Guidelines for Complications of Cancer Treatment Vol VIII

Part B

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Dedicated to
All our patients at
The Tata Memorial Hospital

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Preface

Treatment of cancer by various specialties of Surgical, Medical and Radiation Oncology has seen impressive progress in recent times. This is reflected in the explosion of published medical literature focusing on improved perioperative outcomes of modern surgery and the ever improving outcomes associated with chemotherapy and radiotherapy. The rapid development of targeted treatment has only served to usher in heightened optimism and galvanize cancer research. There has been a more structured approach towards long-term goals of recurrence and death, producing robust evidence for their efficacy or otherwise. But such is not the case for 30-day complications and its impact on morbidity / mortality and its management.

According to the Centre for Evidence-Based Medicine, "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."

The eighth volume on Evidence Based Management Guidelines brought out by the Tata Memorial Centre attempts to address this issue of complications of modern cancer treatment through an evidence based perspective. It represents a continuation of our commitment to improve cancer care in India.

Not only is the best available evidence presented in this volume, but areas where evidence is lacking are also highlighted. It is sincerely hoped that this volume would not only enable cancer specialists to improve the standard of care when it comes to management of cancer treatment related complications but will also serve as a stimulus for investigators to undertake more clinical research to address unanswered questions to many common complications.

We look forward to your feedback to further improve the quality and applicability of these guidelines in our country.

February, 2009
Mumbai, India

R. A. Badwe
Director, Tata Memorial Centre

Section — I

General

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Complications In Breast Cancer Surgery

Breast is a surface organ and breast surgeries are mainly associated with non-life threatening, minor morbidities. The major complications are possibly due to accidental axillary vein injuries or may be related to any associated reconstructive surgery. The most commonly encountered problems are a consequence of axillary lymph node dissection and neurological symptoms.

For ease of understanding and discussions these complications can be broadly grouped as under:

1. General surgical-wound related complications such as hematoma, infections, flap necrosis, seroma, wound dehiscence, keloids and hypertrophic scars
2. Placement of incisions and cosmesis- mastectomy incision, dog-ear formation, nipple deviation and breast distortion
3. Brachial plexopathy and sensory neurological symptoms
4. Axillary lymph node dissection and lymphoedema
5. Axillary webs

6. Complications after breast reconstruction and implant surgery
7. Treatment related local symptoms (radiation, chemotherapy)
8. Quality of life and early psychosocial implications

General surgical-wound related complications

Most of the minor wound complications after breast surgery are not well documented and managed as outpatients and occur in up to 30% cases. These are mainly minor wound infections, seroma and hematoma managed conservatively.

Wound infection rates postoperatively after breast surgery have been reported in various retrospective studies ranging from 3-15% [1-4] and some Phase III studies of preoperative antibiotics with varied effects on wound infection rates.[5-7] The largest data on wound infection is a meta-analysis reported by Platt et al in 1993 [8]. The wound infection rates were analyzed in 2587 breast surgeries with a 3.8% infection rate, most commonly by staphylococcal skin flora. Most common risk factors in all these studies have been old age, obesity, and diabetes, tobacco smoking and alcohol consumption. Prior open biopsy has also been implicated as a cause of higher wound infection after definitive surgery as compared to needle biopsy [9,10]. Smoking and diabetes are known to affect the small vessels in the skin and lead to delays in wound healing and wound dehiscence, and increase wound infection rates nearly four-fold [2].

Role of preoperative antibiotics

Preoperative and perioperative antibiotics have been variously used to reduce wound infections in surgical procedures. But most of these are biased towards use in only high risk cases or infected cases. As routine use in elective clean cases, antibiotic

prophylaxis has been studied in multiple retrospective and prospective randomized trials. Some studies have clearly shown a reduction up to 40% in infection rates [1,6,10], while the meta-analysis by Platt et al [8] showed a reduction in wound infection rates by 38% when used in high-risk cases. On the other hand, various studies failed to show any difference in rate of wound infection after breast surgery [11,7] but did show a delay in onset of wound infection (17.7 days versus 9.6 days) [11].

Formation of seroma and repeated aspirations increases the risk for postoperative infections after breast surgery. This risk especially is higher during the adjuvant chemotherapy and extra care needs to be taken to follow strict asepsis during seroma aspirations. Any signs of infection in the form of fever, raised counts, turbid aspiration from the axilla or frank pus require immediate intervention with incision and drainage with a corrugated rubber drain insertion to avoid disseminated sepsis. The aspirate should be cultured to assess the antibiotic sensitivity.

Seroma formation after breast surgery

Breast is an organ with a very rich lymphatic drainage into the axillary lymph nodes, internal mammary nodes and the supraclavicular lymph nodal basins. At the same time, due to the axillary dissection (usually till level II or level III as in most cases), the lymphatic channels open up and account for the large amount of seroma in the axillary cavity after breast conservation surgery, and under the flaps after a mastectomy. Due to the absence of inherent clotting factors in the lymph fluid, and low fibrinogen and fibrinolytic activity [12], the lymphatic channels remain open for a longer period and account for the large amount of seroma. Seroma formation is seen in 70-80% cases after complete axillary clearance with definitive breast surgery for cancer [13]. Sentinel node biopsy

promises to reduce this risk of seroma by limiting the axillary dissection.

In the immediate postoperative period this seroma is taken care of by a closed suction drainage which is left in for a period of 10-12 days. After this, the drain is taken out and continued seroma is managed by a simple percutaneous needle aspiration using a wide bore needle (mostly an 18 G) with a 20 c.c. disposable syringe under strict asepsis. Usually due to the insensate flaps after axillary dissection, this procedure is an absolutely painless procedure. Seroma prevents the mastectomy flaps from adhering to the chest wall and impairs the healing process. In addition, the use of external breast prosthesis is also difficult in presence of excessive seroma. However, seroma is advantageous after a breast conservation surgery as it helps in reforming the breast contour by filling up the lumpectomy cavity and helps improve cosmesis. Generally, the seroma lasts for 4-6 weeks with gradual reduction in the volume collecting, and dries up nearly completely with gradual obliteration of the open lymphatic channels with setting in of fibrosis. Persistent seroma and large volumes of aspirations are noted mainly in women with a higher body mass (obesity) [14].

Various methods have been suggested and tested for reducing postoperative seroma. Such as shortening the duration of closed low-pressure suction drainage (from 2 weeks to 2 days) [15]. There was no difference in infection rates and lymphoedema. But the duration of seroma aspiration increased with shorter durations of drainage (73% with 10-day axillary drain; 86% with 2-days axillary drainage; and 97% where no drain was used).

Compression and strapping of axilla and chest wall [16,17] and even suturing of flap to muscle to reduce dead space [18] have been suggested as methods for reducing seroma. Reducing shoulder movements also appear to reduce

seroma [19,20]. Use of electrocautery has been implicated as the cause for larger volumes of seroma [21]. The same was tested in a randomized controlled trial [14] of electrocautery versus using a knife and ligatures during axillary clearance. There was no difference in volumes and duration of seroma formation in either arm. The other randomization was between corrugated drainage versus low-pressure suction drain. Again no difference was noted between both interventions.

Injection of sclerosing agents have also been attempted unsuccessfully in reducing seroma. Agents such as tetracycline, bovine thrombin, fibrin glues and sealants have failed to produce any reduction in seroma formation [22,23,24,25].

Hematoma

The incidence of hematoma formation has reduced considerably after the advent of the electrocautery. Use of sharp dissection using the knife was associated with higher incidence of hematoma. Minor hematoma may be managed conservatively and are usually self-limiting. Larger collections imply bleeding which needs to be checked surgically. The primary preventive measure is to ensure meticulous hemostasis taking care of all the named and unnamed tributaries of the axillary vessels, and chest wall perforators, using judiciously ligatures or surgical clips where necessary for hemostasis. Any concomitant medication such as aspirin or anticoagulant therapy should be discontinued in case a major surgery is being contemplated.

Neuropathic pain and paresthesia

Following axillary clearance and disconnection of the intercostobrachial and medial cutaneous nerve of the arm, there is frequently a ‘burning pain’, ‘piercing pain’, or even a ‘constricting pain’ which is invariably stimulated by cold contact or even a cold breeze. The numbness may actually be

preceded by increased sensory hyperesthesia in 20-30% cases [26,27]. Most of this pain may reduce over a period of time but a chronic pain still persists for long periods with waxing and waning by external stimulation [28]. This pain is considerably significant in younger women, larger tumors, post-radiation and chemotherapy, and in women with poor coping skills. In fact, antidepressants are sometimes prescribed to manage such neuropathic pain [29].

Damage to the lateral thoracic nerve to serratus anterior can result in permanent deformity of 'winging of the scapula' and intractable pain. Care should be taken not to venture too close to the nerve during axillary dissection especially while using an electrocautery for dissection. Transection of the medial and lateral pectoral nerves can permanently denervate the pectoralis muscle and cause cosmetic and functional disability.

Saving the intercostobrachial nerve was considered as a way of reducing postoperative neuropathic pain. Unfortunately, this may not be so as traction on the nerve or partial nerve damage (neuropraxia) eventually results in more intractable neuropathic pain and distress.

Proper Incision Planning

Proper placement of incisions in both breast conservation surgery and at the time of mastectomy goes a long way in improving quality of life of the woman. At the time of lumpectomy, incisions in upper half of the breast should be circumferentially planned while in the lower half, radial incisions are preferred for better cosmetic outcome. In case an excision of skin ellipse is necessary, a radial incision is better to avoid nipple deviations and poor cosmetic outcome.

An important precaution to be remembered at the time of mastectomy incisions is to not allow the lateral most point of incision to cross the anterior axillary line and to use a tear-drop or pear-shaped incision with point on medial aspect and

broader excision laterally to allow a flat scar later without the 'dog-ear' finish. Not only is the scar more acceptable, but also makes it easier to use the breast prosthesis later.

Dog-ears are especially more common in obese and heavy built women with thick axillary fat pads. Sometimes a Halsted's oblique incision or closing the transverse incision as a 'T' or 'Y'-shape may help in reducing the 'dog-ear' formation [30].

Breast Cellulitis and 'Recall' Reactions

There is a known skin reaction seen in patients who have previously received taxane-based (especially docetaxel) chemotherapy at the time of radiation therapy to the breast after breast conservation surgery. This 'recall' can be very distressing with severe exfoliation of skin and patient may even need to be hospitalized [31]. The main line of treatment is steroids and conservative management with rest and antibiotics.

Axillary Lymph Node Dissection and Lymphoedema

It is a standard procedure to carry out levels I, II and III clearance of axillary lymph nodes in case of invasive breast cancer more than 1cm in size. With complete axillary clearance, lymphoedema of the upper limb is a known entity. It is seen in 13-27% of women with breast cancer after surgery [32,33]. The incidence of postoperative lymphoedema can be reduced by aggressive physiotherapy, and prevention of upper extremity trauma or infection.

A prospective audit was carried out during October 2007 to April 2008 at the Breast Services outpatients' clinic at TMH to assess the incidence of lymphoedema in the follow up patients after completion of breast cancer treatment (unpublished results). Of the 496 women studied, 76 (15.3%)

had significant lymphoedema. The factors that increased the risk for lymphoedema were BMI more than 25% (p=0.007), surgery on the dominant side (p=0.045), and post-mastectomy (as compared to BCT) (p<0.001). Surgery on dominant hand increased risk of developing lymphoedema 1.7 times (HR 1.76, 95% CI 1.01-3.05. p=0.045); BMI >25% increased lymphoedema 5.3 times (HR=5.38, 95% CI 1.5-18.2, p=0.007); at 20-25% BMI, risk increased by 3.4 times (HR=3.4, 95% CI 0.98-12.2, p=0.05).

Axillary Webs

Axillary webs are tight bands of scar tissue developing after an axillary clearance in 10% cases. They appear like a cord-like structure across the axilla, along the arm occasionally reaching the thumb, and may sometimes even be painful. But their main effect is a tightness and limitation of movement at the shoulder. The treatment is to only observe and allow this to resolve on its own. It mostly disappears without any sequelae.

Post Breast Reconstruction Disasters

Breast reconstruction using free flaps is commonly offered for multicentric disease and involves extensive surgery at the donor site with sometimes skin grafting performed to cover the defects. Free microvascular surgery carries the inherent risk of vascular accidents with venous or arterial thrombosis. The consequences can be disastrous. Not only is there a failure of procedure but there is also major loss of tissue cover for the primary site and the psychological stress for the patient is extreme. The donor site also carries a risk of hematoma, seroma, flap necrosis and hypertrophic scars. Breast implants may need to be removed early in the postoperative period in case of wound infection. Implants also carry a risk of rupture or displacement.

References:

1. Prophylaxis against wound infection following herniorrhaphy or breast surgery.

Platt R, Zucker JR, Zaleznik DF, Hopkins CC, Dellinger EP, Karchmer AW, Bryan CS, Burke JF, Wikler MA, Marino SK, et al. J Infect Dis. 1992 Sep;166(3):556-60.

Abstract: The effect of perioperative antibiotic prophylaxis on definite wound infections was assessed for 3202 herniorrhaphies or selected breast surgery procedures. Patients were identified preoperatively and monitored for greater than or equal to 4 weeks. Thirty-four percent of patients (1077/3202) received prophylaxis at the discretion of the surgeon; 86 definite wound infections (2.7%) were identified. Prophylaxis recipients were at higher risk for infection, with a higher proportion of mastectomies, longer procedures, and other factors. Patients who received prophylaxis experienced 41% fewer definite wound infections (odds ratio [OR], 0.59; 95% confidence interval [CI], 0.35-0.99; P = .04) and 65% fewer definite wound infections requiring parenteral antibiotic therapy (OR, 0.35; 95% CI, 0.15-0.88; P = .02) after adjustment for duration of surgery and type of procedure. Additional adjustment for age, body mass index, the presence of drains, diabetes, and exposure to corticosteroids did not change the magnitude of this effect meaningfully. The effect of prophylaxis was similar for all procedures studied. In the absence of formal guidelines, surgeons at these institutions administered prophylaxis preferentially to patients at highest risk.

PMID: 1500739 [PubMed - indexed for MEDLINE]

2. Smoking as a risk factor for wound healing and infection in breast cancer surgery.

Sørensen LT, Hørby J, Friis E, Pilsgaard B, Jørgensen T. Eur J Surg Oncol. 2002 Dec;28(8):815-20.

AIM: Clinical studies suggest that smoking is associated with wound necrosis after breast cancer surgery. However, the significance of smoking as a risk factor for wound infection, skin flap necrosis, and epidermolysis when adjusting for other potential risk factors remains to be studied. METHODS: From June 1994 through August 1996, 425 patients underwent breast cancer surgery as simple mastectomy, modified radical mastectomy, or breast conserving surgery. The patients were evaluated postoperatively for wound infection, skin flap necrosis, and epidermolysis. Association between these complications and 17 patient, operative, and postoperative variables were analyzed by three separate multiple logistic regression analyses. RESULTS: When compared to non-smoking, smoking was significantly associated with wound infection after all types of surgery (light smoking (1-14 grams per day): [odds ratio (OR)=2.95, 95% confidence interval (95% CI)=1.07-8.16], and heavy smoking (>/=15 grams per day): OR=3.46 (1.52-7.85). A similar significant association was found as regards skin flap necrosis and epidermolysis after simple mastectomy and modified radical mastectomy: both light and heavy smoking were predictive for skin flap necrosis: light smoking: OR=6.85 (1.96-23.90), heavy smoking: OR=9.22 (2.91-29.25) and for epidermolysis: light smoking: OR=3.98 (1.52-10.43) and heavy smoking: OR=4.28 (1.81-10.13). No significant dose-response relation was disclosed. Other risk factors and confounders associated with complicated wound healing were adjusted for in the analysis: diabetes, obesity, alcohol, NSAIDs, duration of surgery, and surgical experience. CONCLUSION: Independent of other risk factors,

smoking is predictive for post-mastectomy wound infection, skin flap necrosis, and epidermolysis.

PMID: 12477471 [PubMed - indexed for MEDLINE]

3. Wound complications after modified radical mastectomy compared with tylectomy with axillary lymph node dissection.

Vinton AL, Traverso LW, Jolly PC. Am J Surg. 1991 May;161(5):584-8.

Tylectomy with axillary lymph node dissection and radiotherapy (TAD) has become an accepted treatment for early breast cancer and has been shown to result in equal 5- and 8-year survival when compared with modified radical mastectomy (MRM). In order to determine the safety of TAD with respect to wound complications and to identify potential risk factors, we reviewed the charts of 560 patients undergoing MRM (n = 387) and TAD (n = 173) at Virginia Mason Medical Center from 1983 through 1989. The incidence of infection, seroma, hematoma, and epidermolysis were compared, and obesity, age 60 years or older, smoking, antibiotics, and wound drainage were examined as possible risk factors. There were more wound complications in the MRM group versus the TAD group (49% versus 35%; p less than 0.01), specifically more seromas (29% versus 18%; p less than 0.01) and epidermolysis (18% versus 0%). In the MRM group, age 60 years or older was associated with seroma (p less than 0.01) and smoking was associated with epidermolysis (p less than 0.01). In the TAD group, obesity was associated with infection. In both groups, volume of drainage from closed suction wound drains greater than 30 mL in the 24 hours prior to removal of the last drain was associated with seroma (p less than 0.05).

PMID: 2031542 [PubMed - indexed for MEDLINE]

4. Preoperative core needle biopsy as an independent risk factor for wound infection after breast surgery.

Witt A, Yavuz D, Walchetseder C. et al. Obstet Gynecol. 2003 Apr;101(4):745-50.

OBJECTIVE: Diverging findings concerning the rate of postoperative wound infections in patients undergoing breast surgery have been reported, and little is known regarding the possible risk factors for these infections and their relative importance. We assessed risk factors for wound infection, placing particular emphasis on the influence of preoperative procedures such as core needle biopsy. METHODS: In a prospective evaluation of 326 patients undergoing breast surgery, we identified risk factors for wound infections by univariate analysis and subsequent step-wise multiple logistic regression. Assessment of wound infection was based on a simple wound scoring system. RESULTS: Of the 326 patients, 50 (15.3%) developed wound infections. As expected, after univariate analysis a higher proportion of post surgical infections was observed in patients with diabetes (33.3% versus 14.3%; odds ratio [OR] = 3.00, 95% confidence interval [CI] 1.109, 8.157; P =.03) and malignant tumors (21.2% versus 6.8%; OR = 3.716, 95% CI 1.762, 7.849; P <.001). Patients with wound infections were significantly older than those without (mean age 63.73 versus 51.44 years, P <.001). Surprisingly, patients who underwent core needle biopsy, which in most cases was performed within 1-3 days before breast surgery, were also at significantly higher risk for developing a wound infection (22.3% versus 9.6%; OR = 2.718, 95% CI 1.454, 5.076; P =.001). This effect remained unchanged when controlled for potential confounders by step-wise multiple logistic regression. CONCLUSION: In breast surgery, the independent risk factors for wound infections are older age and preoperative core needle biopsy.

PMID: 12681880 [PubMed - indexed for MEDLINE]

5. Long-acting versus short-acting cephalosporins for preoperative prophylaxis in breast surgery: A randomized double-blind trial involving 1,766 patients.

Thomas R, Alvino P, Cortino GR, et al. Chemotherapy. 1999 May-Jun;45(3):217-23.

Postoperative infectious complications after breast surgery may result in significant morbidity, psychological trauma, and additional costs. We assessed the efficacy of preoperative antibiotic prophylaxis for surgery in a randomized, double-blind trial of 1,766 patients undergoing breast surgery. From January 1, 1996 to August 31, 1997, all eligible patients were assigned randomly to receive a single dose of ceftriaxone (2 g) or ceftazidime (2 g) given intravenously at the induction of anesthesia, with no further doses. The groups were similar with respect to age, operative procedure, operative time and time to discharge after operation. The patients who received ceftriaxone prophylaxis had 54.4% fewer overall infections than those who received ceftazidime prophylaxis. Wound infection occurred in 0.45% of the ceftriaxone recipients (2 of 883) and 0.91% of the ceftazidime recipients (8 of 883). This prospective randomized double-blind study showed that the long-acting regimen containing ceftriaxone is more cost-effective than the short-acting ceftazidime in preventing postoperative infections in patients subjected to breast surgery.

PMID: 10224345 [PubMed - indexed for MEDLINE]

6. Perioperative antibiotic prophylaxis for herniorrhaphy and breast surgery.

Platt R, Zaleznik DF, Hopkins CC, Dellinger EP, et al. N Engl J Med. 1990 Jan 18;322(3):153-60.

We assessed the efficacy of perioperative antibiotic prophylaxis for surgery in a randomized, double-blind trial of 1218 patients undergoing herniorrhaphy or surgery involving the breast, including excision of a breast mass, mastectomy,

reduction mammoplasty, and axillary-node dissection. The prophylactic regimen was a single dose of cefonicid (1 g intravenously) administered approximately half an hour before surgery. The patients were followed up for four to six weeks after surgery. Blinding was maintained until the last patient completed the follow-up and all diagnoses of infection had been made. The patients who received prophylaxis had 48 percent fewer probable or definite infections than those who did not (Mantel-Haenszel risk ratio, 0.52; 95 percent confidence interval, 0.32 to 0.84; P = 0.01). For patients undergoing a procedure involving the breast, infection occurred in 6.6 percent of the cefonicid recipients (20 of 303) and 12.2 percent of the placebo recipients (37 of 303); for those undergoing herniorrhaphy, infection occurred in 2.3 percent of the cefonicid recipients (7 of 301) and 4.2 percent of the placebo recipients (13 of 311). There were comparable reductions in the numbers of definite wound infections (Mantel-Haenszel risk ratio, 0.49), wounds that drained pus (risk ratio, 0.43) Staphylococcus aureus wound isolates (risk ratio, 0.49), and urinary tract infections (risk ratio, 0.40). There were also comparable reductions in the need for postoperative antibiotic therapy, non-routine visits to a physician for problems involving wound healing, incision and drainage procedures, and readmission because of problems with wound healing. We conclude that perioperative antibiotic prophylaxis with cefonicid is useful for herniorrhaphy and certain types of breast surgery.

PMID: 2403655 [PubMed - indexed for MEDLINE]

7. Antibiotic prophylaxis for post-operative wound infection in clean elective breast surgery.

Gupta R, Sinnett D, Carpenter R, et al. Eur J Surg Oncol. 2000 Jun;26(4):363-6.

Antibiotic prophylaxis has been used to good effect in the prevention of post-operative wound infections in patients

undergoing gastrointestinal operations. We have assessed the use of a single dose of intravenous antibiotic (Augmentin 1.2 g), given with induction of anaesthesia as prophylaxis, against post-operative wound infection in women undergoing clean, elective breast surgery. Three hundred and thirty-four patients were recruited. Of the 164 receiving antibiotic prophylaxis 29 (17.7%) had wound infections compared with 32 (18.8%) in the placebo group (P=0.79). There were no significant differences in any other post-operative infective complications. Antibiotic prophylaxis is probably not required in clean, elective breast surgery. Copyright 2000 Harcourt Publishers Ltd.

PMID: 10873356 [PubMed - indexed for MEDLINE]

8. Perioperative antibiotic prophylaxis and wound infection following breast surgery.

Platt R, Zucker JR, Zaleznik DF, et al. J Antimicrob Chemother. 1993 Feb;31 Suppl B:43-8.

The effectiveness of perioperative antibiotic prophylaxis against wound infections following breast surgery was investigated by meta-analysis of published data from a randomized clinical trial and an observational data set, which included a total of 2587 surgical procedures, including excisional biopsy, lumpectomy, mastectomy, reduction mammoplasty and axillary node dissection. There were 98 wound infections (3.8%). Prophylaxis was used for 44% (1141) of these procedures, cephalosporins accounted for 986 (86%) of these courses of antibiotics. Prophylaxis prevented 38% of infections, after controlling for operation type, duration of surgery and participation in the randomized trial (Mantel-Haenszel Odds Ratio = 0.62, 95% confidence interval = 0.40-0.95, P = 0.03). There was no significant variation in efficacy according to operation type or duration. We conclude that antibiotic prophylaxis significantly reduces the risk of

postoperative wound infection following these commonly performed breast procedures.

PMID: 8449845 [PubMed - indexed for MEDLINE]

9. Complications of mastectomy and their relationship to biopsy technique.

Lipshy KA, Neifeld JP, Boyle RM, et al. Ann Surg Oncol. 1996 May;3(3):290-4.

BACKGROUND: Wound complication rates after mastectomy are associated with several factors, but little information is available correlating biopsy technique with the development of postmastectomy wound complications. Fine-needle aspiration (FNA) biopsy is an accurate method to establish a diagnosis, but it is unknown whether this approach has an impact on complications after mastectomy. METHODS: Charts of 283 patients undergoing 289 mastectomies were reviewed to investigate any association between biopsy technique and postmastectomy complications. RESULTS: The diagnosis of breast cancer was made by FNA biopsy in 50%, open biopsy in 49.7%, and core needle biopsy in 0.3%. The overall wound infection rate was 5.3% (14 of 266), but only 1.6% when FNA biopsy was used compared with 6.9% with open biopsy ($p = 0.06$). Among 43 patients undergoing breast reconstruction concomitantly with mastectomy, the infection rate was 7.1% (0% after FNA, 12% after open biopsy). Neither the development of a postoperative seroma (9.8%) nor skin flap necrosis (5.6%) was influenced by the biopsy technique used. CONCLUSIONS: These data suggest that wound infections after mastectomy may be reduced when the diagnosis of breast cancer is established by FNA biopsy.

PMID: 8726185 [PubMed - indexed for MEDLINE]

10. Does re-operation predispose to postoperative wound infection in women undergoing operation for breast cancer?

Tran CL, Langer S, Broderick-Villa G, et al. Am Surg. 2003 Oct;69(10):852-6.

Re-operations for breast cancer predispose to a higher risk of postoperative wound infections than primary procedures. We accomplished a retrospective chart review of 320 women who underwent multiple breast cancer procedures between 10/97 and 8/02. The mean number of procedures was 2.4 (range, 2-5). The overall incidence of wound infection was 6.1 per cent. Wound infections developed, on average, 12 days after surgery (range, 2-30). There was a statistically significant difference in the incidence of wound infection comparing the initial procedure versus the subsequent operation (1.6% vs. 9.4%, P <0.001). This was also seen with re-operation after an operative biopsy compared to operation after a core biopsy (11.1% vs. 9.7%, P < 0.01). The incidence was increased to 22.0 per cent when the initial operation involved lymph node dissection (sentinel lymph node biopsy or complete axillary lymph node dissection). Wire localization did not increase the incidence of postoperative wound infections, and prophylactic antibiotics were associated with a decreased incidence of wound infection in the re-operative setting. The incidence of wound infection is increased with reoperation after operative biopsy compared to operation after core biopsy and is further increased when the initial biopsy involved lymph node dissection.

PMID: 14570362 [PubMed - indexed for MEDLINE]

11. A prospective, randomized double-blind study of the use of antibiotics at the time of mastectomy.

Wagman LD, Tegtmeier B, Beatty JD, et al. Surg Gynecol Obstet. 1990 Jan;170(1):12-6.

The ability of perioperative cefazolin to reduce the incidence of postoperative wound infection in patients undergoing

ablative surgical treatment for carcinoma of the breast was tested in this prospective, randomized, double-blinded study. From May 1983 until December 1985, 118 women were divided into two groups at random. Group 1 consisted of 59 patients and received cefazolin and group 2 was made up of 59 patients who received a placebo. The groups were similar with respect to age, operative procedure, operative time and time to discharge after operation. Three infections occurred among those in group 1 and five among those in group 2 ($p = 0.72$). The time to onset of infection was delayed in the patients in group 1 versus those in group 2 (17.7 days versus 9.6 days, $p = 0.04$). Six of eight infections occurred in patients in whom an interval between biopsy and definitive surgical treatment was present. Prophylactic antibiotics in mammary operations did not reduce postoperative wound infections in this study.

PMID: 2403697 [PubMed - indexed for MEDLINE]

12. The composition of serous fluid after axillary dissection.

Bonnema J, Ligtenstein DA, et al. Eur J Surg. 1999 Jan;165(1):9-13.

OBJECTIVE: To analyse the composition of the serous fluid formed after axillary dissection. DESIGN: Descriptive study. SETTING: University hospital and teaching hospital, The Netherlands. SUBJECTS: 16 patients whose axillas were dissected as part of a modified radical mastectomy for stage I or II breast cancer. MAIN OUTCOME MEASURES: Chemical and cellular composition of axillary drainage fluid on the first, fifth, and tenth postoperative days compared with the same constituents in blood and with reported data on the composition of peripheral lymph. RESULTS AND CONCLUSION: On the first postoperative day the drainage fluid contained blood contents and a high concentration of creatine phosphokinase (CPK). After day one it changed to a

peripheral lymph-like fluid but containing different cells, more protein, and no fibrinogen, making coagulation impossible. The reduction in the fluid production must be caused by other wound healing processes, such as formation of scars and connective tissue.

PMID: 10069628 [PubMed - indexed for MEDLINE]

13. Seroma following breast cancer surgery.

Pogson CJ, Adwani A, et al. Eur J Surg Oncol. 2003 Nov;29(9):711-7.

BACKGROUND: Seroma is a common problem following breast cancer surgery causing patient discomfort and prolongation of hospital stay. METHODS: This manuscript reviews the relevant literature obtained by an extensive search of the medline database. In addition papers were also derived from the reference lists of retrieved articles. RESULTS AND CONCLUSION: The advantages and disadvantages of the various methods to deal with seroma are discussed. Based on this an individual patient based policy can be formulated.

PMID: 14602488 [PubMed - indexed for MEDLINE]

14. Influence of surgical technique on axillary seroma formation: a randomized study.

Nadkarni MS, Rangole AK, et al. ANZ J Surg. 2007 May;77(5):385-9.

The aim of this study was to evaluate the influence of surgical technique in the form of electrocautery and suction drains on seroma formation following surgery for breast cancer. A prospective randomized study was carried out. One hundred and sixty patients with breast cancer who underwent surgery were allocated to four arms using a 2 x 2 factorial design. This method enabled us to evaluate the independent effect of two different causative factors on the incidence of

postoperative seroma formation using a single dataset with limited numbers. The main outcome measure was postoperative seroma formation defined as a postoperative axillary collection requiring more than one aspiration after removal of the drain. The incidence of seroma in our institution is 90%. Incidence of postoperative seroma was 88.3% if electrocautery was used, which reduced to 82.2% if surgery was carried out using scissors for dissection and ligatures for haemostasis (P = 0.358). There was no influence on the incidence of seroma formation whether suction drain (84.6%) or corrugated drains (86.1%) were used (P = 0.822). The use of electrocautery in axillary dissection does not adversely affect postoperative seroma formation after surgery for breast cancer. The use of different drainage techniques has no bearing on the postoperative seroma formation. The surgical technique has no influence on the rate of seroma formation after surgery for breast cancer.

PMID: 17497983 [PubMed - indexed for MEDLINE]

15. Reduced use of drains following axillary lymphadenectomy for breast cancer.

Talbot ML, Magarey CJ. ANZ J Surg. 2002 Jul;72(7):488-90.

BACKGROUND: Axillary dissection is frequently performed during the treatment of operable breast cancer, and is associated with certain morbidities. Accumulation of axillary fluid, otherwise known as a seroma, is a frequent complication that appears to be related to the degree of dissection. Based on empirical evidence, surgeons have attempted to reduce the occurrence and duration of seromas by using suction drainage, but this concept has been challenged by several authors. OBJECTIVES: To determine if the natural history of seroma fluid accumulation after axillary surgery is altered by the duration of suction drainage or non-placement of a drain. METHODS: Ninety consecutive patients having axillary

dissection for breast cancer had either prolonged suction drainage (mean 9.6 days), short duration drainage (2 days), or had no drain placed. Seromas were aspirated and the time to cessation of fluid accumulation determined, as well as any other wound complications. RESULTS: There was no difference in the number of wound complications or the duration of fluid accumulation between the three groups, being 26.6, 25.7, and 27.9 days, respectively. Patients having no drains placed required more frequent aspirations. CONCLUSIONS: The duration of seroma fluid accumulation is not altered by the placement of a suction drain following axillary lymphadenectomy.

PMID: 12123509 [PubMed - indexed for MEDLINE]

16. External compression dressing versus standard dressing after axillary lymphadenectomy.

O'Hea BJ, Ho MN, Petrek JA. Am J Surg 1999 Jun;177(6):450-3

BACKGROUND: Closed-catheter drainage after axillary lymph node dissection (ALND) for breast cancer may constitute a significant inconvenience to the recovering patient, and may also serve as portals of entry for bacteria. Any intervention that could reduce the volume and duration of postoperative drainage would be beneficial. The purpose of this study was to determine whether an external compression dressing after ALND would decrease postoperative drainage, afford earlier drain removal, and reduce subsequent seroma formation. PATIENTS AND

METHODS: One hundred thirty-five women undergoing definitive surgical treatment for breast cancer were randomized to receive a compression dressing (n = 66) or standard dressing (n = 69). They were also stratified for modified radical mastectomy (MRM; n = 74) or breast conservation therapy (BCT; n = 61). All patients had ALND. The compression

dressing consisted of a circumferential chest wrap of two 6-inch Ace bandages, held in place by circumferential Elastoplast bandage, and it was applied by the same nurse. This dressing remained intact until postoperative day 4. Patients in the standard dressing group (control) were fitted with a front-fastening Surgibra only. Drains were removed when the total daily amount was <50 cc. Postoperative drainage volume, total days with drain, and frequency of seroma formation were recorded for each patient. RESULTS: After 4 days, wound drainage in both groups was nearly identical (compression = 490 cc, standard = 517 cc; P = 0.48). Total days with drain were also similar (compression = 6.4 days, standard = 6.1 days; P = 0.69). The compression dressing did not reduce seroma formation. In fact, there was a statistically significant increase in the number of seroma aspirations per patient in the compression group (compression = 2.9, standard = 1.8; P <0.01). The increase in seroma aspirations was more significant in MRM patients (compression = 3.1, standard = 1.7; P <0.01) than in BCT patients (compression = 2.6, standard = 1.8; P = 0.20). CONCLUSIONS: External compression dressing fails to decrease postoperative drainage and may increase the incidence of seroma formation after drain removal. Thus, routine use of a compression dressing to reduce postoperative drainage after ALND for breast cancer is not warranted.

PMID: 10414691 [PubMed - indexed for MEDLINE]

17. Axillary padding as an alternative to closed suction drain for ambulatory axillary lymphadenectomy: a prospective cohort of 207 patients with early breast cancer.

Classe JM, Dupre PF, François T, et al. Arch Surg. 2002 Feb;137(2):169-72; discussion 173.

HYPOTHESIS: Axillary lymphadenectomy performed without the use of a drain but with padding of the axilla is

feasible and safe on an outpatient basis in the setting of conservative surgery for breast cancer. DESIGN: Prospective clinical study. SETTING: Public oncology center. PATIENTS: Two hundred seven patients were treated in our oncology center between January 11 and December 28, 1999, by means of this method of axillary lymphadenectomy based on axillary padding without a drain. One-day surgery was offered to each patient. INTERVENTION: At the end of each functional axillary lymphadenectomy, the axilla was padded with the use of axillary aponeurosis and local muscles. Axillary suction drains were not used at all in this series of patients. MAIN OUTCOME MEASURES: Prospective assessment was performed, without randomization, with regard to the length of hospital stay, the reasons for postoperative conversion from 1-day surgery to traditional hospitalization, and postoperative complications. RESULTS: Eighty-seven (42.0%) of the 207 patients underwent a 1-day procedure. In the 1-day surgery group, 87 (84.5%) of the 103 patients benefited from a true 1-day surgery procedure. The main reasons for conversion were nausea and anxiety rather than surgical complications. Hospital stay never exceeded 3 days. The most common postoperative complication was axillary seroma, with an average incidence of 22.2%. CONCLUSION: Breast-preserving surgery with axillary lymphadenectomy and padding of the axilla, precluding the use of a drain, is feasible and safe on a 1-day surgery basis for selected consenting patients.

PMID: 11822954 [PubMed - indexed for MEDLINE]

18. Effect of closing dead space on seroma formation after mastectomy—a prospective randomized clinical trial.

Coveney EC, O'Dwyer PJ, et al. Eur J Surg Oncol 1993 Apr;19(2):143-6

To evaluate the effect of closing dead space on seroma formation after mastectomy, 39 patients undergoing 40

mastectomies with axillary node clearance were randomized to undergo suturing of skin flaps to underlying muscle or conventional skin closure. Duration of closed suction drainage, 72 h, and shoulder exercises, commencing on the first post-operative day, were standardized for both groups. Closed suction drainage was significantly less ($P < 0.05$) in the group that had flaps sutured 272 +/- 46 ml vs 393 +/- 39 ml. Also fewer patients in the flap sutured group developed seromas, 5 (25%) vs 17 (85%) chi 2 = 12.2 $P < 0.001$. Three patients in the group that had conventional skin closure had breakdown of wound edges, two developing a prolonged serous discharge, while none occurred in the sutured group. A functional range of shoulder motion was attained at 6 months in 14 (70%) patients in the flap sutured group compared with nine (45%) in the conventional skin closure group (P = NS). These results confirm the value of suturing skin flaps to underlying muscle in reducing local morbidity after mastectomy and suggest that this technique should be included in the closure of all mastectomy wounds.

PMID: 8491318 [PubMed - indexed for MEDLINE]

19. Early versus delayed shoulder motion following axillary dissection: a randomized prospective study.

Lotze MT, Duncan MA, Gerber LH, et al. Ann Surg. 1981 Mar;193(3):288-95.

The role and timing of physical therapy following axillary dissection for melanoma, or in conjunction with modified radical mastectomy has not been extensively studied. A prospective randomized clinical trial was carried out over an 18-month period in the Surgery Branch, National Cancer Institute (NCI) and Department of Rehabilitation Medicine, Clinical Center, in which patients were assigned to receive one of two postoperative physical therapy regimens. Patients were assigned to receive graduated increases in allowed range of motion (ROM), either beginning on postoperative day 1

(early) or day 7 (delayed). All patients were advanced to full pain-free ROM when the suction catheters were removed. A total of 36 patients with 40 axillary dissections (19 for melanoma, 21 for breast cancer) were included in this study. Patients randomized to receive early motion had more total wound drainage (805 +/- 516 cc vs. 420 +/- 301 cc, $p < 0.01$), more days of drainage (10.3 +/- 5.3 vs. 6.2 +/- 2.7, $p < 0.01$), and later postoperative day of discharge (12.8 +/- 5.1 days vs. 9.2 +/- 4.0 days, $p < 0.02$) than did patients who started motion on day 7. Wound complications including infection and small areas of skin breakdown occurred more frequently in the early group (seven patients vs. one patient, $p < 0.02$). No significant differences in the per cent of patients achieving functional ROM could be identified between these two groups at one, three or six months after operation. Transient serratus anterior palsy (12 patients) and latissimus dorsi palsy (2 patients) occurred in approximately 30% of all patients, regardless of group (breast vs. melanoma, early vs. delayed), but returned to normal in all patients. The early institution of flexion and abduction exercises following axillary dissection thus appears to have a deleterious effect on wound healing and drainage. Adequate functional ROM is attained in all patients with a minimum of complications when active motion exercises are delayed for up to 7 days after axillary dissection.

PMCID: PMC1345064

PMID: 7011221 [PubMed - indexed for MEDLINE]

20. Delayed shoulder exercises in reducing seroma frequency after modified radical mastectomy: A prospective randomized study.

Schultz I, Barholm M, Gröndal S. Ann Surg Oncol. 1997 Jun;4(4):293-7.

BACKGROUND: Seromas and impaired shoulder function are well-known complications after modified radical

mastectomy for breast cancer. Early postoperative physiotherapy is a common treatment to avoid shoulder dysfunction. The aim of this study was to evaluate if the frequency of postoperative seromas could be reduced, without increasing shoulder dysfunction, by delayed postoperative shoulder exercises. METHODS: In a prospective study 163 patients with breast cancer undergoing modified radical mastectomy were randomized to physiotherapy starting on postoperative day 1 or day 7. Patients were seen by the surgeons and the physiotherapists during hospital stay and in the outpatient department. Seromas and other complications were registered by the surgeons. The physiotherapists instructed the patients pre- and postoperatively and assessed shoulder function. RESULTS: There was a significantly higher incidence of postoperative seromas in the group of patients that started physiotherapy postoperative day 1 (38%) compared to the group that started physiotherapy postoperative day 7 (22%) ($p < 0.05$). There was no significant difference between the groups in the late outcome of shoulder function. CONCLUSION: The incidence of seromas after modified radical mastectomy for breast cancer is reduced by delaying shoulder exercises one week postoperatively. Earlier postoperative physiotherapy is not necessary to avoid impaired shoulder function.

PMID: 9181227 [PubMed - indexed for MEDLINE]

21. Electrocautery as a factor in seroma formation following mastectomy.

Porter KA, O'Connor S,Rimm E, et al. Am J Surg 1998 Jul;176(1):8-11.

BACKGROUND: Electrocautery has been postulated as a factor in the risk of seroma formation after mastectomy. METHODS: Eighty consecutive mastectomies in 74 patients were randomly assigned to dissection of the mastectomy flaps

with either scalpel (n = 38) or electrocautery (n = 42). Total volume of fluid output through drains and aspirated from seromas was recorded. Other factors investigated included the type of drain utilized, estimated blood loss, and complications.

RESULTS: Seromas developed in 16 wounds in the electrocautery group compared with 5 in the scalpel group (38% and 13%, respectively; P = 0.01). Other factors with an independent risk for seroma included use of Jackson-Pratt drains compared with Blake drains (P = 0.006), and lower estimated blood loss (P = 0.006). No differences in characteristics of patients or in other complications were noted. CONCLUSIONS: Use of electrocautery to create skin flaps in mastectomy reduced blood loss but increased the rate of seroma formation.

PMID: 9683123 [PubMed - indexed for MEDLINE]

22. Intraoperative topical tetracycline sclerotherapy following mastectomy: A prospective, randomized trial.

Rice DC, Morris SM, Sarr MG, et al. J Surg Oncol 2000 Apr;73(4):224-7

BACKGROUND AND OBJECTIVES: Postoperative wound seromas are a frequent and troublesome occurrence after mastectomy. Recent reports have suggested the efficacy of topical sclerosants at reducing their formation. METHODS: A prospective, randomized, double-blinded trial was performed to examine the effect of intraoperatively administered topical tetracycline on the occurrence of postoperative mastectomy seromas. Thirty-two women were randomized to the control arm (normal saline) and 30 women to the tetracycline arm. In the treatment group, 100 ml (2 g) of tetracycline solution was administered topically to the chest wall and skin flaps prior to skin closure. The control group received an equal volume of normal saline. Patients were

monitored for the development of postoperative wound seroma. RESULTS: There were no significant differences between groups regarding total volume of closed suction drainage, numbers of patients leaving hospital with drains in place, or duration of catheter drainage.

Seroma formation 2 weeks postoperatively was greater in the tetracycline group than the control group (53% vs. 22%, P = 0.01). There were no differences between groups regarding the degree of postoperative pain, wound infection, or seroma formation 1 month postoperatively. CONCLUSIONS: Topical tetracycline is not effective at preventing post-mastectomy wound seromas.

PMID: 10797336 [PubMed - indexed for MEDLINE]

23. Seroma formation following axillary dissection for breast cancer: risk factors and lack of influence of bovine thrombin.

Burak WE Jr, Goodman PS, Young DC, et al. J Surg Oncol 1997 Jan;64(1):27-31

BACKGROUND: Seromas of the axillary space following breast surgery can lead to significant morbidity and delay in the initiation of adjuvant therapy. A prospective, randomized study was undertaken to evaluate the effect of bovine spray thrombin on seroma formation following either modified radical mastectomy (MRM) or lumpectomy with axillary dissection (LAD). In addition, risk factors for seroma formation were analyzed and identified. METHODS: A total of 101 patients were randomized to receive either bovine thrombin (20,000 units) (treatment group) or no thrombin (control group) applied to their axilla following either MRM or LAD. Drains were left in place until the preceding 24-hour drainage was < 40 milliliters. The numbers of days the drains were in place and wound complications (including seroma

formation) were recorded. RESULTS: Forty-nine (n = 49) patients were assigned to the treatment gorup and 52 (n = 52) to the control group. MRM was performed on 60 patients (59%) and LAD on 41 (41%). Eighteen of the 49 patients (37%) in the thrombin group developed a seroma in comparison to 21 of the 52 control patients (40%) (P = 0.71). Significant risk factors for seroma formation included increased age, patient weight, initial 72-hour wound drainage, and LAD. No statistically significant differences were observed between treatment and control groups with respect to time to drain removal, or the incidence of other wound complications. CONCLUSION: Although thrombin by itself appears to have no effect on subsequent seroma development following axillary dissection, the identification of predictive variables will be helpful in designing future trials aimed at reducing the incidence of this common complication of breast surgery.

PMID: 9040797 [PubMed - indexed for MEDLINE]

24. Sealing of postoperative axillary leakage after axillary lymphadenectomy using a fibrin glue coated collagen patch: A prospective randomised study.

Berger A, Tempfer C, Hartmann B, et al. Breast Cancer Res Treat. 2001 May;67(1):9-14.

Seroma formation after axillary lymphadenectomy in women with breast cancer remains a problem despite many efforts to reduce surgery-related morbidity. In a prospective, randomised, open, parallel-group, controlled clinical trial we evaluated the effect of a fibrin-glue coated collagen patch (TachoComb H, Nycomed Pharma AS, Denmark) on volume and duration of postoperative axillary drainage, duration of hospital stay, and procedural safety. Sixty patients were included in the study. Patients did not differ with respect to general characteristics, such as age, body mass index, treatment

modality, and tumor stage distribution. In 29 patients, a fibrin-glue coated collagen patch was applied from the apex axillae to the thoracic longus nerve and half a patch was applied to the lateral border of the axillary nerve-vessel bundle. Thirty-one patients were randomised to standard closure of the axillary lymphadenectomy area. The mean duration of axillary drainage was 3.8 +/- 1.9 days in the fibrin-glue treatment group and 3.9 +/- 1.8 days in the control group (p = NS). The mean total drainage volume was 338.5 +/- 251.8 ml in the fibrin-glue treatment group and 370.8 +/- 314.6 ml in the standard closure group (p = NS). The mean length of post-operative hospital stay was 9.1 +/- 2.7 days in the fibrin-glue treatment group and 9.3 +/- 3.6 days in the standard closure group (p = NS). Seven patients (25%) and eight patients (25%) were diagnosed with local inflammation in the fibrin-glue treatment group and the standard closure group, respectively (p = NS). Seroma formation after drain removal was found in 11 patients (39%) in the fibrin-glue treatment group and in 13 patients (42%) in the standard closure group (p = NS). In summary, we observed no statistically significant differences with respect to axillary drainage time, drainage volume, and length of hospital stay, local inflammation, and seroma formation after drainage removal.

PMID: 11518470 [PubMed - indexed for MEDLINE]

25. Fibrin sealant reduces the duration and amount of fluid drainage after axillary dissection: A randomized prospective clinical trial.

Moore M, Burak WE Jr, Nelson E, et al. J Am Coll Surg. 2001 May;192(5):591-9.

BACKGROUND: Patients who have axillary dissections during lumpectomy or modified radical mastectomy for breast carcinoma accumulate serosanguinous fluid, potentially

resulting in a seroma. Currently accepted practice includes insertion of one or more drains for fluid evacuation. This multicenter, randomized, controlled, phase II study was undertaken to evaluate whether a virally inactivated, investigational fibrin sealant is safe and effective when used as a sealing agent to reduce the duration and volume of serosanguinous fluid drainage and to determine the dose response of this effect. STUDY DESIGN: Patients undergoing lumpectomy or modified radical mastectomy were randomized to treatment with 4, 8, or 16 mL of fibrin sealant or control (no agent) at the axillary dissections site. Patients undergoing modified radical mastectomy also received an additional 4 or 8 mL of fibrin sealant at the skin flap site. Efficacy was evaluated by the number of days required for wound drainage and the volume of fluid drainage compared with control. Safety was confirmed by clinical course, the absence of viral seroconversion, and no major complications attributable to the sealant. RESULTS: The 4-mL axillary dissection dose of fibrin sealant significantly reduced the duration and quantity of fluid drainage from the axilla following lumpectomy ($p < or = 0.05$). In the modified radical mastectomy patients, a 16-mL axillary dissection dose combined with an 8-mL skin flap dose was significantly effective in reducing the number of days to drain removal ($p < or = 0.05$) and fluid drainage ($p < or = 0.01$). There were no fibrin sealant patient viral seroconversions and no major complications attributable to the sealant. A number of wound infections were noted, although this may represent a center-specific effect. CONCLUSIONS: Application of fibrin sealant following axillary dissection at the time of lumpectomy or modified radical mastectomy can significantly decrease the duration and quantity of serosanguinous drainage. The viral safety of the product was also supported.

PMID: 11333096 [PubMed - indexed for MEDLINE]

26. Pain and other symptoms during the first year after radical and conservative surgery for breast cancer.

Tasmuth T, von Smitten K, Kalso E. Br J Cancer. 1996 Dec;74(12):2024-31.

This study assessed pain, neurological symptoms, oedema of the ipsilateral arm, anxiety and depression occurring in women treated surgically for breast cancer, the impact of these symptoms on daily life and how they evolved during the 1 year follow-up. Ninety-three consecutive patients with non-metastasized breast cancer who were treated during 1993-94 were examined before surgery and after 1, 6 and 12 months. They were asked about pain, neurological symptoms and oedema in the breast scar region and/or ipsilateral arm. Sensory testing was performed, and gripping force and the circumference of the arm were measured. Anxiety and depression were evaluated. One year after surgery, 80% of the women had treatment-related symptoms in the breast scar region and virtually all patients had symptoms in the ipsilateral arm. The incidence of chronic post-treatment pain was higher after conservative surgery than after radical surgery (breast area: 33% vs 17%, NS; ipsilateral arm: 23% vs 13%, NS). Numbness occurred in 75% and oedema of the ipsilateral arm in over 30% of the patients after both radical and conservative surgery. Phantom sensations in the breast were reported by 25% of the patients. No difference in psychic morbidity was detected after the two types of surgery. Both the anxiety and depression scores were highest before surgery, decreasing with time, and were significantly correlated with preoperative stressful events.

PMID: 8980408 [PubMed - indexed for MEDLINE]

27. Pain and other symptoms after different treatment modalities of breast cancer.

Tasmuth T, von Smitten K, Hietanen P, et al. Ann Oncol. 1995 May;6(5):453-9.

PURPOSE: The aim of this study was to analyse the risk factors that predispose women to chronic symptoms related to the treatment of breast cancer. PATIENTS AND METHODS: A questionnaire was sent to 569 women who had undergone modified radical mastectomies with axillary evacuation (MRM) or breast resection with axillary evacuation (BCT). RESULTS: Pain, paraesthesias and strange sensations were reported by half of the patients. The chronic pain slightly affected the daily lives of about 50% of the patients and moderately or more the daily lives of about 25% of the patients. Pain was reported significantly more often after BCT than after MRM both in the breast scar (BS) and in the ipsilateral arm (IA). The patients with chronic pain were significantly younger and had larger primary tumours. Postoperative complications increased the incidence of chronic pain in the IA. The highest incidence of pain in the IA was reported by patients who had had both radio- and chemotherapy. The fact that the incidence of pain (IA) had a significant correlation with the incidence of paraesthesias, oedema, strange sensations and muscle weakness may be an indication of nerve injury. CONCLUSIONS: Chronic pain was more common after breast-conserving surgery than after radical surgery. Surgical complications and postoperative radiotherapy and chemotherapy increased the risk of chronic pain and other symptoms. Modifications in the treatment protocol and preclusion of postoperative complications may be necessary in order to minimize chronic treatment-related symptoms.

PMID: 7669710 [PubMed - indexed for MEDLINE]

28. Coping, catastrophizing and chronic pain in breast cancer.

Bishop SR, Warr D. J Behav Med. 2003 Jun;26(3):265-81.

This cross-sectional study investigated the relationships between individual differences in coping and catastrophizing, and markers of adaptation to chronic pain associated with breast cancer. Sixty-eight breast cancer patients with chronic pain due to either cancer or cancer-treatment were administered self-report instruments that assess active and passive coping, catastrophizing, pain, disability, and mood disturbance. Regression analyses were performed to investigate the unique contribution of differences in coping and catastrophizing to the various markers of adaptation. Both active and passive coping explained unique variance in self-reported disability; active coping was associated with less disability while passive coping was associated with greater disability. Catastrophizing explained unique variance in anxiety and depression scores; higher levels of catastrophizing were associated with greater emotional distress. The results suggest that coping and catastrophizing may contribute to different outcomes in chronic pain in breast cancer patients and provides preliminary evidence that they may be important targets of psychological treatments.

PMID: 12845938 [PubMed - indexed for MEDLINE]

29. Venlafaxine in neuropathic pain following treatment of breast cancer.

Tasmuth T, Härtel B, Kalso E. Eur J Pain. 2002;6(1):17-24.

Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. However, adverse effects are a major problem. Venlafaxine has no anticholinergic effects and could have a better compliance. The aim of the study was to evaluate the effectiveness of venlafaxine in neuropathic pain.

The study was a randomized, double-blind, crossover comparison of venlafaxine and inactive placebo. The study lasted 10 weeks. The number of tablets (18.75 mg) taken daily was increased by one at a 1 week interval. Pain intensity and pain relief were registered daily by a diary and by a questionnaire and a computer program (Painscreen) on each visit. Adverse effects were evaluated with the diaries and a 10-item list on each visit. Also, anxiety and depression were measured on each visit. Venous blood samples were collected before the treatment and at 4 weeks for the determination of the serum levels of venlafaxine and its three metabolites. Thirteen patients were analysed. The average daily pain intensity as reported in the diary (primary outcome) was not significantly reduced by venlafaxine compared with placebo. However, the average pain relief (diary) and the maximum pain intensity (retrospective assessment by the computer program) were significantly lower with venlafaxine compared with placebo. Anxiety and depression were not affected. Adverse effects did not show significant differences between treatments. The two poor responders had low venlafaxine concentrations whereas the two slow hydroxylizers had high venlafaxine concentrations and excellent pain relief. Thus, higher doses could be used in order to improve pain relief.

PMID: 11888224 [PubMed - indexed for MEDLINE]

30. Eliminating the dog-ear in modified radical mastectomy.

Farrar WB, Fanning WJ. Am J Surg. 1988 Nov;156(5):401-2.

Inadequate attention has been paid to optimal closure of the postmastectomy incision in patients not desirous of breast reconstruction. Herein, we describe the use of a basic plastic

surgical technique at the time of mastectomy to eliminate the dog-ear deformity at the axillary end of the incision. The technique is conceptually simple and expedient, and gives an excellent cosmetic result.

PMID: 3189710 [PubMed - indexed for MEDLINE]

31. Case 2. Radiation recall associated with docetaxel.

Morkas M, Fleming D, Hahl M. Challenges in oncology. J Clin Oncol. 2002 Feb 1;20(3):867-9.

No abstract available. Publication Types: Case Reports

PMID: 11821473 [PubMed - indexed for MEDLINE]

32. Arm edema in breast cancer patients.

J Erickson VS, Pearson ML, Ganz PA, et al. Natl Cancer Inst. 2001 Jan 17;93(2):96-111.

The improvement in the life expectancy of women with breast cancer raises important questions about how to improve the quality of life for women sustaining complications of breast cancer treatment. In particular, attention to common problems, such as arm edema, is of critical importance. We reviewed published breast cancer guidelines and literature identified via MEDLINE(R) searches in an effort to summarize the research literature pertinent to management of breast cancer-related arm edema, including incidence, prevalence, and timing; risk factors; morbidity; prevention; diagnosis; and efficacy of non-pharmacologic and pharmacologic interventions. We found that arm edema is a common complication of breast cancer therapy that can result in substantial functional impairment and psychological morbidity. The risk of arm edema increases when axillary dissection and axillary radiation therapy are used. Recommendations for preventive measures, such as avoidance of trauma, are available, but these measures have not been well studied. Non-pharmacologic treatments, such as massage

and exercise, have been shown to be effective therapies for lymphedema, but the effect of pharmacologic interventions remains uncertain. Comparing results across studies is complicated by the fact that the definitions of interventions and measures of outcomes and risk stratification vary substantially among studies. As arm edema becomes more prevalent with the increasing survival of breast cancer patients, further research is needed to evaluate the efficacy of preventive strategies and therapeutic interventions.

PMID: 11208879 [PubMed - indexed for MEDLINE]

33. Complications of level I and II axillary dissection in the treatment of carcinoma of the breast.

Roses DF, Brooks AD, Harris MN, et al. Ann Surg. 1999 Aug;230(2):194-201.

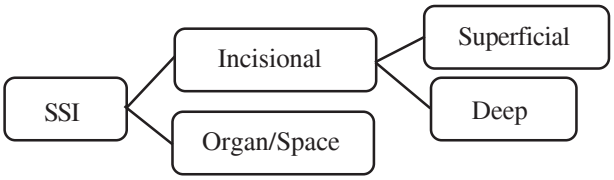
OBJECTIVE: To assess the complications of level I and II axillary lymph node dissection in the treatment of stage I and II breast cancer, with breast-conservation surgery and mastectomy. SUMMARY BACKGROUND DATA: The role of axillary dissection for staging, and as an effective means of controlling regional nodal disease, has long been recognized. As small and low-grade lesions have been detected more frequently, and as its therapeutic impact has been questioned, axillary dissection has increasingly been perceived as associated with significant complications. METHODS: Two hundred patients, 112 of whom had breast-conservation surgery with axillary dissection and 88 of whom had total mastectomy with axillary dissection, were evaluated 1 year or more after surgery for arm swelling as well as nonedema complications. All patients had arm circumference measurements at the same four sites on both the operated and nonoperated sides. RESULTS: No patient had an axillary recurrence. The mean difference in circumference on the nonoperated versus operated side was 0.425 cm +/- 1.39 at the midbiceps (p <

0.001), 0.315 cm +/- 1.27 at the antecubital fossa ($p < 0.001$), 0.355 cm +/- 1.53 at the midforearm ($p < 0.005$), and 0.055 cm +/- 0.75 at the wrist (n.s.). Seven patients (3.5%) had mild swelling of the hand. Heavy and obese body habitus were the only significant predictors of edema on multivariate analysis. One hundred fifty-three (76.5%) patients had numbness or paresthesias of the medial arm and/or axilla after surgery; in 125 (82%) of these, the problem had lessened or had resolved on follow-up assessment. CONCLUSIONS: The characterization of a level I and II axillary dissection as a procedure with significant complications does not appear justified based on this experience.

PMCID: PMC1420861

PMID: 10450733 [PubMed - indexed for MEDLINE]

Surgical Site Infections



Criteria for defining a Surgical Site Infection (SSI) [1]

Superficial Incisional SSI

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness,

or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.

4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathology or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Microbiology of SSI

In clean surgical procedures, Staphylococcus aureus from the exogenous environment or the patient's skin flora is the usual cause of infection. In clean-contaminated, contaminated, and dirty, the polymicrobial aerobic and anaerobic flora closely resembling the normal endogenous microflora of the surgically resected organ is the most frequently isolated pathogens. [2]

Guidelines for prevention of SSI [3]

Rankings of CDC recommendations

Category 1A: Strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiologic studies

Category 1B: Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale

Category II: Suggested for implementation and supported by suggestive clinical or epidemiologic studies or theoretical rationale

No recommendation: Practices for which insufficient evidence or no consensus regarding efficacy exists.

Recommendations

A. Preparation of the patient

Category 1A: Treat remote infection before elective operation; postpone surgery until treated; Do not remove hair from operative site unless necessary to facilitate surgery; If hair is removed, do immediately before surgery, preferably with electric clippers

Category 1B: Control serum blood glucose perioperatively; Cessation of tobacco use 30 days before surgery; Do not withhold necessary blood products to prevent SSIs; Shower or bath on night before operative procedure; Wash incision site before performing antiseptic skin preparation with approved agent

Category II: Prepare skin in concentric circles from incision site; Keep preoperative stay in hospital as short as possible

Unresolved: Improve nutritional status; Use of mupirocin in nares; Improve oxygenation of wound space; Taper or discontinue systemic steroid use before elective surgery

B. Antimicrobial prophylaxis

The strength of evidence represents only support for or against prophylaxis and does not apply to the antimicrobial choice, dose, or dosage regimen.

Category 1A: Select (if indicated) an antimicrobial agent with efficacy against expected pathogen; Intravenous route used to ascertain adequate serum levels during operation and for at most a few hours after incision closed; Before elective colorectal operations, in addition to parenteral agent, mechanically prepare the colon by use of enemas and cathartics. Administer nonabsorbable oral antimicrobial agents in divided doses on the day before the operation

Category 1B: Do not routinely use vancomycin for antimicrobial prophylaxis

Surgical Wound Classification[4]

Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage.

Class II/Clean-Contaminated: An operative wound in which the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination.

Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.

Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

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Anaesthesia and Perioperative Management

Maintenance of Euthermia

Body temperature often decreases in anesthetized patients. Severe hypothermia tends to occur more often in longer operations, including abdominal or thoracic surgery. Approximately one-half of patients develop hypothermia to a core temperature of <36.0°C, and approximately one-third of patients develop hypothermia to a core temperature of <35°C during surgery. Cancer surgeries are frequently duration complex, requiring opening of more than one serous cavity, prolonged, are associated with major fluid shifts, and conducted on older patients. All these factors lead to loss of heat and development of hypothermia. Perioperative hypothermia can have a wide range of underappreciated, detrimental effects. These include increased rates of wound infection, morbid cardiac events, blood loss, and increased length of stay in both recovery and hospital. Maintaining core temperature at or above 36°C can be beneficial for the patient and cost effective.

Hypothermia can be reduced by the use of forced air warming blankets, irrigation fluid that has been warmed in a heating cabinet, and by warming intravenous fluid.

Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty

Harald Schmied, Andrea Kurz, Daniel I Sessler, Sybille Kozek, Albert Reiter Lancet 1996;347:289-92.

Background - In-vitro studies indicate that platelet function and the coagulation cascade are impaired by hypothermia. However, the extent to which perioperative hypothermia influences bleeding during surgery remains unknown.Accordingly, authors tested the hypothesis that mild hypothermia increases blood loss and allogeneic transfusion requirements during hip arthroplasty.

Methods - Blood loss and transfusion requirements were evaluated in 60 patients undergoing primary, unilateral total hip arthroplasties who were randomly assigned to normothermia (final intraoperative core temperature $36.6 \pm 0.4\ ^0C$ or mild hypothermia ($35.0 \pm 0.5\ ^0C$). Crystalloid, colloid, scavenged red cells, and allogeneic blood were administered by strict protocol.

Findings - Intra- and postoperative blood loss was significantly greater in the hypothermic patients: 2.2 ± 0.5 Lt vs 1.7 ±0.3) Lt, $p<0.001$). Eight units of allogeneic packed red cells were required in seven of the 30 hypothermic patients, whereas only one normothermic patient required a unit of allogeneic blood ($p<0.05$ for administered volume). A typical decrease in core temperature in patients undergoing hip arthroplasty will thus augment blood loss by approximately 500 mL.

Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial

S. M. Frank, L. A. Fleisher, M. J. Breslow, M. S. Higgins, K. F. Olson, S. Kelly and C. Beattie

Objective: To assess the relationship between body temperature and cardiac morbidity during the perioperative period.

Design: Randomized controlled trial comparing routine thermal care (hypothermic group) to additional supplemental warming care (normothermic group).

Setting: Operating rooms and surgical intensive care unit at an academic medical center. *Subjects*: Three hundred patients undergoing abdominal, thoracic, or vascular surgical procedures who either had documented coronary artery disease or were at high risk for coronary disease.

Outcome Measure: The relative risk of a morbid cardiac event (unstable angina/ischemia, cardiac arrest, or myocardial infarction) according to thermal treatment. Cardiac outcomes were assessed in a double-blind fashion.

Results: Mean core temperature after surgery was lower in the hypothermic group (35.4+/-0.1 degrees C) than in the normothermic group (36.7+/-0.1 degrees C) (P<.001) and remained lower during the early postoperative period. Perioperative morbid cardiac events occurred less frequently in the normothermic group than in the hypothermic group (1.4% vs 6.3%; P=.02). Hypothermia was an independent predictor of morbid cardiac events by multivariate analysis (relative risk, 2.2; 95% confidence interval, 1.1-4.7; P=.04), indicating a 55% reduction in risk when normothermia was maintained. Postoperative ventricular tachycardia also occurred less frequently in the normothermic group than in the hypothermic group (2.4% vs 7.9%; P=.04).

Conclusion: In patients with cardiac risk factors who are undergoing noncardiac surgery, the perioperative maintenance of normothermia is associated with a reduced incidence of morbid cardiac events and ventricular tachycardia.

Perioperative Normothermia to Reduce the Incidence of Surgical-Wound Infection and Shorten Hospitalization

Kurz A, Sessler DI, Lenhardt R. The Study of Wound Infection and, for Temperature Group. N Engl J Med 1996;334:1209-15.

Background Mild perioperative hypothermia, which is common during major surgery, may promote surgical-wound infection by triggering thermoregulatory vasoconstriction, which decreases subcutaneous oxygen tension. Reduced levels of oxygen in tissue impair oxidative killing by neutrophils and decrease the strength of the healing wound by reducing the deposition of collagen. Hypothermia also directly impairs immune function. Authors tested the hypothesis that hypothermia both increases susceptibility to surgical-wound infection and lengthens hospitalization.

Methods Two hundred patients undergoing colorectal surgery were randomly assigned to routine intraoperative thermal care (the hypothermia group) or additional warming (the normothermia group). The patients' anesthetic care was standardized, and they were all given cefamandole and metronidazole. In a double-blind protocol, their wounds were evaluated daily until discharge from the hospital and in the clinic after two weeks; wounds containing culture-positive pus were considered infected. The patients' surgeons remained unaware of the patients' group assignments.

Results The mean (±SD) final intraoperative core temperature was 34.7±0.6°C in the hypothermia group and 36.6±0.5°C in the normothermia group ($P<0.001$). Surgical-wound infections were found in 18 of 96 patients assigned to hypothermia (19 percent) but in only 6 of 104 patients assigned to normothermia (6 percent, $P = 0.009$). The sutures were removed one day later in the patients assigned to hypothermia than in those assigned to normothermia ($P = 0.002$), and the duration of

hospitalization was prolonged by 2.6 days (approximately 20 percent) in the hypothermia group (P = 0.01).

Conclusions Hypothermia itself may delay healing and predispose patients to wound infections. Maintaining normothermia intraoperatively is likely to decrease the incidence of infectious complications in patients undergoing colorectal resection and to shorten their hospitalizations.

Management of Massive Blood Transfusion

Complications of major blood loss and massive transfusion may jeopardize the survival of patients from many specialties, and challenge haematological and blood transfusion resources. Avoidable deaths of patients with major haemorrhage are well recognized, and generally agreed that speciality-specific guidelines are needed to ensure effective management. Since acute massive blood transfusion is relatively rare but when occurs is a clinical emergency, management of such situations depend on understanding basic physiology and pathophysiology. The guidelines issued by various societies are generally based on expert opinion and retrospective reviews.

Clinical Resource Efficiency Support Team (CREST), Northern Ireland Guidelines for the management of acute massive blood loss

Definition:

Massive blood loss may be defined as:

- Loss of one blood volume within a 24 hour period. (7% of lean body weight (5 litres in an adult) – 8 to 9% in a child.
- Loss of 50% of blood volume within 3 hours.
- Loss of blood at a rate in excess of 150 ml. per minute.

Priorities:

- Restoration of circulation to re-establish adequate perfusion.
- Haemostasis of visual bleeding points.
- Integrated care, by appropriate staff
- Positive patient identification and documentation of care.

Resuscitation:

- Principles of airway management and resuscitation apply.
- Arrest visible haemorrhage: replace blood volume by rapid infusion of WARM crystalloids and/or colloids through multiple large bore cannulae.
- Transfuse preferably fully crossmatched blood, if time permits, or if irregular antibodies are known to be present. Alternatively, if more urgent, uncrossmatched group specific blood should be given if 1/3 of the patient's estimated blood volume has been lost. In extreme emergency use group O Rhesus D negative blood. O Rhesus D positive blood is acceptable for post menopausal female and male patients.
- Avoid hypothermia by using fluid warmers.

Laboratory investigations:

- Arrange for early initial, and serial assessment of FBC; blood gas analysis, blood biochemistry and a Coagulation Screen.
- Blood group and cross match Packed Cells (8 Units for an adult – pro.rata. for a child). Further crossmatch is not required after replacement of 1 blood volume (8 Units in adults) as the cells by then are unrepresentative.
- Repeat estimations every 4 hours, or more frequently, after component therapy.

Blood Component Therapy:

Red cells:

Red cells transfused in optimal additive solution contain no plasma or other cellular fractions. Dilutional coagulopathy may occur.

Platelets:

Platelet levels will fall due to blood loss and haemodilution and should be anticipated when volume replacement exceeds 1.5 times the estimated total blood volume.

Recommendations (grade C, level IV).

- There is consensus that the platelet count should not be allowed to fall below $50 \cdot 10^9$ / L in patients with acute bleeding (BCSH, 1988; Consensus Conference on Platelet Transfusion, 1998; Stainsby et al, 2000).
- A higher target level of $100 \cdot 10^9$ / L has been recommended for those with multiple trauma or central nervous system injury (Development Task Force of the College of American Pathologists, 1994; Horsey, 1997).

Cryoprecipitate:

Cryoprecipitate is a blood fraction containing concentrated fibrinogen (factor 1), fibronectin, factor VIII and Von Willebrand Factor and is the definitive therapy in fibrinogen deficiency. Serial estimations of fibrinogen, PT and APPT are mandatory. Fibrinogen levels should be maintained above 1 g/l. Average replacement would be 1 unit/5 kg. body weight (15 to 20 units for an adult).

Fresh frozen plasma (FFP):

FFP is indicated in Acute Disseminated Intravascular Coagulation (DIC) or during Massive Transfusion where DIC is anticipated. When PT and APPT are prolonged to more

than 1.5 times control values but fibrinogen levels are greater than 1 g/l and there is active bleeding, then transfusion at 12–15 ml/kg (approximately 4 packs for an adult) will increase levels of the required coagulation factors. The potential risk of blood borne infection, including HIV and hepatitis, from transfusion of FFP is similar to that for whole blood. Although ''formula replacement'' is not recommended it has been suggested that FFP should be considered after loss of one blood volume.

The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital.

Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB: J Trauma 2007, 63:805-813 [1]

Background : Patients with severe traumatic injuries often present with coagulopathy and require massive transfusion. The risk of death from hemorrhagic shock increases in this population. To treat the coagulopathy of trauma, some have suggested early, aggressive correction using a 1:1 ratio of plasma to red blood cell (RBC) units.

Objective: To determine whether the ratio of plasma to RBCs transfused would affect survival by decreasing death from hemorrhage.

Design: Retrospective chart review.

Setting: United States Army combat support hospital in Iraq.

Subjects: 246 patients who received a massive transfusion (≤ 10 units of RBCs in 24 hours) from November 2003 to September 2005. Three groups of patients were constructed according to the plasma to RBC ratio transfused during massive transfusion.

Intervention: None.

Outcome: Hospital mortality rates and the cause of death were compared among groups. Multivariable logistic regression was used to determine the independent association between plasma to RBC ratio and hospital mortality.

Results -For the low ratio group the plasma to RBC median ratio was 1:8 (interquartile range (IQR), 0:12-1:5), for the medium ratio group, 1:2.5 (IQR, 1:3.0-1:2.3), and for the high ratio group, 1:1.4 (IQR, 1:1.7-1:1.2) ($p<0.001$). Median Injury Severity Score (ISS) was 18 for all groups (IQR, 14-25). For low, medium, and high plasma to RBC ratios, overall mortality rates were 65%, 34%, and 19%, ($p<0.001$); and hemorrhage mortality rates were 92.5%, 78%, and 37%, respectively ($p < 0.001$). Upon logistic regression, plasma to RBC ratio was independently associated with survival (odds ratio 8.6, 95% confidence interval 2.1-35.2).

Conclusions- In patients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.

Management of postoperative Pain

Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management Anesthesiology 2004; 100:1573–81

Post operative pain in the perioperative setting is defined as pain that is present in a surgical patient because of preexisting disease, or the surgical procedure (with associated drains, chest or nasogastric tubes, or complications). Some of the adverse

outcomes that may result from the undertreatment of perioperative pain are thromboembolic and pulmonary complications, increase length of stay in the intensive care unit or hospital, hospital readmission for further pain management, needless suffering, impairment of health-related quality of life, and development of chronic pain.

Adverse outcomes associated with the management of perioperative pain are respiratory depression, brain or other neurologic injury, sedation, circulatory depression, nausea, vomiting, pruritus, urinary retention, impairment of bowel function, and sleep disruption.

The following terms describe the strength of the findings.

- **Supportive**: Meta-analyses of a sufficient number of adequately designed studies indicate a statistically significant relationship (P _ 0.01) between a clinical intervention and a clinical outcome.
- **Suggestive**: Information from case reports and descriptive studies permits inference of a relationship between an intervention and an outcome. This type of qualitative information does not permit a statistical assessment of significance.
- **Equivocal**: Qualitative data are not adequate to permit inference of a relationship between an intervention and an outcome and (1) there is insufficient quantitative information, or (2) aggregated comparative studies have found no significant differences among groups or conditions. The lack of scientific evidence in the literature is described by the following terms.
- **Silent**: No identified studies address the relationship of interest.
- **Insufficient**: There are too few published studies to investigate a relationship between an intervention and an outcome.

- **Inadequate**: The available studies cannot be used to assess the relationship between an intervention and an outcome. These studies either do not meet the criteria for content as defined in the "Focus" of these Guidelines, or they do not permit a clear causal interpretation of findings because of methodologic concerns.

Institutional Policies and Procedures for Providing Perioperative Pain Management

Anesthesiologists offering perioperative analgesia services should

- Provide (where appropriate with other healthcare professionals) ongoing education and training to ensure that hospital personnel are knowledgeable and skilled with regard to the effective and safe use of the available treatment options within the institution.
- Use standardized, validated instruments to facilitate the regular evaluation and documentation of pain intensity, the effects of pain therapy, and side effects caused by the therapy
- Be available at all times to consult with ward nurses, surgeons, or other involved physicians, and should assist in evaluating patients who are experiencing problems with any aspect of perioperative pain relief.
- Do so within the framework of an Acute Pain Service, and participate in developing standardized institutional policies and procedures.

Preoperative Evaluation of the Patient

A directed pain history, physical examination, and a pain control plan should be included in the anesthetic preoperative evaluation.

Preoperative Preparation of the Patient

- Patient preparation for perioperative pain management should include appropriate adjustments or continuation of medications to avert an abstinence syndrome, treatment of preexistent pain, or preoperative initiation of therapy for postoperative pain management (**Insufficient evidence**).
- Anesthesiologists offering perioperative analgesia services should provide, in collaboration with others as appropriate, patient and family education regarding their important roles in achieving comfort, reporting pain, and in proper use of the recommended analgesic methods **(Supportive evidence)**.

Perioperative Techniques for Pain Management

The Task Force supports the use of epidural, PCA, and regional techniques including but not limited to intercostals blocks, plexus blocks, and local anesthetic infiltration of incisions by anesthesiologists when appropriate and feasible

- Anesthesiologists who manage perioperative pain should utilize therapeutic options such as epidural or intrathecal opioids, systemic opioid PCA, and regional techniques, after thoughtfully considering the risks and benefits for the individual patient. These modalities should be used in preference to intramuscular opioids ordered "as needed." The therapy selected should reflect the individual anesthesiologist's expertise, as well as the capacity for safe application of the modality in each practice setting. This capacity includes the ability to recognize and treat adverse effects that emerge after initiation of therapy **(Supportive evidence)**
- Special caution should be taken when continuous infusion modalities are used, as drug accumulation may contribute to adverse events. **(Insufficient evidence)**

Multimodal Techniques for Pain Management

Administration of two analgesic agents that act by different mechanisms via a single route provide superior analgesic efficacy with equivalent or reduced adverse effects. **(Supportive evidence)** The literature is **insufficient** to evaluate the postoperative analgesic effects of oral opioids combined with nonsteroidal anti-inflammatory drugs (NSAIDs). The Task Force believes that NSAID, COXIB or acetaminophen administration has a dose-sparing effect for systemically administered opioids. Two routes of administration, when compared with a single route, may be more effective in providing perioperative analgesia. **(Suggestive evidence)** The literature is **insufficient** to evaluate the efficacy of pharmacologic pain management combined with nonpharmacologic, alternative or complementary pain management when compared to pharmacologic pain management alone.

- Whenever possible, anesthesiologists should employ multimodal pain management therapy.
- Unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COXIBs, or acetaminophen. In addition, regional blockade with local anesthetics should be considered.
- Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events. The choice of medication, dose, route, and duration of therapy should be individualized.

Patient Subpopulations

Some patient groups are at special risk for inadequate pain control, and require additional analgesic considerations. Patient populations at risk include (1) pediatric patients, (2) geriatric patients, and (3) critically ill or cognitively impaired

patients, or other patients who may have difficulty communicating.

Pediatric Patients

Absence of parents, security objects, and familiar surroundings may cause as much suffering as the surgical incision.

- Aggressive and proactive pain management is necessary to overcome the historic under treatment of pain in children.
- Peri-operative care for children undergoing painful procedures or surgery requires developmentally appropriate pain assessment and therapy.
- Analgesic therapy should depend on age, weight, and comorbidity, and unless contraindicated should involve a multimodal approach.
- Behavioral techniques, especially important in addressing the emotional component of pain, should be applied whenever feasible.
- Sedative, analgesic, and local anesthetics are all important components of appropriate analgesic regimens for painful procedures.
- As many analgesic medications are synergistic with sedating agents, it is imperative that appropriate monitoring be employed during the procedure and recovery.

Geriatric Patients

- Pain assessment and therapy should be integrated into the perioperative care of geriatric patients. Pain assessment tools appropriate to a patient's cognitive abilities should be employed.

- Extensive and proactive evaluation and questioning may be necessary to overcome barriers that hinder communication regarding unrelieved pain.
- Anesthesiologists should recognize that geriatric patients might respond differently than younger patients to pain and analgesic medications, often because of co-morbidity. Vigilant dose titration is necessary to ensure adequate treatment while avoiding adverse effects such as somnolence in this vulnerable group, who are often taking other medications (including alternative and complementary agents).

Other Groups

Patients who are critically ill, cognitively impaired (e.g., Alzheimer's disease), or who otherwise have difficulty communicating (e.g., cultural or language barriers) present unique challenges to peri-operative pain management.

- Anesthesiologists should recognize that patients who are critically ill, cognitively impaired, or have communication difficulties may require additional interventions to ensure optimal peri-operative pain management.
- Anesthesiologists should consider a therapeutic trial of an analgesic in patients with elevated blood pressure and heart rate or agitated behavior, when causes other than pain have been excluded.

Management of difficult airway

A large number of these malignancies are related to head and neck region mainly in men due to prevalence of tobacco chewing largely in rural population. Primary malignancy or metastatic tumors at the region of head neck especially laryngeal level, or mediastinum may cause airway obstruction.

Obstruction can occur at the level of larynx, trachea or bronchi depending on site of tumor. When subjected to surgery anaesthetist frequently encounters difficult intubation.

Practice Guidelines for Management of the Difficult Airway

An Updated Report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway

Anesthesiology 2006; 104:847–64

Definition- A difficult airway is defined as the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with face mask ventilation of the upper airway, difficulty with tracheal intubation, or both. The difficult airway represents a complex interaction between patient factors, the clinical setting, and the skills of the practitioner.

1. Difficult face mask ventilation: (a) It is not possible for the anesthesiologist to provide adequate face mask ventilation due to one or more of the following problems: inadequate mask seal, excessive gas leak, or excessive resistance to the ingress or egress of gas.

(b) Signs of inadequate face mask ventilation include (but are not limited to) absent or inadequate chest movement, absent or inadequate breath sounds, auscultatory signs of severe obstruction, cyanosis, gastric air entry or dilatation, decreasing or inadequate oxygen saturation (SpO2), absent or inadequate exhaled carbon dioxide, absent or inadequate spirometric measures of exhaled gas flow, and hemodynamic changes associated with hypoxemia or hypercarbia (e.g., hypertension, tachycardia, arrhythmia).

2. Difficult laryngoscopy: (a) It is not possible to visualize any portion of the vocal cords after multiple attempts at conventional laryngoscopy.

3. Difficult tracheal intubation: (a) Tracheal intubation requires multiple attempts, in the presence or absence of tracheal pathology.

4. Failed intubation: (a) Placement of the endotracheal tube fails after multiple intubation attempts.

Evaluation of the Airway

1. History- An airway history should be conducted, whenever feasible, prior to the initiation of anesthetic care and airway management in all patients. The intent of the airway history is to detect medical, surgical, and anesthetic factors that may indicate the presence of a difficult airway (suggestive evidence)
2. Physical Examination- An airway physical examination should be conducted whenever feasible, prior to the initiation of anesthetic care and airway management in all patients. The intent of this examination is to detect physical characteristics that may indicate the presence of a difficult airway. (suggestive evidence)
3. Additional Evaluation- Additional evaluation may be indicated in some patients to characterize the likelihood or nature of the anticipated airway difficulty. (suggestive evidence)

Components of the Preoperative Airway Physical Examination

Airway Examination Component	Nonreassuring Findings
Length of upper incisors	Relatively long
Relation of maxillary and mandibular incisors during normal jaw closure	Prominent "overbite" (maxillary incisors anterior to mandibular incisors)

Relation of maxillary and mandibular incisors during voluntary protrusion	Patient mandibular incisors anterior to (in mandible front of) maxillary incisors
Interincisor distance	Less than 3 cm
Visibility of uvula	Not visible when tongue is protruded with patient in sitting position (e.g., Mallampati class greater than II)
Shape of palate	Highly arched or very narrow
Compliance of mandibular space	Stiff, indurated, occupied by mass, or nonresilient
Thyromental distance	Less than three ordinary finger breadths
Length of neck	Short
Thickness of neck	Thick
Range of motion of head and neck	Patient cannot touch tip of chin to chest or cannot extend neck

Basic Preparation for Difficult Airway Management- At least one portable storage unit that contains specialized equipment for difficult airway management should be readily available. If a difficult airway is known or suspected, the anesthesiologist should

a. Inform the patient (or responsible person) of the special risks and procedures pertaining to management of the difficult airway.

b. Ascertain that there is at least one additional individual who is immediately available to serve as an assistant in difficult airway management.

c. Administer face mask preoxygenation before initiating management of the difficult airway. The uncooperative or pediatric patient may impede opportunities for preoxygenation.

d. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management. Opportunities for supplemental oxygen administration include (but are not limited to) oxygen delivery by nasal cannulae, face mask, laryngeal mask airway (LMA), insufflation, or jet ventilation during intubation attempts; and oxygen delivery by face mask, blow-by, or nasal cannulae after extubation of the trachea. (supporttive evidence)

Suggested Contents of the Portable Storage Unit for Difficult Airway Management

1. Rigid laryngoscope blades of alternate design and size from those routinely used; this may include a rigid fiberoptic laryngoscope
2. Tracheal tubes of assorted sizes
3. Tracheal tube guides. Examples include (but are not limited to) semirigid stylets, ventilating tube changer, light wands, and forceps designed to manipulate the distal portion of the tracheal tube
4. Laryngeal mask airways of assorted sizes; this may include the intubating laryngeal mask airway and the LMA-ProsealTM
5. Flexible fiberoptic intubation equipment
6. Retrograde intubation equipment
7. At least one device suitable for emergency noninvasive airway ventilation. Examples include (but are not limited to) an esophageal tracheal Combitube, a hollow jet ventilation stylet, and a transtracheal jet ventilator

8. Equipment suitable for emergency invasive airway access (e.g.,cricothyrotomy)
9. An exhaled CO2 detector

Strategy for Intubation of the Difficult Airway

An assessment of the likelihood and anticipated clinical impact of four basic problems that may occur alone or in combination:

a. difficult ventilation
b. difficult intubation
c. difficulty with patient cooperation or consent
d. difficult tracheostomy

2. A consideration of the relative clinical merits and feasibility of three basic management choices:
    a. awake intubation versus intubation after induction of general anesthesia
    b. use of noninvasive techniques for the initial approach to intubation versus the use of invasive techniques (i.e., surgical or percutaneous tracheostomy or cricothyrotomy)
    c. preservation of spontaneous ventilation during intubation attempts versus ablation of spontaneous ventilation during intubation attempts
3. The identification of a primary or preferred approach to:
    a. awake intubation
    b. the patient who can be adequately ventilated but is difficult to intubate
    c. the life-threatening situation in which the patient cannot be ventilated or intubated
4. The identification of alternative approaches that can be employed if the primary approach fails or is not feasible.

5. The use of exhaled carbon dioxide to confirm tracheal intubation.

Techniques for Difficult Airway Management

Techniques for Difficult Intubation	Techniques for Difficult Ventilation
Alternative laryngoscope blades	Esophageal tracheal Combitube
Awake intubation	Intratracheal jet stylet
Blind intubation (oral or nasal)	Laryngeal mask airway
Fiberoptic intubation	Oral and nasopharyngeal airways
Intubating stylet or tube changer	Rigid ventilating bronchoscope
Laryngeal mask airway as an intubating conduit	Invasive airway access
Light wand	Transtracheal jet ventilation
Retrograde intubation	Two-person mask ventilation
Invasive airway access	

Strategy for Extubation of the Difficult Airway

The anesthesiologist should have a preformulated strategy for extubation of the difficult airway. This strategy will depend, in part, on the surgery, the condition of the patient, and the skills and preferences of the anesthesiologist.

The preformulated extubation strategy should include

1. A consideration of the relative merits of awake extubation versus extubation before the return of consciousness.

2. An evaluation for general clinical factors that may produce an adverse impact on ventilation after the patient has been extubated.
3. The formulation of an airway management plan that can be implemented if the patient is not able to maintain adequate ventilation after extubation.
4. A consideration of the short-term use of a device that can serve as a guide for expedited reintubation. This type of device is usually inserted through the lumen of the tracheal tube and into the trachea before the tracheal tube is removed. The device may be rigid to facilitate intubation and/or hollow to facilitate ventilation. (insufficient data)

Follow-up Care

The anesthesiologist should document the presence and nature of the airway difficulty in the medical record. The intent of this documentation is to guide and facilitate the delivery of future care. Aspects of documentation that may prove helpful include (but are not limited to)

1. A description of the airway difficulties that were encountered.The description should distinguish between difficulties encountered in face mask or LMA ventilation and difficulties encountered in tracheal intubation.
2. A description of the various airway management techniques that were employed. The description should indicate the extent to which each of the techniques served a beneficial or detrimental role in management of the difficult airway. (insufficient data)

Monitoring for awareness under anaesthesia

Intraoperative awareness under general anesthesia is a rare occurrence, with a reported incidence of 0.1–0.2%.1–4 Significant psychological sequelae (e.g., post–traumatic stress

disorder) may occur after an episode of intraoperative awareness, and affected patients may remain severely disabled for extended periods of time. Surgeries for cancer due to their complexities associated with massive blood loss, haemodyanamic instability and sharing of airway or difficult airway may have episodes of lighter planes of anaesthesia making awareness possible.

Practice Advisory for Intraoperative Awareness and Brain Function Monitoring

A Report by the American Society of Anesthesiologists Task Force on Intraoperative Awareness Anesthesiology 2006; 104:847–64

Definition- Intraoperative awareness occurs when a patient becomes conscious during a procedure performed under general anesthesia and subsequently has recall of these events. For the purpose of this Advisory, recall is limited to explicit memory and does not include the time before general anesthesia is fully induced or the time of emergence from general anesthesia, when arousal and return of consciousness are intended. Dreaming is not considered intraoperative awareness.

Preoperative Evaluation- An evaluation should include, if possible, a review of a patient's medical records for previous occurrences of awareness or other potential risk factors, a patient interview to assess level of anxiety or previous experiences with anesthesia, and a physical examination. Potential risk factors to consider for patients undergoing general anesthesia include substance use or abuse (e.g., opioids, benzodiazepines, cocaine), a history of awareness, a history of difficult intubation or anticipated difficult intubation, chronic pain patients using high doses of opioids, cardiac surgery, cesarean delivery, trauma and emergency surgery,

reduced anesthetic doses in the presence of paralysis, planned use of muscle relaxants during the maintenance phase of general anesthesia, total intravenous anesthesia, the planned use of nitrous oxide-opioid anesthesia, ASA physical status of IV or V, and limited hemodynamic reserve. The consensus of the Task Force is that patients whom the individual clinician considers to be at substantially increased risk of intraoperative awareness should be informed of the possibility of intraoperative awareness when circumstances permit.

Preinduction Phase of Anesthesia- Because intraoperative awareness may be caused by equipment malfunction or misuse, the Task Force believes that there should be adherence to a checklist protocol for anesthesia machines and equipment to assure that the desired anesthetic drugs and doses will be delivered. These procedures should be extended to include verification of the proper functioning of intravenous access, infusion pumps, and their connections. The decision to administer a benzodiazepine prophylactically should be made on a case-by-case basis for selected patients (e.g., patients requiring smaller dosages of anesthetics). The Task Force cautions that delayed emergence may accompany the use of benzodiazepines.

Intraoperative Monitoring- Intraoperative monitoring of depth of anesthesia, for the purpose of minimizing the occurrence of awareness, should rely on multiple modalities, including clinical techniques (e.g., checking for clinical signs such as purposeful or reflex movement) and conventional monitoring systems (e.g., electrocardiogram, blood pressure, HR, end-tidal anesthetic analyzer, capnography). The use of neuromuscular blocking drugs may mask purposeful or reflex movements and adds additional importance to the use of monitoring methods that assure the adequate delivery of anesthesia. It is the consensus of the Task Force that brain function monitoring is not routinely indicated for patients

undergoing general anesthesia, either to reduce the frequency of intraoperative awareness or to monitor depth of anesthesia

Intraoperative and Postoperative Interventions- the decision to administer a benzodiazepine intraoperatively after a patient unexpectedly becomes conscious should be made on a case-by-case basis. Practitioners should speak with patients who report recall of intraoperative events to obtain details of the event and to discuss possible reasons for its occurrence

Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial

Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Lancet. 2004 May 29;363(9423): 1757-63

Background: Awareness is an uncommon complication of anaesthesia, affecting 0.1-0.2% of all surgical patients. Bispectral index (BIS) monitoring measures the depth of anaesthesia and facilitates anaesthetic titration. In this trial we determined whether BIS-guided anaesthesia reduced the incidence of awareness during surgery in adults.

Methods: Authors did a prospective, randomised, double-blind, multicentre trial. Adult patients at high risk of awareness were randomly allocated to BIS-guided anaesthesia or routine care. Patients were assessed by a blinded observer for awareness at 2-6 h, 24-36 h, and 30 days after surgery. An independent committee, blinded to group identity, assessed every report of awareness. The primary outcome measure was confirmed awareness under anaesthesia at any time.

Findings: Of 2463 eligible and consenting patients, 1225 were assigned to the BIS group and 1238 to the routine care group. There were two reports of awareness in the BIS-guided group and 11 reports in the routine care group (p=0.022). BIS-guided

anaesthesia reduced the risk of awareness by 82% (95% CI 17-98%).

Interpretation: BIS-guided anaesthesia reduces the risk of awareness in at-risk adult surgical patients undergoing relaxant general anaesthesia. With a cost of routine BIS monitoring at US16 dollars per use in Australia and a number needed to treat of 138, the cost of preventing one case of awareness in high-risk patients is about 2200 dollars.

Anesthesia awareness and the bispectral index

Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, Saager L, Turner MS, Rao S, Bottros M, Hantler C, Jacobsohn E, Evers AS. N Engl J Med. 2008 Mar 13;358(11):1097-108

Background: Awareness during anesthesia is a serious complication with potential long-term psychological consequences. Use of the bispectral index (BIS), developed from a processed electroencephalogram, has been reported to decrease the incidence of anesthesia awareness when the BIS value is maintained below 60. In this trial, Authors sought to determine whether a BIS-based protocol is better than a protocol based on a measurement of end-tidal anesthetic gas (ETAG) for decreasing anesthesia awareness in patients at high risk for this complication.

Methods: Authors randomly assigned 2000 patients to BIS-guided anesthesia (target BIS range, 40 to 60) or ETAG-guided anesthesia (target ETAG range, 0.7 to 1.3 minimum alveolar concentration [MAC]). Postoperatively, patients were assessed for anesthesia awareness at three intervals (0 to 24 hours, 24 to 72 hours, and 30 days after extubation).

Results: Authors assessed 967 and 974 patients from the BIS and ETAG groups, respectively. Two cases of definite

anesthesia awareness occurred in each group (absolute difference, 0%; 95% confidence interval [CI], -0.56 to 0.57%). The BIS value was greater than 60 in one case of definite anesthesia awareness, and the ETAG concentrations were less than 0.7 MAC in three cases. For all patients, the mean (+/- SD) time-averaged ETAG concentration was 0.81+/-0.25 MAC in the BIS group and 0.82+/-0.23 MAC in the ETAG group (P=0.10; 95% CI for the difference between the BIS and ETAG groups, -0.04 to 0.01 MAC).

Conclusions: Authors did not reproduce the results of previous studies that reported a lower incidence of anesthesia awareness with BIS monitoring, and the use of the BIS protocol was not associated with reduced administration of volatile anesthetic gases. Anesthesia awareness occurred even when BIS values and ETAG concentrations were within the target ranges. Authors findings do not support routine BIS monitoring as part of standard practice.

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008

Dellinger RP, Levy MM, Carlet JM, et al. for the International Surviving Sepsis Campaign Guidelines Committee. Crit Care Med 2008; 36: 296–327.

Phases of surviving sepsis campaign

- Phase I: Barcelona Declaration
    - o October 2002:ESICM, SCCM & International Sepsis Forum
    - o Aim: Reduce relative mortality due to severe sepsis / septic shock by 25% in 5 years. (Crit Care 2003;(1):1-2)
- Phase II: Creation of Guidelines for Management of Severe Sepsis & Septic Shock
    - o Sponsored by 11 international medical societies. (ICM 2004; 30:536-555, CCM 2004;32:858-871)
- Phase III: Evaluate impact on clinical outcome
    - o Updated Surviving Sepsis Guidelines

- The current guidelines are actually the update to the original guidelines published in 2004. There were several differences in the guidelines: in the process of funding, grading of evidence and actual recommendations themselves.
- The 2004 guidelines were funded from unrestricted educational grants from industry, this was heavily criticized. In the current version of the guidelines, no industry grants were used for committee meeting.
- The guidelines process included a modified Delphi method, a consensus conference, several subsequent meetings of subgroups and key individuals, teleconferences and electronic-based discussions among subgroups and members of the entire committee, and two follow-up group meetings in 2007.
- The GRADE Methodology (Table 1) was used for determining the quality of evidence. Depeding on the quality of evidence, relative importance of the outcomes, baseline risks of outcomes, magnitude of relative risk, including benefits, harms, and burden, absolute magnitude of the effect, precision of the estimates of the effects and costs of interventions, the committee made either Strong or Weak recommendations.
    - o A strong recommendation in favor of an intervention reflects that the desirable effects of adherence to a recommendation will clearly outweigh the undesirable effects.
    - o A weak recommendation in favor of an intervention indicates that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these tradeoffs.

Table 1. Determination of the quality of evidence

- Underlying methodology
  - A. RCT
  - B. Downgraded RCT or upgraded observational studies
  - C. Well-done observational studies
  - D. Case series or expert opinion
- Factors that may decrease the strength of evidence
  1. Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias
  2. Inconsistency of results (including problems with subgroup analyses)
  3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
  4. Imprecision of results
  5. High likelihood of reporting bias
- Main factors that may increase the strength of evidence
  1. Large magnitude of effect (direct evidence, RR _2 with no plausible confounders)
  2. Very large magnitude of effect with RR _5 and no threats to validity (by two levels)
  3. Dose-response gradient
- The SSC guidelines are discussed in several thrust areas: initial resuscitation and infection issues, haemodynamic support and adjunctive therapy, and other supportive therapy of severe sepsis.
- In the description below
  - o (no and alphabet in bracket represent grade of evidence eg, (1C)),

- S – Strong Recommendation –Committee Recommends
- W – weak recommendation Committee Suggests
- 2004 (alphabet): Grade of evidence as in 2004 guidelines

Initial resuscitation and infection issues

- Immediate resuscitation when hypotension or serum lactate > 4 mmol/L;
  - Do not delay pending ICU admission (1C) S
- Resuscitation goals (1C) S
  - CVP 8–12 mmHg (if MV 12-15 mmHg)
  - Mean arterial pressure > 65 mm Hg
  - Urine output > 0.5 mL/kg/hr
  - $ScvO_2$ > 70% or SvO_2 > 65%
    - 2004 B & B
- If ScvO2 target not achieved (2C) W
  - Consider further fluid
  - PRBCs to hematocrit of > 30% and/or
  - Start dobutamine infusion, maximum 20 μg/kg/min
- Diagnosis
- Obtain cultures before antibiotics provided this does not significantly delay antimicrobial administration (1C) S
  - Obtain two or more BCs
  - One or more BCs should be percutaneous
  - One BC from each vascular access device in place > 48 hrs

- Culture other sites as clinically indicated
- Perform imaging to confirm & sample any source of infection (1C) S

- Antibiotic therapy
  - IV antibiotics within 1st hr in sepsis (1D) & septic shock (1B) S
  - Broad-spectrum(1B) S
  - Reassess antimicrobial regimen daily
- Combination therapy
  - Pseudomonas infections (2D) W
  - Empiric therapy in neutropenic patients (2D) W
  - Comb therapy > 3–5 days & de-escalation following susceptibilities (2D) W
    - 2004 grade B & E
- Antibiotic therapy
  - Duration of therapy 7–10 days; longer if (1D) S
  - Slow response
  - Undrainable foci of infection
  - Immunologic deficiencies Stop antimicrobial therapy if cause is found to be noninfectious
    - 2004 D & E
- Source Control
  - Establish infection site ASAP (1C) & within first 6 hrs (1D) S
  - Evaluate focus amenable to source control measures (e.g. abscess drainage, tissue debridement) (1C) S

- Source control ASAP after successful initial resuscitation (1C) S (exception: infected pancreatic necrosis) (2B) W

- Source control measure
  - Maximum efficacy
  - Minimal physiologic upset (1D) S
  - Remove intravascular access devices if potentially infected (1C) S
    - 2004 E

Haemodynamic support and adjunctive therapy

- Fluid therapy
  - Fluid-resuscitate using crystalloids or colloids (1B) S
  - Target CVP > 8 mm Hg (12 mmHg if MV) (1C) S
  - Use fluid challenge
    - Till associated with hemodynamic improvement (1D) S
  - Fluid challenge
    - 1 L Crystalloids or 300–500 mL colloids over 30 mins. (1D) S
    - Reduce rate when cardiac filling pressures increase without concurrent hemodynamic improvement (1D) S
- 2004 E
- Vasopressors
  - Maintain MAP > 65 mm Hg (1C) S
  - Use NE & Dopa as initial vasopressors (1C) S

- Epinepphrine, phenylephrine and vasopressin NOT initial vasopressors (2C). W
- Vasopressin 0.03 units/min may be added to NE.
  - 2004 E & D

- Vasopressors
  - Epinephrine first alternative agent when poor response to NE or Dopa (2B). W
  - Do not use low-dose dopamine for renal protection (1A) S
  - In pts needing vasopressors, insert an arterial catheter ASAP (1D) S
    - 2004 B & E

- Inotropic therapy
  - Use dobutamine in patients with myocardial dysfunction (1C) S
  - DO NOT increase cardiac index to supranormal levels (1B) S
  - Aim for adequate O_2 delivery
    - 2004 E & A

- Steroids
  - IV hydrocortisone
  - hypotension refractory to fluids & vasopressors (2C) W
  - ACTH stimulation test not recommended (2B) W
  - Hydrocortisone preferred to dexamethasone (2B) W
  - Fludrocortisone optional if hydrocortisone used (2C) W

- Wean steroids once vasopressors not required (2D) W
- Hydrocortisone dose < 300 mg/day (1A) S
- Do not use steroids to treat sepsis in absence of shock (1D) S
  - 2004 C, E, A, E

- rhAPC (recombinant Human Activated Protein C)
  - Consider rhAPC in adult septic pts with high risk of death (APACHE II > 25 or MOF) if not contraindicated (2B, 2C (for postoperative patients).) W
  - rhAPC should not be used for adult septic patients with risk of death (APACHE II < 20 or one organ failure) (1A) S
    - 2004 B

Other supportive therapy of severe sepsis

- Blood product administration
  - Give red blood cells when hemoglobin decreases to 7.0 g/dL (70 g/L) to target a hemoglobin of 7.0–9.0 g/dL in adults A higher hemoglobin level may be required in special circumstances (e.g., myocardial ischaemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis) (1B).
    - 2004 B
  - Do not use erythropoietin to treat sepsis-related anemia. Erythropoietin may be used for other accepted reasons (1B)
  - Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures (2D)

- Do not use antithrombin therapy (1B)
  - 2004 B

- Transfuse platelets
  - when counts < 5000/mm^3, regardless of bleeding (2D) W
  - With counts 5000–30,000/mm^3 with significant bleeding risk
  - Higher platelet counts (50,000/mm^3) for surgery or invasive procedures
    - 2004 B, E, E

- Mechanical ventilation of sepsis-induced ALI/ARDSSet a Target V_T of 6 mL/kg (predicted) in patients with ALI/ARDS (1B) S
  - Target an initial upper limit plateau pressure < 30 cm H_2O. Consider chest wall compliance when assessing plateau pressure. (1C) S
  - Allow $PaCO_2$ to increase above normal, if needed, to minimize plateau pressures and tidal volumes (1C) S
  - Set PEEP to avoid extensive lung collapse at end-expiration (1C) S
    - 2004 B, C, E
  - Consider using the prone position for ARDS patients requiring potentially injurious levels of FiO_2 or plateau pressure, provided they are not put at risk from positional changes (2C) W
  - Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45°) unless contraindicated (1B) S, between 30° and 45° (2C) W
    - 2004 E, C

- Mechanical ventilation of sepsis-induced ALI/ARDS
    - Noninvasive ventilation may be considered in the minority of ALI/ARDS patients with mild to moderate hypoxemic respiratory failure. The patients need to be hemodynamically stable, comfortable, easily arousable, able to protect/clear their airway, and expected to recover rapidly (2B) W
- New Recommendation, absent in 2004 guidelines
- Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing mechanical ventilation (1A) S
    - SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H2O or a T piece.
    - Before the SBT, patients should be
    - Arousable, hemodynamically stable
    - have no new potentially serious conditions
    - have low ventilatory and PEEP requirement
    - Require FIO_2 levels can be given with face mask or nasal cannula
        - 2004 A
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS (1A) S
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion (1C) S
    - New Recommendation, absent in 2004 guidelines
- Sedation, analgesia, and neuromuscular blockade in sepsis
    - Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients (1B) S

- Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Re-titrate if necessary (1B) S
- Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions (1B) S
  - 2004 B, B, E

- Glucose control
  - Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU (1B) S
  - Aim to keep blood glucose < 150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment (2C) W
    - 2004 D
  - Provide a glucose calorie source and monitor blood glucose values every 1–2 hrs (4 hrs when stable) in patients receiving intravenous insulin (1C) S
    - 2004 E
  - Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values (1B) S
    - New Recommendation, absent in 2004 guidelines

- Renal replacement
  - Intermittent haemodialysis and CVVH are considered equivalent (2B) S

- CVVH offers easier management in hemodynamically unstable patients (2D) W
  - 2004 B

- Bicarbonate therapy
  - Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion induced lactic acidemia with pH > 7.15 (1B) S
    - 2004 C

- Deep vein thrombosis prophylaxis
  - Use either low-dose UFH or LMWH, unless contraindicated (1A) S
  - Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated (1A) S
  - Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis (2C) W
  - In patients at very high risk, LMWH should be used rather than UFH (2C) W
    - 2004 A

- Stress ulcer prophylaxis
  - Provide stress ulcer prophylaxis using H2 blocker (1A) or proton pump inhibitor (1B). Benefits of prevention of upper gastrointestinal bleed must be weighed against the potential for development of ventilator-acquired pneumonia. S
    - 2004 A

- Consideration for limitation of support
    - Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations (1D) S
        - 2004 E

Dellinger RP, Levy MM, Carlet JM, et al for the International Surviving Sepsis Campaign Guidelines Committee. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296–327 and Int Care Med. 2008; 34: 17-60.

OBJECTIVE: To provide an update to the original Surviving Sepsis Campaign clinical management guidelines, "Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock," published in 2004. DESIGN: Modified Delphi method with a consensus conference of 55 international experts, several subsequent meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. This process was conducted independently of any industry funding. METHODS: We used the GRADE system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations. A strong recommendation indicates that an intervention's desirable effects clearly outweigh its undesirable effects (risk, burden, cost), or clearly do not. Weak recommendations indicate that the tradeoff between desirable and undesirable effects is less clear. The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. In areas without complete agreement, a formal process of resolution was developed and applied. Recommendations are grouped into those directly targeting severe sepsis, recommendations targeting general care of the

critically ill patient that are considered high priority in severe sepsis, and pediatric considerations. RESULTS: Key recommendations, listed by category, include: early goal-directed resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures prior to antibiotic therapy (1C); imaging studies performed promptly to confirm potential source of infection (1C); administration of broad-spectrum antibiotic therapy within 1 hr of diagnosis of septic shock (1B) and severe sepsis without septic shock (1D); reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate (1C); a usual 7-10 days of antibiotic therapy guided by clinical response (1D); source control with attention to the balance of risks and benefits of the chosen method (1C); administration of either crystalloid or colloid fluid resuscitation (1B); fluid challenge to restore mean circulating filling pressure (1C); reduction in rate of fluid administration with rising filing pressures and no improvement in tissue perfusion (1D); vasopressor preference for norepinephrine or dopamine to maintain an initial target of mean arterial pressure > or = 65 mm Hg (1C); dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy (1C); stress-dose steroid therapy given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and clinical assessment of high risk for death (2B except 2C for post-operative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, target a hemoglobin of 7-9 g/dL (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless

contraindicated (1B); avoiding routine use of pulmonary artery catheters in ALI/ARDS (1A); to decrease days of mechanical ventilation and ICU length of stay, a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (1C); protocols for weaning and sedation/analgesia (1B); using either intermittent bolus sedation or continuous infusion sedation with daily interruptions or lightening (1B); avoidance of neuromuscular blockers, if at all possible (1B); institution of glycemic control (1B) targeting a blood glucose < 150 mg/dL after initial stabilization (2C); equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1A); use of stress ulcer prophylaxis to prevent upper GI bleeding using H2 blockers (1A) or proton pump inhibitors (1B); and consideration of limitation of support where appropriate (1D). Recommendations specific to pediatric severe sepsis include: greater use of physical examination therapeutic end points (2C); dopamine as the first drug of choice for hypotension (2C); steroids only in children with suspected or proven adrenal insufficiency (2C); a recommendation against the use of recombinant activated protein C in children (1B). CONCLUSION: There was strong agreement among a large cohort of international experts regarding many level 1 recommendations for the best current care of patients with severe sepsis. Evidenced-based recommendations regarding the acute management of sepsis and septic shock are the first step toward improved outcomes for this important group of critically ill patients.

PMID: 18058085 [PubMed - indexed for MEDLINE]
PMCID: PMC2249616

Rivers E, Nguyen B, Havstad S, et al for Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345: 1368-77

BACKGROUND: Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit. METHODS: We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups. RESULTS: Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy (P = 0.009). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (+/-SD) central venous oxygen saturation (70.4+/-10.7 percent vs. 65.3+/-11.4 percent), a lower lactate concentration (3.0+/-4.4 vs. 3.9+/-4.4 mmol per liter), a lower base deficit (2.0+/-6.6 vs. 5.1+/-6.7 mmol per liter), and a higher pH (7.40+/-0.12 vs. 7.36+/-0.12) than the patients assigned to standard therapy (P < or = 0.02 for all

comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0+/-6.3 vs. 15.9+/-6.4, P < 0.001). CONCLUSIONS: Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.

PMID: 11794169 [PubMed - indexed for MEDLINE]

Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006; 34: 1589-96

OBJECTIVE: To determine the prevalence and impact on mortality of delays in initiation of effective antimicrobial therapy from initial onset of recurrent/persistent hypotension of septic shock. DESIGN: A retrospective cohort study performed between July 1989 and June 2004. SETTING: Fourteen intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States. PATIENTS: Medical records of 2,731 adult patients with septic shock. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: The main outcome measure was survival to hospital discharge. Among the 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103-1.136, p<.0001). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease

in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12-2.48). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Median time to effective antimicrobial therapy was 6 hrs (25-75th percentile, 2.0-15.0 hrs). CONCLUSIONS: Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock. Despite a progressive increase in mortality rate with increasing delays, only 50% of septic shock patients received effective antimicrobial therapy within 6 hrs of documented hypotension.

PMID: 16625125 [PubMed - indexed for MEDLINE]

Finfer S, Bellomo R, Boyce N, et al for SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004; 350: 2247-56.

BACKGROUND: It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU. METHODS: We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization. RESULTS: Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups

had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups (P=0.85). There were no significant differences between the groups in the mean (+/-SD) numbers of days spent in the ICU (6.5+/-6.6 in the albumin group and 6.2+/-6.2 in the saline group, P=0.44), days spent in the hospital (15.3+/-9.6 and 15.6+/-9.6, respectively; P=0.30), days of mechanical ventilation (4.5+/-6.1 and 4.3+/-5.7, respectively; P=0.74), or days of renal-replacement therapy (0.5+/-2.3 and 0.4+/-2.0, respectively; P=0.41). CONCLUSIONS: In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

PMID: 15163774 [PubMed - indexed for MEDLINE]

LeDoux D, Astiz ME, Carpati CM, et al. Effects of perfusion pressure on tissue perfusion in septic shock. Rackow EC. Crit Care Med. 2000; 28: 2729-32

OBJECTIVE: To measure the effects of increasing mean arterial pressure (MAP) on systemic oxygen metabolism and regional tissue perfusion in septic shock. DESIGN: Prospective study. SETTING: Medical and surgical intensive care units of a tertiary care teaching hospital. PATIENTS: Ten patients with the diagnosis of septic shock who required pressor agents to maintain a MAP > or = 60 mm Hg after fluid resuscitation to a pulmonary artery occlusion pressure (PAOP) > or = 12 mm Hg. INTERVENTIONS: Norepinephrine was titrated to MAPs of 65, 75, and 85 mm Hg in 10 patients with septic shock. MEASUREMENTS AND MAIN RESULTS: At each level of MAP, hemodynamic parameters (heart rate, PAOP, cardiac index, left ventricular stroke work index, and systemic vascular resistance index), metabolic parameters (oxygen delivery, oxygen consumption, arterial lactate), and regional perfusion

parameters (gastric mucosal Pco2, skin capillary blood flow and red blood cell velocity, urine output) were measured. Increasing the MAP from 65 to 85 mm Hg with norepinephrine resulted in increases in cardiac index from 4.7+/-0.5 L/min/m2 to 5.5+/-0.6 L/min/m2 ($p < 0.03$). Arterial lactate was 3.1+/-0.9 mEq/L at a MAP of 65 mm Hg and 3.0+/-0.9 mEq/L at 85 mm Hg (NS). The gradient between arterial P(CO2) and gastric intramucosal Pco2 was 13+/-3 mm Hg (1.7+/-0.4 kPa) at a MAP of 65 mm Hg and 16+/-3 at 85 mm Hg (2.1+/-0.4 kPa) (NS). Urine output at 65 mm Hg was 49+/-18 mL/hr and was 43+/-13 mL/hr at 85 mm Hg (NS). As the MAP was raised, there were no significant changes in skin capillary blood flow or red blood cell velocity. CONCLUSIONS: Increasing the MAP from 65 mm Hg to 85 mm Hg with norepinephrine does not significantly affect systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchnic perfusion.

PMID: 10966242 [PubMed - indexed for MEDLINE]

Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet. 2000; 356: 2139-43

BACKGROUND: Low-dose dopamine is commonly administered to critically ill patients in the belief that it reduces the risk of renal failure by increasing renal blood flow. However, these effects have not been established in a large randomised controlled trial, and use of dopamine remains controversial. We have done a multicentre, randomised, double-blind, placebo-controlled study of low-dose dopamine in patients with at least two criteria for the systemic inflammatory response syndrome and clinical evidence of early renal dysfunction (oliguria or increase in serum creatinine concentration). METHODS: 328 patients admitted to 23

participating intensive-care units (ICUs) were randomly assigned a continuous intravenous infusion of low-dose dopamine (2 microg kg(-1) min(-1)) or placebo administered through a central venous catheter while in the ICU. The primary endpoint was the peak serum creatinine concentration during the infusion. Analyses excluded four patients with major protocol violations. FINDINGS: The groups assigned dopamine (n=161) and placebo (n=163) were similar in terms of baseline characteristics, renal function, and duration of trial infusion. There was no difference between the dopamine and placebo groups in peak serum creatinine concentration during treatment (245 [SD 144] vs 249 [147] micromol/L; p=0.93), in the increase from baseline to highest value during treatment (62 [107] vs 66 [108] micromol/L; p=0.82), or in the numbers of patients whose serum creatinine concentration exceeded 300 micromol/L (56 vs 56; p=0.92) or who required renal replacement therapy (35 vs 40; p=0.55). Durations of ICU stay (13 [14] vs 14 [15] days; p=0.67) and of hospital stay (29 [27] vs 33 [39] days; p=0.29) were also similar. There were 69 deaths in the dopamine group and 66 in the placebo group. INTERPRETATION: Administration of low-dose dopamine by continuous intravenous infusion to critically ill patients at risk of renal failure does not confer clinically significant protection from renal dysfunction.

PMID: 11191541 [PubMed - indexed for MEDLINE]

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. [No authors listed] N Engl J Med. 2000; 342:1301-8

BACKGROUND: Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress

syndrome. We therefore conducted a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients. METHODS: Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter, randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 ml per kilogram of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 ml per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less. The primary outcomes were death before a patient was discharged home and was breathing without assistance and the number of days without ventilator use from day 1 to day 28. RESULTS: The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent, P=0.007), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean [+/-SD], 12+/-11 vs. 10+/-11; P=0.007). The mean tidal volumes on days 1 to 3 were 6.2+/-0.8 and 11.8+/-0.8 ml per kilogram of predicted body weight (P<0.001), respectively, and the mean plateau pressures were 25+/-6 and 33+/-8 cm of water (P<0.001), respectively. CONCLUSIONS: In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use.

PMID: 10793162 [PubMed - indexed for MEDLINE]

Sprung CL, Annane D, Keh D, et al for CORTICUS Study Group.Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008; 358: 111-24

BACKGROUND: Hydrocortisone is widely used in patients with septic shock even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin. METHODS: In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test. RESULTS: Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, P=0.69) or between those who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, P=1.00). At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died (P=0.51). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock. CONCLUSIONS: Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed.

PMID: 18184957 [PubMed - indexed for MEDLINE]

Complications After Limb Salvage Surgery : Evidence Based Guidelines

Abstract

Limb Salvage Surgery has become a standard of care even in developing nations like India. Endoprosthetic reconstruction, allografts, rotationplasty or autografting are the commonly used reconstructive methods. Prosthesis are commonly used due to immediate stability and mobility and the excellent cosmesis and function. Some complications are encountered with other modality of limb salvage procedure, whereas the others are endoprosthetic-unique. Expectedly, there is an increased incidence of complications compared to a routine orthopaedic operation, especially in the long term survivors. The major causes of such a relatively high rate of complications include (1) extensive excision of soft tissue, leading to change of biomechanical ergonomics, little soft tissue constraints or support for a long replacement segments, and decreased local defence to infection, (2) increased stress on the implants due to higher activity level in the youthful active individuals, relatively narrower medullary canals with less cancellous bone for fixation, (3) special needs for the stability resulting an

increased mechanical constraints placed directly within the endoprosthesis, thus raising the local stress transferred to the prosthesis, and to the prosthesis-bone interface, (4) poor immunological, hematological, or nutritional status resulting from chronic oncologic diseases or chemotherapy. It in turn accelerates the wear processes of the components, induces the wear particulate disease and local osteolysis, as well as to cause the aseptic loosening eventually. The common complications include wound necrosis, aseptic loosening, fatigue fracture, local osteolysis, joint contracture, dislodgement/dislocation, nerve or vascular injury, rotational deformity, leg length discrepancy, infection, periprosthectic fracture, etc. Some patients need revision of the construct and, at times, an amputation. Early detection and early correction of minor complications has an important role of preventing the major complications, thus reduces the necessity of reoperation, and at times, amputation. We will review in detail the literature and evidence related to infection and vascular complications. Guidelines based on the published evidence is provided related to infection and vascular complications.

1. Introduction

The advent of adjuvant chemotherapy, imaging techniques and surgical techniques improved the survival rate and functional outcomes of the patients with malignant bone tumors around the knee in the recent three decades. Taking osteosarcoma as an example, new generation neoadjuvant chemotherapy reduces lung metastasis, improves the 5-year survival rate, decreases the tumor size, and permits a closer surgical resection margin for the malignant bone tumor. Different kinds of limb salvage procedures provide better overall functional outcomes of extremity and bettert body image as compared to those with amputees without the expense of increased local recurrence and shortening the survival time. The principle of limb salvage surgery is to widely resect the

local tumor and to preserve as much as possible of the normal soft tissue, thus providing a well-functioning, tumor-free, and painless limb. The modern imaging techniques clearly demonstrate the local extent of tumor and permit a guide for a safe level of wide resection. A successfully salvaged limb in the well-selected patients can improve pscyche, simplify the rehabilitation process and preserve intact body image. The distal femur and proximal tibia are the common sites of the malignant bone neoplasms. Thus many options of limb salvage operation around the knee have been developed, including resection-arthrodesis of knee joint, reconstruction of the knee using bone graft (autograft, allograft, allograft/endoprosthetic composite), endoprosthesis reconstruction, Ilizarov leg lengthening technique, rotationplasty. The selection of a proper procedure is determined on individual basis. The histopathological diagnosis/grading, tumor extent, presence of lung metastasis, local involvement, patient's age, life and work needs, etc. all may influence the choice of any limb salvage procedure.

Compared with the allograft and autograft reconstruction options, the endoprosthesis reconstruction of limb after wide resection of malignant tumor avoids the problems of disease transmission and limited source of supply that may be encountered in autograft or allograft reconstructions and in pediatric patients. Tumor endoprostheses can provide a wide available range of size and custom design to fit the needs of each patient. Many design principles and concepts have been evolved from clinical experience in the recent three decades to improve the function and decrease the complications. Thus the endoprosthetic reconstruction becomes an alternative to allograft or autograft in the limb salvage procedures and has become more and more common recently. We also have designed our own custom-made tumor endoprosthesis for reconstruction in the limb salvage procedures since 2000.

Megaprosthesis is the most attractive option with excellent cosmesis, and immediate mobility and stability. High costs and limited longevity have been the major drawbacks. Fixed hinge designs have shown high rates of aseptic loosening (35% at 10 years) compared to the rotating hinge with a hydroxyapatite coated collar (zero at 10 years)[1]. A bone ingrowth madreporic surface at the bone–implant junction for extracortical bridging is equally effective in extracortical fixation, seals the cement interface and prevents loosening[2]. Fatigue failures are rare with super-alloys like titanium and chrome-cobalt. Tibial yoke failures seen with the rotating hinge should reduce with a stronger forged component[1,2]. Rebushing is required more commonly in the fixed hinge implant[1] and generally after 5 years[3]. Uncemented stems with madreporic surface Facilitating bone ingrowth in a fixed hinge implant had only 2% aseptic loosening at 10 years but had a high fracture rate through screw holes in the stem[4].

Imported modular tumour prostheses for the knee cost about Rs 4 lakhs in the Indian market. This is generally out of reach of most of our patients. We have reported our results with an indigenous fixed hinge stainless steel prosthesis in osteosarcoma[5]. Inorder to reduce the breakage of the stainless steel intramedullary stem, since December 2006, we have changed to a modular system with the intramedullary stems now made in titanium. Corrosion between the stainless steel taper and titanium stem may not be of clinical concern[6].

The most common site for the complications was in the distal femur and/or proximal tibia, followed by proximal femur[7-10]. This may be because of larger circumference of bone coupled with a thinner soft tissue cover as well as the fact that a majority of tumors occur around the knee. Comparing the two femoral groups(proximal femur and distal femur), an important mechanical difference is the amount of offset of the tip of the prosthesis from the weight-bearing axis from the center of the

femoral head to the center of the knees. Telemetric studies by Taylor et al[10] have demonstrated that, in a cemented prosthesis, most of the force is transmitted rapidly to the tip of the prosthesis. An increment in offset will increase the bending moment around the prosthesis and this may explain the greater loosening of distal femoral replacements[7,10].

Better surgical technique and the better design of endoprostheses have reduced complications and improved the long-term results. However, either early or late complications may occur, including wound necrosis, deep wound infections, joint instability, subluxation or dislocation, joint stiffness, malalignment of patella, fatigue fracture, prosthetic loosening, polyethylene wear, leg length discrepancy, local recurrence, and soft tissue healing problems. The overall complication rate is between 20-41%, including mechanical failure (5-16%), dislocation or instability(5-8%), aseptic loosening rate 2-37%, polyethylene wear 2%, local recurrence(4-11%), wound complication (2-6%), infection (5-15%), neuropraxia [5,7,9,11-25]. The expandable prosthesis has the highest complication rate, may be up the 70%[11-12,16,26].

The occurrence of complications may impair the function and quality of life of the patents. The early detection and early correction of minor complications, such as worn polyethylene bushing, resulted in a significant reduction of implant failure and eventual disaster[17]. Thus it may prevent the occurrence of major complications, such as an accelerated process of bone resorption, aseptic loosening, secondary osteoarthritis, fatigue, etc. The necessity of late event of reoperation and at times amputation also can be avoided.

The postoperative complications after endoprosthetic reconstruction can occur early or late, or be grouped into prosthesis-unique or not, however, they are closely related and some of them are difficult to group. In general, early

complications are usually more related to the patient's status, medical or surgical treatment. The late complications are related to the implant or construct or the long-term tissue response. The occurrence of complications is related to multiple factors. They may be related to the poor nutritional and immune status, lengthy operation, extensive dissection and resection of soft tissue resulting in an inadequate soft tissue cover, longer exposure of the wound resulting in infection, etc. In addition, the use of a relatively smaller stem due to the smaller medullary canal in pediatric patients, young and active individuals with more activity level, little soft tissue support or constraint for stability of fixation, wear particle disease due to larger surface of exposure, higher mechanical stress transferred to the prosthesis and the prosthesis-bone interface may be also encountered in the tumor-endoprosthetic reconstruction. All these factors may contribute to either early or late complications after endoprosthetic reconstruction. The improvement of the surgical technique and chemotherapy protocols have dramatically decreased the iatrogenic complications. Improvement in implant technology have reduced implant specific complications.

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Infection in Limb Salvage Surgery : Incidence, Treatment and Diagnosiss. Evidence Based Guidelines

The Incidence

Infection is a serious complication after Endoprosthetic reconstruction. It often leads to amputation and retards or contraindicates postoperative chemotherapy. The infection rate in the literature varies widely, ranging from 2% to 40%[1-10]. This incidence of infection after tumor resection and limb salvage surgery, by endoprosthesis or allograft, is much higher than after conventional orthopaedic surgery. This is not unexpected as these patients have longer operations, there is a large amount of tissue exposed at the time of surgery, and they frequently are immuno-compromised as a result of neoadjuvant chemotherapy. Results using endoprostheses have shown infection rates varying from none in the humerus to 33% in the proximal tibia[11-14]. The highest infection rates occur after proximal tibial reconstruction and in children who have frequent lengthening procedures. The overall infection rate in more than 650 patients with long-term follow-up was 9.6%[11-15]. The inexperienced surgeon may have a higher incidence of wound complications in the early learning course.

An infection can have disastrous consequences; It may delay the planned adjuvant chemotherapy and, at times, the limb may end up with an amputation.

The Treatment of Infection

Treatment of an infected tumor endoprosthesis is much like treatment of an infected regular hip or knee replacement except that after tumor resection there is a dramatically larger expanse of potentially infected tissue. The possibility of excision arthroplasty or arthrodesis, which might be considered options at the hip and knee respectively, are not available because of the amount of bone removed at the time of the initial tumor resection. Consequences of failing to control the infection are persistent pain, stiffness, and discharging sinuses that eventually could lead to amputation, something that rarely is required after infected hip or knee replacements. The options for controlling infection include debridement, lavage, irrigation, and one- or two-stage revisions[16-21].

Infection at the site of a total joint arthroplasty can be classified into four basic categories[22]: Type I (early postoperative), Type II (late chronic), Type III (acute hematogenous), and Type IV (positive intraoperative cultures with clinically unapparent infection). Acute postoperative infection occurs within 4 weeks of surgery and is initially treated with debridement with retention of the prosthesis and intravenous antibiotics. Local high concentration of antibiotic can be achieved by using antibiotic impregnated cement beads. Type III or Acute hematogenous infection occurs when bacteremia causes seeding at the site of arthroplasty and is treated exactly as in Type I infection. For a type IV infection, a course of intravenous antibiotics is recommended.

Late chronic infection is the most difficult to manage. The current standard of care for type II or late chronic infection is

considered to be two-stage revision arthroplasty including removal of the prosthesis and cement, thorough débridement, placement of an antibiotic-impregnated cement spacer, a course of intravenous antibiotics, and a delayed second-stage revision arthroplasty[16-21,23]. Two-stage revision surgery was first described in 1983 by Insall et al., who demonstrated the necessity of removing the implants as well as the cement and of introducing antibiotic therapy for definitive treatment[24]. Bengston et al[25] showed the advantages of a two stage procedure. One-stage procedures were not successful and one or two attempts to control the infection by leaving the intramedullary component of the prosthesis in situ also were unsuccessful. Donati and Biscaglia[26] experienced similar results and recommended removal of the prosthesis and use of a cement spacer in all chronic infections.

Garvin and Hanssen[27] reviewed twenty-nine studies and found that two-stage procedures without antibiotic-loaded cement had a better success rate (82% of 158 joints) than one-stage exchange arthroplasties (58% of sixty joints), although systemic antibiotics were used for both procedures[27]. With the addition of antibiotic cement, the rates of successful eradication of the infection increased to 91% (385 of 423 joints) for the two stage technique and 82% (976 of 1189 joints) for the one-stage revision. Two-stage revision arthroplasty without the use of spacers allows complete removal of foreign materials, with later reimplantation after eradication of the infection. However, this procedure has several disadvantages as soft-tissue contractures and joint instability may develop and the patient will have difficulty with mobility. From a technical perspective, the disadvantage of the procedure is that it makes reimplantation during the second-stage operation more difficult as a result of arthrofibrosis and the loss of tissue planes. Antibiotic-impregnated cement spacers provide direct local delivery of antibiotics while preserving patient mobility

and facilitating reimplantation surgery. This operative treatment decreases cost and improves patient outcomes as well as addresses some of the disadvantages of two-stage revision procedures in which spacers are not used. Lee et al[28] also reported that one-stage treatment was not successful in any of their patients whereas a two stage revision resulted in control of infection in all the cases. The authors conclude that two stage revision should be used despite disadvantages such as long hospitalisation, more bone loss, more disuse osteoporosis, difficulty of revision operation, and shortening of the affected limb. They recommend that one stage revision should be used only for poor general condition of the patient, low-grade infection, or long delay of chemotherapy.

There are two types of antibiotic-impregnated cement spacers that are typically used in two-stage revisions of total hip and knee arthroplasties: nonarticulating (block or static and articulating (mobile). Nonarticulating spacers allow local delivery of a high concentration of antibiotics and at the same time function to maintain joint space for future revision procedures. Their disadvantages include a limited range of motion of the joint after the operation, resulting in quadriceps or abductor shortening, scar formation, and bone loss. For large Tumor defects these are chosen due to the difficulty in fabricating articulating spacers. Grimer et al[29] reported their experience with thirty-four patients with infected massive endoprostheses treated with two-stage revision procedures with an antibiotic impregnated cement spacer constructed with two cement gun liners and a Kuntscher nail. This non-articulating spacer provided temporary stability and also allowed a high dose of local antibiotic concentration. The overall success rate for controlling infection was 91% at 1 year and 74% at 5 years with six patients requiring an amputation.

In contrast, articulating spacers permit more joint motion and can improve function prior to the second-stage reimplantation. From a technical perspective, improved joint function and decreased scar formation after resection arthroplasty can facilitate exposure during reimplantation. Although the distinction between articulating and nonarticulating spacers is somewhat controversial, use of a well-molded, well-fitted articulating spacer that restores soft-tissue tension and allows a greater degree of joint motion has been reported to have a better outcome than use of a nonarticulating spacer, which may limit joint freedom[30]. As previously stated, articulating spacers are practically difficult to fabricate for the knee but could be used for the hip.

The steps for carrying out the procedure are well described[29].The first-stage procedure involves complete removal of the implant, all the infected surrounding tissues, any scar tissue, and as much intramedullary cement as possible. If the prosthesis was not loose then approximately 1 cm of bone was removed from the junction of the bone with the prosthesis to allow the prosthesis to be jacked out using a distractor. In most patients the prosthesis was loose and could be removed easily. The thick fibrous layer around the prosthesis was removed along with the adjacent scar tissue that often was edematous. Care was taken in revisions around the knee because this scar tissue often was in intimate contact with the popliteal vessels or the posterior tibial vessels and nerve, and all of these structures are at risk during this procedure. The intramedullary cement is removed using appropriate extraction techniques that may include the use of chisels, drills, and ultrasonic extractors. In most patients it proved impossible to remove all the cement as it had fanned out beyond the tip of the intramedullary stem in the metaphysis of the bone. Provided the cement was not obviously loose or infected, this imperfection in technique was accepted. One of the key

features of a two-stage revision is to ensure that a spacer of sufficient size is used to maintain a cavity into which the endoprosthesis will fit at the time of the second stage. A spacer was used of the appropriate length made up inside a cement gun with a Kuntscher nail inside to provide strength. Once the cement has set the outer plastic sleeve is removed and the spacer is ready to be inserted. Appropriate antibiotics were added depending on the sensitivities of the isolated organisms. The most common addition was vancomycin, which was used when appropriate at a dose of 1 g per mix of cement. Primary wound healing is essential after this procedure and adequate soft tissue cover must be available. In the thigh this was not usually a problem but all revisions of the proximal tibia required a medial head of gastrocnemius muscle flap if they had not already had one. Intravenous antibiotics were commenced once appropriate fluid and tissue samples had been taken for microbiologic culture at the start of the operation, and were continued for a minimum of 5 days. The antibiotics were changed depending on the sensitivities of the organisms obtained from the cultures. No patient required long-term intravenous antibiotics and most patients went home after 7 to 10 days taking at least one but usually two oral antibiotics. At 3 weeks the wound was checked and the spacer cavity aspirated to ensure absence of any residual infection. If these cultures proved positive then the systemic antibiotics were changed or the spacer was removed and replaced with a new one incorporating the appropriate antibiotics. In all patients, a sterile aspirate was achieved before proceeding to the second stage. The second stage procedure was done a minimum of 6 weeks after the first procedure. The mean time between the two stages was 10 weeks with a maximum of 34 weeks. At the second stage the wound was reopened and the fluid was sent for culture. The spacer and the pseudocapsule that formed were removed back to healthy muscle. The intramedullary canal was cleaned and all granulation tissue was removed.

The new endoprosthesis then was inserted and the wound was closed over a surgical drain. Intravenous antibiotics again were continued until the cultures taken at the time of the operation became available. Oral antibiotics were continued until all indices of infection (temperature and erythrocyte sedimentation rate) had returned to normal. After the second-stage procedure, the patients were allowed to begin full weightbearing after 48 hours and joint movement was allowed when the wound was seen to be healing.

In most of the infections with a cemented endoprosthesis the implant will be loose or there will be inevitable spread of infection along the bone-cement interface, therefore, removal of the implant and the bone cement is essential. In an uncemented implant like KMFTR or HMR system, infection may not track along the bone-prosthesis interface and there may be scope for not removing the prosthesis or doing a one-stage revision. Holzer et al[31] reported on 18 patients with a mean followup of 52 months treated by one-stage revision surgery without removing the intramedullary stem and had success in 14 of 18 patients. Their success rate at 6 months was 77.8%, somewhat lower than in two stage revision, but problems with late recurrence of infection do not seem to have arisen in their series. This approach of one-stage revision surgery with preservation of the prosthesis in infected hip replacement was condemned by Crockarell et al[32] who found that by 6 years the success rate had fallen to 14%, compared with an optimistic figure of greater than 80% after 6 months. Prolonged followup is essential to confirm the success of any procedure for infection, and early results can be misleading. A significant incidence of late reinfection is linked to previous radiotherapy or additional operative procedures for revision or servicing the endoprosthesis.

Reinfection of a revised endoprosthesis is generally disastrous. Grimer et al in their series[29] reported that four of the seven

patients had an amputation. Two other patients died from metastatic disease with an infected endoprosthesis still in situ. In only one patient the infection could be controlled and the patient avoided amputation of the limb. These results are worse than those for reinfection after conventional joint replacements. This is not unexpected as the option of arthrodesis or resection arthroplasty is not possible in patients with tumors, the importance of controlling infection with the first revision cannot be understated. Radiation has been linked with persisting infection after the revision[29]. Inability to obtain adequate soft tissue cover may be another factor. Late reinfections seemed to develop after additional surgeries to the prosthesis for causes unrelated to infection despite the use of prophylactic antibiotics and careful asepsis. It seems that surgical stimulus can act as a potent source of infection and all patients are made aware of this risk before every additional surgical procedure to their prosthesis[28].

The functional results after revision surgery for infection can be good. Patients who have revision surgery have as good a functional outcome as those patients with primary endoprostheses for range of movement and everyday functional capacity[29]. The success rate of two-stage revision surgery for infected endoprostheses in patients who have not had radiotherapy and who do not have additional surgery is only a little worse than the success rate for infected hip and knee replacements. The same principles of treatment have been used, but because of the extent of the surgical field it is necessary to have appropriate soft tissue cover to allow primary wound healing at first- and second-stage surgeries. The onset of infection in a patient with a tumor endoprosthesis is a disaster but one that can be resolved. Prevention clearly is more desirable. The article on prophylaxis of infection deals with these strategies. Infections of allografts and after other procedures are managed keeping the same principles in mind.

Diagnosis of Infection

The diagnosis of infection after total joint arthroplasty continues to pose a challenge, particularly when it presents as a subacute or low-grade infection. Currently, there is no universally accepted diagnostic test or modality that is absolutely accurate or reliable for the determination of infection. The diagnosis of periprosthetic infection relies on clinical suspicion and a combined armamentarium of serological and imaging modalities[33], with isolation of organisms from the intraoperative culture samples constituting the "gold standard" for ultimate diagnosis[34,35].

Serological tests, including the erythrocyte sedimentation rate and the C-reactive protein level, are frequently used to screen for septic and aseptic failure of total joint arthroplasty and have a relatively high sensitivity and specificity when combined[36]. However, their specificity and sensitivity vary depending on the cutoff values chosen[34]. The role of analysis of synovial fluid for determination of the leukocyte count and neutrophil percentage, although frequently employed, remains unclear. The indicators of periprosthetic infection based on joint fluid analysis still remain unknown[34,36].

There are also numerous limitations related to the use of radiographic or radioisotope imaging modalities. Plain radiographs can impart very important information regarding the cause of failure of a total joint arthroplasty. Infection can cause radiographic changes at the bone-cement or bone-prosthesis interface, including periosteal and endosteal reactions, osteopenia, and osteolysis[33,34]. Rapid and progressive loosening of cemented and cementless implants in the absence of any mechanical cause raises the possibility of infection[36]. However, there is no marked difference between infection and aseptic failure of total joint arthroplasty with regard to these radiographic parameters[3]. Therefore, plain radiography is neither sensitive nor specific for infection and

its main role is confined to ruling out aseptic etiologies. A technetium-99m bone scan is sometimes performed for the initial assessment of pain at the site of an arthroplasty and has been reported to have a sensitivity of 33%, a specificity of 86%, a positive predictive value of 30%, and a negative predictive value of 88% for the detection of infection at the site of a total joint replacement[37]. The indium-111-labeled leukocyte scan has a more promising role in the detection of periprosthetic infection, with a sensitivity of 77%, a specificity of 86%, a positive predictive value of 54%, and a negative predictive value of 95%[38]. These two imaging modalities can be combined to achieve greater results, and this has become the radionuclide imaging modality of choice for the diagnosis of periprosthetic infection[39]. The combined bone scan, despite its relatively high accuracy, has a few drawbacks. It is a labor-intensive test that is often performed over two days as it requires the handling of the patient's white blood cells. In addition, the test involves numerous preparation steps and is prone to processing errors[39,41].

In recent years, a potential role of fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning for the diagnosis of periprosthetic infection has been explored[39-41]. The test relies on the detection of inflammatory cells, particularly macrophages and neutrophils, with an increased glucose uptake in areas of infection[34]. It has higher imaging resolution and easier and faster penetration ability into infected tissues, and it can be performed within sixty minutes[40]. Some authors have reported reliable results, with an accuracy ranging from 91% to 95%, when the FDG-PET scan has been compared with a triple-phase technetium bone scan[40,41]. However, in one study in which FDG-PET scanning was compared with combined technetium-99m/indium-111-labeled leukocyte scanning, FDG-PET scanning demonstrated poor accuracy, ranging from 47% to 71%[39]. In a more recent study[42],

FDG-PET scanning had a positive predictive value of 80% and a negative predictive value of 98.5% for the diagnosis of infection at the site of total hip arthroplasty when increased uptake around the stem-bone interface was used as the criterion for infection. With further research, this new and promising modality may have an important role in the diagnosis of periprosthetic infection.

Culture of aspirated fluid from around the joint should be confirmatory for infection. However, contamination can reduce the value of this test. The predictive value of a positive culture of aspirated fluid will be higher if the test is used to confirm rather than to screen for infection[42].

Besides microbiologic testing, aspirated joint fluid also can be analyzed with respect to cell count and differentials. Spangehl et al. reported that a leukocyte count of >50 × 103 cells/îL combined with a neutrophil percentage of >80% was highly suggestive of infection[43]. A recent study demonstrated that a joint fluid leukocyte count of 1700 cells/μL yielded a positive predictive value of 73% and negative predictive value of 98%, whereas a neutrophil percentage of ?65% yielded a positive predictive value of 94% and negative predictive value of 99%[44]. A more recent study[42] showed that a fluid white blood-cell count cutoff value of 1760 cells/μL yielded a 99% positive predictive value and an 88% negative predictive value. However, the cutoff value of their neutrophil percentage was slightly higher (73%) and had a similar positive predictive value (96%) but had a slightly lower negative predictive value (91%).

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Antibiotic Prophylaxis in Orthopaedic Prosthetic Surgery

Prevention of surgical infection consists of perioperative measures like:

1. augmenting the host response
2. optimizing the wound environment
3. decreasing the bacterial load introduced into the surgical wound by clean air technology and surgical site preparation.
4. Antibiotic prohylaxis: The administration of systemic antibiotics immediately before surgery is the most effective prophylactic measure in the prevention of infection[1].
    a. perioperative prophylaxis to diminish the quantity and consequences of the bacterial contamination that occurs inevitably during the surgery.
    b. Postoperative prophylaxis to reduce the risk of joint infection caused by the transient bacteremias associated with infection or instrumentation at remote sites.

5. A systematic review of 25 RCT's on antibiotic prophylaxis for total hip replacement was published in 1999[2]. The overall rate of surgical wound infection across all the included trials of antimicrobial prophylaxis for THR surgery was 1% (2.1% when total knee replacement (TKR) patients were included). Staphylococcus aureus and Staphylococcus epidermidis were the most frequently isolated pathogens in the trials included in the present review.

   a. Surgical wound infection (SWI) rates can be statistically significantly reduced when an antimicrobial is used prophylactically, compared with placebo or no intervention.

   b. However, trials to date provide inconclusive evidence on the optimal antimicrobial prophylaxis regimen. The comparative efficacy of antimicrobial prophylaxis for THR (and TKR) surgery was difficult to demonstrate, mainly due to the low infection rates and the small sample sizes of the trials.

   c. Cephalosporins (first and second generation) were the most commonly studied antibiotics. There is no convincing evidence to suggest that third-generation cephalosporins are more effective than first- and second-generation cephalosporins in preventing SWIs in THR surgery.

   d. The duration of the antimicrobial prophylactic regimen examined in the included trials varied from a single dose to a 14-day course. There is no evidence to suggest that administering antimicrobial prophylaxis for more than 1 day postoperatively reduces the number of infections following THR surgery. Extending the duration of a regimen for longer than 24 hours may not only

be wasteful, but potentially hazardous in terms of toxicity, and the increased risk of developing bacterial resistance.

e. The antimicrobial prophylaxis examined in the review were administered parenterally, orally, or in antibiotic-loaded cement. The results of trials in this area are inconclusive. The cost and ease of administration should, therefore, be used to determine which route should be used.

f. These reviews are from elective total joint Arthroplasty and cannot be directly applied to Oncology reconstructions. This is an inherently higher risk group. However broad principles emerge from the data which can be applied.

Selection of antimicrobial agent

The optimal antibiotic should have activity against common organisms in prosthetic joint infections (Staphylococcus or Streptococcus spp); a long half-life; excellent tissue penetration; a lack of toxicity; and be relatively inexpensive.

1. Cefazolin, a first-generation cephalosporin, meets all the desired criteria[3] and is the most widely used antibiotic at present. Vancomycin and clindamycin are recommended as alternative agents for patients who have a true type I b-lactam allergy, manifested by immediate urticaria, laryngeal edema, or bronchospasm[4].
2. The use of vancomycin in orthopedic surgery prophylaxis should be limited:
    a. Vancomycin is an inferior antistaphylococcal agent for methicillin-susceptible strains, compared with cephalosporins and penicillinase-resistant penicillins[5,6]. There are no prospective comparative data on the clinical efficacy of cephalosporin

(cefazolin or cefuroxime) or penicillin (nafcillin or oxacillin) compounds versus vancomycin for prevention of infections associated with surgical implants.

b. A high frequency of MRSA infection in an institution is an indication for the use of vancomycin for prophylaxis[7]. Wiesel and Esterhai[8] recommend administration of vancomycin in institutions where the prevalence of MRSA is greater than 10% to 20%. There is no consensus about what constitutes a high prevalence of methicillin resistance, however, and no evidence that routine use of vancomycin for prophylaxis in institutions with perceived high risk of MRSA infection results in fewer surgical site infections than the use of cefazolin[9].

c. Vancomycin is appropriate for surgical prophylaxis for patients with known MRSA colonization[9].

3. Teicoplanin has proved to be an effective and safe prophylactic agent in prosthetic implant surgery especially when there is a high risk of infection with MRSA[10-14]. It is not available in the United States. Restricted use is advised to prevent antibiotic resistant strains. For surgical procedures requiring a tourniquet, such as total knee arthroplasty, regional administration of a single dose of teicoplanin achieved a high concentration in the operative field, and resulted in a rate of postoperative infection similar to those of conventional prophylactic regimens[15].

4. The use of daptomycin for prophylaxis in orthopedic surgery needs to be investigated.

5. Antimicrobial prophylaxis with third- and fourth-generation cephalosporins is not indicated, because most

are less active than cefazolin against staphylococci, their use promotes emergence of resistance, and they are more expensive than more effective alternatives[16].

6. In a small study investigating the contaminating bacteria in primary hip arthroplasty[17] and their sensitivity to the prophylactic antibiotics currently in use, impressions (627) of the gloved hands of the surgical team in 50 total hip arthroplasties were obtained on blood agar. The gloves were changed after draping, at intervals of 20 minutes thereafter, and before using cement. Changes were also undertaken whenever a visible puncture was detected. The culture plates were incubated at 37°C for 48 hours. Isolates were identified and tested for sensitivity to flucloxacillin, which is a recognised indicator of sensitivity to cefuroxime. They were also tested against other agents depending upon their appearance on Gram staining. Contamination was detected in 57 (9%) impressions and 106 bacterial isolates. Coagulase negative staphylococci were seen most frequently (68.9%), but Micrococcus (12.3%), diphtheroids (9.4%), Staphylococcus aureus (6.6%) and Escherichia coli (0.9%) were also isolated. Of the coagulase-negative staphylococci, only 52.1% were sensitive to flucloxacillin and therefore to cefuroxime. In another study from Wrightington Hospital, Wigan, UK,(9) where tissue samples were collected for bacteriological study during primary and revision hip surgery, coagulase-negative staphylococcus was the most common isolate (43.4%), 55% being methicillin-resistant. In light of above, the authors question whether cefuroxime is the most appropriate agent for antibiotic prophylaxis since staphylococci represented 75% of contaminating isolates, nearly half of which were resistant to it. They recommend that the antibiotic policy

should be based on the isolates from any institute and their antibiotic sensitivity pattern.

Timing and dosage of antimicrobial prophylaxis

The goal of antimicrobial prophylaxis is to achieve serum and tissue drug levels that exceed, for the duration of the operation, the minimum inhibitory concentrations for the organisms likely to be encountered.

a. Peak serum and bone concentration of antibiotics typically occur within 20 minutes of systemic administration[3]. It is therefore reasonable to administer a prophylactic antibiotic 30 to 60 minutes before skin incision[9].

b. Vancomycin infusion should begin within 60 minutes before skin incision, to prevent antibiotic-associated reactions.

a. Arthroplasties that require a tourniquet should have the entire antimicrobial dose before the tourniquet is inflated[9].

b. For prolonged procedures, or procedures associated with extensive blood loss, an additional intraoperative dose of antibiotic is advised[18,19].

c. For obese patients, higher doses of cefazolin (2 g) are required[16].

Duration of antimicrobial prophylaxis

The optimal duration has yet to be determined.

1. Several studies have reported no additional benefit when prophylaxis was continued beyond 24 hours[20-24].
2. The current consensus on the duration of prophylaxis for a routine joint arthroplasty is a single preoperative dose, followed by two to three postoperative doses[25] to minimize toxicity, cost, and antimicrobial resistance.

3. There is no evidence to support prophylactic antibiotics beyond 24 hours after surgery, although some surgeons choose to continue prophylaxis until all indwelling catheters are out[26].

Surgical site preparation

Introduction of a foreign body decreases the number of bacteria required to produce a clinical infection[27]. The risk of infection is also influenced by additional factors, such as patient health, the length of operation, and adequacy of circulation. Strict adherence to aseptic techniques during each case is essential to control the number of infections. Preparation of the patient before operation is important. Several disinfectants can be used to remove bacteria from the patient's skin[26]. Clipping hair immediately before an operation is associated with a lower risk of surgical site infections than shaving or clipping the night before an operation[7]. Appropriate draping of the patient is mandatory, but does not guarantee the prevention of infection.

Clean air technology

Various techniques are used to minimize the number of airborne bacteria in the operating room, such as laminar air flow, ultraviolet light, limitation of traffic, and wearing of surgical facemask under an overlapping hood[25]. Not all of these measures have gained widespread acceptance. Laminar air flow can result in a 90% reduction of bacteria in the wound, and 60% reduction of airborne bacteria in the operating room[28]. Vertical laminar airflow is considered more effective than horizontal airflow in reducing airborne contamination, especially in the absence of body exhaust suits[25,29]. With the use of clean air technology and laminar air flow, various studies have demonstrated a significant reduction in infection rates to 0.5%-1% [21,30,31]. These studies were not prospective, however, and included confounding factors that were not controlled for,

such as concomitant use of prophylactic antibiotics. Other studies did not find a statistically significant difference between the two operating room environments[32]. Currently, the role of laminar airflow in the prophylaxis is controversial if prophylactic antibiotics are used.

Control measures for methicillin-resistant Staphylococcus aureus

MRSA has become an important cause of surgical wound infections, with an increased incidence within both hospitals and the community. Monthly bacterial colonization rates vary between 6.6% and 23%, with an MRSA infection rate of 3%[33,34]. This are likely to be higher in India. Simple measures, such as meticulous hand hygiene, patient screening, careful surveillance of infections, and prompt implementation of isolation policies, are essential components of control[35-37]. Preoperative nasal carriage of S. aureus represents a risk factor for surgical site infections[7]. Up to 5.3% of orthopedic patients are colonized with methicillin-resistant strains of staphylococci on hospital admission[38]. Current guidelines advocate screening for MRSA carriage in patients at high risk (ie, patients who have spent more than 5 days in acute or long-term care centers)[39].

Intranasal mupirocin has been evaluated in the prevention of surgical site infections. Although intranasal mupirocin reduced nasal carriage of S aureus, several studies failed to demonstrate a significant reduction in surgical site infection rates[40-42]. In one study, the rate of endogenous S aureus infections was five times lower in the mupirocin group than in placebo group (0.3% and 1.7%, respectively), although this difference was not statistically significant[40]. Other studies have shown a potential benefit in reduction of surgical site infections by using mupirocin. One study that used a historical control group showed a significant reduction in the surgical site infection

rate from 2.7% to 1.3%, with a nonsignificant reduction of S aureus surgical site infection from 1.1% to 0.7%[43]. Another study that used mupirocin in conjunction with preoperative triclosan shower showed a marked decrease in the incidence of MRSA surgical site infections from 23 per 1000 operations to 3.3 to 4 per 1000 operations, after the introduction of a mupirocin-based protocol[44]. Although a consensus has not been reached regarding the relationship between mupirocin nasal decolonization and the reduction of S aureus surgical site infections, identification of patients colonized with MRSA is important, because vancomycin or teicoplanin prophylaxis is indicated for these patients.

Optimization of the total joint arthroplasty patient

Unlike in a routine Arthroplasty setting, in an Oncology patient, there is not much time to optimise factors such as obesity or nutrition. Most patients are on immunosuppressive chemotherapy. Patients at high risk for infection, such as those with rheumatoid arthritis, the elderly, malnourished, obese, diabetic, or otherwise immunosuppressed, may benefit from the optimization of these risk factors, or may require more intensive prophylaxis to minimize their risk of sepsis[25].

1. Patients with preoperative lymphocyte counts of less than 1500 cells/mm3 and an albumin level of less than 3.5 g/dL had five and seven times more frequent major wound complications, respectively[45].
2. Glycemic control is desirable in diabetic patients undergoing elective implant surgery, although no reports of the effect of normalizing serum glucose levels in the setting of total hip arthroplasty have been published[7,25].
3. Smoking cessation or abstaining from tobacco is highly recommended[7].

Surgical technique

Adherence to meticulous surgical technique is essential in reducing the infection rates after joint arthroplasty.

1. There is strong evidence to support the use of impenetrable disposable clothing and drapes, as opposed to using permeable gowns[46].
2. The operative site should be cleansed with an antiseptic agent, and covered with an antiseptic adhesive tape before incision. A plastic drape impregnated with slow-release iodophor inhibits skin recolonization and lateral migration of bacteria from scrubbed areas not involving the incision[25].
3. Efforts should be made to minimize the duration of surgery, because prolonged operative time increases the rate of infection[47,48].
4. Although the method of gloving is controversial, double gloving is still recommended over single gloving[1]. A cloth outer glove significantly reduces the number of punctures to the innermost glove compared with wearing double latex gloves[49].
5. Surgical staff should wear hoods and masks, although the wearing of masks is controversial[29].
6. Gore-Tex gowns may prevent dispersion of bacteria up to 1000 times more effectively than cotton gowns[50].
7. Several operative instruments, such as suction tips and splash basins, are reported as sources of bacterial contamination. Frequent exchanging of the suction tip, and use of a clean suction tip at the time of preparation of the femoral canal, is recommended to minimize bacterial contamination[1].
8. In addition, delicate tissue handling and prevention of extensive dissection from the underlying fascia help reduce the extent of devitalized tissue[25].

9. Saline irrigation of the wound contributes to a 12% to 56% reduction of the wound bacterial counts, and prevents tissue desiccation[4,25]. The addition of antibiotics to the irrigation solutions remains controversial[51,52], but may be reasonable during orthopedic procedures[4]. Most commonly used is a triple antibiotic solution of neomycin, polymyxin, and bacitracin, because it provides the most complete coverage against common microorganisms known to cause infection[51]. More studies are needed before routine implementation of this technique.
10. There is insufficient evidence to support or refute the routine use of closed surgical drainage in implant orthopedic surgery[53]. If used, drain removal should be accomplished early to prevent retrograde contamination of the wound[25].

Antibiotic-impregnated bone cement

The use of antibiotic-impregnated cement for primary and revision joint arthroplasty is becoming the standard of practice in Europe and Scandinavia[54]. It has been approved by the Food and Drug Administration in the United States for use only in infected joint arthroplasty. There are no established guidelines for use of these agents for prophylaxis in the United States[9], although the antibiotic-impregnated bone cements have been extensively studied.

1. A large prospective multicenter randomized Swedish study (1688 consecutive total hip arthroplasties) found a statistically significant difference at 5-year follow-up between deep infection rates in patients treated with systemic antibiotics (1.9%) compared with patients who had gentamicin-impregnated cement (0.8%). At 10-year follow-up the difference between the two groups (1.6% versus 1.1%) was not significant[55].

2. Another small prospective randomized trial comparing the effect of cefuroxime impregnated cement versus systemic administration of cefuroxime found no statistically significant difference in respect to incidence of superficial or early deep wound infections between the two groups[56].
3. Two trials (one in patients with diabetes mellitus) in patients undergoing total knee arthroplasty comparing infection rates in patients who received cefuroxime impregnated bone cement and those who had standard bone cement found a significant reduction in deep infections in the antibiotic cement group[57,58].
4. A large Norwegian study found that patients who received both systemic prophylaxis and antibiotic-impregnated cement had the lowest risk of revision. Those who received only systemic antimicrobial prophylaxis had a revision rate because of infection that was 1.8 times higher. The authors concluded that systemic antibiotics, combined with antibiotic-impregnated cement, provide the best prophylaxis for total hip arthroplasty[59].
5. In a recent review, Bourne[54] suggested that consideration should be given for use of antibiotic-impregnated bone cements during primary joint arthroplasty. Before the use of antibiotic-impregnated cement can be recommended for routine primary joint arthroplasties, however, randomized trials are needed to study the rate of infection, the risk of antimicrobial resistance, and assessment of cost-benefit[8,54]. Antibiotic-impregnated cement has a more definitive role in high-risk patients, such as the immunocompromised, the elderly, or those requiring revision surgeries[54].
6. In a study of 91 infected total hip arthroplasties caused by coagulase-negative staphylococci, emergence of

gentamicin-resistant organisms occurred in 88% of patients who underwent primary hip arthroplasty with gentamicin-impregnated cement, and in only 16% of patients who had not received gentamicin-impregnated cement[60].

A number of criteria must be met for antibiotics to be effective when mixed with methylmethacrylate: thermal stability, water solubility, bactericidal effect at tissue level, gradual release, minimal or absent development of antimicrobial resistance or allergic reactions, and lack of compromise of mechanical integrity[61]. Concerns about the routine use of antibiotic impregnated bone cement for prophylaxis of infection include mechanical effects of mixing antibiotics to acrylic bone cement, occurrence of an allergic reaction, emergence of antimicrobial resistance, and cost[4]. Many antibiotics used in bone cement are heat-stable, and demonstrate highly effective bactericidal activity for at least 7 to 10 days, or even up to 10 years[54,62,63]. In addition, low doses of antibiotics may not weaken the bone cement[54]. Allergic reactions are not seen with gentamicin, a commonly used antibiotic in bone cement[54], whereas other antibiotics, such as penicillin or cephalosporins, are best avoided because of their potential allergenicity[61].

Postoperative prophylaxis

From the moment of implantation, total joint arthroplasty is vulnerable to infection during episodes of transient bacteremia. The risk of hematogenous seeding lasts throughout the lifetime of prosthesis, and may result from infection or manipulation at distant body sites. Some of the more common origins of hematogenous infection are the oral cavity, skin, genitourinary tract, and gastrointestinal tract[25]. The aim of postoperative prophylaxis is to protect the total joint arthroplasty from hematogenous seeding. Currently, there are relatively few generally accepted indications for postoperative prophylaxis.

Antibiotic prophylaxis for dental and urological patients with total joint arthroplasty

The most critical period for hematogenous seeding is up to 2 years after joint placement[64], occurring at a frequency of 0.14 cases per 1000 joint-years, whereas the annual rate after the first 2 years is only 0.03 cases per 1000 joint-years[65]. The routine use of dental prophylaxis is not recommended for most patients with total joint arthroplasty after two years. Prophylaxis is considered for immunocompromised patients undergoing dental procedures with a high bacteremic risk. 1st generation cephalosporin or clindamycin for those allergic to cephalosporin is recommended as a single dose (2g cephalexin or 600mg clindamycin) 1 hour before the procedure. The recommendations are similar for urologic procedures except that ciprofloxacin or levofloxacin 500mg can be used. URINE INFECTION IF PRESENT PUTS A HIGHER RISK AND SHOULD BE TREATED BEFORE MANIPULATION[66].

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Vessel Related Issues in Sarcoma: Evidence Based Guidelines

Incidence

Vessel invasion by primary malignant musculoskeletal neoplasms is uncommon. Approx. 3-4% of bone sarcomas[1] and 4.5%-10% of soft tissue sarcomas[1,2] demonstrate vascular involvement. Most of the time tumors juxtaposed to vessels without encasement are resectable by excising the tumor along with the vascular adventitia, provided that an effective adjuvant was used (radiotherapy for soft tissue sarcomas or chemotherapy for osteosarcoma) or the tumor was of low histologic grade[3]. In these cases, the goal of the surgery was to obtain wide or wide with focally marginal surgical margins[3]. If adequate margins are not obtainable, a vascular resection and reconstruction or an amputation is necessary. Vascular resection typically is not needed until there is more than 50% encasement of major vessels by tumor[3].

Imaging

Nevertheless, decision making before surgical treatment in patients with musculoskeletal tumors of the limb requires accurate delineation of the presence and level of vascular

involvement. several factors limit the radiologic assessment of neurovascular structures:

(1) Arteries and veins are small structures, placing great demands on imaging studies to depict the structures and their relationship to a tumor.

(2) the vessels are often not parallel to the imaging plane

(3) normal anatomic relationships are distorted by the presence of a tumor mass.

(4) It can be difficult or impossible to differentiate edema in the reactive zone surrounding a tumor and the tumor itself at imaging limiting the evaluation of the neurovascular structures present within that abnormal tissue.

(5) Non-invasive cross-sectional imaging techniques such as CT and MRI can demonstrate whether a tumor is close to or in contact with a neurovascular structure, but usually cannot differentiate mere contact, adherence or subtle invasion. Gross encasement of a vessel can be diagnosed reliably only when a tumor mass clearly surrounds the vessel. Irregularity of vessel walls shown at angiography can be due to tumor encasement or atherosclerosis.

In the Radiology Diagnostic Oncology Group multiinstitutional collaborative trial[1] which compared CT and MRI in local staging of malignant musculoskeletal neoplasms, the positive predictive value of CT and MRI for neurovascular involvement by sarcomas in that study was only 6± 27%, with a negative predictive value of 92±99%. Panicek et al[1] emphasise the importance of excellent image quality and recommend large imaging matrices and small field-of-view imaging focused on the local tumor site along with appropriate MRI surface coils. For CT, they suggest that intravenous contrast material delivered by rapid bolus injection should be used to optimize the delineation of vessels. Special CT or MRI angiographic

sequences may be of value. They caution against the tendency to over-diagnose invasion based solely on the demonstration of contact between tumor and neurovascular structures as the incidence of actual invasion found at surgery is very low.

Feydi et al[4] prospectively evaluated the accuracy of contrast–enhanced MR angiography in the evaluation of vascular invasion by bone and soft-tissue tumors and referenced the finding against those found at surgery. The presence of MR imaging findings of partial or total or MR angiographic findings of stenosis had a sensitivity of 79%, specificity of 100%, positive predictive value of 100%, negative predictive value of 85%, and accuracy of 90% in the detection of vascular involvement. They conclude that the findings of stenosis were sensitive and specific in the detection of arterial invasion. MR imaging evidence of partial or total encasement is highly specific in the detection of vascular invasion, while MR imaging evidence of a gap between the tumor and the vessels excludes an arterial invasion.

The decision of whether or not to resect blood vessels and to what extent depends on preoperative MR/CT imaging and intraoperative findings. Despite the high accuracy of preoperative cross-sectional imaging, precise intraoperative differentiation between mere contact and invasion of vascular structures remains difficult. Intraoperative decisions about vessel resection may be improved by the use of intraoperative intravascular ultrasonography (IVUS) to visualize vascular infiltration by soft tissue sarcoma[5]. Hunerbein et al in their study of 20 patients found IVUS provided high-resolution images of tumour and vessels, and allowed accurate assessment of vascular infiltration. Both IVUS and MRI had a high sensitivity in the assessment of vascular infiltration (18 of 20 patients), but the combination of these two modalities increased the accuracy. In comparison with preoperative MRI, intraoperative IVUS improved the assessment of vascular

involvement in four of the 20 patients. In three of these four patients, IVUS confirmed resectability and demonstrated a tissue layer between tumour and vessels. In only one patient did IVUS disclose infiltration of the popliteal artery, which appeared displaced but not involved by tumour on MRI. The major advantage of IVUS was its ability to confirm the absence of vascular involvement in several patients, thereby avoiding unnecessary resection of major vessels. The authors point out that although high-resolution ultrasonography can evaluate direct vascular infiltration, it is often impossible to visualize remote tumour sites owing to the limited field of view of the transducer. MRI therefore remains indispensable for accurate visualization of large and bulky tumours and a combination of MRI and IVUS may improve assessment of resectability of soft tissue sarcoma in close proximity to major vessels. Other disadvantages of IVUS include the learning curve and the costs of additional technical equipment.

Surgical Management

Most of the time tumors juxtaposed to vessels without encasement are resectable by excising the tumor along with the vascular adventitia, provided that an effective adjuvant is used (radiotherapy for soft tissue sarcomas or chemotherapy for osteosarcoma) or the tumor was of low histologic grade. In these cases, the goal of the surgery is to obtain wide or wide with focally marginal surgical margins. If adequate margins are not obtainable, a vascular resection and reconstruction or an amputation is necessary. Data gathered from literature[3,6-9] indicates that patients can avoid amputation, despite malignant involvement of major vessels to their extremities. Though the complication rate observed in this subset of patients is significant, local control and the incidence of major complications is acceptable. Although only a few series are reported in literature, most have shown that for vessel involvement, a resection and reconstruction of the vessels is

an excellent alternative to amputation with very good local control and limb preservation rates. Often a major nerve is sacrificed but the function in the lower limb is still good.

Leggon et al reported their experience with 14 patients of limb sarcoma with vessel reconstruction[3]. They also analysed the literature till 1996 and reported that amputation was not necessary as vessels could be reconstructed and limbs successfully salvaged (88%) despite a high rate of local complications. In half their cases a major nerve was also resected with the vessels. They reported a 26% infection rate for prosthetic grafts compared to 3% with the autogenous vein graft. The pooled cases from literature also showed similar findings.

The german group[5] reported their experience with 21 cases of vessel resection in lower extremity STS with vessel reconstruction. Vein was reconstructed only if greater saphenous vein (GSV) was not patent or previously removed. 43% incidence of vessel infiltration was reported. Local control rate was 86% and the limb survival rate was 94%. Good function was retained and patients were happy that an amputation was avoided. They conclude that vessel infiltration is a possible negative prognostic factor in extremity STS and the use of the autologous vein has not proven to be superior to synthetic grafts with respect to the long-term patency rate after limb-salvage surgery.

Tsukushi et al[6] analysed 25 cases of vascular reconstruction, 13 with both artery and vein and 12 with only the artery reconstructed after resection of soft tissue sarcomas involving the vessels as judged on MRI. They found no difference in outcomes of the two groups implying no advantage of the additional vein reconstruction. Though the patency rates of the vein were much lower, there did not appear any difference between autogenous vein graft and the PTFE graft. No local recurrence was observed, which is remarkable considering that

these were large and deep-seated soft tissue sarcomas. This justifies the increased operating time as well as increased magnitude of surgery. Interestingly , on histology, only 24% of these cases showed actual vascular infiltration. The complication rate of extensive resection associated with vascular reconstruction is high, and active use of flap transfers may help mitigate complications and postoperative severe edema.

Mckay et al reported from their experience of 7 cases that The SFV conduit is a versatile option for major vascular reconstruction, providing good long-term patency rates with acceptable morbidity and mortality. It provides a better size match for the larger diameter proximal limb vessels. Patency of the saphenous vein was a prerequisite.

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Section — II

Head and Neck

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Oral Incompetence

Oral competence is controlled by a complex neuromuscular mechanism consisting of:

– The orbicularis oris muscle.
– Motor supply from the buccal branches of facial nerve.
– Sensory innervation to the upper lip is provided by branches of infraorbital nerve and that of lower lip by mental nerve, both branches of trigeminal nerve.

Etiology

- Injury to sensory/motor (Facial Nerve) innervation of lip.
- Extensive resections of the cheek or loss of bony support to lips (upper and lower alveolus).
- Breach in continuity of lip or orbicularis muscle.

Symptoms and Signs

- Continuous drool of saliva.
- Difficulty in holding liquids in the oral cavity.
- Inability to achieve oral seal.

Management

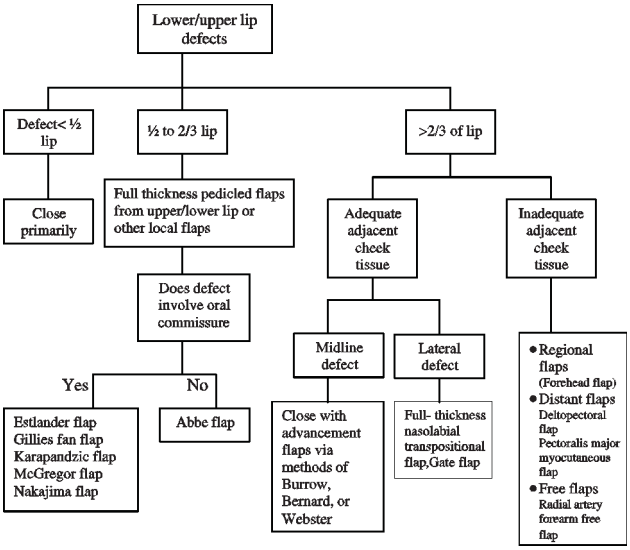
Principles

- The most important considerations are-
    - o Adequate gingivo-labial sulcus creation.
    - o Tight oral commissure.
    - o Bony support to lips (upper and lower alveolus).
    - o Sufficient height of lower lip so that it touches the upper lip or vice – versa.
- Lower lip has no definitive central structure like philtral column and therefore can donate larger amounts of tissue for upper lip reconstruction.
- For the sake of oral continence, muscle restoration in the upper lip is little less important than it is in the lower lip because the upper lip functions more like a curtain, while the lower lip functions more like a dam.
- Surgical reconstruction may leave the lips with reduced sensation and elasticity. Reconstruction techniques that use full-thickness nasolabial tissue may also dennervate the upper lip muscle to a great degree. Patients who have reduction of lip sensation in addition to poor sulcus depth have tendency to drool.
- Injury to Sensory/motor innervation of lip- management involves primary repair of the nerve and if required facial reanimation.
- Extensive resections of the cheek not involving lip – manage by forehead flap or free radial artery forearm flap to give adequate soft tissue replacement with special concern for adjusting the angle of the mouth on the diseased side at the same level as that of the normal side.
- Loss of bony support to lips (upper and lower alveolus) – free fibula osteocutaneous flap is the flap of choice as it provides bony support as well as soft tissue. As the

flap is insensate and has no motor function, the primary concerns for competence are to maintain occlusion and to provide adequate sulcus depth and height so that the lips come in contact with each other.

- Breach in continuity of lip or orbicularis muscle.Lip reconstruction can best be accomplished by following the algorithm below.

Algorithm for Reconstruction of Lower/Upper-Lip Defects



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Osteoradionecrosis of the Mandible

Definition

- When irradiated bone becomes devitalized and exposed through the overlying periosteum or mucosa without healing for 3 months, without evidence of recurrence of tumor.
- The final diagnosis is most often based on a radiological evidence of bony necrosis within the radiation field or histological evidence of necrotic bone at the time of resection.

Incidence

- The true frequency of ORN is impossible to determine because of poor reporting. The overall incidence of ORN has decreased over the last 3 decades. ORN incidence over the years has ranged from 3.0-11.8%.
- ORN is rare in patients who receive less than 60 gray (Gy) radiation therapy (conventional fractionation). However, the incidence maybe higher in patients who receive combined chemotherapy and radiation.
- ORN affects the mandible more than any other bones of the face and neck. Its incidence in the mandible is between 2% and 22% and affecting the body most often.

- The incidence is usually lower after hyperfractionated radiotherapy at 72–80 Gy, or moderately accelerated fractionated radiotherapy together with a boost of 64–72 Gy.
- Its incidence can be decreased with the use of intensity-modulated radiotherapy.
- The incidence is higher in dentate than in edentulous patients.

Clinical presentation

- Pain, chronic non-healing fistulae, sinus through the skin or alveolar mucosa, exposed bone in a region that has been irradiated.
- Dysaesthesia, halitosis, dysgeusia.
- The interval between radiation and occurrence of ORN varies from 4-12 months. It may sometimes manifest after longer intervals in the presence of trauma.
- May present earlier with history of trauma, post radiotherapy.

Various staging systems have been proposed based on severity and response to treatment

Factors influencing the occurrence of ORN

- Size and site of tumor: Larger tumors in proximity to the mandibular alveolus, in the presence of other factors may predispose to ORN.
- Dose of radiation: The type of radiation, whether external beam or brachytherapy or a combination of the two, the volume radiated, proximity and dose to the adjacent bone, fractionation, dose per fraction and total dose play an important role in the manifestation of ORN.
- Type of Mandibular resection: Resection of large segments of the mandible, especially the posterior segment may predispose to ORN.

- Injury or dental extractions: Any stimulus that initiates or stimulates cell division post radiotherapy, can cause manifestation of ORN.
- Infection, immune deficiencies and malnutrition.

Etiology

- Radiation injury.
- Trauma in the form of dental extractions, biopsies.
- Infection.

Pathogenesis

Various theories have been proposed:

- Release of histamine.
- Exposure of bone to radiotherapy above a critical dose, local injury; and infection (Watson, Scarborough et al.) with underlying tissue changes like thickening of arterial and arteriolar walls, loss of osteocytes and osteoblasts, filling of bony cavities with inflammatory cells.
- Hypoxic-hypocellular-hypovascular theory (Marx): Formation of hypoxic-hypocellular-hypovascular tissue and breakdown of tissue driven by persistent hypoxia that can cause a chronic non-healing wound. This forms the basis of hyperbaric oxygen therapy for ORN.
- Radiation-induced fibroatrophic theory: Activation and dysregulation of fibroblastic activity that leads to atrophic tissue within a previously irradiated area.
- Three distinct phases can be identified:

  Prefibrotic phase: Changes in endothelial cells predominate, with acute inflammatory response.

  Constitutive organized phase: Abnormal fibroblastic activity predominates with disorganization of extracellular matrix.

Late fibrotic phase: Attempted tissue remodelling occurs with formation of fragile healed tissues.

- The underlying mechanism seen by microradiographic analysis of affected bone reveals:
  - Progression resorption of osteoclasts, unaccompanied by osteogenesis.
  - Periosteocytic lysis.
  - Extensive demineralization.
  - Accelerated aging of bone.

Prevention and treatment

- Dental: Appropriate dental prophylaxis, attention to teeth that are carious and prophylactic application of fluoride to teeth prior to starting radiation.
- Better Radiotherapy techniques with attention to sparing salivary glands and uninvolved oral mucosa whenever possible.
- Avoid trauma and extraction in the post radiated setting. Unnecessary tissue trauma like repeated biopsies should be avoided.
- The use of antibiotic prophylaxis before extractions, though commonplace, has not been validated in any study (LOE 3). However, antimicrobial prophylaxis could be incorporated into the suggested protocol if desired.
- Hyper Basic Oxygen (HBO) has been used both for treatment and prevention of ORN. The results are varied and hence, there is no consensus on the exact regime, number of sessions and duration of therapy (LOE: 2). Marx et al., compared HBO to penicillin in a randomized trial to prevent the development of ORN in patients who had radiotherapy and needed a dental extraction, the results of which suggested that HBO without aggressive surgical management was inadequate since only 15% of

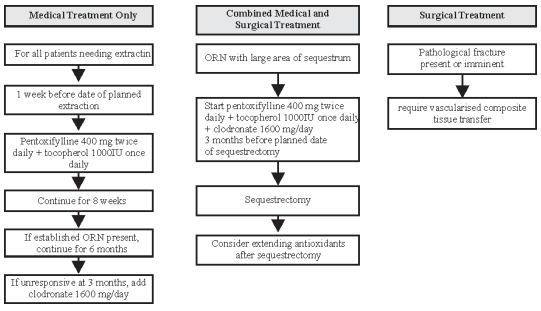
the patients responded to HBO alone. Annane et al., evaluated the role of HBO in treatment of overt ORN in a randomized, placebo controlled trial. The trial had to be concluded prematurely as HBO did not show any benefit over placebo (19% versus 33%), neither did it slow progression of disease or relieve pain. In a recent phase II clinical trial the role of pentoxyphylline and tocopheraol with the addition of clodronate have been evaluated and found to be promising. In the absence of adequately powered prospective trials, prospective data on the use of this new protocol may define the role and place of HBO and these newer protocols.

- Surgical intervention is reserved for pathological fractures, non responding lesions and progressive disease.

Suggested protocols (Delanian S et al., LOE: 2):

Patients requiring dental extractions could be given:

T. Pentoxifylline, 400 mg twice daily, for eight weeks with tocopherol 1000 IU, starting a week before the procedure. If ORN developed then they could be continued for a further 6 months with clodronate prescribed after 3 months if there has been no appreciable response.



Management of ORN

Ref: A Lyons, N Ghazali/ British J of Oral & Maxillofacial Surgery 46 (2008) 653-660

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Xerostomia

Xerostomia is present in 22-26% of the general population. All patients who undergo radiotherapy to the head and neck region have some degree of xerostomia. It can be exacerbated by the use of concomitant or sequential chemotherapy and other drugs

Physiology of saliva production:

- The major salivary glands are well-defined structures: parotid, submandibular and sublingual salivary glands. In contrast the minor salivary glands may vary in number and position from patient to patient and are distributed throughout the oral cavity and pharynx.
- The major salivary glands produce 90% of the saliva, upto 1000 – 1500 ml in a healthy individual, whole day, with 60 – 65% being produced by the parotids, 20-30% by the submandibular and 2-5% by the sublingual salivary glands.
- The saliva from the parotid glands is predominantly serous, while that from the submandibular and sublingual salivary glands is mixed serous and mucinous. The minor salivary glands contain predominantly mucinous acini. In addition saliva also contains inorganic ions, lipids,

amino acids, proteins and traces of hormone like substances. It also contains the enzyme alpha-amylase.

- Saliva helps in mastication, digestion, swallowing and speech. It acts as a lubricant and plays an important role in protecting the oral cavity and teeth from bacteria.
- The cells of the salivary glands and ducts are reverting post-mitotic cells. They do not divide under normal circumstances, but remain capable of dividing to replace lost cells. Regeneration is achieved by proliferation of secretory and duct cells.

Course of xerostomia:

- Clinically, transient, reversible xerostomia can occur with a dose of 6Gy/ 3 fractions.
- Doses greater than 30 Gy to the whole gland can cause permanent xerostomia.
- Parotid glands exposed to > 60 Gy sustain permanent damage with no recovery with time. The serous acini of the parotid gland are more sensitive than the mucinous glands.
- 50-60% reduction of salivary function is seen by the first week after a course of fractionated RT.
- Measurable minimum salivary flow occurs 2-3 weeks after 23 Gy of fractionated RT, with barely measurable salivary flow rates by the end of 7 weeks of fractionated radiotherapy.
- The extent of damage is directly related to the volume of salivary glands irradiated, dose and fractionation of radiotherapy, use of concomitant CT.
- Damage is long lasting and continues for several months after cessation of radiotherapy.
- Radiation causes reduction in salivary flow, changes in its electrolyte and immunoglobulin composition,

reduction in salivary pH, decreased transparency, yellow brown discoloration.

- It is associated with oral pain, discomfort, increased incidence of dental caries, oral infection, difficulty in speaking, swallowing, decreased nutritional intake and weight loss and a significant impairment in the QOL.

Pathogenesis

- Most severe and irreversible form results from loss of salivary acinar cells.
- Lack of wetting medium → reduction in response of chemoreceptors on tongue and palate → failure of salivary response.
- Minimal and thickened saliva (mucinous) is a barrier to dietary, mechanical and thermal stimulation of taste buds.
- Affects central stimulation of the salivary gland and salivary secretion.
- Tongue mucosa becomes atrophic.

Assessment

- Subjective and objective criteria: Patient symptoms and distress, alteration in lifestyle and food habits.
- Clinical examination: Examination by the clinician.
- Salivary scintigraphy: use of isotopes to evaluate the functional ability of the salivary glands, the salivary flow rates in the stimulated and unstimulated states, pre and post treatment.
- Sialometry: Spit method: by asking the patient to collect saliva over a definite time interval, both unstimulated and stimulated, after administration of a sialogogue.

  Cannulation of the duct: The Stenson's duct is cannulated and the saliva is collected in a cup (Lashley's cups) placed over the opening, at rest and after stimulation, after a definite time.

- RTOG, EORTC and CTCAE, version 3 for scoring of xerostomia (CoxJD et al., Trotti A et al.).

All these evaluations are carried out both pre and post treatment and at regular intervals thereafter to estimate the damage and evaluate recovery, if any.

Prevention & treatment

Best method to treat xerostomia is to prevent it. Good and appropriate attention to dental prophylaxis prior to radiotherapy is mandatory. Aggressive measures attending to maintenance of oral hygiene during and after treatment are essential in preventing the sequelae to xerostomia.

- **Pharmacologic agents:**
  - **Fluoride agents** to maintain optimal oral hygiene: 0.4% stannous fluoride gel to minimize dental caries (Chambers MS et al.).
  - **Antimicrobials** to prevent dental caries and oral infection.
  - **Saliva substitutes** like carboxymethyl cellulose. Have moistening and lubricating properties, provide prolonged wetness of the oral mucosa and may provide palliation by providing wetness to relieve discomfort (LOE 2).
  - **Sialogogues** that stimulate saliva production
  - **Pilocarpine:** Is the only sialogogic agent approved by the FDA for radiation induced xerostomia. Studies have shown pilocarpine to have efficacy in patients with radiation induced xerostomia (LOE 1).

    Data from a randomized RTOG trial (Scrantino CW et al.) suggest that there is some improvement in objective saliva measurements in patients receiving pilocarpine during radiation as compared

to those that received placebo. However there was no difference in the patient's perception of xerostomia for patients receiving pilocarpine when compared to the placebo arm. In two trials conducted by Johnson and colleagues and LeVeque et al., significantly more patients treated with pilocarpine reported an improvement in xerostomia as compared to the control group. In addition in the study by LeVeque, there was a decrease in the use of oral comfort agents in patients treated with pilocarpine.

Based on the results of randomized trials the CCOPG (Cancer Care Ontario Practice Guidelines) arrived at a few suggestions regarding the use of Pilocarpine in patients on radiotherapy, suffering from post radiotherapy xerostomia, provided there are no medical contra-indications to the use of pilocarpine. (2.5 – 10mg, bid or tid dosage). The exact duration of treatment is not known.

- ➢ Other cholinergic agents with sialogogic properties.

Cevimeline - Studies are ongoing to evaluate its efficacy in xerostomia in Sjogrens' syndrome.

- Radioprotectors like Amifostine:

  The FDA has approved the use of Amifostine for prevention of xerostomia in patients undergoing radiotherapy for the head and neck region. This recommendation was based on the results of a phase III randomized trial conducted by Brizel et al., which revealed that there was a decrease in the incidence of Grade 2 or higher chronic xerostomia from 57% to 34% in patients receiving amifostine. Also, there was no

difference in the disease related parameters in both arms suggesting that amifostine selectively protects the salivary glands and not the tumor cells. The dose recommended was 200 mg/m^2 of amifostine given daily as a slow i.v. push over 3 minutes, 15-30 minutes before each fraction of radiotherapy. A systematic review by Sasse AD et al., suggests that amifostine significantly reduces the side effects of radiation therapy. The efficacy of radiotherapy was itself not affected by the use of this drug and patients receiving amifostine were able to achieve higher rates of complete response.

Though the US FDA has approved the use of Amifostine to prevent RT induced xerostomia, its use is suggested only in a protocol setting till further robust evidence is available to support its routine use. This is because there remain concerns regarding the possible protection of tumor, the logistics of daily administration and the incidence of significant side-effects with its administration. The use of amifostine has also been evaluated through the subcutaneous route to evaluate its efficacy and obviate the problem of daily i.v. administration (Koukourakis MI).

- **Salivary gland transfer techniques:**

  Various salivary gland transfer techniques to transfer the uninvolved salivary gland into areas not within the radiation portals have been used. These are especially effective for the submandibular salivary glands as these are responsible for resting saliva production.

- **Salivary gland sparing radiotherapy techniques:**

  The incidence and severity of xerostomia is a direct function of the radiotherapy doses, the volume irradiated, the dose per fraction and the type of radiation. Various measures like the use of brachytherapy, use of customized blocks in an attempt to protect adjacent critical structures have been used over the years. The recent thrust however

has been on techniques like IMRT, IGRT, 3DCRT which offer the ability to spare the major salivary glands. There is evidence to suggest that when carefully executed they result in significant subjective and objective improvement in xerostomia (LOE 3). It maybe possible to reduce the incidence of permanent xerostomia with the use of these techniques. However, care should be taken that the target be covered adequately.

O'Sullivan et al., used ipsilateral radiotherapy portals to treat cancers of the tonsil. In their study of 228 patients, after a mean follow-up of 7 years, the three year acturial control rate was 77%, while the cause-specific survival was 76%. With careful selection of patients and attention to planning it was possible to deliver adequate doses to the target volume and at the same time protect adjacent critical structures.

Eisbruch and colleagues, Chao et al., have evaluated prospectively the role of IMRT in being able to save the parotid glands. Various objective and subjective criteria have been used for the evaluation. The investigators concluded that it was possible to significantly reduce the dose to the salivary glands with the use of IMRT, with no adverse effect on tumor control. Though patients had xerostomia during therapy, the spared salivary glands showed recovery with time.

Though most of the results of these techniques is from well-conducted prospective, non-randomized series they prove that it is possible to effectively spare the salivary glands and prevent the ensuing sequelae without compromising tumor control. This has a definite impact on outcome and quality of life of patients with head and neck cancers being treated on aggressive, multimodality regimes.

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Mucositis

Mucositis is an inflammatory response of mucosal epithelial cells to the cytotoxic effects of radiation and chemotherapy

Pathogenesis

Phase I: Vascular phase – release of free radicals, resulting in increased vascular permeability

Phase II: Epithelial phase: Impaired cell division, reduction in the epithelial turn over, erythema

Phase III: Ulcerative phase: microbial colonization of mucosal surface

Phase IV: Healing phase: hematopoietic recovery

Clinical effects

- Frequent treatment breaks: leading to inferior local control rates.
- Pain.
- Malnutrition.
- Local and systemic infection.
- Need for feeding tube placement.
- Hospitalization.

- Deterioration in the Quality of life.
- Increased mortality.

Incidence of oral mucositis

Conventional RT: 80%

RT+ Chemotherapy: 90%

RT Altered fractionation: 100%

Grade III-IV mucositis

Conventional fractionation: 25-45%

R Taltered fractionation : 52%

Weight loss due to mucositis: 3-6.7kg

Timing of mucositis

- Conventional: begins at 1-2 weeks, ulcerative mucositis develops after 30 Gy.
- Accelerated: peaks within 3 weeks.
- Interstitial implant: begins 7-10 days, peaks after 2 weeks.
- Limited to the field of radiation and resolves 3-6 weeks after completion of radiotherapy.

Risk factors

Patient related

- Young age (rapid epithelial mitotic rate) and very old.
- Poor nutritional status.
- Poor oro-dental hygiene during therapy (ill fitting dentures, periodontal disease, caries).
- Comorbidities affecting distribution or excretion of chemotherapeutic drugs (renal, hepatic etc).
- Neutrophil count before treatment.

Type of cancer: high risk for mucositis

- CT induced: hematological malignancies due to use of intensive CT.
- RT induced: head & neck cancers.

Other non cancer adjuvant medications causing xerostomia: opiates, phenothiazines, sedatives, anti-hypertensives.

Continued smoking, alcohol consumption.

Radiation related

- Total cumulative dose.
- Dose per fraction.
- Volume of irradiation.
- Overall treatment time.
- Technique of RT (conformal vs. non-conformal. external vs. brachytherapy).
- Quality of radiation (photons, electrons, protons).
- Radio-protectants.

Management

Prevention/ Treatment

Oral care:

- Reduces microbial flora.
- Reduces pain, bleeding.
- Prevents infection.
- Decreases risk of dental complications.

Components

- Tooth brushings, flossing, oral rinses.
- Dental examination and treatment prior to RT.

Toxicity grading

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	none	Oral soreness, erythema	Oral erythema, ulcers, can swallow solids	Oral ulcers, requires liquid diet only	Oral alimentation not possible
NCI-CTC (chemo)	none	Painless erythema, ulcers or mild soreness in absence of lesions	Painful erythema, oedema or ulcers but can eat or swallow	Painful erythema, oedema or ulcers requiring IV hydration	Severe ulceration or requires parenteral or enteral nutrition or prophylactic intubation
NCI-CTC (Rad)	none	Erythema of the mucosa	Patchy pseudomembranous reaction (patchy < 1.5 cm in diameter and noncontiguous)	Confluent pseudomembranous reation (continous patches >1.5 cm)	Necrosis or deep ulceration, may include bleeding not induced by minor trauma or abarasion

Oral care protocol

1. Brush all tooth surfaces for at least 90 seconds, twice daily using soft brush. Allow tooth brush to air dry before storing.
2. Floss at least once daily.
3. Rinse mouth 4 times.
4. Avoid alcohol, tobacco or irritating foods (acidic, hot, rough, spicy).
5. Use water based moisturizer for lips.
6. Maintain adequate hydration.

Oral rinse: salt and sodium bicarbonate gargles: one tea spoon each of salt and sodium bicarbonate per pint of water (LOE 1)

Benzydamine hydrochloride

Nonsteroidal drug with analgesic, anesthetic, anti-inflammatory and antimicrobial properties. Rinse the oral cavity with benzydamine 15ml- 8-10 times.

Cryotherapy: Ice chips or ice cold water for prevention of mucositis. Useful in patients receiving high dose chemotherapy regimens.

Pain management

Includes use of topical analgesics, anesthetics as well as systemic agents. In severe mucositis pain controlled analgesia with morphine may be considered.

Radiation therapy:

Use of conformal blocks to avoid mucosal radiation, 3D conformal therapy and intensity modulated radiation therapy may reduce high doses to the mucosa.

Palifermin

Recombinant human keratinocye growth factor that stimulates growth of epithelial cells.

Shown to decrease the severity and duration of mucositis associated with chemotherapy.

Dose: 60microgm/kg/day via IV for 3 days before conditioning regimen.

Not recommended

Chlorhexidine gargles

- No benefit over salt soda gargles (LOE 1).
  - ➢ May contain alcohol.
  - ➢ Rinse induced discomfort.
  - ➢ Taste alteration.
  - ➢ Teeth staining.
- Antimicrobial lozenges: Not recommended (LOE 2).
- Sucralfate: Not recommended (LOE 2).
- Radioprotectors.
- Amifostine: No benefit for oral mucositis.
- Growth factors and cytokines: Conflicting results. Not useful for oral mucositis.

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Problems Associated with Free Tissue Transfers

- Free tissue transfers have revolutionized oncoreconstruction.
- It affords transfer of well vascularised composite tissues that nearly matches the requirement in a single stage from distant donor sites.
- Good vascularity of tissues ensures prompt healing of wound and this allows early institution of adjuvant Chemotherapy/Radiotherapy.
- However it has certain disadvantages like specialized equipment and expertise is required, operations are long, failure is usually total and technique relies on suitable vessels at recipient site.
- Although infrequent, there are still multiple problems associated with the free tissue transfers.
- These problems can be classified as:

1) Recipient site (Surgical site) problems
2) Donor site problems
3) General problems

1) Recipient site problems

- The majority of recipient site complications are related to vascular thrombosis. The incidence of vascular thrombosis requiring urgent re exploration is about six percent.
- Venous thrombosis far outnumbers the arterial thrombosis.
- Majority of vascular thrombosis occurs within 3 days of surgery.
- Late thrombosis mainly results from local infection, subsequent fistula formation or mechanical compression.
- There is no difference in the rates of exploration or flap failure as a function sex or age.
- Potential for thrombosis exists in all microvascular anastomosis.
- The use of drugs to prevent thrombosis is heavily debated and not universally agreed.
- There is no level I evidence of utility of these drugs or superiority of one drug over another as prophylaxis in prevention of thrombosis.
- At our centre, we do not use any thromboprophylactive agents because of their potential side effects and unproven benefit.

2) Monitoring Flap Viability

- Clinical monitoring of flap by response to prick by hypodermic needle is most common and reliable.
- Normal color, temperature, absence of congestion or edema and slow bright red blood on needle prick is the sign of adequate perfusion of flap.
- A flap with venous congestion is edematous, bluish, cold and on needle prick shows brisk and profuse flow of dark blood.

- A flap with arterial blockade shows loss of tissue turgor, cold, blanched and on needle prick there is no flow of blood.
- Urgent re exploration and remedy of the cause of vascular compromise can salvage the flap.
- There is good correlation between time from detection of thrombosis to re exploration and chances of survival of flap i.e. the longer the time between thrombosis and re exploration the fewer the chances of successful salvage of flap.
- If the flap does not have an external skin paddle for monitoring i.e. totally buried flap, an implantable Doppler can be used for monitoring.
- At re exploration, venous thrombosis has greater chances of successful salvage than arterial thrombosis.
- When thrombosis is encountered at re exploration, clot evacuation is attempted by heparinized saline irrigation and gentle compression of flap.
- If clot is adherent to vessel, thrombolytic therapy with streptokinase/Urokinase or tissue plaminogen activator is tried.
- All patients with thrombosis where the flap is salvaged receive systemic heparinization in the form of bolus heparin at the time of re exploration and followed post operatively with heparin infusion. The target of therapy is to mention activated partial thromboplastin time 2 – 2.5 times control value.
- Subsequently after 3-5 days patients is switched over to oral warfarin therapy which is continued for a month. The target of warfarin therapy is to maintain the INR around 2.
- No reflow phenomenon is seen in cases where the re exploration was delayed. It refers to a condition where

restoration of vascular flow to tissues fails to result in tissue perfusion. This indicates non-salvageable flap.

- Haematoma is next common indication for re exploration.
- Commonest predisposition factor for haematoma is use of heparin, uncontrolled blood pressure.
- Presence of bleeder in the recipient bed is more common than bleeder in the flap.
- Minor haematoma can be removed by the bed side while major haematoma require removal under GA.

Other less common complications at the recipient site include:-

- Salivary fistula.
- Intra Oral dehiscence.
- Seventh Nerve weakness (esp. marginal mandibular branch).
- Skin necrosis.
- Abscess adjacent to flap.
- Infected bone graft.
- Prosthesis removal.
- Dysphagia.
- Lip necrosis.
- Microstomia.
- Oral incompetence.

Donor site complication

These include:-

- Hematoma at the donor site – when under the forearm graft, it can lift the graft off the bed and result in graft loss. In the Fibula donor site, if the overlying skin is closed primarily, it can lead to compartment syndrome. Urgent opening of wound and haematoma evacuation is required.

- Graft loss is commonly due to shearing forces and haematoma.
- Tendon exposure at the forearm or peroneal tendons in the leg. This may require tendon debridement and delayed skin grafting.
- Wound dehiscence and delayed healing.
- Seroma at the donor site especially in latissimus dorsi bed, or anterolateral thigh flap bed.
- Radius bone fracture in case of radial Osteomyocutaneous flap.
- Distal Limb Ischemia - It is a very rare but dreaded complication.
- It can happen with Radial artery Forearm Flap harvest even after checking preoperatively negative Allen's test. Limb perfusion should be checked after flap raising and if found to be inadequate, vein graft may be used to restore vessel continuity or flap vessel may be re anastomosed back.
- In the leg there is less than one percent chance of the peroneal vessel being the dominant supply of leg known as "Peronea magna". If fibula from such a leg is harvested, it may critically compromise foot vascularity.
- To avoid this problem, it is mandatory that posterior tibial and dorsalis pedis vessel is clinically palpable before surgery. In case any one vessel is not clinically palpable, color Doppler examination of leg vessels is warranted.
- There is no need for invasive angiography to assess leg vessel as color Doppler examination is reasonably adequate.
- Rectus abdominis and iliac crest free flaps may lead to abdominal or inguinal hernia.

General Complications

- Deep vein thrombosis – Murray & Neligan et al., (2008) have reported higher incidence of deep vein thrombosis in Cancer patients especially those undergoing lower limb microvascular reconstruction.
- Injury to adjacent neuro vascular pedicle.
- Neuropraxia due to tension/traction on nerves.
- Second primary squamous cell carcinoma arising in the free flap tissue.

Medical Complication

Since these Cancer Patients are elderly people they have many other co morbidities associated with them. The predisposing factors for cancer also promote many of medical problems in the same patient. Cancer, in addition, causes immuno suppression. On top of this, cancer excision followed by Free Flap reconstruction leads to prolonged and extensive surgical trauma. This accounts for a number of medical complications seen in this population of patients like-

- Myocardial infarct.
- Cardiac arrest.
- Cerebrovascular accidents.
- Respiratory arrest.
- Pneumonia.
- Hypo parathyroidism.
- Alcohol withdrawal.
- Peptic Ulceration.
- Hematemesis.
- Death post MI.

These medical complications should be managed on their own merit.

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Nerve Injuries
(Recurrent and Superior Laryngeal Nerve)

During thyroidectomy the external branch of the superior laryngeal nerve (EBSLN) and the recurrent laryngeal nerve (RLN) are at risk. Nerve injuries may be temporary or permanent. The incidence of transient temporary RLN injury is around 5% and permanent injury occurs in 2% to 3% of cases in most series. The most important cause for permanent RLN injury is division of the nerve. In malignant thyroid disease every attempt is made to preserve a functioning nerve. However, occasionally the nerve may be sacrificed, if the disease cannot be dissected off the nerve and if it is the only site of residual disease.

Surgical Considerations

Knowledge of anatomy and meticulous surgical techniques is a must. Proper identification of nerves during surgery is documented to reduce the incidence of damage to these structures[1].

Recurrent Laryngeal Nerve (RLN)

a. Relation in the Beahr's triangle:
RLN forms the third boundary of a triangle formed by the common carotid artery and the inferior thyroid artery low down in the tracheo-oesophageal groove.

b. Relation to Inferior thyroid artery (ITA):
RLN lies posterior to ITA in the majority of cases however, it may lie anterior or traverse between the branches of ITA.

c. Relation to the Zukerkandl's tubercle:
Zukerkandl's tubercle is a lateral projection of the thyroid lobe formed by the fusion of the medial and lateral thyroid analges. The RLN lies posterior to this tubercle with the superior parathyroid lying further posterior to the RLN.

d. Relation to the Berry's Ligament: the RLN may penetrate the Berry's ligament which is a posterior condensation of the pretracheal fascia binding the thyroid to the cricoid and upper tracheal rings.

e. Relation to the cricothyroid joint: the RLN enters the larynx anteromedial to the cricothyroid joint.

f. Non recurrent Laryngeal nerve: seen in 1% of cases a RLN may be non recurrent and is usually associated with an anomalous subclavian artery.

Unilateral RLN damage results in a vocal cord paralysis. The symptoms depend on the degree of abduction of the vocal cord. If the vocal cord is paralysed in the paramedian position voice will be almost normal. If the vocal cord is paralysed in the cadaveric position the gap between the cords being more results in a whisper with a poor cough reflex. The final position that the cords take is apparent only after 6 months.

Bilateral cord damage can result in both cords being either in the paramedian position or in abduction. If cords are in the

paramedian position, it will result in a reduced glottic air space which would necessitate a tracheostomy. On the other hand, if both cords are paralysed in abduction, the patient will have severe aspiration, which may also necessitate a tracheostomy.

External branch of the Superior Laryngeal Nerve:

a. Relation to the Joll's triangle:

   The EBSLN lies deep to the superior pole of the thyroid gland as it passes to the cricothyroid muscle in the sternothyrolaryngeal (Joll's) triangle formed laterally by superior thyroid pole, superiorly by the attachments of the strap muscles and medially by the midline.

b. Relation to the superior thyroid pole:

   Depending on the distance of the EBSLN from the superior pole of the thyroid gland, Cernea et al., proposed a classification given below. In their study there was a more than 50% incidence of the EBSLN being less than 1 cm from the superior thyroid pole suggesting need for meticulous dissection of the individual superior thyroid artery branches as close to the gland whilst trying to identify the nerve.

EBSLN Types

Type I EBSLN crosses the Superior thyroid artery (STA) 1cm cranial to the upper pole of the thyroid gland.

Type II EBSLN crosses the STA < 1 cm cranial to the upper pole of the thyroid gland.

Type III EBSLN crosses the STA while covered by the Upper pole of the thyroid gland.

Type IV EBSLN does not cross the trunk of the STA at all, but runs dorsal to the artery.

When the EBSLN is damaged unilaterally, it usually goes unnoticed by a normal individual. A trained singer will notice a change in pitch variation, with inability to go to a higher pitch and may affect the singing career. Hence in a professional voice user extreme care should be taken to preserve the EBSLN and the patient should be adviced of this possibility. On examination the damaged side will show a bowed vocal cord wrinkly or wavy in appearance and at a lower level than the opposite cord.

Bilateral EBSLN damage causes a lower pitch voice which is weaker and breathy. The singing will be severely affected at higher notes but not the conversational speech.

2. Nerve Monitoring

a. Per primum setting:

The literature is divided on the routine use of nerve monitoring for identifying and preserving nerves during thyroidectomy. In a large prospective study across 7133 nerves at risk, Thomusch O et al., showed a significant reduction in RLN damage with neuro-monitoring

Other studies by Shino M et al., and Dralle H et al., (2008) have not shown to reduce the incidence of nerve trauma intra-operatively. In a large retrospective study, Dralle et al., analyzing outcomes of 30,000 nerves at risk failed to show any advantage with neuro-monitoring.

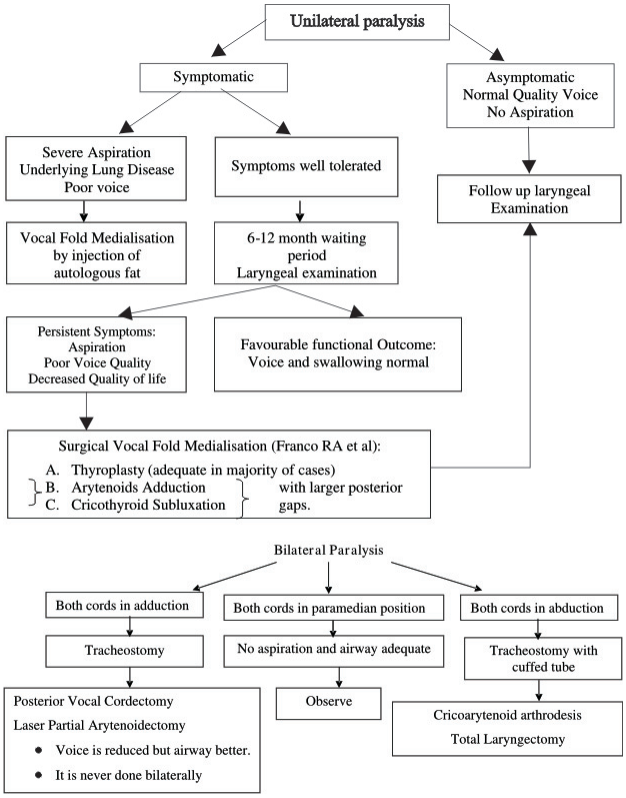
b. Revision Surgery:

In the re-operative setting a study from Mayo Clinic, Yarbrough et al., failed to show any added advantage of neuromonitoring over visual identification and meticulous surgical technique. More over addition of neuromonitoring significantly added to the cost of the procedures.

In summary, the best method for nerve preservation is a thorough understanding of normal anatomy of the nerve

along with its variations, and a meticulous dissection with clear delineation of the nerve along its entire length up to the point of entry into the larynx. Caution has to be exercised with use of electrocautery with preferential use of bipolar over unipolar whilst dileaneating the nerves and achieving hemostasis. During surgery magnification with loupe or microscope are proved to be better than conventional dissection.

Management:



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Hypocalcemia Following Thyroidectomy

Hypocalcaemia is the presence of low serum calcium levels in the blood, usually taken as less than 2.1 mmol/L or 9 mg/dL or an ionized calcium level of less than 1.1 mmol/L or 4.5 mg/dL. This is a result of hupoparathyroidism due to decreased functioning of parathyroid glaands

Postoperative hypocalcaemia can be transient or permanent, the latter when the duration of hypocalcaemia is more than 6months postoperative.

Etiology

Vascular damage

Direct Trauma

Inadvertent or intended removal of parathyroid glands during surgery.

Incidence

Transient – 0.6-83%- probably because of reversible ischaemia to the glands

Permanent – 1-6% (usually <2% in most centers)

Risk factors

Central compartment (Level VI) clearance (bilateral has higher rates)

Lateral neck dissection

Total thyroidectomy has higher rates as compared to subtotal or hemithyroidectomy

Thyroid cancer associated with thyrotoxicosis

Lesser rates seen in centres which perform larger volumes of thyroid surgery

Diagnosis

Clinical

Hypocalcaemia presents with signs of generalized neuromuscular irritability including paraesthesia, muscle cramps, laryngospasm, tetany and seizures. This neuromuscular irritability can also be displayed through elicitation of Chvostek's and Trousseau's Sign.

- Chvostek's sign: Tapping of face just anterior to ear and below zygomatic arch, produces twitching of ipsilateral facial muscles suggestive of neuromuscular excitability caused by hypocalcaemia.
- Trousseau's sign: Inflating a sphygmomanometer about 20mmHg above the systolic blood pressure produces a muscle contraction including flexion of wrist and metacarpophalangeal joints, hyperextension of fingers and flexion of thumb on the palm, suggestive of neuromuscular excitability caused by hypocalcaemia.

Serum calcium

Total calcium < 9mg/dl (2.1mmol/L)

Ionised calcium- < 4.5mg/dl (1.1mmol/L)

Prevention

- Thorough knowledge of the thyroid-parathyroid anatomy.
- Meticulous surgical procedure.
- Capsular ligation of branches of the inferior thyroid artery as opposed to truncal ligation, may decrease rates of hypocalcemia
- A drop of 75% baseline PTH or Postoperative PTH below 7-15pg/mL is considered as predictors for future hypocalcaemia.
- Scenario of Unavoidable/Accidental damage to parathyroids – Parathyroid auto transplantation (PTHAT)
  - Preferred site – Sternocleidomastoid.
  - In case of extensive neck dissections, can use pectoralis major for implantation.
  - In cases of surgery for medullary thyroid cancer associated with MEN II A & IIB – Forearm is the preferred choice.

* PTHAT – After confirming the cut tissue is parathyroid gland in frozen section, 1mm slices of removed parathyroid gland are prepared and these are inserted into a pocket made in the sternocleidomastoid muscle.

Management of hypocalcaemia:

Depends on severity and presenting symptoms.

Mainstay of treatment - Symptomatic patients require iv calcium + oral calcium & Vit D3.

Asymptomatic patients can be managed with oral supplements alone.

*It is also essential to measure serum magnesium in any patient who is hypocalcaemic, as correction of hypomagnesaemia must be done to overcome PTH resistance before serum calcium will return to normal.

Goal – To raise serum calcium levels by 2-3mg/dL with administration of 15mg/kg elemental calcium over 4-6hrs.

- Serum calcium <6mg/dL – IV calcium gluconate 1mg/ml/hr. (calcium gluconate contains 90mg elemental calcium/ 10ml ampoule).
- Acute conditions - 1-2ampoules diluted in 50-100ml 5%dextrose over 10mins).

* Calcium gluconate preferred to calcium chloride due the latter's tendency for local tissue irritation.

- Addition of oral calcium supplementation concurrently with 1-2g elemental calcium and 0.5-1µg/day.
- Maintenance therapy once serum calcium levels are >7mg/dL – Oral supplements with elemental calcium 15mg/kg/day (calcium carbonate 1-3g/day).
- Vitamin D3: Commonly used - Calcitriol - 0.25-0.5mg up to four times daily.
    - Ergocalciferol – less expensive, longer duration of action - 50,000 – 100000 IU/Day.
    - If administration of therapy is needed acutely, Calcitriol should be administered for first three weeks and then tapered off as the dose of ergocalciferol becomes effective.

Diet rich in calcium is advised

Regular follow up:

- Serum calcium evaluation every 3-6months.
- Evaluation of serum calcium is important as excessive calcium consumption may lead to hypercalciuria with nephrocalcinosis and/or nephrocalcinosis, hence it is mandatory to monitor calcium annually with 24hr urine calcium (<4mg/kg/24hr).

- Annual Ophthalmologist evaluation for cataract screening.

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Pharyngocutaneous Fistula (PC Fistula)

- PC fistula is the commonest complication following laryngectomy. The incidence varies widely from 7-50% in various studies.
- Fistulae generally occur in the immediate postoperative period, anytime between 5-15 days. However, occurrence of late fistulae especially during or after adjuvant therapy is also known.

Signs and symptoms

- Erythema and edema of the skin flaps and suture lines
- Elevated and turbid drain output
- Frank salivary leak from the suture line.
- Cough due to aspiration if the fistula is trickling into the stoma
- Constitutional symptoms like fever, malaise may precede the onset of fistula.

Diagnosis

- Is usually clinical (see above)
- Estimation of drain amylase or a conray swallow can be used as confirmatory tests, though they are rarely required

Risk factors

- Poor nutritional status and a low serum albumin.
- Pre/postoperative hemoglobin level
- Co-morbid conditions such as diabetes
- Previous chemoradiotherapy
- Pyriform sinus cancers requiring partial pharyngectomy or laryngeal cancers requiring an extended laryngectomy where part of the pharyngeal mucosa is excised

Prevention

- Surgical technique is of utmost importance
- General principle is to perform a tension free and vascularised anastomosis
- When indicated, use of pedicled or microvascular flaps to augment inadequate mucosa and achieve a tension free anastomosis
- There is no proven impact of the type closure (T vs Verical vs Horizontal), type of suture material used (vicryl vs catgut), pattern of closure (continuous vs interrupted), initiation of feeding (late vs early) and preoperative tracheostomy on PC fistula.
- In individuals with high risk factors, a levator scapulae muscle rotation or a pectoralis major myofascial flap may be used to cover the exposed carotid arteries to prevent a carotid blowout.

Management

- Majority of fistulae respond well to conservative management.
- There is no consensus on duration of observation following a PC fistula.

- Based on our institutional practice, we recommend two weeks of conservative therapy for non-radiated tissue. The conservative therapy may be 4-6 weeks in radiated tissue.
- Surgical intervention is recommended for
    1) Large and high output fistulae
    2) Skin breakdown.
    3) Major blood vessel exposure/bleeding

General Measures

- Nil per orally
- Enteral feeding and correction of any attendant anemia or hypoproteinaemia.
- Appropriate antibiotics which may be guided by culture sensitivity reports

Wound management

- Local wound care that consists of frequent change of dressing thereby allowing good drainage of saliva. We prefer putting corrugated drains as the drainage is better and they do not get blocked. Also a continuous negative suction drain may impede the closure of the fistula
- All attempts should be made to divert the fistula away from the stoma to prevent aspiration into lungs
- In case of aspiration because of drainage into the stoma, a cuffed tracheostomy tube will help in preventing the same.

Surgical intervention

- Surgical closure may utilize healthy tissue around the fistula.

- However, more often than not, insertion of a well-vascularized tissue is performed such as pectoralis major flap.
- Free flaps are not advisable because of the infected recipient site; however they can be used for long standing fistulae where there is no evidence of infection.

Adjuvant Radiotherapy

- Most centers do not recommend adjuvant radiotherapy in the presence of a fistula as this impedes the closure of the fistula and can lead to catastrophic complications like a carotid blowout.
- However, one study has reported that any delay of RT greater than six weeks post-operatively increases the rates of neck recurrence from 2.0% to 29.0%. Hence a judicious decision regarding starting adjuvant therapy is required.

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Post-Laryngectomy Tracheostomal Stenosis

Only decrease in the size of tracheostoma does not amount to tracheostomal stenosis. Even a 50% reduction in size of tracheostoma may not cause any problem in normal healthy individual.

Tracheostomal stenosis is characterized by one or more of the following features

- Needs to be stented with a tube
- Leads to respiratory compromise
- Does not allow trained bronchial toilet
- Does not allow maintenance of tracheo-esophageal prosthesis.

Incidence: 4% - 42%

Classification: Montgomery classification

- Vertical slit – prominent sternocleidomastoid (SCM) heads
- Concentric – Cicatricial scar
- Inferior shelf – Redundant skin

Risk factors (LOE-5)

Patient factors

- Fat neck
- Bulky SCM heads
- Enlarged thyroid
- Poor nutrition
- Steroids
- Tendency to develop keloid
- Female sex

Treatment related factors

- Tension on suture line of tracheostoma: leads to partial or complete dehiscence and healing by secondary intension causing excessive scarring.
- Infection: usually secondary to pharyngo-cutaneous fistula.
- Tracheal division: There is no consensus regarding the method of tracheal division (beveled vs. straight) at the time of laryngectomy.
    - o A bevelled tracheal cut gives a larger cross sectional area, less tension and interrupts circular scar formation along the tracheal ring, hence may cause less stenosis.
    - o On the other hand, a straight tracheal cut gives complete tracheal ring for support, avoids infection and granulations on exposed tracheal cartilage, and therefore may cause lesser stenosis.
- Use of a postoperative tracheostomy tube: No consensus with contradictory reports in literature.
- Primary Tracheo-esophageal puncture: A few studies have shown it to increase incidence of tracheostomal stenosis (LOE-3)

- Previous tracheostomy – no conclusive evidence.
- Previous radiotherapy – no conclusive evidence.

Prevention

Following steps should be taken to prevent post-laryngectomy tracheostomal stenosis.

- Creation of wide stoma. This is done by suturing the entire cartilegenous part of the trachea to the skin of the lower flap and suturing the membranous portion to the upper skin flap
- Avoid de-vascularisation of trachea.
- Tension-free suturing of trachea to skin.
- Proper hemostasis and drainage of surgical wound to prevent hematoma formation around tracheostoma.
- Prevent exposure of tracheal cartilage.
- Cutting of clavicular heads of SCM (recommended by some).
- Excision of redundant skin.
- Adequate antibiotic cover.
- Diversion of pharyngo-cutaneous leak away from tracheostoma.

Treatment

- Asymptomatic or mildly symptomatic tracheostomal stenosis can be treated by use of Larytube or Larybutton.
- Mild stenosis can be treated by repeated serial dilatation using increasing sizes of non cuffed tracheostomy tubes (Montgomery maneuver).
- Severe stenosis requires surgical correction by various plastic surgery procedures
    - o Multiple Radial incisions.
    - o CO2 laser incisions

- o Circumferencial excision and insertion of vascularised flaps.

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Chondroradionecrosis

Introduction and incidence

Radiation induced chondronecrosis is a well documented but relatively rare complication of irradiating laryngeal and hypopharyngeal tumours.

Although the incidence of chondronecrosis by histology is seen in about 18-26% of laryngectomy specimens, 3-5% of the irradiated patients have symptoms attributable to it (in retrospect). Diagnosis is challenging and the condition is probably under diagnosed and underreported due to similarity of symptoms and signs to those of a recurrence. A high index of suspicion and repeated negative biopsies in spite of persisting symptoms and stable appearance on cross sectional imaging point to the diagnosis. Absence of recurrence can be definitively concluded only on detailed histopathological study of the laryngectomy specimen.

Pathogenesis

Irradiation of the laryngeal cartilage leads to disrupted collagen synthesis, hypoxia and hypocellularity of the tissues which is unable to maintain its normal tissue turnover. Changes in the cartilage usually occur when the perichondrium is breached

by trauma or tumor, exposing the underlying irradiated cartilage and making it susceptible to infection and perichondritis resulting in necrosis and laryngeal collapse. Healthy cartilage is avascular and chondroradionecrosis of the larynx is largely due to poor vascular and lymphatic flow, caused by endothelial damage and fibrosis. This, when combined with further insult such as previous or repeated surgical intervention and infection, create a demand for tissue repair, which is beyond the capabilities of the irradiated cartilage promoting its breakdown.

Predisposing factors

Factors affecting the onset of laryngeal chondroradionecrosis are;

Radiation dose: Doses >70Gy to the cartilage may increase the probability of chondroradionecrosis. This may occur due to inappropriate dose prescription points and/or lack of tissue compensators leading to a higher dose to the larynx where the tissue separation is minimum.

Radiation technique: Modern techniques like IMRT offer the ability to control the dose to the larynx to some degree. However careful planning and meticulous plan implementation, treatment delivery and Quality Assurance measures are needed to ensure that the laryngeal doses are within tolerance.

Fractionation schedule: Although there is no direct evidence, it is likely that accelerated fractionation schedules, if inappropriately delivered, may increase the incidence of chondroradionecrosis.

T Stage: Patients with a large pretreatment tumor and a tumor abutting or involving the thyroid cartilage seem to be at higher risk for chondroradionecrosis.

Concomitant chemotherapy may compound the problem due to increase in the effective radiation dose and delayed tissue healing.

Trauma from repeated instrumentation and premature and often unnecessary *biopsies* can initiate and accelerate the process. In addition, coexisting hypoxia, general debility and malnourishment may predispose the patient to chondroradionecrosis.

Clinical Features

Symptoms are nonspecific and very often mimic those of a recurrence.

Chandler classification of laryngeal radionecrosis (Chandler, 1979)

Grade	Symptoms	Signs
I	Slight hoarseness; slight mucosal dryness	Slight edema; telangectasia
II	Moderate hoarseness; moderate mucosal dryness	Slight impairment of cord motility; moderate edema and erythema
III	Severe hoarseness with dyspnea; moderate odynophagia and dysphagia	Severe impairment of cord motility or fixation of one vocal cord; marked edema; skin changes
IV	Respiratory distress; severe pain, severe odynophagia; weight loss; dehydration	Fistula; fetor oris; fixation of skin to larynx; laryngeal constriction and edema occluding airway; fever

Arytenoid cartilage is reported to be the most commonly affected by histologic necrosis (51%) followed by thyroid , cricoid and epiglottic cartilages at 34%, 9% and 3% respectively

Imaging

The CT appearance of laryngeal chondroradionecrosis is often nonspecific. The soft-tissue and cartilaginous changes observed in these patients can mimic local tumour recurrence. Progressive crico-arytenoidal sclerosis with surrounding soft-tissue swelling, anterior dislocation, and sloughing of the arytenoid may be signs of chondroradionecrosis. Gas bubbles around the thyroid cartilage and fragmentation and collapse of the thyroid cartilage are highly suggestive of laryngeal chondroradionecrosis.

Although difficult, a PET CT scan provides additional information to help in distinguishing tumour from inflammatory necrosis. Of particular utility is the ability to guide a confirmatory biopsy, when a focus of high tracer uptake is seen surrounded by an area of milder uptake.

Management

The initial management consists of antibiotics and anti inflammatory agents usually combined with steroids for all patients.

Chandler I and II chondroradionecrosis: Patients may be managed conservatively for 6-8 weeks with anti-inflammatory agents and antibiotics. In addition, humidification, analgesia and tube feeding help symptomatically and in tissue healing.

Chandler III and IV chondroradionecrosis: A tracheotomy is often needed in moderate to severe cases. A total laryngectomy is required in cases of proven tumour recurrences and in those with a functionless larynx with significant aspiration when

despite repeated negative biopsies recurrence has not been documented. More conservative surgical approaches include debridement and a pedicled flap or submucosal resection of the necrotic cartilage.

Role of Hyperbaric Oxygen: Administration of hyperbaric oxygen to necrotic tissues promotes healing by improving oxygenation, enhancing collagen and fibroblast formation, stimulating leuckocyte and anti-infective activity and initiating and promoting neovascularisation. Although protocols vary, preliminary data (London et al, Flintisis et al) has shown encouraging results with the use of hyperbaric oxygen with reduced need for laryngectomy and preservation of function. Flintisis et al., reported 18 patients with severe chondroradionecrosis (2 had grade 3 and 16 had grade 4) treated with adjunctive hyperbaric oxygen therapy. Thirteen patients (72.2%) had a major improvement after HBO therapy, and none of them required total laryngectomy. All patients preserved their voice and deglutition in good or normal condition.

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Swallowing Dysfunction after Treatment for the Oro-Hypopharynx and Larynx

Incidence

- Following Chemoradiotherapy (CTRT): 15- 50%
- Following total laryngectomy- 10-60%
- Swallowing is worse with CTRT as compared to total laryngectomy (LOE-3)
- Combination of radiotherapy and surgery for the larynx significantly increases swallowing problems as compared to surgery alone
- Gastrostomy tube dependence is seen in nearly 15-30% of patients after treatment for oro-hypopharyngeal cancers
- Aspiration has been reported in 28-68% of patients treated with CTRT in various studies. Most of this aspiration is silent and can be made out only on videofluroscopy or on a Modified Barium Swallow (MBS). Detecting aspiration is important as this may lead to aspiration pneumonitis in a small percentage of patients.

- As high as 52% patients are detected to have strictures one to three months after CTRT if intensive monitoring is performed with MBS and videofluroscopy.

Etiology

After surgery

- laryngectomy with partial pharyngectomy
- post operative pharyngocutaneous fistulae
- damage to pharyngeal plexus
- strictures

After CTRT

Combination of

- salivary gland dysfunction,
- mucositis,
- post RT fibrosis and
- strictures

Methods of assessment

1) Modified Barium Swallow with esophageal phase

   The MBS study is a dynamic assessment of swallowing performed by a speech pathologist under videofluoroscopic guidance. This study delineates the various stages of swallowing with its attendant abnormalities.

   The MBS will outline the possible cause of dysphagia and can help monitor treatment of these patients.

2) Fibreoptic Endoscopic Evaluation of Swallowing (FEES) - is now gaining acceptance as a complementary modality to diagnose swallowing dysfunction along with the MBS.

Commonest dysfunction on MBS after treatment for HN cancers-(LOE-3)

Decreased epiglottic movement

Decreased base of tongue contact with posterior pharyngeal wall,

Decreased laryngeal elevation

Decreased bolus propulsion

Strictures

Preventive measures

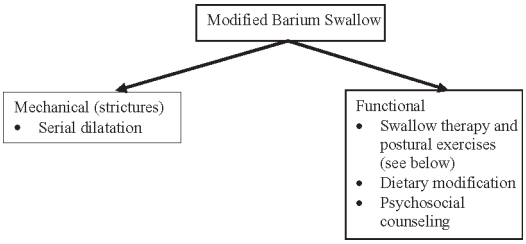
During surgery

- Appropriate use of reconstruction after total laryngectomy with partial pharyngectomy has shown promising results. (LOE-3)
- Adequate augmentation techniques in the form of pedicled or free tissue flaps should be used if remnanat unstretched mucosa is less then 3cm. No increase in stricture rates if primary closure performed when remnant unstretched mucosa is between 3-8cm (Hui et al) (LOE-3)

During CTRT

- Use of Intensity Modulated radiotherapy (IMRT) can decrease injury to mucosa and salivary glands and improve swallowing.(LOE III)
- Encourage oral feeds during treatment, especially in patients with gastrostomy tubes, as these patients are known to become gastrostomy dependant.
- Use of Amifostine has shown to significantly decrease dysphagia when combined with CTRT because of the attendanrt decrease in xerostomia (LOE-3)

Management



Postural exercises

Disorder for which posture appropriate (symptom of disorders)	Posture flow	Effects of oropharyngeal dimensions and bolus
Inefficient oral transit (reduced posterior lingual propulsion of bolus	Chin up	Uses gravity to clean oral cavity from bolus
Delay in triggering the pharyngeal swallow (blous past ramus of mandible, but pharyngeal swallow is not triggered)	Chin down	Widens valleculae to prevent bolus entering airway, narrows airway entrance ,reducing risk of aspiration
Reduced posterior motion of the tongue base (residue in valleculae)	Chin down	Pushes tongue base close to the posterior pharyngeal wall
Reduced closure of laryngeal entrance and vocal folds (aspiration during swallow)	Chin down	Puts epiglottis is more protective position: narrows laryngeal entrance

	Head rotated to the damaged side	Improves vocal fold closure by applying extrinsic pressure
Unilateral pharyngeal paresis (residue on one side of the pharynx)	Head rotated to the damaged side	Eliminates damaged side of pharynx from bolus path
Unilateral oral and pharyngeal weakness on the same side (residue in mouth and pharynx on same side)	Head tilt to stronger side	Direct bolus down stronger side by gravity
Reduced pharyngeal contraction (residue spread throughout pharynx)	Lying down on one side	Eliminates the effect of gravity on pharyngeal residue
Cricopharyngeal dysfunction (residue in pyriform sinuses)	Head rotated	Pulls cricoid cartilage away from posterior pharyngeal wall, reducing resting pressure in crico pharyngeal sphincter

Rationale for application of Postural techniques to various swallowing disorders.

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Hypothyroidism After Treatment for Head Neck Cancers

Incidence

- Pretreatment- 5%
- Overall 10-70%
- Non laryngeal resections with RT-12% (LOE-3)
- Highest incidence in patients undergoing total laryngectomy with thyroid lobectomy with RT-48-70% (LOE-3)
- Post RT alone-5 and 10yr rates of hypothyroidism are-20&27% repectively (LOE-3)

Risk Factors

- Thyroid lobectomy (with laryngectomy) followed by RT
- Higher doses of radiotherapy
- Unilateral versus bilateral RT to neck
- Pre-existing thyroiditis
- Presence of antimicrosomal thyroid antibodies in patient's pretreatment samples (LOE 3)

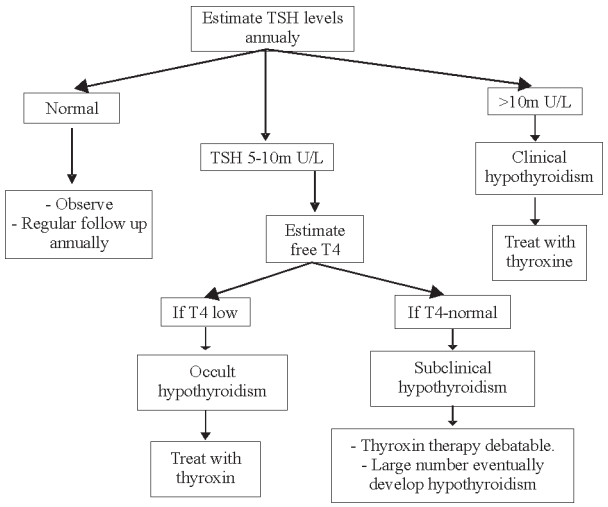
Diagnosis

- Average time to hypothyroidism with Sx+RT-6 months RT alone-1-3 years
- All patients should be tested for hypothyroidism prior to start of treatment, if suspected
- Post treatment, the first test should be performed between 3-6 months and six monthly after that for the first two years
- Most hypothyroidism will be detected within the first 2 years after treatment

Treatment

Supplementation with Thyroxine guided by TSH levels is treatment of choice.

Treatment Algorithm



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Management of Facial Nerve Injury

Incidence

- In superficial parotidectomy with dissection and preservation of the nerve:
  - Temporary palsy – 16% - 47%.
  - Permanent palsy – 0% - 9%.
- Recovery of paresis (temporary) usually takes 2-3 months, sometimes longer.

Etiology

Surgery – inadvertent injury or palsy due to extensive dissection. Extensive tumor involvement may require deliberate nerve sacrifice.

Evaluation

House-Brackman Scale -

I - Normal.

II - Mild dysfunction (slight weakness, normal symmetry at rest).

III - Moderate dysfunction (obvious but not disfiguring weakness with synkinesis, normal symmetry at rest).

IV - Moderately severe dysfunction (obvious and disfiguring asymmetry, significant synkinesis).

V - Severe dysfunction (barely perceptible motion).

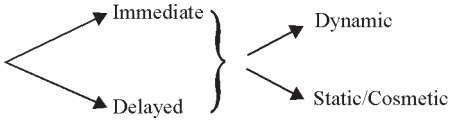
VI - Total paralysis (no movement).

Management

Factors deciding management:

- Presence of a proximal healthy and viable nerve stump
- Ability to identify and isolate distal nerve branches
- Time elapsed since surgery.
- Functional status of facial muscles.

Facial nerve rehabilitation:



If facial nerve is structurally intact –

- Observe. Facial nerve regeneration after Wallerian degeneration may take months to.
- Post operatively corneal protection maybe necessary. Static procedures like tarsorraphy / gold weight implants maybe required at a later date to protect the cornea.

After transection – Immediate repair gives best results.

1. End to end anastomosis – In the presence of adequate proximal and distal stump a tension free anastomosis can be achieved.

   The nerve endings are freshened, and sutures of 8-0 / 9-0 nylon are used, with 2 or 3 sutures applied to the epineurium.

2. Interposition or cable graft (to be used if a section of the nerve has been excised and primary suturing not possible because of nerve loss):
   - Greater auricular nerve - most commonly used.
   - Sural nerve – up to 35cms available.
   - Ansa hypoglossi.
   - Medial antebrachial cutaneous nerve.
3. If proximal stump is unavailable:
   - Hypoglossal – facial nerve anastomosis:
     - Technically easy
     - Anastomosis lies far peripherally, thus leading to an early reinnervation. (3-4 months)
     - Can be done as end to end or an interposition graft. (jump anastomosis)
   - Cross facial nerve grafts – It is helpful when the proximal nerve segment is unavailable for use but there is always the potential risk of disruption of innervation to the donor site, hence not recommended.
4. Muscle transfer:
   - If proximal nerve is not available and particularly if the hypoglossal nerve is sacrificed.
   - Masseter or temporalis muscle are most commonly used.
5. **Delayed**:-Success depends upon the time elapsed and the functional status of the facial muscles.
   - Up to 2yrs – Recovery expected
   - 2-3yrs – Recovery possible
   - 3-5yrs – recovery questionable
   - 5yrs – Recovery not expected

The functional status of the facial muscles needs to be accessed with EMG studies:

- Voluntary potentials – Facial nerve intact – Reanimation not attempted unless facial function does not return for 18 months. If, after 18 months, voluntary potentials are present, but no apparent facial function –"sub clinical innervation" – Transection and reinnervation surgery is warranted.
- Nascent and polyphasic potentials – Seen during active phase of reinnervation – Reanimation surgery contraindicated till end result is apparent.
- Fibrillation potentials – Denervated muscle – Reanimation procedure warranted.
- Electric silence – Muscles has undergone denervation atrophy – Nerve grafting or transfer futile – Muscle transfer indicated.

Reanimation procedures:

- Depends on the presence of a viable proximal and distal nerve stumps.
- Proximal and distal branches available – Interposition grafts.
- Only distal branches available – cross facial nerve grafts or Hypoglossal- facial nerve anastomosis as described earlier.
- Muscle transposition – When no significant facial musculature exists for reinnervation.

Static/cosmetic procedures:

- Done along with reanimation procedures while awaiting nerve regeneration.
- Patients unable or unwilling to undergo muscle transposition surgery.

Prevention of corneal exposure

- Tarsorraphy.
- Gold upper eyelid weights.
- Eyelid springs.

Facial rehabilitation and symmetry

- Static facial slings – Fascia lata strips or Gore-Tex soft tissue patch for facial suspension.
- Rehabilitation of orbital area – Brow lift, eyelid repositioning.
- Senile ectropion – Corrected by eyelid repositioning procedures, such as lateral strip technique or eyelid shortening procedure.

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Frey's Syndrome

Frey's syndrome or auriculotemporal syndrome is characterized by profuse sweating, frequently accompanied by flushing of the facial skin during meals.

Incidence

1. Varies according to the diligence with which the diagnosis is sought & the time elapsed after parotidectomy.
2. 10% pts will experience definite symptoms.
3. If asked, 30 – 40% will admit to gustatory sweating.
4. Minors test (see below) – 95% will show some evidence of gustatory sweating.

Etiology

It occurs due to aberrant regeneration of the sectioned parasympathetic nerve fibers with the sectioned cutaneous sympathetic fibers. For this to occur, the sympathetic fibers must also be sectioned, a common occurrence after parotidectomy and parotid trauma. The resulting aberrant regeneration and parasympathetic innervations of the sweat glands and vessels results in local vasodilatation (gustatory

flushing) and localized sweating (gustatory sweating) during meals.

Prevention (LOE-3)

Various methods described in literature are

1. Minimize the parotid wound bed while adequately removing the pathology.
2. Thick skin flaps.
3. Rotation of the superficial musculoaponeurotic (SMAS) layer to ameliorate the parotidectomy defect. It involves placating the SMAS layer to the sternocleidomastoid muscle and perichondrium of the external ear.
4. Interposition of barriers to prevent aberrant reinnervation of parasympathetic fibers.
   - The temporoparietal flap is a reliable and versatile flap and has close proximity to the parotid bed.
   - Implantation of materials like lyophilized dura, polygalactin, expandable polytetrafluroethylene and human dermal matrix has been used. These materials however increase the chance of a parotid fistula. Less resorbable implants are better barriers but have a higher incidence of fistulas.
   - Sternocleidomastoid muscle flap to fill the defect – Doubtful value and masks recurrences.

Treatment: (LOE-3)

Detection

Testing for Frey's syndrome has in general been limited to the evaluation of sweating. The most frequently used method of sweat secretion assessment for gustatory sweating was originally described by Victor Minor, a Russian neurologist.

The affected area is painted with iodine solution and starch powder is sprayed on it after it has dried. The water in the sweat produces blue coloring by a reduction reaction of the iodine -starch mixture. Minor test is seen as a topographic method, allowing accurate mapping of the involved surface. Dole and Thaysen further simplified the process by the use of paper coated with iodine. In the Iodine – Sublimated Paper Histogram (ISPH) method regular office paper is sublimated with iodine and acquires the property of changing color when wetted. The paper is than digitized and a histogram algorithm applied to measure the area of color change. Mapping of the facial surface to be treated, by the ISPH method, gives excellent topographic information.

Grading of Frey's syndrome (Luna-Ortiz)

- Clinical manifestations
  - o Yes 1
  - o No 0
- Extent of the affected area
  - o 0.1–2.0 cm 1
  - o 2.1–4.0 cm 2
  - o >4.0 cm 3
- Excessive focal sweating 3
- Unpleasant smell sweating 3
  - ➢ Mild Frey's syndrome 1–3 points
  - ➢ Severe Frey's syndrome 4 or more points

Treatment

There is no definitive treatment. Reassurance and explanation usually suffice for mild symptoms.

Other options :

1. Intracutaneous injection of botulinum toxin in the involved area – Simple, effective, & first line treatment option. Map the affected area with ISPH method and then inject botulinum toxin. Consensus on the exact method of botulinum toxin injection treatment is lacking but experimental data favors the 10 – mm inter – injection distance and an injection dose of 0.1ml. May be repeated.
2. Interposition of a subcutaneous barrier – Re-elevation of skin & interposition of various tissue barriers like dermal graft & temporoparietal fascia between the cheek skin and the parotid gland.
3. Local and systemic application of anticholinergic drug - Contraindicated in pts with glaucoma. Side effects are blurred vision and dry mouth.
   - Scopolamine – penetrates skin easily & blocks cholinergic transmission. Applied as solution and cream - Dosage varies from 0.25% to 3%
   - Glycopyrrolate – A quaternary ammonium compound penetrates skin slowly.
4. Sectioning of some portion of the efferent neural arc
   - Tympanic neurectomy – Varied success and recurrences reported. Technically difficult.
   - Auriculotemporal nerve – Not done anymore.
5. Radiotherapy – Should it be indicated, the incidence of gustatory sweating is low.

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Shoulder Dysfunction or Painful Shoulder Syndrome After Neck Dissection

Shoulder dysfunction or 'Painful shoulder syndrome' is one of the commonest complications of neck dissection. This syndrome consists of following features

- Pain
- Drooping of shoulder.
- Inability to abduct arm above 90^0.
- Decreased flexion of arm.
- Forward rotation of scapula making the acromion process and medial edge of scapula prominent.
- Sterno-clavicular joint subluxation (in severe cases).
- Gleno-humeral joint capsulitis and fibrosis (in severe cases).

Shoulder dysfunction not only has impact on appearance and function, it is one of the significant quality of life issues after neck dissection

Incidence:

Depends upon the type of neck dissection. (LOE-3)

Classical Radical Neck Dissection (RND)	66– 100%.
Modified radical ND (MRND)	28 – 45%.
Supra-omohyoid ND (SOHD) &other selective ND	15 –20%.

Etiology

- Injury to spinal accessory nerve is the most important cause of shoulder dysfunction after neck dissection. Complete transection of the nerve is almost always associated with shoulder dysfunction. Other causes of injury are
    a. Thermal injury by electro-cautery
    b. Traction injury
    c. De-vascularisation of nerve

These injuries most commonly occur while dissecting level IIb and level V lymph nodes

The other causes are

- Injury to cervical plexus of nerves supplying scapulo-humeral girdle muscles like rhomboids, levator scapulae and scalenes causing their weakness.
- Secondary glenohumeral stiffness resulting from postoperative forced immobility also contributes to shoulder dysfunction (LOE-3).

Diagnosis

- Assessment of active and passive movements of shoulder joint
- Goniometric evaluation

- EMG studies on scapulo-humeral and gleno-humeral muscles
- Use of questionnaires like Constant Modified Questionnaire can also be used

Prevention

Following steps should be taken to minimize the incidence of shoulder dysfunction after neck dissection.

1. Selective node dissection rather than comprehensive neck dissection in N0 neck.
2. Modified Radical Neck dissection (MRND) with preservation of spinal accessory nerve rather than Radical Neck dissection (RND), provided it is oncologically safe, in N+ neck.
3. Minimal handling of nerve to avoid traction injury,
4. Avoid thermal injury by using bipolar cautery.
5. Avoid de-vascularisation of nerve.
6. Clearance of level V nodes only in N+ neck.
7. Clearance of level IIb nodes only when nodes at other levels positive for metastasis (recommended by some)
8. Post-operative shoulder physiotherapy

Treatment

- Early post-operative shoulder physiotherapy including both active and passive movements
- Progressive Resistance Exercise Training (PRET) is found to be more effective than routine physiotherapy. (LOE-1)
- In advanced cases with muscular atrophy, capsular adhesions and fibrosis, no treatment is found to be effective.

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Chyle Fistula after Neck Dissection

Incidence

- Occurs in 1-5.8% patients after neck dissection.
- More common in radical and modified neck dissections than selective neck dissections.
- Commonly injured during level IV nodal clearance.
- Most common on the left, but one fourth of all chyle fistulae occur on the right side.

Prevention

- Knowledge of anatomy of the chyle duct and its relation with other neurovascular structures in the neck.
- The chyle duct may end as a leash of terminal ducts. Inadvertent damage of some may occur which goes unrecognized during surgery. It therefore is important to address each of these during surgery.
- Dissection and identification of the chyle duct in every neck dissection is not recommended.
- If the undamaged chyle duct is identified, it should be left undisturbed.
- Serial clamping and ligation of tissue in the region of the chyle duct may prevent fistulae (LOE-5).

- After every neck dissection, put the patient in trendelenburg position and ask the anesthetist to provide positive pressure ventilation (valsalva manoevre). This helps identify any latent leaks and if present, it should be underrun with 3.0/4.0 non absorbable suture material. (LOE-3) Use of coloured suture material like black silk may help in identifying the chyle duct if re-exploration is required.

Management (LOE 3)

Chyle fistula, though a rare complication after neck dissection, has significant associated morbidity and an important cause of prolonged hospital stay. Correct management of this complication is of utmost importance as excessive chyle loss may lead to hypoproteinaemia, hyponatremia, hypochloremia, lymphocytopenia and an overall immunocompromised status of the postoperative patient. To add to this, wound breakdown and infections are common problems with chyle fistulae.

General measures

- Bed rest.
- Head elevation.
- Strict input/output and weight charting.

Wound management

- Pressure dressings may be applied.
- Local wound care with dressings.
- Aspiration under sterile precautions if not adequately drained.

Dietary management

Enteral feeding with diet low in long chained triglycerides (LCTs) and high in medium chained triglycerides (MCTs).

Rationale:

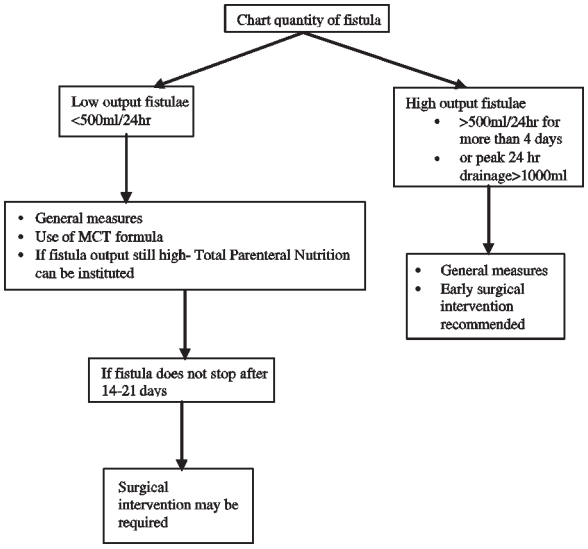
LCTs, which constitute 70% of dietary fat, enter the blood through chyle. MCTs on the other hand are directly absorbed from the intestine into the portal circulation. Hence, foods rich in MCTs (e.g. coconut oil) need to be administered to patients with chyle leaks. Premade formulae containing MCTs are also available.

Total Parenteral Nutrition- Can be considered in patients on medical management experiencing significant weight loss. However, TPN is expensive and requires infrastructure and has its attendant risks. It may therefore be better to stop medical management and surgically manage the chyle leak .

Surgical management

- Re-exploration with identification of the leak and suturing with non absorbable suture material. Patient may be administered fat in the form of cream enterally (thru ryle's tube) 1-2 hours prior to surgery to help identify the exact site of leak intraoperatively.
- Use of gelfoam or surgical may help in sealing the leak, however not routinely recommended.
- Muscle flaps (e.g. levator scapulae flap) have been described by some to seal the area (LOE-5).
- If leak persists, thoracoscopic ligation of the thoracic duct may help (LOE-3).

Algorithm for management of fistulae



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CSF Leak after Craniofacial Resections

Cerebrospinal fluid (CSF) leak is the most important post-operative complication following surgeries of the skull base (both anterior and lateral skull base). It can be life-threatening and lead to various other CNS complications like meningitis, cerebritis , epidural and brain abscess, increasing overall morbidity and mortality.

Incidence

Earlier series reported very high CSF leak rates of upto 71%. However improvements in techniques of skull base reconstruction have seen a reduction in these figures. Recent series of malignant lesions of anterior skull base report an overall complication rate of 39% and CSF leak rate of 2%.

Radiographic features that predict CSF leak include.

1) Dural and brain involvement.
2) cribriform plate involvement
3) proximity to eustachian tube.

Prevention

The main principle to prevent CSF leakage after skull base resection is to create an anatomical and functional seal between intracranial and extracranial contents by

a) water-tight dural closure either primarily or by use of a free patch grafts
   a. pericranial patch
   b. fascia lata
   c. synthetic grafts are best avoided unless absolutely necessary.

b) Use of vascularised pericranial graft to reinforce the dural closure, if required.

   The vascularized pericranial flap is the workhorse for anterior skull base reconstruction. It derives its supply from the supraorbital and supratrochlear arteries. The flap is passed below and beyond the dural suture line and fixed to the dura or the bone of the skull base. If the orbital roofs are intact, then the pericranial flap may be sufficient to support the brain without bony reconstruction. Autologous or synthetic tissue glue may be used to reinforce the closure and promote a water-tight seal.

   In some cases with a large postoperative cavity, the dead space has to be occluded to prevent infection and to provide support to the overlying brain. This may be done by

   i) local Temporalis muscle flap: medial transposition of temporalis muscle is an effective way of constructing anterolateral skull base defects. Care should be taken to preserve its attachment to the coronoid process to preserve its blood supply. It may be used with a part of cortical bone attached

to the muscle to recreate the orbital roof. It is limited by its narrow arc of rotation.

ii) Pedicled myocutaneous flaps: These may be derived from pectoralis major, trapezius, latissimus dorsi, or sternocleidomastoid muscle. They offer more bulk and coverage then the local flaps; however some authors have reported higher complication rates, when compared to the free flaps.

iii) Free tissue transfer (free flaps): These flaps have revolutionized the skull base reconstruction. They provide large volume of flexible vascularised tissue and are ideal in case of extensive resection involving removal of dura, bone, muscle and skin .They are optimal for patients who have undergone previous surgery or radiotherapy. These flaps can be harvested from latissimus dorsi, rectus abdominus, radial forearm, scapula, paascapula, and anterolateral thigh.

c) Repair of the large bony defect by vascularised bone graft or titanium mesh, if required.

d) Lastly, the judicious use of lumbar drainage to decrease CSF pressure and to provide alternate drainage till the wound heals. Prophylactic lumbar drainage is a contentious issue with divided opinion on its use. With improving methods of reconstruction, it is best to reserve it for early postoperative leaks or to prophylactically use it to support a suboptimal repair.

Diagnosis of Leak

➢ The diagnosis is usually evident in most cases. Very occasionally the leak is intermittent and clinically

difficult to appreciate. Characteristics of CSF (to be distinguished from nasal/lacrimal secretions

- o CSF is clear and odourless
- o Typical halo – sign when drop is placed on a cloth (30-90% specificity)
- o Biochemical analysis – high sugar (>30mg/dl is virtually diagnostic, low proteins and high chloride)
- o beta2 transferrin corroborates the presence of CSF in the fluid. This test is very specific for the presence of CSF (more than 90%). However it may not be easily available.

➢ Anatomical localization of the site of leak is seldom a problem in the postoperative patient. However a baseline CT or MRI is useful to:

- o Confirm the adequacy of the repair and look for any local collection.
- o To check for pneumocephalus and follow it in subsequent scan. (if it increases, it denotes inadequate repair of skull base and lumbar drain in these cases would be counterproductive and would require surgical intervention)
- o To rule out presence of raised ICP in form of cerebral edema and hydrocephalus , which would lead to a high pressure CSF leak and require primary treatment

Management of established leaks

In the setting of a postoperative leak, there have been no randomized trials to suggest the most desirable treatment. A **graded approach** to management is advisable.

Conservative treatment

It is logical to give an adequate trial of conservative methods like bed rest, serial lumbar punctures and lumbar drainage. Results with more conservative approaches are variable, but are welcome when they occur.

a) Position: Head elevation between 45 to 75 degrees is preferred for postoperative cranial leaks. This allows the brain to fall down and ensures a tight seal between the brain and the basal repair.

b) Lumbar drain: Lumbar drainage should be considered whenever position alone does not significantly reduce or stop the leak. Early use of lumbar drain before a tract is formed is preferable. Drainage should be continued for 2 to 3 days after the stoppage of leak to allow healing. Repeated lumbar drainage via puncture is an alternative, though a drain is the best to ensure complete dryness.

c) Prophylactic antibiotics are given as a norm. Appropriate specific antibiotics capable of eliminating the potential pathogen should be used. A swab from the PNS during surgery is advisable prior to starting antibiotics. If patient develops meningitis, when on prophylactic antibiotics, the antibiotics are changed to cover the appropriate organism after culture and sensitivities are checked.

Indications for prompt surgical intervention include:

a) Leaks associated with obvious disruption or destruction of skull base

b) High pressure leaks acting as a safety valve for hydrocephalus.

c) High volume leaks that cannot be controlled by position and drainage.

d) Failure of adequate trial of conservative treatment.

e) Delayed postoperative CSF leak

Operative Techniques include:

1) Endoscopic repair :(extradural repair)
   It is advised for discrete and definable normal pressure leaks .The key is to identify and seal the leaks with some combination of dural graft or substitute, bone or bone substitute and packing.
2) Open repair (Craniotomy) :
   This is indicated when there is extensive dehiscence of the skull base, or a previous endoscopic approach has failed.

   The repair can be an intradural or an extradural repair. The principles are identical to those described in the prevention of leaks.

Lumbar drains are used after endoscopic and open extradural repairs to allow the leak to heal. They are avoided after intradural repairs to allow raised CSF pressure to push the graft onto the dura and promote sealing of the leak.

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Complications Associated with use of Chemotherapy Agents for Treatment of Head and Neck Cancers

Introduction

- The current indications for chemotherapy in head neck cancers include-
  - definitive concurrent chemoradiation (for organ preservation or in unresectable tumors), - (LOE-1)
  - post-operative adjuvant chemoradiation[2,3] (in cases with perinodal extension or close margins) - (LOE-1)
  - and neoadjuvant triplet based chemotherapy in selected cases of unresectable locally advanced head neck cancers.[4,5] – (LOE-2) and borderline resectable cases – (LOE-5)

  Chemotherapy has been shown to provide survival advantage in the above- mentioned scenarios

Drugs used –

- Drugs which are commonly used in treatment of head and neck cancer include cisplatin, carboplatin, 5-fluorouracil, docetaxel, paclitaxel and ifosfamide.

- Cisplatin, as single agent is the currently recommended drug for concurrent chemoradiotherapy protocols[6] and forms the backbone of the triplets used as neoadjuvant chemotherapy.[4,5] (LOE-1)
- Neoadjuvant chemotherapy is based on taxane-based triplets – docetaxel, cisplatin and 5 FU or paclitaxel, cisplatin and 5 FU – (LOE-1). Other triplet which has been used in some neoadjuvant studies is paclitaxel, ifosfamide and cisplatin – (LOE-3).

Toxicity Profile

- Chemotherapy side effects can be divided into –

hematological - All the above mentioned drugs have the propensity to cause myelosuppression . anemia, neutropenia, leucopenia, thrombocytopenia, febrile neutropenia.

non-hematological -mucositis, nausea, vomiting, diarrhea, constipation, weight loss, lethargy, alopecia, neurotoxicity, ototoxicity, nephrotoxicity, skin rashes etc. • Cisplatin can result in nephrotoxicity, ototoxicity and neurotoxicity. • Carboplatin has more myelosuppressive potential than Cisplatin. However its potential to cause nephrotoxicity, ototoxicity and neurotoxicity is much less than cisplatin. • Paclitaxel causes peripheral neuropathy, myelosuppression, alopecia, diarrhea, hypersensitivity reactions and rarely bradyarrythmias. • Docetaxel can result in mucositis, myelosuppression, fluid retention and skin rashes. • 5- FU causes mucositis, loose motions, vomiting, hand-foot syndrome and rarely can result in coronary vasospasm.

Grading of toxicities is done usually with the help of National Cancer Institute common toxicity criteria (ctc). This makes assessment of toxicity more objective and helps in deciding dose modification.

Following is the example of hematological toxicity grading.

Toxicities		Normal	Grade-I	Grade-II	Grade-III	Grade-IV
Hematology						
Hemoglobin	Men Women	14-18 g/dl 12 to 16 g/dl	10-13.9g/dl	8.0 - 99g/dl	6.5 - 7.9 g/dl	<6.5 g/dl
Leulceyte (Total WBC		4000 - 11000 cells/mm^3	3000-3999 cells/mm^3	8.0 - 9.9 g/dl cells/mm^3	1000-1999 cells/mm^3	<1000 cells/mm^3
Neutraphile/		>2000 cells/mm3	1500-1999 cells/mm^3	1000-1499 cells/mm^3	500 to 999 cells/mm^3	<500 cells/mm^3
Platelets		150000-450000 cells/mm^3	750000-149999 cells/mm^3	50000-74999 cells/mm^3	10000-49999	<10000 cells/mm^3

- Different drugs have varying potential to cause these side effects, more so when they are used as combination. – (LOE-2)
- Use of cisplatin based chemotherapy (100 mg/m2 every 3 weekly for three doses) along with radiation increases the risk of grade 3-4 mucositis, dysphagia, anemia, leucopenia and thrombocytopenia by 14-43% over radiation alone. –(LOE-1)
- Cisplatin can result in grade 3 /4 neurotoxicity and nephrotoxicity in 1% and 10% of patients respectively.[7,8] – (LOE-2)
- The use of weekly cisplatin (20-40 mg/m2) reduces the risk of nephrotoxicity but can still cause myelosuppression. There is no head-to-head comparison available for weekly and three-weekly cisplatin in the setting of concurrent chemoradiation, however it seems to be more tolerable and has theoretically better radiosensitizing effect.[9] –(LOE-3). Given the better toxicity profile and almost similar cumulative dose, once-weekly is the preferred regimen at our centre.
- The number of treatment related deaths have also been numerically higher in concurrent chemoradiation arm

in many trials though the difference did not reach statistical significance.[6] –(LOE-2)

- The most frequent and distressing toxicity of cisplatin is nausea and vomiting. It can result in both acute and delayed emesis (>90% risk) so much so that it has been used as a model to describe acute and delayed emesis.[10] –(LOE-2)
- Incidence of ototoxicity, nephrotoxicity and neurotoxicity is less with carboplatin however it is more myelosuppressive. – (LOE-1)
- The combination chemotherapy (taxanes based triplets or cisplatin and 5-FU combination)[4,5] which is used in neoadjuvant setting can cause grade 3 / 4 neutropenia (52-76%), anemia(9-12%), thrombocytopenia (5-18%), leucopenia (22-41%), febrile neutropenia (2-5%), alopecia (0-20%), stomatitis (4-11%), nausea and vomiting (4.5-6%),anorexia (0.6-4%), diarrhea (2-4%), constipation (0.6%), ototoxicity (0-3%), and neurotoxicity (0.6-1%). – (LOE-2)

Etiology

- These side-effects of chemotherapeutic regimens are due to their cytotoxic action on rapidly proliferative normal cells of bone marrow, hair follicles, and gastro-intestinal tract mucosa resulting in anemia, leucopenia, thrombocytopenia, alopecia, mucositis and diarrhea.
- Antineoplastic agents may cause emesis through effects at a number of sites.[10] (LOE-2)
    - Action of chemotherapy drugs on small bowel which results in neurotransmitter mediated stimulation of the nucleus tractus solitarius (NTS), and the area postrema through vagal nerve.

- direct interaction with the area postrema, which is accessible to blood and cerebrospinal fluid–borne emetic stimuli.
- Through cerebral cortex.

- Cisplatin induced nephropathy occurs due to tubular injury caused by platinum DNA adduct formation. – (LOE-4)
- The ototoxicity due to cisplatin is cumulative and it occurs due to cochlear damage and it leads to loss of high frequency acuity.
- Cisplatin related peripheral neuropathy is likely due to irreversible accumulation of inorganic platinum in the neurons and it is also cumulative.
- Cisplatin and carboplatin can result in vasospasm and can lead to myocardial ischemia and cerberovascular events
- Paclitaxel disrupts neuronal microtubule dynamics by stabilizing the microtubules against depolymerization and leads to neuropathy due to demyelination and axonal degeneration.
- There is a risk of acute hypersensitivity reactions during infusion of paclitaxel and carboplatin.

Prevention

- Prevention of side-effects allows administration of chemotherapy in time and in full doses thus maintaining the dose intensity to attain the desired effects.
- The key for prevention is appropriate selection of cases. Patients who are elderly and those with poor performance status and multiple co-morbidities should not be taken for chemoradiation or neoadjuvant chemotherapy.[11] – (LOE-2). Calculation of creatinine-clearance (Cockroft-Gault formula – (140-age) X body weight / 72 X serum

creatinine in males, 0.85 X (140-age) X body weight / 72 X serum creatinine in case of females) is an important pre-requisite in selecting patients for cisplatin based concurrent chemoradiation and neoadjuvant chemotherapy. Patients with calculated creatinine clearance < 50 mL/min should not be taken for these treatments.

- Most of the patients with head neck cancer are nutritionally compromised due to poor oral intake and are prone for treatment related toxicities. Insertion of feeding tubes before commencement of treatment may be helpful in such patients.- (LOE-3)
- To prevent the myelosuppression use of prophylactic G-CSF is recommended with regimens which have more than 20% incidence of febrile neutropenia (taxanes based triplets). Patients who have had grade 3 / 4 leucopenia, neutropenia or febrile neutropenia can be given G-CSF during next cycle. –(LOE-1)
- There is no role of amifostine in the prevention of chemotherapy-induced thrombocytopenia.[12]- (LOE-2)
- Prevention of chemotherapy induced nausea and vomiting in head neck cancer patients requires the use of aprepitant, 5-HT3 receptor antagonist and dexamethasone prior to administration of chemotherapy and dexamethasone and aprepitant for 3 days after chemotherapy.[10,13] – (LOE-1)
- To avoid the nephrotoxicity associated with cisplatin, hydration with normal saline 2-3 hours before and 4-6 after the administration plays an important role. It prevents the hydrolysis of cisplatin in the tubules and reduces its time of contact with tubular epithelium. – (LOE-3)
- Amifostine may have a role in preventing the cisplatin induced nephrotoxicity. Amifostine is given

intravenously over 15 minutes in dose of 910 mg/m2 30 minutes before administration of cisplatin.[12] – (LOE-2)

- Administration of other nephrotoxic drugs (aminoglycosides, non-steroidal anti-inflammatory drugs) should be avoided. Patients with impaired renal function should not be given cisplatin.
- Role of amifostine in preventing neurotoxicity due cisplatin and paclitaxel has not been supported by the studies.[12] – (LOE-2)
- Use of premedication (dexamethasone, H1 and H2 receptor blockers) before the paclitaxel infusion can avoid the development of hypersensitivity reactions.- (LOE-1)
- Maintenance of oral hygiene with any oral protocol which include saline rinses, flossing and regular brushing helps in preventing the development of oral mucositis.- (LOE-2)
- Some patients who have dihydropyrimidine deficiency develop severe life-threatening myelosuppression and mucositis after treatment with 5-FU and require dose modification. Identification of these patients by mutational analysis can prevent life-threatening toxicities.

Management

- In most cases the occurrence of nausea and vomiting can be effectively prevented by the above mentioned regimen of antiemetics; however management of breakthrough vomiting is largely empirical and includes benzodiazepines and phenothiazines. Importance of hydration and electrolyte replacement needs no emphasis.- (LOE-4)

- Treatment of febrile neutropenia requires risk assessment as per the Infectious disease society of America (IDSA) guidelines and administration of oral or intravenous antibiotics and growth factors. – (LOE-2)
- Development of nephrotoxicity requires temporary or permanent discontinuation or dose modification of cisplatin. Aggressive hydration, potassium, sodium and magnesium supplementation helps to avoid further tubular damage.- (LOE-3)
- For the drug-induced grade 3 /4 neuropathy and ototoxicity, discontinuation of cisplatin or paclitaxel is required. In patients with lesser grade of toxicity dose modification can be considered. Amitriptyline and gabapentin help reducing the neuropathic pain. - (LOE-4)
- Chemotherapy-induced diarrhea requires hydration and electrolyte replacement .Lopermaide can be used in patients with 5-FU related diarrhea. Octreotide is helpful in patients who do not respond to loperamide(LOE-2)
- Treatment of mucositis requires good pain management with opioid or non-opioid analgesics depending on the severity of pain and response to first line therapy. - (LOE-3)
- There is no role of acyclovir or chlorhexidine mouthwash in treatment of mucositis.-(LOE-2).

Targeted therapy :

The role of targeted therapy is gradually increasing in head neck cancer. Presently the only FDA approved drug is cetuximan (monoclonal antibody directed against epidermal growth factor receptor) - along with radiation for treatment of locally advanced head neck cancer and in patients with recurrent/metastatic head neck cancer as first line treatment along with chemotherapy - (LOE-1). This drug is well tolerated

in most of the patients. The common side effects include-hypersensitivity reaction during infusion, acneiform skin reaction and diarrhea and hypomagnesemia. Addition of cetuximab to radiotherapy or chemotherapy does not result in higher incidence of toxicity. In most of the cases the infusion reaction can be managed with discontinuation of infusion, antihistaminics and occasionally steroids are required. In most of the patients these reaction do not occur during next infusion. Acneiform rashes can be managed with topical applicationof steroids, and oral doxycycline. In cases with grade 4 or recurrent grade 3 toxicity, does reduction or discontinuation is required -(LOE-2). role of other drugs like Geftinib and Erlotinib - epidermal growth factor receptor tyrosine kinase inhibitors is limited to phase II trials with marginal activity.

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Section — III

Radiotherapy

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Complications of Abdomino-Pelvic Radiotherapy

Introduction:

Radiation therapy is an established treatment modality in the management of patients with gynecological, gastrointestinal and genitourinary malignancies. The radiation can be either external beam (teletherapy) alone, internal (brachytherapy) or combination. Radiation therapy (external alone or combination of external and brachytherapy) is given in different settings depending on the intent of treatment. It could be in radical radiation, post or peri-operative adjuvant, salvage or palliative settings. In recent past there has been a paradigm shift towards use of concomitant chemoradiation for radiosensitization. The classical example to illustrate use of radiation in various settings is cervical cancers. In stage II/III cervical cancers radical radiation therapy with / without concomitant chemotherapy is the treatment of choice. Radiation is also given as adjuvant postoperative treatment in patients with high risk histo-pathological features like, tumor size, positive margins, lymphovascular invasion or positive lymph nodes in cervical and endometrial cancers after radical surgery and risk stratification . In cases where para aortic lymph

nodes are involved or suspected to be involved, the pelvic field is extended to encompass the para aortic nodes too, where large fields are used. In post surgery recurrences, radiation therapy has also resulted in modest control rates (2). For palliation of symptoms like profuse vaginal discharge, bleeding, bone metastasis, brain metastasis, palliative radiation works wonders.

Majority of the side effects in abdomino-pelvic region are due to irradiation of small bowel, recto-sigmoid, bladder, kidneys, liver femoral heads and bone marrow etc. The severity of complications depend on the radiation threshold doses, volume, repair time etc. Before going into details of anticipated toxicities, complications and management, it is worthwhile to know some radiation therapy basics.

Radiation treatment and Dose Response Relationships:

The aim of radiation therapy is to achieve maximal tumor kill while limiting injury to the normal surrounding tissues. Solid tumors have a variable fraction of clonogenic cells that have the property to divide and proliferate like any other normal tissues in the body. Thus one must eradicate all clonogenic tumor cells so as to achieve a cure. To improve the chances of cure, radiation doses may have to be increased, which results in increased acute reactions which is acceptable to a certain degree. However, it is the risk of late reactions which has to be reduced so as to minimize the morbidity in the surviving patient.

Radiation tolerance doses

The radiation doses for a particular tumor depends on dose response curve, but to a large extent limited by radiation tolerances of the surrounding tissues and organs. For eg. Tolerance of cervix and uterus is usually more than 200Gy.

With these doses, the rate of necrosis is less than 1%. Tolerance doses of the upper vagina and surface of the distal vagina are 140 Gy and 100Gy, respectively. Threshold doses reported for vesico-vaginal fistula is 150Gy and for recto-vaginal fistula is 80 Gy (4). Hence a combination of external and brachytherapy is offered to cervical cancers. The radiation induced side effects and their manifestations depend on the type of tissues receiving radiation i.e. early or late responding normal tissues and the radiation tolerances. Early responding tissues like, the skin and intestinal mucosa have a high cell turnover rate and they express radiation injury earlier, at about 2 to 3 weeks. Conversely, late responding tissues, like spinal cord, rectum, bladder, or kidneys have a slow cell turnover or non-proliferating, thus expressing radiation injury many years later after treatment.

Classification of Radiation Induced Reactions

Broadly, reactions may be divided into acute, subacute and late. Acute reactions are those which manifest while on treatment or within 3 months, subacute reactions arise between 3 to 6 months and late reactions become apparent after 6 months of treatment. Adverse event (AE) reporting in oncology has evolved from unceremonious metaphors to a highly systematized method. The Common Terminology Criteria for Adverse Events (CTCAE) is the principal system for describing the severity of AE's commonly encountered in oncology clinical studies. CTCAE clinical descriptors have been developed empirically during more than 30 years of use. The method of data collection is clinician based. Limitations of the CTC system include potential for incomplete reporting and limited guidance on data analysis and presentation methods.

Early reactions manifest clinically during the course of radiotherapy, and are generally due to mitotic-linked cell death in rapidly dividing tissues and secondary impaired tissue

function. In general, with conventionally fractionated radiotherapy, the acute normal tissue reactions are within tolerable limits. However, with development of newer strategies of delivering radiation like, concurrent chemo-radiotherapy, accelerated fractionation, and hyper-fractionation, the chances of severe acute radiation toxicity are increased manifold.

Variables affecting normal tissue tolerance

Variables impacting normal tissue tolerance maybe classified into host, organ, tumor, and treatment related factors.

Host-related factors include age, individual response to radiation, and comorbid conditions like, collagen vascular disease and diabetes mellitus.

Organ-related variables include pre-radiation organ function compromise or loss, volume of organ irradiated, geographical variation in the radiosensitivity within the organ, and the functional organization of the organ (i e, whether it is a serial or parallel type and if damage to one part affects only that portion or has more widespread effect).

Treatment-related variables include total dose, fraction size, overall treatment time, beam energy and volume irradiated. In a classic pelvic radiation field, the small and large bowel mainly recto-sigmoid, and urinary bladder are at an increased risk of treatment-related complications.

The common complications encountered in routine clinical practice have been discussed in subsequent paragraphs.

Gastrointestinal toxicity:

A : Small Bowel

At the start of pelvic radiation therapy, most patients will have normal gastrointestinal functions. While on therapy, the normal tissues around the tumour will undergo radiation effects. The

sigmoid colon and rectum being in close proximity to the tumour will be affected the most. Similarly, in postoperative cases and in extended field treatments including para-aortic nodes, a sizeable amount of small bowel tends to get irradiated. The intestines are an important dose-limiting organ in abdomino-pelvic radiotherapy.

Severity and frequency of gut toxicity depends on total dose, fractionation, volume of bowel irradiated, concurrent administration of chemotherapy and co-morbidities like pelvic inflammatory disease, hypertension, inflammatory bowel disease, HIV infection and thin body habitus. For instance, the incidence of severe late toxicity in women treated for cervical cancer was 10 - 15% at 20 years with a 30-40% incidence of chronic diarrhea, and a late small bowel obstruction of 9-30% requiring surgery at 5-years.

Acute bowel toxicity manifests clinically as enteritis and ulceration in the intestine with loss of epithelial integrity and increased secretion of mucus. Patients manifest with chronic diarrhea with resultant tissue edema and hyperemia. These symptoms may be severe enough to require an alteration in the treatment plan, they are usually transient and cease shortly after completion of radiation therapy.

Delayed intestinal dysfunction may continue to worsen into the late stage effects, typically presenting 6 months to 3 years after radiation therapy. In a retrospective study by Olopade et al., 90% of patients undergoing pelvic radiation reported a permanent change in their bowel habit after treatment, with nearly 50% reporting adverse effects on quality of life measures.

Diagnosis, Prevention and Management

Diagnostic tests used in the workup of patients with recurrent abdominal symptoms post radiation therapy includes imaging,

like ultrasonography, CT scan, endoscopy, tests for malabsorption (eg, fecal fat excretion, lactose absorption test Schilling test), and maldigestion (eg, xylose breath test), measurement of intestinal transit, microflora assessment tests, and histopathological examination of mucosal biopsies.

Anti-peristaltic drugs, like loperamide or codeine phosphate when taken 30-60 min prior to meals may often be sufficient to manage diarrhea and malabsorption. Patients must be advised to avoid unabsorbed sugars, spices, chilies and starches and a dietician reference is recommended. Symptomatic therapy is helpful in reducing distress in the acute period. Nausea and vomiting are usually responsive to antiemetics like metochlopramide or, in severe cases, ondansetron or granisetron (5-hydroxytryptamine antagonists) maybe given. Henriksson et al., found that sucralfate significantly reduced the frequency of defecation and improved the stool consistency, with lowered requirements of symptomatic treatment with loperamide.

B: Recto-sigmoid toxicities

Rectosigmoid toxicity is dose limiting during pelvic radiotherapy. Total doses of less than 40Gy rarely cause clinically significant symptoms. Nevertheless, pelvic tumors are usually treated to doses in the range of 50-70Gy, which result in significant acute morbidity, including abdominal pain, cramps, diarrhea and hematochesia. In a few patients, these symptoms may require treatment interruptions or other modifications that hinder optimal completion of planned treatment. Some patients may develop symptoms of chronic injury, usually after a latent period of few months or years.Perez et al., in their study of 1456 patients from Mallinckrodt found a 1-4% incidence of major rectal complications when patients received doses less or equal to 8000 Gy, versus a rate of 9% at doses greater than 8000 Gy. Schultheiss in a study from Fox Chase, suggested that the dose resulting in 5% and 50%

complication rate of late rectal toxicity is nearly 65 Gy and 78 Gy, respectively.

Diagnosis, prevention and management

The assemblage of symptoms contributing to late proctitis was alluded to as long as 15 years ago and the RTOG defined proctitis as "being characterized by rectal irritation or urgency (tenesmus), presence of mucous or blood in the stool and, in some patients frequent loose bowel actions. More recently, the LENT/SOMA (Late Effect on Normal Tissues/ Subjective Objective Management Assessment) scoring system for late radiation injuries has been introduced which lists six different symptoms of proctitis.

A patient presenting to the clinic must be questioned about the presence and severity of various gastrointestinal symptoms as stated above. Clinician must distinguish tenesmus from detecation frequency.

A rectal examination with assessment of the sphincteric tone, proctoscopy and sigmoidoscopy is necessary. Counseling is a helpful tool as majority patients may be reassured if they are educated that they will get intermittent bleeding (particularly when they are constipated which should be avoided at all costs), that bleeding will subside over years.

Kocchar et al., documented the benefit of sucralfate in delayed radiation proctitis. They stated that sucralfate enemas being better tolerated and cheaper rendering a better clinical response should be the considered for short-term treatment for chronic proctitis. Other studies have shown that sucralfate is ineffective in cases of acute radiation proctitis.

A Cochrane review has summarised the evidence for treatment of rectal bleeding from radiotherapy. Sucralfate enemas (2 g sucralfate suspension made-up with 30–50 mL water in a bladder syringe injected twice a day via a lubricated foley

catheter passed through the anus into the rectum) are more effective than corticosteroid or mesalazine enemas. Various endoscopic treatment options exist: use of argon plasma coagulation (APC), laser therapy, or formalin applied to affected mucosa. In our institute, APC is widely practiced though strongly contraindicated in case of rectal ulcers as perforation rates are high as reported in literature. Formalin is known to decrease mucosal blood flow and can be used in two ways. It can be rectally inserted as a 4% suspension between 20 to 80 mL, for a holding time of 15min under general anesthesia. A review which included 16 studies with 202 patients found response rates ranging from 55% and 100% with 7% adverse outcomes. Formalin 10% soaked pads applied topically to the mucosa under endoscopic guidance results in excellent response rates of 90% with serious complication rate of 1%.

Likewise, the use of hyperbaric oxygen has shown the most promising benefits. The principle of this therapy is that oxygen gradient promotes angiogenesis and tissue restructuring in ischemic anoxic tissues. There is no level I evidence available supporting its use, though there is a systematic review that well summarizes the effectiveness of hyperbaric oxygen in the management of radiation-induced bleeding. The main drawback is that they are all retrospective studies that lack uniformity in symptoms and response criteria scoring and its efficacy needs to be validated in larger randomized controlled setting.

Bladder toxicity

The urinary bladder is an important dose- limiting pelvic organ which gets directly irradiated in gynecological malignancies both throughout external therapy as well as during brachytherapy. With this technique dose to the posterior/ inferior walls of the bladder are often very high. During and

after radiation therapy, bladder irritation varies from mild dysuria with infrequent hematuria to protracted bladder spasm, continous hematuria, necrosis and may be eventual vesico-vaginal or urethra-vaginal fistula. The overall rate of urinary sequelae in cancer cervix patients is frequently reported in the 8-12% range, while the rate of moderate/ severe sequelae is in the 2-6% range.

While (ICRU 38) report attempts to make the reporting of the bladder dose uniform, it is clear that this technique is laden with uncertainties, which was confirmed in various studies.

Acute symptoms include pain during micturition, increased urinary frequency, and urgency. The reported incidence of these acute symptoms varies widely from 23 to 80% among patients receiving pelvic radiation for various tumors. The symptoms are usually subjective, occasionally severe, and therefore may not always be appreciated and reported by the patient.

Diagnosis, Prevention and Management

A careful history, physical examination, and urinalysis is usually sufficient to assess the degree of bladder dysfunction. Patients should be evaluated for the presence of obstructive or irritative symptoms. An urge incontinence must be distinguished from stress incontinence. A urinary tract fistula must be ruled out in women with large volume or continuous incontinence.

The suprapubic region and abdomen must be palpated to assess bladder distention and tenderness. A meticulous gynecological examination must be performed to exclude the presence of inflammatory conditions or fistula. A carefully collected, clean urine sample should be examined for the presence of bacteria and red and white cells. Urinary infection can greatly augment the effects of radiation which requires prompt attention. Urine cytology and culture sensitivity is also helpful in indicating the source of infection.

Acute symptoms usually subside several weeks following radiation. Management of these early symptoms is directed toward symptom relief. In cases of dysuria, phenazopyridine hydrochloride, a topical analgesic 200mg orally, thrice a day is frequently used to relieve the symptoms. While prescribing this drug, the patients urine will become orange/ red. Symptoms due to modest reduction in bladder capacity, such as mild urinary frequency and urgency maybe managed with antispasmodics like, oxybutinin chloride and the newer drug tolterodine, which is better tolerated helps to relaxes the bladder smooth muscles by inhibiting the muscarinic effects of acetylcholine. This drug is effective in relieving symptoms of frequency and urgency. The dose is 5 mg thrice a day. Majority of these acute reactions are self- limiting and it is very difficult to analyze due to its subjective nature.

Bladder storage capacity defects and outlet resistance must be identified. Severe decrease in the bladder capacity may be treated with bladder augmentation using a segment of intestine. Urethral strictures are successfully managed with simple endoscopic incisions. Though, recurrent or complex stricture may require open surgical repair. In some patients with fixed urethral strictures and adequate bladder capacity, intermittent catheterization may suffice.

Severe haemorrhage caused by radiation maybe treated with cystoscopy and selective cauterization of bleeding points followed by irrigation with various agents like normal saline, alum, silver nitrate or dilute formalin. Early institution of hyperbaric oxygen therapy (HBOT) has also shown positive results in many studies. In a study by Chong et al, 60 patients received an average of 33 HBOT treatments. HBOT therapy was delivered at 2.36 atmosphere absolute pressure, with 90 minutes of 100% oxygen breathing per treatment. Nearly 80% had either total or partial resolution of hematuria. When treated within 6 months of hematuria onset, 96% had complete or

partial symptomatic resolution (P = 0.003). They concluded that delivery of HBOT therapy within 6 months of hematuria onset results in a greater therapeutic response rate.

Severe injuries not amenable to the above management strategies may require construction of continent urinary reservoirs from small or large intestine. Vesico-vaginal fistulas may be repaired using a variety of surgical approaches. The principles of repair include meticulous surgical technique, excision of the fistula site, multilayer closure, use of well-vascularized tissue, when possible, and interposition of omentum, muscle, peritoneum or fat.

Skin and Subcutaneous Tissues:

As mentioned earlier skin is an early reacting tissue by virtue of rapidly dividing epithelial cells and subcutaneous fibro-fatty tissue the late reacting tissues. So radiation induced acute toxicities are commonly seen in skin ranging from erythema, dry desquamation (peeling), moist desquamation and ulceration. Local hygiene, quality of radiation (cobalt / linac), skin folds and area of skin surface radiated. All these factors are also applicable to development of subcutaneous fibrosis (mild, woody to stony hard). The skin toxicities can be managed conservatively by superficial cleaning, applying smoothening ointments like aloederm, steroids and barrier hydrocolloid dressings or 1% GV paint. Chronic non healing ulcerations are best treated with grafts. Severe symptomatic woody / stony fibrosis may also require surgical intervention and reconstruction.

Hematological toxicities

In adults, a major portion of hematopoietic tissue lies in skull, sternum, ribs, vertebrae and pelvic bones (35-40%). In pelvic radiation therapy, a large amount of marrow gets irradiated which can be measured in the peripheral blood by levels of

granulocytopenia, thrombocytopenia and anemia. An easy way to circumvent and prevent this problem is by decreasing doses of chemotherapy and not infrequently, concomittant administration of injectable colony stimulating factors.

Pelvic fibrosis (vaginal, parametrial)

Vaginal function is compromised both after surgery and radiation therapy. Surgery results in vaginal shortening while radiotherapy reduces the length, pliability and transudative lubrication of the vagina. In a study by Jensen et al., reported lack of lubrication in 35% patients, mild to severe dyspareunia in 55%, low or no sexual interest in 85% and a dissatisfied sexual life in 30%. Ovarian ablation further causes estrogen deficiency, which results in thinning and atrophy of the skin of the vulva and vaginal mucosa. In a study from our institute, it was reported that counseling about vaginal hygiene, sexual activity and use of vaginal dilator helps to alleviate majority of the symptoms. At follow up, a successful increase in vaginal length was seen between 1st and 4th month.

Bilateral lower limb lymphedema

Lower limb lymphedema occurs as a result of venous or lymphatic obstruction secondary to regional nodal dissection, thrombophlebitis, tumor emboli and pelvic RT. Conservation management in the form of limb elevation, manual lymphatic drainage and compression stockings may be of benefit.

Osteoradionecrosis (ORN) bilateral femoral head : ORN is a pathological entity which comprises of non traumatic, aseptic, avascular necrosis of bone, most likely due to decreased blood flow skeletal tissues. With radiation therapy to the pelvis, the incidence of ORN is 2-20%, affecting proximal ends of long bones, head of femur, sacrum etc. It occurs within few months of RT or may occur after several years too. Risk is usually

increased with concurrent administration of chemotherapeutic drugs like, cisplatin, vincristine and adriamycin.

Pelvic Insufficiency Stress Fractures (PIF's) : PIF are an important complication of pelvic RT which commonly occurs with normal stress in bones with diminished elastic flexibility. Commonly affects bones like neck of femur, vertebrae and pelvic bones. Majority of the patients are asymptomatic while few may report pain aggravated on motion. Less aggressive diagnostic studies reveal an incidence of PIF in 2-30% of irradiated bones, while the more sophisticated MRI has revealed an incidence as high as 89%. Majority of the patients improve symptomatically with conservative management.

Lumbosacral plexopathy: This entity has been occasionally reported in patients with pelvic tumors treated to doses above 60 - 67.5Gy. Characteristically, patients will present with lower motor neuron weakness of legs along with muscle fasciculations and loss of deep tendon reflexes.

Premature menopause: Pelvic RT results in iatrogenic premature menopause wherein the ovaries undergo atresia, and hormone production ceases. Ovarian hormones play a significant role in the maintenance of bone mineralization, integrity of the cardiovascular system, libido, maturation and maintenance of the breasts and vagina.

Strategies to reduce complications

With the emergence of advanced technologies, newer strategies to improve the therapeutic ratio, such that the effect on the tumor may be increased with subsequent decrease in the complication rates has become the dictum and the main driving force of modern Radiation Oncology. This goal is applicable in the treatment of every possible site of the human body. This goal can be achieved by two principal methods: a) Physical method, by use of sophisticated 3DCRT (3D conformal

radiation therapy), IMRT (intensity-modulated radiotherapy) techniques, simultaneous integrated IMRT boost, proton therapy etc which allows precise delivery and dose escalation of radiation while sparing the neighboring normal tissues and, b) Biological method, wherein treatment is delivered over time (fractionation), allowing the sparing of late normal tissue toxicity; combining radiation with chemotherapy or targeted agents so as to overcome the repopulation and radio-resistance of hypoxic tumors.

With the above advances in treatment strategies, have the potential in further improvements in survival and probably reduction in late sequelae. However, till date there is no substantial data including late toxicities to support. These complications are a trade-off in the pursuit to cure pelvic malignancies. Thus it has become imperative that the radiation oncologist is aware of the patho-physiology and the treatment options for these patients who manifest the complications. On recognition of problems, referral pathways should be laid such that the suffering patient can see a specialist.

Summary and Conclusions

To summarize, patients receiving abdomino-pelvic radiation will encounter acute grade I-III gastro-intestinal, genitourinary and skin toxicities which are treatable. The radiation induced late sequelae are preventable. This needs careful selection of cases, appropriate and optimum radiation planning (external and / or brachytherapy), limiting doses to adjacent critical organs / tissues, careful follow-up evaluation to identify toxicities at the earliest and immediate appropriate treatment measures. In order to achieve this apart from the Radiation Oncologist and the treating team and other members of the multi-disciplinary team (Surgical and Medical Oncologist) should be aware of the anticipated effects following radiation therapy and the knowledge that timely intervention would to a large extent abort them.

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Radiation Induced Second Malignant Neoplasm

Introduction:

With sustained and continuous improvements in screening, early detection, and therapy mortality from cancer has consistently reduced over the years resulting in improved cancer-specific survival. In the United States, 5 year survival for all cancers increased from 50% to 66% in adults and from 61% to 79% in children from 1975-1979 to 1996-2002 (1). In the latter years, the 10 year survival rates were 59% in adults and 75% in children. Development of second malignant neoplasm (SMN) is probably one of the most sinister late events in long-term cancer survivors. The risk of second malignancies is often expressed as observed versus expected ratio (O/E ratio) calculated by dividing the observed number of new cases by the number expected if patients in the cohort experienced same cancer rates as the general reference population. It is a measure of strength of association. Another tool often used is excess absolute risk (EAR), defined as excess cancers per 10,000 person-years at risk (PYR) and calculated as [(O-E)/PYR X 10,000]. It is the difference between the subsequent cancer rate in the cohort being evaluated and the

rate expected in the standard population which is used to measure the overall burden due to subsequent cancers.

Burden:

The Surveillance, Epidemiology & End Results (SEER) data on SMN based on nine cancer registries involving over 2 million cancer patients reported an overall 14% higher risk of new malignancies (O/E=1.14; 95%CI=1.14-1.15) in cancer survivors than would be expected in general population [Table I].

In the SEER database (2), nearly 14% of all patients developed a second cancer by 25 years of follow-up (cumulative incidence of 5.0%, 8.4%, 10.8%, and 13.7% at 5, 10, 15, and 25 years, respectively). The aetiology of SMN can reflect the late sequelae of treatment; the influence of lifestyle factors, environmental exposures, and host factors; and combinations of influences, including gene-environment and gene-gene interactions. Travis and colleagues (3) categorized SMN into three major groups according to dominant etiologic factors (ie. treatment-related, syndromic, and those attributable to shared etiologic influences) underscoring the non-exclusivity of these delineations. The incidence of second primary cancer however varied according to age group (1). In childhood cancers, the all-cause mortality and overall risk of subsequent cancer was very high (O/E=6.13), as compared to the elderly population where the risk of a SMN was much less (O/E=0.93). In a subgroup analysis (2), the incidence of subsequent primary cancers was evaluated in a cohort of 23,819 2-month survivors of childhood cancer diagnosed at ages less than 18 years during 1973-2000 and followed for an average of 8.3 years. Childhood cancer survivors were at more than 6-fold increase in risk of developing a new cancer relative to the general population (O/E=6.07, O=352, EAR=15 per 10,000 person-years). The cumulative incidence of second cancers at 25 years after

Table I: Risk of subsequent cancer after any initial cancer by age at initial diagnosis

	Total			Males			Females		
Age at Initial diagnosis	**0**	**0/E**	**EAR**	**0**	**0/E**	**EAR**	**0**	**0/E**	**EAR**
All ages	185,407	1.14*	21	100,428	1.11*	22	84,979	1.17*	21
00-17	351	6.13*	15	176	6.44*	15	175	5.84	15
18-29	1,401	2.92*	22	562	3.39*	22	839	2.67*	23
30-39	4,909	2.37*	39	1,530	2.88*	40	3,379	2.20*	38
40-49	13,537	1.16*	39	4,466	1.83*	52	9,071	1.52*	34
50-59	34,159	1.27*	32	15,957	1.33*	46	18,202	1.21*	24
60-69	62,286	1.13*	23	35,986	1.11*	25	26,300	1.14*	22
70-79	52,321	1.02*	4	32,419	1.00*	0	19,902	1.05*	9
80-115	16,443	0.92*	-19	9,332	0.92*	-26	7,111	0.93*	-14

adjusting for competing causes of death was 3.5% (95% CI=3-4.1%) [Figure I]. The most common types of childhood cancers were leukemias, lymphomas, cancers of the central nervous system (CNS), and bone and soft tissue sarcomas [Figure II]. Most common were subsequent primary cancers of the female breast, brain, bone, thyroid gland, and soft tissue, as well as melanoma of the skin and acute non-lymphocytic leukemia.

Radiation Associated Malignancies:

Radiation Therapy (RT) and Chemotherapy (CT) are integral components of multimodality management of vast majority of cancers in the definitive setting. Although radiation induced or rather radiation associated malignancies (RAM) have been known for decades, the benefits of radiation and chemotherapy in disease control and overall survival far outweighs this very small risk. Internationally accepted criteria (Cahan and Murray) for diagnosing RAM (4, 5) include all of the following:

(a) The tumor arose in a previously irradiated field.

(b) The new tumor is histologically different from the original condition.

(c) There was no evidence of the new tumor at the time of radiation therapy.

(d) A latency period existed between irradiation and the development of the new tumor.

Mechanism of RAM: Treatment with RT may repair impairment of chromosomes and thus lead to several point and segment mutations. These mutations and genetic changes lead to second malignancies in patient, years after they are cured of the original cancer. Cells outside the irradiated field also express some of these cellular and genetic abnormalities called as radiation-induced 'bystander effect'. It refers to the induction of biological effects in cells that are not directly

traversed by a charged particle but are in close proximity to cells that are bombarded by the charged particle (6).

Tumor Types: Radiation is known to induce both leukaemia and solid tumor. Latent period for secondary leukaemia is usually shorter (around 5 years) while for solid tumor, the median is around 10 years. Amongst solid tumors it can cause both sarcomas and carcinomas. Sarcomas can be in soft tissue or bone; common types are osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, angiosarcoma and chondrosarcoma. Incidence of radiation associated sarcoma is reported to be 0.03- 0.25% of all patients receiving therapeutic irradiation. In some cases radiation carcinogenicity is modified by life-style (e.g. higher incidence of lung cancer among survivors of Hodgkin's lymphoma with smoking) or by genetic influence (e.g. higher incidence of osteosarcoma in patients with hereditary retinoblastoma and germ line mutation of RB gene).

Dose-Risk Relationship: Relationship between radiation dose and cancer risk comes from studies of Japanese atomic bomb survivors, individuals with occupational radiation exposure, diagnostic radiology and use of RT for management of non-malignant diseases. For most solid tumor there is a linear relationship up to 5 Gy and for leukaemia linear increase in risk up to 1.5-2 Gy. These observations have led to the belief that risk of RAM is higher in the tissues exposed to intermediate doses, while tissue exposed to lethal doses in the range of >30 Gy, radiation is often lethal and does not induce carcinogenesis. There is also variation in the sensitivity of different organs with regards to cancer induction by radiation with sites such as thyroid, breast and bone marrow being more sensitive.

Impact of newer radiation technology: Rapid advancements in technology have ushered in the era of high-precision radiotherapy such as three-dimensional conformal radiation

therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) in contemporary oncologic practice. The incidence of RAM is hypothesised to increase with the use of new techniques compared to conventional RT due to following reasons:

(a) More number of beams is used for treatment in 3D-CRT and IMRT which resulting in a more conformal dose distribution to target but at the expense of low-doses to more normal body volume outside target area.

(b) The beam ON time is longer with these techniques resulting in is higher total body low-dose exposure due to more leakage and scatter.

At the same time it is expected that 3D-CRT/IMRT may result in irradiation of smaller volumes which may possibly reduce the whole-body integral dose that might reduce incidence of RAM. Therefore exact risk modelling with 3D-CRT/IMRT is difficult as the spatial distribution of dose, sensitivity of various irradiated organs and leakage are variable. Studies with longer follow up of patients treated with conformal techniques will probably answer these questions (7).

Disease-specific SMNs:

Hodgkin's disease: Long-term survivors of Hodgkin's disease (HD) are at increased risk of leukaemia, non-Hodgkin's lymphoma (NHL) and solid tumor which have been correlated with carcinogenicity of alkylating agents of chemotherapy and radiotherapy. In a study of 1319 patient of HD (majority patients with early stage disease) treated at Dana Faber Cancer Institute between 1969 to 1997 with a median follow up of 12 years, 15 and 20 years cumulative incidence of SMN was 14% and 23% respectively. Relative risk (RR) for leukaemia, NHL and solid tumor were 82.5, 16.5 and 3.5 respectively which corresponds to excess absolute risk of 14.2, 14.3 and 59 per 10,000 person-years. RR was significantly higher for combined

modality treatment than RT alone (6.1 vs. 4%, p=0.015). Relative risk was higher with bigger RT field size corresponding to 2.1, 4.2 and 5.1 for mantle, subtotal nodal irradiation (STNI) and total nodal irradiation (TNI) respectively (8). A recent study by Constine et al., (9) has found positive correlation of risk of SMN with radiation dose. The standardized incidence ratio (SIR) were 11.7, 12.5, and 16.5 with doses <25 Gy, 25-35 Gy and >35 Gy respectively (p=0.0085). Apart from the carcinogenicity of radiation therapy and chemotherapy, risk of second primary is also influenced by other known aetiologies of the solid tumor. Young age at mantle irradiation is associated with significantly higher risk of breast cancer. Smoking has been reported to multiply the occurrence of carcinoma lung in HD survivors. With the use of non alkylating chemotherapy drugs, abbreviated RT fields and doses, the incidence of SMN in long-term survivors of HD is likely to decrease.

Head and Neck Cancer: The mucosa of the upper aero-digestive tract is at risk of 'field carcinogenesis' and is associated with increased risk of second malignancies. This increased risk is largely attributed to consumption of tobacco and alcohol. Recent SEER data of 27,985 patients with localized squamous cell HNC (excluding thyroid and salivary gland tumor) treated from 1973 -1997 was analysed to estimate the risk of second head and neck cancers with or without RT. Details of RT doses and use of tobacco and alcohol was not available. It showed 15 year incidence of second head and neck carcinomas to be 7.7% with and 10.5% without RT (HR 0.71, p=0.0001). This data suggests potential benefit of RT in eliminating occult foci of second cancer (10).

Testicular Cancer: Both leukemias and various solid tumor including gastrointestinal, bladder, prostate lung and contralateral testes cancers have been reported in long-term survivors of testicular cancers. These have been largely

attributed to use of cisplatin based chemotherapy and radiotherapy; and tumor of contralateral testis due to underlying predisposition. In a cohort study by Travis et al., relative risk of SMN was 2.0, 1.8 and 2.9 with RT alone, CT alone and combined CT & RT respectively (11).

Breast Cancer: Breast cancer patients are at a high risk of contralateral breast cancer due to underlying predisposition factors, radiotherapy associated lung cancer and sarcomas, chemotherapy induced leukemias , tamoxifen induced endometrial cancers and various genetic cancer syndromes. Risk of contralateral breast cancer is two to five folds in patient with breast cancer but role of RT in this risk is not clear. RT on the other hand is clearly linked to lung carcinomas (1.5 to 3 times risk), sarcomas and esophageal cancers. With the use of IMRT and accelerated partial breast irradiation (APBI), the risk of RT associated SMN is likely to decrease (12, 13, 14).

Prostate Cancer: Patient with prostate cancer are at increased risk of bladder, colorectal, lung carcinoma and sarcomas. SMN could be due to radiation carcinogenesis, vigilant screening, incidental finding on investigation done for RT complications or due to base line high level due to genetic/environmental factors. The RR for bladder carcinoma after RT for carcinoma prostate is variable (between 1-1.5) with a latency period of 5-10 years. RR of bladder cancer is reportedly higher after post-prostatectomy RT probably due to irradiation of more bladder volume. There is also modest increase in risk of rectal cancer after RT with RR varying between 1.2-1.5. Patients treated with brachytherapy have been reported to have lower incidence of secondary bladder and rectal cancers compared to external beam RT (1.6 vs. 5.8%; p=0.0623). With the increasing use of IMRT and seed brachytherapy, incidence of SMN is again likely to change in course of time (15, 16, 17).

Cervical Cancer: Patients with cervical cancer are at increased risk of SMN due to shared infectious aetiology (eg. cancer

vulva, anal canal and oropharynx) and treatment with RT & CT (eg. rectal, bladder cancers and pelvic sarcomas). In a large study of over 1 lakh patients of cervical cancer with long follow-up, the RR of SMN was 1.3. In last few years cisplatin based concurrent chemotherapy has become standard of care for locally advanced cervical cancer; however, its impact on SMN remains to be seen (18).

Leukemias: The term secondary leukemia indicates both acute myeloid leukemia (AML) evolving from previous myelodysplasia (MDS) and acute leukemia developing after exposure to environmental or therapeutic toxins or radiation (therapy-related). Secondary leukemias account for 10-30% of all AML. The majority of secondary leukemias resulting from the use of cytotoxic drugs can be divided into two well defined groups depending on whether the patient has received 1) alkylating agents or 2) drugs binding to the enzyme DNA-topoisomerase II. Alkylating agents related leukemias are very similar to post MDS leukemias being characterized frequently by a preleukemic phase, trilineage dysplasia, frequent cytogenetic abnormalities involving chromosomes 5 and 7 and a poor prognosis. Secondary leukemias related to therapy with topoisomerase II inhibitors are not preceded by a preleukemic phase and show frequently balanced translocations involving chromosome 11q23. Therapy related leukemias are a major problem in patients treated for Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, polycythemia, breast cancer, ovarian carcinoma, or testicular carcinoma.

Retinoblastoma: Overall risk of any second malignancies amongst hereditary retinoblastoma survivors is reported to be 20 times higher than the general population. Risk of second malignancies amongst survivors of hereditary retinoblastoma patients treated with combination of radiotherapy and chemotherapy is reported to be higher than hereditary retinoblastoma patients treated otherwise.

Conclusion:

Incidence of SMN is increasing with improved cancer survival, better awareness, and closer surveillance and rigorous follow-up. Contrary to popular belief all SMN cannot be attributed to radiation therapy, rather aetiology of SMN is a complex interaction of various host and treatment related factors. Still the risk of malignancy development following irradiation is low and should be weighed against the risks of death and carcinogenicity from other factors, toxicity of chemotherapy, morbidity and mortality of surgery, and existing alternatives to radiotherapy in the treatment of cancer patients. Potential carcinogenicity should not be regarded as a contraindication to the use of radiotherapy. With the increasing incidence of SMN, there is a need for population-based registries to document, analyse, and interpret the data pertaining to these SMN. Risk of SMN is not equal among all cancer patients. There is need to develop methods to identify patients at high risk of SMN based on molecular and genetic factors. These high-risk subgroups should be counselled about the risk of SMN, regarding life-style modification (eg. smoking cessation, high-fibre & low-fat diet, regular physical exercise etc.) and close long-term follow up. The options of early and frequent screening and chemoprevention strategies also need to be evaluated appropriately.

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18. Chaturvedi AK, Engels EA, Gilbert ES, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. *J Natl Cancer Inst* 2007;99:1634-43

Suggested Reading:

1. Goldsby R, Burke C, Nagarajan R, et al: Second solid malignancies among children, adolescents, and young adults diagnosed with malignant bone tumors after 1976: follow-up of a Children's Oncology Group cohort

   Cancer 2008;113((9):2597-2604

BACKGROUND: The growing number of individuals surviving childhood cancer has increased the awareness of adverse long-term sequelae. One of the most worrisome complications after cancer therapy is the development of second malignant neoplasms (SMNs).

METHODS: The authors describe the incidence of solid organ SMN in survivors of pediatric malignant bone tumors who were treated on legacy Children's Cancer Group/Pediatric Oncology Group protocols from 1976 to 2005. This retrospective cohort study included 2842 patients: 1686 who were treated for osteosarcoma (OS) and 1156 who were treated for Ewing sarcoma (ES).

RESULTS: The cohort included 56% boys/young men and 44% girls/young women, and the median age at primary diagnosis was 13 years. The median length of follow-up was 6.1 years (range, 0-20.9 years). In this analysis, 64% of patients were alive. Seventeen patients with solid organ SMN were identified. The standardized incidence ratio was 2.9 (95% confidence interval [CI], 1.4-5.4) for patients who were treated for OS and 5.0 (95% CI, 2.6-9.4) for patients who were treated for ES. The median time from diagnosis to development of solid SMN was 7 years (range, 1-13 years). The 10-year cumulative incidence of solid organ SMN for the entire cohort was 1.4% (95%CI 0.6%-2%).

CONCLUSIONS: The magnitude of risk of solid SMNs was modest after treatment for malignant bone tumors. However,

radiation-related solid SMNs will increase with longer follow-up. Because nearly 33% of patients die from their disease, recurrence remains the most significant problem. The development of improved therapies with fewer long-term consequences is paramount. Follow-up should focus on monitoring for both recurrence of primary malignancies and development of SMNs.

2. Constine LS, Tarbell N, Hudson MM, et al: Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose

   Int J Radiat Oncol Biol Phys 2008;72(1):24-33

PURPOSE: Subsequent malignant neoplasms (SMNs) are a dominant cause of morbidity and mortality in children treated for Hodgkin's disease (HD). We evaluated select demographic and therapeutic factors associated with SMNs, specifically gender and radiation dose.

METHODS AND MATERIALS: A total of 930 children treated for HD at five institutions between 1960 and 1990 were studied. Mean age at diagnosis was 13.6 years, and mean follow-up was 16.8 years (maximum, 39.4 years). Treatment included radiation alone (43%), chemotherapy alone (9%), or both (48%).

RESULTS: We found that SMNs occurred in 102 (11%) patients, with a 25-year actuarial rate of 19%. With 15,154 patient years of follow-up, only 7.18 cancers were expected (standardized incidence ratio [SIR] = 14.2; absolute excess risk [AER] = 63 cases/10,000 years). The SIR for female subjects, 19.93, was significantly greater than for males, 8.41 ($p < 0.0001$). After excluding breast cancer, the SIR for female patients was 15.4, still significantly greater than for male patients ($p = 0.0012$). Increasing radiation dose was associated with an increasing SIR ($p = 0.0085$). On univariate analysis, an increased risk was associated with female gender, increasing

radiation dose, and age at treatment (12-16 years). Using logistic regression, mantle radiation dose increased risk, and this was 2.5-fold for female patients treated with more than 35 Gy primarily because of breast cancer. CONCLUSIONS: Survivors of childhood HD are at risk for SMNs, and this risk is greater for female individuals even after accounting for breast cancer. Although SMNs occur in the absence of radiation therapy, the risk increases with RT dose.

3. Rusthoven K, Chen C, Raben D, et al: Use of external beam radiotherapy is associated with reduced incidence of second primary head and neck cancer: a SEER database analysis

   Int J Radiat Oncol Biol Phys 2008;71(1):192-198

PURPOSE: Patients with head and neck cancer have a significant risk of developing a second primary cancer of the head and neck. We hypothesized that treatment with external beam radiotherapy (RT) might reduce this risk, because RT can eradicate occult foci of second head and neck cancer (HNCA).

METHODS AND MATERIALS: The data of patients with Surveillance, Epidemiology, and End Results Historic Stage A localized squamous cell carcinoma of the oral cavity, larynx, and pharynx were queried using the Surveillance, Epidemiology, and End Results database. For patients treated with or without RT, the incidence of second HNCA was determined and compared using the log-rank method. Cox proportional hazards analysis was performed for each site, evaluating the influence of covariates on the risk of second HNCA.

RESULTS: Between 1973 and 1997, 27,985 patients were entered with localized HNCA. Of these patients, 44% had received RT and 56% had not. The 15-year incidence of second HNCA was 7.7% with RT vs. 10.5% without RT (hazard ratio

0.71, p <0.0001). The effect of RT was more profound in patients diagnosed between 1988 and 1997 (hazard ratio 0.53, p <0.0001) and those with pharynx primaries (hazard ratio 0.47, p <0.0001). On multivariate analysis, RT was associated with a reduced risk of second HNCA for pharynx (p <0.0001) and larynx (p = 0.04) tumors. For oral cavity primaries, RT was associated with an increased risk of second HNCA in patients treated before 1988 (p <0.001), but had no influence on patients treated between 1988 and 1997 (p = 0.91).

CONCLUSION: For localized HNCA, RT is associated with a reduced incidence of second HNCA. These observations are consistent with the eradication of microscopic foci of second HNCA with external beam RT.

4. Nguyen F, Rubino C, Guerin S, et al: Risk of a second malignant neoplasm after cancer in childhood treated with radiotherapy: correlation with the integral dose restricted to the irradiated fields

   Int J Radiat Oncol Biol Phys 2008;70(3):908-15

PURPOSE: After successful treatment of cancers in childhood, the occurrence of second malignant neoplasm (SMN) came to the fore. Few studies have considered the relationship between the radiation dose received and the risk of developing an SMN. To take into account the heterogeneity of the dose distribution so as to evaluate the overall risk of an SMN after a childhood cancer, we therefore focused on the integral dose restricted to the irradiated fields.

METHODS AND MATERIALS: The study was performed in a cohort of 4,401 patients who were 3-year survivors of all types of childhood cancer treated between 1947 and 1986 in France and Great Britain. For each patient, the integral dose was estimated for the volume inside the beam edges.

RESULTS: We found a significant dose-response relationship between the overall risk of an SMN and the estimated integral

dose. The excess relative risk for each incremental unit of the integral dose was only 0.008 in a linear model and 0.017 when a negative exponential term was considered, when adjusted for chemotherapy. The risk of SMN occurrence was 2.6 times higher in the case of irradiation. However among patients who had received radiotherapy, only those who had received the highest integral dose actually had a higher risk.

CONCLUSIONS: The integral dose in our study cannot be considered as a good predictor of later risks. However other studies with the same study design are obviously needed to evaluate the use of the integral dose as a tool for decision making concerning different radiotherapy techniques.

5. Maule M, Scélo G, Pastore G, Risk of second malignant neoplasms after childhood central nervous system malignant tumours: an international study

   Eur J Cancer 2008;44(6):830-9

PURPOSE: The aim of this study was to assess the risk of second malignant neoplasms (SMNs) other than central nervous system (CNS) neoplasms after childhood CNS cancer in an international multicentre study.

METHODS: Individual data on cases of CNS cancer in children (0-14 years) and on subsequent SMNs were obtained from 13 population-based cancer registries contributing data for different time periods in 1943-2000. Standardised incidence ratios (SIRs) with 95% confidence intervals (CI), absolute excess risk and cumulative incidence of SMNs were computed.

RESULTS: We observed 43 SMNs in 8431 CNS cancer survivors. The SIR was 10.6 (4.85-20.1) for thyroid cancer (nine cases), 2.75 (1.01-5.99). for leukaemia (six cases) and 2.47 (0.90-5.37) for lymphoma (six cases). The SIRs were highest in the first 10 years after CNS cancer diagnosis. The cumulative incidence of non-CNS SMNs was 3.30% (0.95-

5.65%) within 45 years after a CNS cancer diagnosis. Within 15 years, the cumulative incidence was highest for cases diagnosed after 1980 (0.56%, 95% CI: 0.29-0.82%).

CONCLUSION: This population-based study indicates that about one every 180 survivors of a childhood CNS cancer will develop a non-CNS SMN within the following 15 years. The excess is higher after glioma and embryonal malignant tumour than after another CNS tumour.

Radiation Induced Cardiac & Pulmonary Complications

Cardiac Complications

Pumping action of the heart is due to synchronized contraction of the myocytes which is the basic unit of cardiac musculature. Sinus node initiates electrical stimulus (action potential) which propagates through atrioventricular node and HIS-purkinje system to ventricular myocytes which causes contraction. The release of calcium from sarcoplasmic reticulum into the sarcoplasm which in turn catalyze the cross bridging of the actin and myosin filaments producing myocyte contraction. Cross bridging can only occur if the filaments are in their normal, relaxed state. If the myocytes are already stretched as in anthracycline-induced cardiomyopathy, then such cross bridging is impaired. Moreover, the myocytes must return to their resting state to respond to the action potential for the next contraction.

The myocardial blood supply is a critical system. Rich capillary network of the heart muscle is an important target because of inherent sensitivity of the endothelial cells, which essentially constitute the vessel wall. The endothelial lining of muscular arteries (epicardial and subepicardial) are also vulnerable to

radiation damage though supporting vasculature prevents severe early injury in these arteries, delayed lesions may result from damage and subsequent proliferation and migration of medial smooth myocytes. The epicardium and pericardium are lined by a single layer of mesothelial cells that form a closed sac. A strong collagen lamina external to the mesothelium forms a nondistensible wall. It is not clear whether blood capillaries, mesothelium or fibroblasts of pericardium, is the main target of radiation that leads to pericarditis with effusion.

Pathophysiological Aspects:

Radiation induced heart damage (RIHD) has been recognized as a complication of therapeutic irradiation since the sixties. Patients treated for Hodgkin and non-Hodgkin lymphoma and breast cancer have been the most carefully studied group. The pericardium is the most common site of RIHD. Patterns of injury range from pericardial effusions to acute fibrinous pericarditis to constrictive pericarditis. Both the parietal and visceral pericardium are at risk but the parietal layer is more commonly involved. It is normally less than 1 mm in thickness and is composed of a layer of collagenous connective tissue with variable amounts of adipose tissue, small blood vessels and lined by mesothelial cells. The pericardial sac is a closed or potential space containing up to 50 cc of straw-colored serous fluid. Pericardial effusions can develop with or without concomitant tamponade physiology. This will depend on the rate of development and accumulation of fluid. Stewart and Farjado report effusions with volumes as large as 700 cc but in the majority of cases the volumes are far less. Spontaneous resolution usually occurs in case of chronic or delayed onset effusions (i.e., following completion of irradiation) but can take up to 2 years to clear. As much as 20% of these patients progress to fibrous constrictive pericarditis.

Acute fibrinous pericarditis can present with classic signs and symptoms identical to other forms of acute pericarditis. Two temporal patterns have been observed, firstly early acute pericarditis occurring during treatment (likely caused by tumor lysis) and secondly, delayed onset acute pericarditis. Chronic fibrosing pericarditis with constrictive physiology can develop months, years, or decades following therapy. Unlike other forms of the disease, fibrous bands or adhesions between the parietal and visceral layers are uncommon. Instead, there is collagenous thickening of both layers, usually with a predominance of changes in the parietal pericardium. Thickening varies from 1 to 7 mm with disproportionate involvement of the anterior pericardial region. Microscopically, dense eosinophilic cicatricial collagen bands containing altered vessels are seen. The small arteries display fibrointimal proliferation and medial muscular hypertrophy.

Radiation damages the myocardium by injuring capillary endothelial cells, which causes the obstruction of the capillary lumen and the formation of fibrin and platelet thrombi. This process leads to ischemia and then to myocardial cell death and fibrosis. Damaged myocardium is characterized by non-specific, diffuse interstitial fibrosis, but it rarely encompasses the entire myocardium. The severity of fibrosis can differ markedly from one region to another. Another pattern is the cardiomyopathic type of RIHD. The morphological changes in this group include marked thickening of the endocardium by increased numbers of collagen and to a lesser extent elastin fibers.

The incidence of clinically significant radiation induced valvular disease is unknown. The microscopic findings of valvular tissues examined at the time of valve replacement or necropsy are nonspecific and include diffuse fibrosis with or

without calcification. Inflammation and other cellular components are absent. Left-sided valves are more commonly affected and show regurgitant changes. Valves are normally devoid of vascular structures in any of the three layers and the etiology is unlikely ischemic in origin. Accelerated changes caused by radiation to preexisting abnormalities or damage may be an important factor in the evolution of clinical valvular dysfunction and may be the high pressures in the left-sided chambers that cause persistent stress-related injury to damaged valves and chemotherapy have synergistic effect.

Conduction disturbances are classified as early and late in onset. Early electrical alterations are common but transient. Late conduction abnormalities occur months to years after treatment and include infranodal blocks, atrioventricular nodal bradycardia, and all types of heart block, including complete heart block.

The clinical presentation of coronary artery damage is similar to atherosclerotic coronary disease. The morphologic features in radiation-induced arteriosclerosis (RIAS) are similar to those seen in classic atherosclerotic coronary disease. Subtle differences include the increased proximal location often with involvement of the coronary ostia in RIAS. A variety of microscopic patterns are seen, including fibrous, fibrocalcific, and fibro fatty lesions with abundant cholesterol and lipid. Focal or multiple patchy foci of medial and adventitial fibrosis is suggestive of healed arteritis and favors a radiation etiology. Late alterations in the large elastic arteries such as the pulmonary arteries and aorta have not been thoroughly studied. Cases of acute rupture have been reported and most cases occur in the setting of other local complications such as infection or fistula formation. Fajardo and Lee reported two cases of de novo aortic rupture that demonstrated aortic adventitial necrosis or severe necrosis of the elastic layer.

Cardiac Morbidity & Mortality

Cardiovascular mortality contributes for approximately 10-15% of all causes of mortality. The various cardiac complications that have been observed after Hodgkin's disease treatment includes pericarditis, pancarditis, pericardial effusion, pericardial fibrosis, congestive heart failure, valvular defects, conduction defects, and coronary artery disease. The most common fatal cardiovascular complication has been acute myocardial infarction secondary to coronary artery disease.

Radiation related factors associated with Cardiac Toxicity:

Several types of damage were recognized, including pericardial, myocardial and vascular. The risk of acute radiation pericarditis and delayed constrictive pericarditis after irradiation for HD have been clearly associated with the volume of heart irradiated and the dose of radiation received. Stewart and Fajardo and Stewart et al. estimated that the threshold for significant pericardial injury is 40Gy if more than 60% of the heart is included in the radiation field and 15% if less than 15% of the cardiac volume is irradiated. Studies from the Stanford and University of California were the first ones to indicate a dose-response relationship for radiation pericarditis and myocardial injury. Also frequency of radiation related cardiac damage is related to the technique of irradiation employed. The original mantle field technique employed equally weighted anterior and posterior fields, high dose-rate pulmonary irradiation, and no subcarinal block. Pericarditis was diagnosed in 17.1% (43/251) of patients who received this treatment. The use of a "thin lung block" to decrease the dose rate to the lungs, and the addition of a subcarinal block to decrease the amount of pericardium treated to the full dose decreased the frequency of pericarditis to 2.5%. The frequency of pericarditis was 3.2% in a series of adult

patients treated using the original mantle field technique, with the treatment delivered over a longer period of time using smaller radiation fractions, and was 0% - 2.5% among pediatric patients treated using an equally weighted anterior-posterior mantle technique. The frequency of radiation related pericarditis was correlated with the total pericardial radiation dose.

Relationship between radiation pericarditis and whole pericardium RT dose

	Dose in cGy			
	<599	**600-1500**	**1501-3000**	**>3000**
Pericardial Irradiation (No. of patients)	198	42	123	14
Pericarditis	14(7.1%)	5(11.9%)	3(18.7%)	7(50%)
Pericarditis requiring treatment	3(1.5%)	4(9.5%)	8(6.5%)	5(35.7%)

The risk of pericarditis rose steeply above doses of 40Gy when subcarinal block was not used. It was clearly seen in these studies that the incidence of pericarditis was dependent on the volume of heart irradiated and the total dose of irradiation received. Among patients treated at Stanford, the risk of death from cardiac diseases other than acute myocardial infarction have reduced significantly after the use of subcarinal block and radiation doses of 30Gy or less.

Byhardt et al., confirmed the increased risk of pericardial damage associated with the use of an anteriorly weighted mantle field. Twenty-four of 83 patients (28.9%) who received this treatment developed radiographic evidence of a pericardial

effusion a mean of 150 days after the completion of thoracic irradiation. The frequency of pericarditis was correlated with the size of the mediastinal mass, but not with the radiation dose, suggesting that, within the dosage range examined, the amount of pericardium included within the radiation volume was the most critical variable.

The risk of premature coronary artery disease has varied with treatment technique, use of chemotherapy, age at treatment, and duration of observation. Hence it has been difficult to establish a clear relationship between radiation dose, volume of heart irradiated, and coronary-artery disease risk. Investigators at Princess Margaret Hospital found no significant increase in the risk of acute myocardial death in patients with stage I & II disease who received mantle field irradiation to a dose of 35Gy with fraction size of 1.8Gy. In another study Glanzmann et al. observed a very high risk of acute myocardial infarction or sudden death of 8.6 (CI, 4.5-15.3) in men who received approximately 40Gy in 1.5-1.8Gy per fraction but observed no excess risk among women who received similar treatment [RR 1.7(CI, 0.04-9.6)]. It was also observed that the excess risk was confined to those who had known risk factors for coronary artery disease, including smoking, diabetes, hypertension, obesity, or hypercholesterolemia [RR, 2.36 (CI, 1.42-3.68) with risk factors vs. 0.96 (CI, 0.20-2.77) with no known risk factors].

The relationship between radiation dose, cardiac volume and subsequent development of valvular heart disease has also been difficult to discern due to the relatively small number of events, prolonged latency period for the development of valvular heart disease, and evolving radiation techniques. Glanzmann et al. in a study reported the latency of valvular abnormality after mediastinal irradiation using echocardiographic studies in 144 patients. Twenty-nine percent had aortic or mitral valvular thickening apparent on echocardiography. The cumulative

incidence of valvular thickening at 10 years after irradiation was 8% and rose to 45% at 20 years with grade 3 changes in 4.1%. Patients who had echocardiograms 1-6 years after a baseline echocardiogram, 8% of patients with normal heart valves at initial study developed valvular thickening and 37% of those with abnormal valves showed progression of valvular abnormality.

Future Directions:

Currently available evidence suggests a strong relationship between "Volume of Normal Tissue Irradiated", "Total Radiation Dose", "Fraction Size of Radiation Dose", "Interaction with Chemotherapeutic Agents", and "Associated Co morbidities" as major factors influencing the development and severity of Cardiopulmonary complications associated with thoracic irradiation as in Lung cancer, Breast Cancer, Hodgkin's disease etc. Advanced radiation therapy technologies like, Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), Helical Tomotherapy etc. which primarily aim at reducing the dose to normal tissues while delivering the intended dose to the target volume would help reduce the radiation related adverse effects significantly. Optimal dose intensity and sequencing of various treatment modalities (Radiotherapy, Chemotherapy, & Surgery) would further reduce the incidence of acute and late adverse effects of treatment.

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Suggested Reading:

J Clin Oncol. 2007 Sep 1;25(25):3991-4008. Epub 2007 Jun 18.

American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects.

Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, Hagerty KL, Somerfield MR, Vaughn DJ; ASCO Cancer Survivorship Expert Panel.

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PURPOSE: To review the evidence on the incidence of long-term cardiac or pulmonary toxicity secondary to chemotherapy, radiotherapy, or trastuzumab in symptomatic and asymptomatic cancer survivors. METHODS: An American Society of Clinical Oncology Panel reviewed pertinent information from the literature through February 2006. RESULTS: Few studies directly addressing the benefits of screening for long-term cardiac or pulmonary toxicity in asymptomatic cancer survivors who received chemotherapy, radiotherapy, or trastuzumab were identified. The reviewed literature included primarily retrospective and cross-sectional studies describing the incidence of cardiac and pulmonary late effects. Anatomic and/or functional abnormalities have been associated with use of all currently available anthracyclines and their derivatives. Trastuzumab-related cardiac dysfunction rarely causes death, and in most cases is reversible with improvement in cardiac function on drug discontinuation and/or treatment with cardiac medications. The estimated aggregate incidence of radiation-induced cardiac disease is 10% to 30% by 5 to 10 years post-treatment, although the incidence may be lower with modern techniques. Radiation pneumonitis is reported in 5% to 15% of lung cancer patients receiving definitive external-beam radiation therapy. A minority of patients may develop progressive pulmonary fibrosis; late complications include cor pulmonale and respiratory failure. Bleomycin-induced pneumonitis is an acute rather than late effect of treatment. Late pulmonary complications in bone marrow or stem cell transplantation patients who develop interstitial pneumonitis include idiopathic pneumonia

syndrome and bronchiolitis obliterans. CONCLUSION: An increased incidence of cardiac and/or pulmonary dysfunction is observed in cancer survivors. Research is needed to identify high-risk patients, and to determine the optimal screening strategies and subsequent treatment.

Radiother Oncol. 1998 Jan;46(1):51-62.

Cardiac risk after mediastinal irradiation for Hodgkin's disease.

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PURPOSE: To evaluate the risk of cardiac lesions after conventionally fractionated irradiation (Rt) of the mediastine with or without chemotherapy (Ct) in patients with Hodgkin's disease (HD) and to relate them to known cardiovascular risk factors.

PATIENTS AND METHODS: Between 1964 and 1992, 352 (total group) patients with HD were treated with curative intention using Rt with or without Ct including the mediastine and had a follow-up of at least 1 year. More than 96% of the patients had a complete follow-up. One hundred forty-four patients (64% of the living patients, heart study group) have regular follow-up in our department and had a special heart examination including rest and exercise ECG, echocardiography and myocardial perfusion scintigraphy (112 patients). Doses per fraction in the anterior heart region were between 1.3 and 2.1 Gy. Total doses were between 30.0 and 42.0 Gy in 93% of cases. The mean length of follow-up was 11.2 years (range 1.0-31.5 years). Other cardiovascular risk factors evaluated were body mass index, blood pressure, smoking history, diabetes mellitus, hypercholesterolemia and history of coronary artery disease before Rt.

RESULTS: In the total group, the risk of fatal cardiac ischemic events and/or of sudden unexpected death was significantly higher than expected with a relative risk of 4.2 for myocardial infarction and 6.7 for myocardial infarction or sudden death. In female patients and in patients without other cardiovascular risk factors, the risk of fatal or non-fatal ischemic cardiac events was not significantly different from the expected value. In the subgroup with no cardiovascular risk factors and treatment without Ct, there was no ischemic or other major cardiac event. Echocardiography showed valvular thickenings in a large amount of the patients (the cumulative risk after 30-year follow-up was above 60%) but mostly without hemodynamic disturbance. In patients without hypertension and without coronary artery disease, findings of perfusion scintigraphy and echocardiographic evaluation of systolic and diastolic function were normal. Treatment with Ct was not a significant risk factor for cardiac events but the number of patients whose treatment included adriamycin and with a follow-up exceeding 10 years is to low for a definitive evaluation. CONCLUSIONS: In patients without the usual cardiovascular risk factors (smoking, hypertension, obesity, hypercholesterolemia, diabetes mellitus) the risk of serious cardiac lesions after conventionally fractionated irradiation of the mediastinum with an intermediate total dose between 30 and 40 Gy is low. Also the cardiac risk of the combination of this irradiation with Ct including adriamycin with a total dose between 200 and 300 mg/m2 seems low but further long-term observation is necessary.

Lancet Oncol. 2005 Aug;6(8):557-65

Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries.

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BACKGROUND: Radiotherapy for early breast cancer can decrease breast cancer mortality but increase other mortality, mainly from heart disease and lung cancer. The mean cardiac dose from irradiation of a left-sided breast cancer can be two or three times that for a right-sided breast cancer. The mean ipsilateral (ie, on the same side as the breast cancer) lung dose can also be two or three times the mean contralateral lung dose. Particularly during the 1970s, when typical heart and lung exposures were greater than now, the laterality of an irradiated breast cancer could measurably affect cardiac mortality and mortality from cancer of the right or the left lung decades later. This study aimed to assess the hazards in the general US population from routine cancer-registry and death-certificate data.

METHODS: We analysed data for 308 861 US women with early breast cancer of known laterality (left-sided or right-sided) who were registered in the US Surveillance Epidemiology and End Results (SEER) cancer registries during 1973-2001 and followed prospectively for cause-specific mortality until Jan 1, 2002.

FINDINGS: 115 165 (37%) received radiotherapy. Among those who did not, tumour laterality was of little relevance to subsequent mortality. For women diagnosed during 1973-82 and irradiated, the cardiac mortality ratio (left versus right tumour laterality) was 1.20 (95% CI 1.04-1.38) less than 10 years afterwards, 1.42 (1.11-1.82) 10-14 years afterwards, and 1.58 (1.29-1.95) after 15 years or more (trend: 2p=0.03). For women diagnosed during 1983-92 and irradiated, the cardiac mortality ratio was 1.04 (0.91-1.18) less than 10 years afterwards and 1.27 (0.99-1.63) 10 or more years afterwards.

For women diagnosed during 1993-2001 and irradiated the cardiac mortality ratio was 0.96 (0.82-1.12), with none yet followed for 10 years. Among women irradiated for breast cancer who subsequently developed an ipsilateral or contralateral lung cancer, the lung cancer mortality ratio (ipsilateral versus contralateral) for women diagnosed during 1973-82 and irradiated was 1.17 (0.62-2.19), 2.00 (1.00-4.00), and 2.71 (1.65-4.48), respectively, less than 10 years, 10-14 years, and 15 or more years afterwards (trend: 2p=0.04). For women irradiated after 1982 there is, as yet, little information on lung cancer risks more than 10 years afterwards.

INTERPRETATION: US breast cancer radiotherapy regimens of the 1970s and early 1980s appreciably increased mortality from heart disease and lung cancer 10-20 years afterwards with, as yet, little direct evidence on the hazards after more than 20 years. Since the early 1980s, improvements in radiotherapy planning should have reduced such risks, but the long-term hazards in the general populations of various countries still need to be monitored directly.

Lancet. 2005 Dec 17;366(9503):2087-106.

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.

Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y; Early Breast Cancer Trialists' Collaborative Group (EBCTCG).
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BACKGROUND: In early breast cancer, variations in local treatment that substantially affect the risk of locoregional recurrence could also affect long-term breast cancer mortality. To examine this relationship, collaborative meta-analyses were

undertaken, based on individual patient data, of the relevant randomised trials that began by 1995.

METHODS: Information was available on 42,000 women in 78 randomised treatment comparisons (radiotherapy vs no radiotherapy, 23,500; more vs less surgery, 9300; more surgery vs radiotherapy, 9300). 24 types of local treatment comparison were identified. To help relate the effect on local (ie, locoregional) recurrence to that on breast cancer mortality, these were grouped according to whether or not the 5-year local recurrence risk exceeded 10% (<10%, 17,000 women; >10%, 25,000 women).

FINDINGS: About three-quarters of the eventual local recurrence risk occurred during the first 5 years. In the comparisons that involved little (<10%) difference in 5-year local recurrence risk there was little difference in 15-year breast cancer mortality. Among the 25,000 women in the comparisons that involved substantial (>10%) differences, however, 5-year local recurrence risks were 7% active versus 26% control (absolute reduction 19%), and 15-year breast cancer mortality risks were 44.6% versus 49.5% (absolute reduction 5.0%, SE 0.8, 2p<0.00001). These 25,000 women included 7300 with breast-conserving surgery (BCS) in trials of radiotherapy (generally just to the conserved breast), with 5-year local recurrence risks (mainly in the conserved breast, as most had axillary clearance and node-negative disease) 7% versus 26% (reduction 19%), and 15-year breast cancer mortality risks 30.5% versus 35.9% (reduction 5.4%, SE 1.7, 2p=0.0002; overall mortality reduction 5.3%, SE 1.8, 2p=0.005). They also included 8500 with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy (generally to the chest wall and regional lymph nodes), with similar absolute gains from radiotherapy; 5-year local recurrence risks (mainly at these sites) 6% versus 23% (reduction 17%), and 15-year breast cancer mortality risks 54.7% versus 60.1% (reduction

5.4%, SE 1.3, 2p=0.0002; overall mortality reduction 4.4%, SE 1.2, 2p=0.0009). Radiotherapy produced similar proportional reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy), so large absolute reductions in local recurrence were seen only if the control risk was large. To help assess the life-threatening side-effects of radiotherapy, the trials of radiotherapy versus not were combined with those of radiotherapy versus more surgery. There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer (rate ratio 1.18, SE 0.06, 2p=0.002) and a significant excess of non-breast-cancer mortality in irradiated women (rate ratio 1.12, SE 0.04, 2p=0.001). Both were slight during the first 5 years, but continued after year 15. The excess mortality was mainly from heart disease (rate ratio 1.27, SE 0.07, 2p=0.0001) and lung cancer (rate ratio 1.78, SE 0.22, 2p=0.0004). INTERPRETATION: In these trials, avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (eg, the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality. Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.

Pulmonary Complications

Radiation therapy (RT) is an important treatment modality for thoracic and breast malignancies. Incidental irradiation of the normal lungs is unavoidable and often dose-limiting. Toxicity of the respiratory system is a common side effect that can result in significant morbidity.

Pathophysiological Aspects:

The functional unit of the lung is the pulmonary lobule. It lies entirely within the lung parenchyma and consists of the terminal bronchiole and that segment of the respiratory parenchyma that it serves. Reactive oxygen species generated by radiation are toxic to parenchymal cells. The most radiosensitive subunit of the lung is the alveolar/capillary complex and injury to this causes diffuse alveolar damage. This initiates a cascade of molecular events, creating a self-sustaining cycle of inflammation and chronic oxidative stress. The culminating event is replacement of normal lung parenchyma by fibrotic tissue. The range of respiratory compromise can extend from acute lethal events to varied degrees of chronic pulmonary decompensation which manifest at years after the initial cancer therapy. When the entire lung is irradiated with a single large fraction as in total body irradiation, there is a steep dose–response relationship starting at 8.2 Gy. Conversely, treatment with multiple daily fractions to a whole lung dose of 17.5 Gy appears to be well tolerated.

Factors influencing pulmonary toxicity

Patient Related Factors	Treatment Related factors
Performance status	Volume of lung irradiated, and the
History of smoking	Dose received by the lung
Chronic Obstructive Pulmonary Disease	Percentage of total normal lung volume exceeding the dose of 20Gy
Pulmonary function tests (FEV1, DCLO)	Mean lung dose
Tumour site	Fractionation of radiotherapy Use of chemotherapy

Pneumonitis

The clinical syndrome of pneumonitis usually occurs l-3 months after completion of radiation or drug therapy. Symptomatic pneumonitis occurs in approximately 5- 15% of patients irradiated for mediastinal lymphoma, lung, or breast cancer.

Clinical features: Clinical features depend on the degree of pulmonary involvement. There may be lowgrade fever, nonspecific respiratory symptoms such as congestion, cough, and fullness in the chest. Severe cases could manifest with dyspnea, pleuritic chest pain, cough or blood stained sputum. Generally after the transient acute phase, there is the intermediate phase which can progress to the eventual fibrotic phase.

Diagnostic modalities: The chest x-ray (CXR) may reveal a diffuse infiltrate corresponding to the radiation field. This appears as a result of an acute exudative edema that is initially faint and may become prominent later. Computed tomography scans are more sensitive and detect abnormalities in > 50% of patients. Ventilation/perfusion scans are very frequently abnormal following thoracic irradiation. Perfusion defects are seen more commonly than ventilation defects and approximately correspond to the irradiated volume. Using planar images, perfusion and ventilation abnormalities are seen in 53-95% and 35-45% of irradiated patients, respectively.

Pulmonary Fibrosis

In contrast to the acute reaction, chronic effects of cytotoxic therapy are observed from months to years following treatment. Pulmonary fibrosis develops insidiously in the previously irradiated field, and stabilizes after 1 or 2 years.

Symptoms: Symptoms related to pulmonary fibrosis are proportional to the extent of the lung parenchyma involved and the patients' preexisting pulmonary reserves. Most patients with radiation fibrosis are asymptomatic. Advanced cases may manifest with chronic respiratory failure, dyspnea on effort, reduced exercise tolerance, orthopnea, cyanosis and finger clubbing. Symptoms are generally minimal if fibrosis is limited to less than 50% of one lung.

Diagnostic modalities: Radiologic changes consistent with fibrosis are seen in most patients who have received lung irradiation even if they did not develop acute pneumonitis. Whether there is always an acute phase that precedes lung fibrosis is still unknown, though most authors believe this is likely the case. Chest x-rays have the appearance of linear streaking, radiating from the area of previous pneumonitis. which may extend outside the irradiated region. There may be concomitant regional contraction, pleural thickening, and tenting of the diaphragm. There may also be resultant compensatory hyperinflation of adjacent or contralateral lung tissue. Findings of pulmonary fibrosis are usually seen 12 months to 2 years after radiation. Computerized tomography is currently favored to image diagnosis. Eventually, the previously irradiated lung can develop dense fibrotic nodules, especially in the area of previous tumor. Fibrosis usually results in mild deterioration in pulmonary function. This may result in decreased maximum inspiratory volume and tidal volume usually with mild to moderate increase in respiratory rate. In case of small volume involvement, pulmonary function tests do not demonstrate significant change, owing to the functional compensation of adjacent lung regions. Hence, diffusion capacity may be the best assessment of whole organ function because it is least likely to be effected by compensatory changes in unirradiated portions of the lung.

Measurable end points of Pulmonary toxicity

Clinical	Radiological	Pulmonary function tests	Nuclear Medicine tests	Newer biochemical tests
Symptoms (cough, fever , dyspnoea)	CXR CT/HRT (Total aerated lung volume,	VC FEV1 FEV1/FVC%	VP scan Gallium scan Tc ^{99}DTPA aerosol	TGF b(S) Surfactant (S) Surfactant (BAL)
Signs (Respiratory Rate, ronchi or wheeze, cyanosis)	total opacified volume)	DLCO%		Cytokines (BAL) ACE (BAL) PG I2 (BAL) GAG (BAL) Laminin (BAL) Fibronectin (BAL)

CXR= Chest X Ray, CT= Computed Tomograpy HRCT= High resolution CT, DLCO%= Carbon monoxide diffution capacity, FEV1 (Forced expiratory volume in 1 second) , VP= Ventilation Perfusion, (S)= serum, (BAL)= Broncho alveolar lavage

Prevention of Pneumonitis and Lung fibrosis

Ideally, pulmonary toxicity should be prevented. While administering radiotherapy, the normal lung volumes and doses should be minimized and given in accordance to accepted tolerance. In case of any concomitant drug therapy monitoring of symptoms/signs, pulmonary function tests, and chest x-rays can aid detecting problems early and the causative agent can be withdrawn.

The omission of Elective nodal irradiation (ENI) considerably reduces V20. It has been seen that the shape of the planning target volume (PTV) in the transverse plane (expressed as an elliptical index) affects the conformity of the V20 isodose to the PTV..

Fluorodeoxyglucose-positron emission tomography (FDGPET)/ CT is a functional nuclear medicine study that has been shown to be more accurate than CT in determining the extent of NSCLC. Preliminary studies have shown that co-registered PET/CT alters GTV delineation in about 50% of NSCLC patients compared with targeting using CT alone. PET is especially useful in differentiating disease from atelectasis, something often difficult to discern in a conventional CT scan. This in turn leads to reduction in target volumes and consequent sparing of more normal lung.

Four dimensional (4D) imaging is becoming increasingly utilized for treatment planning in radiotherapy (RT). Generally, 4DCT information is used to (1) determine the tumor margin to account for the extent of tumor motion on patient specific basis or to (2) choose a gating phase and window for respiratory-gated RT (gated-RT) treatment planning. 4D-CT derived patient-specific margins have been shown to lead to a reduction of the tumor margin in RT plan, which in turn significantly reduces the ipsilateral lung toxicity. Gated-RT plans lead to significant reductions of V20, V40, and Normal tissue complication probability (NTCP). (J Antony, abstract)

Useful radiation therapy planning parameters for identifying at risk cases

In conventional fractionation, various studies have implicated percent of the total lung volume exceeding 20 Gy (*V*20), the effective volume (*V*eff) and the total lung volume mean dose, and location of the tumor primary (upper versus lower lobes) to be statistically significant relative to the development of > Grade 2 pneumonitis. (graham) Continuous hyperfractionated accelerated radiotherapy (CHART) involves giving 3 fractions of small dose per fraction per day for 12 days.(Peter Jenkins). In relation to acute radiation pneumonitis, CHART has been shown to have a superior therapeutic index than conventionally fractionated radiotherapy. V20 and mean lung dose are useful factors for predicting the risk of pulmonary complications in CHART therapy.

Management of Pneumonitis and Lung fibrosis

Corticosteroids form the mainstay in recovery from pneumonitis caused by varied etiological agents. In general the treatment for pneumonits is a dose of 30-60 mg of prednisone per day for 2-3 weeks with subsequent tapering. Superadded infection should be treated by antibiotics, oxygen may be required in severe cases along with other supportive measures. Smoking should be strictly avoided. There should be awareness about the risks of general anaesthesia in such patients.

Future directions

Our understanding of the molecular mechanisms underlying radiation lung injury continues to evolve. Predicting which patients will suffer from this complication is a challenge at present. Ideally, individual phenotype- and genotype-based risk profiles should be able to identify patients who are sensitive to RP. The predictive power of biomarkers might be increased if they are coupled with radiogenomics, e.g.,

genotyping analysis of single nucleotide polymorphisms in transforming growth factor beta1, transforming growth factor beta1 pathway genes, and other cytokines. Genetic variability and the complexity of RP and its underlying molecular mechanisms make identification of biological risk predictors challenging. Further research is needed to develop more effective risk predictors of RP. Understanding new molecular mechanisms such as those involving cytokine release in the initiation of the fibrosis process provide new opportunities for prevention and treatment. Appropriate agents such as certain interferons that inhibit fibrosis-promoting growth factors hold potential to be used during therapy, resulting in enhanced therapeutic ratio.

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Suggested Reading:

Br J Cancer. 2008 Jun 3;98(11):1870-5. Epub 2008 May 27. Links

Incidence of interstitial pneumonitis among breast cancer patients: a 10-year Danish population-based cohort study.

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Chemotherapy and radiation therapy may increase risk for interstitial pneumonitis (IP) in breast cancer patients, but there are little current population-based data on IP incidence in these patients. We assessed population-based incidence rates (IRs) of IP among Danish breast cancer patients and compared these with IRs for the Danish general population. Through the Danish Cancer Registry, we identified all Danish breast cancer patients (n=35 823) diagnosed between 1994 and 2004. Treatment data were obtained from the Danish Breast Cancer Cooperation Group database, and data on IP, from the Danish National

Registry of Patients. We computed IRs of IP among breast cancer patients and age-standardised incidence rate ratios (SIRs) comparing breast cancer patients with the general population. During follow-up, 28 breast cancer patients were registered with an IP diagnosis (IR=17.3 per 100,000 person-years (p-y) (95% confidence intervals (95% CI): 11.7-24.6)). When follow-up was restricted to 1 year after the first breast cancer diagnosis, eight patients with IP were identified (IR=23.4 per 100,000 p-y (95% CI: 11.0-44.1)). The SIR comparing breast cancer patients with the general population was 8.4 (95% CI: 5.7-11.9). Thus, although IP is a rare adverse event among breast cancer patients, its risk is substantially higher than that in the general population.

J Thorac Oncol. 2007 Sep;2(9):864-74.

Predicting risk of radiation-induced lung injury.

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Radiation-induced lung injury (RILI) is the most common, dose-limiting complication of thoracic radio- and radiochemotherapy. Unfortunately, predicting which patients will suffer from this complication is extremely difficult. Ideally, individual phenotype- and genotype-based risk profiles should be able to identify patients who are resistant to RILI and who could benefit from dose escalation in chemoradiotherapy. This could result in better local control and overall survival. We review the risk predictors that are currently in clinical use—dosimetric parameters of radiotherapy such as normal tissue complication probability, mean lung dose, V20 and V30—as well as biomarkers that might individualize risk profiles. These biomarkers comprise a variety of proinflammatory and

profibrotic cytokines and molecules including transforming growth factor beta1 that are implicated in development and persistence of RILI. Dosimetric parameters of radiotherapy show a low negative predictive value of 60% to 80%. Depending on the studied molecule, negative predictive value of biomarkers is approximately 50%. The predictive power of biomarkers might be increased if they are coupled with radiogenomics, e.g., genotyping analysis of single nucleotide polymorphisms in transforming growth factor beta1, transforming growth factor beta1 pathway genes, and other cytokines. Genetic variability and the complexity of RILI and its underlying molecular mechanisms make identification of biological risk predictors challenging. Further investigations are needed to develop more effective risk predictors of RILI.

Int J Radiat Oncol Biol Phys. 2003 Jun 1;56(2): 360-6.

Radiation pneumonitis following treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART).

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PURPOSE: To determine whether partial volume lung irradiation influences the risk of developing acute radiation pneumonitis after the treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART).

METHODS AND MATERIALS: We conducted an analysis of 32 patients treated with CHART at the Gloucestershire Oncology Center. Twelve patients were treated using conventional two-dimensional treatment techniques and

received elective nodal irradiation (ENI). Their treatment plans were subsequently recapitulated using a three-dimensional treatment planning system. Twenty patients were planned using this system from the outset. For these patients, elective nodal irradiation was omitted. Dose-volume histograms (DVH) were constructed and several parameters analyzed for their ability to predict for the development of pneumonitis. RESULTS: Univariate analysis revealed that the percentage lung volume receiving more than 20 Gy (V20) and the mean lung dose are of predictive value for the development of pneumonitis after CHART. There is a strong correlation between these two parameters. Importantly, partial volume lung irradiation using CHART appears to be better tolerated than conventionally fractionated radiotherapy. The omission of ENI considerably reduces V20. Using a commonly employed 3-beam technique it was also noted that the shape of the planning target volume (PTV) in the transverse plane (expressed as an elliptical index) affects the conformity of the V20 isodose to the PTV. This influences the scope for dose escalation with irregularly shaped tumors.

CONCLUSIONS: In relation to acute radiation pneumonitis, CHART appears to have a superior therapeutic index than conventionally fractionated radiotherapy. V20 and mean lung dose are useful factors for predicting the risk of this complication. The use of these parameters will aid the selection of optimal treatment plans and provides a basis for future dose escalation studies.

Int J Radiat Oncol Biol Phys. 1999 Sep 1;45(2): 323-9.

Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC).

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PURPOSE: To identify a clinically relevant and available parameter upon which to identify non-small cell lung cancer (NSCLC) patients at risk for pneumonitis when treated with three-dimensional (3D) radiation therapy. METHODS AND

MATERIALS: Between January 1991 and October 1995, 99 patients were treated definitively for inoperable NSCLC. Patients were selected for good performance status (96%) and absence of weight loss (82%). All patients had full 3D treatment planning (including total lung dose-volume histograms [DVHs]) prior to treatment delivery. The total lung DVH parameters were compared with the incidence and grade of pneumonitis after treatment.

RESULTS: Univariate analysis revealed the percent of the total lung volume exceeding 20 Gy (V20), the effective volume (Veff) and the total lung volume mean dose, and location of the tumor primary (upper versus lower lobes) to be statistically significant relative to the development of > or = Grade 2 pneumonitis. Multivariate analysis revealed the V20 to be the single independent predictor of pneumonitis.

CONCLUSIONS: The V20 from the total lung DVH is a useful parameter easily obtained from most 3D treatment planning systems. The V20 may be useful in comparing competing treatment plans to evaluate the risk of pneumonitis for our individual patient treatment and may also be a useful parameter upon which to stratify patients or prospective dose escalation trials.

Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1187-203.

Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems.

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Toxicity of the respiratory system is a common side effect and complication of anticancer therapy that can result in significant morbidity. The range of respiratory compromise can extend from acute lethal events to degrees of chronic pulmonary decompensation, manifesting years after the initial cancer therapy. This review examines the anatomic-histologic background of the lung and the normal functional anatomic unit. The pathophysiology of radiation and chemotherapy induced lung injury is discussed as well as the associated clinical syndromes. Radiation tolerance doses and volumes are assessed in addition to chemotherapy tolerance and risk factors and radiation-chemotherapy interactions. There are a variety of measurable endpoints for detection and screening. Because of the wide range of available quantitative tests, it would seem that the measurement of impaired lung function is possible. The development of staging systems for acute and late toxicity is discussed and a new staging system for Late Effects in Normal Tissues (LENT) is proposed.

Radiation Myelopathy

Introduction:

Spinal Cord is a very eloquent part of CNS. The densely packed tracts, the complex neuronal networks and the vascular supply make it a very sensitive structure to not only surgical interventions but to Radiation Therapy. All the more, it spans a long course in the body and thus is an important dose limiting organ in the treatment of tumors of head and neck, lung, mediastinum, Hodgkin's disease and the primary and metastatic tumors of the cord itself.

Etiopathogenesis:

The knowledge about pathogenesis is evolving with few autopsy studies and numerous animal studies. The cells involved are almost all the cells seen in spinal cord, i.e. Oligodendrocytes, Microglia, Vascular endothelial cells and Neurons. Ionizing radiations lead to early and late orchestra of events involving altered gene expressions and cytokine mediated auto- and paracrine effects, vasculopathies, loss of oligodendrocyte precursor cell population and microgliosis.[1]

There is not much evidence of acute radiation injury to the spinal cord *during* therapeutic radiation and any neurodefecit

worsening during the treatment should be carefully evaluated for acute vascular, mechanical events or tumor progression.[2]

Radiation injury to the spine is a very rare clinical complication. Before making a diagnosis of radiation myelopathy, three crucial points should be kept in mind[3]

1. Rule out other common causes as tumor progression or spinal metastasis.
2. Check that symptoms have rational pattern, for e.g. only pain is never the symptom but typical sensory motor deficits at and below the anatomical site of irradiated cord are.
3. Third, the dose and time to expression of injury must be consistent with a spinal cord radiation injury. For sensory motor deficits as seen in delayed radiation myelopathy, a latency of less than 6 months is rare, and patients who received cord doses of less than 50 Gy are not generally at risk for radiation myelopathy.

It may manifests either as an early-delayed, transient, essentially reversible adverse event known as 'Transient Radiation Myelopathy' or a late and irreversible serious event known as 'Delayed Radiation Myelopathy'. Both the events can be more systematically understood using the *Late Effects of Normal Tissues* (LENT) paradigm.[4]

Transient Radiation Myelopathy:

Clinical detection : The clinical pattern, first described in 1964 by Jones[5] , is generally limited to Lhermitte's sign, characterized by brief unpleasant sensations of numbness, tingling, and/or often electric-like feelings going down from the neck to the spine and to the extremities and triggered by the flexion of the neck. The clinical entity was characterized by Lhermitte in conjunction with injuries and multiple sclerosis.[6] He noted that the symptomatology was most

probably secondary to damage to the cervical spinal cord resulting in demyelination. The clinical latency period corresponded to the normal survival of the myelin, since damaged oligodendrocytes are not capable of carrying out myelin synthesis. As the oligodendrocytes recover, myelin synthesis is resumed and the resolved disease does not return.

Time Course of Events: This may present after 1 to 6 months of radiation therapy and in almost all the patients uneventfully subsides in next 2 to 6 months.

Dose/Time/Volume: In series of head and neck patients, Fein DA et al.[7] found that a global incidence of 3.6% (40 cases out of a group of 1112 patients receiving 30 Gy or more). The dose incidence relationship is listed in the table. The risk was also increased with a fraction size over 2 Gy.

Dose (Gy)	**Incidence (%)**
30 to 39.9	2
40 to 44.9	4
45 to 49.9	3
50 or more	8

Chemical/Biologic Modifiers: Concomitant use of intrathecal and intravenous chemotherapeutic agents known to be associated with neurotoxicity include methotrexate, cisplatin, cytarabine, and others. However, the contribution of the intrathecal component is unclear.[1]

Radiological Imaging: No definite CT or MRI findings may be seen. Imaging thus may be only done to rule out other causes if suspected.

Laboratory Tests: Myelin basic protein may be released into the cerebrospinal fluid. However it is essentially a clinical diagnosis.

Differential Diagnosis: This sign is nonspecific, and other causes should be considered in patients[8], including chemotherapy (cisplatin or docetaxel), spinal tumor, vitamin B12 deficiency, herpes zoster, or even radiation induced worsening of preexisting multiple sclerosis .[9]

Pathologic Diagnosis: Pathological diagnosis is not required. Its need may arise only to rule out other causes like tumor progression.

Management: There is no known specific treatment for this condition, and none is required, as recovery occurs in most cases. Corticosteroids like dexamethasone have been proven beneficial in animal models.[10]

Follow up: Early-delayed spinal cord disorder is not predictive of a possible evolution to the much more serious progressive myelopathy. Patients may be convinced about the temporariness of the symptoms and subjected to routine follow up.[11]

Delayed Radiation Myelopathy

Clinical detection: Delayed radiation myelopathy may begin abruptly or more often in a progressive way; the patients complain of sensory and/or motor deficits leading to para- or quadriparesis. A typical initial clinical presentation is a Brown-Sequard's syndrome, consisting of a motor deficit associated with ipsilateral sensory loss affecting tactile, vibration, and proprioception on one side, and contralateral sensory loss affecting mainly temperature and pain sensory modalities. In some patients, a transverse myelopathy develops with bilateral leg weakness and sensory loss up to the irradiated region. Some patients also experience pain. Bladder and bowel sphincter as well as diaphragmatic dysfunction (in upper cervical spinal cord lesions) are possible. The evolution of delayed radiation myelopathy varies; in some patients the symptoms stabilize, while in others they progress to a complete deficit.

Time Course of Events: The onset may happen 6 months to 10 years after the radiation therapy.

Dose/Time/Volume: A rare event as it is and today much feared by the Radiation Oncology community[12], statistically accurate estimates are thus lacking. Much of the evidence is thus form some patients treated in 1970-80s (see table) using high dose per fraction, animal studies, dose models and careful ventures in dose escalations.

Author	Year	Doses	Cases	Incidence
Eichhom et al.[13]	1972	27 * 2.45 Gy	Ca Lung	17.4% (8/46)
Abramson et al.[14]	1973	10 * 4 Gy	Ca Lung Radical RT	3.8% (4/103)
Miller et al. [15]	1977	10 * 4 Gy	Ca Lung Radical RT	4% (4/97)
Choi et al. [16]	1980	27 * 2.54 Gy	Ca Lung PORT	17% (8/46)
Dische et al. [17]	1981	6 * 5.8 Gy	Ca Lung Radical RT	11% (8/71)
Fitzgerald et al. [18]	1982	10 * 4 Gy	Ca Lung	17%(6/45)

The 5% probability of delayed radiation myelopathy in 5 years (TD5/5) and 50% in 5 years (TD 50/5) values were described by Emami etal.[19] as:

Volume	1/3rd (5 cm.)	½ (10 cm)	3/3 (20 cm)
TD 5/5	50 Gy	50 Gy	47 Gy
TD 50/5	70 Gy	70 Gy	-

This underlies the traditional prescriptions of keeping the cord dose below 45Gy/ 23-25#/4.5-5 weeks. Few salient clinical studies that challenged these estimates when treated by conventional fractionation (1.8 to 2 Gy/#/day) found the incidence as:

Dose	Incidence	Comments	Author
>30 Gy	0.18%	in 1112 Head & Neck Patients	Marcuss and Millon[20]
45 to 50 Gy	0.42 %		
56 to 65 Gy	0.7%	Only 1 in 144 Patients Head & Neck Patients treated by parallel opposed bilateral beams.	McCuniff and Liang[21]

The present dose response estimates are:

Dose		Probable Incidence of Delayed Radiation Myelopathy
45 Gy	in 1.8 to 2 Gy/#	< 0.2%
50 Gy	in 1.8 to 2 Gy/#	< 1% [12]
57 – 67 Gy	in 1.8 to 2 Gy/#	5% [12,21]
68 – 73 Gy	in 1.8 to 2 Gy/#	50% [17,22]

Dose per fraction relationship: Dosed higher than conventional doses may be associated with higher incidence, however experimental and clinical studies have not shown benefit of reducing dose per fraction.[23]

Dose length (volume) relationship: The evidence is conflicting. While some studies show that incidence increases[24,25] with the length irradiated, many do not. [25,26]

Segment of Cord: Although assumed classically that dorsal cord has lower tolerance than cervical, this holds true no more. All segments are supposed to carry equal risk.

Reirradiation: In most of the animal experiments including primates, much of the recovery takes place within 2 years, thus reirradiation if required can be done if 2 years have elapsed

since previous treatment, although weighing the risk and benefits.[1]

Chemical/Biologic Modifiers: As in transient myelopathy, concomitant use of intrathecal and intravenous chemotherapeutic agents known to be associated with neurotoxicity include methotrexate, cisplatin, cytarabine, and others. In randomized studies by Jeremic et al. investigating the role of concurrent cisplatin with hyperfractionated radiotherapy in the treatment of head and neck (n=101)[27] and lung cancers (n=336)[28], after cord doses of greater than 50 Gy there were no cases of radiation myelitis in patients receiving concomitant cisplatin. The contribution of the intrathecal component is unclear. In a series of 149 patients with cranial parameningeal rhabdomyosarcoma treated with both systemic and intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) and concurrent radiotherapy to the primary tumor (with or without additional radiotherapy to the whole brain and spine), five patients developed ascending myelitis resulting in quadriplegia at 5.5–9 months after initiation of therapy (3.4%). They had received radiotherapy doses of 40–55 Gy to the upper cervical cord [29]. As with the treatment with radiation therapy alone, no dose response curves exist for chemoradiation at present. Thus it appears that when treating young patients by aggressive chemoradiation with good expected survival, cord dose should be respected by using conventional fractionation and total dose not higher than traditional limits of 40 to 45Gy.

Radiological Imaging: Spinal cord MRI is helpful[30.]

Early findings: May be normal during initial few weeks.

Delayed findings: The locations of nonspecific lesions correlate with the site of radiation.

Late findings: Years later may show spinal- cord atrophy without any signal abnormality; a case of cystic formation in late-delayed radiation myelopathy has also been reported[31].

PET scan findings have been described as increased [18F] deoxyglucose and [15O]butanol uptakes, but a diminished [11C]methionine accumulation.

MRI Study	Early (weeks)	Delayed (month(s))	Late (years)
General finding	*There may be NO Change.*	Cord edema. No SOL.	Cord atrophy
T1		Hypointense	Iso/Hypointense
T2		Diffusely hyperintense	Iso/Hyperintense
T1 Contrast		50-60% enhancement[32]	No enhancement

Laboratory Tests: Moderately elevated protein and Myelin basic protein is the most common finding in the CSF but lacks any specificity. Somatosensory evoked potentials show changes correlated to the extent of the lesions[33] whereas spinal conduction velocity is decreased[34].

Differential Diagnosis: Epidural metastasis or compression secondary to vertebral metastases must be excluded for lymphoma and carcinoma. Exclusion diagnosis rules out other demyelinating diseases, paraneoplastic syndromes, degenerative spondylitis and hypertrophic arthritis in the intervertebral foramen.

Pathologic Diagnosis: Essentially a clinicoradiological diagnosis. In case SOL is visible image guided FNAC or biopsy may be done to rule out recurrences.

Management: Corticosteroid as dexamethasone, which has proven CNS activity and long half life is used with an intensive intravenous schedule followed by slow oral tapering to stabilize progress. Most patients become steroid dependent. Most other interventions are experimental with vague clinical benefits. Hyperbaric Oxygen Therapy (HBOT) has been reported to stabilize as by Angibaud et al.[35] Anticoagulation has also been

tried[36]. Novel therapies as stem cell therapy are still in preclinical stage[37]

Follow up: The patient is seen every day or week until relief is obtained and then at 1- to 3-month intervals. Intensive nursing and rehabilitative care are essential, and medico legal implications should be carefully assessed. Like other spinal cord injury patients, most patients ultimately succumb to pneumonitis, bed sores, septicemia or pulmonary thromboembolism. A dedicated spinal or neuro rehabilitation program can ensure best possible care.

Prevention:

Careful Radiation Therapy planning in which care is taken to not to exceed the dose to spinal cord more than 45 to 50 Gy using conventional fractionation by using various techniques as going off cord after an initial phase, using oblique spine sparing portals, using spinal blocks, careful matching of field junctions etc. are examples of methods used during conventional planning. Modern high precision photon, proton or charged particle Radiation Therapy whenever available can also ensure lower doses to cord. A strict Quality Assurance (QA) program for all the steps and equipments of treatment like dosimetry, setup, and treatment delivery is essential to ensure coherence of planning and final treatment. Care should be taken to avoid potential neurotoxic chemotherapeutic agents during radiation therapy if spinal cord is getting substantial dose.

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Suggested Reading:

Radiation response of the central nervous system

Int J Radiat Oncol Biol Phys. 1995; 31(5): 1093- I112.

T. E. Schultheiss, Ph.D.,et al.

This report reviews the anatomical, pathophysiological, and clinical aspects of radiation injury to the central nervous system (CNS). Despite the lack of pathognomonic characteristics for CNS radiation lesions, demyelination and malacia are consistently the dominant morphological features of radiation myelopathy. In addition, cerebral atrophy is commonly observed in patients with neurological deficits related to chemotherapy and radiation, and neurocognitive deficits are associated with diffuse white matter changes. Clinical and experimental dose-response information have been evaluated

and summarized into specific recommendations for the spinal cord and brain. The common spinal cord dose limit of 45 Gy in 22 to 25 fractions is conservative and can be relaxed if respecting this limit materially reduces the probability of tumor control. It is suggested that the 5% incidence of radiation myelopathy probably lies between 57 and 61 Gy to the spinal cord in the absence of dose modifying chemotherapy. A clinically detectable length effect for the spinal cord has not been observed. The effects of chemotherapy and altered fractionation are also discussed. Brain necrosis in adults is rarely noted below 60 Gy in conventional fractionation, with imaging and clinical changes being observed generally only above 50 Gy. However, neurocognitive effects are observed at lower doses, especially in children. A more pronounced volume effect is believed to exist in the brain than in the spinal cord. Tumor progression may be hard to distinguish from radiation and chemotherapy effects. Diffuse white matter injury can be attributed to radiation and associated with neurological deficits, but leukoencephalopathy is rarely observed in the absence of chemotherapy. Subjective, objective, management, and analytic (SOMA) parameters related to radiation spinal cord and brain injury have been developed and presented on ordinal scale.

Radiation tolerance of the spinal cord: doctrine, dogmas, data

Archive of Oncology. 2000,8 (3):131-4.

Lilia Gocheva, Institute of Oncology Sremska Kamenica, Yugoslavia

Radiation damage to the spinal cord is one of the most feared complications in the treatment of cancer with radiation therapy. There is no uniformly accepted definition of the term ‘tolerance’ and this fact reflects differences in the clinical

acceptability of the types of treatment related morbidity. Having in mind this fact, to say a dose to the spinal cord of 45 Gy in 23-25 fraction represents cord tolerance, is true only insofar as most radiotherapists accept its use and very few will tolerate in practice a higher dose. Many studies have attempted to define the risk factors associated with chronic progressive radiation myelopathy with differing conclusions. In the present paper the following main factors are discussed in detail: total dose, dose per fraction, length (volume) of the spinal cord irradiated segment of spinal cord and reirradiation of the cord to control the malignant disease. A number of conclusions are obtained regarding the relative influence of these risk factors, particularly for the range of doses usually given incidentally to the spinal cord in the treatment of tumors in the region of the cord. It is obvious that the sample size in the clinical studies is not adequate to define the multiple risk factors of chronic progressive radiation myelopathy. In fact, the sample size required may be so large that the exact risks may never be completely defined. It is unfortunate that the standard of practice for limiting incidental dose to the spinal cord is determined more by litigation than by clinical judgment. Tumoricidal dose should never be compromised for the purpose of limiting, where such liming forces even greater probability of compromising the tumoricidal dose.

Tolerance of normal tissue to therapeutic irradiation.

Int J Radiat Oncol Biol Phys. 1991 May 15;21(1):109-22

Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M.Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110.

The importance of knowledge on tolerance of normal tissue organs to irradiation by radiation oncologists cannot be overemphasized. Unfortunately, current knowledge is less than

adequate. With the increasing use of 3-D treatment planning and dose delivery, this issue, particularly volumetric information, will become even more critical. As a part of the NCI contract N01 CM-47316, a task force, chaired by the primary author, was formed and an extensive literature search was carried out to address this issue. In this issue, in this manuscript we present the updated information on tolerance of normal tissues of concern in the protocols of this contract, based on available data, with a special emphasis on partial volume effects. Due to a lack of precise and comprehensive data base, opinions and experience of the clinicians from four universities involved in the contract have also been contributory. Obviously, this is not and cannot be a comprehensive work, which is beyond the scope of this contract.

Radiation Induced Central Nervous System Complications

Introduction

Radiation therapy (RT) is an important component of treatment of cancer. However, RT may cause acute and late complications as a side effect in a proportion of patient. RT induced complications to the central nervous system (CNS) may occur after treatment of primary brain tumour, metastatic brain tumour, prophylactic cranial RT (ALL, lymphoma, small cell lung cancer) and also after treatment of head and neck cancer (temporal lobe necrosis, radiation myelitis).

CNS complications after RT are dependent upon several patient and treatment related factors. Toxicity profile of focal RT is entirely different from cranio-spinal (CSI) or whole brain RT (WBRT). Important late toxicities after RT in brain tumour are mainly neuropsychological, neurological function and neuroendocrine impairment, and also radiation induced second malignancy. Apart from these above complications other relatively less described ones are cardiovascular accident (CVA), radiation induced necrosis, growth / sexual function impairment, radiation induced optic neuropathy (RION), radiation myelitis and skin toxicities (e.g permanent hair loss).

Complications are mainly described according to the radiation portals (e.g focal conformal RT, CSI and WBRT) or grade of the tumour (high and low grade). Grade and site of disease, age of presentation, radiation energy used (cobalt / Linear accelerator) and also intensity of treatment regimen (fraction schedule, total RT dose) have an important role in the development of acute and late complications. Acute toxicities are defined as complications occurring within 2 months after complications of treatment. Late complications usually occur after 2-3 years, however may be observed even many years after completion of treatment. The incidence and prevalence of toxicity also varies with the duration of follow up (e.g neuropsychological and neuroendocrine impairment has shown to increase with longer follow up). Few complications like radiation induced CVA and radiation necrosis (pesudoprogression) have been described only in recent literatures.

In last few years there is a paradigm shift from earlier used larger conventional portals to current practice of imaging based planning and multiple smaller conformal portals. Irradiated normal tissue and thus complication profile of treatment has changed in last few decades. The toxicity evaluation tools have also evolved in recent years. Thus, it is imperative to interpret the complication rate and severity with respect to the follow up data, treatment schedules, toxicity evaluation tools used and also patient demographic profile.

Evidences of CNS complications after radiation therapy

Neuropsychological function

Neurological function assessment is traditionally being done by clinical examination, Karnofsky performance status (KPS) and neurological performance status (NPS). These are simple tests, require minimum expertise and are used to detect any

sensory or motor impairment. Numerous batteries of tests are being used in clinical practice to evaluate neurocognitive and psychological function. Among them, Wechsler Intelligent scoring system (WISC), Bhatia Scoring system and Vitoba Paknikar (VP) in blind patients are commonly used in India. Intelligent quotient (IQ) is described as global IQ (GQ) or full scale IQ (FSIQ), performance IQ (PQ), memory IQ (MQ) and verbal IQ (VQ). These IQ scores are assessed by different verbal questionnaire and performance domain. In children below 16 years, FSIQ, PQ and VQ are assessed as the neuropsychological battery where as in adults additional MQ is also assessed. Total score depends upon the task performed and total time taken. Neurocognitive function is assessed by LOTCA (Lowenstein Occupational Therapy Cognitive Assessment) battery of test. LOTCA is a direct observational and verbal communication method of assessment.

- Majority of neurocognitive function assessment data are obtained from either whole brain RT or CSI and had shown deterioration of function after RT. However, these data were obtained from studies which used mostly telecobalt machine and suboptimal radiation techniques. Thus, neuropsychological function should be evaluated in the light of modern RT techniques and newer assessment tools.
- Intelligence quotient (IQ) measurement is benchmark for measurement of changes in cognitive function. Declines in IQ are mostly as a result of failure to learn at a rate that is appropriate for the age of the child, rather than from a loss of previously acquired knowledge.
- A significant number of children and young adults may exhibit low IQ levels even before starting RT suggesting other factors such as tumour, surgery etc to be responsible as well (Carpentieri 2003; Jalali 2007)

- IQ decline is associated with several patient and treatment related risk factors such as younger age at time of treatment, longer time since treatment, hydrocephalus, RT schedule and dose, volume of irradiated normal brain.
- Loss of cerebral white matter and failure to develop white matter at a rate appropriate to the developmental stage may be responsible for changes in IQ score.
- Decline in IQ function after CSI is estimated to be 4 points per years and is cumulative. Young age and radiation dose were the most significant factor influencing fall in IQ score. Decline in performance quotient (PQ) is more than verbal quotient (VQ).
- However, the decline in IQ scores may be of lesser magnitude after focal conformal RT (3D-CRT) as demonstrated in recent studies. There is paucity of prospective data about neuropsychological status in patients with brain tumours, especially for focal partial brain RT.
- Studies with relatively short follow up have shown the superiority of conformal RT with or without stereotactic guidance (3D-CRT and SCRT) in maintaining long-term cognitive scores when compared to conventional RT (Merchant 2006; Jalali 2006).
- After RT, reading appears more vulnerable than other academic skills and may decline over time despite stable intellectual functioning. Math and spelling performance remained stable. Supratentorial tumor location and multiple surgeries were predictive of worse reading performance.
- Control of tumor is the most important factor for stabilizing neurocognitive function. In metastatic brain tumour control of the disease had shown to have significant impact on preserving neurocognitive function.

- Randomized trial in craniospinal radiation dose (36 Gy versus 23.6 Gy) had shown that with lower dose of CSI (23.6 Gy) there is significantly less reduction of both neuropsychological and neuroendocrine function compared with higher dose CSI (36 Gy) (Mulhern 1998).
- Randomized study had shown that lower age (<7 years) and higher radiation dose (>23.6 Gy) have deleterious effect of cognitive function. However, patients with recurrent disease also had significantly worse quality of life and cognitive function.
- In PNET 3 study, health status was significantly poorer in the group treated with CSI plus chemotherapy than in the CSI alone arm, and there were also trends to poorer outcomes for behavior and quality of life scores.
- Prophylactic cranial radiation (PCI) in acute leukemia (ALL) had shown to reduce neurocognitive function and has been assessed by randomized trial with long term follow up data. Poorer performance after PCI was independent of sex of the patient, time since treatment and age at diagnosis. Data suggest that addition of 2,400 cGy PCI cranial in ALL increases the risk for mild global loss in intellectual and neuropsychologic ability.
- Randomized trials had shown that young ALL patients treated with lower dose of PCI (18 Gy) had significantly less reduction of Full-Scale, Verbal, and Performance IQ as measured with WISC Scale compared with 24 Gy PCI. Thus, reducing PCI dose from 2400 cGy to 1800 cGy reduces neurotoxicity to acceptable levels.

Neurological function assessment by activity of daily living

Functional activity is assessed by more objective methods with activity of daily living measurements (ADL). Activity of daily living (ADL) is a battery of tests done to assess 'functional

activity' of a person, essentially in terms of degree of performance activity regarding movement, eating, cooking, self care, bathing, clothing etc. People with low score are more dependent on others to do their daily living then with those with higher scores. Depending upon the performance activity, this evaluation also helps to identify patients, who may require support for daily living and the efficacy of supportive care in improving their functional activity. ADL is most commonly assessed by modified Barthel's Index. However, FIM FAM (Functional independence measurement and functional activity measurement) scoring system is a recently being used to assess ADL activities as a comprehensive tool and encompasses cognitive parameters as well.

- Activity of daily living (ADL) is a validated method to assess the functional status of a patient.
- Barthel's Index (BI) has been used in the evaluation of efficacy of supportive care or any sort of intervention (radiotherapy or surgery), primarily in elderly patients with high-grade glioma. BI has shown to improve after RT in HGG and also in brain metastasis.
- There are sparse data regarding BI score in pediatric low grade brain tumour patients treated with RT. However, in our prospective series there was no deterioration in BI domain scores at 3 year follow up (Jalali 2008).

Endocrine function

Neuroendocrine function assessment is done by serum hormone level estimation of different pituitary hypothalamic (PHA) hormone axis. Estimation is done in thyroid hormone (T3, T4, TSH), growth hormone (unstimulated and stimulated GH), sex hormone (LH, FSH, testosterone), cortisol (cortisol) and prolactin hormone axis (prolactin).

- RT to brain has been implicated as one of the most important factor associated with neuroendocrine dysfunction after long term follow up.
- Radiation dose and volume of brain irradiated had shown significant correlation. Majority of the literature has come from either craniospinal radiation (CSI) or from whole brain RT.
- Both in whole brain RT and CSI, PHA receives high dose and thus functional impairment is expected even years after RT. Growth hormone (GH) seems to be the most sensitive hormone as it's serum level is the first to decline after RT. GH is followed by thyroid hormone releasing hormone (THRH) and cortisol level decline. Impairment of the circadian hormonal surge is considered as an early sign of hormone axis deficit.
- Frequency, delay of appearance and severity of deficiency depends upon RT dose delivered, age of the patient and treatment schedule.
- After conventional whole brain RT (WBRT) with dose more than 18 Gy, impairment of normal growth hormone (GH) secretion are the first and most common recognized deficit.
- After CSI, 50% to 80% of patients develop signs of GH deficiency, 30-50% develops primary hypothyroidism and 30-40% develops cortisol deficiency.
- Functional disturbances of thyroid and adrenal glands due to PH axis deficiency are less common and usually seen only after RT dose >40 Gy.
- Few chemotherapeutic regimens used in brain tumor are also associated with decline in endocrine function.
- Patients with hormonal dysfunction presents with early or delayed puberty or growth retardation. Girls may frequently experience an early and rapid pubertal

development after brain tumor therapy, with reduction in height due to accelerated bone maturation.

- In medulloblastoma, after CSI dose of 36 Gy, 75% had hormone axis impairment with majority (70%) having GH axis deficit while cortisol and thyroid axis were usually preserved. Younger patients had significantly higher GH deficiency after RT. Laughton et al., had showed 93% (±4%) deficit in GH axis, 65% (±7%) thyroid axis deficiency and 38% (±6%) patient had cortisol axis deficiency at 4 year follow up after CSI.
- It seems HP axis deficiency is dose dependent and lower radiation dose is associated significantly less hormone axis deficiency.
- In a prospective study , GH axis deficiency was observed in 41% of pediatric brain tumor patients treated with chemotherapy and surgery (Clarson et al).
- There were further significant impairment in both GH and thyroid axis after treatment with CSI. Few other studies on medulloblastoma/PNET patients treated with CSI (±chemotherapy) had shown to be associated with decline in endocrine function.
- After whole brain RT in metastatic brain tumor, 50% patient developed hormone axis deficit in at least one axis. In patients receiving prophylactic cranial RT, higher RT dose is associated with significantly more endocrine dysfunction. Studies have also shown correlation between the endocrine dysfunction and severity of neurocognitive impairment after RT.
- Prospective evaluation of endocrine function after focal RT is sparse. There are evidences of 'dose-effect' relationship between RT dose and HP axis deficit. With focal RT as HP axis is expected to be spared, it is assumed

that there will be higher probability of preservation of endocrine function.

- Among literatures with focal RT, pediatric patients suffering from germinoma treated with low dose focal radiation (25 Gy) had shown to preserve endocrine function.
- Dosimetric study of Intensity modulated radiotherapy (IMRT) in brain tumor has shown superior target coverage and sparing of PH axis. But, there are no mature data to comment about the clinical outcome. Stereotactic conformal radiotherapy (SCRT) has dosimetric superiority over other focal RT techniques as it requires lesser PTV margin. Thus, it will be interesting to assess the endocrine function status after treatment with SCRT. Few studies that had assessed endocrine function in patients treated with SCRT had shown promising outcome. In TMH data with SCRT, only 17.5% of patients developed additional hormone axis deficiencies at 2 and 3 year follow up (Dutta 2008).
- Stereotactic Intensity modulated radiotherapy (SIMRT) may have the highest probability of sparing PH axis function in tumors close to sellar region. Long term follow up of pediatric brain tumor patients treated with proton beam therapy will be interesting to observe in respect to neuroendocrine function preservation.

Second malignancy

Second malignancy data is obtained either from retrospective series, large randomized trial as secondary end point or recently from population based SEER data.

- In SEER data the cumulative incidence of second cancer among all cancer patients were 5.0%, 8.4%, 10.8%, and 13.7% at 5, 10, 15, and 25 years, respectively.

- Highest relative risk of second cancer is in young cancer survivors and is estimated to be 5.6.
- Second malignancies after treatment of brain tumour with radiation are meningioma, sarcoma and glioma.
- Cumulative risk of developing a second brain tumour over the first 10 years after treatment was 1.3% (95% CI 0.4% -3.9%) and over 20 years 1.9% (0.7% -5.0%).
- Relative risk of second brain tumour compared with incidence in the normal population was 9.38 (3.05 to 21.89). Cumulative incidence of brain tumors at 20 years after cranial RT in acute lymphoblastic leukemia (ALL) was 1.39% (95% CI, 0.63%- 2.15%). Thus, second malignancy is relatively uncommon after RT in primary brain tumour.

Cerebrovascular accident (CVA)

An increased incidence of cerebrovascular accidents (CVA) and related mortality has been reported in patients with pituitary adenoma treated with RT. Possible risk factors include hypopituitarism, irradiation and extensive surgery, but none are proven causes at present.

- Brada et al., reported an increased mortality in a series of 334 irradiated patients with a 4.1-fold excess of CVA in pituitary tumour. However, increase in CVA may be related to endocrine dysfunction rather than RT itself.

Radiation induced necrosis

RT induced necrosis is usually observed in 1-2% after high dose RT.

- However, RT induced necrosis ('pseudo-progression') is increased up to 14% after treatment with concurrent RT and Temozolomide. This increased contrast enhancement after RT is called 'pseudo-progression'.

Pseudo-progression needs to be differentiated from true progression.

Radiation myelitis

Radiation myelitis though rare is seen in brain tumour patients treated with CSI or posterior fossa tumour.

- Higher probability of myelitis occurs with higher RT dose (>50Gy). Majority of acute radiation myeliis are self limiting. Late onset myelitis is permanent and associated with significant neurodeficit.

Radiation induced Optic neuropathy (RION)

The optic chiasm is radiosensitive and blindness from damage well documented. Risk of damage following RT is 1-2% with latency period 2 months – 4 yrs. Gadolinium MR has defined the injury due to injury to the vaso nervorum. Risk is related to dose and dose per fraction

- RMH experience: 411 patients, 1962-1986, 45-50Gy RT, visual deterioration, assumed to be RT induced, 1.5% (Brada et al., Clin Endo, '93)
- University of Florida: 141 patients, 1965-1993, 45-55Gy, vision worse in 2% (McCord et al., IJROBP, '97)
- PMH, 160 patients: 1972-1986, 40-50Gy, no visual deterioration (Tsang et al., IJROBP, '94). IIIrd to VIth nerves in the cavernous sinus exposed to a mean dose of 14.2Gy (5 – 30Gy) and these had no new neuropathies
- Radiation tolerance of structures to single fraction treatment: Radiation related optic neuropathy was picked up earliest by a delay or reduction in the amplitude of visual evoked potentials <10Gy : No RON;10-15Gy: 26.7%;> 15Gy: 77.8%

Suggested Reading:

A) Neuropsychological function

1. **Neuropsychological Functioning after Surgery in Children Treated for Brain Tumor.** Carpentieri SC, Waber DP, Pomeroy SL, Scott RM, Goumnerova LC, Kieran MW. Neurosurgery 2003;52: 1348-57.

OBJECTIVE: To describe the neuropsychological functioning of children treated with surgery only for localized brain tumors in Dana-Farber Cancer Institute Protocol 92-077. Subsequent reports will describe the neuropsychological functioning of children treated with surgery and stereotactic radiation therapy on Dana-Farber Cancer Institute 92-077.

METHODS: The intellectual functioning of 106 patients was evaluated within 3 months after surgery. An in-depth assessment of the neuropsychological functioning, including an impairment index, was conducted for a subset of 77 school-age children (6-16 yr old) across six functional domains. Descriptive statistics were generated; binomial distribution analyses were performed to assess whether the proportion of individuals with impaired performance on each measure exceeded normative expectations. The impairment index assessed whether poor performance was attributable to a few children or reflected the performance of the cohort as a whole.

RESULTS: Although the Full Scale IQ was within normative expectations, the Verbal IQ was higher than the Performance IQ with 45% of individuals showing a significant discrepancy ($P < 0.01$) between these scales. There was an increased prevalence of poor performance for measures of motor output, verbal memory, and visuospatial organization. The distribution of the impairment index indicated moderate impairment across the school-age cohort rather than severe impairment in a few patients.

CONCLUSION: The results document a moderate level of neuropsychological morbidity among children with brain tumors before stereotactic radiation therapy, presumably referable to the tumor itself and the surgery. The extent to which stereotactic radiation therapy may increase this burden will be assessed in follow-up studies evaluating the longitudinal neuropsychological data.

2. **Predicting change in academic abilities after conformal radiation therapy for localized ependymoma.** Conklin HM, Li C, Xiong X, Ogg RJ, Merchant TE. J Clin Oncol.2008;26(24):3965-70

PURPOSE: Conformal radiation therapy (CRT) aims to limit the highest radiation dose to the tissue volume at risk while sparing surrounding normal tissues. This study investigated whether treatment of childhood ependymoma with CRT would preserve cognitive function. Academic competence was chosen as the primary outcome measure given it is a measure of applied cognitive abilities in a child's natural setting.

PATIENTS AND METHODS: Eighty-seven pediatric patients diagnosed with ependymoma received CRT in which doses ranging from 54.0 to 59.4 Gy were prescribed to the postoperative tumor bed with a 10-mm clinical target volume margin. Cognitive testing was conducted at the start of CRT, 6 months, and annually after the start of CRT. The median length of follow-up was 59.6 months. Academic testing included subtests from the Wechsler Individual Achievement Test (WIAT) and the Achenbach Child Behavior Checklist. RESULTS: Linear mixed models with random coefficients revealed a modest but significant decline in reading scores during follow-up (WIAT slope estimate -0.064 +/- 0.028 points/month; P = .026). Math and spelling performance remained stable. Supratentorial tumor location and multiple surgeries were predictive of worse reading performance at CRT

baseline. Male sex, longer symptomatic interval, pre-CRT chemotherapy, pre-existing endocrine deficiencies, hydrocephalus, and younger age at CRT (< 5 years) were predictive of a significant decline in reading scores over time.

CONCLUSION: CRT may result in better long-term cognitive outcomes when compared to conventional radiation therapy approaches. Reading appears more vulnerable than other academic skills and may decline over time despite stable intellectual functioning.

3. **Neuropsychological profile in children with low-grade brain tumours before starting treatment with focal RT: baseline data from an ongoing randomised trial.** Jalali R, Dutta D, Goswami S, Develekar R, Sarin R, Dinshaw KA. Neurooncol; Oct 2007: 588

The objective was to report neuropsychological profile and activities of daily living in the pediatric patient population with residual/progressive low-grade brain tumors before starting focal radiotherapy (RT). The aim is to report the baseline pre-RT data collected in an ongoing prospective randomized trial comparing stereotactic conformal RT versus conventional RT in these patients to generate level 1 evidence for the efficacy of high-precision RT techniques. Between April 2001 and April 2007, out of 93 children and young adults (5–25 years) accrued so far, the present analysis focuses on 60 pediatric patients (46 males, 14 females) in the age group of 5–16 years. Prior surgery was in the form of partial excision in 29 patients, subtotal excision in 16 patients, and biopsy in 15 patients. Tumor subtypes included 18 chiasmatic-hypothalamic gliomas, 17 craniopharygiomas, 14 cerebellar astrocytomas, 8 supratentorial low-grade gliomas, and 3 ependymomas. Patients underwent a detailed baseline neuropsychological evaluation as per designed protocol. Neuropsychological function was assessed by Wechsler

Intelligence Score Chart (WISC), which included measurement of ageadjusted intelligence quotients (verbal quotient, performance quotient, fullscale intelligence quotient [IQ]). A Lowenstein Occupational Therapy Cognitive Assessment (LOTCA) battery, which measured cognitive parameters of visual, spatial, visuomotor, and attention, was performed in 41 suitable patients. Anxiety was measured by State-Trait Anxiety Inventory for Children (STAIC) (C1—state and C2—trait) and activities of daily living by the modified Barthel's index. Binomial distribution analyses were performed to assess whether the proportion of patients with impaired performance on each measure exceeded normal expectations. As many as 32 (60.4%) of the 53 evaluable patients had full-scale IQ values below normal expected levels at baseline before starting RT, although the overall mean verbal IQ (87.9), performance IQ (85.33), and full-scale IQ (84.6) were only slightly less than the expected values. Proportion of patients with less-than-expected scores was seen significantly more (p 5 0.003) in the performance IQ domain (34 patients, 64%) than in the verbal IQ domain (24 patients, 45%). A significantly higher number of patients showed severe anxiety (score more than 30) in the state C1 form (19 out of 41 evaluable patients patients, 46%) than in the trait C2 form (14 patients, 34%) (p =0.008). In the LOTCA battery, the proportion of patients with less-than-expected scores was seen significantly more in the visual (p =0.007), orientation (p=0.001), and spatial perception (p = 0.001) than visuomotor, motor praxia, thinking, and attention domains. The mean score of Barthel's index was 18.21 (range 10–20). Our prospective study in children with residual/progressive benign and low-grade brain tumors after prior surgery demonstrates a considerable pre-RT cognitive and neuropsychological morbidity. These suggest that factors other than RT, such as tumor and surgery, could have a possible impact on neuropsychological parameters. Performance IQ rather than verbal IQ was seen to be impaired in a greater

number of patients. Cognition was poorer in some specific domains than others. We are collecting prospective follow-up data to show the further impact of various RT techniques on these parameters.

4. **Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study.** Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. J Clin Oncol. 1998;16(5): 1723-8.

PURPOSE: The purpose of this study was to test the hypothesis that survivors of medulloblastoma who were younger at diagnosis and those who received standard-dose cranial irradiation (SRT) of 36 Gy would have a lower performance on standardized tests of cognitive function and achievement than children who were older and those treated with reduced-dose cranial irradiation (RRT) of 23.4 Gy.

PATIENTS AND METHODS: Eligible patients had been treated on Pediatric Oncology Group (POG) study 8631 for low-risk medulloblastoma that randomized patients to receive RRT or SRT after surgical resection. Those who were alive and free of progressive disease 6.1 to 9.9 years from completion of treatment were eligible for this study. Of the 35 eligible patients, 22 patients (13 SRT, nine RRT) participated in a battery of tests that included intellectual and academic development as well as ratings of health-related quality of life.

RESULTS: Patients were stratified by treatment group (SRT v RRT) and into younger (Y) and older (O) groups by the median age at diagnosis (8.85 years), which resulted in four groups that we hypothesized would show neuropsychologic test scores in the following order: Y/SRT less than Y/RRT less than O/SRT less than O/RRT. Evidence to support the

hypothesized ordering of groups in terms of neuropsychologic toxicity was obtained with regard to Performance Intelligence Quotient (IQ), Full Scale IQ, Attention, Reading, and Arithmetic.

CONCLUSION: Children treated for medulloblastoma experienced less severe neuropsychologic toxicity when treated with 23.4 Gy instead of 36 Gy cranial irradiation. Older children experienced less toxicity than children who were younger at the time of irradiation.

5. **Neuropsychological status in children and young adults with benign and low-grade brain tumors treated prospectively with focal stereotactic conformal radiotherapy.** Jalali R, Goswami S, Sarin R et al., Int J Radiat Oncol Biol Phys 2006; 66(4):S14–S19

Purpose: To present prospective neuropsychological data at baseline and follow-up in children and young adults with benign and low-grade gliomas treated with focal stereotactic conformal radiotherapy (SCRT). Methods and Materials: A total of 22 patients (age 4–25 years) with residual/progressive benign and low-grade brain tumors considered suitable for SCRT underwent detailed and in-depth neuropsychological and cognitive testing at baseline before SCRT. The test battery included measurement of age-adjusted intelligence quotients (IQs) and cognitive parameters of visual, spatial, visuomotor, and attention concentrations. Anxiety was measured using the State-Trait Anxiety Inventory for Children and Hamilton Anxiety Rating Scale for patients >16 years old. Patients were treated with high-precision conformal radiotherapy under stereotactic guidance to a dose of 54 Gy in 30 fractions. All neuropsychological assessments were repeated at 6 and 24 months after SCRT completion and compared with the baseline values. Results: The baseline mean full-scale IQ before starting RT for patients <16 years was 82 (range, 33–105). For those

>16 years, the corresponding value was 72 (range, 64–129). Of 20 evaluable patients, 14 (70%) had less than average IQs at baseline, even before starting radiotherapy. The verbal IQ, performance IQ, and full-scale IQ, as well as other cognitive scores, did not change significantly at the 6- and 24-month follow-up assessments for all patients. The memory quotient in older children and young adults was maintained at 6 and 24 months after SCRT, with a mean value of 93 and 100, respectively, compared with a mean baseline value of 81 before RT. The mean anxiety score in children measured by the C1 and C2 components of the State-Trait Anxiety Inventory for Children (STAIC) was 48 and 40, respectively, which improved significantly to mean values of 30 and 26, respectively, at the 24-month follow-up assessment ($p = 0.005$). The mean depression score in patients >16 years old was 23 at baseline and had improved to 17 and 14 at the 6-month and 24-month follow-up assessments, respectively. Conclusion: Our data demonstrated neuropsychological impairment in a cohort of young patients with benign and low-grade tumors even before starting radiotherapy. SCRT, however, did not result in any additional worsening. These encouraging results need to be validated in a study with a larger number of patients and longer follow-up.

6. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG).

Bull KS, Spoudeas HA, Yadegarfar G, Kennedy CR; J Clin Oncol. 2007 20;25(27):4239-45.

PURPOSE: To compare quality of survival after craniospinal irradiation (CSI) alone with survival after CSI plus chemotherapy (CT) for medulloblastoma.

PATIENTS AND METHODS: Follow-up study of surviving UK patients with medulloblastoma diagnosed between 1992 and 2000 treated according to one or other treatment arm of the PNET 3 controlled trial. R

ESULTS: Seventy three percent of all 147 eligible patients ages 6.6 to 24.3 years were assessed at a mean of 7.2 years after diagnosis. Health status was significantly poorer in the group treated in the CSI plus CT arm of the trial than in the CSI alone arm, and there were also trends to poorer outcomes for behavior and quality of life scores. The CSI plus CT group were also significantly more restricted physically and needed more therapeutic and educational support. Body mass index, stature, and other endocrine outcomes were similar in the two treatment arms, except for the trend in increased frequency of medical induction of puberty in the CSI plus CT group. CONCLUSION: The addition of CT to CSI for medulloblastoma was associated with a significant decrease in health status. The effect of the addition of other CT regimens to CSI on quality of survival should be evaluated.

B. Endocrine function

1. Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. Heikens J, Michiels EM, Behrendt H, Endert E, Bakker PJ, Fliers E. Eur J Cancer. 1998;34(10):1592-7.

The occurrence of neuro-endocrine deficiencies following craniospinal irradiation for medulloblastoma is well known, but data concerning the spectrum and prevalence of endocrine abnormalities in adulthood are scarce. We studied endocrine function in 20 (median age 25 years) adult subjects, 8-25 years (median 16 years) after therapy. The radiation dose to the whole cranium and spinal axis was 35 +/- 2.6 Gray (mean +/- standard deviation) with a boost to the posterior fossa of 18 +/- 3.7 Gray. 13 subjects had received additional chemotherapy. In

15 of 20 (75%) subjects, endocrine abnormalities were observed. In 14 (70%), growth hormone (GH) secretion was impaired; 7 (35%) subjects had an absolute GH deficiency, while 7 (35%) showed subnormal responses to insulin-induced hypoglycaemia. In contrast, only 20% (4) of these subjects showed impairment of the hypothalamus-pituitary-thyroid (HPT) axis, while 15% (3) showed central impairment of hypothalamus-pituitary-gonadal (HPG) function. Central impairment of the HPG axis was associated with impaired GH secretion in all cases. Central adrenal insufficiency was not observed. Basal levels of prolactin were normal in all subjects. Young age at treatment was a determinant of GH deficiency in adulthood (P = 0.014). Neither post-treatment interval, nor the use of chemotherapy were determinants of central endocrine impairment in adulthood. In long-term survivors of medulloblastoma, GH deficiency has a high prevalence. In contrast, impairment of the HPG and HPT axis is less common, while central adrenal insufficiency was not observed.

2. **Prospective analysis of endocrine function in children with residual/recurrent low grade brain tumours treated with high precision stereotactic conformal radiotherapy.** Dutta D, Shah N, Gupta T, Munshi A, Jalali R. J Clin Oncol 26:2008 (May 20 Suppl; abstr 2049)

Background: We report prospective neuroendocrine function in children and young adults with residual/recurrent low-grade brain tumours treated with high-precision stereotactic conformal radiotherapy (SCRT). Methods: 57 patients (median 13 yrs, range 5- 25 yrs; 42 male, 15 females) with low-grade brain tumours treated with SCRT comprise the present patient population. The histologic types included 18 craniopharyngioma, 16 optic chiasmatic glioma, 12 cerebral gliomas and 6 patients with cerebellar astrocytoma. Patients

had undergone surgical procedure including biopsy in 19 and partial excision in 38 patients. Results: At a median follow-up of 27.5 months, 51 patients have controlled disease. Four patients have died of disease progression and 1 patient is alive with progression yielding 2 and 3 year overall survival of 90% and 85% respectively. Before starting radiotherapy, 30 out of 57 patients (53%) had hormone deficiency in at least one axis requiring replacement. This implies that factors other than radiotherapy such as tumour and surgery may also be responsible. Hormone dysfunction was significantly more in sellar tumour (27 of 38 patients, 71%; p=0.006) and tumours close to PHA (0.001). At baseline, hormone dysfunction was seen significantly more in GH axis (27 patients, 48%), corticosteroid axis (23 patients, 40%) than thyroid axis (10 patients, 17.5%) and sex hormone axes (1 patient, 2%). At 2- and 3-year follow-ups, hormone deficiency in at least 1 axis was seen in 14/29 patients (48%) and 11/22 patients (50%) respectively. At 2-year follow-up, three patients developed additional deficiency (1 each in thyroid, steroid and sex-hormone axis). At 3-year follow-up, only 1 more patient (14%) developed additional deficiency. Conclusions: More than half of patients with low-grade brain tumours before radiotherapy had hormone deficiency in at least one axis, with maximum deficiency seen in sellar tumours. Hormone dysfunction was seen in a very small number of patients at 2- and 3-year follow-ups in this cohort of patients treated with SCRT. Validation of these encouraging results will come from maturation of data in a larger number of patients at a longer follow-up.

C. Vascular events

1. Cerebrovascular mortality in patients with pituitary adenoma.

Brada M, Ashley S, Ford D, Traish D, Burchell L, Rajan B. Clin Endocrinol (Oxf). 2002;57(6):713-7.

OBJECTIVE: To assess cerebrovascular mortality in a UK cohort of patients with pituitary adenoma known to have increased incidence of cerebrovascular accidents (CVA).

METHODS: A total of 334 patients treated at the Royal Marsden Hospital (RMH) between 1962 and 1986 with surgery and postoperative radiotherapy were followed up via the NHS Central Register (NHSCR) to identify deaths and emigrations. The causes of death were assessed by NHSCR-based death certificates and coded according to the 9th revision of ICD. Follow-up was censored at age 85, on emigration or cancellation of NHSCR. Thirteen patients could not be traced. A total of 4982 person-years was accumulated in the cohort. Expected numbers of deaths were computed from the national age-, sex- and period-specific mortality rates for England and Wales.

RESULTS: In the pituitary adenoma cohort, 128 deaths were observed compared to 80.9 expected [relative risk (RR) of death 1.58 (95% CI: 1.32-1.90)]. There were 33 cerebrovascular deaths compared with 8.04 expected (RR 4.11, 95% CI 2.84-5.75). Three deaths were from subarachnoid haemorrhage compared to 0.54 expected (RR 5.51, 95% CI 1.14-16.09). There was an increased cerebrovascular mortality in women (RR 6.93, 95% CI 4.29-10.60) compared to men (RR 2.4, 95% CI 1.24-4.20; P = 0.002) and in patients having debulking surgery (RR 5.19, 95% CI 3.50-7.42) compared to biopsy/no surgery (RR 1.33, 95% CI 0.27-3.88; P = 0.02). The RR in patients with nonsecretory tumours was 3.65 (95% CI 2.26-5.58), compared with 5.23 (95% CI 2.25-10.30) in secretory tumours (P = 0.4). The effect of age at radiotherapy was not significant (P = 0.4).

CONCLUSION: Patients with pituitary adenoma treated with surgery and radiotherapy have an increased risk of cerebrovascular mortality compared to the general population,

which mirrors the increased incidence of CVA. The possible risk factors include hypopituitarism, radiotherapy and extent of surgery but none are at present proven causes. The evaluation of new treatment strategies should not only assess intermediate end-points of tumour and endocrine control but should concentrate on long-term survival with particular emphasis on CVA incidence and mortality.

D. Radiation induced necrosis

1. Pseudoprogression (PsPr) after concurrent radiotherapy (RT) and temozolomide (TMZ) for newly diagnosed glioblastoma multiforme (GBM).

Clarke JL, Abrey LE, Karimi S, Lassman AB. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 2025)

Background: Increased contrast enhancement on brain imaging following chemoradiotherapy is often interpreted as progression of disease (PD). However, there is growing evidence that radiographic and even clinical worsening may result from effects of therapy, i.e. PsPr, rather than from true PD. Methods: 80 patients (pts) with GBM were treated in an IRB-approved phase 2 clinical trial with concurrent RT and TMZ followed by adjuvant TMZ. MRI was performed post-RT. PsPr was defined as increased contrast enhancement on the initial post-RT MRI scan that improved without changing chemotherapy, or as histologically documented necrosis. True PD was defined as continued progression on subsequent scans, or histologically documented viable tumor. MR perfusion imaging with relative cerebral blood volume (rCBV) and FDG PET imaging were collected in subsets of patients. Results: There were 33 pts with increased enhancement on the initial post-RT MRI; 8 (24%) had PsPr, 17 (52%) had true PD, and 8 (24%) discontinued TMZ (PsPr vs. true PD unknown). Of the 8 pts with PsPr, 2 had MR perfusion scans; both demonstrated increased rather than decreased rCBV. Two others had FDG PET scans; both showed hyper- rather than

hypometabolism. Of the 17 patients with true PD, 5 had MR perfusion scans: 4 had increased rCBV and 1 had decreased rCBV; none had PET scans. The single patient with histologically documented PsPr had at the time of surgery, after 2 cycles of adjuvant TMZ, both increased rCBV and hypermetabolic PET scan; perfusion imaging was not performed with his first post-RT MRI. 6 of the 8 pts with PsPr were clinically worse at their post-RT visit; 7 of the 17 with true PD were clinically worse. Conclusions: At least 24% of our pts with increased contrast enhancement post-RT had PsPr; the incidence could be as high as 48% if all 8 pts who discontinued TMZ for a worsening scan actually had PsPr. MR perfusion, FDG PET, and clinical status were not predictive of PsPr versus true PD. It may be reasonable to consider findings on the post-RT MRI as a new baseline, rather than an assessment of response to chemo-RT, because of the high (24-48%) risk of PsPr. This approach would also minimize the likelihood of overestimating the benefits of second-line treatment.

E. Second malignancy

1. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years.

Minniti G, Traish D, Ashley S, Gonsalves A, Brada M J Clin Endocrinol Metab. 2005 Feb;90(2):800-4

We assessed the risk of second brain tumors in a cohort of patients with pituitary adenoma treated with conservative surgery and external beam radiotherapy. Four hundred and twenty-six patients (United Kingdom residents) with pituitary adenomas received radiotherapy at the Royal Marsden Hospital (RMH) between 1962 and 1994. They were followed up for 5749 person-years. The cumulative incidence of second intracranial tumors and systemic malignancy was compared

with population incidence rates through the Thames Cancer Registry and the National Health Service Central Register (previously OPCS) to record death and the potential causes. Eleven patients developed a second brain tumor, including five meningiomas, four high grade astrocytomas, one meningeal sarcoma, and one primitive neuroectodermal tumor. The cumulative risk of second brain tumors was 2.0% [95% confidence interval (CI), 0.9-4.4%] at 10 yr and 2.4% (95% CI, 1.2-5.0%) at 20 yr, measured from the date of radiotherapy. The relative risk of second brain tumor compared with the incidence in the normal population was 10.5 (95% CI, 4.3-16.7). The relative risk was 7.0 for neuroepithelial and 24.3 for meningeal tumors. The relative risks were 24.2 (95% CI, 4.8-43.5), 2.9 (95% CI, 0-8.5), and 28.6 (95% CI, 0.6-56.6) during the intervals 5-9, 10-19, and more than 20 yr after radiotherapy (four cases occurred >20 yr after treatment). There was no evidence of excess risk of second systemic malignancy. An additional 10-yr update confirmed our previous report of an increased risk of second brain tumors in patients with pituitary adenoma treated with surgery and radiotherapy. The 2.4% risk at 20 yr remains low and should not preclude the use of radiotherapy as an effective treatment option. However, an increased risk of second brain tumors continues beyond 20 and 30 yr after treatment.

F. Radiation induced optic neuropathy

Radiation-induced optic neuropathy.

Danesh-Meyer HV. J Clin Neurosci. 2008; 15(2):95-100

Radiation-induced optic neuropathy (RION) is a devastating late complication of radiotherapy to the anterior visual pathway resulting in acute, profound, irreversible visual loss. It is thought to be a result of radiation necrosis of the anterior visual pathway. Visual loss may be unilateral or bilateral; simultaneous or sequential. RION occurs commonly between

10-20 months, with an average of 18 months after treatment; but the onset may range from three months to 9 years. Cumulative doses of radiation that exceed 50 Gy or single doses to the anterior visual pathway or greater than 10 Gy are usually required for RION to develop. Several factors are associated with a higher risk for developing RION or for RION occurring with lower total doses of radiation. These include age, pre-existing compression of the optic nerve and chiasm by tumour, concurrent chemotherapy or previous external beam radiation. MRI, the investigation of choice for identifying radiation injury to the visual pathway, may show abnormalities before the loss of vision. Typically, the unenhanced T1- and T2-weighted images show no abnormality, but the optic nerve will show enhancement on T1-weighted images with MRI. Treatment with systemic corticosteroids, anticoagulation and hyperbaric oxygen has been generally unsuccessful and disappointing. If visual dysfunction is detected early, hyperbaric oxygen might be beneficial if treatment is initiated within 72 hours of visual loss. Because of the poor prognosis associated with RION, the risk of its potential development should be factored into the decision to irradiate the brain.

Section — IV

Medical Oncology

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Febrile Neutropenia

Neutropenia is well known complication of chemotherapy. Neutropenia predisposes to infections which is a major cause of morbidity and mortality. Specific guidelines is provided for diagnosis, treatment and prevention of febrile neutropenia. This guidelines should be used in conjunction with patient evaluation, host factors analysis and especially microbes and antimicrobial sensitivity pattern at the local place.

Definition

Fever is defined as single oral temperature 38.3 C or more orally or 38 C or more over 1 hour without obvious cause. A patient with neutropenia and signs of infection should be treated as febrile neutropenia.

Initial Evaluation

A site specific history and examination should be done. Culture should be obtained and antibiotic should be started immediately. Common sites of infection such as gastrointestinal tract, lung, sinus, ears, perivagina, perirectum, skin, groin and central venous catheter shold be examined. Important features to consider are co-morbid features, last chemotherapy date and recent antibiotic use. (level-3)

Initial investigations – Complete blood count, blood urea nitrogen, serum creatinine, liver function test should be done in all patients. Oxygen saturation, chest X-rays and urine analysis should be done depending on patients symptoms. (level-3)

Cultures

Two blood samples should be obtained for culture. There are three options: 1) Both samples can be from periphreral blood, 2) one from peripheral blood and one from catheter, 3) both from catheter. In the absence of clinical signs and symptoms routine cultures from other sites are not recommended. (level-3)

Initial empiric antibiotic therapy-

All neutropenic patients with signs and symptoms of infection should receive empiric antibiotic to decrease mortality.

Following factors should be considered before deciding antibiotics-

Patient infection risk assessment

The antimicrobials susceptibilities of organism isolated locally

The most common potentially infecting organisms, incidence of extended spectrumbeta-lactamase producing Gram negative rods (ESBL), vancomycin resistant enterococci (VRE) and colonization with with or previous infection with methicillin resistant S. aureus (MRSA).

Potential sites of infections

Bactericidal Antibiotics with antipseudomonal coverage

Clinical instability

Drug allergy

Recent antibiotic use

Approach to initial antibiotic use –

It is important to risk stratify the patients:

High Risk- if any features are present

Inpatient at the time of development of fever

Significant clinical co-morbidity or clinically unstable

Prolonged severe neutrpenia: <or equal to 100 cells/mcl and more than 7 days

Hepatic insufficiency (5 times the normal of hepatic enzymes)

Renal insufficiency (creatinine clearance <30 ml/min)

Uncontrolled progressive cancer

Pneumonia or other complex infections at clinical presentation

Mucosistis grade 3-4

Low Risk- none of above factors and most of the following

Outpatient status at the time of development of fever

No associated acute comorbid conditions

Anticipated short duration of severe neutropenia (<100 cell/mcl for < 7 days)

Good performance status (ECOG 0-1)

No hepatic insufficiency

No renal insufficiency

There is other risk group classification(MASCC RISK-INDEX, TALCOTT RISK ASSESSMENT) but none of them has been validated in India. The above mentioned risk stratification is relatively easy to use.(level-2)

In high risk group, patient may receive IV antibiotics as in-patient

In low risk group, patient may receive IV or Oral antibiotics as in-patient, few select patients may receive out patient treatment with adequate outpatient infrastructure established. Eg- review laboratory results to ensure no critical value, 24 hours home care givers available, home telephone, access to emergency facilities, distance less than one hour from from medical center, able to take oral medicines, not on prior fluroquinolones, patient education and follow up after 12-24 hours. (level-2)

Antibiotics

Intravenous Monotherapy- (level-1)

Cefepime, Imipenem, Meropenem, Piperacillin+Tazobactum

Ceftazidime

Intravenous antibiotic Combination therapy-(level-2)

Aminoglycosides + Antipsudomonal penicillin+/- beta-lactamase inhibitor, Aminoglycoside + extended spectrum cephalosporin (cefepime, ceftazidime), Ciprofloxacin + antipseudomonal penicillin

Use of vancomycin or linozelid is not routinely recommended

Oral antibiotic combination-(level-2)

Ciprofloxacin + Amoxicillin/clavulanate

Penicillin allergic patients may use ciprofloxacin + clindamycin

Role of Vancomycin- (level-3)

Vancomycin should not be routinely considered part of initial empiric therapy. Vancomycin may be considered part of empiric therapy in following clinical situations-

Serious catheter related infection

Blood culture positive for gram positive infection till sensitivity report is available

Known colonization with Penicillin/Cephalosporin resistant pneumococci or methicillin resistant Staph aureus

Hypotension or Septic Shock without identified organism

Soft tissue infection

Risk factors for viridans group streptococcal bacteremia-severe mucositis, prophylaxis with quinolones or Trimethoprim + Sulfamethoxazole

Vancomycin should be discontinued in 2-3 days if a resistant gram positive infection is not identified and if clinically appropriate

Empiric therapy for patients who are clinically unstable-

Empiric therapy in unstable patients may include broad spectrum beta-lactum (imipenem, meropenem, piperacillin + tazobactum) and aminoglycosides and vancomycin and antifungals if patient is not on antifungal prophylaxis. Treatment may be modified after final reports. Stress dose of steroids are recommended for patients in septic shock.

(Hydrocortisone 50 mg every 6 hours with or without fludrocortisones oral 50 mcg daily)

Role of Drotrecogin alpha (Xigris) or recombinant human activated protein (APC) in neutropenic patients has not been defined.

Empiric antifungal therapy in persistent neutropenia(level-2)

Empiric antifungal therapy may be started after 4-7 days of antibiotic if patient does not respond clinically. Fluconazole, Amphotericin B, Lipid Amphotericin B preparation, Itraconazole solution and caspofungin has been successfully used. Inspite of non-inferiority not proven in randomized trial for voriconazole with respect to liposomal Amphotericin B, most guidelines recommend its use in empiric setting due to

trial design issues.1 Fluconazole should not be used in empiric setting if it was used in prophylaxis and has limitation due to lack of activity against molds.

Pre-emptive antifungal therapy- (level-3)

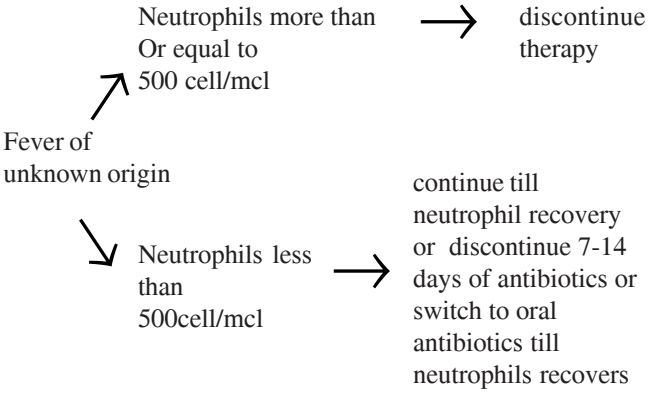
This is a new concept which involves Chest and Sinus CT Scan, laboratory markers or both to decide antifungal therapy. For this to be used in clinical practice serology assay needs to be validated. Evidence is preliminary at present for its routine use.

Follow up of patients with neutropenic fever-

Daily evaluation by health care professional is important. Regular review of previously obtained culture should be done. Repeat blood cultures for clearance of blood infections are needed. Evaluate drug toxicity and end organ toxicity (LFT and renal function test twice a week). Overall response needs to be evaluated between 3-5 days.

Follow up therapy of responding patients-

It is important to consider if patient has documented infection or not



Documented infections Suggested duration of therapy →

Skin and soft tissue 7-14 days Blood stream infection uncomplicated Gram –ve 10-14 days Gram +ve 7-14 days S aureus- 2 weeks after –ve blood Culture and –ve transesophageal ECHO Yeast >/= 2 weeks after negative culture Consider catheter removal for blood stream infection with candida, S aureus, P aeruginosa, Corynebacterium jeikeium, Acinetobacter, Bacillus,yeast, Molds, VRE, Stenotrophomonas Maltophilia

Sinusitis 10-21 days Bacterial pneumonia 10-21 days Molds minimal 12 weeks Viral-HSV/ VZV- 7-10 days of antiviral

Follow up therapy of non-responding patients-

In non-responding patients also it important to categorize if infection is documented

Fever of unknown origin

- Stable → continue same antibiotics → add anti Fungal activity against Molds
- Unstable → broaden coverage for anaerobes, Resistant Gram +ve, Gram –ve Consider adding G-CSF Ensure coverage for candida → For fever >/= 4 days

Duration of treatment may depend upon clinical course, neutropenia recovery and toxicities.

Documented infection	→	Appropriate antibiotic for isolated pathogen Consider G-CSF Consider granulocyte transfusion for life threatening bacterial and fungal infections

Therapy for invasive fungal infections

Invasive Candidiasis- (level-2)

Invasive Candida infection is an important fungal infection. The crude mortality rate for candidemia varies from 23-50%. Fluconazole, AmphotericinB, Voriconazole and Caspofungin may be used for invasive candidiasis. It appears that caspofungin had favourable response rate and better safety profile as compared to Amphotericin B. As number of patients with neutropenia in the studies evaluating these drugs in invasive candidiasis is small, the optimal therapy for these patients remains undefined.

Invasive Aspergillosis: (level-2)

Invasive Aspergillosis is common in patients with prolonged neutropenia. Voriconazole has better efficacy as compared to amphotericin B. In neutropenic patients also response was higher and is considered standard of care. Other antifungals may also be used eg- ampotericin B, Lipid preparation of amphotericin B, caspofungin. Combination antifungals voriconazole with caspofungin, amphotericin B with caspofungin has shown better efficacy as compared to single agent in smaller trials. At present it is not possible to recommend combination antifungals for aspergillosis.

Zygomycosis and other mold infections:

Frequency of zygomycosis infection appears to be increasing. There is no level 1 evidence for treatment recommendation. These patients should receive amphotericin B (Preferably lipid preparation) and aggressive surgical debridement. Invasive Fusarium infection needs treatment with voriconazole, amphotericin B (preferably lipid preparation). Scedosporium species are resistant to amphotericin B and they need to be treated with Itraconazole or voriconazole.

Prophylaxis for infections- (level-1)

Antibacterial prophylaxis during neutropenia:

There has been evidence of antibiotic prophylaxis decreasing the risk of all cause mortality, infection related mortality. There are important risk involved with its use. There are immediate side effects, potential for selection of resistant organism. At present fluoroquinolones may be used in patients with expected duration of neutropenia for more than 7 days. It is also important to review the resistant pattern for the fluoroquinolones at the individual center before starting the use of this drug.

Antibacterial agents-

Overall risk of infection	Examples	Febrile neutropenia risk category	Antimicrobial Prophylaxis
Low	Standard chemotherapy for solid tumors Anticipated neutropenia less than 7 days	Low	Bacterial-none Fungal- none Viral- none unless prior HSV episode
Intermediate	Autologous HSCT Lymphoma Multiple Myeloma CLL Purine analogs Anticipated neutropenia 7-10 days	Usually high	Bacterial-consider fluroquinolones Fungal- consider fluconazole during neutropenia and for anticipated mucositis Viral-during neutropenia and at least 30 days after 30 days HSCT

Overall risk of infection	Examples	Febrile neutropenia risk category	Antimicrobial Prophylaxis
High	Allogeneic HSCT Acute leukemia- Induction Consolidation GVHD treated high dose steroids Anticipated neutropenia more than 10 days	Usually high	Bacterial-consider fluroquinolones Viral-during neutropenia and at least 30 days after HSCT Fungal-consider appropriate antifungals

Gram positive agents	DOSE	Spectrum	Comments
Vancomycin	15mg/kg IV every 12 hrs	Gram +ve organism except VRE	Not used routinely except with certain risk factors
Linezolid	600 mg PO/IV 12 hrs	Gram positive organism including VRE	Thrombocytopenia (0.3-10%) Not for routine use Treatment option for VRE and MRSA
Broad spectrum agents			
Cefepime	2 gm IV every 8 hr	Broad activity against most Gram +ve and Gram –ve organisms Not active against most anaerobes, MRSA, Enterococcus	Use for suspected / proven CNS infection with susceptible organism

Broad spectrum agents	DOSE	Spectrum	Comments
Cefepime	2 gm IV every 8 hr	Broad activity against most Gram +ve and Gram –ve organisms Not active against most anaerobes, MRSA, Enterococcus	Use for suspected / proven CNS infection with susceptible organism
Ceftazidime	2 gm IV every 8 hr	Relatively poor Gram +ve activity Breakthrough streptococcal infection Not active against most anaerobes, MRSA, Enterococcus	Use for suspected / proven CNS infection with susceptible organism

Broad spectrum agents	DOSE	Spectrum	Comments
Imipenem/ cilastatin	500mg IV every 6hr	Broad spectrum activity against most gram +ve	Imipenem may have low threshold for seizure
Meropenem	1 gram IV every 8hr (2 gm every 8hr for meningitis)	and gram –ve and anaerobes Not active against VRE and MRSA	threshold in patients with CNS infection/ CNS malignancies or renal dysfunction
Piperacillin/ Tazobactum	4.5 gram IV 6 hr	Broad spectrum activity against most gram +ve and gram –ve and anaerobes Not active against VRE and MRSA	Not recommended for meningitis May result in false positive galactomannan essay

Broad spectrum agents	DOSE	Spectrum	Comments
Tigecycline	100 mg load than 50 mg IV 12 hr	Broad spectrum activity gram –ve, anaerobes, VRE, MRSA Poor activity against pseudomonas	Poor activity against blood stream infection Nausea Not studied in neutropenic patients
Ciprofloxacin	500-750 mg PO every 12 hr or 400 mg IV every 8-12 hr	Active against gram –ve and atypical (eg-legionella) organism No activity against anaerobic organisms	Avoid empiric therapy if fluroquinolones used as prophylaxis Oral antibiotic combination with (amoxicillin/ clavulanate or clindamycin) In combination with antipseudomonal penicillin in high risk patients

Broad spectrum agents	DOSE	Spectrum	Comments
Levofloxacin	500-750 mg oral or IV daily	Active against gram –ve and atypical (eg-legionella) organism Limited activity against anaerobic organisms Prophylaxis in neutropenic patients	Limited studies as empirical therapy
Aminoglycosides	Dosing indivisualized with monitoring of levels	Activity primarily against gram –ve organism	Nephotoxicity and ototoxicity limit use
Antifungal agents			
Fluconazole	400 mgIV/PO daily	Active against candida Active against dimorphic fungi	Candida krusei is always resistant and Candida glabrata has variable resistance Inactive against molds

Broad spectrum agents	DOSE	Spectrum	Comments
Itraconazole	200 mg IV 12 hrly for 4 doses, followed by 200 mg daily. Oral 400 mg daily	Active against Candida and Aspergillosis Active against dimorphic fungi	Contraindicated in significant cardiac dysfunction as it has negative inotropic effect IV formulations may worsen preexisting renal dysfunction
Voriconazole	6 mg/kg IV 12 hrly for 2 doses, then 4 mg/kg every 12 hrs	Active against Candida and Aspergillus Active against dimorphic fungi	Zygomycetes are resistant IV formulation may worsen renal impairment

Broad spectrum agents	DOSE	Spectrum	Comments
Amphotericin B desoxycholate	0.5-1.5 mg/kg/day IV	Broad spectrum activity candida, aspergillus (except aspergillus terreus), dimorphic fungi, zygomycetes	Infusional and renal toxicity including electrolyte wasting Saline loading may reduce renal toxicity
Liposomal amphotericin B	3 mg/kg /day IV		Less infusional and renal toxicity as compared to Ampho B
Amphotericin B lipid complex	5 mg/kg/day IV		Less infusional and renal toxicity as compared to Ampho B
Caspofungin	70 mg IV, then 50 mg IV daily	Active against candida and aspergillus	Primary therapy for candidemia and invasive candida Salvage therapy for aspergillus Excellent safety profile

Role of G-CSF-

Primary Prophylaxis:

	Risk category	Role of G-CSF
	High(>20%)	CSF
Evaluation of risk	Intermediate	Consider
of Febrile neutropenia	(10-20%)	CSF
Following chemotherapy	Low (<10%)	No CSF

Secondary Prophylaxis:

Febrile neutropenia or Dose limiting neutropenic event	If G-CSF used earlier dose reduction If no prior G-CSF than it should be used

Suggested Reading-

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12. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Eng J Med. 2004;351:1391-1402

Chemotherapy Induced Nausea and Vomiting

Burden of the Disease

Chemotherapy induced nausea and vomiting remains one of the most distressing side effects of chemotherapy. It is a result of either treatment-related toxicity or complications directly or indirectly related to the cancer. Inadequately controlled emesis impairs functional activity and quality of life for patients, increases the use of health care resources, and may occasionally compromise adherence to treatment. Overall, approximately 70% to 80% of cancer patients on chemotherapy experience nausea and/or vomiting and over 20% are forced to postpone or refuse potentially curative treatment.

Types of Chemotherapy Induced Nausea Vomiting

1. **Acute CINV:** Acute nausea and vomiting develops within the first 24 hrs after chemotherapy administration. No single neurotransmitter is likely to be responsible for all chemotherapy-induced nausea and vomiting, but it appears that serotonin is particularly important in the pathophysiology of acute vomiting.

2. **Delayed CINV:** Nausea and vomiting occurring more than 24 hours after chemotherapy administration. Unlike acute CINV, delayed vomiting is due to substance P dependent pathways i.e. through Nk1 receptors.

3. **Anticipatory CINV:** Nausea and vomiting that occurs as a result of a conditioned response to prior episodes of CINV. It is a classically conditioned response to stimuli such as smell, sight of chemotherapy room and thought of previous CINV. It depends on many variables such as young age, female sex, state of anxiety and degree of motion sickness.

4. **Breakthrough CINV:** Nausea and vomiting that happens inspite of optimal preventive treatment. It is usually due to inadequate prophylaxis.

5. **Refractory CINV**: Nausea and vomiting that recurs in subsequent cycles of therapy in spite of all previous preventive and rescue treatments. It is due to inadequate prophylaxis, inadequate treatment and use of highly emetogenic regimens.

Emetogenic Levels of Intravenously Administered Antineoplastic Agents

The recent clinical practice guidelines make antiemetic recommendations based on the risk categories. Both the American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC) classify chemotherapy induced nausea & vomiting as high (> 90%), moderate (> 30% to 90%), low (10% to 30%), and minimal (< 10%) emetic risk.

Level I	Level II	Level III	Level IV
(Minimal risk, <10%)	(Low risk, 10-30%)	(Moderate risk, 31-90%)	(High risk, >90%)
Bevacizumab	Bortezomib	Carboplatin	Carmustine
Bleomycin	Cetuximab	Cyclophosphamide	Cisplatin
Busulfan	Cytarabine(d”	(<1.5g/m2)	Cyclophosphamide
Cladribine	100mg/m2)		(>1.5g/m2)
Fludarabine	Topotecan	Cytarabine	Dacarbazine
Vinblastine	Docetaxel	(>1g/m2)	Mechlorethamine
Vincristine	Etoposide	Daunarubicin	Streptozocin
Vinorelbine	Flourouracil	Doxorubicin	
	Gemcitabine	Epirubicin	
	Ixabepilone	Idarubicin	
	Lapatinib	Ifosfamide	
	Methotrexate	Irinotecan	
	Mitomycin	Oxaliplatin	
	Mitoxantrone		
	Paclitaxel		
	Pemetrexed		

Recommended Treatment Options

Acute nausea & vomiting

Emetogenic potential	Antiemetics
High	Serotonin Antagonist + Dexa + Aprepitant (I,A)
Moderate	
A) Anthracycline + cyclophosphamide (AC) based	Serotonin Antagonist + Dexa + Aprepitant (II,A)
B) Non AC based	Serotonin Antagonist + Dexa (I,A)
Low	A single agent such as Dexamethasone. (I, A).
Minimal	No routine prophylaxis. (V, D).

Delayed nausea & vomiting

Emetogenic potential	Antiemetics
High	Dexa + Aprepitant (II,A)
Moderate	
A) AC based	Dexa or Aprepitant (II,A)
B) Non AC based	Dexa (I,A) or Serotonin Antagonist (II, B)
Low	No routine prophylaxis.
Minimal	No routine prophylaxis.

Specific Problem Recommendations	
Multiple day Chemotherapy	As acute CINV on chemotherapy days As delayed CINV 1-2 days after chemotherapy Aprepitant & Palanosetron have not been investigated (II,A).
Refractory nausea vomiting	Add Dopamine antagonist to Serotonin Antagonist + Dexa (V, D).
Anticipatory nausea vomiting	Lorazepam or similar drugs Behavioural techniques. (V, D).
High dose chemotherapy	Dopamine antagonist + Serotonin Antagonist + Dexa (III,C).

Types & doses of Antiemetics

Drug & Schedule	Oral Dose (mg)	I.V. dose(mg)
Serotonin antagonist (OD)		
Ondansetron	16 - 24	8
Granisetron	2	1
Tropisetron	5	5
Dolasetron	100	100
Palonosetron (one/week)	N. A.	0.25
Dopamine antagonist (tds to qid)		
Metoclopramide	20 – 30	—
Prochlorperazine	10 - 20	—
Domperidone	20	Not for I.V. use
Metopimazine	15 – 30	Only as continuous infusion
Corticosteroids (OD)		
Dexamethasone	20	8 – 20
Prednisolone	100 - 150	
Methyl Prednisolone	Not for oral use	100
Neurokinin Antagonist		
Aprepitant OD	125 mg day 1 followed by 80 mg on day 2, 3 after chemotherapy.	When combined with steroids, dose of steroid to be reduced by 50-75%
Others (1 -4 times daily)		
Lorazepam	1-2	

Evidence Based Management Guidelines

The treatment recommendations that follow reflect a composite of the consensus recommendations of various randomized controlled trials.

Highly Emetogenic Chemotherapy

The three drug regimen mentioned above is now a standard of care in highly emetogenic chemotherapy. This regimen when compared with two-drug regimen (5HT3 antagonist and Dexamethasone) in various randomized phase-3 trials has shown significant reduction in acute (Day 1) emesis i.e. 7-17% vs 19-33% respectively. Various placebo controlled multicentric phase three trials have also shown aprepitant to have significant effect on delayed vomiting which translated into better quality of life. Schmoll et al demonstrated in their phase three study that Aprepitant plus Dexamethasone when compared with 5HT3 antagonist plus Dexamethasone had significant reduction in delayed CINV (21% vs 36% respectively). (**Level I, A)**

Moderate emetogenic therapy (anthracyclines based)

Aprepitant when added to 5HT3 antagonist and Dexamethasone therapy to prevent emesis in breast cancer patients on anthracycline based chemotherapy, significantly decreased day1 to day5 emesis. Heersted et al carried out a double blind phase three study of 866 patients in which experimental arm (i.e. arm managed with three drugs 5HT3+ Dexa+ Aprepitant) had significantly less day 1-5 vomiting when compared with control arm (i.e. arm managed with 5HT3 + Dexamethasone). (**Level II, A)**

Moderate emetogenic therapy (non anthracyclines based)

The recommendation of two-drug regimen (5HT3 antagonist and Dexa) for the prevention of acute emesis in this group is

supported by a meta-analysis, which examined 11 randomized trials that used 5-HT_3 receptor antagonists with moderately emetic chemotherapy. It demonstrated that the risk of acute emesis was decreased with the use of 5-HT_3 receptor antagonists (odds ratio = 0.47; 95% CI, 0.39 to 0.58) and that the risk was further reduced when drugs in this class were combined with dexamethasone. **(Level I , A)**

Similarly for the prevention of delayed emesis, dexamethasone as a single agent is recommended as demonstrated by the Italian group in their phase three trial. This trial demonstrated that dexamethasone was superior to placebo in decreasing delayed emesis (87% *v* 77%, respectively; $P < .02$), that dexamethasone plus 5-HT_3 antagonist was not superior to dexamethasone alone (92% *v* 87%, respectively), and also that the combination was associated with more constipation**. (Level I, A)**

Low Emetic Risk

In this group, Dexamethasone, as a single agent is recommended for both acute and delayed emesis. A meta-analysis of 32 RCTs involving 5,613 patients demonstrated that dexamethasone was superior to placebo or no treatment for complete protection from acute emesis (odds ratio = 2.22; 95% CI, 1.89 to 2.60) and for complete protection from delayed emesis (odds ratio = 2.04; 95% CI, 1.63 to 2.56). (**Level I, A)**

Management of Anticipatory Nausea and Vomiting

- Good control of emesis in previous chemotherapy doses.
- Behavior therapy with systemic desensitization. (**Level V, D**)
- Drugs like alprazolam (0.5 – 2mg po qid) or olanzapine.

Management of refractory and breakthrough Nausea and vomiting

Though there are no clear guidelines for this type of CINV, combination antiemetic therapy consisting of different classes of antiemetic drugs is one approach that can be used in some patients. The addition of dopamine-receptor antagonists (metoclopramide), and agents such as benzodiazepines or neuroleptics (Olanzapine) to the standard treatment can be considered. (**Level V, D)**

Multiple Day Chemotherapy

$5HT_3$ receptor antagonist and dexamethasone during each day of chemotherapy followed by Dexamethasone for delayed emesis after the last day of chemotherapy is the standard of care. The role of Aprepitant in this setting is not yet proven (**Level II, A).**

1. Evidence-Based Recommendations for Cancer Nausea and Vomiting

Arash N, Sydney MD, Karl AL, et al. *J Clin Oncol 2008;* 26: 3903-10

The experience of patients living with cancer and being treated with chemotherapy often includes the symptoms of nausea and vomiting. To provide a framework for high-quality management of these symptoms, we developed a set of key targeted evidence-based standards through an iterative process of targeted systematic review, development, and refinement of topic areas and standards and consensus ratings by a multidisciplinary expert panel as part of the RAND Cancer Quality–Assessing Symptoms Side Effects and Indicators of Supportive Treatment Project. For nausea and vomiting, key clinical standards included screening at the initial outpatient and inpatient visit, prophylaxis for acute and delayed emesis in patients receiving moderate to highly emetic chemotherapy,

and follow-up after treatment for nausea and vomiting symptoms. In addition, patients with cancer and small bowel obstruction were examined as a special subset of patients who present with nausea and vomiting. The standards presented here for preventing and managing nausea and vomiting in cancer care should be incorporated into care pathways and should become the expectation rather than the exception.

2. American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006

Mark G.K, Paul J.H, Mark R.S, et al. J Clin Oncol 2006; 24:2932-47.

PURPOSE: To update the 1999 American Society of Clinical Oncology guideline for antiemetics in oncology.UPDATE METHODOLOGY: The Update Committee completed a review and analysis of data published from 1998 thru February 2006. The literature review focused on published randomized controlled trials, and systematic reviews and meta-analyses of published phase II and phase III randomized controlled trials. RECOMMENDATIONS: The three-drug combination of a 5-hydroxytryptamine-3 (5-HT_3) serotonin receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy of high emetic risk. For persons receiving chemotherapy of high emetic risk, there is no group of patients for whom agents of lower therapeutic index are appropriate first-choice antiemetics. These agents should be reserved for patients intolerant of or refractory to 5-HT_3 serotonin receptor antagonists, neurokinin-1 receptor antagonists, and dexamethasone. The three-drug combination of a 5-HT_3 receptor serotonin antagonist, dexamethasone, and aprepitant is recommended for patients receiving an anthracycline and cyclophosphamide. For patients receiving other chemotherapy of moderate emetic risk, the Update Committee continues to recommend the two-drug combination of a 5-HT_3 receptor

serotonin antagonist and dexamethasone. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended for the prevention of delayed emesis. The Update Committee no longer recommends the combination of a 5-HT_3 serotonin receptor antagonist and dexamethasone for the prevention of delayed emesis after chemotherapeutic agents of high emetic risk. CONCLUSION: The Update Committee recommends that clinicians administer antiemetics while considering patients' emetic risk categories and other characteristics.

3. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group

Hesketh PJ, Grunberg SM, Gralla RJ, et al. J Clin Oncol. 2003; 21:4112-9

Purpose: In early clinical trials with patients receiving highly emetogenic chemotherapy, the neurokinin antagonist aprepitant significantly enhanced the efficacy of a standard antiemetic regimen consisting of a type-three 5-hydroxytryptamine antagonist and a corticosteroid. This multicenter, randomized, double-blind, placebo-controlled phase III study was performed to establish definitively the superiority of the aprepitant regimen versus standard therapy in the prevention of chemotherapy-induced nausea and vomiting (CINV). PATIENTS AND METHODS: Patients receiving cisplatin > or = 70 mg/m2 for the first time were given either standard therapy (ondansetron and dexamethasone on day 1; dexamethasone on days 2 to 4) or an aprepitant regimen (aprepitant plus ondansetron and dexamethasone on

day 1; aprepitant and dexamethasone on days 2 to 3; dexamethasone on day 4). Patients recorded nausea and vomiting episodes in a diary. The primary end point was complete response (no emesis and no rescue therapy) on days 1 to 5 post cisplatin, analyzed by a modified intent-to-treat approach. Treatment comparisons were made using logistic regression models. Tolerability was assessed by reported adverse events and physical and laboratory assessments. RESULTS: The percentage of patients with complete response on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), as were the percentages on day 1, and especially on days 2 to 5 (P <.001 for all three comparisons). CONCLUSION: Compared with standard dual therapy, addition of aprepitant was generally well tolerated and provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy.

4. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment

H. J. Schmoll, M. S. Aapro, S. Poli-Bigelli et al. Ann Oncol 2006; 17:1000-1006.

Background: We compared an aprepitant regimen with a control regimen of ondansetron + dexamethasone given for 4 days. Patients and methods: Patients scheduled to receive cisplatin ≥ 70 mg/m^2 were randomized to either the aprepitant regimen (aprepitant, ondansetron and dexamethasone on day 1; aprepitant and dexamethasone on days 2–3; dexamethasone on day 4) or control regimen (ondansetron + dexamethasone on days 1–4). Patients recorded vomiting, nausea and rescue therapy use. The primary end point was complete response

(no vomiting and no use of rescue therapy) in the overall phase (days 1–5 post-cisplatin). Results**:** Complete response rates were higher in the aprepitant than control group in the overall (72% versus 61%; $P = 0.003$), acute (day 1; 88% versus 79%; $P = 0.005$) and delayed phases (days 2–5; 74% versus 63%; $P = 0.004$), as were rates of [s]no vomiting (overall 77% versus 62%, $P \geq 0.001$; acute 89% versus 81%, $P = 0.004$; delayed 79% versus 64%, P 0.001). Rates of no rescue therapy were similar between groups. Conclusions: Compared with an antiemetic regimen in which ondansetron + dexamethasone were given for 4 days, the aprepitant regimen was superior in the acute, delayed and overall phases of chemotherapy-induced nausea and vomiting. The aprepitant regimen should be considered a new standard of antiemetic therapy for cisplatin-treated patients. www.ClinicalTrials.gov Identifier: NTC00090207

5. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy.

Herrstedt J, Muss HB, Warr DG, et al Cancer 2005;104:1548-55.

Background: An aprepitant (APR) regimen was evaluated for prevention of nausea and emesis due to moderately emetogenic chemotherapy (MEC) over multiple cycles.

Methods: The authors performed a randomized, double-blind study. Eligible patients with breast carcinoma were naïve to emetogenic chemotherapy and treated with cyclophosphamide alone or with doxorubicin or epirubicin. Patients were randomized to receive either an APR regimen (Day 1: APR 125 mg, ondansetron [OND] 8 mg, and dexamethasone [DEX] 12 mg before chemotherapy and OND 8 mg 8 hrs later; Days

2-3: APR 80 mg every day) or a control regimen (Day 1: OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hrs later; Days 2-3: OND 8 mg twice per day). Data on nausea, emesis, and use of rescue medication were collected. The primary end point was the proportion of patients with a complete response (CR; no emesis or use of rescue therapy) in Cycle 1. Efficacy end points for the multiple-cycle extension were the probabilities of a CR in Cycles 2-4 and a sustained CR rate across multiple cycles.

Results: Of 866 patients randomized, 744 (85.9%) entered the multiple-cycle extension, and 650 (75.1%) completed all 4 cycles. Overall, the CR was greater with the APR regimen over the 4 cycles: 53.8% versus 39.4% for Cycle 2, 54.1% versus 39.3% for Cycle 3, and 55.0% versus 38.4% for Cycle 4. The cumulative percentage of patients with a sustained CR over all 4 cycles was greater with the APR regimen (P = 0.017).

Conclusions: The APR regimen was more effective than a control regimen for the prevention of nausea and emesis induced by MEC over multiple chemotherapy cycles.

6. Dexamethasone Alone or in Combination with Ondansetron for the Prevention of Delayed Nausea and Vomiting Induced by Chemotherapy

The Italian Group for Antiemetic Research. N Engl J Med 2000; 342:1554-59.

Background The prevention of delayed nausea and vomiting caused by moderately emetogenic chemotherapy for cancer has not been studied systematically. *Methods* We enrolled patients who were scheduled to receive chemotherapy for the first time in a double-blind, randomized, multicenter study. All the patients received ondansetron combined with dexamethasone for prophylaxis against emesis that might occur

within 24 hours after the start of chemotherapy (acute emesis). They were then divided into two groups: patients who did not have either vomiting or moderate-to-severe nausea (the low-risk group) and patients who had one or both (the high-risk group). Patients in the low-risk group were then randomly assigned to one of the following regimens, given on days 2 through 5 after the start of chemotherapy: oral placebo, 4 mg of dexamethasone given orally twice daily, or 8 mg of ondansetron in combination with 4 mg of dexamethasone, given orally twice daily. Patients in the high-risk group were randomly assigned to receive oral dexamethasone alone or in combination with ondansetron at the same doses as those used in the low-risk group. *Results* Among the 618 patients in the low-risk group, there was a complete absence of both delayed vomiting and moderate-to-severe nausea in 91.8 percent of those who received ondansetron combined with dexamethasone, 87.4 percent of those who received dexamethasone alone, and 76.8 percent of those who received placebo. The proportions of patients who were protected by dexamethasone combined with ondansetron or by dexamethasone alone were significantly greater than the proportion protected by placebo ($P<0.001$ and $P<0.02$, respectively). Of the 87 patients in the high-risk group, complete protection was achieved in 40.9 percent of those treated with ondansetron and dexamethasone and in 23.3 percent treated with dexamethasone alone (P not significant). ·*Conclusions* The best way to prevent delayed nausea and vomiting in patients receiving moderately emetogenic chemotherapy is to control these complications within the first 24 hours after the start of chemotherapy. Dexamethasone alone provides adequate protection against delayed emesis in patients at low risk (those who have not had acute emesis).

Late Effects in Childhood Cancer Survivors: Guidelines for Evaluation & Monitoring

Introduction

Survival after the diagnosis of cancer in children has become a rule rather than an exception. Currently, more than 70% of children with cancer in developed countries survive at least 5 years and most survivors are cured. [1,2] Consequent to this success arise challenges inherent in coordinating life long health care for a high risk group of patients predisposed to a variety of cancer related complications. Cancer-related sequelae that persist or develop 5 years after the cancer diagnosis are termed late effects.

Magnitude of late effects & its determinants

Approximately 30-40,000 cases of childhood cancer occur in our country annually. Even with conservative estimates of 10-20% long-term cure, approximately 3.5 -7,000 survivors are added to our population each year. Two-third of survivors are known to have at least one late effect of their cancer therapy and of these, one third have serious or life threatening complications. [3] The incidence of most late effects increases

with age, often becoming clinically apparent decades after therapy.[4]

The degree of late effects is essentially a function of 3 types of factors which include a) tumor-related factors such as histology, site and biology b) treatment-related factors such as type of radiation therapy(dose/fraction size/volume/machine energy), chemotherapy (type/ dose/ schedule), and surgery (site/technique), and c) host-related factors such as developmental status, genetic predisposition, organ function, premorbid state, inherent tissue sensitivity and capacity of normal tissue repair.

Long Term Follow up at Tata Memorial Hospital

To prevent or ameliorate late effects by early diagnosis with therapeutic intervention, a common approach is to adopt an individualized life long health care plan for each survivor encompassing screening, surveillance and prevention that incorporates risks which in turn depends on the site of underlying malignancy, the type & intensity of treatment and age at treatment. One such model was established at St. Jude Children's Research Hospital, USA.[5] Drawing inspiration from the same, the Tata Memorial Hospital After Completion of Therapy (ACT) Clinic was initiated as a follow up clinic for long term survivors of childhood cancer in February 1991. [6] The aims of the clinic are to monitor growth, development, and sexual maturation, as well as the somatic late effects of therapy and to apply corrective measures whenever feasible.

Our ACT model addresses 3 basic facets of childhood cancer survivor care by providing 1) longitudinal care at a tertiary cancer centre by a single physician coordinator who integrates patient care, education and research; 2) ongoing communication with primary care provider to ensure continuity of follow up; and 3) education and empowerment of survivors

to increase their awareness about late effects, need for surveillance and lifestyle factors that influence late effects.

From February 1991 to February 2007, 978 survivors were registered in the Tata Memorial ACT Clinic[7]. The presence of late effects in survivors can be recorded and the severity of specific complications can be graded according to Garre's grading system or according to the Common Terminology Criteria for Adverse Events (version 3), a scoring system developed through the National Cancer Institute [8]. This system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5).In Tata Memorial ACT Clinic, grading is done according to a simpler Garre's grading system developed in Italy [9]. Overall, 488 (50%) survivors exhibited no evidence of cancer-related complications (grade 0). 205 (21%) survivors had asymptomatic laboratory changes detected by health screening prescribed by the study protocol e.g., screening for transfusion-transmitted infection (grade 1). 85 (8%) had moderate symptomatic changes that could be corrected by simple therapeutic interventions e.g., thyroid hormone replacement therapy for compensated biochemical hypothyroidism (grade 2). 164 (17%) survivors had severe impairments such as cosmetic changes, reproductive dysfunction and learning deficits requiring special educational support (grade 3). 36(4%) survivors experienced life threatening events such as late primary cancer recurrence, the development of a subsequent malignant neoplasm, or death (grade 4).

Long Term Guidelines for Survivors of Childhood Cancers ;-

There are various guidelines for long term follow up for survivors. One of the frequently used guidelines is by Children's Oncology Group (COG-LTFU Guidelines).[10,11] These are risk-based, exposure-related clinical practice

guidelines for screening & management of late effects resulting from therapeutic exposures used during treatment for pediatric malignancies. There are no randomized control trials based on which level 1 evidence can be generated for formulation of guidelines. Hence these guidelines represent a statement of consensus from a panel of experts .The guidelines are both evidence based (utilizing established association between therapeutic exposures & late effects to identify high risk categories) & grounded in the collective clinical experience of experts (matching the magnitude of risk with the intensity of screening recommendations)[12]. To make evidence based recommendations for the long term follow up of survivors, a scoring system is used in COG Guidelines. Each score relates to the strength of association of the identified late effect with the specific therapeutic exposure based on current literature, and is coupled with a recommendation for periodic health screening based on collective clinical experience of panel of experts.

Explanation of Scoring Used in COG-LTFU Guidelines [13] :

Score	Statement of consensus
1	There is uniform consensus of the panel that (1) There is high-level evidence linking the late effect with therapeutic exposure and(2) the screening recommendation is appropriate based on collective clinical experience of panel members.
2A	There is uniform consensus of the panel that (1) There is lower-level evidence linking the late effect with therapeutic exposure and(2) the screening recommendation is appropriate based on collective clinical experience of panel members.

Contd...

Contd...

Score	Statement of consensus
2B	There is non-uniform consensus of the panel that (1) There is lower-level evidence linking the late effect with therapeutic exposure and (2) the screening recommendation is appropriate based on collective clinical experience of panel members.
3	There is major disagreement that the recommendation is appropriate.

The COG Guidelines emphasize the need for a thorough history & physical examination as the primary assessment for cancer related late effects during periodic screening. Recommendation & frequency of investigations are based on the score; thus reducing the burden of unnecessary investigations. Details on system wise late effects, possible causative agents, recommended evaluation & frequency of monitoring for late effects can be accessed on the COG website (www.survivorshipguidelines.org).

However, stringent COG guidelines are difficult to adopt in developing countries like India due to logistic and financial constraints. To ensure compliance on ongoing basis, a more practical follow up strategy is suggested by the Scottish guidelines [14] for long-term follow-up of childhood cancer survivors based on the intensity of therapy received.[15] The three levels of follow up recommended are summarized in table below. To optimize the follow-up of long-term survivors each centre should adopt its own policy keeping in mind the basic guiding principles of existing international standards and strategies.

Level	Treatment	Method of follow up	Frequency	Example
A	- surgery alone - low risk chemotherapy	postal or telephone	1-2 yrs	- Wilms st1/2 - LCH (single system disease)
B	- chemotherapy - low dose cranial irradiation less than or equal to 24 Gy	Nurse or primary care-led (with appropriate training protocols)	1-2 yrs	majority of patients (e.g. All in first remission)
C	- radiotherapy except low dose cranial irradiation - mega therapy	medically supervised long term follow up clinic	annual	- brain tumors - post BMT - stage 4 pts (any tumor type)

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Selected Abstracts:

1) Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia.

Pui CH, Cheng C, Leung W, et al. N Engl J Med. 2003;349:640-9

Backgraound: Children who survive acute lymphoblastic leukemia are at risk for leukemia-related or treatment-related complications, which can adversely affect survival and socioeconomic status. We determined the long-term survival and the rates of health insurance coverage, marriage, and employment among patients who had attained at least 10 years of event-free survival. METHODS: A total of 856 eligible patients were treated between 1962 and 1992 in 13 consecutive clinical trials. Survival rates, the cumulative risk of a second neoplasm, and selected indicators of socioeconomic status were analyzed for the entire group and for patients who did or did not receive cranial or craniospinal radiation therapy during initial treatment. RESULTS: Fifty-six patients had major adverse events, including 8 deaths during remission, 4 relapses, and 44 second neoplasms (41 of them radiation-related); most of the second neoplasms were benign or of a low grade of malignant potential. The risk of a second neoplasm was significantly higher in the 597 patients who received radiation therapy (irradiated group) than in the 259 patients who did not receive radiation therapy (nonirradiated group) (P=0.04; estimated cumulative risk [+/-SE] at 20 years, 20.9+/-3.9 percent vs. 0.95+/-0.9 percent). The death rate for the irradiated group slightly exceeded the expected rate in the general U.S. population (standardized mortality ratio, 1.90; 95 percent confidence interval, 1.12 to 3.00), whereas that for the

nonirradiated group did not differ from the population norm (standardized mortality ratio, 1.75; 95 percent confidence interval, 0.34 to 5.00). The rates of health insurance coverage, marriage, and employment in the nonirradiated group were similar to the age- and sex-adjusted national averages. Despite having health insurance rates similar to those in the general population, men and women in the irradiated group had higher-than-average unemployment rates (15.1 percent vs. 5.4 percent and 35.4 percent vs. 5.2 percent, respectively), and women in the irradiated group were less likely to be married (35.2 percent vs. 48.8 percent). CONCLUSIONS: Children with acute lymphoblastic leukemia who did not receive radiation therapy and who have attained 10 or more years of event-free survival can expect a normal long-term survival. Irradiation is associated with the development of second neoplasms, a slight excess in mortality, and an increased unemployment rate.

2) Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study.

Hudson MM, Mertens AC, Yasui Y, et al Jama. 2003;290:1583-92

CONTEXT: Adult survivors of childhood cancer are at risk for medical and psychosocial sequelae that may adversely affect their health status. OBJECTIVES: To compare the health status of adult survivors of childhood cancer and siblings and to identify factors associated with adverse outcomes. DESIGN, SETTING, AND PARTICIPANTS: Health status was assessed in 9535 adult participants of the Childhood Cancer Survivor Study, a cohort of long-term survivors of childhood cancer who were diagnosed between 1970 and 1986. A randomly selected cohort of the survivors' siblings (n = 2916) served as a comparison group. MAIN OUTCOME MEASURES: Six

health status domains were assessed: general health, mental health, functional status, activity limitations, cancer-related pain, and cancer-related anxiety/fears. The first 4 domains were assessed in the control group. RESULTS: Survivors were significantly more likely to report adverse general health (odds ratio [OR], 2.5; 95% confidence interval [CI], 2.1-3.0; P<.001), mental health (OR, 1.8; 95% CI, 1.6-2.1; P<.001), activity limitations (OR, 2.7; 95% CI, 2.3-3.3; P<.001), and functional impairment (OR, 5.2; 95% CI, 4.1-6.6; P<.001), compared with siblings. Forty-four percent of survivors reported at least 1 adversely affected health status domain. Sociodemographic factors associated with reporting at least 1 adverse health status domain included being female (OR, 1.4; 95% CI, 1.3-1.6; P<.001), lower level of educational attainment (OR, 2.0; 95% CI, 1.8-2.2; P<.001), and annual income less than 20 000 dollars (OR, 1.8; 95% CI, 1.6-2.1; P<.001). Relative to those survivors with childhood leukemia, an increased risk was observed for at least 1 adverse health status domain among those with bone tumors (OR, 2.1; 95% CI, 1.8-2.5; P<.001), central nervous system tumors (OR, 1.7; 95% CI, 1.5-2.0; P<.001), and sarcomas (OR, 1.2; 95% CI, 1.1-1.5; P =.01). CONCLUSION: Clinicians caring for adult survivors of childhood cancer should be aware of the substantial risk for adverse health status, especially among females, those with low educational attainment, and those with low household incomes.

3) Status of long term survivors after cancer in childhood.

Garre Mc Gandus, S.Cesanaet B,et al . American Journal of Pediatric hematoncology.1994;16: 2 143-152.

PURPOSE: This study aims at defining the frequency and severity of late effects in a series of 288 long-term survivors of childhood cancer treated from 1962 to 1982 at the Giannina

Gaslini Children's Research Hospital of Genoa, Italy. PATIENTS AND METHODS: All cases with a diagnosis of malignancy in childhood and a minimum of 2.5 years from discontinuation of treatment were considered eligible. For all cases the study included physical, endocrinological, and psychological examination. Groups of patients selected according to treatment underwent cardiac, pulmonary, orthopedic, and ophthalmologic evaluation. The sequelae observed were scored according to a grading system in which asymptomatic subclinical defects are distinguished from those that are sufficiently symptomatic to require some type of corrective measure. RESULTS: Overall, 200 of 288 cases (69.4%) presented with some kind of abnormality. Symptomatic changes were present in 92 cases (42%); in these, severe and life-threatening late toxicity was reported in 61 (21.2%) and 12 cases (4.2%), respectively. The major risk factors appeared to be irradiation, type of tumor, and whether the patient had received therapy before 1974. CONCLUSIONS: In our experience, this study demonstrates that there was a true excess of morbidity caused by the disease and its treatment in long-term survivors from almost any kind of childhood cancer. It also sheds light on how to prevent, diagnose, and adequately treat these patients and proposes specific criteria for the evaluation of the severity of delayed toxicity in long-term survivors of cancer in childhood.

4) Risk-based health monitoring of childhood cancer survivors: a report from the Children's Oncology Group

Nunez SB, Mulrooney DA, Hudson MM. Curr Oncol Rep. 2007; 6 :440-52

Because of therapeutic advances over the past 50 years, long-term survival is now a reality for nearly 80% of children and adolescents diagnosed with cancer. The growing population

of childhood cancer survivors is notable for its vulnerability to adverse health outcomes, many of which may not become clinically apparent until years after therapy completion. Early detection, prevention, and ameliorative interventions provide the opportunity to reduce cancer-related morbidity and mortality. This review is intended to complement the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. The objective of this review is to familiarize readers with the diverse health risks experienced by childhood cancer survivors that stem from the heterogeneous therapeutic interventions required to achieve disease control.

5) Long term follow up care in developing countries

P Kurkure, Pediatric blood cancer 2007,SLO62; 49:2

Because of improvements in Cancer therapy over last several decades more children are surviving cancer than ever before. Approximately 40,000 new childhood cancers are projected annually in India. Even with conservative estimates of 10-20% long term cure 3.5 – 7000 survivors are added to population each year. This is expected to increase exponentially with improved survival rates. The potential Public Health implication of such large number of high risk individuals in society are evident. There is a increasingly felt need for optimal delivery of health care to this growing, vulnerable population. Drawing inspiration from efforts at St. Jude Children Research Hospital, USA, follow-up clinic for long term survivors of childhood cancer was initiated at Tata Memorial Hospital in February 1991. This clinic was appropriately named After Completion of Therapy (ACT) Clinic to emphasize that ACTs are needed beyond therapy to achieve ²CURE ² in its full dimensions. Aims of this clinic are to monitor growth, development, sexual maturation and somatic late effects of therapy and to apply corrective measures whenever feasible.

Our ACT model has 3 basic facets; providing longitudinal care at a tertiary care centre. Second, ongoing communication with primary care provider ensures continuity of follow up and finally education and empowerment of survivors sensitizes them towards need for continued surveillance and healthy life style. From Feb 1991 to Feb. 2007, 978 survivors (off therapy and disease free for >2 years) have been enrolled in ACT clinic. Clinical characteristics of survivors are shown in Table I. Highlights of observations are 1) striking male preponderance (3:1) among survivors suggestive of preferential treatment to male child in our society. 2) Less frequent (8%) grade III sequel in survivors of hematolymphoid malignancies vis-à-vis. Solid tumors(26%) highlighting need for fine tuning of protocols.3) 212/978 (22%) survivors received cranial irradiation (CI) 142(15%) of these failed to attain normal growth potential and half had learning disabilities. CI should preferably be avoided. 4) Increased risk of death attributed to late recurrence and SMN. Long term follow up strategy should be effective as well as cost-effective and should include survivors' perspective. A special bond established between the survivors and the ACT team consolidates these efforts. The parents use the ACT platform to vocalize their fears, hopes, aspiration and look forward to continue the interaction which is risk/need based. Risk based follow up care may be the most appropriate method in our country with diverse socio–demographic, religious and cultural milieu. Creation of nationwide ACT clinics with tight linkage to primary care providers would be the right beginning. It would be important to sensitize primary care practitioners regularly regarding problems of survivors. Indian National Training Program in Practical Pediatric Oncology (INTPP) could play an important role in this direction.

Tumor Lysis Syndrome

Definition: Tumor lysis syndrome (TLS) is characterized by a group of metabolic derangements including hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia.caused by the massive and abrupt release of cellular components into the blood after the rapid lysis of malignant cells. It is observed most frequently in patients with malignancies with high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy such as acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma after the initiation of cytotoxic therapy.

Pathogenesis and Clinical Consequences

The release of intracellular metabolites, including nucleic acids, proteins, phosphorus, and potassium after the initiation of cytotoxic chemotherapy or cytolytic antibody therapy can overwhelm normal homeostatic mechanisms, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia. In some cases, TLS can lead to acute renal failure and even death due to uric acid or calcium phosphate precipitation, xanthine crystallization, tumor infiltration in the kidney, tumor-associated obstructive uropathy, drug associated nephrotoxicity, and/or acute sepsis.

The relative risk of developing TLS is significantly higher in patients with high uric acid levels (8 mg/dL) and high phosphorus levels.

Clinical manifestations: The clinical features of TLS may include nausea, vomiting, diarrhea, anorexia, lethargy, edema, fluid overload, hematuria, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possible sudden death. Although symptoms may occur before the start of chemotherapy, they are observed more commonly within 12 to 72 hours after the initiation of cytoreductive therapy. Complications resulting from TLS can compromise the efficacy or further administration of chemotherapy.

Classification

There is currently no universally accepted system for classification and grading. The most recent and preferred is Cairo and Bishop classification system based on defining laboratory or clinical TLS (LTLS or CTLS). This system distinguishes between patients who do not require therapeutic intervention versus those experiencing life-threatening clinical abnormalities.

This classification and grading system is currently being used by Children's Oncology Group

Under this system, LTLS is considered to be present if levels of two or more serum values of uric acid, potassium, phosphate, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after the initiation of treatment (Table 1). CTLS requires the presence of LTLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias/ sudden death, and seizures (Table 2). LTLS is considered to be either present or absent (Table 1), whereas

the grade of CTLS is defined by the maximal grade of the clinical manifestation (Table 2).

Incidence and Risk Factors

TLS occurs most frequently in patients with NHL and other hematologic malignancies, particularly Burkitt's lymphoma, ALL, and acute myeloid leukemia (AML). The overall incidence of LTLS and CTLS ranges from 14%-17% and 3%-5% in patients with AML, 21%-30% and 5%-8% in those with ALL, and 19%-40% and 6%-20% in patients with NHL, respectively. The syndrome is observed less frequently in other hematologic malignancies, including chronic lymphocytic leukemia on fludarabine (0.5%), NHL treated with the anti-CD20 monoclonal antibody rituximab (0.04% to 0.05%) and promyelocytic leukemia (<0.05%). Although occurrences are rare, a literature review revealed 45 case reports of TLS in patients with solid tumors, with a mortality rate of one in three in this patient set. Certain intrinsic tumor-related factors, therapy related factors and several conditions may predispose patients to developing TLS (Table 3-4)

Guidelines for prevention and management

The potential severity of complications resulting from the development of TLS necessitates measures for prevention in high-risk patients and prompts treatment in the event that symptoms arise. Recognition of risk factors, close monitoring of at-risk patients, and appropriate interventions are the key to preventing or managing TLS.

Management of Hyperuricemia

Fluids and hydration: Aggressive hydration and diuresis are fundamental to the prevention and management of TLS. The combination of hydration and enhanced urine flow promotes

the excretion of uric acid and phosphate by improving intravascular volume, renal blood flow, and glomerular filtration. Vigorous hydration is recommended for all patients in the intermediate to- high risk groups or for those with diagnosed LTLS or CTLS, with the exception of patients presenting with renal failure or oliguria. It is important to attempt to achieve equal fluid intake and urinary output if at all possible.

Pediatric patients should receive 2 to 3 L/m^2/d (or 200 mL/kg/d if<10 kg; volume adapted to patient age, cardiac function, and urine output) IV of a solution consisting of one quarter of normal saline/5% dextrose. Urine output should be monitored closely and be maintained within a range of 80 to 100 mL/m^2/h (4 to 6 mL/kg/h if < 10 kg). If there is no evidence of acute obstructive uropathy and/or hypovolemia, diuretics may be used to maintain output within this range if necessary. Potassium, calcium, and phosphate should be withheld initially from hydration fluids. Urine-specific gravity should be monitored and maintained at <1.010 **(level of evidence: V; grade of recommendation: D).** Guidelines for hydration in adult patients are the same as those for pediatric patients. Fluid intake should be maintained at approximately one to two times maintenance, with a urine output of 80 to 100 mL/m^2/h **(level of evidence: V; grade of recommendation: D**).

Alkalinization: Historically, alkalinization had been recommended for pediatric patients receiving treatment for hyperuricemia, particularly those treated with allopurinol, to promote excretion of uric acid in the urine. However, this practice is currently not recommended, because there is no unequivocal evidence of efficacy. Further, alkalinization may increase the risk of precipitation of calcium phosphate crystals. Because of these potential complications and lack of evidence of benefit, alkalinization is only indicated for patients with metabolic acidosis, in which case sodium bicarbonate may be considered based on the standards of the institution.

Alkalinization for patients who will receive treatment with allopurinol is controversial. Alkalinization is additionally not required in patients receiving rasburicase

(level of evidence: V; grade of recommendation: D).

Allopurinol Administration

Allopurinol is a xanthine analog which, when converted in vivo to oxypurinol, acts as a competitive inhibitor of xanthine oxidase, thereby blocking the conversion of the purine metabolites xanthine and hypoxanthine to uric acid. Use of allopurinol has been shown to decrease the formation of uric acid and to reduce the incidence of obstructive uropathy caused by uric acid precipitation in patients at risk for developing TLS. The use of allopurinol can be considered as a prophylactic option for patients with a medium to high risk of developing TLS (Table 4). Allopurinol is contraindicated in patients with a pre-existing allergy to allopurinol or who develop a severe hypersensitivity reaction while receiving treatment with this agent.

In pediatric patients, allopurinol is administered at a dose of 50 to 100 mg/m2 every 8 hours orally (maximum dose, 300 mg/m2/d) or 10 mg/kg/d divided every 8 hours (maximum dose, 800 mg/d). For patients unable to take allopurinol orally, IV administration may be considered, at a dose of 200 to 400 mg/m2/d in one to three divided doses (maximum dose, 600 mg/d). Treatment with allopurinol should be initiated in intermediate to high risk patients no more than 12 to 24 hours before the start of induction chemotherapy. Treatment may be continued until uric acid levels are normalized, and tumour burden, WBC count, and other laboratory values have returned to low-TLS risk levels as defined in Table 4. It should be noted that allopurinol only prevents the formation of uric acid and does not reduce uric acid produced before the initiation of treatment. Therefore, for patients with pre-existing severe

hyperuricemia (> 7.5 mg/dL), treatment with rasburicase is preferred **(level of evidence: II; grade of recommendation: B).**

Allopurinol can also cause an increase in serum levels and crystal deposition of the purine precursors xanthine and hypoxanthine, which can result in acute obstructive uropathy. Because allopurinol is excreted by the kidneys, a dose reduction of 50% is recommended in patients with renal insufficiency. The guidelines for allopurinol dosages and administration for adult patients are the same as those for pediatric patients. Treatment may be started 1 to 2 days before the start of induction chemotherapy and may be continued for up to 3 to 7 days afterwards, based on the ongoing risk of TLS development **(level of evidence: II; grade of recommendation: B).**

Recombinant Urate Oxidase

Urate oxidase converts uric acid into allantoin, which is five to 10 times more soluble in urine than uric acid. A recombinant form of urate oxidase with a high specific activity is available. Rasburicase is much more effective in reducing the level of uric acid, creatinine and achieving the control of other metabolites involved in tumour lysis syndrome. The use of recombinant urate oxidase (rasburicase) is recommended for the treatment of pediatric patients with hyperuricemia associated with LTLS or CTLS, or in the initial management of patients considered to be at high risk of developing TLS (Table 4).

In addition, for patients in the intermediate-risk group, rasburicase is recommended if urate nephropathy develops despite prophylactic treatment with allopurinol **(level of evidence: II; grade of recommendation: B).** Rasburicase is contraindicated in patients with a known G6PD deficiency and in pregnant or lactating females. Screening for G6PD

deficiency should include a thorough history of prior drug-induced hemolytic anemia, ethnic background, and available semiquantitative laboratory tests. Definitive testing, including measurement of RBC NADPH formation is preferred.

The US Food and Drug Administration–approved dosing guidelines recommend 0.15 to 0.2 mg/kg once daily in 50 mL of normal saline as an IV infusion over 30 minutes for 5 days. However, rasburicase has demonstrated activity even at lower doses and for shorter duration. Therefore, a dose of 0.10 to 0.2 mg/kg daily, dependent on whether the intention is prevention or treatment may be used (Table 5). Duration of treatment can range from 1 to 7 days. In Tata memorial hospital, a single dose has proven adequate for most patients. It is important that uric acid levels be monitored regularly and used as a guide to modulate dosing with rasburicase. Treatment is not necessary when uric acid is extremely low or no longer detectable.

Potential serious adverse reactions are rare and include anaphylaxis, rash, hemolysis, methemoglobulinemia, fever, neutropenia (with or without fever), respiratory distress, sepsis, and mucositis. At room temperature, rasburicase will cause the degradation of uric acid within blood samples, thereby interfering with accurate measurement. Therefore, samples should immediately be placed on ice until the completion of assay, which is preferably done within 4 hours of collection. Guidelines for rasburicase usage in adults are identical to those provided above for pediatric patients. **(level of evidence: II; grade of recommendation: B).**

Management of Hyperphosphatemia

It is of particular importance to treat hyperphosphatemia in pediatric patients (Table 6). For asymptomatic hyperphosphatemia, initial treatment consists of eliminating phosphate from intravenous solutions, maintaining adequate

hydration, and the administration of phosphate binders. For severe hyperphosphatemia, hemodialysis, peritoneal dialysis, or continuous venovenous hemofiltration should be used **(level of evidence: V; grade of recommendation: D).**

Aluminum hydroxide 50 to 150 mg/kg/d is administered in divided doses orally or nasogastrically every 6 hours. Its use should be limited to 1 to 2 days to avoid cumulative aluminum toxicity. Because pediatric patients might find the taste of aluminum hydroxide objectionable, other phosphate binders, such as calcium carbonate (eg, low calcium levels), sevelamer hydroxide, and lanthanum carbonate may alternatively be used. Calcium carbonate should not be used in patients with elevated calcium levels. Phosphate clearance has been found to be better with hemodialysis as compared with continuous venovenous hemofiltration or peritoneal dialysis. The above recommendations are valid for adult patients **(level of evidence**: V; grade of recommendation: D).

Management of Hyperkalemia

In pediatric patients, oral and IV sources of potassium should be eliminated as long as the risk of TLS exists (Table 6). Immediate intervention is indicated if serum potassium is greater than 7.0 to 7.5 mEq/L or the ECG shows widening of QRS complex. For asymptomatic patients, the standard treatment is sodium polystyrene sulfonate 1 g/kg administered orally or rectally (avoid this route in neutropenic patients). For symptomatic patients, more intense intervention is recommended, such as rapid-acting insulin (0.1 U/kg administered IV) and glucose infusion (25% dextrose 2 mL/kg).Sodium bicarbonate (1 to 2 mEq/kg administered via IV push) can be given to induce influx of potassium into cells. Calcium gluconate (100 to 200 mg/kg/dose) via slow infusion with ECG monitoring for bradycardia can be given for treatment of life-threatening arrhythmias. However, sodium

bicarbonate and calcium should not be administered through the same line **(level of evidence: V; grade of recommendation: D).** Elevated potassium levels should be verified immediately with a second sample to rule out fictitious hyperkalemia from hemolysis during phlebotomy. Patient ECG and cardiac rhythm should be closely followed, along with evaluation of electrolyte levels. The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: D).**

Management of Hypocalcemia

For asymptomatic pediatric patients, no intervention is recommended (Table 6). Symptomatic patients may be treated with calcium gluconate 50 to 100 mg/kg IV, administered slowly with EKG monitoring **(Level of evidence: V; grade of recommendation: D).** Care must be taken because increased calcium might increase the risk of calcium phosphate precipitation in the tissues and consequential obstructive uropathy. The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: D**).

Monitoring during treatment:

Check laboratory and clinical TLS parameters 4 to 6 hours after the initial administration of chemotherapy. The TLS parameters consist of levels of uric acid, phosphate, potassium, creatinine, calcium, and LDH, as well as fluid input and urine output. For all patients, uric acid levels should be re-evaluated 4 hours after administration of rasburicase and every 6 to 12 hours thereafter until resolution of TLS, for example, until normalization of LDH levels **(level of evidence: V; grade of recommendation: D).**

For adult intermediate-risk patients, patients should be monitored for at least 24 hours after the completion of chemotherapy. For multiagent chemotherapeutic regimens in

which the different drugs are administered over several days, monitoring should continue for 24 hours after the administration of the final agent of the first cycle. If rasburicase is not used in the initial management of the patient, electrolyte levels should be determined 8 hours after chemotherapy. If TLS has not occurred after 2 days, the likelihood is essentially zero that the patient will experience TLS **(level of evidence: V; grade of recommendation: D).**

For pediatric and adult patients at high risk of TLS, cytotoxic chemotherapy should only be administered once patients are located in a facility with ready access to dialysis. Although dialysis usage has been reduced since the introduction of rasburicase, as many as 3% of

patients (1.5% of pediatric patients and 5% of adult patients) still require this procedure. A nephrology specialist should therefore be notified in advance regarding high-risk patients. A renal consultation be obtained immediately if urine output is progressively decreasing, if there is persistent or elevated urea, phosphate or potassium levels, or in the case of life threatening hypocalcemia.

Summary of guidelines for management of tumor lysis syndrome:

High-Risk Patients

Adequate hydration and urine output are of high importance in preventing TLS. Along with hydration, rasburicase is indicated for high risk patients with pretreatment hyperuricemia (>7.5mg/dl) and/or evidence of urate nephropathy (renal dysfunction). The dose is 0.1-0.2 mg/kg/day as single daily infusion over 30 minutes for 1 dose. It may be repeated if required. In other patients, allopurinol may be used initially but these patients should be intensively monitored

and should have ready access to rasburicase as well as intensive care unit facilities if his or her clinical condition deteriorates. Allopurinol may be stopped and resumed at cessation of rasburicase. A renal expert should be notified regarding the patient in case dialysis is required. **(level of evidence: II; grade of recommendation: A).**

Intermediate-risk patients:

For intermediate-risk pediatric patients, in addition to hydration, allopurinol may be used as an initial antihyperuricemic treatment as described in allopurinol Administration. Initial management with a single dose of rasburicase might also be considered in pediatric patients with evidence of urate nephropathy (renal dysfunction). **(level of evidence: V; grade of recommendation: D).**

Low-risk:

For pediatric patients unlikely to develop TLS, a watch-and-wait approach with close monitoring is appropriate **(level of evidence: V; grade of recommendation: D).** The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: B).**

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change From Baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or 1.45 mmol/L for adults	25% increase
Calcium	≥ 1.75 mmol/L	25% decrease

NOTE. Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy.

Table 2. Cairo-Bishop clinical Tumor Lysis Syndrome (Definition and Grading)

	Grade					
Complication	0	1	2	3	4	5
Creatinine*	1.5 x ULN	1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN	Death
Cardiac arrhythmia*	None	Intervention not indicated	Non urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

NOTE. Laboratory tumor lysis syndrome and at least one clinical complication.
Abbreviations: ULN, upper limit of normal; CHF, congestive heart failure; ADL, activities of daily living.
* Not directly or probably attributable to therapeutic agent.

If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 µmol/L; 12 to < 16 years, both male and female, 88 µmol/L; 16 years, female 105.6 µmol/L, male 114.4 µmol/L.

Table 3 Risk Factors for Tumor Lysis Syndrome

Characteristic	Risk Factor
Tumor type	Burkitt's lymphoma Lymphoblastic lymphoma Diffuse large-cell lymphoma ALL Solid tumors with high proliferative rates and rapid response to therapy
Tumor burden/ extent of disease	Bulky disease (>10 cm) Elevated LDH (> 2x ULN) Elevated WBC (>25,000/μL)
Renal function	Preexisting renal failure Oliguria
Baseline uric acid	Baseline serum/plasma uric acid > 450 μmol/L (7.5 mg/dL)
Effective and rapid cytoreductive therapy	Disease-specific therapy, varies according to tumor type

Abbreviations: ALL, acute lymphoblastic leukemia; LDH, lactate dehydrogenase

Table 4 Patient Stratification by Risk

	Risk		
Type of Cancer	**High**	**Intermediate**	**Low**
NHL	Burkitt's, lymphoblastic, B-ALL	DLBCL	Indolent NHL
ALL	WBC 100,000	WBC 50,000-100,000	WBC 50,000
AML	WBC 50,000, monoblastic	WBC 10,000-50,000	WBC 10,000
CLL		WBC 10,000-100,000, Tx w/fludarabine	WBC 10,000
Other hematologic malignancies (including CML and multiple myeloma) and solid tumors		Rapid proliferation with expected rapid response to therapy	Remainder of patients

Abbreviations: NHL, non-Hodgkin's lymphoma; B-ALL, Burkitt's acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia, CLL, chronic lymphocytic leukemia; Tx, treatment; CML, chronic myeloid leukemia.

Table 5 Recommended Rasburicase Dosing

Tumor Lysis Syndrome Profile	Baseline Uric Acid		Dose (mg/kg)	Duration*
	mg/dL	mmol/L		
High risk	> 7.5	450	0.20	Based on plasma uric acid levels
Intermediate risk	< 7.5	450	0.15	Based on plasma uric acid levels
Low risk	< 7.5	450	0.10	Clinical judgment

* The average duration of therapy is 2 days, but can vary from 1 day to 7 days. Dosages as low as 0.05 mg/kg have been used successfully in groups of patients in at least one clinical trial.

Table 6 Management of Electrolyte Abnormalities

Abnormality	Management Recommendation
Hyperphosphatemia	
Moderate, 2.1 mmol/L	Avoid IV phosphate administration Administration of phosphate binder
Severe	Dialysis, CAVH, CVVH, CAVHD, or CVVHD
Hypocalcemia, 1.75 mmol/L	
Asymptomatic	No therapy
Symptomatic	Calcium gluconate 50-100 mg/kg IV administered slowly with ECG monitoring
Hyperkalemia	
Moderate and asymptomatic, 6.0 mmol/L	Avoid IV and oral potassium ECG and cardiac rhythm monitoring
	Sodium polystyrene sulphonate
Severe (> 7.0 mmol/L) and/or symptomatic	Same as above, plus: Calcium gluconate 100-200 mg/kg by slow IV infusion for life-threatening arrhythmias
	Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV
	Sodium bicarbonate (1-2 mEq/kg IV push). However, sodium bicarbonate and calcium should not be administered through the same line.
	Dialysis
Renal dysfunction (uremia)	Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemo- or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD, or CVVHD)

Abbreviations: IV, intravenous; CAVH/CAVHD, continuous arterial-venous hemodialysis; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis.

1. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence- based review.

Coiffier B, Altman A, Pui CH, et al J Clin Oncol. 2008 ;26:2767-78.

PURPOSE: Tumor lysis syndrome (TLS) has recently been subclassified into either laboratory TLS or clinical TLS, and a grading system has been established. Standardized guidelines, however, are needed to aid in the stratification of patients according to risk and to establish prophylaxis and treatment recommendations for patients at risk or with established TLS. METHODS: A panel of experts in pediatric and adult hematologic malignancies and TLS was assembled to develop recommendations and guidelines for TLS based on clinical evidence and standards of care. A review of relevant literature was also used. RESULTS: New guidelines are presented regarding the prevention and management of patients at risk of developing TLS. The best management of TLS is prevention. Prevention strategies include hydration and prophylactic rasburicase in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring for low-risk patients. Primary management of established TLS involves similar recommendations, with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia. Alkalinization is not recommended. Although guidelines for rasburicase use in adults are provided, this agent is currently only approved for use in pediatric patients in the United States. CONCLUSION: The potential severity of complications resulting from TLS requires measures for prevention in high-risk patients and prompts treatment in the event that symptoms arise. Recognition of risk factors, monitoring of at-risk patients, and appropriate interventions are the key to preventing or managing TLS. These guidelines should assist in the prevention

of TLS and improve the management of patients with established TLS.

2. Tumour lysis syndrome: new therapeutic strategies and classification.

Cairo MS, Bishop M. Br J Haematol. 2004 ;127:3-11.

Tumour lysis syndrome (TLS) describes the metabolic derangements that occur with tumour breakdown following the initiation of cytotoxic therapy. TLS results from the rapid destruction of malignant cells and the abrupt release of intracellular ions, nucleic acids, proteins and their metabolites into the extracellular space. These metabolites can overwhelm the body's normal homeostatic mechanisms and cause hyperuricaemia, hyperkalaemia, hyperphosphaetemia, hypocalcaemia and uraemia. TLS can lead to acute renal failure and can be life-threatening. Early recognition of patients at risk and initiation of therapy for TLS is essential. There is a high incidence of TLS in tumours with high proliferative rates and tumour burden such as acute lymphoblastic leukaemia and Burkitt's lymphoma. The mainstays of TLS prophylaxis and treatment include aggressive hydration and diuresis, control of hyperuricaemia with allopurinol prophylaxis and rasburicase treatment, and vigilant monitoring of electrolyte abnormalities. Urine alkalinization remains controversial. Unfortunately, there have been few comprehensive reviews on this important subject. In this review, we describe the incidence, pathophysiological mechanisms of TLS and risk factors for its development. We summarise recent advances in the management of TLS and provide a new classification system and recommendations for prophylaxis and/or treatment based on this classification scheme.

3. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis.

Goldman SC, Holcenberg JS, Finklestein JZ, et al
Blood. 2001;97:2998-3003.

Standard therapy in the United States for malignancy-associated hyperuricemia consists of hydration, alkalinization, and allopurinol. Urate oxidase catalyzes the enzymatic oxidation of uric acid to a 5 times increased urine soluble product, allantoin. Rasburicase is a new recombinant form of urate oxidase available for clinical evaluation. This multicenter randomized trial compared allopurinol to rasburicase in pediatric patients with leukemia or lymphoma at high risk for tumor lysis. Patients received the assigned uric acid-lowering agent for 5 to 7 days during induction chemotherapy. The primary efficacy end point was to compare the area under the serial plasma uric acid concentration curves during the first 96 hours of therapy (AUC(0-96)). Fifty-two patients were randomized at 6 sites. In an intent-to-treat analysis, the mean uric acid AUC(0-96) was 128 +/- 70 mg/dL.hour for the rasburicase group and 329 +/- 129 mg/dL.hour for the allopurinol group (P <.0001). The rasburicase versus allopurinol group experienced a 2.6-fold (95% CI: 2.0-3.4) less exposure to uric acid. Four hours after the first dose, patients randomized to rasburicase compared to allopurinol achieved an 86% versus 12% reduction (P <.0001) of initial plasma uric acid levels. No antirasburicase antibodies were detected at day 14. This randomized study demonstrated more rapid control and lower levels of plasma uric acid in patients at high risk for tumor lysis who received rasburicase compared to allopurinol. For pediatric patients with advanced stage lymphoma or high tumor burden leukemia, rasburicase is a safe and effective alternative to allopurinol during initial chemotherapy.

4. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial.

Jeha S, Kantarjian H, Irwin D, et al. Leukemia. 2005;19:34-8.

The recombinant urate oxidase, rasburicase (Elitek, Sanofi-Synthelabo, Inc.), has recently received regulatory approval for the prevention and treatment of hyperuricemia in children with leukemia, lymphoma, and solid tumors. Prior to approval, 682 children and 387 adults in the US and Canada received rasburicase on compassionate-use basis. Uric acid concentration declined rapidly in both adult and pediatric patients after rasburicase treatment. Similar responses were observed in patients treated with subsequent courses. Possible drug-related adverse events, including allergic reactions, were uncommon. These data confirm that rasburicase is effective and safe for the treatment and prophylaxis of children and adults with malignancy-associated hyperuricemia.

5. Reduced-dose rasburicase (recombinant xanthine oxidase) in adult cancer patients with hyperuricemia.

Trifilio S, Gordon L, Singhal S, et al Bone Marrow Transplant. 2006;37:997-1001.

Recombinant urate oxidase (rasburicase) lowers uric acid levels rapidly to very low levels at the labeled dose of 0.15-0.2 mg/kg daily for 5 days. Our past experience showed that a lower dose (3 mg) lowered uric acid levels sufficiently in most patients. A retrospective review was conducted to determine the effect of a fixed 3 mg dose of rasburicase in 43 adult patients with cancer undergoing hematopoietic stem cell transplantation or receiving chemotherapy who had elevated or rising uric

acid levels (6.4-16.8 mg/dl; median 9.6). Six patients received a second dose of rasburicase (3 mg in four patients and 1.5 mg in two patients) 24 h later. Patients received allopurinol, adequate hydration, as well as other supportive therapy as required. Uric acid levels declined by 6-95% (median 43%) within the first 24 h after rasburicase administration, and levels at 48 h were 9-91% (median 65%) lower than the baseline levels. Serum creatinine changed by < or =10% in 21 patients, increased by >10% in four patients and decreased by >10% in 18 patients. No significant renal dysfunction developed in any of the patients. We conclude that rasburicase is effective in lowering uric acid levels at a fixed dose of 3 mg, which is much lower than the recommended dose.

Pulmonary Toxicity of Antineoplastic Therapy

Many drugs can produce damage to the lungs, airways, pleura, and pulmonary circulation. The most common are listed in Table 1.The most common pattern is interstitial lung disease (ILD). Although drug-induced ILD accounts for only 3% of all causes of ILD, it represents an important subtype of this disorder, since discontinuation of the medicine may lead to significant improvement [1].

The diagnosis of cytotoxic lung damage depends upon an appropriate history of drug exposure, histological evidence of lung injury, and exclusion of other causes of pulmonary disease. Because there is no single diagnostic test capable of definitively confirming the diagnosis of chemotherapy-associated pulmonary toxicity, it remains a diagnosis of exclusion[2].

The typical clinical presentation in patients with chemotherapy-induced pulmonary fibrosis is the insidious onset of dyspnoea and nonproductive cough. Fever is common but not consistently present and chills are usually absent. Physical examination usually reveals crackles. The chest radiograph may be initially unremarkable for weeks before the typical diffuse interstitial infiltrative pattern appears. The only specific

radiographic pattern is the hilar lymphadenopathy seen in association with methotrexate use [3]. Pulmonary function tests demonstrate a restrictive pattern with decreased lung volumes and diffusing lung capacity for carbon monoxide (DL_{CO}). DL_{CO} is the most sensitive component of the pulmonary function tests, with decreases typically occurring before clinical symptoms or radiographic changes in patients treated with bleomycin [4].

Bronchoalveolar lavage (BAL) is indicated in patients with unclear ILD, and there is a good correlation between the type of inflammatory cells obtained by BAL and lung biopsy. Approximate normal percentages in nonsmokers include more than 80% macrophages, up to 15% lymphocytes, up to 3% neutrophils, up to 0.5% eosinophils, and up to 5% mast cells. BAL may narrow the differential diagnosis by excluding infection or worsening underlying pathology in addition to grouping disorders according to the cell profile

Table 1 Antineoplastic Agent Associated With Pulmonary Toxicity[5]

Class	Agents
Cytotoxic antibiotics	Bleomycin,mitomycin
Anitimetabolites	Methotrexate, Cytarabine, Fludrbine
Alkylating agents	Busulfan, Cyclopho-sphamide, Chrombucil, melphalan
Microtuble inhibitors	Taxanes,Vinca alkaloids
Topoisomerase inhibitors	Irinotecan
Monoclonal antibodies	Trastuzumab, Rituximab, Bevacizumab,Cetuximab
Small molecule targeted agents	Imatinib,Geftinib, Erlotinib
Miscellaneous	ATRA,Asparaginase

Though there are many chemotherapeutic drugs which may affect pulmonary function below we discuss the most common drugs causing pulmonary toxicity.

Bleomycin: Although the pathophysiology of bleomycin-induced lung injury is not completely understood, one of the putative mechanisms is the lack of bleomycin hydrolase, an enzyme responsible for the inactivation of bleomycin in normal and tumoral tissues [6]. Owing to the low activity of bleomycin hydrolase in the skin and lungs, these organs are the most commonly affected by bleomycin toxicity [7]. Pulmonary fibrosis following exposure to bleomycin is estimated to occur in approximately 10% of patients [8] The risk factors for the development of pulmonary toxicity in patients treated with bleomycin include the cumulative dose, age, use of radiation therapy, renal dysfunction, and high concentrations of inspired oxygen. The incidence of bleomycin-related pulmonary toxicity appears to be directly related to the cumulative dose, occurring in 3% to 5% of patients receiving a total dose of less than 300 units and 20% of those receiving doses higher than 500 units [9].

Bleomycin should be discontinued in patients with highly suspicious or documented lung toxicity. Although there is no proven effective therapy, patients are usually treated with high-dose corticosteroids. Patients surviving the pneumonitis episode almost always recover completely with no residual pulmonary symptoms or radiologic abnormalities.

Methotrexate: The incidence of pulmonary toxicity in patients receiving methotrexate is approximately 7%[10]. Risk factors in patients with rheumatoid arthritis include age older than 60, rheumatoid pleuropulmonary involvement, previous use of disease-modifying antirheumatic drugs, low serum albumin, and diabetes mellitus

Fludrabine:The incidence of fludarabine-related lung toxicity in patients with chronic lymphoproliferative disorders in a

study involving 105 patients was 8.6%. Patients presented with fever, hypoxemia, and infiltrates in the radiograph. Symptoms developed from 3 days after initiating therapy to 6 days after the seventh cycle. Trail of corticosteroids is beneficial in some cases & it should be tried[11]

Busulfan: It was the first cytotoxic drug associated with the development of pulmonary toxicity. The onset of respiratory symptoms may occur from 6 weeks to 10 years following exposure to busulfan, with most cases occurring within 3.5 years[12]. The most common symptoms include dyspnea, dry cough, weight loss, and fever over a period of weeks to months. The withdrawal of the offending medicine should be done promptly and the use of corticosteroids has been associated with anedoctal responses. Once pulmonary toxicity develops, the prognosis is usually poor, with most patients developing progressive respiratory failure with eventual death. The median survival for these patients is approximately 5 months[13]

Carmustine: Possible risk factors for the development of pulmonary toxicity in patients receiving carmustine-based chemotherapy include preexisting pulmonary disease, a history of smoking, and thoracic radiation. In a study involving long-term survivors from childhood brain tumors, the mortality rate was 12% for early pulmonary fibrosis, defined as disease presenting within 3 years of exposure to carmustine, and 35% for late fibrosis, defined as disease appearing after 8 to 20 years [14].

To summarize

Symptoms of pulmonary toxicities are nonspecific and frequently misinterpreted as caused by the underlying disorder, particularly in patients with thoracic malignancies. The lack of a pathognomonic diagnostic test makes it essentially a diagnosis of. exclusion Treatment usually consists of withdrawal of the suspected offending agent and the use of

corticosteroids with variable responses. High clinical suspicion with early discontinuation of the likely offending medicine represents the best approach to decrease the incidence of severe toxicity, particularly in drugs with known cumulative effect, and achieve a better outcome.

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Nephrotoxicity of Chemotherapeutic Drugs

Nephrotoxicity is an inherent adverse effect of certain anticancer drugs. Mechanisms of nephrotoxicity include chemotherapy induced damage to vasculature or structures of the kidneys, haemolytic uraemic syndrome and prerenal perfusion deficits. Patients with cancer are frequently at risk of renal impairment secondary to disease-related and iatrogenic causes.

Evaluation of Renal Function: In humans, the assessment of renal function is mainly done by the measurement of glomerular filtration rate (GFR) (1). Normal values, which are related to age, sex, and body size, are approximately 130 mL/min/1.73 m^2 in young men and 120 mL/min/1.73 m^2 in young women. Mean values decline as people age (2). Serum creatinine is dependent on age, gender, race, body size, diet, certain drugs, and laboratory analytic methods (3). In early renal disease, GFR can decrease substantially, without changes in serum creatinine. In late renal disease, the serum creatinine level may rise disproportionately as GFR falls. The serum creatinine does not significantly change until the Creatinine clearance rate (CCR) is less than 70 mL/min/1.73 m^2 therefore the use of a single reference range for serum creatinine to

distinguish between a normal GFR and an abnormal one can be misleading (2).

Risk Factor: risk factors for nephrotoxicity includes age older than 60 years, hypertension, diabetes, cardiovascular disease, concomitant use of nonsteroidal anti-inflammatory drugs, intravascular volume depletion, either due to external losses, reduced intake, or fluid sequestration, and urinary tract obstruction secondary to underlying tumor and underlying disease as patients with multiple myeloma because of prerenal uremia from hyperviscosity syndrome (1)

Important Nephrotoxic Chemotherapeutic Agents:

1. Cisplatin: Causes both acute and chronic renal failure. Acute injury manifest as azotemia and a rising serum creatinine level .Chronic injury presents as decrease in GFR without an increase in serum creatinine or CCR. The chronic form of injury is only partially reversible (4). Cisplatin also induces several electrolyte disorders; the most common one is hypomagnesemia. The hypomagnesemia results from a proximal tubular defect interfering with magnesium reabsorption and thereby increasing fractional excretion (5). Prevention of cisplatin nephrotoxicity primarily involves sodium chloride hydration. This standard prophylaxis usually consists of giving 2 to 3 L of normal saline over 8 to 12 hours on the day of cisplatin administration. Prophylactic use of magnesium supplementation reduces the risk of nephrotoxicity (6). Management of cisplatin nephrotoxicity requires that the drug to be discontinued, the dosage be reduced substantially, or by another drug if possible.
2. Carboplatin: Sixty to seventy percent of carboplatin is excreted by the kidneys. Degree of myelosuppression

associated with use of carbopltin correlates with carboplatin clearance (7). Calculation of carboplatin dose requires estimation of CCR.

3. Antitumor Antibiotics:

   The antitumor antibiotic mitomycin C has been associated with a syndrome of renal failure and microangiopathic hemolytic anemia that commonly seen after 6 months of therapy. It appears in up to 20% of patients receiving total doses of 100 mg or more (8).It is characterized by the abrupt onset of a microangiopathic hemolytic anemia with schistocytes; increased fibrin degradation products; thrombocytopenia; and renal abnormalities consisting of azotemia, proteinuria, and hematuria.

4. Ifosfamide and Cyclophosphamide: These causes two type of genitourinary toxicities. The first is hematuria due to hemorrhagic cystitis, requires the use of the uroprotective compound, mesna. Most patients who receive ifosfamide develop microscopic hematuria, and a significant number of patients develop gross hematuria (9). This hematuria may be severe enough to require modification of dose or discontinuation of the drug.

   The second renal toxicity of ifosfamide consists of a proximal tubular defect, which clinically manifest as a Fanconi-like syndrome (10). Mesna does not appear to protect against the proximal tubular abnormality induced by ifosfamide (11).

5. Methotrexate: In normal doses about 90% of drug is excreted unchanged in urine. When given in high doses, methotrexate precipitate in the renal tubules and collecting ducts because the high concentration exceeds the solubility of methotrexate at pH 5.0(12).Prevention

of methotrexate induced nephropathy includes brisk, diuresis alkalinization of the urine to keep the urinary pH above 7.0 and monitoring serum creatinine and methotrexate levels (13).

6. Bleomycin : Bleomycin does not directly cause renal toxicity. It is excreted primarily by the kidneys, so dose adjustment is required in the presence of renal insufficiency or failure.
7. Bevacizumab: It may induce nephrotic proteinuria and severe hypertension If a treated patient develops more than moderate proteinuria without the nephrotic syndrome, then the drug should be temporarily held as the proteinuria generally resolves (14).
8. Bisphosphonates : Pamidronate and zoledronic acid are commonly used Both drugs undergo renal excretion .Pamidronate should not be administered in the presence of severe renal impairment or if the serum creatinine rises more than 0.5 mg per dL during treatment (15). Zoledronic acid may be dosed based on CCR (16).

Table 1 Chemotherapeutic Drugs not Requiring Dose Modification in Renal Failure (17)

Actinomycin D	Gemcitabine	Teniposide
Amsacrine	Idarubicin	6-Thioguanine
Busulfan	Melphalan (p.o.)	Thiotepa
Chlorambucil	6-Mercaptopurine	Vinblastine
Daunorubicin	Mitoxantrone	Vincristine
Docetaxel	Paclitaxel	Vindesine
Doxorubicin	Procarbazine	Vinorelbine
5-Fluorouracil		

Table 2 Chemotherapeutics Requiring Dose Modification in Renal Failure: Suggested Percentage Dose for Glomerular Filtration Rate (17)

	> 60 mL/min	30 - 60 mL/min	10 - 30 mL/min	<10 mL/min
Bleomycin	NC	50	Omit	Omit
Capecitabine	NC	75	Omit	Omit
Carboplatin	Dose determined by Calvert formula (18)			
Cisplatin	NC	50	Omit	Omit
Cyclophosphamide	NC	NC	NC	50
Cytosine arabinoside	NC	50	Omit	Omit
Dacarbazine	NC	75	50	Omit
Epirubicin	NC	NC	NC	50
Etoposide	NC	NC	NC	50
Fludarabine	NC	75	50	Omit
Hydroxyurea	NC	75	75	50
Ifosfamide	NC	75	50	Omit
Melphalan (i.v.)	NC	75	75	50
Methotrexate	NC	50	Omit	Omit
Mithramycin	NC	75	50	Omit
Mitomycin	NC	75	50	Omit
Nitrosoureas	NC	Omit	Omit	Omit
Pamidronate	NC	Omit	Omit	Omit
Pemetrexed	NC	50	Omit	Omit
Pentostatin	NC	50	Omit	Omit
Topotecan	NC	75	50	Omit
Zoledronate	NC	75	Omit	Omit

NC –No change

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Mucositis and Gastrointestinal Toxicities of Chemotherapy

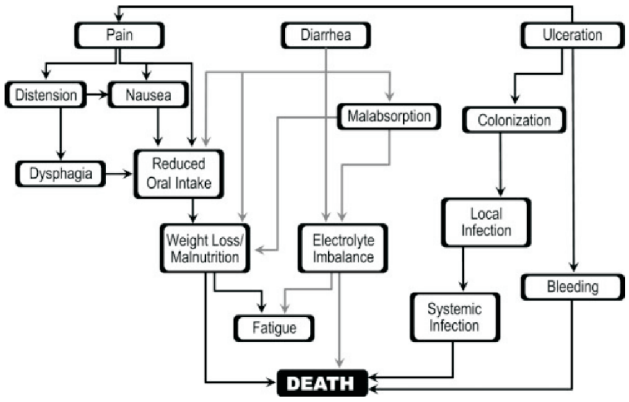
Introduction and epidemiology -Advent of intensive chemotherapy regimens including high dose chemotherapy to improve the cure rates in malignancies has led to higher incidence of hematological and non-hematological toxicities. Increasing use of growth factors take care of hematological toxicity to a certain extent thus making non-hematological toxicity an important concern for medical oncologists. Non-hematological toxicities such as mucositis (oral and gastrointestinal), diarrhea are well recognized with several standard dose chemotherapy regimens and high dose chemotherapy. They can be debilitating due to severe pain, bleeding, increase frequency of infections, poor oral intake and weight loss and thus lead to chemotherapy delays and dose reduction compromising the cure. For patients receiving high dose chemotherapy treatment, a 1-point increase in an oral mucositis score has been found to be associated with a significant increase in days with fever, risk of infection, additional days of total parenteral nutrition, use of intravenous narcotic analgesics, total hospital charges, and 100-day mortality. Apart from physical effects mucositis can have marked psychological effects and may become an important barrier for continuation of chemotherapy.

The incidence of mucositis involving oral cavity and gastrointestinal mucosa varies between 5-15% with standard dose chemotherapy whereas it can be as high as 80-100% with high dose chemotherapy and stem cell transplantation. However, considering the risk of mucositis with each cycle of chemotherapy in solid tumors, the overall burden is higher in this subgroup than in hematological malignancies. The reported incidence of diarrhea varies from 1-3% with most chemotherapy regimens however combinations such as irinotecan and oxaliplatin can increase the risk to 16-25%.Alimentary mucositis (AM) is the term which is recommended by the mucositis study group of Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology to describe cancer therapy associated mucosal injury of the alimentary tract (mouth to anus). This unifying term acknowledges the similarities along the entire GI tract while allowing for regional differences that require discussion of oral and GI mucositis separately at times based on pathophysiologic responses and clinical characteristics.

Pathogenesis- Mucosal injury is the first step in the development of mucositis. It results in changes in mucosa, submucosa and connective tissue matrix mediated by a number of pro-inflammatory cytokines, reactive oxygen species, ceramide pathway and a number of other transcription factor including NF-kb. The resultant degradation of connective tissue matrix and upregulation of number of other genes lead to apoptosis of clonogenic stem cells in basal layer of epithelium. This coupled with reduced proliferative capacity of surrounding epithelium leads to ulceration of mucosa. The ulcerative phase is further compounded by the bacterial colonization and the resultant cytokine release due to bacterial cell wall components. Ultimately healing occurs by the migration of healthy epithelium from wound margins. The

pathogenesis is similar for gastrointestinal mucositis, however the manifestations are different due to morphologic and functional differences. In most cases the diarrhea, abdominal pain and bloating appear by day 3 and settle around day 7 of chemotherapy. The oral mucositis starts manifesting around day 7.

Clinical manifestations- Alimentary mucositis can result in following manifestations represented in the diagram below



Factors affecting the incidence

1. Drugs –Use of certain chemotherapeutic agents like -5-Fluorouracil, Methotrexate, Melphalan, Irinotecan , Docetaxel , Capecitabine results in higher incidence of mucositis (30%)
2. Multiagent combination chemotherapy regimens
3. High dose chemotherapy
4. Patients with poor performance status, poor nutritional status and underlying bad oral hygiene
5. Chemoradiation protocols
6. Gender- Females might be more predisposed than males.

7. Obesity – Probably due to over dosing as a result of failure to adjust dosage to ideal body weight
8. Genetic predisposition – some preliminary work suggests a possibility that some individuals are more prone for development of mucositis than others.

Prevention and treatment of mucositis and diarrhea-

Advancements in terminology and in the assessment of AM in patients receiving cytoreductive cancer therapies have resulted in better patient management practices and enhanced drug development to reduce toxicity. Several attempts are in progress to develop models for assessing risk of mucositis in any given patient. The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) have developed the guidelines based on available evidence for prevention and treatment of chemotherapy associated mucositis which were first published in 2004 and have been updated in 2007.

To prevent the development of oral mucositis following standard chemotherapy following methods have been suggested -

1. Basic oral care, its importance in maintaining mucosal health, integrity, and function is well accepted. The purpose of basic oral care is to reduce the impact of the oral microbial flora, reduce cancer therapy–related symptoms of pain and bleeding, and prevent soft tissue infections that may have systemic sequelae. In addition, maintenance of good oral hygiene will reduce the risk of dental complications, including caries and gingivitis. For these reasons, basic oral care is an important component of care of the patient with cancer The

acceptable oral protocol include regular brushing with soft bristle tooth brush, flossing, bland rinses and moisturizers along with educating patient, family and health care team the importance of oral care.(level of evidence, III; grade of recommendation, B). Dental consultation and treatment should be done prior to the start of treatment.

2. Cryotherapy with bolus doses of 5-FU.- The panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 minutes of oral cryotherapy to prevent oral mucositis (level of evidence, II; grade of recommendation, A). It was hypothesized that placing ice chips in the mouth, starting 5 minutes before 5-FU bolus injection and continuing for a total of 30 minutes, would cause cooling of the oral cavity, which would lead to vasoconstriction. It was suggested that the vasoconstriction would allow less 5-FU to reach the oral mucosa, thereby attenuating 5-FUinduced mucositis. It should be noted that oral cryotherapy is not expected to be useful in preventing oral mucositis in patients receiving 5-FU by continuous infusion or in patients undergoing administration of such agents as methotrexate, doxorubicin, or other agents with a long serum half-lives.

3. The panel does not recommend the use of systemic glutamine, acyclovir in the prevention of oral mucositis. (level of evidence, II; grade of recommendation, B)

For prevention of mucositis caused by high dose chemotherapy with or without total body irradiation plus haematopoietic stem cell transplantation the panel recommends

1. Use of keratinocyte growth factor-1 (KGF1) (palifermin) at a dose of 60 mg/kg per day for 3 days prior to

conditioning treatment and for 3 days post-transplantation for the prevention of oral mucositis (Level I evidence, grade A recommendation)

2. Cryotherapy can be used in patients receiving high-dose melphalan (Level II evidence, grade A recommendation).

3. Use of granulocyte- macrophage colony stimulating factor mouth-washes is not recommended by the panel. (Level II evidence, grade C recommendation).

Treatment of oral mucositis

1. Palliative care (including pain management) Palliation of mucositis and acute oral pain is an important component of patient care. Approaches include the use of systemic analgesics and other individual agents, coating agents, and topical anesthetics/analgesics. The panel recommends patient-controlled analgesia (PCA) with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT (level of evidence, I; grade of recommendation, A). Control of mucositis-induced pain is achieved by PCA with intravascular morphine sulfate. Use of morphine in other setting is not evidenced based, however analgesics can be used as per the local clinical practice. The panel does not recommend the use of topical anesthetic based mixtures in treatment of mucositis.

2. The panel recommends that chlorhexidine not be used to treat established oral mucositis (level of evidence, II; grade of recommendation, A)

Prevention of gastrointestinal mucositis

The basic bowel care should include adequate hydration, consideration of lactose intolerance and bacterial colonization.

Treatment of gastrointestinal mucositis

1. The panel recommends either ranitidine or omeprazole for the prevention of epigastric pain after treatment with cyclophosphamide, methotrexate, and 5-FU or after treatment with 5-FU with or without folinic acid chemotherapy (level of evidence, II; grade of recommendation, A).
2. Chemotherapy-induced diarrhea is a common clinical problem associated with certain drugs used to treat colon cancer and other solid tumors (5-FU, irinotecan) and with high-dose chemotherapy coupled with HSCT. Irinotecan-induced diarrhea occurs in 2 phases: an acute syndrome (within the first 24 hours), which is mediated by acetylcholine and blocked by atropine, followed by a delayed phase, which is inflammatory. Octreotide, a somatostatin analogue, regulates intestinal water and electrolyte transport, inhibits gut hormones. When loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT, the panel recommends octreotide at a dose of at least 100 mg administered subcutaneously twice daily (level of evidence, II: grade of recommendation, A).

Future Directions and Areas of Research

1. The prevalence of mucositis is largely remains unreported therefore there is a need for studies reporting the exact prevalence using standard nomenclature, cost of therapy, prevention and treatment.
2. More research is required to assess the risk assessment based on genetics
3. Development of other agents which are cost effective

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Hepatotoxicity of Chemotherapeutic Agents

Toxic liver injury by chemotherapeutic drugs can cause any known pattern of injury, including necrosis, steatosis, fibrosis, cholestasis, and vascular injury (1). Liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer .Other factors responsible for liver toxicity includes antibiotics, analgesics, antiemetics, or other medications.

Preexisting medical problems, tumor, immunosuppression, hepatitis viruses and other infections, and nutritional deficiencies or total parenteral nutrition all may affect a host's susceptibility to liver injury. Most hepatotoxic drug reactions are idiosyncratic, due to immunologic mechanisms or variations in host metabolic response (2).

ALKYLATING AGENTS: These includes mechlorethamine, melphalan, chlorambucil **,** Cyclophosphamide , Ifosfamide and busulfan**.**

The liver cytochrome P-450 system converts cyclophosphamide to form, aldophosphamide which inside the cell converts into phosphoramide mustard and acrolein and these two compounds are highly cytotoxic and represent active forms of the drug. In spite of its requirement for hepatic

metabolism for activity, cyclophosphamide is an uncommon hepatic toxin, and only a few reports of elevated hepatic enzymes are attributed to the drug (3). Ifosfamide is an alkylator and elevations of hepatic enzymes have rarely been reported during therapy. Rodriquez et al. showed that 7 of 32 patients who were being treated with ifosfamide in doses of 600 to 1,200 mg per m^2 developed elevations of the transaminases and these were transient (4).

Melphalan is rapidly hydrolyzed in plasma, and approximately 15% is excreted unchanged in the urine. At usual doses, it is not associated with hepatotoxicity, but it produce transient abnormalities in liver function tests at the high doses used in hematopoietic stem cell transplantation (HSCT) (5).

Busulfan after administration is rapidly cleared from the blood. Hepatic metabolism is apparently not important. In standard doses, busulfan rarely causes hepatic dysfunction but has been implicated to cholestatic hepatitis (6). As a group, the alkylating agents are seldom implicated as hepatotoxins and can usually be given in the face of altered liver function with relative safety. The possible exception to this is cyclophosphamide, which requires adequate liver function for activation to its active metabolites (7). Antimetabolites :

Most commonly used antimetabolites are cytosine arabinoside (ara-C), 5-fluorouracil (5-FU), 6- mercaptopurine (6-MP), azathioprine (AZ), 6-thioguanine, fludarabine, pentostatin, gemcitabine and MTX.

Ara-C induced liver toxicity includes increased SGOT/PT , cholestatic jaundice and intrahepatic cholestasis and this usually reversible (8).Fludarabine is a purine antimetabolite . Reversible elevation of the serum transaminases to two to three times normal has been described (9).

5 Flurouracil commonly causes steatosis which usually remains subclinical. Hepatotoxicity is rare (10).

Capecitabine is the prodrug for 5-FU and causes hepatotoxcity. Out of 875 patients who were evaluated for toxicity in clinical trials, grade 3 hyperbilirubinemia occurred in 15.2% of patients and grade 4 occurred in 3.9%. Grade 3 or 4 hyperbilirubinemia occurred in 22.8% of patients with hepatic metastases at baseline (n = 566) and 12.3% of patients without hepatic metastases (n = 309). Administration of capecitabine should be interrupted if hyperbilirubinemia of grade 2 grade 3, or grade 4 occurs until the hyperbilirubinemia resolves or decreases in intensity to grade 1(11).

Gemcitabine is commonly associated with elevated levels of transaminases, but this is seldom of clinical significance. Three cases of fatal cholestatic hepatotoxicity have been reported and current recommendations are for dose reduction in patients with an elevated serum bilirubin. An elevated bilirubin level of greater than 1.6 mg per dL requires that the dose be started at 800 mg per m^2 and escalated only if tolerated (12).

Hepatotoxicity induced by 6-MP may occur in a variety of settings, especially when the dose of the drug exceeds the usual daily dose of 2 mg per kg, and may present as either hepatocellular or cholestatic liver disease . Elevations of aminotransferases and serum lactate dehydrogenase are quite common after high-dose MTX therapy, with an incidence of about 14 % (13). Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis are seen with chronic low dose as in rheumatoid arthritis and where the cumulative dose >2 g. (14). For the development of toxicity, cumulative dose is more important than duration of therapy.

Antitumor Antibiotics:

The antitumor antibiotics include doxorubicin, daunorubicin, idarubicin, mitoxantrone, bleomycin, mitomycin, and dactinomycin. Doxorubicin, an anthracycline antibiotic. It is extensively metabolized in the liver. Impaired liver function

delays excretion and eventually results in increased accumulation in plasma and tissues. Reducing the amount of doxorubicin administered decreases the values similar to those of patients with normal liver function who are receiving higher doses.

For bleomycin most human studies have found a very low incidence of liver dysfunction; a review of more than 1,000 patients who were treated with bleomycin concluded that hepatic toxicity was not consistently reported, and it could not be specifically ascribed to bleomycin (15).

Microtubule Targeting Drugs: Vinca Alkaloids

vincristine is excreted primarily by the liver but has seldom been implicated as a hepatotoxin. It has produced hepatotoxicity when used in combination with radiation. Vincristine and vinblastine are excreted primarily by the liver into the bile.

Taxanes:

Paclitaxel and docetaxel are members of spindle inhibitors. Both are extensively excreted by the liver. AST Levels that were more than twice normal and bilirubins of 1.5 mg per dL, dose of paclitaxel should be less than 135 mg per m^2, those with bilirubins of 1.6 to 3.0 mg per dL dose of paclitaxel is 75 mg per m^2 or less, and those with bilirubins above 3 mg per dL dose of paclitaxel is 50 mg per m^2(16).

Topoisomerase II Inhibitors

Etoposide is excreted primarily in the bile but is not usually considered hepatotoxic at standard doses (17) . At high doses, etoposide causes hyperbilirubinemia, elevated aminotransferases, and elevated alkaline phosphatase activity approximately 3 weeks after administration (18).

Topotecan causes elevation of transaminases in fewer than 10% of patients and significant elevations of liver enzymes are uncommon (19).

Irinotecan can cause severe transaminitis which is often reversible.Usually seen in patients with hepatic metastases (20).

Miscellaneous Agents:

Cisplatin is a rare cause of hepatic toxicity, but minor AST elevations are common at usual therapeutic dose. Cisplatin-induced acute hepatic injury is dose related. (21).

Oxaliplatin is renally eliminated and can be given to patients with severe liver dysfunction due to metastatic colorectal cancer (22).

L-asparaginase (L-Asp) hydrolyzes L-asparagine in serum. Hepatic toxicity is quite frequent with L-Asp. The mechanism of hepatotoxicity involves impaired protein synthesis from asparagine depletion. Decreased serum levels of albumin, ceruloplasmin, haptoglobin, transferring and coagulation factors II, VII, IX, X, and fibrinogen are common. Moderate elevations of aminotransferase, bilirubin, and alkaline phosphatase also occur. These common changes with L-Asp are usually mild and reversible (23).

Bortezomib is metabolized by the liver and clearance may decrease with hepatic impairment. Hyperbilirubinemia and portal vein thrombosis have also been reported (24).

Hepatic Veno-Occlusive Disease:

High-dose chemotherapy such as tin stem cell transplant may result in a specific pattern of hepatotoxicity known as VOD. Drugs implicated to cause this includes busulfan , Cyclophosphamide, Carmustine (BCNU),Lomustine.

Combination Chemotherapy:

Combination chemotherapy uses several chemotherapeutic agents, each with a different mechanism of action and toxicity profile. Along with the potential for greater tumor kill, however, the possibility for enhanced toxicity occurs.

Adjuvant chemotherapy for breast cancer with cyclophosphamide, daunorubicin, and 5-FU has produced that liver function abnormalities developed in 77% of patients (25). These abnormalities appeared within the first 3 months of therapy and normalized in 90% of patients within a year of cessation of treatment.

General Guidelines for Chemotherapy Dosage Based on hepatic Function (27)

Drug Recommended Dose Reduction for Hepatic Dysfunction.

Bleomycin : No dose reduction is necessary.

Busulfan: No dose reduction is necessary.

Carboplatin: No dose reduction is necessary.

Chlorambucil : No dose reduction is necessary.

Cisplatin: No dose reduction is necessary.

Cyclophosphamide: Reduce by 25% if bilirubin 3.0–5.0 mg/dL or SGOT > 180 mg/dL. Omit if bilirubin > 5.0 mg/dL.

Cytarabine : No formal recommendation for dose reduction. Dose reduction may be necessary in patients with hepatic dysfunction.

Dacarbazine: No dose reduction is necessary.

Dactinomycin: Reduce dose by 50% if bilirubin > 3.0 mg/dL.

Daunorubicin: Reduce dose by 25% if bilirubin 1.5–3.0 mg/dL. Reduce dose by 50% if bilirubin > 3.0 mg/dL. Omit if bilirubin > 5.0 mg/dL.

Docetaxel: Omit if bilirubin > 1.5 mg/dL, SGOT > 60 mg/dL, or alkaline phosphatase > 2.5 × upper limit of normal.

Doxorubicin: Reduce dose by 50% if bilirubin 1.5–3.0 mg/dL. Reduce dose by 75% if bilirubin 3.1–5.0 mg/dL. Omit if bilirubin > 5.0 mg/dL.

Etoposide Reduce dose by 50% if bilirubin 1.5–3.0 mg/dL or SGOT 60–180 mg/dL. Omit if bilirubin > 3 mg/dL or SGOT > 180 mg/dL.

Fludarabine: No dose reduction is necessary.

5-Fluorouracil: Omit if bilirubin > 5.0 mg/dL.

Ifosfamide: No dose reduction is necessary.

Imatinib : Omit if bilirubin > 3 mg/dL or SGOT > 5 × ULN. Once bilirubin < 1.5 or SGOT < 2.5 × ULN, reduce dose from 400 mg to 300 mg or from 600 mg to 400 mg.

Irinotecan : No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary.

Melphalan: No dose reduction is necessary.

6-Mercaptopurine: No dose reduction is necessary.

Methotrexate: Reduce dose by 25% if bilirubin 3.1–5.0 mg/dL or SGOT > 180 mg/dL. Omit if bilirubin > 5.0 mg/dL.

Oxaliplatin: N/A.

Paclitaxel: dose reduction if bilirubin 1.5–3.0 mg/dL or SGOT 60–180 mg/dL. Omit if bilirubin > 5.0 mg/dL or SGOT > 180 mg/dL.

Vincristine: No dose reduction if bilirubin < 1.5 mg/dL and SGOT < 60 mg/dL.

Reduce by 50% if bilirubin 1.5–3.0 mg/dL and SGOT 60–180 mg/dL. Omit if bilirubin > 3.0 mg/dL or SGOT > 180 mg/dL.

N/A– not available. ULN– upper limit of normal.

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Dermatologic Toxicity of Antineoplastic Therapy

The function of human skin to serve as a protector, a sensor, a temperature regulator, and an overall window into the body's ever-changing states is amazing. The unique ability of the skin to proliferate and repair itself rapidly makes it a common incidental target for chemotherapeutic drugs. The most common reaction are listed in Table 1[1]. Because skin reactions can range from benign to life threatening, the presence of a cutaneous complication does not necessarily require cessation of the drug.

Table 1

Major cutaneous reaction patterns associated with chemotherapy are
Alopecia
Acral erythema
Radiation Recall
Radiation Enhancement
Photosensitivity
Hyperpigmentation
Nail changes
Hypersensitivity

Alopecia

Common drugs causing alopecia are given below (Table 2)[1]

Table 2

Cyclophosphamide	Ifosfamide
Daunorubicin	Paclitaxel
Doxorubicin	Vinblastine
Etoposide	Vincristine

At any given time, 85% of hair on the human scalp is in this growth phase or anagen[2] when an antimitotic chemotherapeutic agent is initiated, the abrupt cessation of mitotic activity in rapidly dividing hair matrix cells causes the hair shaft to thin and break at the surface of the skin. The resulting alopecia is termed anagen effluvium[3] In general; anagen effluvium typically starts in the first few days to weeks after the chemotherapy. The degree, timing, and impact of hair loss depend on the agent given, its half-life, dose, schedule, and route of administration.

It has been shown, for example, that taxanes in lower doses given once weekly cause a less severe alopecia than taxanes given in higher doses every third week. Docetaxel's course is unique with hair loss being sudden and complete, usually during the third week after a patient's first 1-hourinfusion[4]

Although chemotherapy-induced alopecia primarily affects scalp hairs, other sites such as, these hairs face, arms, legs, and groin may be involved. Fortunately, however, the process is usually reversible with cessation of the agent and most patients show regrowth after 3 to 4 months[5.] Regrowth can occur because chemotherapy usually spares the stem cells in the hair follicle bulb.A notable exception to this is busulfan, which has been reported to induce a permanent alopecia by destruction of the lower hair follicle region[6] Interestingly,

because 15% of scalp hairs are not in anagen at any given timemay escape the affects of chemotherapy which results in clinically patchy, incomplete patterns of hair loss.

Acral Erythema

Acral erythema, also called palmar-plantar erythrodysesthesia syndrome and toxic erythema of the palms and soles. It is most commonly caused by bleomycin,capecitabine,cytarabine, docetaxel, doxorubicin, flurouracil & tegafur. The toxicity appears to be both due to cumulative dose and peak concentration of drug.

The formulation of the drug also plays a role. With liposome-encapsulated doxorubicin, occasionally severe and dose-limiting acral erythema appears in up to 51% of patients[7]The liposome formation prohibits excretion of the drug by preventing the binding of drug to the plasma proteins. Its coating, a hydrophilic polyethylene glycol, prevents its uptake by the reticuloendothelial system[8]The mode of administration also plays a role. 5-Fluorouracil given as a bolus has a very low occurrence rate of acral erythema; with a continuous regimen, it is much higher. Discontinuation of the offending drug will usually resolve this reaction. Reducing the dose or changing the timing or type of delivery can be beneficial as well

Radiation Recall (RR) and Radiation Enhancement (RE)

The most common RR & RE offenders are doxorubicin & dactinomycin. Radiation recall occurs when a chemotherapy drug causes an inflammatory response in skin that has been previously irradiated whereas radiation enhancement exists when a drug increases the radiation therapy toxicity. The involved drug and radiation are normally given within a week of each other for enhancement[9]. Radiation recall is not as time

dependent, occurring from 8 days to 15 years after radiation therapy. The shorter the time interval the more severe the reaction is. The higher doses of the initial radiation may play a role as well. The mechanism of action is not clear but theories implicate both microvasculature effects, stem cell damage with defective repair mechanisms, and impaired cutaneous immunologic action[9]

Hyperpigmentation and Nail Change

Hyperpigmentation of the skin and nails and nail changes are very common with chemotherapeutic drugs. The common drugs causing these changes are arsenic trioxide, bleomycin, cisplatin, flurouracil, methotrexate and hydroxyurea. Hair changes may also occur with regrowth. Many theories have been suggested, including a direct toxic effect on melanocytes, increased drug presence due to vascular changes, and increased toxicity of the skin secondary to eccrine gland drug secretion. Increased levels of adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH) and drug-induced depletion of tyrosinase inhibitors have been suggested as potential factors[9]Postinflammatory hyperpigmentation from a variety of cutaneous eruptions is also seen.

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Cancer Induced Anemia (CIA)

Introduction

The past two decades have seen dramatic strides taken in the management of cancer. Longer survival amongst patients has been attributed to the availability of better diagnostic tools, improved surgical techniques, precise delivery of radiation, superior cytotoxic drugs, and the advent of targeted therapy. The advances in supportive care have also significantly contributed to improvement in morbidity and quality of life in cancer patients. Despite these positives common toxicities associated with cancer therapy exist and anemia remains a condition that is often overlooked, under treated, or just ignored. Its existence has a detrimental impact on clinical and treatment outcomes as well as a patient's health-related quality of life. The lack of a standard definition regarding what constitutes symptomatic anemia requiring an intervention and the suboptimal assessment tools does magnify the problem of cancer related anemia. Treatment interventions are directed toward the underlying etiology and include iron supplementation, blood transfusion, and administration of recombinant human erythropoietin.

Anemia and Cancer – incidence, etiology and pathogenesis

Anemia is common both at baseline and develops increasingly while on treatment. The European Cancer Anemia Survey (ECAS) cited 50% baseline anemia rate (Hemoglobin < 12 g/dL) among patients with hematological malignancies, and a 41% baseline anemia rate amongst solid tumors patients [1]. A longitudinal analysis further revealed that 72% of patients with hematological malignancies and 66% of patients with solid tumors became anemic at some point during the course of their treatment.[1] Groopman and Itri reported that the most significant rates of anemia requiring transfusion existed in patients with lung, gynecologic, and genitourinary tumors, with the incidence ranging from 50% to 60%. [2]

Type of Cancer	Prevalence of Anemia (Hemoglobin < 12 g/dL)
Hematologic malignancies[1]	72%
Solid tumors[1]	66%
Colorectal cancer[3]	67%
Lung cancer[3]	63%
Cervical cancer[3]	82%

A number of factors contribute to the high incidence of cancer-related anemia and these include:

1. Chemotherapy and radiation-induced myelosuppression,
2. Bleeding and hemolysis
3. Marrow infiltration by tumor,
4. Nutritional deficiencies
5. Cytokine-mediated anemia of chronic disease.

The pathogenesis of chronic anemia in cancer results from an interaction between the tumor cells and the host's own immune

system. There is an upregulation of specific inflammatory cytokines such as interleukin-1 (IL-1), gamma interferon (IFN-γ) and tumor necrosis factor alpha (TNF-α) which cause decreased differentiation of erythroid precursors, interference with normal iron utilization and inhibition of normal hypoxia-driven EPO production[4,5] . Renal impairment, caused by nephrotoxic agents and a blunted response EPO response to anemia in cancer patients further compound the problem.[6-8] Chronic anemia in some cancer patients may be exacerbated by an anemia-inducing factor, generated by tumor cells, which causes a diminished erythrocyte life span.[9,10] .

Absolute or functional iron deficiency is another factor in the aetio-pathogenesis of anemia in cancer patients.(11) Absolute iron deficiency (ID), defined by the exhaustion of iron stores in macrophages and hepatocytes, is reflected in the serum ferritin values (40 to 100 ng /ml). However, despite this iron deficient erythropoiesis may still occur or paradoxically may even be elevated. This is called functional ID, defined as an imbalance between iron needs in the bone marrow and iron supply by macrophages. Common causes for absolute iron deficiency in cancer patients include poor dietary iron, compromised oral intake and blood loss. Altered iron homeostasis by the over expressed cytokines interfere with the iron homeostasis by trapping iron within macrophages making it unavailable for utilization. Blunted response of the erythroid progenitors to the erythropoietin also adds to the functional iron deficiency in cancer patients. (12)

Diagnosis of CIA

Serum ferritin, although useful for diagnosing absolute iron deficiency, may not be a reliable indicator of iron stores in cancer patients on recombinant human erythropoietin (rHuEPO). Serum ferritin increases with inflammation, and high levels may be seen in patients with ACD and cancer. The

most accurate method for detecting functional iron deficiency in these patients is the measurement of the percentage of hypochromic RBCs or reticulocyte hemoglobin content. Such measurements, however, require specialized instrumentation that is not widely available. Consequently, the best method for evaluating available iron stores at the present time is the transferrin saturation (TSAT). A TSAT of 20% to 30% generally indicates sufficient iron stores to support erythropoiesis in rHuEPO- treated patients. [14] Thus, functional iron deficiency can be identified when serum ferritin is normal (100-300 ng/ml), transferrin saturation is at least or less than 20%, and when there are more than 10% of hypochromic cells on PS.

Management of anemia in cancer

Assessing risk factors

It is important to identify the risk group who are most likely to be affected and prone to develop anemia. These include

- Patients receiving myelosuppressive chemotherapy or a large area of radiation therapy
- A low hemoglobin level (10-12 g/dl) at the initiation of cytotoxic therapy.
- Administration of platinum-containing regimens

Assessing anemia in cancer

There is no standard. However, it is important to treat the individual and set aside gender specific differences in normal hemoglobin levels. The trigger point will and has to vary for an intervention, be it using blood transfusion or growth factor support. The assessment should include the evaluation of current blood counts, pertinent laboratory values at baseline and assessment of physical symptoms (eg, pulmonary, cardiac, fatigue). Any change in trends related to these findings over

time may represent increasing anemia severity, even if the hemoglobin level has not decreased to very low levels. Assessment also needs to ascertain underlying condition such as nutritional deficiencies, inflammation, infection, hemolysis, blood loss, and other diagnoses in the context of cancer for an optimal intervention to be designed.

Assessing CIA- the NCCN recommendation 2008

The NCCN have laid out certain broad parameters which help assess cancer related anemia and gives a broad framework for adopting strategies to treat the same.. the recommendations are as follows-

- Initial review should include a complete blood count with indices and peripheral blood smear.
- The following studies should be completed if clinically indicated: reticulocyte count, iron studies, B12 and folic acid estimation, stool guaiac, LDH, fractionated bilirubin and reticulocyte count, bone marrow examination, direct Coombs's test, creatinine and/or creatinine clearance.
- If immediate correction is necessary, transfusion should be considered.
- If hemoglobin is 10-11gm/dL, consider erythropoietin therapy after counseling regarding risks and benefits of Erythrocyte stimulating agents in those who are symptomatic or at riskm of developing symptomatic anemia.

Grading of CIA

Standard grading systems define severe anemia as a hemoglobin level lower than 8 g/dl (grade 3 or higher), and this hemoglobin level is also a transfusion trigger. However, several published reports have used different criteria for baseline assessment of hemoglobin values including hematocrit

levels, to define anemia and this makes comparison of many studies complex or neigh impossible. Assessment of the entire scope of potential symptoms is challenging because there is no instrument designed to examine the complete range of findings. Yellen et al developed and validated two instruments to measure the impact of anemia-related symptoms, particularly fatigue, in patients with cancer: the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scale and the Functional Assessment of Cancer Therapy-Anemia (FACT-An). The latter encompasses the FACT-F and additional questions related to anemia. [12, 13]

Impact of anemia in cancer treatment outcomes

Severe anemia cause numerous physiologic complications including dyspnea, headache, fatigue, dizziness decreased cognitive, sleep, and sexual function and significant debilitation. Anemia may delay surgical interventions, chemotherapy cycles and may require dose reductions or delays of myelosuppressive agents, thereby a decrease in the overall intensity of the treatment. Tumor hypoxia also may limit the effectiveness of oxygen-dependent chemotherapy. Data particularly those involving radiation therapy, suggest that anemia has an effect on survival. Patients with head and neck, cervical, ovarian, or vulvar cancer have been shown to be particularly affected.[14, 15] A secondary analysis of RTOG 85-27, a study on patients with head and neck malignancy treated with radiation therapy, estimated that 5-year survival rate among patients with normal hemoglobin was 35.7%, as compared with 21.7% among patients with anemia.[15]

A randomized, placebo-controlled study of 375 patients with diagnoses of solid tumors or hematologic malignancies undergoing non-platinum-based chemotherapy was conducted. The study arm received recombinant human erythropoietin

(rHuEPO) whiles the other received placebo. The treatment group demonstrated significantly improved hemoglobin levels. The Kaplan-Meier survival estimates at 12 months were 60% versus 49% in favor of the intervention group. These results, however, were not significant. Anemia in relation to cancer has also shown to increase the vascular endothelial factor levels and also seem to function through induction of cachexia in cancer patients. Studies using erythropoietin has shown to improve quality of life in the treatment as compared to those who did not receive the same, a reflection of improved oxygenation status.

Treating Cancer-Related Anemia

While simultaneously correction of nutritional deficiencies cannot be overemphasized, transfusion of red blood cells and/or the administration of exogenous hematopoietic growth factors are the simplest way of treating anemia in cancer patients. Recombinant human erythropoietin (EPO-A) effectively treats anemia by increasing Hemoglobin levels. Three independent open-label, nonrandomized, prospective studies, published by clearly demonstrated that EPO increased Hemoglobin by approximately 1.8 g/dL to 2.0 g/dL and decreased the number of transfusions in more than 7000 cancer patients receiving cytotoxic chemotherapy. The increase in Hemoglobin levels were noted when EPO was administered at a starting dose of 150 mcg/kg or 10,000 U thrice weekly.

In the study by Gabrilove et al involving patients with nonmyeloid malignancies on chemotherapy, a schedule of once-weekly EPO (40,000 U) was used [16]. The increase in mean Hemoglobin was 1.8 g/dl in the responders, and the subsequent reduction in transfusion requirements were similar to those results observed when EPO was given more frequently. The various other studies are summarized in Table 2.

Darbopoietin Vs Epoetin Alfa: Is There any Difference?

Compared with Erythropoietin alfa, Darbopoietin has an increased number of sialic-containing N-linked carbohydrate chains, which renders it less susceptible to catabolism thereby increasing its serum half-life 3-fold. Pooled data from 3 clinical trials in which 300 mcg of darbopoietin was given every 2 weeks to patients undergoing multicycle chemotherapy demonstrated a baseline change in Hemoglobin >/= 2 g/dL in 71% of the 115 patients included.[22] Similarly, in a dose-finding study, Darbopoietin was given as either a 3-mcg/kg or a 5-mcg/kg injection every 2 weeks, while EPO was given at a dose of 40,000 units (increased to 60,000 U after 4 weeks when Hemoglobin increase was < 1 g/dL). Patients who achieved hematologic response were 66% and 84% for the two Darbopoietin doses respectively as compared to 63% response rate for epoetin alfa [22].

Although there are currently no published head-to-head studies comparing EPO with darbepoetin alfa, a pilot study by Glaspy et al [23] explored the feasibility and safety of Darbopoietin alfa as a front loading dose (4.5mcg/kg/week for 4 weeks) followed by 3 different maintenance dosing (1.5, 2.25 and 4.5 mcg/kg/week), against once-weekly EPO (40000 units/ week increased to 60000 units at 6 weeks) as an active control. There was a marked increase in Hemoglobin concentration noted early in all the Darbopoietin arms with no decrease in efficacy when frequency was reduced. However, the increase was still smaller than the mean change of 2 g/dl seen in previous trials with erythropoietin alfa. The study though not powered to detect differences between treatment arms did however suggest a higher activity for Darbopoietin. [24,25]

Table 3. Improvements in Hemoglobin Levels With Darbopoietin vs Epoetin Alfa [27]

Treatment Arm	Mean Change in Hemoglobin	Patients Achieving Response
Group 1	1.35 g/dL	59%
Group 2	1.35 g/dL	58%
Group 3	1.28 g/dL	65%
Group 4	1.03 g/dL	49%

Glaspy JA, et al. Cancer. 2003; 97:1312-1320.

Iron Therapy

Iron deficiency is a reality in patients with cancer and it is imperative to identify and replenish the same when adopting other measure to correct anemia of cancer. Even though there is an element of impaired iron absorption, utilization and metabolism in cancer patients oral iron intake can be useful. However poor compliance to oral therapy is met with due to GI disturbances induced by oral iron make it a less attractive option. Under the circumstances options of parenteral iron therapy has been used to good effect. With the current availability of iron sucrose, the toxicity associated with parenteral iron therapy are less frequent. Auerbach [26] compared the utility of oral iron versus IV iron versus no iron at all in cancer patients. Iron dextran was given either as bolus dose or as an infusion. There were statistically significant differences in mean end point hemoglobin levels between the IV bolus group and the no-iron arm. The mean Hb increase for both the IV iron groups were significantly higher than the no-iron and oral iron arms ($P < .02$). However there was no difference between the no-iron and oral iron groups suggesting poor results with oral therapy [26]. In another study Henry et al compared ferric gluconate infusion once weekly with oral iron and no supplementation. There was a significantly larger increase in mean Hb from baseline to end point in the infusional

arm (2.4 g/dl) compared to patients on oral iron or no iron. Mean Hb increase was 1.6 g/dL in the oral iron arm, and 1.5 g/dL (95% CI, 1.1 to 1.9) in the no-iron arm. The difference in Hb increase between these two arms was not significant. [27] The summary of the 2 studies are mentioned in table -4

Table 4 Iron therapy- Summary of results from randomized studies

Auerbach 157 patients [18]	**No Iron**	**Oral Iron**	**IV dextrann bolus**	**IV dextran infusion**
EPO 40000U/weekly	given	given	given	given
Hb increase (gm/dl)	0.9	1.5	2.5	2.4
Henry et al 187 patients [19]	IV Ferric gluconate once a week	Oral Ferrus sulphate	No Iron	
Hb increase (gm/dl)	2.4	1.5	1.4	

Conclusions

Cancer related problems is not limited to the disease itself, but can be exacerbated by the treatment regimens as well. Supportive care measures have demonstrated an ability to not only alleviate side effects but also to significantly improve the quality of life of affected patients. Given the high prevalence of anemia in cancer patients on chemotherapy, the concurrent use of erythropoietic agents including EPO and darbepoetin alfa have demonstrated an ability to increase hemoglobin levels, improve quality of life and perhaps survival also in patients being treated for cancer.

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