Guidelines for Complications of Cancer Treatment

Part A

Editors

Dr. S. V. Shrikhande MS, MD
Senior Professor
Tata Memorial Hospital

Dr. C. S. Pramesh, MS, FRCS
Senior Professor
Tata Memorial Hospital

Published by
Tata Memorial Hospital
Mumbai

Tata Memorial Hospital
Dr. Ernest Borges Road, Parel
Mumbai 400 012. INDIA.
Tel.: +91-22-2417 7000 Fax: +91-22-2414 6937
Email: crs@tmc.gov.in
Website: http: //tmc.gov.in

Evidence Based Management of Cancers in India Vo. VIII Year 2009

Three Parts
Set ISBN: 978-81-904583-6-8

Guidelines for Complications of Cancer Treatment
Part A ISBN: 978-81-904583-7-5

Guidelines for Complications of Cancer Treatment
Part B ISBN: 978-81-904583-8-2

Guidelines for Molecular Imaging and PET-CT in Cancer
Part C ISBN: 978-904583-9-9

Set ISBN: 978-81-904583-6-8
Part C ISBN : 978-81-904583-7-5

Published by the Tata Memorial Hospital, Mumbai,
Printed at the Sundaram Art Printing Press, Mumbai.

Dedicated to
All our patients at
The Tata Memorial Hospital

Contents

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

Complications of Esophageal Surgery

Contributors

Rajesh Mistry
C S Pramesh

Complications of Esophageal Surgery

- Pulmonary complications
  - Neoadjuvant chemotherapy (LOE 1)
  - Neoadjuvant chemoradiation (LOE 1)
  - Transhiatal vs transthoracic (LOE 1)
  - Prevention (LOE 5)
- Anastomotic leaks
  - Route of reconstruction (LOE 1)
  - Conduit used (LOE 3)
  - Site of anastomosis (LOE 3)
  - Type of anastomosis (stapled vs handsewn) (LOE 1)
- Cardiac complications
  - Prevention (LOE 3)
- Recurrent laryngeal paresis / palsy
  - Three field vs two field (LOE 1)
- Chylothorax
  - Diagnosis (LOE 3)
  - Management (LOE 4)
- Delayed gastric emptying
  - Pyloric drainage (LOE 1)
  - Management (LOE 3)
- Anastomotic stricture
  - Type of anastomosis (stapled vs handsewn) (LOE 1)

Introduction

Surgery for oesophageal cancer is known to be associated with significant morbidity and mortality, the reasons being manifold. It is one of the most complex surgical procedures involving intervention in minimum of two and often three anatomical sites (thorax, abdomen and neck). Patients are generally elderly with associated co morbidities and compromised nutritional status. Several reviews have reported statistically significant association between hospital and surgeon volume of esophageal surgery and outcome in terms of mortality and morbidity. Therefore while surgery continues to play an important role in management of patients with esophageal cancer, it is important to focus on the 'downside' of this procedure and evolve guidelines to minimize and manage the same. The complications are discussed under following headings:

1. Pulmonary complications
2. Anastomotic leak
3. Gastric tube necrosis
4. Recurrent nerve palsy
5. Chylothorax
6. Cardiac complications
7. Diaphragmatic herniation
8. Functional complications: dysphagia due to anastomotic stricture, delayed gastric emptying, gastro-oesophageal reflux and dumping.
9. Video Assisted Thoracoscopic Oesophagectomy (VATS) and complications.

1. Pulmonary Complications

The incidence of post operative pulmonary complications range from 2% to 33% and are a major source of morbidity. The large variation is in part due to variable definition of what

constitutes pulmonary complication. Patient factors such as advanced age, compromised nutritional and performance status predispose to increased pulmonary complication. Several authors have investigated role of pre-operative pulmonary function as predictor of pulmonary morbidity and a few have reported FEV1 of < 65% to be associated with increased risk pulmonary complications (LOE3). Pre-operative factors such as neo-adjuvant treatment has been implicated to increase the risk of pulmonary complications. However, a meta-analysis performed by Urschel did not find significant increase in pulmonary complications among patients receiving induction chemotherapy (LOE 1). Induction chemo-radiation on the other hand, is reported to cause significant increase in the risk of pulmonary complications. van Meerten reported pulmonary complications in 41% of patients in a Phase II study of neoadjuvant chemo-radiation. However, the meta analysis by Urschel showed only a non-statistically significant trend towards increased pulmonary complications after neoadjuvant chemoradiation (LOE 1).

Surgical approach and extent of mediastinal lymph node dissection are also factors implicated in pulmonary complications. Orringer reports 2% incidence of pulmonary complications in over a thousand patients who underwent transhiatal oesophagectomy. Hulscher et al, in a Phase III trial comparing the two approaches reported pulmonary complications rates of 27% and 57% in trans hiatal and trans thoracic approach respectively. A meta analysis comparing transhiatal with transthoracic esophagectomy showed no difference in incidence of pulmonary complications in studies which had a comparative group (LOE 1). Extended lymph node dissection (total mediastinal/3-field dissection) can cause tracheo-bronchial devascularisation and abnormal fluid shift. This increases the risk of pulmonary complications. A small randomized trial comparing two with three field lymphadenectomy showed similar pulmonary complication

rates. A large ongoing randomized trial comparing two with three field lymphadenectomy showed a definite trend towards increased pulmonary complications with three field lymphadenectomy (personal communication, LOE 1). A meta analysis on the route of reconstruction showed similar pulmonary complications after either a posterior mediastinal or a retrosternal route (LOE 1).

Prevention (LOE 5)

Proper patient selection

Pre-operative counseling regarding smoking cessation

Antibiotic prophylaxis

Meticulous surgery

Preservation of bronchial artery when possible

Post operative (epidural) analgesia

Fluid restriction

Chest physiotherapy

Bronchoscopic aspiration of secretions

Tracheostomy when indicated

2. Anastomotic Leak

Anastomotic leak is an important cause of morbidity and mortality following oesophagectomy. The incidence reported in literature ranges from 1% to 30%. The wide variability is due to absence of standard definition and threshold for reporting a leak. Broadly, leaks are classified as minor and major depending on its severity. Lerut has proposed four grades of leak: Radiological without clinical signs (Grade I), Clinical minor (Grade II), Clinical major with sepsis (Grade III) and Conduit necrosis (Grade IV). Poor nutritional status is an important patient factor predisposing to leak. Among the preoperative factors, induction chemo radiation is associated with higher leak rates. Operative factors that potentially impact

leak rates are the conduit organ, site and route of anastomosis and anastomotic technique. Stomach is more robust than colon and hence leak rates are higher with coloplasty than with gastric tube (LOE 3). Intra thoracic anastomosis requiring smaller length of gastric tube, generally have lesser incidence of leak than cervical anastomosis (LOE 3). A meta analysis on the route of reconstruction showed no significant difference in anastomotic leaks between posterior mediastinal and retrosternal routes (LOE 1).

Various techniques of anastomosis (single layer, double layer, continuous, interrupted and mechanical) have been described in the literature with aim of minimising the leak rates. Some authors have reported reduction in the leak rates with mechanical or semi mechanical anastomosis; however randomized trials and a meta analysis do not reveal significant difference in leaks with the two techniques (LOE 1).

Absence of tension at the anastomosis and good vascularity of the conduit is of paramount importance. Ischemic preconditioning of stomach by preoperative embolization of left gastric, right gastric and splenic arteries has not been shown to reduce the leak rates (LOE 4). 'Super charging' with micro vascular anastomosis have also been described to improve the vascularity of the conduit (LOE 4). Division of interclavicular ligament beneath the sternal notch and at times, resection of the ipsilateral sternoclavicular joint is recommended to protect against venous obstruction caused by extrinsic compression while using the retrosternal route. Absence of serosa and longitudinal orientation of the oesophageal muscle confers inherent disadvantage over other enteral anastomosis; hence reinforcement with peritoneal patch has been described.

Diagnosis of leak could be radiological or clinical. Routine contrast swallow does not rule out leaks conclusively. This is particularly true of cervical anastomosis. Early leaks are generally clinically obvious and major. The presenting feature

could be tachycardia, tachypnea, fever, arrhythmia or collection/crepitus in the neck. A CT thorax could reveal mediastinal widening, mediastinal or pleural collection and secondary pneumonia. Minor cervical leaks generally lateralize in the neck and in absence of chest or mediastinal contamination can be managed conservatively. Nutritional support is provided by enteral feeding (jejunostomy) till leak heals. Orringer advocates early anastomotic dilatation to prevent obstruction and promote flow through anastomotic lumen rather than fistula. Intra thoracic leaks tend to be more serious. Negative intra-pleural pressure generally causes diffuse contamination of the pleural cavity and mediastinum with grave consequences. Grade III leaks need aggressive surgical management which includes adequate drainage and at times disconnection. Leaks resulting from ischemic necrosis require disconnection, resection of necrosed gastric tube, gastrostomy and cervical oesophagostomy.

3. Gastric Tube Necrosis

Gastric tube necrosis is the most dreaded complication of esophagectomy and is associated with very high mortality. It is reported to occur in 2% to 10% of patients. The causes are intrinsic vascular insufficiency due to atherosclerosis, conduit torsion, and technical mishap. Presentation could be acute with rapid deterioration of patient's general condition if the necrosis is extensive. Rising levels of lactate and metabolic acidosis on arterial blood gas analysis could be indicative of necrosis. Bedside endoscopy will confirm the diagnosis. Early diagnosis and re-operation are advisable. Surgery involves disconnection and resection of necrosed gastric tube followed by gastrostomy and cervical oesophagsotomy. Coloplasty should be performed to restore gastro-intestinal continuity after complete recovery. However salvage rates are dismal. Gastric conduit is based on right gastro-epiploic artery and the vascular arch. Generally it is also possible to preserve the right gastric artery. There is no consensus on the amount of fundus that should be resected or

the width of the gastric conduit; however it is advisable to avoid a very narrow tube and resect as much fundus as possible without compromising the length of the conduit. If vascularity of the conduit is in doubt at surgery, delayed reconstruction is an option. The conduit can be hitched to the cervical wound where it can be closely watched for viability.

4. Cardiac Complications

The commonest cardiac complication is rhythm disturbances (atrial fibrillations). Age, pre existing cardiac disease, and mediastinal dissection are predisposing factors. However very often it could be manifestation of anastomotic leak causing mediastinitis. Atrial fibrillation occurring after oesophagectomy generally responds to beta blocker or Amiodarone. Prophylactic medication has been tried without success. (LOE 3)

5. Recurrent Nerve Palsy/Paresis

The incidence of unilateral recurrent nerve palsy following oesophagectomy is upto 50%. It is more common following cervical anastomosis and dissection of nodes along the recurrent nerves in the upper mediastinum. Three field lymph node dissection as described by Akiyama also may result in bilateral recurrent nerve palsy. There is a definite increase in the rate of recurrent laryngeal nerve paresis after three field esophagectomy compared to two field lymphadenectomy (LOE 1). The best way to avoid inadvertent nerve injury is by preventing direct retraction of the trachea while mobilizing the oesophagus in the neck. In most cases, vocal cord function recovers in three to six months. In our experience, permanent palsy is observed in 6% of cases (LOE 3). In the immediate post operative period, palsy results in ineffective cough and aspiration. The latter is overcome by restricting oral intake to solids and administering liquids through a jejunostomy tube. In cases of bilateral nerve palsy, a tracheostomy may become

necessary. If the cord movement does not recover or is not compensated by the contra lateral functioning cord, medialisation of the paralysed cord may be needed. (LOE 5)

6. Chylothorax

The occurrence of chylothorax following oesophagectomy is not uncommon. High postoperative drainage through inter costal drain, which persists without showing signs of reduction should raise suspicion of thoracic duct leakage. It turns 'milky' following jejunostomy feeds. Fluid triglyceride level of more than 110mg/dl is strongly suggestive of chyle and level less than 50mg/dl rules out chylothorax (LOE 3). Presence of chylomicron in the fluid is also indicative of thoracic duct leak. The best way to prevent chylothorax is to be familiar with the anatomy of thoracic duct in the thorax (between the azygous vein and descending aorta). While dissecting the lymph nodes one should carefully avoid injury to the duct or electively identify and ligate with or without its resection. Prolonged leakage leads to nutritional and immunological depletion with grave consequences. Initially, conservative management with fat free feeds/medium chain triglyceride diet can be attempted; however, if the leakage continues to be more than a litre over 24 hours or more than 10ml/kg/day for more than five days, early surgical intervention is recommended (LOE 4). Identification of leakage site in the thoracic duct can be aided by pre operative jejunostomy feed with cream (LOE 4). Thoracoscopic magnification is useful for identification of the injured duct and it's clipping. Radiological embolisation of the thoracic duct has also been described for difficult cases. In situation where it is impossible to identify the duct or ligation has failed pleurodesis/pleurectomy may be attempted.

7. Diaphragmatic herniation

This is a rare complication, which can occur in the early postoperative period. Presentation could be in form of

tachypnoea, abdominal distension or signs of sepsis resulting from bowel ischemia or perforation. The condition can prove fatal unless diagnosed early. A CT scan can confirm diagnosis. It is observed more frequently after resection for carcinoma of the cardia where a cuff of diaphragm is often removed. There is suggestion that it occurs more frequently after laparoscopic mobilization of stomach. We have had four such cases in our experience of over 750 cases. Some surgeons advocate routine narrowing of the diaphragmatic hiatus around the gastric tube to prevent this complication.

8. Functional complications

A. Delayed gastric emptying

Gastric atony and pyloric spasm causing delayed emptying is not uncommon after oesophagectomy and reconstruction with gastric conduit. Distal passage of food bolus through the stomach tube is largely a function of gravity. Generally, delayed emptying is temporary from which patient recovers gradually with passage of time. Avoiding broad and voluminous gastric tube helps in adequate emptying. Medical treatment with prokinetics (metoclopramide, cisapride, bethanechol, and domperidone) or erythromycin, a motilin agonist, may be useful to overcome the delay in early postoperative period (LOE 3). Drainage procedures such as pyloroplasty, pyloromyotomy and dilatation (we perform intra-operative pyloric dilatation with a sponge holder through gastrotomy before completing tubularisation of stomach) are described to overcome delay with varying degree of success. A meta analysis on the use of pyloric drainage procedures showed no difference in delayed gastric emptying regardless of a pyloric drainage procedure being performed (LOE 1). Most centres in Japan do not perform drainage and resort to endoscopic balloon dilatation in the event of obstruction. One disadvantage of drainage procedure is higher incidence of reflux observed in many studies.

B. Gastric Oesophageal reflux

This is a common complain of many patients under going oeosphagectomy. It is more frequent with cervical anastomosis. Pyloric drainage and placement of gastric conduit in the posterior mediastinum may be predisposing factors. Instructing patient to sleep with head end slightly elevated can minimize it (LOE 5). Avoiding meals before going to bed or lying down is useful. There should be three or four hours between last meal/snack and bedtime. Symptomatic reflux is treated with proton pump inhibitor and prokinetics (LOE 4).

C. Dumping

The incidence of dumping after oesophgectomy is variable ranging from 25% to 50%. 'Early' dumping occurs within 45 minutes of meal and 'late' occurs 2 to 3 hours after meals. Early dumping results from rapid entry of food and fluids directly into the small intestine, producing decreased blood pressure and increased blood flow to the intestines. Low blood sugar caused by excess insulin produced in response to sudden dumping of foods and fluids into the intestine results in late dumping. Symptoms of early dumping are weakness and fainting, sweating, irregular or rapid heartbeat, decreased blood pressure, flushing of skin, dizziness, shortness of breath, vomiting, and severe abdominal cramps. This may or may not end in explosive diarrhea. Symptoms of late dumping are dizziness, faintness, sweating, exhaustion, low blood pressure, headache or anxiety. Both forms of dumping are exaggerated by over-distention of the stomach and meals that have high content of refined mono- and disaccharide sugars. The best treatment of dumping is dietary modification. Usually, it resolves gradually over a period of 4 to 6 months. Taking small meals and separating solids from liquids and avoiding refined sugars minimizes the symptoms.

D. Anastomotic stricture

This is generally a delayed complication, which impacts the quality of life. The incidence reported in the literature is highly variable and ranges from 1% to 51%. Presenting feature is gradually increasing dysphagia. A contrast swallow and endoscopy can confirm the diagnosis. Early strictures are generally benign; anastomotic recurrence should be ruled out in delayed strictures. Postoperative anastomotic leak predisposes to strictures. Acid reflux also predisposes anastomosis to stricture formation. Double-layered anastomosis may be more predisposed to stricture formation than single layered anastomosis (LOE 3). Mechanical anastomosis with circular staplers have been shown to have a higher rate of stricture formation in some studies but a meta analysis failed to show a difference in stricture rates (LOE 1). On the other hand semi mechanical anastomosis described by Orringer and its modification using series of GIA staplers increases the cross sectional area of the anastomosis which in turn reduce the incidence of stricture formation. Most strictures respond to few dilatations. However strictures following leaks or vascular insufficiency could be resistant to dilatation and frustrating to treat.

9. Video Assisted Thoracoscopic Oesophagectomy and complications.

The two popular approaches for oesophagectomy are trans hiatal and trans thoracic oesophagectomy. One of the reasons why THE is preferred by general surgeons is potential for lower pulmonary morbidity associated with the procedure. Postero-lateral thoracotomy involves cutting of muscles, retraction of chest wall which can cause inadvertent fractures of rib(s). Therefore thoracotomy is generally associated with severe pain, which interferes with patients cough effort and chest physiotherapy. On the other hand THE is a blind procedure

and hence there is risk of injury to thoracic duct, azygous vein, recurrent nerve and tracheo-bronchial tree. Also, it is not possible to do mediastinal lymph node dissection and the circumferential margin is very close to oesophageal wall. VATS provides all the advantage of THE (since it does not involve cutting of muscles and retraction of ribs) and allows thoracic dissection under vision. Thus theoretically it should have pulmonary complication rate comparable to THE. However review of published literature and our own experience show that pulmonary complication rate is comparable to TTE (LOE 3). Need for one lung ventilation and mediastinal dissection that is similar to open TTE could be the reasons for comparable pulmonary complication. VATS is also associated with a steep learning curve and lack of tactile sensation is a distinct disadvantage. Till results of large, preferably phase III studies are available, VATS will continue to be an investigational approach in the hands of experienced surgeons.

Suggested Reading

1. Urschel JD, Urschel DM, Miller JD. A meta-analysis of randomized controlled trials of route of reconstruction after esophagectomy for cancer. Am J Surg 2001; 182: 470-5
2. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003; 185: 538- 43
3. Urschel JD, Blewett CJ, Young JE et al. Pyloric drainage (pyloroplasty) or no drainage in gastric reconstruction after esophagectomy: a meta-analysis of randomized controlled trials. Dig Surg 2002; 19: 160-4
4. Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant

chemotherapy and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2002; 183: 274-9

5. Swisher SG, Deford L, Merriman KW, et al: Effect of operative volume on morbidity, mortality and hospital use after esophagectomy for cancer. J Thorac Cardiovasc Surg 2000; 119: 1126-32
6. Law S, Wong KH, Kwok KF, et al: Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004; 240: 791-800
7. Orringer MB, Marshall B, Iannettoni MD: Transhiatal esophagectomy for treatment of benign and malignant esophageal disease. World J Surg 2001; 25: 196-203
8. Avendano CE, Flume PA, Silvestri GA, et al: Pulmonary complications after esophagectomy. Ann Thorac Surg 2002; 73: 922-6
9. Hulscher JBF, Tijssen JGP, Hugo O, et al: Transthoracic versus transhiatal resection for carcinoma of the esophagus: A meta-analysis. Ann Thorac Surg 2001; 72: 306-313
10. Hulscher JB, van Sandick JW, de Boer A, et al: Extended transthoracic resection compared with limited transhiatal resection for advanced adenocarcinoma of the esophagus. N Engl J Med 2002; 347: 1662-9
11. Law S, Fok M, Chu KM, Wong J: Comparison of hand-sewn and stapled esophagogastric anastomosis after esophageal resection for cancer: a prospective randomized controlled trial. Ann Surg 1997; 226: 169-73
12. Urschel JD, Blewett CJ, Bennett WF, et al. Handsewn or stapled esophagogastric anastomoses after esophagectomy for cancer: meta-analysis of randomized controlled trials. Dis Esoph 2001; 14: 212-7

13. Orringer MB, Marshall B, Iannettoni MD: Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. J Thorac Cardiovasc Surg 2000; 119: 277-88.

14. Eric K. Hoffer, Robert D. Bloch, Michael S. Mulligan, John J. Borsa and Arthur B. Fontaine :Treatment of Chylothorax. Percutaneous Catheterization and Embolization of the Thoracic Duct. AJR 2001; 176:1040-2.

15. Van Sandick JW, Knegiens JL, van Lanschott JJ, et al: Diaphragmatic herniation following oesophagectomy. Br J Surg 1999; 86:109-12

16. Burrows WM. Gastrointestinal function and related problems following esophagectomy. Seminar in Thorac Cardiovasc Surg 2004; 16: 142-151,.

17. Luigi Bonavina, Greta Saino, Davide Bona, Medhanie Abraham, Alberto Peracchia. Journal of Laparoendoscopic & Advanced Surgical Techniques. December 1, 2001, 11(6): 367-9.

18. Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al: Minimally invasive esophagectomy: Outcomes in 222 patients. Ann Surg 2003; 238: 486-95

Section — II

Stomach

Contributors

PJ Shukla

SV Shrikhande

R Maharaj

Complications of Lymphadenectomy

- D 1 vs D2 dissection level of evidence LOE 1.
- D1 vs D3 LOE 1.
- D2 vs D2 with aortic nodal dissection LOE 1.
- Low Maruyama index surgery for gastric cancer LOE 1.

Introduction

Gastric carcinoma ranks among the fourth most common cancer in the world with a high incidence in Japan and the Andes region. Proximal gastric cancers are more common in the West than in Asia. The first successful gastrectomy for gastric carcinoma was performed by Billroth in 1881 and since several lymph nodes were also removed, he performed the first lymph node dissection as well.Since then numerous variations to the extent of gastric resection and lymphadenectomy as well as reconstruction of the gastrointestinal tract has been described, all of which have their inherent complications.

Complications of lymphadenectomy

The extent of lymphadenectomy in gastric cancer has been a source of controversy for decades. The Japanese Reseach Society for the Study of Gastric Cancer (JRSGC) as well as the American Joint Comittee on Cancer (AJCC) and the

International Union against Cancer (UICC) have standardised the nomenclature regarding the lymph node echelons surrounding the stomach. The perigastric lymph nodes along the lesser curve (echelons 1,3 and 5) and the echelons along the greater curvature (echelons 2,4 and 6) and grouped as N1 nodes. The left gastric (echelon 7), common hepatic (echelon 8), celiac (echelon 9), splenic hilum (echelon 10)and splenic artery (echelon 11) are grouped as N2 nodes. The nodes in the hepatoduodenal ligament (echelon 12), posterior pancreaticoduodenal (echelon 13), nodes at the base of the superior mesenteric vessels (echelon 14) and the middle colic nodes (echelon 15) are the N3 nodes while the para-aortic nodes (echelon 16) are N4. The extent of lymph node dissection is classified D1-4 depending on the groups of lymph nodes removed. As recommended by the JRSGC, a pancreaticosplenectomy was performed in order to facilitate dissection of echelons 10 and 11. The more common, major complications identified following lymphadectomy were intra-abdominal collections, anastomotic leaks, pancreatic fistulae and pulmonary complications.

The first evidence of a survival benefit following extended lymphadenectomy came in 1981 when Kodama reported a 39% 5 year survival for D2 dissections compared to 18% for D1 dissections (level of evidence LOE:2). Since then numerous randomized and non-randomized trials were designed to hypothesise whether the removal of additional positive lymph nodes improved survival. To date, two well powered randomised controlled trials have been conducted namely the British MRC Gastric Cancer Surgical Trial (LOE 1) and the Dutch Gastric Cancer Trial (LOE1). The randomized trials by Dent et al. and Robertson et al. were both underpowered.

In the British MRC Gastric Cancer Surgical Trial, 737 patients were initially registered however 337 were ineligible due to advanced disease detected on staging laparoscopy. The remaining 400 were equally randomized to either the D1 or

D2 groups. The postoperative mortality was statistically significantly higher in the D2 group as compared to the D1 group (13% vs 6.5%; p=0.04). The postoperative complication rate was also statistically significantly higher in the D2 group (46% vs 28%; p< 0.001).

In the Dutch Gastric Cancer Trial, 996 patients were registered and 711 were randomized to the D1 and D2 groups. As with the MRC trial, the postoperative mortality was statistically significantly higher in the D2 as compared to the D1 group (10% vs 4%; p=0.004) and the postoperative complication rate was also higher in the D2 group (43% vs 25%; p<0.001).

Results of the MRC and Dutch Trial

	D1	D2	P value
Dutch Trial	Morbidity:25%	Morbidity:43%	< 0.001
	Mortality: 4%	Mortality: 10%	0.004
MRC Trial	Morbidity:28%	Morbidity:46%	<0.001
	Mortality:6.5%	Mortality:13%	0.04

Pancreaticosplenectomy has been regarded as a risk factor for postoperative morbidity and mortality . In addition, as surgeon experience increased, the need for pancreaticosplenectomy to facilitate the removal of echelons 10 and 11 when performing a total gastrectomy was questioned. In a Cochrane Systematic Review by McCulloch et al.(LOE 1) a subgroup analysis revealed that the perioperative mortality and morbidity were similar in both both groups when the spleen and pancreas were preserved. Incidentally, in both these trials there was no statistical difference in the overall survival for the D1 vs the D2 groups.

Two non-randomized trials by the German Gastric Carcinoma Study Group (LOE 2)and the Italian Gastric Cancer Study Group Multicenter Trial (LOE 2) revealed an improved overall survival of D2 compared with D1 dissection. This survival

difference has been attributed to the stage migration effect, also known as the Will Rogers phenomenon, where the more extensive the lymphadenectomy, the greater the chances of detecting involved nodes leading to an improvement in stage specific survival but not overall survival.

In a randomized trial by the Taiwanese group led by Wu (LOE 1),110 patients were randomized to the D1 group and 111 to the D3 group. The postoperative complications identified were anastomotic leak, intra-abdominal abscesses, pancreatic leaks and pulmonary complications. These postoperative complications were significantly higher in the D3 vs the D1 group. There were no mortalities in either group.

In a randomised trial by Sano et al. of the Japan Clinical Oncology Group (LOE 1), 523 patients were randomised to D2 lymph node dissection and D2 lymph node dissection plus para-aortic node dissection. There was no statistical difference in terms of major morbidity and mortality in either group. The postoperative complications identified were similar to the trial by the Taiwanese group.

Critics of this one size fits all approach have, on the other hand, supported the Maruyama Index to predict the extent of lymphadenectomy required for individualised patients. The Maruyama programme was introduced based on data from numerous patients and the possibility of lymph node involvement can be predicted once a patient's preoperative and intraoperative parameters are fed into the programme. The extent of surgery can therefore be tailored for each patient.

Conclusion

The extent of lymphadenectomy has been and continues to be a source of controversy for many decades. The morbidity and mortality rates appear proportional to the extent of lymphadenectomy however this association correlates with concomitant pancreaticosplenectomy.

Extended lymph-node dissection for gastric cancer.

Bonenkamp JJ, Hermans J, Sasako M et al. N Engl J Med. 1999;340:908-914.

BACKGROUND: Curative resection is the treatment of choice for gastric cancer, but it is unclear whether this operation should include an extended (D2) lymph-node dissection, as recommended by the Japanese medical community, or a limited (D1) dissection. We conducted a randomized trial in 80 Dutch hospitals in which we compared D1 with D2 lymph-node dissection for gastric cancer in terms of morbidity, postoperative mortality, long-term survival, and cumulative risk of relapse after surgery.

METHODS: Between August 1989 and July 1993, a total of 996 patients entered the study. Of these patients, 711 (380 in the D1 group and 331 in the D2 group) underwent the randomly assigned treatment with curative intent, and 285 received palliative treatment. The procedures for quality control included instruction and supervision in the operating room and monitoring of the pathological results.

RESULTS: Patients in the D2 group had a significantly higher rate of complications than did those in the D1 group (43 percent vs. 25 percent, P<0.001), more postoperative deaths (10 percent vs. 4 percent, P= 0.004), and longer hospital stays (median, 16 vs. 14 days; P<0.001). Five-year survival rates were similar in the two groups: 45 percent for the D1 group and 47 percent for the D2 group (95 percent confidence interval for the difference, -9.6 percent to +5.6 percent). The patients who had R0 resections (i.e., who had no microscopical evidence of remaining disease), excluding those who died postoperatively, had cumulative risks of relapse at five years of 43 percent with D1 dissection and 37 percent with D2 dissection (95 percent confidence interval for the difference, -2.4 percent to +14.4 percent).

CONCLUSIONS: Our results in Dutch patients do not support the routine use of D2 lymph-node dissection in patients with gastric cancer.

Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group.

Cuschieri A, Weeden S, Fielding J et al. Br J Cancer. 1999;79:1522-1530

Controversy still exists on the optimal surgical resection for potentially curable gastric cancer. Much better long-term survival has been reported in retrospective/non-randomized studies with D2 resections that involve a radical extended regional lymphadenectomy than with the standard D1 resections. In this paper we report the long-term survival of patients entered into a randomized study, with follow-up to death or 3 years in 96% of patients and a median follow-up of 6.5 years. In this prospective trial D1 resection (removal of regional perigastric nodes) was compared with D2 resection (extended lymphadenectomy to include level 1 and 2 regional nodes). Central randomization followed a staging laparotomy. Out of 737 patients with histologically proven gastric adenocarcinoma registered, 337 patients were ineligible by staging laparotomy because of advanced disease and 400 were randomized. The 5-year survival rates were 35% for D1 resection and 33% for D2 resection (difference -2%, 95% CI = -12%-8%). There was no difference in the overall 5-year survival between the two arms (HR = 1.10, 95% CI 0.87-1.39, where HR > 1 implies a survival benefit to D1 surgery). Survival based on death from gastric cancer as the event was similar in the D1 and D2 groups (HR = 1.05, 95% CI 0.79-1.39) as was recurrence-free survival (HR = 1.03, 95% CI 0.82-1.29). In a multivariate analysis, clinical stages II and III, old age, male sex and removal of spleen and pancreas

were independently associated with poor survival. These findings indicate that the classical Japanese D2 resection offers no survival advantage over D1 surgery. However, the possibility that D2 resection without pancreatico-splenectomy may be better than standard D1 resection cannot be dismissed by the results of this trial.

Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach.

McCulloch P, Nita ME, Kazi H, et al. Cochrane Database Syst Rev. 2004;(4):CD001964

BACKGROUND: Surgeons disagree about the merits and risks of radical lymph node clearance during gastrectomy for cancer.

OBJECTIVES: To evaluate survival and peri-operative mortality after limited or extended lymph node removal during gastrectomy for cancer.

SEARCH STRATEGY: We searched MEDLINE, EMBASE, CancerLit, LILACS, Central Medical Journal Japanese Database and the Cochrane register, references from relevant articles and conference proceedings. We contacted known workers in the field.

SELECTION CRITERIA: Studies published after 1970 which reported 5 year survival or postoperative mortality rates, and clearly defined the node dissection performed, were considered. We excluded studies which overtly included patients receiving perioperative chemotherapy, and comparisons with clear systematic treatment allocation bias. Randomised controlled trials (RCTs), non-randomised comparisons and observational studies were considered separately.

DATA COLLECTION AND ANALYSIS: Three reviewers selected trials for inclusion. Quality assessment and data extraction were performed independently by two reviewers.

Results of trials of similar design were pooled. Meta-analysis was performed separately for randomised and non-randomised comparisons.

MAIN RESULTS: Two randomised and two non-randomised comparisons of limited (D1) versus extended (D2) node dissection and 11 cohort studies of either D1 or D2 resection were analysed. Meta-analysis of randomised trials did not reveal any survival benefit for extended lymph node dissection (Risk ratio = 0.95 (95% CI 0.83 - 1.09), but showed increased postoperative mortality (RR 2.23, 95% CI 1.45 - 3.45). Pre-specified subgroup analysis suggested a possible benefit in stage T3+ tumours (RR = 0.68, 95% CI 0.42-1.10). Non-randomised comparisons showed no significant survival benefit for extended dissection (RR 0.92, 95% CI 0.83 -1.02), but decreased mortality (RR 0.65, 95% CI 0.45-0.93). Subgroup analysis showed apparent benefit in UICC stage II and IIIa. Observational studies of D2 resection reported much better mortality and survival than those of D1 surgery, but the settings were strikingly different.

REVIEWERS' CONCLUSIONS: D2 dissection carries increased mortality risks associated with spleen and pancreas resection, and probably with inexperience and low case volumes. Randomised studies show no evidence of overall survival benefit, but possible benefit in T3+ tumours. These results may be confounded by surgical learning curves and poor surgeon compliance. Non-randomised comparisons suggest a possible survival benefit for D2 in intermediate UICC stages. Observational studies show high 5 year survival and low operative mortality after D2 dissection in experienced units, and poor results after D1 dissection in non-specialist units. Further studies, with precautions to eliminate learning curve effects, contamination and non-compliance, are needed to evaluate D2 dissection in intermediate stage gastric cancer.

Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer.

Degiuli M, Sasako M, Ponti A, et al. Br J Cancer. 2004;90:1727-1732.

Curative resection is the treatment of choice for potentially curable gastric cancer. Two major Western studies in the 1990s failed to show a benefit from D2 dissection. They showed extremely high postoperative mortality after D2 dissection, and were criticised for the potential inadequacy of the pretrial training in the new technique of D2 dissection, prior to the phase III studies being initiated. The inclusion of pancreatectomy and splenectomy in D2 dissection was associated with increased morbidity and mortality. Following these results, we started a phase II trial to evaluate the safety and efficacy of pancreas-preserving D2 dissection. The results of this trial regarding the safety of pancreas preserving D2 dissection were published in 1998. In this paper, we present the survival results of this phase II trial to confirm the rationale of carrying out a phase III study comparing D1 vs D2 dissection for curable gastric cancer. Italian patients with histologically proven gastric adenocarcinoma were registered in the Italian Gastric Cancer Study Group Multicenter trial. The study was carried out based on the General Rules of the Japanese Research Society for Gastric Cancer. A strict quality control system was achieved by a supervising surgeon of the reference centre who had stayed at the National Cancer Center Hospital, Tokyo, to learn the standard D2 gastrectomy and the postoperative management. The standard procedure entailed removal of the first and second tier lymph nodes. During total gastrectomy, the pancreas was preserved according to the Maruyama technique. Complete follow-up was available to death or 5 years in 100% of patients and the median follow-up time was 4.38 years. Out of 297 consecutive patients registered, 191 patients were enrolled in the study between

May 1994 and December 1996. The overall morbidity rate was 20.9%. The postoperative in-hospital mortality was 3.1%. The overall 5-year survival rate among all eligible patients was 55%. Survival was strictly related to stage, depth of wall invasion, lymph node involvement and type of gastrectomy (distal vs total). Our results suggest a survival benefit for pancreas-preserving D2 dissection in Italian patients with gastric cancer if performed in experienced centres. A phase III trial among exclusively experienced centres is urgently needed.

Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group.

Siewert JR, Böttcher K, Roder JD, et al. Br J Surg. 1993;80:1015-1018

In a prospective multicentre study of 2394 patients with gastric carcinoma the prognostic relevance of systematic lymph node dissection was evaluated. Of 1654 patients undergoing resection, 558 had a standard lymph node dissection, defined as fewer than 26 nodes in the specimen, and 1096 underwent radical lymphadenectomy, i.e. 26 or more nodes in the specimen. Radical dissection significantly improved the survival rate in patients with Union Internacional Contra la Cancrum (UICC) stages II and IIIA tumours. Multivariate analysis identified radical dissection as an independent prognostic factor in the subgroups of patients with UICC tumour stages II and IIA. Radical dissection conferred no survival advantage in patients with pN2 tumours. There was no significant difference in morbidity and mortality rates between radical and standard lymph node dissection. Radical lymphadenectomy improves survival in patients with UICC gastric cancer stages II and IIIA, and should be the recommended treatment for such patients.

Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501.

Sano T, Sasako M, Yamamoto S, et al. J Clin Oncol. 2004;22:2767-2773.

PURPOSE: Radical gastrectomy with regional lymphadenectomy is the only curative treatment option for gastric cancer. The extent of lymphadenectomy, however, is controversial. The two European randomized trials only reported an increase in operative morbidity and mortality, but failed to show survival benefit, in the D2 lymphadenectomy group. We conducted a randomized controlled trial to compare the Japanese standard D2 and D2 + para-aortic nodal dissection.

PATIENTS AND METHODS: Only experienced surgeons in both procedures from 24 Japanese institutions participated in the study. Patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) who were surgically fit were intraoperatively randomized. Postoperative morbidity and hospital mortality were recorded prospectively in a fixed format and were compared between the two groups in this study.

RESULTS: A total of 523 patients were randomized between July 1995 and April 2001. Postoperative complications were reported in 24.5% of all patients. Although the morbidity for the extended surgery group (28.1%) was slightly higher than the standard group (20.9%), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the two groups. Hospital mortality was reported at 0.80%: one patient in each group died of operative complications,

while one from each group died of rapid progressive cancer while inpatient.

CONCLUSION: Specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Para-aortic lymphadenectomy could be added without increasing major surgical complications in this setting.

Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer.

Wu CW, Hsiung CA, Lo SS, et al. Br J Surg. 2004;91(3):283-287.

BACKGROUND: A randomized comparison of D1 (level 1 lymphadenectomy) and D3 (levels 1, 2 and 3 lymphadenectomy) dissection was performed to evaluate morbidity and effects on survival from gastric cancer.

METHODS: A total of 221 patients were studied after resection for gastric cancer, 110 after D1 surgery and 111 after D3 surgery.

RESULTS: The morbidity rate was higher after D3 than after D1 resection (17.1 (95 per cent confidence interval (c.i.) 10.1 to 24.1) versus 7.3 (95 per cent c.i. 2.4 to 12.2) per cent respectively; P = 0.012). The difference was largely related to abdominal abscess (8.1 per cent after D3 versus none after D1 resection; P = 0.003). The D3 group had an anastomotic leak rate of 4.5 per cent whereas there was no leakage in the D1 group (P = 0.060). All anastomotic leaks were minor and were managed non-operatively with nutritional support. Patients who had D3 resection had longer operating times, greater blood loss and postoperative drain outputs, and more patients needed blood transfusion. There was no death in either group. The hospital stay was longer after D3 than D1 surgery (mean(s.d.) 19.6(13.9) (range 10-98) versus 15.0(4.0) (range 10-30) days; P = 0.001).

CONCLUSION: Extended lymphadenectomy for gastric cancer is associated with more complications than limited lymphadectomy but this does not lead to significant mortality. Copyright 2004 British Journal of Surgery Society Ltd.

Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial.

Peeters KC, Hundahl SA, Kranenbarg EK, et al. World J Surg. 2005;29:1576-1584

A quantitative estimate of residual nodal disease after gastric cancer surgery, the Maruyama index of unresected disease (MI), proved to be a strong independent predictor of survival in a large U.S. adjuvant chemoradiation study in which surgical undertreatment was frequent. Data from the Dutch D1-D2 Lymphadenectomy Trial permit an opportunity to assess the prognostic value of this variable in a cohort with lower-stage disease treated with minimum D-1 lymphadenectomy and no adjuvant chemoradiation. Blinded to survival, and excluding those cases with missing information, the MI was calculated for 648 of the original 711 patients treated with curative intent. Survival was assessed by log-rank and multivariate Cox regression analysis. All patients have been followed for a minimum of 11 years. Overall Dutch trial findings were not affected by the absence of 63 cases with incomplete data. As expected, the median MI was 26, much lower than in the previous U.S. study. In contrast to the D level, MI < 5 proved to be a strong predictor of survival by both univariate and multivariate analysis. The MI was an independent predictor of both overall survival [P = 0.016; hazard ratio (HR) = 1.45; 95% confidence interval (CI) 1.07-1.95] and relapse risk (P = 0.010; HR = 1.72; 95% CI 1.14-2.60). A strong dose-response reaction with respect to the MI and survival was also observed. We conclude that in this trial low-MI surgery is associated with enhanced survival, whereas outside of certain subgroups

routine D2 lymphadenectomy is not. This observation suggests that surgeons might have more of an impact on patient survival by achieving a low-MI operation than a particular D level. A compelling dose-response effect reveals that the MI is a quantitative yardstick for assessing the adequacy of lymphadenectomy in gastric cancer.

Anastomotic Failure

- Total vs subtotal gastrectomy LOE 1.
- Risk factors LOE 3.
- Hand sewn vs stapled anastomosis LOE 3.
- Management of anastomotic leak LOE 2.

Anastomotic Failure

Following gastric resection, intestinal continuity must be re-established however keeping in mind the inherent risk and dreaded complication of anastomotic failure.

Following a total gastrectomy for tumours of the mid or promixal third of the stomach , continuity is re-established by an oesophagojejunostomy. For tumours of the distal third of the stomach however a distal gastrectomy can be performed. In a randomised trial by the Italian Gastrointestinal Tumour Study Group (LOE1), 618 patients with distal gastric cancer were randomised to have either a total gastrectomy or a subtotal gastrectomy provided that an adequate margin of 6cm could be attained. Results showed similar survival for both groups however with a slight increase in mortality in the total gastrectomy group. Subtotal gastrectomy has become the procedure of choice for distal gastric tumours.

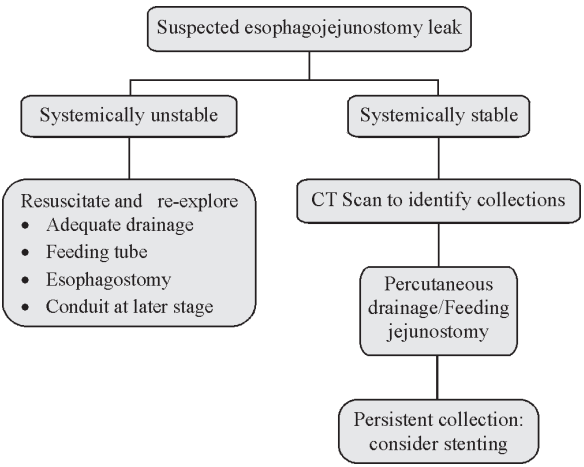
Patients at risk for increased morbidity and mortality, including anastomotic failure are patients with poor nutritional state and advanced age. In a review by Persiani et al. from the University of Rome (LOE 3)found higher rates of morbidity and mortality in the age group over 64years. In addition, a review of 364 patients by Nishi et al. from the Kansai Medical University in Japan (LOE 3) underscored the need for adequate perioperative nutrition to prevent the complication of anastomotic leakage.

Leakage from an oesophago- or gastrojejunostomy leads to escape of large quatities of intestinal fluid with a heavy bacterial load in the peritoneal cavity or posterior mediastinum. The patient usually persents between the 7^{th} to 10^{th} postoperative days with pain, pyrexia and increase in the drain output. Following initial stabilisation, a CT scan is performed and any collection is drained percutaneously. The patient is commenced on intravenous antibiotics and kept nil orally. Nutritional status is maintained by a feeding jejunostomy. If clinical signs persist, repeat CT scans are warranted to ensure adequate drainage (Sasako et al: LOE 2 and Lang H et al: LOE 3). At present, there are reported cases of the successful use of metallic stents in the treatment of anastomotic leaks that persist with conservative management .If the patient remains unwell or presently initially with evidence of diffuse peritonitis, then re-exploration is necessary. In these patients with invariably low physiologic reserve, aggressive peritoneal lavage with wide drainage and esophagostomy is required with the option of a colonic conduit at a later stage.

The dreaded complication of anastomotic failure is better prevented. In an article by Takeyoshi et al, data from 390 patients who underwent esophageal anastomosis either hand sewned or stapled, following a gastrectomy for gastric carcinoma were reviewed. The incidence of anastomotic leak was significantly lower in the stapled group while there was no difference in the anastomotic stricture rate.

In conclusion, esophagojejunal and gastrojejunal anastomosis are associated with a definite risk of anastomotic failure. Management comprise optimization of risk factors, early recognition of clinical signs and prompt institution of treatment (please see algorithm).

Algorithm for the management of anastomotic leaks following gastric resection



Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group.

Bozzetti F, Marubini E, Bonfanti G, et al. Ann Surg 1999;230:170-178.

OBJECTIVE: To evaluate the impact of subtotal (SG) versus total (TG) gastrectomy on the oncologic outcome of patients with cancer of the distal stomach from 28 Italian institutions.

SUMMARY BACKGROUND DATA: There is controversy over whether SG and TG have a different impact on the

5-year survival probability of patients with cancer of the distal half of the stomach.

METHODS: The present analysis involved 618 patients randomized during surgery to SG (315) or TG (303), provided there was at least 6 cm from the proximal edge of the tumor to the cardia, there was no intrapertoneal or distant spread, and it was possible to remove the tumor entirely. Both surgical treatments included regional lymphadenectomy.

RESULTS: Four patients died after SG and seven after TG. Median follow-up was 72 months after SG (range 2 to 125) and 75 months after TG (range 7 to 113). Five-year survival probability as computed by the Kaplan-Meier method was 65.3% for SG and 62.4% for TG. The test of equivalence led to the conclusion that the two procedures may be considered equivalent in terms of 5-year survival probability. The analysis of survival using a multivariate Cox regression model showed a statistically significant impact on survival of tumor site, tumor spread within the gastric wall, extent of resection to the spleen plus or minus neighboring organs or structures, and relative frequency of metastasis in resected lymph nodes.

CONCLUSIONS: Both procedures have a similar survival probability. The authors believe that SG, which has been reported to be associated with a better nutritional status and quality of life, should be the procedure of choice, provided that the proximal margin of the resection falls in healthy tissue.

Management and results of proximal anastomotic leaks in a series of 1114 total gastrectomies for gastric carcinoma.

Lang H, Piso P, Stukenborg C, et al. Eur J Surg Oncol. 2000;26:168-171

AIMS: The management of anastomotic leakage of the oesophago-jejunostomy after total gastrectomy for gastric carcinoma was evaluated in a retrospective study.

PATIENTS AND METHODS: Over a 30-year period, a total of 1114 oesophago-jejunostomies were performed during total gastrectomy for gastric cancer. In 83 cases (7.5%) a leak of the oesophago-jejunostomy was diagnosed.

RESULTS: Frequency of anastomotic leakage was independent of the type of reconstruction and of surgical radicality. Therapeutic management was conservative in 58 cases (69.9%), with placement of a naso-jejunal tube along the anastomoses and with percutaneous drainage of intraabdominal abscesses. In 25 patients re-operation with resuturing of the anastomoses or surgical drainage of an abscess was performed. Mortality was 11/58 (19%) after conservative treatment of the anastomotic leakage and 16/25 (64%) after re-operation.

CONCLUSION: Conservative management with a naso-intestinal tube and percutaneous drainage of intraabdominal abscesses is realistic for anastomotic leaks. Re-operation results in a high morbidity and should only be considered when conservative management is not successful.

Treatment of gastrojejunal anastomotic leak with a covered metallic stent.

Kwak HS, Lee JM, Jin GY, et al.
Hepatogastroenterology. 2003;50:62-64

Although the incidence rates of anastomotic leaks after radical gastrectomy in a patient with gastric cancer are generally low, when the complication ensues, morbidity and mortality rates rise, varying between 18% and 30%. We used self-expandable, covered metallic stent to occlude the leakage site in a patient with recurrent postoperative anastomotic leaks. The deployment of the covered stent was successful, and immediate leak occlusion was obtained after the procedure. During

follow-up, the patient had unrecognized passage of the stent per rectum and showed no anastomotic leak on upper gastrointestinal series. We suggest that implementation of covered metallic stent should be considered as a valuable, alternative therapeutic option for the treatment of intractable postoperative anastomotic leak after radical gastrectomy.

Determinants of surgical morbidity in gastric cancer treatment.

Persiani R, Antonacci V, Biondi A, et al. J Am Coll Surg. 2008;207:13-19.

BACKGROUND: The occurrence of early surgical complications after gastrectomy as a treatment for gastric cancer has been reported to have a negative impact on longterm survival. The aim of this study was to identify treatment-related factors that can predict morbidity and mortality in patients undergoing operations for gastric cancer.

STUDY DESIGN: The charts of 388 patients who underwent different operations for gastric cancer at A Gemelli General Hospital, Catholic University of Rome, Italy, between January 1992 and April 2007, were reviewed. Patients were grouped according to the type of surgical treatment performed. The study end points were postoperative morbidity, mortality, and the length of hospital stay after surgery.

RESULTS: Overall morbidity and mortality rates were 16.2% (63 patients) and 2.3% (9 patients), respectively. Overall morbidity rates were higher in patients more than 64 years of age, when a gastric tumor was resected along with the spleen, and when an extended lymphadenectomy was performed. Patients older than 64 years had longer postoperative hospital stays, and Roux-en-Y gastrojejunostomy was predictive of a shorter stay. Mortality was not influenced by any surgically related factors.

CONCLUSIONS: Age, splenectomy, and extended lymphadenectomy were independently associated with the development of complications after gastric cancer operations. After subtotal gastrectomy, Roux-en-Y gastrojejunostomy was associated with a shorter postoperative length of stay than conventional Billroth I and Billroth II reconstructions.

Risk factors in relation to postoperative complications in patients undergoing esophagectomy or gastrectomy for cancer.

Nishi M, Hiramatsu Y, Hioki K, et al. Ann Surg. 1988;207:148-154

To clarify the risk factors contributing to postoperative complications in the elderly patients (over 70 years) undergoing esophagectomy and/or gastrectomy, 364 patients with primary cancer seen were evaluated. As a result, some characteristic patterns of stress response in the elderly could be detected as follows: the disorders of the vital organs were more important indices for the development of postoperative complications rather than age, and a reduction in the maximum response of the stress hormones to surgical procedures in aged patients was noted; moreover, the functional variability of target organ in the aged group was confirmed. Studies on the hormonal response to surgery suggest that the restriction of fluid replacement is advisable until the third postoperative day, maintaining the host on the dry side, to prevent cardiopulmonary complications. As the nutritional status in the patients with esophageal and gastric cancer goes from bad to worse with the advancing clinical stages, adequate perioperative nutrition is imperative to prevent complications such as anastomotic leakage, wound dehiscence, and/or infections. For the treatment of anastomotic leaks after esophagectomy and esophagogastrectomy, more than 45 kcal/kg/d must be provided, and the serum albumin level must be

restored to 3.5 g/dL in order to achieve spontaneous healing of small anastomotic leakages.

Esophageal anastomosis following gastrectomy for gastric cancer: comparison of hand-sewn and stapling technique.

Takeyoshi I, Ohwada S, Ogawa T, et al.
Hepatogastroenterology. 2000;47:1026-1029.

BACKGROUND/AIMS: During the past 4 years, we have experienced a marked reduction in the incidence of esophageal anastomotic leakage and/or stricture coinciding with the use of a mechanical circular stapler for gastric cancer patients.

METHODOLOGY: We reviewed medical records of gastric cancer patients who underwent a total or proximal gastrectomy, and compared the leakage or stricture of stapled anastomosis with the hand-sewn anastomosis technique. A total of 390 esophageal anastomosis were performed between January 1978 and August 1997. Two types of mechanical circular staplers were used (EEA and CDH).

RESULTS: Anastomotic leakage occurred in 13 (3.3%) of 390 cases; three (4.5%) of 66 cases with hand-sewn anastomosis, and 10 (3.1%) of 324 cases with stapled anastomosis (EEA: 4.5%, CDH: 0%). The anastomotic leakage rate was significantly lower in the CDH stapler group than in the EEA stapler group. Anastomotic stricture occurred in one (1.5%) of 66 cases of hand-sewn anastomosis, and 16 (4.9%) of 324 cases of stapled anastomosis (EEA: 5.9%, CDH: 2.9%). There were no significant differences in the stricture rate between the hand-sewn group and the stapler group.

CONCLUSIONS: Stapling anastomosis using a CDH stapler led to a reduction in the incidence of anastomotic leakage. Surgeons must, however, continue to be aware of anastomotic stricture.

Duodenal Stump Leakage

- Use of tube duodenostomy Level of Evidence LOE 2
- Use of end tube duodenostomy LOE 3
- Conventional vs tube duodenostomy vs Nissen vs Bancroft closure LOE 2
- Use of proximal duodenojejunostomy LOE 3

Duodenal Stump Leakage

Duodenal stump leakage or blow-out is undeniably one of the most potentially catastrophic complications following gastric resection. It may follow a total gastrectomy with oesophagojejunostomy or subtotal gastrectomy with a Billroth 2 reconstruction. Although the incidence varies from 3-5%, the mortality associated with duodenal blow is as high as 50%. The difficult duodenum most commonly presents itself in surgery for peptic ulcer disease and though the present day gastric surgeon will operate much less on this disease as compared to his predecessors, much can be learnt from their experiences.

Several factors may account for a leaking duodenal stump:

- Severely diseased duodenal stump with remnant disease

- Suture line haemorrhage with resultant infection and necrosis
- Postoperative pancreatitis
- Malnutrition
- Afferent loop syndrome

A duodenal stump leak usually presents between the 2nd to 5th postoperative days with sudden onset of upper abdominal pain associated with tachycardia, pyrexia and features of localised peritonitis. Following initial stabilisation, a CT scan is performed to determine the presents of a fluid collection in the hepato-renal fossa or extravasation of oral contrast. Management comprise percutaneous drainage of the fluid collection together with decompression of the afferent loop via endoscopically/fluoroscopically guided nasojejunal intubation .A nasojejunal tube can also be placed in the efferent loop for the purpose of enteral feeding since prolonged hospitalisation is anticipated.

Failing these conservative measures, exploration is warranted. The aim of exploration would be thorough peritoneal lavage, with wide and adequate drainage of Morrison's pouch. In a review article by Tsuei and Schwartz (LOE 2), the use of a tube duodenostomy has been detailed. An end duodenostomy is placed through the suture line and allows for a controlled fistula to form while a lateral duodenostomy is placed through a healthy portion of the antimesenteric aspect of the duodenum and allows for decompression similar to a proximal stoma in a colorectal anastomosis. In a retrospective review by Isik et al.(LOE 3), an end tube duodenostomy was performed in a total of 31 patients, either primarily in the case of a difficult duodenum or secondarily following a duodenal stump leak. There was a leak rate of 3.2% in the secondary group with no leaks in the primary group. A concomitant biliary T-tube was inserted in 61% of the patients.The conclusion was that tube duodenostomy is a safe, simple and effective method in both the prevention and treatment of duodenal stump leak.

In view of the potential devastation of a duodenal blow-out, identifying the difficult duodenum is imperative in order to implement appropriate and effective closure. In a review of 200 patients by Burch et al. (LOE 2), the duodenal stump was closed either conventionally, with the use of a tube duodenostomy or employing either the Nissen or Bancroft closure. The Nissen closure uses the anterior duodenal wall for closure while the Bancroft employs the distal antral mucosa. There was a leak rate of 2.5% in the conventional closure group, 33% in the tube duodenostomy group and 0% in both the Nissen or Bancroft closure groups. The Nissen or Bancroft closures were concluded to be the methods of closure for a difficult duodenum. In a retrospective review by Carlo et al. (LOE 3), 7 patients with a difficult duodenum underwent a proximal duodenojejunostomy in which an end to end anastomosis is performed using the Roux limb of a Roux-en-Y reconstruction brought up for the gastrojejunostomy. There were no leaks in this group however of 5 similar patients who underwent conventional closure, there were two leaks of which there was one mortality.

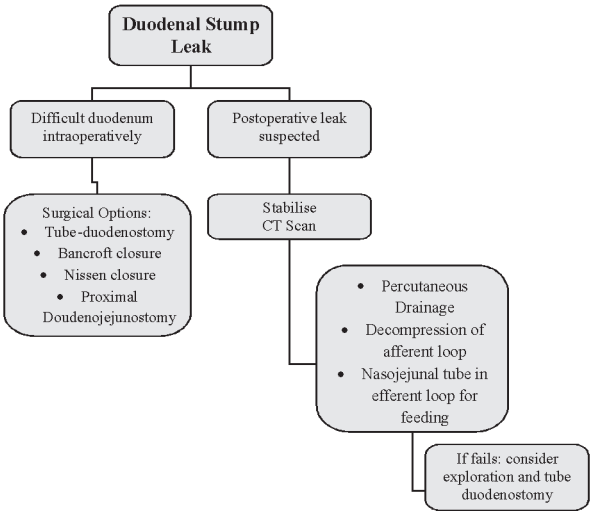
In conclusion, an algorithm for the management of a duodenal stump leak is presented.

A life-saving but inadequately discussed procedure: tube duodenostomy. Known and unknown aspects.

Isik B, Yilmaz S, Kirimlioglu V, et al. World J Surg. 2007;31(8):1616-1624

OBJECTIVE: The most successful method of managing the difficult duodenum, including the stump leakage, has been the tube duodenostomy technique, but it has not gained wide acceptance and is rarely used. The purpose of this study is to describe the details of the procedure for indication, technical approach, and postoperative care. METHODS: During the period from 1998 to 2006, a tube duodenostomy was

Algorithm for the management of duodenal stump leak.



performed in 31 patients for possible insecure duodenal stump closure during gastric resection, postoperative duodenal stump leakage, duodenal leak after primary closure of duodenum for perforation or injury, or anostomotic leak after choledochoduodenostomy. All of the tube duodenostomies were performed through the open end of the duodenum. We also inserted a T-tube into the common bile duct in 19 of 31 patients (61.2 %) with tube duodenostomy.

RESULTS: A tube duodenostomy was performed in the primary operation in 15 of 31 patients. None of those 15 patients required a second operation, and there were no leaks and no deaths. Among the larger group (31 patients), there was one (3.2 %) duodenal stump leak after tube duodenostomy, and it ceased spontaneously; one patient had a subhepatic collection after removal of the duodenostomy tube, and three patients had associated incisional infections. Two patients died;

one after a myocardial infarction and the other from irreversible sepsis. The mean length of hospital stay was 26.9 days.

CONCLUSIONS: We conclude that tube duodenostomy is a simple, effective, and safe method to prevent rupture of an insecure duodenal stump or to treat the leakage from the duodenal stump or primary repair on the duodenum.

Proximal duodeno-jejunostomy for the safe management of the difficult duodenal stump.

Carlo VM, Vargas O, Ramírez Schon G, et al. Bol Asoc Med P R. 1996;88(10-12):89-91.

Seven patients with peptic ulcer disease had severe scarring of the duodenum, making its closure at the time of gastrectomy difficult. They were managed intraoperatively with proximal duodeno-jejunostomy as a means to avoid the catastrophic complication of disruption of the duodenal stump closure with its consequent peritonitis. The jejunum used for this anastomosis was an extension of the long limb of a Roux en Y which is brought up to perform the gastrojejunostomy. The end to end duodeno-jejunostomy is performed proximal to a side to side gastrojejunostomy, hence the name, proximal duodeno Jejunostomy. These seven patients had no unexpected immediate postoperative complications during the thirty days following surgery and were all discharged from the hospital well. During the same three and a half year period twenty five other patients were submitted to gastrectomy and had two duodenal stump leaks after conventional closures. One patient died and the other survived after prolonged intensive care stay. These differences were not statistically significant. These duodenojejunostomies are non-functional anastomoses and should consequently stricture, but in one patient it remained open and he developed bile reflux gastritis in spite of the Roux en Y gastrojejunostomy constructed to avoid this complication. These anastomoses should be constructed as stenotic as possible.

Management of the difficult duodenal stump.

Burch JM, Cox CL, Feliciano DV, et al. Am J Surg. 1991;162:522-526.

Leakage from the duodenal stump has been the most feared complication of the Billroth II reconstruction following gastric resection. The purpose of our study was to evaluate four methods of duodenal stump closure in 200 patients. One hundred and forty-seven (74%) patients had duodenal ulcers; 28 (14%) had gastric ulcers; and 25 (13%) had a variety of other inflammatory conditions. The most common indication for operation was acute hemorrhage (51%), followed by perforation (24%), intractability (15%), and obstruction (10%). Conventional duodenal closures were performed in 160 (80%) patients, Nissen's closure in 25 (13%), Bancroft's closure in 6 (3%), and tube duodenostomy in 9 (5%). Duodenal leaks occurred in four (2.5%) patients with conventional closures and in three (33%) patients with tube duodenostomies. No leaks occurred in patients with Nissen's or Bancroft's closures. The hospital mortality rate for the series was 9.5%; however, no patient who developed a duodenal leak died. We conclude that Nissen's and Bancroft's closures were safe and effective, but that tube duodenostomy did not reliably prevent uncontrolled leakage.

Delayed Gastric Emptying

- Risk factors Level of Evidence, LOE: 3
- Definition/grading LOE: 1
- Use of erythromycin LOE 1
- Antecolic vs retrocolic gastrojejunostomy LOE 2
- Billroth 1 vs Roux-en-Y LOE 3

Delayed Gastric Emptying

Delayed gastric emptying (DGE), also termed gastroparesis occurs in 5 to 25% of patients following gastric resection. In a retrospective review of 416 patients by Bar-Natan et al (Level of Evidence, LOE: 3), the incidence of DGE was 24%.The preoperative risk factors identified were diabetes mellitus and malnutrition while the postoperative risk factors were sepsis, anastomotic failure or edema, pancreatitis and multiple organ failure. In addition, disruption of the autonomic innervations along the pyloric region can account for DGE in the absence of the above factors.

The precise definition of DGE has eluded physicians for some time, making the true incidence difficult to assess how the two parameters of nasogastric aspiration and time to oral intake

was taken into account. A consensus was however made in November 2007 by the International Study Group of Pancreatic Surgery (ISGPS) (LOE: 1). DGE was defined according to three grades. Grade A when the patient required a nasogastric tube (NGT) from the 4th to the 7th postoperative day (POD) or reinsertion due to vomiting after the 3rd POD together with the inability to tolerate orally by the 7th POD but able to tolerate orally by the 14th POD. Grade B was defined as the need for nasogastric aspiration for between the 7th and 14th POD together with the inability to tolerate orally by the 14th POD but able to do so by the 21st POD. Grade C DGE is present when the patient requires nasogastric aspiration for more than the 14th POD and the inability to tolerate an unlimited diet after the 21st POD.

Grades of delayed gastric emptying

	Nasogastric tube requirement	**Time to oral intake**
Grade A	4th to 7th POD	7th POD
Grade B	7th to 14th POD	14th POD
Grade C	after 14th POD	After 21st POD

The ISGPS definition and grading of DGE aids in not only standardization but allows a management algorithm to be plotted. Patients with grade A DGE can usually be managed conservatively while patients with grade B will require prokinetic therapy. Grade C patients tend to have prolonged hospital stay requiring nutritional support with possibly jeopardizing their ability to tolerate adjuvant therapy if indicated.

Many lesions can be learnt from the trials of prokinetic drugs following pancreaticoduodenectomy. In a randomized

controlled trial by Yeo et al. (LOE 1), 118 patients were randomized to be given erythromycin 200mg intravenously every 6 hours or a placebo from the 3rd to 10th POD. A dual phase radionuclide gastric emptying study was then performed on the 10th day. The erythromycin group exhibited a 37% reduction in DGE as compared to the placebo group. In another randomized controlled trial by Ohwada et al. (LOE 1), 31 patients were randomized to either low dose erythromycin (1mg/kg every 6 hours) or a placebo group. Gastroduodenal motility studies performed on the 30th POD revealed an increase in phase 3 migratory motor complexes with a resultant 75% reduction in DGE. Based on this, low dose erythromycin was considered superior to high dose.

For patient with grade C DGE, surgery is a last resort however success rate is low. As a result, preventation is imperative. Some studies suggest that the type of reconstruction may influence the risk of DGE. In a prospective analysis by Hartel et al. (LOE 2), 100 consecutive patients underwent a retrocolic reconstruction following pancreaticoduodenectomy and 100 consecutive patients underwent antecolic reconstruction. All patients were well matched for age as well as medical and surgical complications. The incidence of DGE was significantly less in the antecolic group ($p< 0.001$). In addition, in a retrospective analysis by Murakami et al. (LOE 3), 132 patients were analyzed and the incidence of DGE following a retrocolic Billroth 1 reconstruction was 81% while the incidence following antecolic Roux-en-Y was 10% ($p<0.001$).

In conclusion, DGE is common following gastric resection though antecolic Roux-en-Y reconstruction appears to have the lowest incidence and since low dose erythromycin has been successfully used in the management of DGE, both can be combined to decrease morbidity.

Delayed gastric emptying after gastric surgery.

Bar-Natan M, Larson GM, Stephens G, Massey T. Am J Surg. 1996;172:24-28.

BACKGROUND: The reported incidence of delayed gastric emptying (DGE) after gastric surgery is 5% to 25% and usually is based on operations for peptic ulcer disease. Ongoing improvements in perioperative care, nutritional support, and new prokinetic drugs may have had a beneficial effect on the frequency and course of postoperative DGE.

METHODS: We therefore studied our recent experience with DGE in 416 patients who had gastric surgery for ulcer disease (283), cancer (92), or trauma and other indications (41) between January 1985 and December 1993. DGE was defined as inability to eat a regular diet by postoperative day 10.

RESULTS: DGE occurred in 99 of 416 patients (24%). In 75 of these 99 patients, a postoperative contributing factor for DGE was identified. These factors were sepsis (32), anastomotic edema and leaks (23), obstruction (4), pancreatitis (3), multiple system organ failure (5), and miscellaneous conditions (8). In 24 patients there was no obvious cause for DGE; these patients recovered with nutritional support and time. Re-operation specifically for gastric stasis was not performed. Among the 99 patients with DGE, 67% were eating by day 21, 92% by 6 weeks, and 100% by 10 weeks. Significant risk factors for DGE were diabetes (55%), malnutrition (44%), and operations for malignancy (38%). The Whipple procedure had the highest incidence of DGE (70%), highly selective vagotomy the lowest (0%), while truncal vagotomy had no significant effect. The response to metoclopramide was 20% and unpredictable.

CONCLUSION: DGE continues to affect a considerable number of our patients (24%) after gastric surgery and is particularly common in patients with diabetes, malnutrition,

and gastric or pancreatic cancer. However, gastric motility does return in 3 to 6 weeks in most patients and the need for re-operation for gastric stasis is rare.

Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial.

Yeo CJ, Barry MK, Sauter PK, et al. Ann Surg. 1993;218:229-237

OBJECTIVE: This study tested the hypothesis that erythromycin, a motilin agonist, reduces the incidence of early DGE after pancreaticoduodenectomy.

SUMMARY BACKGROUND DATA: Delayed gastric emptying (DGE) is a leading cause of morbidity after pancreaticoduodenectomy, occurring in up to 40% of patients. The pathogenesis of DGE has been speculated to involve factors such as peritonitis from anastomotic leaks, ischemia to the antropyloric muscles, and gastric atony in response to resection of the duodenal pacemaker or reduction in circulating motilin levels.

METHODS: Between November 1990 and January 1993, 118 patients undergoing pancreaticoduodenectomy completed this prospective, randomized, placebo-controlled trial. The patients received either 200 mg of intravenous erythromycin lactobionate every 6 hours ($n = 58$), or an identical volume of 0.9% saline ($n = 60$) from the third to tenth postoperative days. On the tenth postoperative day, a dual phase radionuclide gastric emptying study was performed.

RESULTS: The erythromycin and control groups were comparable regarding multiple preoperative, intraoperative, and postoperative factors. The erythromycin group had a 37% reduction in the incidence of DGE (19% vs. 30%), a significantly reduced ($p < 0.05$) need to reinsert a nasogastric

tube for DGE (6 vs. 15 patients), and a significantly reduced ($p < 0.01$) per cent retention of liquids at 30 minutes and solids at 30, 60, 90, and 120 minutes. No major adverse reactions to erythromycin were observed.

CONCLUSIONS: Erythromycin is a safe, inexpensive drug that significantly accelerates gastric emptying after pancreaticoduodenectomy and reduces the incidence of DGE by 37%. These data support the use of erythromycin to decrease early DGE after pancreaticoduodenectomy.

Low-dose erythromycin reduces delayed gastric emptying and improves gastric motility after Billroth I pylorus-preserving pancreaticoduodenectomy.

Ohwada S, Satoh Y, Kawate S, et al. Ann Surg. 2001;234:668-674

OBJECTIVE: To test the hypothesis that early and low doses of erythromycin reduce the incidence of early delayed gastric emptying (DGE) and induce phase 3 of the migratory motor complex in the stomach after Billroth I pylorus-preserving pancreaticoduodenectomy (PPPD).

SUMMARY BACKGROUND DATA: Delayed gastric emptying is a leading cause of complications after PPPD, occurring in up to 50% of patients. High doses of erythromycin (200 mg) accelerate gastric emptying after pancreaticoduodenectomy and reduce the incidence of DGE, although they induce strong contractions that do not migrate to the duodenum.

METHODS: Thirty-one patients were randomly assigned to either the erythromycin or control groups. The patients received erythromycin lactobionate (1 mg/kg) every 8 hours, or H2-receptor antagonists and gastrokinetic drugs from days 1 to 14 after surgery. On postoperative day 30, gastroduodenal motility was recorded in 14 patients.

RESULTS: Preoperative, intraoperative, and postoperative factors were comparable in the erythromycin and control groups. The erythromycin group had a shorter duration of nasogastric drainage, earlier resumption of eating, and a 75% reduction in the incidence of DGE. Erythromycin was an independent influence on nasogastric tube removal, and preservation of the right gastric vessels was a significant covariate. Low doses of erythromycin induced phase 3 of the migratory motor complex and phase 3-like activity, with the same characteristics as spontaneous phase 3, in 86% of patients: two had quiescent stomachs and the others had spontaneous phase 3 or phase 3-like activity.

CONCLUSIONS: Low doses of erythromycin reduced the incidence of DGE by 75% and induced phase 3 of the migratory motor complex after Billroth I PPPD. Low doses of erythromycin are preferable to high doses in the unfed period after PPPD.

Effect of antecolic reconstruction on delayed gastric emptying after the pylorus-preserving Whipple procedure.

Hartel M, Wente MN, Hinz U, et al. Arch Surg. 2005;140:1094-1099.

HYPOTHESIS: Antecolic duodenojejunostomy prevents delayed gastric emptying (DGE) after a pylorus-preserving Whipple (ppW) procedure better than retrocolic duodenojejunostomy.

DESIGN: A single operation team's experience with antecolic and retrocolic duodenojejunostomy in ppW is analyzed on a prospective database using univariate and multivariate models.

SETTING: Tertiary referral center that focuses on pancreatic diseases.

PATIENTS AND INTERVENTIONS: One hundred consecutive patients undergoing a ppW procedure with retrocolic reconstruction between January 1, 1996, and December 31, 2001, and 100 consecutive patients undergoing a ppW procedure with antecolic reconstruction between January 1, 2002, and December 31, 2003. Characteristics such as median age, median hospital stay, sex, diagnosis, previous operations, blood loss, surgical and medical complications, American Society of Anesthesiologists risk groups, stent implantation, and especially DGE were matched for the comparison groups.

MAIN OUTCOME MEASURES: We compared DGE, characteristics, and perioperative variables in patients with antecolic vs retrocolic reconstruction after ppW.

RESULTS: The DGE occurred significantly more often in patients with retrocolic reconstruction than in those with antecolic reconstruction ($P < .001$). The antecolic and retrocolic study groups were comparable in age ($P = .25$), sex ($P = .48$), and postoperative surgical ($P = .19$) and medical ($P = .054$) complications. The univariate analysis between patients with and without DGE did not show significant differences regarding diagnosis, previous operations, blood loss, surgical and medical complications, American Society of Anesthesiologists classification, or stent implantation. In the multivariate analysis, only the type of reconstruction ($P = .006$) and sex ($P = .04$) seemed to affect DGE.

CONCLUSION: We recommend antecolic duodenjejunostomy in patients undergoing a ppW procedure regardless of their diagnosis.

An antecolic Roux-en Y type reconstruction decreased delayed gastric emptying after pylorus-preserving pancreatoduodenectomy.

Murakami Y, Uemura K, Sudo T, et al. J Gastrointest Surg. 2008;12:1081-1086.

The aim of this study was to identify a preferable procedure reducing the incidence of delayed gastric emptying (DGE) after pylorus-preserving pancreatoduodenectomy (PPPD). Data on 132 consecutive patients with pancreatobiliary disease, who underwent PPPD, were collected retrospectively. A retrocolic Billroth I type reconstruction (B-I group) and an antecolic Roux-en Y type reconstruction (R-Y group) were performed for 54 and 78 patients after PPPD, respectively. Clinical measures of DGE were compared between the two groups. The incidence of DGE was 81% in B-I group and 10% in R-Y group ($P < 0.001$). The type of reconstruction ($P < 0.001$), operative time ($P = 0.016$), and postoperative complications ($P = 0.001$) were significantly associated with DGE by univariate analysis. Only the type of reconstruction ($P < 0.001$) was identified as an independent factor, which was associated with DGE by multivariate analysis. An antecolic Roux-en Y type duodenojejunostomy could be a useful reconstruction method after PPPD to prevent the occurrence of DGE.

Dumping Syndrome

- Risk Factors. Level of Evidence LOE 2
- Billroth 1 vs Roux-en-Y LOE 3
- Billroth 1 vs Billroth 2 vsRoux-en-Y LOE 2
- Dietary modification LOE 3
- Use of acarbose LOE 3
- Use of octreotide LOE 3

Dumping Syndrome

Dumping syndrome can occur following gastric resection. The small or absent gastric pouch together with the loss of pyloric sphincter tone leads to unregulated flow of hyperosmolar contents into the small intestines. Initial symptoms, due to the fluid shift into the small intestines, are characterized by sweating, bloating and diarrhoea and are termed early dumping. Late dumping is due to the reactive hypoglycaemia and leads to sweating, palpitations and sometimes altered conscious level. The incidence of dumping syndrome is approximately 10% however, in patients with known risk factors like malnutrition, the incidence is approximately 45% (Rivera et al. Level of Evidence LOE: 2)

Following gastric resection, continuity can be re-established by a gastroduodenostomy (Billroth 1), gastrojejunostomy (Billroth 2) or a Roux-en-Y reconstruction. In a Quality of Life Study by Nunobe et al. (LOE: 3), 229 patients underwent a Billroth 1 reconstruction and 214 patients underwent a Roux-en-Y reconstruction. At 5 years, patients with the Roux-en-Y were less likely to experience symptoms of either early or late dumping as compared to patients who underwent the Billroth 2 reconstruction. There were no nutritional differences in either group. Schwiezer et al. in a prospective analysis (LOE 2) of 53 patients who underwent a subtotal gastrectomy with either a Billroth 1, Billroth 2 or Roux-en-Y found that postgastrectomy symptoms including dumping was significantly less ($p< 0.05$) in the Roux-en-Y group.

Initial management of Dumping Syndrome comprise dietary modification. In a study by Kellogg et al. (LOE 3), 14 patients were given a high carbohydrate diet on day 1 and a low carbohydrate diet on day 2. Blood glucose and insulin levels were done at regular intervals on both days and the results were compared. The high carbohydrate day exhibited early hyperglycaemia with hyperinsulinemia with subsequent hypoglycaemia. There was very little alteration in the blood glucose and insulin levels on the low carbohydrate day. A diet low in carbohydrate, small in volume and regularly spaced throughout the day is recommended for patients with dumping syndrome.

Pharmacological agents are available if dietary modification is ineffective. In a study by Peter (LOE 3), acarbose, an alpha-glucosidase inhibitor known to decrease the absorbed glucose load, improved the symptoms of dumping when given with meals. Long acting octreotide has also been successfully used for the management of dumping. Didden et al. (LOE 3) studied the efficacy of long acting octreotide in 34 patients with severe symptoms of dumping and found a substantial reduction in their symptoms.

Surgery is employed as the last resort if conservative and pharmacological management fails. The Billroth 1 or 2 reconstructions can be converted to a Roux-en-Y since this has been shown to have less symptoms of dumping.

In conclusion, the dumping syndrome is well recognised sequelae of gastric resection which usually responds to dietary modifications or pharmacological intervention.

Postgastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet.

Kellogg TA, Bantle JP, Leslie DB, et al. Surg Obes Relat Dis. 2008 ;4(4):492-499.

BACKGROUND: Some alarming cases of hypoglycemic episodes in patients who have undergone Roux-en-Y gastric bypass have been reported. The syndrome of hyperinsulinemic hypoglycemia with nesidioblastosis after Roux-en-Y gastric bypass has been previously reported and is controversial. It has been suggested that subtotal or total pancreatectomy might be needed to control the symptoms in these patients. We have identified a similar cohort of patients with hyperinsulinemic hypoglycemia for whom we have reviewed patient characteristics and measured the glucose and insulin response to mixed meals.

METHODS: We reviewed the charts of 14 patients identified by clinic follow-up who reported episodes consistent with hyperinsulinemic hypoglycemia (lightheadedness or loss of consciousness after a high-carbohydrate meal). All patients were given a mixed meal consisting of high carbohydrates on day 1 and a low-carbohydrate meal on day 2. The plasma glucose and serum insulin levels were measured before (fasting) and 30, 60, 90, 120, 150, and 180 minutes after the meal.

RESULTS: After a high-carbohydrate meal, 12 of 14 patients demonstrated hyperglycemia associated with hyperinsulinemia at 30 minutes. These patients subsequently became hypoglycemic while the serum insulin was rapidly declining. After reaching a nadir at 120 minutes, the plasma glucose level corrected spontaneously. After a low-carbohydrate mixed meal, the patients demonstrated very little change in plasma glucose and only a modest increase in serum insulin. Of the 12 patients treated with a low-carbohydrate diet, 6 had substantive symptom improvement, and 10 exhibited at least some improvement.

CONCLUSION: The hyperinsulinemic hypoglycemia noted in some patients after Roux-en-Y gastric bypass has many similarities to the dumping syndrome. A low-carbohydrate diet successfully improved symptoms in most of our patients. Approaches to treatment should involve a low-carbohydrate diet and alpha-glucosidase inhibitors rather than pancreatectomy.

[Dumping syndrome in patients submitted to gastric resection]

Rivera I, Ochoa-Martínez CI, Hermosillo-Sandoval JM, et al. Cir Cir. 2007 ;75(6):429-434.

BACKGROUND: We undertook this study to establish the incidence of dumping syndrome after partial or total gastric resection and its association with patient's preoperative nutritional status as well as the clinical behavior with dietary management during a short-term follow-up period.

METHODS: This was a prospective study of consecutive patients >30 years of age and who were submitted to gastrectomy for gastric cancer or complicated ulceropeptic disease during a 48-month period in a highly specialized hospital.

RESULTS: A total of 42 patients were evaluated with a slight female predominance (n = 22, 52.4%). Twenty-nine cases (69%) had subtotal gastrectomy and 13 (31%) had a total gastrectomy. Patients had a medium age of 54.38 +/- 7.56 vs. 66 +/- 13.99 years, respectively (p = 0.034). Reconstruction techniques were Roux-en-Y gastrojejunostomy in 70% and Roux-en-Y esophagojejunostomy in 28.5%. We found dumping syndrome in 45% of the cases associated with acute or chronic undernutrition (p = 0.003). Fifty-three percent of the patients with dumping syndrome improved with adequate dietetic manipulation during a follow-up period of 211 days.

CONCLUSIONS: Although the majority of reconstructions were performed with dysfunctionalized small bowel segments, the incidence of dumping syndrome was 45%. Patient's preoperative nutritional status influenced the presence of clinical manifestations. Adequate dietary management reduced, in 53% of the patients, the presence of dumping symptoms during a short-term follow-up period.

[Postgastrectomy symptoms after partial stomach resection: Billroth I vs. Billroth II vs. reconstruction with roux-Y-loop]

Schweizer W, Blunschi T, Seiler C. Helv Chir Acta. 1994 ;60(4):665-669.

We clinically followed 53 patients after a mean time of 3 years for postgastrectomy symptoms concerning 10 criteria including the Visick grading, dumping after Sigstad, efferent and afferent loop-syndrome, bile reflux, regurgitation and life-quality judged by the patient and the examiner. In our study we included 15 patients after a Billroth I, 15 after Billroth II, 15 patients after a Roux-en-Y reconstruction and 8 patients with a Roux-en-Y reconstruction because of severe disturbance of life quality after a primary Billroth II operation. The Roux-en-Y reconstruction showed significantly better results when

compared to Billroth I and especially Billroth II reconstruction ($p < 0.05$). These results compare well with reports in the literature, where generally only one or two criteria are examined. We conclude that partial gastrectomy with Roux-en-Y reconstruction should be the preferred method provided that the procedure is adequate for the pathology found.

Billroth 1 versus Roux-en-Y reconstructions: a quality-of-life survey at 5 years.

Nunobe S, Okaro A, Sasako M, et al. Int J Clin Oncol. 2007 ;12(6):433-9.

BACKGROUND: In the majority of gastric surgical units across Japan, Billroth 1 is the preferred method of anastomosis following subtotal distal gastrectomy for gastric cancer. However, across Europe and North America, reconstruction using a Roux-en-Y anastomosis is more common. There is a lack of comparative studies of the two methods focusing on long-term outcome. This study evaluated patient outcome, in terms of adverse gastrointestinal complaints and quality of life, at 5 years following surgery.

METHODS: A total of 652 patients had a subtotal distal gastrectomy for early gastric cancer between January 1993 and December 1999. We studied 229 patients with reconstruction by the Billroth 1 procedure and 214 patients with the Roux-en-Y procedure. All patients had an abdominal ultrasound and endoscopy as part of their follow-up. Quality of life was assessed by questionnaire.

RESULTS: We had an 87% response rate from the questionnaire assessment. The results demonstrated that patients were less likely to experience symptoms of either early or late dumping after Roux-en-Y anastomosis than after Billroth 1. In addition, there were significantly fewer patients with gastritis on endoscopy in the Roux-en-Y group. There was no significant difference in the average relative body

weight between the groups. However, patients were more likely to develop gallstones after a Roux-en-Y than after a Billroth 1 reconstruction.

CONCLUSION: The results from this study show that, at 5 years, both symptomatically and functionally, Roux-en-Y reconstruction was superior to the Billroth I method after subtotal distal gastrectomy for gastric cancer. However, the overall outcome in both groups was good, with patient satisfaction scores of around 75% in each group.

Octreotide therapy in dumping syndrome: Analysis of long-term results.

Didden P, Penning C, Masclee AA. Aliment Pharmacol Ther. 2006 1;24(9):1367-1375

BACKGROUND: Octreotide therapy is effective in controlling severe dumping symptoms during short-term follow-up but little is known about long-term results. AIM: To report on the long-term results of patients with severe dumping syndrome treated at the Leiden University Medical Center with subcutaneous or depot intramuscular (long-acting release) octreotide.

METHODS: Follow-up of 34 patients with severe dumping syndrome refractory to other therapeutic measures treated between 1987 and 2005 with octreotide subcutaneous/long-acting release. At regular intervals symptoms, quality of life, weight, faecal fat excretion and gallstone formation were evaluated.

RESULTS: All patients had excellent initial relief of symptoms during octreotide subcutaneous therapy. However, during follow-up 16 patients stopped therapy because of side effects (n = 9) or loss of efficacy (n = 7). Four patients died. Fourteen patients (41%) remain using octreotide (follow-up 93 +/- 15 months), seven are on octreotide subcutaneous and seven on

octreotide long-acting release. Patients with severe dumping (both early and late) do better on subcutaneous than long-acting release despite the inconvenience of frequent injections. Dumping symptoms are reduced by 50% even in long-term users. Body weight continues to increase during therapy despite more pronounced steatorrhoea.

CONCLUSION: The long-term the efficacy of octreotide is much less favourable compared with short-term treatment.

Acarbose and idiopathic reactive hypoglycemia.

Peter S. Horm Res. 2003;60(4):166-167.

BACKGROUND/AIM: Therapy for idiopathic reactive hypoglycemia is ineffective and impractical. Acarbose, an alpha-glucosidase inhibitor, decreases the absorbed glucose load. This study was done to determine the efficacy of acarbose in this syndrome.

METHODS: Six patients with symptoms suggestive of postprandial hypoglycemia were chosen consecutively. Three-hour oral glucose tolerance tests using 75 g of glucose were done on each patient. The patients were then treated with acarbose with each meal.

RESULTS: All patients had symptomatic hypoglycemia during testing. After 4 weeks of acarbose therapy, all patients were asymptomatic on a regular diet.

CONCLUSION: Acarbose is efficacious in the management of idiopathic reactive hypoglycemia.

Section — III

Liver and Bile Duct

Contributors

PJ Shukla

SV Shrikhande

SS Jiwnani

MD Patel

Assessment of Liver Function

- Child class C and hepatic resection LOE 2.
- The Model for End-Stage Liver Disease, or MELD LOE 2
- Multidetector CT volumetry for pre-operative volume calculation LOE 3
- Indocyanine Green Retention-in assessing liver function especially after portal vein embolization LOE 2
- 99m-Tc-galactosyl-human serum albumin scintigraphy correlation with postoperative outcomes LOE 4

Liver resection is the curative therapeutic option for hepatocellular carcinoma, biliary tumors, metastases of colorectal and other extra hepatic tumors, living donor liver transplantation and other benign liver diseases. Perioperative mortality is determined mostly by the extent of preoperative evaluation focused on the liver. After resection, the remnant liver parenchyma must cope with the challenge caused by increased metabolism, portal overflow, decreased vascular bed and biliary tract and oxidative stress following the operation. If the remnant liver is unable to grow up to this challenge, acute liver failure occurs. This maintains the necessity of determining the hepatic functional reserve and the hepatic remnant volume.

Assessment of liver function is a critically important tool for selecting patients for hepatic surgery. It has an increasingly important role, as surgeons attempt to overcome the limits of anatomic constraints and the volume of the tumour to increase resection rates.

Liver resections need to be customized not only according to the tumour burden and the remnant liver volume, but must also take into consideration the functional reserve and underlying liver disease if any.

Assessment for liver resection needs to be four-fold:

Clinical

Biochemical

Volumetric

Functional

Clinical assessment includes identification of co morbid conditions such as obesity, diabetes mellitus, cardiovascular disease and a general assessment of the nutritional status of the patient.

Biochemical parameters such as markers of hepatic synthetic function (albumin, prothrombin time) and excretory function (bilirubin levels) need to be investigated.

Liver volume after major hepatic resection has been critically linked to postoperative tolerance of resection. Careful analysis of outcomes based on liver remnant volume stratified by underlying liver disease has led to recommendations regarding the safe limits of resection.

Hepatic functional reserve can be determined by a variety of laboratory tests, clearance and tolerance tests and functional imaging.

Hepatic Function Assessment Systems

The most widely used classification system for the assessment of liver function is the Child-Pugh system which measures

total bilirubin and albumin levels, presence or absence of ascites, encephalopathy and the prothrombin time/international normalized ratio. Together these parameters give a rough estimate of the synthetic and detoxification capacity of the liver.

Less widely employed alternatives are the Child-Campbell score, Apache III, ANS or ascites and nutrition score, Okuda staging system, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer system (BCLC).

Child-Pugh Scoring System

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points	Units
Bilirubin	<2	2-3	>3	mg/dl
Serum Albumin	>35	28-35	<28	g/dl
INR	<1.7	1.7-2.2	>2.2	No unit
Ascites	none	Suppressed with medication	Refractory	No unit
Encephalopathy	none	Grade I-II	Grade III-IV	No unit

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above, a total score of 5-6 merits a Child-Pugh class A, 7-9 is class B, and class C has a score of 10-15. Child class C patients are not considered fit for hepatic resection (Level of evidence 2a).

The Model for End-Stage Liver Disease, or MELD, is a scoring system for assessing the severity of chronic liver disease. It is calculated according to the following formula:

MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57 [Ln serum creatinine (mg/dL)] + 6.43

This score was primarily designed to assess patients with severe liver disease as candidates for liver transplantation. Inspite of the initial enthusiasm to use this score to predict outcomes in patients undergoing hepatic resection, a retrospective review of over 500 patients by Schroeder et al showed that it should not be used in the setting of elective hepatic resection (LOE 2b). Teh at al showed that MELD fails to predict perioperative outcome in patients undergoing hepatic resection for HCC without cirrhosis. Cuccheti et al used MELD scores on post-operative days 3 and 5 to predict recovery from liver failure after hepatic resection, (LOE 2b).

Liver Volumetry

When the liver remnant is normal or has only mild disease, the volume of liver remnant can be measured directly and accurately by three-dimensional computed tomography volumetry. The liver remnant to be left after resection is termed the future liver remnant (FLR). For patients with marked underlying liver disease a 40% liver remnant is necessary to avoid cholestasis, fluid retention and liver failure. Complications are rare when the standardized FLR is greater than 20% of the total liver volume (TLV) as compared to when it is less than 20%. However CT volumetry for determining the functional residual liver remnant may be inaccurate when the liver to be resected is diseased.

The calculated TLV which has been derived from the close association between patient size and liver size (body surface area and liver size) provides a standardizing estimate of the TLV. The following formula has been validated and is used at M.D. Anderson for calculation of the remnant liver volume.

TLV (cm3) = -794.41 + 1267.28 X BSA (square meters)

Standardized FLR = measured FLR volume / TLV.

Schindl et al used CTAP (angioportography) for liver volumetry and predicting the residual liver volume. They

identified as 26.6% as the critical %RLV needed to decrease postoperative morbidity(LOE 2b). Emirogh and colleagues have demonstrated safety of multidetector CT volumetry by comparing the weight of the rescted liver specimen intra-operatively with the pre-operative volume calculated (LOE 3a).

Indocyanine Green Retention

ICG is a tricarbocyanine dye that binds to albumin and alpha-1 lipoproteins. Its active transfer into the liver parenchymal cells leads to a rapid disappearance from the plasma, and it appears to be solely removed by the liver by secretion into the bile.

Clearance is considered to be impaired when 15% or more of the dye remains within the plasma 15 minutes following the injection of 0.5mg/kg ICG. Although ICG clearance correlates with CP scores and the rate of disappearance of tagged asiaglycoproteins, it is also influenced by the changes in hepatic blood flow.

Akita H et al have utilized ICG retention rates for real time assessment of residual liver function intra-operatively using pulse dye densitometry. Though ICG retention rates at 15 minutes have been used as criteria for defining functional residual reserve and selection of patients for hepatic resection in Japan, there is no consensus regarding widespread acceptance and utilization of this technique due to lack of robust evidence. There is only weak evidence that this test can be useful in assessing liver function and lack of correlation has been described by Wakabayashi and Lam, especially after portal vein embolization (LOE 2b).

99m-Tc-galactosyl-human serum albumin scintigraphy

Utilizing the role of the liver in metabolizing senescent proteins through an active transport process facilitated by hepatocyte membrane receptors, synthetic asialoglycoprotein, galactosyl

human serum albumin (GSA) has been used as a liver scanning agent. The imaging provides volumetric and anatomic information as well as functional assessment of the ability of the liver to clear the synthetic protein.

Dinanat S et al assessed the risk of hepatic dysunction post hepatectomy using both hepatobiliary scintigraphy and volumetry. They found that the uptake in the liver remnant on scintigraphy had better correlation with postoperative outcomes (LOE 4). It has been shown to correlate with the ICG retention as well as histologic cirrhosis indices, in various Japanese studies. Its use, at present is investigational and whether it supplies additional information remains unclear, (LOE 4).

Conclusions

Mortality and morbidity rates after liver resection in cirrhotic and non-cirrhotic patients have decreased in spite of increase in the complexity of liver resections

Various laboratory data and imaging techniques have been used to complement the Child-Pugh score to predict liver failure after hepatectomy and to assess functional hepatic reserve.

The indocyanine green retention test is the most widely used clearance test. Nevertheless, it remains imperfect because it depends both on hepatic blood flow and on the functional capacity of the liver.

Nuclear imaging of the asialoglicoprotein receptors with radiolabelled synthetic asialoglicoproteins provides volumetric information as well a functional assessment of the liver.

In summary, while liver function is complex, a successful liver test to assess quantitative functional hepatic reserve still needs to be established. The combination of the Child-Pugh score, the presence of ascites, the serum bilirubin levels, the

indocyanine green retention (ICG R15) value, and the remnant liver CT volumetry seems to avoid an index of liver failure after hepatic resection. Cases when ICG R15 is above 15% should be combined with portal vein embolization.

1. Evaluation of liver function before living donor liver transplantation and liver resection

Mandli T, Fazakas J, Ther G et al. Orv Hetil 2008;149:779-86.

Liver resection is the curative therapeutic option for hepatocellular carcinoma, biliary tumors, metastases of colorectal and other extrahepatic tumors, living donor liver transplantation and other benign liver diseases. AIM OF STUDY: To summarize the evaluation methods of liver function before living donor liver transplantation and liver resection. METHOD: We summarize the literature about the evaluation of liver function. RESULTS: Perioperative mortality is determined mostly by the extent of preoperative evaluation focused on the liver. After resection the remnant liver parenchyma must cope with the challenge caused by increased metabolism, portal overflow, decreased vascular bed and biliary tract and oxidative stress following the operation. If the remnant liver is unable to grow up to this challenge, acute liver failure occurs. This maintains the necessity of determining the hepatic functional reserve and the hepatic remnant volume. Child-Pugh classification is widely spread to predict outcome. Dynamic functional tests such as indocyanine green retention test, galactosyl human serum albumin scintigraphy and aminopyrine breath tests can be used to evaluate hepatic reserve. To determine remnant liver volume modern imaging processes such as CT volumetry and hepatobiliary scintigraphy are available. CONCLUSION: After the detailed evaluation resection can be limited to an extent which is oncologically radical enough (1% remnant liver tissue/kg) and spares parenchyma which can ensure survival

yet. With careful preoperative examination mortality can be reduced even to reach zero.

2. Impact or preoperative planning using virtual segmental volumetry on liver resection for hepatocellular carcinoma

Yamanaka J, Saito S, Fujimoto J et al. World J Surg 2007;31:1249-255.

BACKGROUND: Accurate assessment of resection volume and vascular anatomy is mandatory in preoperative planning for safe and curative hepatectomy to treat cancer. Accordingly, we examined feasibility and accuracy of a preoperative three-dimensional (3D) computed tomography (CT) scan based simulation in patients with impaired liver function undergoing hepatectomy for hepatocellular carcinoma (HCC). METHODS: Hepatectomy simulation software was programmed to reconstruct detailed 3D vascular structure and calculate liver volume based on hepatic circulation. In 113 patients with HCC, liver resection volume was estimated preoperatively by both simulation and conventional planimetry. For validation, predicted resection volumes were compared with actual resected specimen weights. The resection margin as estimated by the simulation was compared with the margin in the specimen. RESULTS: Simulation showed higher correlation and smaller discrepancy ($r = 0.96$; 9.3 ml) between predicted and actual liver resection volume than conventional planimetry ($r = 0.74$; 174 ml). Simulation showed correlation ($p < 0.01$) between estimated and actual segmental volume, which was not measurable by planimetry. Simulation showed a correlation ($r = 0.84$) between predicted and actual margin, with a difference of 1.6 mm. CONCLUSIONS: Hepatectomy simulation in 3D predicted segmental liver volume and the resection margin accurately. This virtual method should contribute to preoperative planning to achieve safe, curative resection in HCC patients, whose hepatic function is

compromised.

3. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection

M J Schindl, D N Redhead, K C H Fearon et al. Gut 2005; 54: 289-96.

BACKGROUND AND AIMS: Major liver resection incurs a risk of postoperative liver dysfunction and infection and there is a lack of objective evidence relating residual liver volume to these complications. PATIENTS AND METHODS: Liver volumetry was performed on computer models derived from computed tomography (CT) angioportograms of 104 patients with normal synthetic liver function scheduled for liver resection. Relative residual liver volume (%RLV) was calculated as the relation of residual to total functional liver volume and related to postoperative hepatic dysfunction and infection. Receiver operator characteristic curve analysis was undertaken to determine the critical %RLV predicting severe hepatic dysfunction and infection. Univariate analysis and multivariate logistic regression analysis were performed to delineate perioperative predictors of severe hepatic dysfunction and infection. RESULTS: The incidence of severe hepatic dysfunction and infection following liver resection increased significantly with smaller %RLV. A critical %RLV of 26.6% was identified as associated with severe hepatic dysfunction ($p<0.0001$). Additionally, body mass index (BMI), operating time, and intraoperative blood loss were significant prognostic indicators for severe hepatic dysfunction. It was not possible to predict the individual risk of postoperative infection precisely by %RLV. However, in patients undergoing major liver resection, infection was significantly more common in those who developed postoperative severe hepatic dysfunction compared with those who did not ($p=0.030$). CONCLUSIONS: The likelihood of severe hepatic dysfunction

following liver resection can be predicted by a small %RLV and a high BMI whereas postoperative infection is more related to liver dysfunction than precise residual liver volume. Understanding the relationship between liver volume and synthetic and immune function is the key to improving the safety of major liver resection.

4. Relationship between CT volumetry and functional liver volume using technetium-99m galactosyl serum albumin scintigraphy in patients undergoing preoperative portal vein embolization before major hepatectomy: a preliminary study

Nanashima A, Yamaguchi H, Shibasaki S et al. Dig Dis Sci 2006; 51:1190-195.

To clarify the relationship between morphological measurements of hepatic volume by computed tomography (CT-vol) and functional volume (RI-vol) by technetium-99m galactosyl human serum albumin (99mTc-GSA) scintigraphy, and its clinical significance, we examined 16 patients with a background liver status of either normal liver function (n=4), chronic hepatitis or cirrhosis (n=7), or obstructive jaundice (n=5). In five patients who underwent preoperative portal vein embolization (PVE), volumetric measurement was performed 2 weeks after PVE. The mean values of CT-vol and RI-vol of the right lobe were 692+/-147 cm3 (66.1+/-10.7%) and 668+/-159 cm3 (67.8+/-13.2%), respectively, and those of the left lobe were 329+/-138 cm3 (33.9+/-10.6%) and 328+/- 170 cm3 (32.2+/-13.2%), respectively. There were no significant differences in the volume measurements between the two volumetric techniques. Correlations between CT-vol and RI-vol in the right and left lobes were positive and significant (r=0.912 and 0.903, respectively; both P's<0.001). The mean values of post-PVE CT-vol and RI-vol of the right lobe in five patients were significantly different (628+/-149 and 456+/-211 cm3, respectively; P=0.033). However, the mean values of

post-PVE CT-vol and RI-vol of the left lobe were not different (496+/-124 and 483+/-129 cm3, respectively). We propose that volumetric measurement by 99mTc-GSA scintigraphy is useful for detecting changes in functional volume of individual lobes of the liver and is a more dynamic method compared with detection of morphological changes by CT scan.

5. Using indocyanine green test to avoid post-hepatectomy liver dysfunction

Lee CF, Yu MC, Kuo LM et al. Chang Gung Med J 2007;30:333-38.

BACKGROUND: Post-operative hepatic failure is the most important concern for hepatocellular carcinoma (HCC) patients undergoing hepatectomy. The aim of this study was to determine the safe line of hepatectomy to prevent liver failure. METHOD: Clinical profiles of 117 patients with HCC who underwent hepatectomies in Chang Gung Memorial Hospital from Jan. 2002 through Jun. 2003 were reviewed. Patients with heart disease, azotemia, intra-operative blood loss > or = 1500 ml or international ratio of prothrombin time > or = 1.2 were excluded. All 117 patients studied had preoperative 15-minute retention rates of ICG (ICG15). Whole liver volumes (LV) were calculated from the equation: LV (ml) = 706.2 x body surface area (BSA, m2) + 2.4. The resected liver volumes were measured by pathologists. Postoperative liver dysfunction was defined as an international prothrombin ratio of > or = 1.5. RESULTS: Thirteen of the 117 HCC patients experienced postoperative liver dysfunction. The relationship between ICG15 retention rates and the ratio of remnant liver volume (RR) in the patients with postoperative liver dysfunction was established by regression, producing an equation: RR = 1.98 x ICG + 0.3672 ($r = 0.92$, $p < 0.001$). CONCLUSION: Hepatectomies will be safer if the estimated ratio of remnant liver volume prior to surgery is higher than the calculated value of RR = 1.98 x ICG + 0.3672.

6. Preoperative assessment of liver function

Schneider PD. Surg Clin North Am 2004;84:355-73.

At the present time, the decision to resect and the choice of the extent ofa hepatic resection are largely based on surgical judgment. The CP score is the best assessment tool we can now employ. There is uniform agreement that even segmental resections are not possible in the vast majority of Child Class B patients, CP score 7 to 9. The CP score can be augmented by radiographic testing, ICG retention testing, and by assessing tumor extent and the severity of the patient's cirrhosis at surgery.Surgeons need a simple means to assist with liver function evaluation—a test to augment the CP score. Although determining ICG retention is simple, it is questionable whether it adds to one's ability to define the poor-risk patient with better accuracy than the CP score. Abundant data exist to dispute the accuracy and reproducibility of ICG retention. That surgeons use it says more about the fervent desire to find a test that supports clinical judgment in these difficult patients than the scientific validity of the test. Whether a series of tests would better define the Child-Pugh Class A patient who is also a relatively poor risk is not clear at present. Many investigations demonstrate the correlation of various assessment tools with each other, yet nothing distinguishes them in predicting risk beyond what is learned from the CP score. In a group of CP Class A patients, the extent of the disease, the nature of underlying cirrhosis, and the extent of resection provide the clinical backdrop against which a decision for resection must be made. It may well be that one test may not do it, or that one single assessment of the ICG or the 15-minute receptor volume of GSA may be inadequate to project the nuances of liver function. Thus, 99m-Tc GSA scintigraphy will provide volumetric receptor data, as well as kinetic distribution curves, and may prove a useful test in the future. Whether GSA is ultimately to be proven useful requires a correlation of the test with actual clinical outcomes, rather

than correlation with other tests or with the CP score. Discovering which patients are the poor risk Child Class A patients is the desired goal. To have value, the GSA scan must augment, not mimic, the CP score. In view of the fact that experienced surgeons appear to be astute in their ability to select patients for hepatic resection, finding a more refined test will require large numbers of patients at several centers to correlate the test results and the outcomes against the spectrum of postoperative liver failure, including death. It appears that one lesson learned from portal vein embolization is that functional liver volume can be preserved. The compensatory hyperplasia that occurs in the contralateral hepatic lobe demonstrates two important features: (1) function of the opposite lobe has been transferred when evaluated by 99m-Tc-GSA, and (2) one considerable metabolic drain on the postoperative recovery from hepatic resection (ie, liver regeneration) can be attended to before the surgery. Cirrhotic livers do regenerate, but more slowly. Thus, pregrowing the remnant section of liver eliminates one stress on liver reserves following liver resection. For hepatocellular carcinoma or metastasis in cirrhotic patients, portal vein occlusion may be the best way to improve hepatic functional reserve. ICG retention may not corroborate return-to-baseline hepatic function within 2 weeks of portal vein occlusion,but may demonstrate a return to baseline when studied 6 to 8 weeks following the procedure. 99m-Tc-GSA is presently the best means to document compensatory hyperplasia and, possibly, a shift of functional reserve to the planned remnant of a more than four-segment hepatic resection. Whether this will predict the safe outcome of resection remains to be seen.

Measures to Prevent Intraoperative Complications in Liver Resections

- Complete Versus Selective Portal Triad Clamping for Minor Liver Resections LOE 1
- Anterior approach versus conventional approach in right hepatic resection for large hepatocellular carcinoma LOE 2
- Intraoperative blood salvage during liver resection LOE 3
- Intermittent Pedicle Occlusion with Ischaemic Intervals of 15 versus 30 Minutes LOE 2
- How should transection of the liver be performed? LOE 4
- Usefulness of LigaSure for liver Resection LOE 4
- Hilar dissection versus the "Glissonean" approach and stapling of the pedicle for major hepatectomies LOE 3
- Effect of hypoventilation on bleeding during hepatic resection LOE 4
- Routine abdominal drainage for uncomplicated liver resection LOE 1

Liver resection has been increasingly performed over the last 2 decades worldwide due to improved postoperative outcomes and evidence that this approach offers the only curative option

in many patients. Despite the success of liver surgery, excessive blood loss and the need for blood transfusion remain significant risk factors for poor outcome. Furthermore, the use of blood transfusion is associated with poorer long-term survival. Blood loss during liver resection is one of the important factors affecting the peri-operative outcomes of patients.

Complete Versus Selective Portal Triad Clamping for Minor Liver Resections

Both techniques of clamping are equally effective and feasible for patients with normal liver and undergoing minor hepatectomies. In the complete clamping group, the entire hilar pedicle is encircled with a rubber tape to perform a Pringle maneuver with a tourniquet .In the selective clamping group, the control of the intrahepatic portal triad is achieved by a hepatotomy near the corresponding portal pedicle by the "Glissonean" approach technique. However, in cirrhotic patients selective clamping induces less ischemic injury and is recommended by KS Gurusamy et al., in a Cochrane Database of Systematic Review 2008 (Level of Evidence 1).

Anterior approach versus conventional approach in right hepatic resection for large hepatocellular carcinoma

Conventional approach

The liver is mobilized from the retroperitoneum including the division of short venous branches to the inferior vena cava. In the next step the inflow control (either intra- or extrahepatic) is performed by ligation and division of right portal vein and hepatic artery. The outflow is controlled by ligation and division of the right hepatic vein, and possibly, middle hepatic vein. Parenchymal transection is performed according to surgeon's preference and local standards (e.g. stapler, Cusa, etc.).

Anterior approach

Extrahepatic inflow control is maintained by ligation and division of right portal vein and hepatic artery before any mobilization of the right liver lobe. A hanging liver manoeuvre is performed without manipulation of the right lobe. Afterwards, parenchymal transection is performed. This is followed by the outflow control with ligation and division of the right, and possibly, the middle hepatic vein. Finally, the short venous branches of the inferior vena cava are divided and the liver is mobilized out of the retroperitoneum.

Liu CL, et al have shown that the anterior approach results in better operative and survival outcomes compared with the conventional approach. It is the preferred technique for major right hepatic resection for large HCC. Major blood transfusion requirements were lower in the anterior approach in 120 patients (LOE 2).

Intraoperative blood salvage during liver resection

Blood salvage- A blood volume equal to approximately 0.7% of the patient's body weight is collected before the liver transaction. Modest intraoperative blood salvage significantly and safely reduced blood loss during hepatic parenchymal transaction (79 patients Hashimoto T, et al. . 2007- LOE 3).

Effect of CVP

Although reduction of central venous pressure (CVP) is thought to decrease blood loss during liver resection, no consistently effective and safe method for obtaining the desired reduction of CVP has been established.

Intermittent Pedicle Occlusion with Ischaemic Intervals of 15 versus 30 Minutes

There was no difference in the bilirubin ratio when intermittent pedicle occlusion was carried out for 30 or 15 min. By

extension of IPO to 30 min, a greater resection area per unit time was possible with preservation of remnant liver function(108 patients. Esaki M, et al. 2006 – LOE 2b).

How should transection of the liver be performed?

Clamp crushing technique

CUSA

Hydrojet

Dissecting sealer

The clamp crushing technique was the most efficient device in terms of resection time, blood loss, and blood transfusion frequency compared with CUSA, Hydrojet, and dissecting sealer, and has proved to be also the most cost-efficient device (Lesurtel M, et al. 2005 – LOE 4).

Usefulness of LigaSure for liver Resection

The median blood loss during liver transection was less in the LigaSure than in the conventional group The LigaSure system is an effective and safe tool for decreasing liver resection time (60 patients saiura A, et al. 2006- LOE 4).

Hilar dissection versus the "Glissonean" approach and stapling of the pedicle for major hepatectomies

"Glissonean" approach technique - Control of the intrahepatic portal triad is achieved by hepatotomy near the corresponding portal pedicle. The TA-30 vascular stapler is introduced to transect the pedicle. During transection a firm countertraction of the rubber tape is necessary to avoid accidental damage of the bile duct confluence.

Hilar dissection technique - The corresponding hepatic artery and the biliary duct are ligated and cut. The corresponding

portal vein is transected using vascular clamps and closed with a running suture with a nonabsorbable monofilament before transection of the parenchyma.

The two techniques are equally effective procedures for treating hilar structures. Although en bloc stapling transection is faster, hilar dissection is associated with a shorter pedicular clamping time, less cytolysis, and the materials required are less expensive (80 patients ; Figueras J, et al. 2003 – LOE 3).

Effect of hypoventilation on bleeding during hepatic resection

No beneficial effect of reduction of tidal volume on bleeding during hepatic resection (80 patients hasegawa K, et al. 2002 – LOE 4).

Routine abdominal drainage for uncomplicated liver resection

There is no evidence to support routine drain use after uncomplicated liver resections (Gurusamy KS, et al. Cochrane database systemic rev. 2007 – LOE 1).

Ultrasound-guided liver resections for hepatocellular carcinoma

Intraoperative ultrasound has shown to be useful for optimizing the balance between the oncological radicality and the sparing of the highest amount of functioning liver parenchyma. Intraoperative ultrasonography allows the accomplishment of anatomical resections otherwise not possible such as the systematic segmentectomy. If non-anatomical resection is carried out intraoperative ultrasonography guidance allows a better tumor clearance. Precise definition of hepatic vein anatomy and association with color Doppler enables hepatectomies otherwise not possible, expanding the indication at surgical resection (Torzilli G, et al. 2002).

Conclusion

Excessive blood loss and the need for blood transfusion remain the most significant risk factors for poor outcome.

In cirrhotic patients selective clamping induces less ischemic injury and is recommended (LOE 2).

There is no difference when intermittent pedicle occlusionis carried out for 30 or 15 min (LOE 2).

The clamp crushing technique was the most efficient device in terms of resection time, blood loss, and blood transfusion frequency compared with CUSA, Hydrojet, and dissecting sealer, and has proved to be also the most cost-efficient device (LOE 2).

The aid of intraoperative ultrasonography is optimizing the balance between the oncological radicality and sparing of the highest amount of functioning liver parenchyma.

1. Ultrasound-Guided Liver Resections for Hepatocellular Carcinoma

Torzilli G, Leoni P, Gendarini A, et al.
Hepatogastroenterology 2002;49:21-7

Imaging-guided interventional procedures have modified the approach to hepatocellular carcinoma including the surgical one. In fact, liver resections can be carried out with no mortality even if cirrhosis is associated, combining the needs for oncological radicality and liver parenchyma sparing mainly because of the extensive use of intraoperative ultrasonography either for tumor staging or resection-guidance. The aid of intraoperative ultrasonography is therefore optimizing the balance between the oncological radicality and the sparing of the highest amount of functioning liver parenchyma. Intraoperative ultrasonography allows the accomplishment of anatomical resections otherwise not possible such as the

systematic segmentectomy. This is of crucial importance if taking into account that anatomical resections seem able to provide better prognosis than the non-anatomical one. However, if non-anatomical resection is carried out intraoperative ultrasonography guidance allows a better tumor clearance. Precise definition of hepatic vein anatomy and association with color Doppler enables hepatectomies otherwise not possible, expanding the indication at surgical resection. In conclusion, we can affirm that liver resection is an imaging-guided procedure and as every interventional imaging-guided procedure, its features are the highest therapeutic efficacy combined with the minimal invasiveness. Then, with the intraoperative ultrasonography guidance liver resection remains the treatment of choice of hepatocellular carcinoma.

2. Methods of vascular Occlusion for Elective liver Resections.

Gurusamy KS, Kumar Y, Sharma D, et al. Cochrane Database Syst Rev. 2007

BACKGROUND: Vascular occlusion is used to reduce blood loss during liver resection surgery. There is considerable controversy regarding whether vascular occlusion should be used or not during elective liver resections. The method of vascular occlusion employed is also controversial. There is also considerable debate on the role of ischaemic preconditioning before vascular occlusion. OBJECTIVES: To assess the advantages (decreased blood loss and peri-operative morbidity) and disadvantages (liver dysfunction from ischaemia) of vascular occlusion during liver resections. To compare the advantages (in decreasing blood loss or decreasing ischaemia-reperfusion injury) and disadvantages of different types of vascular occlusion versus total, continuous portal triad clamping. SEARCH STRATEGY: We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane

Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded until March 2007. SELECTION CRITERIA: We included randomised clinical trials comparing vascular occlusion versus no vascular occlusion during elective liver resections (irrespective of language or publication status). We also included randomised clinical trials comparing the different methods of vascular occlusion and those investigating the role of ischaemic preconditioning in liver resection. DATA COLLECTION AND ANALYSIS: We collected the data on the characteristics of the trial, methodological quality of the trials, mortality, morbidity, blood loss, blood transfusion requirements, and liver function tests, markers of neutrophil activation, operating time, and hospital stay. We analysed the data with both the fixed-effect and the random-effects models using RevMan Analysis. For each binary outcome we calculated the odds ratio (OR) with 95% confidence intervals (CI) based on intention-to-treat analysis. For continuous outcomes, we calculated the weighted mean difference (WMD) with 95% confidence intervals. MAIN RESULTS: We identified a total of 16 randomised trials. Five trials including 331 patients compared vascular occlusion (n = 166) versus no vascular occlusion (n = 165). Six trials including 521 patients compared different methods of vascular occlusion. Three trials including 210 patients compared ischaemic preconditioning before continuous portal triad clamping (n = 105) versus no ischaemic preconditioning (n = 105). Two trials including 127 patients compared ischaemic preconditioning before continuous portal triad clamping (n = 63) versus intermittent portal triad clamping (n = 64).The blood loss was significantly lower in vascular occlusion compared with no vascular occlusion. The liver enzymes were significantly elevated in the vascular occlusion group compared with no vascular occlusion. There was no difference in the mortality, liver failure, or other morbidities. Four of the

five trials comparing vascular occlusion and no vascular occlusion used intermittent vascular occlusion. Trials comparing complete inflow and outflow occlusion to the liver, ie, hepatic vascular exclusion and portal triad clamping demonstrate significant detrimental haemodynamic changes in hepatic vascular exclusion compared to portal triad clamping. There was no significant difference in the number of units transfused and the number of patients needing transfusion. There was no difference in mortality, liver failure, or morbidity between total and selective methods of portal triad clamping. All four cases of mortality and liver failure in the comparison between the intermittent and continuous portal triad clamping occurred in the continuous portal triad clamping (statistically not significant). Intermittent portal triad clamping does not increase the total blood loss or operating time compared to continuous portal triad clamping. There was no statistically significant difference in the mortality, liver failure, morbidity, blood loss, or haemodynamic changes between ischaemic preconditioning versus no ischaemic preconditioning before continuous portal triad clamping. Liver enzymes used as markers of liver injury were significantly lower in the early post-operative period in the ischaemic preconditioning group. The intensive therapy unit stay and hospital stay were statistically significantly lower in the ischaemic preconditioning group than in the no ischaemic preconditioning group. There was no statistically significant difference in the mortality, liver failure, morbidity, intensive therapy unit stay, or hospital stay between ischaemic preconditioning before continuous portal triad clamping and intermittent portal triad clamping. The blood loss and transfusion requirements were lower in the ischaemic preconditioning group. Aspartate aminotransferase level was lower in the intermittent portal triad clamping group than the ischaemic preconditioning group on the third post-operative day. There was no difference in the peak aspartate

aminotransferase levels or in the aspartate aminotransferase levels on first or sixth post-operative days of aspartate aminotransferase. AUTHORS' CONCLUSIONS: Intermittent vascular occlusion seems safe in liver resection. However, it does not seem to decrease morbidity. Among the different methods of vascular occlusion, intermittent portal triad clamping has most evidence to support the clinical application. Hepatic vascular exclusion cannot be recommended routinely. Ischaemic preconditioning before continuous portal triad clamping may be of clinical benefit in reducing intensive therapy unit and hospital stay.

3. How should transection of the liver be performed?: A prospective randomized study in 100 consecutive patients: comparing four different transection strategies.

Lesurtel M, Selzner M, Petrowsky H et al. Ann of Surg. 2005;242:814-22.

OBJECTIVE: To identify the most efficient parenchyma transection technique for liver resection using a prospective randomized protocol. SUMMARY BACKGROUND DATA: Liver resection can be performed by different transection devices with or without inflow occlusion (Pringle maneuver). Only limited data are currently available on the best transection technique. METHODS: A randomized controlled trial was performed in noncirrhotic and noncholestatic patients undergoing liver resection comparing the clamp crushing technique with Pringle maneuver versus CUSA versus Hydrojet versus dissecting sealer without Pringle maneuver (25 patients each group). Primary endpoints were intraoperative blood loss, resection time, and postoperative liver injury. Secondary end points included the use of inflow occlusion, postoperative complications, and costs. RESULTS: The clamp crushing technique had the highest transection

velocity (3.9 +/- 0.3 cm/min) and lowest blood loss (1.5 +/- 0.3 mL/cm) compared with CUSA (2.3 +/- 0.2 cm/min and 4 +/- 0.7 mL/cm), Hydrojet (2.4 +/- 0.3 cm/min and 3.5 +/- 0.5 mL/cm), and dissecting sealer (2.5 +/- 0.3 cm/min and 3.4 +/- 0.4 mL/cm) (velocity: P = 0.001; blood loss: P = 0.003). Clamp crushing technique was associated with the lowest need for postoperative blood transfusions. The degree of postoperative reperfusion injury and complications were not significantly different among the groups. The clamp crushing technique proved to be most cost-efficient device and had a cost-saving potential of 600 to 2400 per case. CONCLUSIONS: The clamp crushing technique was the most efficient device in terms of resection time, blood loss, and blood transfusion frequency compared with CUSA, Hydrojet, and dissecting sealer, and proved to be also the most cost-efficient device.

4. Hilar dissection versus the "glissonean" approach and stapling of the pedicle for major hepatectomies: a prospective, randomized trial.

Figueras J, Lopez-Ben S, Lladó L, et al. Ann Surg. 2003;238:111-9.

OBJECTIVE: A randomized study was conducted of hilar dissection and the "glissonean" approach and stapling of the pedicle for major hepatectomies to contrast their feasibility, safety, amount of hemorrhage, postoperative complications, operative times, and costs. SUMMARY BACKGROUND DATA: The "glissonean" approach is reported as requiring a shorter portal triad closure time; furthermore, the procedure seems to expedite the transection of the liver. PATIENTS AND METHODS: Between 1998 and 2001, 80 patients were enrolled in this study. The major liver resections included 15 extended right, 7 extended left, 42 right, and 16 left hepatectomies. The patients were randomly assigned to the hilar dissection group (G1; n = 40) or to the "glissonean"

approach and stapling of the portal triad group (G2; n = 40). RESULTS: The groups were equally matched for age, sex, diagnosis, mean resected specimen weight, number of tumoral lesions, type of liver resection performed, and percentage of patients with margin invasion (G1: 4; 10% vs G2: 5; 12.5%). The duration of the 2 procedures was similar (G1: 247 +/- 54 min vs G2: 236 +/- 43 min; P = 0.4). However, the duration of the hilar dissection was shorter for G2 (50 +/- 17 min) versus G1 (70 +/- 26 min; P <0.001). By contrast, the duration of pedicular clamping was shorter for G1 (43 +/- 15 min) versus G2 (51 +/- 15 min; P = 0.015). No differences were observed in the amount of hemorrhage (G1: 887 +/- 510 mL vs G2: 937 +/- 636 mL; P = 0.7), and only 6 patients in G1 and 10 in G2 were transfused (P = 0.26). Morbidity rates were similar for both groups (G1: 23% vs G2: 33%; P = 0.3). Surgical injury of the contralateral biliary duct was not observed. However, 3 patients in G1 and 4 patients in G2 presented a biliary fistula that resolved spontaneously. Postoperative hospital stay was similar (G1: 8 [range, 6-24] vs G2: 9 [range, 5-31] days; P = 0.6). The postoperative levels of alanine transaminase (ALT) during the 2 first postoperative days were lower for G1 than G2. Cost of the surgical material was 1235.80 US dollars for G1 and 1301.10 US dollars for G2. CONCLUSIONS: The 2 techniques are equally effective procedures for treating hilar structures. Although en bloc stapling transection is faster, hilar dissection was associated with a shorter pedicular clamping time, less cytolysis, and the materials required were less expensive.

Evidence Based Management of Post Hepatectomy Liver Dysfunction

- PLF (post-resection liver failure) 50–50 criteria LOE 2
- Doppler analysis of hepatic blood flow to predict liver dysfunction after major hepatectomy LOE 4
- Factors affecting Post-resectional Liver Function LOE 2
- Assessment of remnant liver volume and residual functional reserve LOE 3
- Portal Vein Embolization (PVE) LOE 1
- Intra-operative blood loss prevention LOE 1
- Support of liver function LOE 1

The advances in liver anatomy, surgical techniques and perioperative management have made hepatectomy safer in recent times. However, liver resection is a complex procedure and therefore associated with a high risk of postoperative complications. The reported postoperative complication rates after liver resection are between 22% and 55.5%.

Postoperative complications include bile leakage, sub-phrenic abscess, pleural effusion, wound problems, hemorrhage in surgical sites, liver insufficiency and disorders in other organs.

Liver insufficiency, bile leakage and intra-abdominal hemorrhage are common causes of post operative death.

Surgical complications can be decreased by modified surgical techniques, decreased intra-operative blood loss and duration of surgery, whereas liver failure and medical complications can be decreased by proper selection of patients.

Resection remains an important option for patients with preserved liver function and early HCC because it can achieve survival rates comparable with those of transplantation.

The reported incidence of liver dysfunction after hepatic resection ranges between 0.7 and 9.1%. An inadequate quantity or quality of residual liver mass is a key event in its pathogenesis. In the past decade, mortality after partial hepatic resection ranged from 0 to 5% and although the cause of death after partial hepatic resection is multifactorial, liver dysfunction is the commonest cause.

Definitions

There is lack of a consensus regarding a standard definition of liver insufficiency or dysfunction after resection, but it is recognized that post resection liver insufficiency is characterized as failure of one or more of the hepatic synthetic and excretory functions that include:

hyperbilirubinaemia

hypoalbuminaemia

prolonged prothrombin time

elevated serum lactate and / or

different grades of hepatic encephalopathy

PLF (post-resection liver failure) is quantitatively reasonably well defined by the so-called 50–50 criteria, which describe PLF as prothrombin index <50% (equal to an international standardized ratio >1.7) and serum bilirubin >50 ìmol/L

(2.9 mg/dL) on post-operative day 5. When these 50–50 criteria were fulfilled, patients had a 59% risk of mortality compared with 1.2% when they were not met (sensitivity 69.6% and specificity 98.5%). These 50–50 criteria have been validated recently in a large retrospective study by Balzan et al, which showed a sensitivity of 50% and a specificity of 96.6% for the prediction of PLF-related death in a cohort of patients without underlying liver disease who had undergone major hepatic resection (Level of Evidence 2a).

Mullen JT et al. in their review of 1000 non-cirrhotics undergoing hepatic resection have defined post-resection hepatic insufficiency in terms of peak bilirubin values which can be used to accurately predict liver-related death and worse outcomes after resection.

Pathogenesis

The ability of the liver remnant to surmount the effect of surgical resection depends on its capacity to limit hepatocyte death, to resist metabolic stress, to preserve or recover an adequate synthetic function and to enhance its regenerative power. The factors playing a role in the pathogenesis of post hepatectomy liver insufficiency rely on both the quality and the quantity of remaining liver parenchyma.

Hepatic parenchymal congestion: Hepatic resection leads to augmented sinuisoidal perfusion. Kin Y et al have described the use of Doppler analysis of hepatic blood flow to predict liver dysfunction after major hepatectomy (LOE 4).

Ischemia–reperfusion injury: hepatic ischemia and reperfusion injury triggers a immune response cascade which aggravate hepatic injury.

Reduced phagocytic capacity: Partial hepatic resection causing reduced phagocytic capacity predisposes to infections and liver insufficiency as proposed by Schindl MJ et al (LOE 3).

Factors affecting Post-resectional Liver Function

General risk factors	Liver Characteristics	Surgery Related
Advanced age	Cirrhosis	Remnant liver volume
Comorbid conditions	Steatosis, Cholestasis	Blood loss
Malnutrition	Post chemotherapy toxicity	Duration of surgery

It is essential to identify these risk factors during the pre-operative assessment that includes evaluation of liver volume, anatomy and function. Preventive measures should be applied whenever possible as curative treatment options for post hepatectomy liver dysfunction are limited.

Cirrhosis and other hepatic parenchymal disorders such as cholestasis and steatosis are well known predictors of poor outcome after hepatic resection due to presence of impaired liver function, reduced regenerative capacity, increased risk of coagulopathy and infections (LOE 2a). However, after assessment of residual liver function and careful selection of candidates, resection with limited morbidity has been offered in experienced centers as described by Hong J et al. (LOE 4).

Chemotherapy toxicity, especially with the use of oxaliplatin in colorectal metastases causes sinusoidal injury and leads to an increased incidence of post-resection liver morbidity as reported by Nakano et al. (LOE 3).

An area of intense research and debate is the assessment of remnant liver volume and residual functional reserve which have been identified as the key factors in predicting liver function after resection. Schindl MJ et al from the Edinburgh Liver Surgery and Transplantation Experimental Research group (eLISTER) identified 26% as the critical residual liver volume using computed tomography angioportograms (CTAP) for liver volumetry to prevent post-operative morbidity (LOE 3).

Prolonged duration of surgery and increased blood loss leading to have been reported as independent prognostic factors by various authors (LOE 4).

Togo S et al. retrospectively reviewed 500 patients and the methods instituted for infection control in post hepatectomy patients. They showed a significant decrease in post hepatectomy infection and morbidity rates, 44.7% in 1992 to 9.2% in 2005 (LOE 3).

Malnutrition predisposes to increased post resectional complication rates due to impaired immunity, reduced protein synthesis and decreased regenerative capacity. Fan ST et al. have stressed the need for perioperative nutritional support in patients undergoing hepatic resection for hepatocellular carcinoma (LOE 5).

Prevention

The treatment of post hepatectomy liver failure is largely supportive; hence preventive measures should be instituted especially for extended resections or in cases with limited functional reserve.

When a small residual liver volume is expected, Portal Vein Embolization (PVE) can be used. In a recent meta-analysis by Abulkhir et al., PVE was found to be a safe and effective procedure in inducing liver hypertrophy to prevent postresection liver failure due to insufficient liver remnant (LOE 1).

Excessive intra-operative blood loss can be prevented by maintaining a low CVP during dissection as advocated by Jones et al. (LOE 3). This in combination with other intra-operative maneuvers such as continuous / intermittent portal triad clamping or application of total vascular exclusion that have reported decreased blood loss (LOE 1) (discussed in detail in the previous chapter)

Post hepatectomy liver insufficiency includes features indicating insufficiency of the hepatic synthetic and excretory mechanisms as well as the effects on other systems.

Liver failure: jaundice, coagulopathy, ascites, edema, hepatic encephalopathy

Renal failure: azotaemia and oliguria causing pleural effusion, edema, ascites

Circulatory system: Increased vascular permeability, diffuse intravascular coagulation and peripheral vasodilatation

Respiratory function: Pulmonary edema, adult respiratory distress syndrome

Management of Post-resectional Liver Dysfunction

Circulation	Monitor Central Venous Pressure
	Maintain Mean Arterial Pressure
	Invasive Cardiac Output Monitoring
Renal function	Urine output 0.5 mL/kg/h
Respiratory function	Maintain arterial oxygen saturation
	Monitor central venous oxygen saturation
Coagulation	Monitor INR
	Adequate platelet number and function
	Support with blood and plasma products
Nutrition	Early enteral feeding
	TPN support if required

Support of liver function

In the Cochrane database systematic review of artificial and bioartificial liver systems by Liu et al., they concluded that although artificial liver systems seem to improve the mortality in acute-on-chronic liver failure artificial and bioartificial support systems did not appear to affect mortality in acute liver failure. However, considering the strength of the evidence, additional randomised clinical trials are needed before any support system can be recommended for routine use (LOE 1b).

Otsuka Y et al have demonstrated increased survival for post resection hepatic failure patients undergoing orthotopic liver transplantation as compared to those who did not, 42.2 and 1.4 months respectively (LOE 2b).

Conclusions

The incidence of liver failure after partial hepatic resection ranges between 0.7 and 9.1%. An inadequate quantity or quality of residual liver mass are key events in the pathogenesis of post resection liver insufficiency. Risk factors for the development of complications are small residual liver volume, excessive intra-operative blood loss, need for blood transfusion, malnutrition, advanced age, male gender and pre-existent liver disease. A prerequisite for the avoidance of liver failure is a thorough pre-operative assessment that includes evaluation of liver volume, anatomy and function. Preventive measures should be applied whenever possible as curative treatment options are limited. Management principles focus on support of liver and end-organ function and resemble those applied during acute liver failure and sepsis.

Trends in reported incidence of post hepatectomy liver failure in the last decade

Author	Year Published	Period of Study	Number of cases	Post operative morbidity	Post resectional liver failure (n)	Liver failure (%)
Virani	2007	2001-2004	783	177 (23%)	NA	NA
Benzoni	2006	1989- 2005	287	137 (48%)	26	9.1%
Schroeder	2006	1991- NA	587	188 (32%)	145	32.1%
Sun	2005	2001-2004	146	37 (25%)	1	0.7%
Poon	2004	1989-1996	402	150 (37%)	20	5.0
		& 1996-2003	820	246 (30%)	27	3.3
Rees	1996	1986-1995	150	35 (23%)	1	0.7%

1. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma

Chok KS, Ng KK, Poon RT et al.
Br J Surg 2008; 96:81-7

BACKGROUND: The aim of this retrospective study was to determine the impact of postoperative complications on the long-term outcome of curative liver resection for hepatocellular carcinoma (HCC). METHODS: A total of 863 patients who had curative resection of HCC from December 1989 to December 2004 were included in the analysis. Median follow-up was 35.6 months. RESULTS:Some 288 patients (33.4 per cent) developed postoperative complications. The hospital mortality rate was 5.3 per cent (46 patients). Multiple logistic regression analysis showed that older age and massive intraoperative blood loss were related to a significantly higher complication rate. Demographics of patients with and without postoperative complications were comparable. The former had significantly more blood loss (median 1.1 versus 0.7 litres; $P < 0.001$) and required more transfused blood ($P < 0.001$). The overall survival rates of patients without complications at 1, 3, 5 and 10 years were 83.6, 62.8, 51.5 and 32.1 per cent respectively. Corresponding rates for those with complications were 67.8, 52.4, 41.5 and 26.6 per cent ($P = 0.004$). Cox proportional hazard model analysis revealed that the presence of postoperative complications was independently associated with poor overall survival. CONCLUSION: Postoperative complications can affect overall long-term survival after resection of HCC.

2. Predictive indices of morbidity and mortality after liver resection

Schroeder RA, Marroquin CE, Bute BP et al.
Ann Surg 2006; 243: 373-79

OBJECTIVE: To determine if use of Model for End-Stage Liver Disease (MELD) scores to elective resections accurately predicts short-term morbidity or mortality. SUMMARY BACKGROUND DATA: MELD scores have been validated in the setting of end-stage liver disease for patients awaiting transplantation or undergoing transvenous intrahepatic portosystemic shunt procedures. Its use in predicting outcomes after elective hepatic resection has not been evaluated. METHODS: Records of 587 patients who underwent elective hepatic resection and were included in the National Surgical Quality Improvement Program Database were reviewed. MELD score, CTP score, Charlson Index of Comorbidity, American Society of Anesthesiology classification, and age were evaluated for their ability to predict short-term morbidity and mortality. Morbidity was defined as the development of one or more of the following complications: pulmonary edema or embolism, myocardial infarction, stroke, renal failure or insufficiency, pneumonia, deep venous thrombosis, bleeding, deep wound infection, reoperation, or hyperbilirubinemia. The analysis was repeated with patients divided according to their procedure and their primary diagnosis. Parametric or nonparametric analyses were performed as appropriate. Also, a new index was developed by dividing the patients into a development and a validation cohort, to predict morbidity and mortality in patients undergoing elective hepatic resection. ROC curves were also constructed for each of the primary indices. RESULTS: CTP and ASA scores were superior in predicting outcome. Also, patients undergoing resection of primary malignancies had a higher rate of mortality but no difference in morbidity. CONCLUSION: MELD scores should not be used to predict outcomes in the setting of elective hepatic resection.

3. The "50-50 Criteria" on Postoperative Day 5: An Accurate Predictor of Liver Failure and Death after Hepatectomy.

Balzan S, Belghiti J, Farges O et al Ann Surg 2005; 242 :824-29

Abstract:

Objective: To standardize the definition of postoperative liver failure (PLF) for prediction of early mortality after hepatectomy. Summary Background Data: The definition of PLF is not standardized, making the comparison of innovations in surgical techniques and the timely use of specific therapeutic interventions complex. Methods: Between 1998 and 2002, 775 elective liver resections, including 69% for malignancies and 60% major resections, were included in a prospective database. The nontumorous liver was abnormal in 43% with steatosis >30% in 14%, noncirrhotic fibrosis in 43%, and cirrhosis in 12%. The impact of prothrombin time (PT) <50% and serum bilirubin (SB) >50 [mu]mol/L on postoperative days (POD) 1, 3, 5, and 7 was analyzed. Results: The lowest PT level was observed on postoperative day (POD) 1, while the peak of SB was observed on POD 3. These 2 variables tended to return to preoperative values by POD 5. The median interval between hepatectomy and postoperative death was 15 days (range, 5-39 days). Postoperative mortality significantly increased in patients with PT <50% and SB >50 [mu] ml/L. The conjunction of PT <50% and SB >50 [mu] mol/L on POD 5 was a strong predictive factor of mortality. In patients with significant morbidity, this "50-50 criteria" was met 3 to 8 days before clinical evidence of complications. Conclusions: The association of PT <50% and SB >50 [mu] ml/L on POD 5 (the 50-50 criteria) was a simple, early, and accurate predictor of more than 50% mortality rate after hepatectomy. This criteria could be identified early enough, before clinical evidence of

complications, for specific interventions to be applied in due time.

4. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy

Mullen JT, Ribero D, Reddy SK et al.
J Am Coll Surg 2007; 204: 854-62

BACKGROUND: To establish a reliable definition of postoperative hepatic insufficiency (PHI) in noncirrhotic patients undergoing major hepatectomy. No standard definition of PHI has been established, but one is essential for meaningful comparison of outcomes data across studies. METHODS: Data from 1,059 noncirrhotic patients who underwent major hepatectomy (3 or more liver segments) at 3 centers from 1995 to 2005 were analyzed. Receiver operating characteristics (ROC) analysis of peak postoperative bilirubin ((Peak)Bil) and international normalized ratio ((Peak)INR) were used to define PHI. RESULTS: A total of 669 patients (63%) underwent resection of 3 to 4 liver segments; 390 (37%) underwent resection of 5 or more segments. Complications occurred in 453 (43%). The 90-day all-cause mortality rate was 4.7%, which is 47% higher than the 30-day rate (3.2%). Twenty (1.9%) patients died of causes unrelated to the liver. Of the remaining 1,039 patients, 30 (2.8%) died a median 36 days from liver-related causes (liver failure with or without multiorgan failure). ROC analysis revealed cut-offs that predict liver-related death are (Peak)Bil 7.0 mg/dL (area under the curve 0.982; sensitivity 93.3%; specificity 94.3%) and (Peak)INR 2.0 (area under the curve 0.846; sensitivity 76.7%; specificity 82.0%). (Peak)Bil > 7.0 mg/dL was the most powerful predictor of any (odds ratio [OR] = 83.3) or major complication (OR = 10.0), 90-day mortality (OR = 10.8), and 90-day liver-related mortality (OR = 250) (all $p < 0.0001$).

CONCLUSIONS: PHI defined as (Peak)Bil > 7.0 mg/dL accurately predicts liver-related death and worse outcomes after major hepatectomy. Standardized reporting of complications, PHI, and 90-day mortality is essential to accurately determine the risk of major hepatectomy and to compare outcomes data.

5. Sinusoidal Injury Increases Morbidity after Major Hepatectomy in Patients With Colorectal Liver Metastases Receiving Preoperative Chemotherapy.

Nakano H, Oussoultzoglou E, Rosso E et al.
Ann Surg 2008; 247: 118-24

Abstract:

Objective: To investigate whether sinusoidal injury (SI) was associated with a worse outcome after hepatectomy in patients with colorectal liver metastases (CRLM). Background: Correlation between SI and oxaliplatin-based chemotherapy (OBC) was recently shown in patients with CRLM. However, it has yet to be fully clarified whether SI affects liver functional reserve and outcome after hepatectomy. Patients and Methods: Between 2003 and 2005, 90 patients with CRLM who underwent an elective hepatectomy after preoperative chemotherapies were included. Diagnosis of SI was established pathologically in the nontumoral liver parenchyma of the resected specimens, and perioperative data were assessed in these patients. Results: OBC was significantly associated with a higher incidence of SI. Preoperative indocyanine green retention rate at 15 minutes (ICG-R15) and postoperative value of total-bilirubin were significantly higher, and hospital stay was significantly longer in patients presenting with SI. Multivariate analysis showed that female gender, administration of 6 cycles or more of OBC, abnormal value of preoperative aspartate aminotransferase >36 IU/L, or abnormal value of preoperative ICG-R15 (>10%) were

preoperative factors significantly associated with SI. Among patients undergoing a major hepatectomy, SI was significantly associated with higher morbidity and longer hospital stay. Conclusion: The present study suggests that SI resulted in a poorer liver functional reserve and in a higher complication rate after major hepatectomy. Therefore, female patients who received 6 cycles or more of OBC, or presenting with abnormal preoperative aspartate aminotransferase and ICG-R15 values should be carefully selected before deciding to undertake a major hepatectomy.

6. Liver failure after hepatic resection

Garcea G, Maddern GJ
J Hepatobiliary Pancreat Surg 2008; Epub

INTRODUCTION: The consequence of excessive liver resection is the inexorable development of progressive liver failure characterised by the typical stigmata associated with this condition, including worsening coagulopathy, hyperbilirubinaemia and encephalopathy. The focus of this review will be to investigate factors contributing to hepatocyte loss and impaired regeneration. METHODS: A literature search was undertaken of Pubmed and related search engines, examining for articles relating to hepatic failure following major hepatectomy. RESULTS: In spite of improvements in adjuvant chemotherapy and increasing surgical confidence and expertise, the parameters determining how much liver can be resected have remained largely unchanged. A number of preoperative, intraoperative and post-operative factors all contribute to the likelihood of liver failure after surgery. CONCLUSIONS: Given the magnitude of the surgery, mortality and morbidity rates are extremely good. Careful patient selection and preservation of an obligate volume of remnant liver is essential. Modifiable causes of hepatic failure include avoidance of sepsis, drainage of cholestasis with restoration of enteric bile salts and judicious use of portal triad

inflow occlusion intra-operatively. Avoidance of post-operative sepsis is most likely to be achieved by patient selection, meticulous intra-operative technique and post-operative care. Modulation of portal vein pressures post-operatively may further help reduce the risk of liver failure.

7. Assessment of liver function for successful hepatectomy in patients with hepatocellular carcinoma with impaired hepatic function

Uchiyama K, Mori K, Tabuse K et al
J Hepatobiliary Pancreat Surg 2008; 15: 596-602

BACKGROUND/PURPOSE: This study aimed to construct a formula for assessing liver function in order to prevent post-hepatectomy liver failure. METHODS: A formula was constructed by analyzing data from 28 patients with hepatocellular carcinoma (HCC) with liver cirrhosis operated on between 1981 and 1984. Next, we evaluated the validity of this formula in 207 hepatectomy patients operated on from 1985 to 1999. For 145 hepatectomy patients operated on from 2000 to 2006, this formula was calculated before surgery in order to assess their risk of hepatectomy. RESULTS: The formula for liver functional evaluation, constructed from preoperative hepatic function parameters, was: liver failure score = 164.8 - 0.58 x Alb - 1.07 x HPT + 0.062 x GOT - 685 x K. ICG - 3.57 x OGTT. LI + 0.074 x RW, where Alb is albumin (g/dl); HPT, hepaplastin test (%); GOT, glutamate oxaloacetate transaminase (U/l); K. ICG, K value of indocyanine green clearance test; OGTT. LI, 60-min/120-min glucose level in 75-g oral glucose tolerance test. Linearity index of OGTT; and RW, weight of resected liver(g). We decided that a score below 25 would be safe for hepatectomy. CONCLUSIONS: The mortality rate decreased from 3.9% in 1985-1999 to 1.3% in 2000-2006. This finding allows us to conclude that the formula is valid for assessing the risk of post-hepatectomy liver failure.

8. Preoperative portal vein embolization for major liver resection; a meta-analysis

Abulkhir A, Limongelli P, Healey AJ et al Ann Surg 2008; 247: 49 -57

INTRODUCTION: Preoperative portal vein embolization (PVE) is used clinically to prevent postoperative liver insufficiency. The current study examined the impact of portal vein embolization on liver resection. METHOD: A comprehensive Medline search to identify all registered literature in the English language on portal vein embolization. Meta-analysis was performed to assess the result of PVE and its impact on major liver resection. RESULT: A total of 75 publications met the search criteria but only 37 provided data sufficiently enough for analysis involving 1088 patients. The overall morbidity rate for PVE was 2.2% without mortality. Four weeks following PVE, 85% patients underwent the planned hepatectomy (n = 930). Twenty-three patients had transient liver failure following resection after PVE (2.5%) but 7 patients developed acute liver failure and died (0.8%).The reason for nonresection following PVE (n = 158, 15%) included inadequate hypertrophy of remnant liver (n = 18), severe progression of liver metastasis (n = 43), extrahepatic spread (n = 35), refusal to surgery (n = 1), poor general condition (n = 1), altered treatment to transcatheter artery embolization or chemotherapy (n = 24), complete remission after treatment with 3 cycles of fluoracil and interferon alpha in a patient with hepatocellular carcinoma (n = 1), incomplete pre- or postembolization scanning (n = 8). Of those who underwent laparotomy without resection, (n = 27) reasons included intraoperative finding of peritoneal dissemination (n = 15), portal node metastasis (n = 2), severe invasion of the tumor to the hepatic artery and portal vein (n = 1), and gross tumoral extension precluding curative resection (n = 9).Two techniques were used for portal vein embolization: percutaneous transhepatic portal embolization,

(PTPE) and transileocolic portal embolization, (TIPE). The increase in remnant liver volume was much greater in PTPE than TIPE group (11.9% vs. 9.7%; P = 0.00001). However, the proportion of patients who underwent resection following PVE was 97% in TIPE and 88% PTPE, respectively (P = <0.00001). Although there was no significant difference in patients who had major complications post-PVE, the rate for minor complications was significantly higher among patients who had PTPE (53.6% vs. 0%, P = <0.0001). CONCLUSION: PVE is a safe and effective procedure in inducing liver hypertrophy to prevent postresection liver failure due to insufficient liver remnant.

9. Clinicopathological and intraoperative parameters associated with postoperative hepatic complications

Nanasimha A, Sumida Y, Abo T et al.
Hepatogastroenterology 2007; 54: 839-43

BACKGROUND/AIMS: To predict the risk of liver dysfunction associated complications after hepatectomy, we evaluated perioperative parameters in patients after hepatectomy. METHODOLOGY: We examined 185 consecutive patients who underwent hepatectomy for liver tumors. Background liver was normal liver in 73 patients, chronic viral hepatitis in 49, cirrhosis in 46 and icteric liver in 17. Postoperative complications associated liver dysfunction (long-term ascites, intraabdominal infection and hepatic failure) occurred in 70 (38%) patients. RESULTS: Univariate analysis identified 9 significant parameters associated with postoperative complications (resected volume > or = 50%, intraoperative bleeding volume > or = 1500 mL, liver activity at 15 min by technetium-99m galactosyl human serum albumin scintigraphy of < 0.85, alanine aminotransferase > or = 80 IU/L, total cholesterol < 150 mg/dL, prothrombin activity [PT] < 80%, Liver Damage grade B, histopathological activity index

[HAI] of > or = 8 and hyaluronic acid [HA] of > or = 150 ng/mL). Multivariate logistic regression analysis identified resected volume, intraoperative bleeding, PT and HA levels as four significant independent predictors of post-hepatectomy complication with odds ratios of 7.0, 4.4, 7.5, and 5.4, respectively. CONCLUSIONS: Preoperative assessment and correction of abnormal PT and HA, careful evaluation of resected volume and attempt to reduce intraoperative bleeding are important to avoid postoperative hepatic complications.

10. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study

Ferrero A, Vigano L, Polastri R et al.
World J Surg 2007; 31:1643-651

BACKGROUND: The future remnant liver (FRL) limit for safe major hepatectomy with low risk of postoperative liver failure has not yet been well defined. METHODS: Between April 2000 and September 2004, every patient scheduled for major hepatectomy in our institution underwent CT-volumetry of FRL. Patients with FRL <25% underwent portal vein embolization (PVE). Exclusion criteria were PVE, associated vascular resection and liver cirrhosis. The FRL was correlated with short-term results in patients with normal liver (group A) and those with impaired liver function secondary to neoadjuvant chemotherapy or cholestasis (bilirubin >2 mg/100 ml) (group B). Liver dysfunction was defined as both PT <50% and serum bilirubin level >5 mg/100 ml for three or more consecutive days. RESULTS: A total of 119 patients were analyzed, 72 in group A and 47 in group B. The FRL value was the only significant risk factor for postoperative liver dysfunction in the univariate and multivariate analysis (p = 0.009). The FRL did not correlate with postoperative mortality and morbidity. Bilirubin and prothrombin time (PT) on days 3 and 7 were significantly correlated to FRL in both

groups. In group A, patients with postoperative liver dysfunction had a FRL<30% (3 versus 0; p = 0.005). According to receiving operator characteristic (ROC) curve analysis, a FRL value of 26.5% predicted postoperative liver dysfunction with 66.7% sensitivity, 97.1% specificity, 50% positive predictive value (PPV), and 98.5% negative predictive value (NPV). In group B, patients with postoperative liver dysfunction had a FRL <35% (4 versus 0; p = 0.027). According to ROC curve analysis, a FRL value of 31.05% predicted postoperative liver dysfunction with 75% sensitivity, 79.1% specificity, 25% PPV, and 97.1% NPV. CONCLUSIONS: Hepatectomy can be considered safe when FRL is >26.5% in patients with healthy liver and >31% in patients with impaired liver function.

Bile Leaks After Hepatic Resection

- Cirrhosis and biliary leak LOE 2
- High incidence of bile leak in hepatic resections for left hepatectomy LOE 4
- Hepticojejeunostomy -Independent predictors of leakage LOE 2
- Use of Fibrin glue - incidence of bile leaks LOE 5
- Management of bile leaks LOE 3
- Redo surgery –Increased risk LOE 2
- Closure of persistent bile leaks using various agents LOE 4

Biliary leakage after hepatic resection and extra hepatic biliary tract surgery is a common complication, reported to range form 5% to 15% in various series. It is also a major cause of postoperative morbidity and mortality. Biliary leakage leads to prolonged hospital stay, need for higher antibiotics, repeated radiological imaging and repeated interventions in the form of percutaneous drainage and endoscopic stenting. It can lead to major electrolyte imbalance, nutritional deprivation, sepsis, liver dysfunction and death. Most bile leaks can be treated by conservative management or percutaneous drainage, but some may require exploration and control of the source of leak.

Yamashita et al have described bile leakage as the presence of macroscopic bile in surgical drains beyond seven days.

Types of Bile Leaks

Biliary leakage may occur from the biliary radicles on the hepatic cut surface after resection or anastomotic leakage from a hepaticojejeunostomy.

Risk factors

Risk factors for postoperative bile leakage and intra-operative methods to prevent it are still debatable.

Preoperative Characteristics

Advanced age

Diabetes Mellitus

Malnutrition

Obstructive Jaundice

Peripheral cholangiocarcinoma

Preoperative radiochemotherapy

Cholangitis

Cirrhosis is associated with a decreased risk

Intraoperative Factors

Major hepatectomy

Segment 1 & 4 resection

Left hepatectomy

Extensive hilar dissection

Dissection outside portal scissure

Adjunctive bilio-enteric anastomosis

Prolonged operative time

Increased blood loss

Anatomical and technical variability play an important role in the incidence of biliary leakage. Cirrhosis has been reported to be associated with a lower incidence of biliary leak (LOE 2b). However, surgical procedures in cirrhotic patients are less aggressive with very few patients undergoing major hepatectomies. Tanaka et al as well as Lorenzo reported a lower rate of bilary leak in cirrhotics (LOE 3).

The relationship between the type of hepatectomy and the risk of postoperative bile leak has not been defined clearly. A higher incidence of bile leak has been seen in hepatic resections for left hepatectomy by Lo et al, because of risk of damaging a right posterior biliary duct draining into the left hepatic duct (LOE 4). Yamashita et al. reported central hepatectomy, caudate lobectomy and resection of segments 4, 5 and 8 as high risk factors for bile leak (LOE 3).

The plane of parenchymal transection if extended outside the portal scissures led to higher rate of bile leak in the series reported by Lorenzo et al. There is no reported significant increase in bile leaks on comparing anatomical and non-anatomical resections.

Steve M.M de Castro et al. reviewed more than a thousand patients who underwent heapticojejeunostomy and identified a high body mass index, endoscopic biliary drainage and an anastomosis on the segmental bile ducts as independent predictors of leakage (LOE 2b).

Preventive Methods

There is no consensus regarding the factors to be taken into account to prevent bile leaks.

Common suggested methods incude:

Standardization of surgical technique

Intra-operative bile leak test

Intra-operative cholangiogram

Meticulous dissection

Attention to hemostasis

Confirmation of biliostasis

Suturing of identified/suspected transected bile ducts

Use of hemostatic agents on the cut surface

The role of intra-operative cholangiography or bile leakage tests for prediction of postoperative biliary leaks is debatable. The only randomized trial by Ijichi et al failed to demonstrate any significant difference in prediction of bile leak (LOE 2b). Fibrin glue and other hemostatic agents have been reported to decrease the incidence of bile leaks (LOE 5).

Management

Biliary complications of hepatic resection remain a significant problem in the postoperative period. Although the incidence of postoperative morbidity and mortality after hepatic resection has reduced significantly in the last two decades, the incidence of bile leak has remained the same. This may reflect the increase in complexity of the liver resections being performed. The management of bile leaks is becoming increasingly conservative and relaprotomy is needed only in cases of intractable leak, ascites and sepsis (LOE 3).

The methods commonly used in the management of bile leaks are:

Percutaneous drainage of bilioma

Percutaneous transhepatic biliary drainage with or without stenting

Endoscopic papillotomy with or without stenting

Ethanol injection

Biliary Embosclerosis with cyanoacrylate / acetic acid

Laser ablation

Surgical exploration

Many leaks associated with anastomosis are small and typically resolve without intervention. Larger leaks pose a more significant problem with increased postoperative abdominal pain and subsequent bile peritonitis, as well as a high mortality rate.

Radiological imaging in the form of computed tomography or ultrasound must be done in all cases of definite or suspected bile leak, as well as in patients with clinical features of intra-abdominal collection or early sepsis to document or rule out the presence of a biliary leak (LOE 5). Radiological techniques such a HIDA scan and fistulography are also used for detecting the source of leak. Once a leak is confirmed, it must be determined whether it is localized or diffuse.

Management of localized leaks focuses on minimally invasive techniques and percutaneous drainage either in the form of draining a bilioma or transhepatic drainage in cases of diffuse leaks is safely employed. Transhepatic drainage is feasible even if the intrahepatic biliary radicles are not dilated. Some authors such as Shanatanu B et al prefer the endoscopic route for biliary drainage by a papillotomy and establishing drainage into the duodenum (LOE 4).

There are no standard guidelines in literature regarding the duration for which conservative management should be employed, but most case series have reported continuation of non-surgical methods as long as the drainage continues to decrease or till the patients has clinical evidence of infection or sepsis (LOE 2).

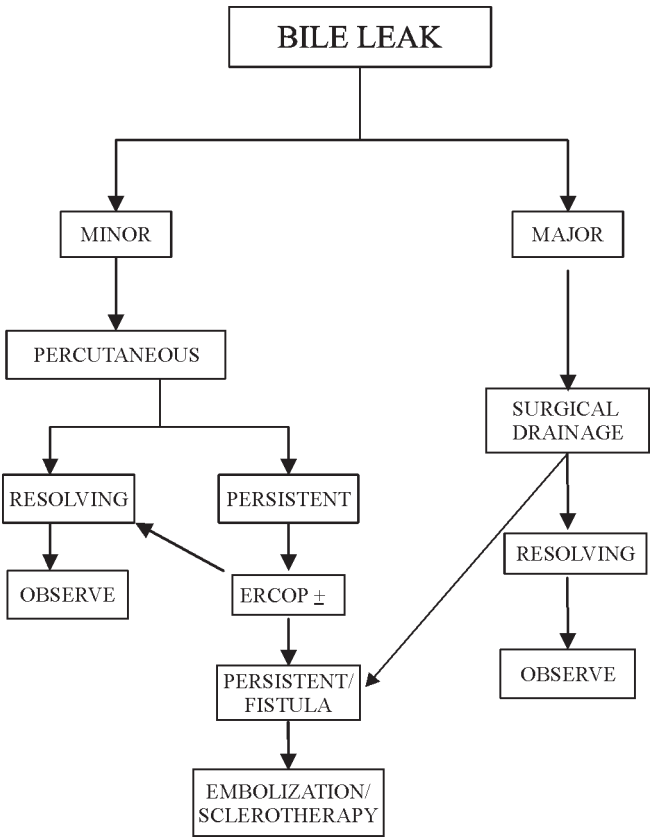
Copious biliary drainage in the immediate post-operative period may signal an injury to major duct or technical failure in a hepaticojejeunostomy, and warrants early surgical exploration to prevent the development of adhesions, sepsis and liver dysfunction. Yamashita et al have advocated identification of perioperative risk factors for postoperative bile leakage as in their experience; redo surgery carried a very

high risk of morbidity and mortality due to traumatization of tissues, increased bleeding and inadequate liver function (LOE 2b).

Recalcitrant or persistent bile leaks, bilio-cutaneous fistulae may also requie surgical intervention if a prolonged conservative approach fails. However, Wael EA Saad et al. have described closure of persistent bile leaks and fistulae using embolization with various sclerosing agents such as ethanol, cyanoacrylate, acetic acid and ablation of persistent biliary fistulae (LOE 4). Investigational methods include the use of laser and cryotherapy as described by Eicher CA et al.

Conclusions

Bile leak is a common complication after hepatic resection, with various general, anatomical and technical risk factors with a significant postoperative morbidity. Preventive methods are not well defined but general principles such as more careful surgical procedures and the use of intraoperative biliary leakage tests in high risk cases may be employed. Most leaks respond to a trial of conservative management in the form of percutaneous or endoscopic drainage, but some may require surgical intervention. With advances in minimally invasive techniques such as intervention radiology and endoscopic procedures, the indications for surgical management are limited.


BILE LEAK
MINOR
MAJOR
PERCUTANEOUS
SURGICAL DRAINAGE
RESOLVING
PERSISTENT
RESOLVING
OBSERVE
ERCOP ±
OBSERVE
PERSISTENT/ FISTULA
EMBOLIZATION/ SCLEROTHERAPY

1. Incidence and Management of Bile Leakage after Partial Liver Resection

D. Erdogan, O.R.C. Busch, O.M. van Delden et al. Dig Surg 2008;25:60-6.

Background/Aims*:* Bile leakage after partial liver resection still is a common complication and is associated with substantial morbidity and even mortality. Methods: A total of 234 consecutive liver resections without biliary reconstruction, performed between January 1992 and December 2004, were analyzed for postoperative bile leakage. Results: Postoperative bile leakage occurred in 6.8% of patients (16/234). In univariate analysis, male gender (p = 0.037), major liver resection (p = 0.004), right-sided hepatectomy (p = 0.005), prolonged operation time (p = 0.001), intraoperative blood loss >500 ml (p = 0.009), red cell transfusion (p = 0.02), tumor size (p = 0.026), duration of vascular occlusion (p = 0.03) and surgical irradicality (p = 0.001) were risk factors. No independent risk factors were associated with bile leakage after liver resection. Bile leakage originated from the resection plane in 10 patients (63%). Endoscopic biliary decompression was performed in 9 patients as initial treatment, and percutaneous drainage of the bile collection was used in 4 patients. Bile leakage resolved spontaneously in 3 patients. Conclusions: Bile leakage is a persisting complication and in this study occurred in 6.8% of patients after partial liver resection. Percutaneous drainage of bile collection with or without endoscopic biliary decompression are effective interventions in the management of most cases of bile leakage.

2. Bile leak after hepatectomy : Predictive factors of spontaneous healing

Luca Viganò M.D, Alessandro Ferrero M.D, Enrico Sgotto M.D et al. Am J of Surg 2008; 196:195-200.

Background: Bile leakage after hepatectomy usually has

spontaneous healing, but some patients require interventional procedures. To identify early predictive factors of conservative management failure. Methods: This study focused on patients with bile leak after hepatectomy without extrahepatic biliary resection from 1996 through 2006. Results: Bile leakage occurred in 34 of 593 patients (5.7%). Conservative management was successful in 26 patients (76.5%). At univariate analysis overall associated resections, vascular associated resections, and drainage output on days 1, 3, and 10 from leak onset were significant negative predictors of spontaneous healing. At multivariate analysis drainage output greater than 100 mL on day 10 was the only independent prognostic factor of conservative management failure (relative risk, 55.985; $P = .008$) with 80% sensitivity, 93.3% specificity, and 90% accuracy. Conclusions: Wait-and-see treatment is successful in most cases. Patients with drainage output greater than 100 mL 10 days after bile leakage diagnosis should be scheduled for interventional treatments.

3. Incidence and management of bile leakage after hepatic resection for malignant hepatic tumours.

Tanaka S, Hirohashi K, Tanaka H et al. J Am Coll Surg 2002;195:484-89.

Background: Bile leakage is one of the frequent and disturbing complications of hepatic resection. Study Design: Clinical records of the 363 patients who underwent hepatic resections without biliary reconstruction for hepatic cancers between January 1994 and June 2001 were reviewed. Postoperative bile leakage was defined as continuous drainage with a bilirubin concentration of 20 mg/dL or 1,500 mg/d lasting 2 days. Leakage that continued longer than 2 weeks or that required surgical intervention was defined as uncontrollable. Differences in incidence and frequency of uncontrollable leakage for the different types of hepatic resection, tumors,

and underlying liver disease were investigated. Outcomes after treatment for uncontrollable bile leakage were also reviewed. Results: Postoperative bile leakage occurred in 26 of 363 patients (7.2%). Although the incidence in patients with cholangiocellular carcinoma (3/9 [33%]) was higher ($p = 0.03$) than in patients with hepatocellular carcinoma, rates of occurrence were similar among the different types of hepatic resection and underlying liver disease. Eight of the 26 patients (31%) had uncontrollable leakage. Two patients required reoperation to control leakage; one of these developed hepatic failure and died 2 months after surgery. Four patients underwent endoscopic nasobiliary drainage 21 to 34 days after hepatectomy, and the leakage resolved within 3 to 21 days. Fibrin glue sealing was effective in two patients whose leaking bile ducts were not connected to the common bile duct. Conclusions: Although meticulous surgical technique can minimize the risk of postoperative bile leakage, some instances of leakage are unavoidable. Nonsurgical treatments, such as nasobiliary drainage or fibrin glue sealing, are preferable to reoperation.

Section — IV

Pancreas

Contributors

PJ Shukla

SV Shrikhande

MA D'Souza

K Singh

Complications of Pancreatic Resection

- Octreotide- Pancreatic fistula and other complications LOE 1
- Octreotide in patients considered to have high risk LOE 3
- Pancreaticojejunostomy (PJ) versus pancreaticogastrostomy (PG) LOE 1
- Pancreatic duct occlusion LOE 1
- Stenting of the main pancreatic duct LOE 1
- Role of magnification in pancreatic anastomosis LOE 3
- Blood supply based technique of PJ LOE 3
- Duct-to-mucosa versus invagination anastomosis LOE 1
- Stapled or hand-sewn closure of the pancreatic remnant after distal pancreatectomy LOE 1
- Comparison of postoperative complications between Pylorus preserving Pancreaticoduodenectomy (PPPD) vs Classical Whipple (cW) LOE 1
- Comparison of postoperative complications between standard and extended resection for pancreatic cancer LOE 1

Pancreatic resectional surgery is technically demanding. Due to the physiological function and anatomy of the pancreas, and the close proximity of celiac and mesenteric vascular systems, complications of pancreatic surgery can be particularly devastating. Despite considerable improvements in surgical techniques and postoperative care leading to a greatly reduced mortality (<5%), the rate of post-operative complications remains persistently high at 30-50%. The main causes of death are post-operative hemorrhage, sepsis due to leakage of the pancreaticoenteric anastomosis after pancreaticoduodenectomy (PD) and cardiovascular and pulmonary complications. Most postoperative complications respond to conservative medical management and radiological and endoscopic interventions. Complications that require re-surgery (2–4%) are associated with a very high mortality up to 70%.

Complications after Pancreatectomy

1. Surgical

Pancreatic fistula / leak (PF)
Hemorrhage
Fluid collection
Abscess
Delayed gastric emptying
Biliary/ Enteric Fistula
Postoperative pancreatitis
Cholangitis
Wound infection

2. Medical

Cardiovascular (angina, myocardial infarction, arrhythmias, stroke, deep venous thrombosis and pulmonary embolism)

Respiratory (atelectasis, pneumonia, respiratory insufficiency)

Renal failure

Hepatic and metabolic disturbances

1. Pancreatic Fistula (PF)

The single most significant cause of morbidity and mortality after pancreatectomy is the development of a pancreatic fistula. The occurrence of a PF increases the length of hospital stay and costs, necessitates additional investigations and procedures, and can cause life threatening complications. Even so there is no universally accepted definition of PF to standardize reporting and compare outcomes between centers. The reported incidence of PF ranges from 2–24%.

Definition

Varying definitions have been used in the past to document PF. The International Study Group on Pancreatic Fistula (ISGPF) definition was intended to standardize the reporting of postoperative PF. The essential components of the ISGPF definition of an anastomotic leak were high amylase content (> 3 times the upper normal serum value), and the presence of fluid, irrespective of the volume, at any time after the 3rd postoperative day. The ISGPF definition has also graded PF (Grades A, B and C) according to the clinical impact on the patient's hospital course and outcome. In a recent publication by Strasberg *et al*, intra abdominal collections along with hemorrhage and peritonitis are all looked upon as a result of pancreatic anastomotic failure. Also, they sought to redefine pancreatic fistulae as 'pancreatic anastomotic failures' (PAF) which includes the entire spectrum of clinically relevant problems that may occur when there is loss of integrity of a pancreatico-enterostomy. They also sought to distinguish fistulae that occur following distal pancreatectomy (DP) or segmental resections or enucleations which did not involve a

pancreatico-enterostomy as a separate entity from PAF. These were termed as pancreatic occlusion failure (POF). POF commonly runs a more benign course (compared to PAF) since enzyme activation does not occur in the absence of a pancreatic anastomosis. Strasberg also states that the definition of PAF should essentially include patients in whom there is a change in management and that asymptomatic fistulae with merely high drain amylase and no change in clinical course should not be considered as an operative complication as proposed by the ISGPF definition. They thus defined PAF and graded its severity into 7 categories in 5 grades based on the Clavien system of grading complications after pancreatic surgery (Table 2). They proposed the adoption of the definition of PF used by the Johns Hopkins group. Furthermore, according to this paper any intra-abdominal fluid collection after pancreatic surgery is a PAF if it cannot be shown to originate from a failure of the other anastomoses performed during a PD and any hemorrhage is PAF unless the pancreatico-enterostomy is shown to be intact.

Clinical Picture

Many leaks are insignificant without clinical symptoms, some can manifest as a pancreatico-cutaneous fistula, a peripancreatic collection or abscess or as delayed gastric emptying, while some present with retroperitoneal sepsis or hemorrhage and death. The suspicion of PF begins whenever there is a deviation in the normal clinical course of a patient who has just undergone a major pancreatic surgery. This may mean a patient who develops unexpected upper abdominal discomfort (often associated with fever), leucocytosis, increasing tachycardia, or just feels unwell after an apparently "normal" initial post-operative recovery. Furthermore, there may be high amylase content of a drain, a persistently high drain output, altered drain color and quality, and other complications such as severe wound infection and hemorrhage.

Table 1

ISGPF Definition: " Output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than 3 times the upper normal serum value"

Grade A	No clinical impact	Absence of peri-pancreatic collections on CT scan; Little / No change in management	Clinically well; no sepsis; no prolongation of hospital stay; delayed removal of operatively placed drains
Grade B	Clinical impact	Drains in place or repositioned to drain collections; Change in management is required	Clinically fairly well; infection requiring specific treatment; prolongation of hospital stay; patients may be discharged with drains in situ and observed in outpatient setting
Grade C	Severe clinical impact	Worrisome peri-pancreatic collections that require percutaneous drainage; Major change in management; ICU care required; possible re-surgery to salvage intractable PF (completion pancreatectomy etc)	Clinical unwell; sepsis requiring aggressive treatment, octreotide and other intensive care support; major prolongation of hospital stay; Associated complications and possibility of mortality

Diagnosis

a. Clinical evaluation

b. Labarotory tests – Drain Amylase, Blood chemistry, CRP

c. Imaging - CT scan
- ERCP
- MRCP
- Fistulography

Routine radiologic evaluation is neither necessary nor recommended for establishing a diagnosis of PF

Preventive Strategies for PF

1. Pharmacological approach to prevent anastomotic leakage- Role of Octreotide and somatostatin analogues.

Octreotide is a synthetic analogue of somatostatin and like somatostatin inhibits pancreatic exocrine secretion. Several prospective randomized controlled trials (RCTs) conducted in Europe evaluated the use of subcutaneous octreotide/ somatostatin in patients undergoing elective pancreatic resection for different indications. The results show that octreotide reduced the development of pancreatic fistula and other complications (Level of evidence - LOE 1). However RCTs by Sarr et al., Yeo et al. and Lowy et al., conducted in the USA failed to show a similar benefit in the peri-operative use of somatostatin analogues in patients undergoing pancreatic resection (LOE 1). Meta-analysis and systematic reviews of octreotide use have also yielded conflicting results (LOE 1). Marked differences in study design and differences in surgical techniques between institutions may account for the variation in outcomes in the above studies. Selective administration of octreotide in patients considered to have high risk pancreas (soft texture, small duct size, and presence of ampullary,

duodenal, cystic or islet cell pathology) may be associated with a decreased incidence of PF (LOE 3).

2. Surgical modifications to prevent anastomotic leakage

Type of pancreatic anastomosis: Pancreaticojejunostomy (PJ) versus pancreaticogastrostomy (PG)

The safe reconstruction of pancreatico-enteric continuity is the key to preventing a PF. PJ and PG are the two most commonly employed techniques for the reconstruction of pancreatico-enteric continuity. PJ can be performed by the dunking method or the duct-to mucosal anastomosis. Earlier uncontrolled studies were in favor of PG. Due to the close proximity of the stomach, a PG was believed to be easier to perform and less prone to ischemia as a result of the rich blood supply of the stomach. However, all the RCTs have failed to show any difference in the overall post-operative complication rate or incidence of PF. Two recent meta-analyses have shown that while non randomized observational studies showed a superiority of PG over PJ, RCTs failed to show superiority of any one technique, thereby concluding that both PJ and PG provided equivalent results (LOE 1).

Pancreatic duct occlusion

Occlusion of the pancreatic duct can be achieved by simple suture ligation of the duct or injection of the duct with non-reabsorbable or reabsorbable glues. Simple duct ligation, advocated in the past, has been largely abandoned due to high PF rates, nearing 50%. However in a recent prospective randomized controlled trial (RCT) by Tran et al. which compared pancreaticojejunostomy with duct occlusion alone there were no significant differences in the morbidity or mortality (LOE 1), but the incidence of diabetes mellitus was higher in patients with duct occlusion. In a study on 51 patients,

Di Carlo et al. used non reabsorbable glue (neoprene) to occlude the pancreatic duct after PD. The authors concluded that intraductal injection of Neoprene after pancreaticoduodenectomy was a safer procedure compared to pancreaticojejunal anastomosis and was not associated with post surgical diabetes (LOE 3).

Stenting of the main pancreatic duct

Stenting of the pancreatic duct during pancreaticoenteric anastomosis facilitates the precise placement of mucosal sutures, diverts pancreatic juice away from the anastomotic site and decreases the risk of inadvertent pancreatic duct occlusion. In doing so, it is believed that the anastomotic integrity improves, thereby reducing the PF rate. The results of this strategy have been encouraging. In a prospective but non-randomized trial in 85 patients, Roder et al. demonstrated that stenting the pancreatic duct reduced the PF rate from 68% to 29.3%, and the median hospital stay from 29 d to 13 d (LOE 2). Poon et al. reported that external drainage of the pancreatic duct with a stent reduced the leakage of PJ after PD (LOE 1). On the other hand, some well designed studies have shown no benefit of internal stenting in preventing PF. Thus the available evidence is conflicting and the use of stents depends on personal choice and experience of the pancreatic surgeon.

Role of magnification in pancreatic anastomosis

Since a duct to mucosa anastomosis is crucial for good outcome, a meticulous approximation assumes great importance. Operating loupes have been used by many experts to allow precise construction of a pancreatic anastomosis. Traverso et al in a retrospective analysis highlighted the role of the operating microscope in constructing a pancreatic anastomosis. Technical errors which may occur during anastomosis include crossing of the sutures, including both

sides of the pancreatic duct while passing the suture, taking unequal and inadequate amounts of pancreatic duct and jejunal mucosa, and incorrect knot placement resulting in air knots. All these events can be avoided by using magnification. The study by Traverso, reported a markedly reduced incidence of PF with the operating microscope compared to operating loupes (LOE 3).

Blood supply based technique of PJ

One of the few modifications which have demonstrated a substantial reduction in the rate of PF after PD was proposed by Strasberg et al. These workers put forward the concept of vascular watershed in the pancreatic neck and its role in ischemia of the cut surface of the pancreatic remnant. In their technique, the blood supply at the cut surface of the pancreas was evaluated, and if necessary, the pancreas was cut back 1.5 cm to 2.0 cm to improve the blood supply (n = 47; 38% patients). Thereafter, the anastomosis was performed meticulously under magnification. The authors concluded that a combination of optimization of blood supply to the pancreatic remnant, and a meticulous technique resulted in reduced PF rate, from previous reports of 10% to 1.6% in their series of 123 resections (LOE 3).

Duct-to-mucosa versus invagination anastomosis

A number of studies have demonstrated a lower rate of PF using the duct-to-mucosa technique for pancreatic anastomosis. However, a prospective RCT by Bassi et al. revealed no significant difference in the morbidity and PF rate between duct-to-mucosa anastomosis and single layer end-to-side pancreaticojejunostomy (LOE 1).

Total pancreatectomy

The rationale for total pancreatectomy is that it allows a more extensive lymphadenectomy, obviates the risk of leak from

the pancreatic anastomosis and decreases the chances of a positive resection margin. However, total pancreatectomy is associated with obligatory diabetes mellitus, decreased immunity because of splenectomy, and loss of pancreatic exocrine function. Most studies have reported either worse survival or no survival difference between total pancreatectomy and standard PD. Total pancreatectomy should not be performed in most cases of carcinoma of the pancreatic head, unless serial positive resection margins are obtained on frozen section examination, or the pancreas is deemed to be very soft with a very high risk of pancreatic leak, and in patients with documented family history of multi-centric disease.

Stapled or hand-sewn closure of the pancreatic remnant after DP

PF remains a major cause of morbidity after DP. A number of techniques have been used to reduce the incidence of PF after DP, including hand-sewn closure, staple closure, combined staple and suture closure, fibrin glue application, serosal jejunal patch and prolamine injection. While hand-sewn closure has stood the test of time, the use of staplers is gaining increasing acceptance, especially with the advent of laparoscopic DP. Knaebel et al performed a meta-analysis that included six studies comparing stapler versus hand-sutured closure, which showed a non-significant combined odds ratio for pancreatic fistula of 0.66 (95% confidence interval 0.35 to 1.26, P = 0.21) in favor of staple closure (LOE 1). However, a large retrospective study of 302 DP's, showed that stapler closure was associated with a higher rate of PF. Thus, the jury is still out and surgeons must follow their own individual experience when dealing with pancreatic remnant after DP. In hand sewn closure, the guiding principle is to make every effort to identify the pancreatic duct, close it with fine sutures and then close the entire stump with sutures (LOE 3).

Management of PF

A diagnosis of PF once established, aggressive and appropriate conservative management is the key to successful outcome. The management in the majority of patients is based on conservative measures. However, interventional radiological assistance is sometimes required, with re-surgery being needed for emergent situations or for intractable PF.

Conservative Management

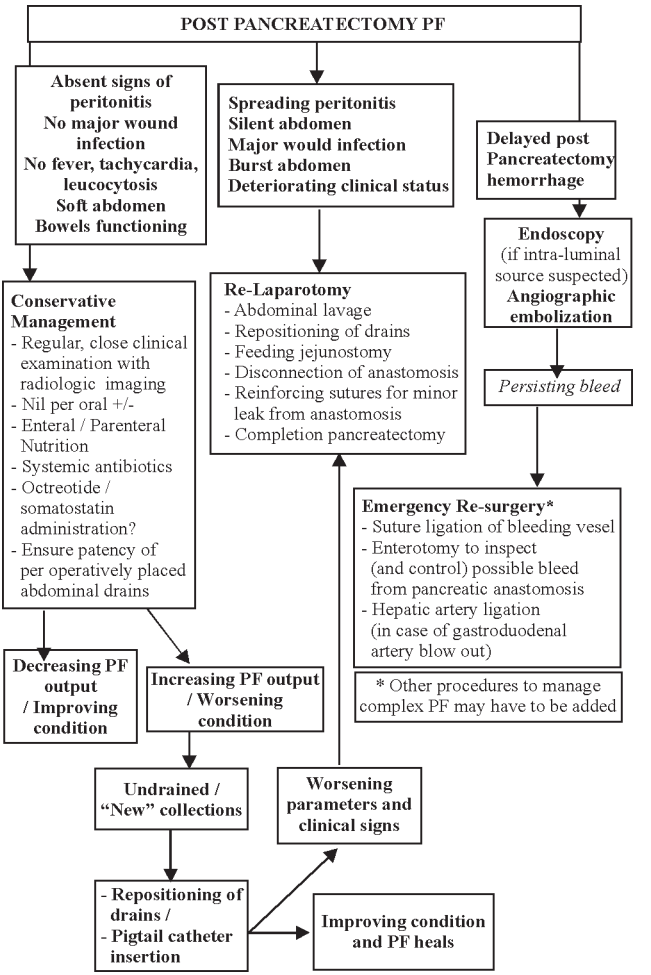
A conservative approach to the management of PF is successful in over 90% patients. This involves clinical evaluation of the patient at short intervals. If the patient does not have any fever, tachycardia, leucocytosis, severe wound infection, and the abdomen is soft (with functioning bowel), and no signs of peritonitis, it is safe to continue with conservative measures. These measures include maintenance of enteral nutrition (through an operatively placed nasojejunal tube or a feeding jejunostomy), nasogastric suction (in the presence of delayed gastric emptying secondary to PF), and appropriate antibiotic coverage. In situations where the abdomen has not "really settled", the option of total parenteral nutrition should be considered. All along, the abdominal drains and the main wound require close attention. The effectiveness of octreotide in aiding the closure of a PF has not provided encouraging results. The interventional radiologist may play a crucial role by image-guided repositioning of operatively placed drains and insertion of percutaneous catheters to drain collections seen on CT scan. Delayed hemorrhage following PF is perhaps best managed by angiography and embolisation of the bleeding vessel. This treatment is successful in stopping the bleeding in 80% patients. The prognosis of patients with post-pancreatectomy hemorrhage depends on whether or not PF is present. The decision-making should be guided by factors such as the time of onset of the bleeding, presence of PF, vascular

pathology, and the underlying disease process. The failure to successfully control hemorrhage by conservative measures like angiographic embolisation may necessitate repeat surgery. Obviously, the management of complications associated with PF requires a multidisciplinary approach, involving the pancreatic surgeon, intensive care team, and interventional radiologists. Reber et al evaluated 437 patients who underwent PD. A total of 55 (12.6%) developed PF; 52 patients (94.5%) had successful conservative management with prolonged tube drainage, 4 required percutaneous drainage and only 3 patients (5.5%) had repeat surgery (LOE 3).

Operative Management

PF can be successfully managed by conservative measures, as described earlier. The indications for surgical intervention in PF include worsening clinical parameters, signs of spreading peritonitis, severe wound infection, wound dehiscence, and delayed hemorrhage. When a decision is made to reoperate a patient with PF, the following measures should be considered: abdominal lavage with repositioning of drains, control of hemorrhage, use of sutures to control a small dehiscence, disconnection of the pancreatic anastomosis, a feeding jejunostomy (if not already in place) and occasionally completion pancreatectomy. In patients with delayed hemorrhage who require repeat surgery, a thorough exploration of the resection site is required and if necessary, ligation of the arterial stumps (including occasionally the common hepatic artery) and inspection of the anastomosis by enterotomy. It is worth noting that with improvements in the results of pancreatic surgery and the success of interventional radiology in managing complications, completion pancreatectomy is seldom required, and it has even been suggested that it should no longer be considered in patients with a PF. The approach to the management of a patient with PF is summarized in Figure1.

Figure 1


POST PANCREATECTOMY PF
Absent signs of peritonitis
No major wound infection
No fever, tachycardia, leucocytosis
Soft abdomen
Bowels functioning
Spreading peritonitis
Silent abdomen
Major would infection
Burst abdomen
Deteriorating clinical status
Delayed post Pancreatectomy hemorrhage
Endoscopy
(if intra-luminal source suspected)
Angiographic embolization
Conservative Management
- Regular, close clinical examination with radiologic imaging
- Nil per oral +/-
- Enteral / Parenteral Nutrition
- Systemic antibiotics
- Octreotide / somatostatin administration?
- Ensure patency of per operatively placed abdominal drains
Re-Laparotomy
- Abdominal lavage
- Repositioning of drains
- Feeding jejunostomy
- Disconnection of anastomosis
- Reinforcing sutures for minor leak from anastomosis
- Completion pancreatectomy
Persisting bleed
Emergency Re-surgery*
- Suture ligation of bleeding vesel
- Enterotomy to inspect (and control) possible bleed from pancreatic anastomosis
- Hepatic artery ligation (in case of gastroduodenal artery blow out)
* Other procedures to manage complex PF may have to be added
Decreasing PF output / Improving condition
Increasing PF output / Worsening condition
Undrained / "New" collections
Worsening parameters and clinical signs
- Repositioning of drains /
- Pigtail catheter insertion
Improving condition and PF heals

2. Post-pancreatectomy hemorrhage (PPH)

Postoperative haemorrhage occurs in 2–15% of patients following pancreatic resection and has a reported mortality between 14 to 38%. The spectrum of PPH is varied; and this is due to differences in the onset and intensity of PPH, underlying diseases, type of operation, co-existent PF, extraluminal or intraluminal manifestation of bleeding, presence of a "sentinel" bleed, and vascular irregularities like arterial erosions and pseudoaneurysms.

Definition

The International Study Group of Pancreatic Surgery (ISGPS) developed an objective, generally applicable definition of PPH based on a literature review and consensus clinical experience (Table 3). Postpancreatectomy hemorrhage is defined by 3 parameters: onset, location, and severity. The onset is either early (< or =24 hours after the end of the index operation) or late (>24 hours). The location is either intraluminal or extraluminal. The severity of bleeding may be either mild or severe. Three different grades of PPH (grades A, B, and C) are defined according to the time of onset, site of bleeding, severity, and clinical impact.

Clinical Picture

Patients with PPH present with signs and symptoms of hemodynamic instability often requiring administration of blood and blood products. Blood may be present in the nasogastric tube and/or the abdominal drains. A "sentinel bleed" is defined as the presence of blood in the drain or gastrointestinal hemorrhage without obvious cause, 24 h prior to an episode of delayed massive hemorrhage. Often the patient has a concomitant PF with accompanying sepsis and the sentinel bleed is of great significance in such patients.

Table 3. Proposed classification of PPH: clinical condition, diagnostic and therapeutic endoscopy consequences

Grade	Time of onset, location, severity and clinical outcome of bleed		Clinical condition	Diagnostic investigations consequence	Therapy endoscopy
A	Early, intra or extraluminal mild		Well	Observation, hemogram, USG and if necessary CT scan	No
B	Early, intra or extraluminal severe	Late, intra or extraluminal, mild	Often well/ intermediate Very rarely life-threatening	Observation, hemogram, USG, angiography, CT scan, endoscopy	Transfusion of fluid/blood, ICU, therapeutic embolisation relaparotomy for early PPH
C		Late intra or extraluminal,	Severely impaired life-threatening	Angiography, CT endoscopy	Localisation of bleeding, angiography and embolisation, (endoscopy) or relaparotomy, ICU

Diagnosis

a. Clinical evaluation

b. Laboratory investigations- Hemogram, Blood chemistry

c. Upper Gastrointestinal endoscopy

d. Radiology – Ultrasound

CT scan

Visceral angiography with selective embolisation

Management (Figures 2 and 3)

1. Early PPH

Early hemorrhage is usually due to technical failure and endoscopy may help to identify the site of bleed. After adequate resuscitation of these patients intraluminal bleed may be managed by a trial of conservative management, including therapeutic endoscopic intervention. Extraluminal bleed may also be managed conservatively initially. However most patients with early PPH require emergency laparotomy.

In case of bleeding from the pancreaticojejunostomy, the jejunal loop is opened opposite to the side that is anastomosed to the pancreas by performing an enterotomy, so that the entire cut surface of the pancreas with the anastomosis is open for examination and the bleeding site can be identified, the vessel identified and under run, followed by a 2 layer closure of the opened jejunum. If the bleeding is from the gastrojejunostomy then an initial attempt to manage small ooze with injection of saline adrenaline or by argon plasma coagulation can be made. Failure of endoscopic intervention or other conservative measures warrants relaparotomy. The anterior wall of the stomach is opened proximal to the anastomosis, removal of blood clots, identification of the bleeding vessel, and placement of appropriate sutures to control the hemorrhage.

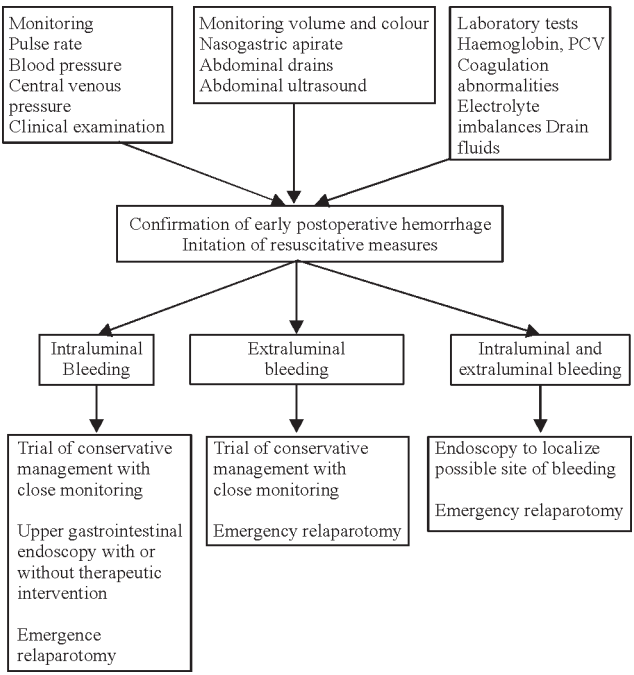
In extraluminal hemorrhage the possible sources of major bleeding are the GDA, inferior pancreaticoduodenal artery, SMA and the portal veins. If the patient fails to stabilize after a trial of conservative management, relaparotomy has to be undertaken without delay. Clot removal, an abdominal wash with warm saline, and careful suctioning enables to identify the bleeding source which tackled with hemostatic clamps followed by transfixation with prolene suture. Often after a thorough abdominal lavage, no specific source of bleeding can be identified; in that case a careful examination of all potential sites followed by precise placement of abdominal drains to detect any re-bleeding that may occur later.

2. Delayed PPH

Delayed massive haemorrhage, especially when associated with pancreatic or bile leak or sepsis, should raise the suspicion of a ruptured pseudoaneurysm. The recommended intervention includes computed tomography scan and selective angiography which offers the option of embolization. Transcatheter arterial embolization (TAE) has been efficacious for the treatment of pseudoaneurysms associated with pancreatitis and post-PD. Emergency surgery for pseudoaneurysms is hazardous and remains the option for haemodynamically unstable patients in whom conservative measures have failed. Surgery has the dual potential of being able to control the hemorrhage as well as deal with sepsis Indications are massive hemorrhage leading to collapse and significant intra-abdominal sepsis associated with hemorrhage. Basic principle is hemostasis and drainage. The vessel is ligated proximally and distally preferably away from the infected region where the tissues may be inflamed and very friable. In wide anastomotic disruption with bleeding pancreatic stumpdirect suturing should be done to achieve hemostasis. If site of blleding is not found, enterotomy should be done to look at one or more of the serosal suture lines which may be the source of bleeding. In case of complete

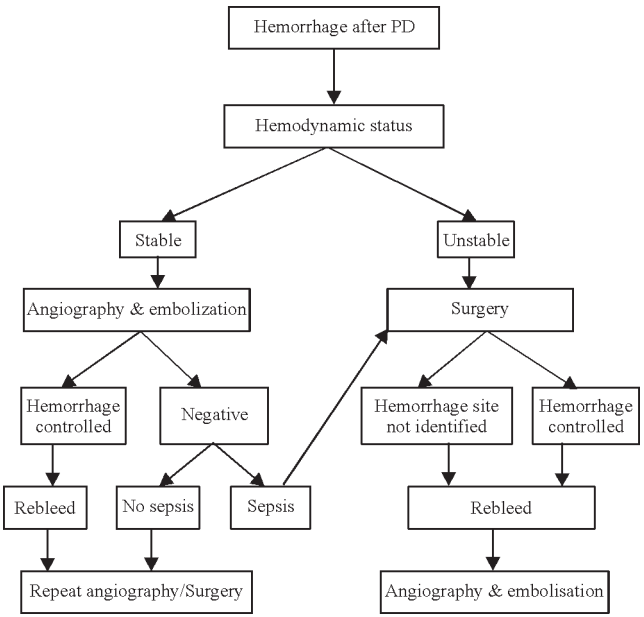
disruption of the pancreaticojejunal anastomosis resuturing is not good in presence of edematous friable tissueCompletion pancreatectomy- the technical difficulties of this procedure in a sick septic and unstable patient combined with the problems of postoperative brittle diabetes argue against this procedure. It should only be used in cases of necrotic pancreas with extensive retroperitoneal sepsis.

Figure 2. Suggested algorithm for treatment of early post PD hemorrhage



(from: Surgery of Pancreatic Tumors by Shrikhande SV et al. (eds), BI Publications, New Delhi 2007)

Figure 3. Suggested algorithm for treatment of late post PD hemorrhage



3. Delayed Gastric Emptying (DGE) after PD

According to definition DGE is said to occur when the nasogastric (NG) tube is left in place for 10 or more days, plus one of the following: emesis after removal of the NG tube, reinsertion of the NG tube, post-operative use of prokinetic agents after the tenth post-operative day or failure to progress with diet. An ISGPS definition with 3 clinical grades based on clinical impact and management has been proposed. Horstmann et al. showed that patients without other complications had a DGE rate of 1% but in the presence of

moderate and severe post-operative complications this rate climbed to 28% and 43% respectively. It is a perception that an intact pylorus leads to a greater incidence of DGE after PD but comparing the incidence of DGE after classical Whipple's and pylorus preserving PD, the results suggest that both procedures are equivalent as regards the occurrence of DGE.

Alternate techniques have been used to reconstitute gastrointestinal continuity after PD with an aim to decrease the incidence of DGE, including use of an undivided Roux-en-Y loop for reconstruction and pyloric dilatation. However there is level 1 evidence that antecolic reconstruction (as opposed to retrocolic duodenojejunostomy/ gastrojejunostomy) is associated with a significantly reduced DGE rate (LOE 1). This is because an antecolic reconstruction avoids the possible torsion or angulation that may occur with a retrocolic anastomosis. There is also convincing evidence that DGE can be reduced by up to 37% with intravenous erythromycin (LOE 1).

4. Enteric and biliary fistula after PD

Biliary and enteric fistulae are uncommon after PD. Biliary fistula occurs in 0.4–4% and indicates leakage from the hepaticojejunostomy. Most biliary fistulae resolve spontaneously with conservative management or non-operative intervention with percutaneous drainage and transhepatic biliary stenting. Early high output biliary fistulae usually require re-operation.

Enteric fistulae occur in 0.4–7.4% and usually indicate a leakage from the gastrojejunostomy. Conservative management including the maintenance of drains, percutaneous drainage, total parenteral or enteral nutrition and the use of octreotide is usually sufficient to heal these fistulae. A re-operation is necessary in if the fistula persists and causes sepsis.

Comparison of postoperative complications between Pylorus preserving pancreaticoduodenectomy (PPPD) vs Classical Whipple (cW)

In a prospective, multi-centre, randomized study by Tran et al, PPPD was compared with cW in 170 consecutive patients. Both procedures were comparable with regards to operative time, blood loss, hospital stay, morbidity, mortality and incidence of DGE. There were also no significant statistical differences between the two groups with regards to overall and disease free survival. In a recent meta-analysis of 2822 patients by Kocher et al., both cW and PPPD had similar morbidity rates, with PPPD having lower mortality and improved long term survival which however was not reflected in the sub group analysis (LOE 1). In a recent Cochrane database systematic review of seven RCTs the authors concluded no relevant differences in mortality, morbidity and survival between PPPD and the cW (LOE 1).

Both PPPD and cW are recommended operations for resectable periampullary and pancreatic head tumors. As a general guideline, the cW is reserved for patients with larger, more extensive tumors or when the tumor is located in the dorsal part of the head of the pancreas or first part of the duodenum.

Comparison of postoperative complications between standard and extended resection for pancreas cancer

Two trials have addressed the role of extended lymphadenectomy. A multicentre,

randomised trial from Italy compared conventional PD with and without extended lymph node resection; 40 patients were randomised to conventional resection and 41 were randomised to additional lymphadenectomy and retroperitoneal soft tissue clearance. There were no significant differences regarding perioperative morbidity and mortality (LOE 1).

The Johns Hopkins group randomised 56 patients with peripancreatic adenocarcinoma to a standard PD and 58 patients to radical PD. Perioperative morbidity and mortality were not significantly different between the two groups. The updated results in 2002 showed 146 patients in the standard PD arm and 148 in the extended PD group. Perioperative mortality was similar in the two groups but the overall complication rate was significantly higher in the extended pancreatoduodenectomy arm (43% vs. 29%, p = 0.01) (LOE 1). Radical pancreatoduodenectomy was not associated with a survival benefit (three year survival of 38% vs. 36% respectively).

References

1. **Postoperative pancreatic fistula: an international study group (ISGPF) definition. Bassi C, Dervenis C, Butturini G et al. International Study Group on Pancreatic Fistula Definition. Surgery. 2005;138:8-13.**

BACKGROUND: Postoperative pancreatic fistula (POPF) is still regarded as a major complication. The incidence of POPF varies greatly in different reports, depending on the definition applied at each surgical center. Our aim was to agree upon an objective and internationally accepted definition to allow comparison of different surgical experiences. METHODS: An international panel of pancreatic surgeons, working in well-known, high-volume centers, reviewed the literature on the topic and worked together to develop a simple, objective, reliable, and easy-to-apply definition of POPF, graded primarily on clinical impact. RESULTS: A POPF represents a failure of healing/sealing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis. An all-inclusive definition is a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity. Three

different grades of POPF (grades A, B, C) are defined according to the clinical impact on the patient's hospital course. CONCLUSIONS: The present definition and clinical grading of POPF should allow realistic comparisons of surgical experiences in the future when new techniques, new operations, or new pharmacologic agents that may impact surgical treatment of pancreatic disorders are addressed.

2. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. DeOliveira ML, Winter JM, Schafer M, et al. Ann Surg. 2006;244:931-7; discussion 937-9.

OBJECTIVE: To define a simple and reproducible classification of complications following pancreaticoduodenectomy (PD) based on a therapy-oriented severity grading system. BACKGROUND: While mortality is rare after PD, morbidity rates remain high. The lack of standardization in evaluating morbidity after PD has severely hampered meaningful comparisons over time and among centers. We adapted a novel classification of complication to stratify morbidity by severity after PD, to test whether the incidence of pancreatic fistula has changed over time, and to identify risk factors in a single North American center. METHODS: The classification was applied to a consecutive series of 633 patients undergoing PD between February 2003 and August 2005. Another series of 141 patients treated between 1987 and 1990 was also analyzed to identify changes in the incidence and severity of fistula. Univariate and multivariate analyses were performed to link respective complications with preoperative and intraoperative parameters, length of hospital stay, and long-term survival. RESULTS: A total of 263 (41.5%) patients did not develop any complication, while 370 (58.5%) had at least one complication; 62 (10.0%) patients had only grade I complications (no need for specific

intervention), 192 patients (30.0%) had grade II (need for drug therapy such as antibiotics), 85 patients (13.5%) had grade III (need for invasive therapy), and 19 patients (3.0%) had grade IV complications (organ dysfunction with ICU stay). Grade V (death) occurred in 12 patients (2.0%). A total of 57 patients (9.0%) developed pancreatic fistula, of which 33 (58.0%) were classified as grade II, 17 (30.0%) as grade III, 5 (9.0%) as grade IV, and 2 (3.5%) as grade V. Delayed gastric emptying was documented in 80 patients (12.7%); half of them were scored as grade II and the other half as grade III. A significant decrease in the incidence of fistula was observed between the 2 periods analyzed (14.0% vs. 9.0%, $P < 0.001$), mostly due to a decrease in grade II fistula. Cardiovascular disease was a risk factor for overall morbidity and complication severity, while texture of the gland and cardiovascular disease were risk factors for pancreatic fistula. CONCLUSION: This study demonstrates the applicability and utility of a new classification in grading complications following pancreatic surgery. This novel approach may provide a standardized, objective, and reproducible assessment of pancreas surgery enabling meaningful comparison among centers and over time.

3. Proposal for definition and severity grading of pancreatic anastomosis failure and pancreatic occlusion failure. Strasberg SM, Linehan DC, Clavien PA et al. Surgery. 2007;141:420-6.

4. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. Connor S, Alexakis N, Garden OJ, et al. Br J Surg. 2005;92:1059-67.

BACKGROUND: The role of somatostatin and its analogues in reducing complications after pancreatic resection is controversial. This is a meta-analysis of the evidence of benefit.

METHODS: A literature search using Medline and ISI Proceedings with exploration of the references identified 22 studies. Of these, ten met the inclusion criteria for data extraction. Estimates of effectiveness were performed using fixed- and random-effects models. The effect was calculated as an odds ratio (OR) with 95 per cent confidence intervals (c.i.) using the Mantel-Haenszel method. Level of significance was set at $P < 0.050$. RESULTS: Outcomes for 1918 patients were compared. Somatostatin and its analogues did not reduce the mortality rate after pancreatic surgery (OR 1.17 (0.70 to 1.94); $P = 0.545$) but did reduce both the total morbidity (OR 0.62 (0.46 to 0.85); $P = 0.003$) and pancreas-specific complications (OR 0.56 (0.39 to 0.81); $P = 0.002$). Somatostatin and its analogues reduced the rate of biochemical fistula (OR 0.45 (0.33 to 0.62); $P < 0.001$) but not the incidence of clinical anastomotic disruption (OR 0.80 (0.44 to 1.45); $P = 0.459$). CONCLUSION: Somatostatin and its analogues reduce the incidence of complications after surgery. Copyright 2005 British Journal of Surgery Society Ltd.

5. Efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. Zeng Q, Zhang Q, Han S et al. Pancreas. 2008 ;36:18-25.

OBJECTIVE: The aim of this study was to evaluate the efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy. METHODS: A literature search of the MEDLINE, EMBASE, and Cochrane databases was used to identify randomized controlled trials that compared somatostatin and its analogues with control group after pancreaticoduodenectomy. Meta-analytical techniques were applied to identify differences in outcomes between the 2 groups. RESULTS: A total of 8 studies were identified according to our inclusion criteria, including

2 studies using somatostatin, 5 studies using octreotide, and 1 study using vapreotide. The use of somatostatin or its analogues did not significantly benefit for reducing the incidence of pancreatic fistula (odds ratio [OR] 95% confidence interval [CI], 0.64-1.37; P = 0.73), total pancreas-specific postoperative complications (OR 95% CI, 0.63-1.42; P = 0.79), delayed gastric emptying (OR 95% CI, 0.50-1.78; P = 0.86), total complication (OR 95% CI, 0.73-1.70; P = 0.61), mortality (OR 95% CI, 0.59-7.72; P = 0.97), and length of postoperative hospital stay (weighted mean difference 95% CI, -7.74 to 4.47; P = 0.60). CONCLUSIONS: The use of somatostatin and its analogues does not significantly reduce postoperative complications after pan-creaticoduodenectomy.

6. Use of octreotide for the prevention of pancreatic fistula after elective pancreatic surgery: a systematic review and meta-analysis. Alghamdi AA, Jawas AM, Hart RS. Can J Surg. 2007;5:459-66.

OBJECTIVE: To assess the effectiveness of octreotide in preventing postoperative pancreatic fistula. Pancreatic fistula is one of the most common complications after elective pancreatic surgery. Several clinical trials have evaluated the use of octreotide to prevent the development of pancreatic fistula after pancreatic surgery with conflicting recommendations. METHODS: We undertook a meta-analysis of 7 identified randomized controlled trials, reporting comparisons between octreotide and a control. The primary outcome was the incidence of postoperative pancreatic fistula, and the secondary outcome was the postoperative mortality. RESULTS: Seven studies, involving 1359 patients, met the inclusion criteria for this review. In these studies, sample sizes ranged from 75 to 252 patients. In total, 679 patients were given octreotide and 680 patients formed the control group. Perioperative octreotide is associated with a significant reduction in the incidence of pancreatic fistula after elective

pancreatic surgery, with a relative risk of 0.59 (95% confidence interval 0.41-0.85, p = 0.004). However, this risk reduction was not associated with a significant difference in postoperative mortality (p > 0.05). CONCLUSIONS: The review revealed that perioperative octreotide is associated with a significant reduction in the incidence of pancreatic fistula after elective pancreatic surgery. However, this risk reduction was not associated with a significant difference in postoperative mortality; further studies are warranted to confirm the results of this metaanalysis and to define which patient subgroups might benefit the most from prophylactic octreotide administration.

7. Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis. Wente MN, Shrikhande SV, Müller MW et al. Am J Surg. 2007 ;193:171-83.

OBJECTIVE: Pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) are the commonly preferred methods of anastomosis after pancreaticoduodenectomy (PD). The ideal choice of anastomosis remains a matter of debate. DATA SOURCES: Articles published until end of March 2006 comparing PJ and PG after PD were searched. STUDY SELECTION: Two reviewers independently assessed quality and eligibility of the studies and extracted data for further analysis. Meta-analysis was performed with a random-effects model by using weighted odds ratios. DATA EXTRACTION AND SYNTHESIS: Sixteen articles were included; meta-analysis of 3 randomized controlled trials (RCT) revealed no significant difference between PJ and PG regarding overall postoperative complications, pancreatic fistula, intra-abdominal fluid collection, or mortality. On the contrary, analysis of 13 nonrandomized observational clinical studies (OCSs) showed significant results in favor of PG for the outcome parameters with a reduction of pancreatic fistula and

mortality in favor of PG. CONCLUSIONS: All OCSs reported superiority of PG over PJ, most likely influenced by publication bias. In contrast, all RCTs failed to show advantage of a particular technique, suggesting that both PJ and PG provide equally good results. This meta-analysis yet again highlights the singular importance of performing well-designed RCTs and the role of evidence-based medicine in guiding modern surgical practice.

8. Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy. McKay A, Mackenzie S, Sutherland F et al. Br J Surg. 2006;93:929-36

BACKGROUND: Pancreaticoduodenectomy is the primary treatment for periampullary cancer. Associated morbidity is high and often related to pancreatic anastomotic failure. This paper compares rates of pancreatic fistula, morbidity and mortality after pancreaticoduodenectomy in patients having reconstruction by pancreaticogastrostomy with those in patients having reconstruction by pancreaticojejunostomy. METHODS: A meta-analysis was performed of all large cohort and randomized controlled trials carried out since 1990. RESULTS: Eleven articles were identified for inclusion: one prospective randomized trial, two non-randomized prospective trials and eight observational cohort studies. The meta-analysis revealed a higher rate of pancreatic fistula associated with pancreaticojejunostomy reconstruction (relative risk (RR) 2.62 (95 per cent confidence interval (c.i.) 1.91 to 3.60)). A higher overall morbidity rate was also demonstrated in this group (RR 1.43 (95 per cent c.i. 1.26 to 1.61)), as was a higher mortality rate (RR 2.51 (95 per cent c.i. 1.61 to 3.91)). CONCLUSION: Current literature suggests that the safer means of pancreatic reconstruction after pancreaticoduodenectomy is pancreaticogastrostomy, but much of the evidence comes from observational cohort study data.

9. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. Lillemoe KD, Cameron JL, Kim MP et al. J Gastrointest Surg. 2004;8:766-72; discussion 772-4.

Despite substantial improvements in perioperative mortality, complications, and specifically the development of a pancreatic fistula, remain a common occurrence after pancreaticoduodenectomy. It was the objective of this study to evaluate the role of fibrin glue sealant as an adjunct to decrease the rate of pancreatic fistula after pancreaticoduodenectomy. One hundred twenty-five patients were randomized after pancreaticoduodenal resection only if, in the opinion of the surgeon, the pancreaticojejunal anastomosis was at high risk for development of a pancreatic anastomotic leak. After completion of the pancreaticojejunal anastomosis, the patients were randomized to topical application of fibrin glue sealant to the surface of the anastomosis or no such application. The primary postoperative end points in this study were pancreatic fistula, total complications, death, and length of hospital stay. A total of 59 patients were randomized to the fibrin glue arm, whereas 66 patients were randomized to the control arm and did not receive fibrin glue application. The pancreatic fistula rate in the fibrin glue arm of the study was 26% vs. 30% in the control group (p = not significant [NS]). The mean length of postoperative stay for all patients randomized was similar (fibrin glue = 12.2 days, control = 13.6 days) and the mean length of stay for patients in whom pancreatic fistula developed was also not different (fibrin glue = 18.9 days, control = 21.7 days). There were no differences with respect to total complications or specific complications such as postoperative bleeding, infection, or delayed gastric emptying. These data demonstrate that the topical application of fibrin glue sealant to the surface of the pancreatic anastomosis in this patient population

undergoing high-risk pancreaticojejunal anastomosis did not reduce the incidence of pancreatic fistula or total complications after pancreaticodudodenectomy. There seems to be no benefit regarding the use of this substance in this setting.

10. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Poon RT, Fan ST, Lo CM et al. Ann Surg. 2007;246:425-33; discussion 433-5.

OBJECTIVE: Pancreatic fistula is a leading cause of morbidity and mortality after pancreaticoduodenectomy. External drainage of pancreatic duct with a stent has been shown to reduce pancreatic fistula rate of pancreaticojejunostomy in a few retrospective or prospective nonrandomized studies, but no randomized controlled trial has been reported thus far. This single-center prospective randomized trial compared the results of pancreaticoduodenectomy with external drainage stent versus no stent for pancreaticojejunal anastomosis. METHODS: A total of 120 patients undergoing pancreaticoduodenectomy with end-to-side pancreaticojejunal anastomosis were randomized to have either an external stent inserted across the anastomosis to drain the pancreatic duct (n = 60) or no stent (n = 60). Duct-to-mucosa anastomosis was performed in all cases. RESULTS: The 2 groups were comparable in demographic data, underlying pathologies, pancreatic consistency, and duct diameter. Stented group had a significantly lower pancreatic fistula rate compared with nonstented group (6.7% vs. 20%, P = 0.032). Radiologic or surgical intervention for pancreatic fistula was required in 1 patient in the stented group and 4 patients in the nonstented group. There were no significant differences in overall morbidity (31.7% vs. 38.3%, P = 0.444) and hospital mortality (1.7% vs. 5%, P = 0.309). Two patients in the nonstented group and none in the stented group died of pancreatic fistula.

Hospital stay was significantly shorter in the stented group (mean 17 vs. 23 days, P = 0.039). On multivariate analysis, no stenting and pancreatic duct diameter <3 mm were significant risk factors of pancreatic fistula. CONCLUSION: External drainage of pancreatic duct with a stent reduced leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy.

11. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. Winter JM, Cameron JL, Campbell KA, Chang DC et al. Gastrointest Surg. 2006;10:1280-90; discussion 1290.

Pancreatic duct stenting remains an attractive strategy to reduce the incidence of pancreatic fistulas following pancreaticoduodenectomy (PD) with encouraging results in both retrospective and prospective studies. We performed a prospective randomized trial to test the hypothesis that internal pancreatic duct stenting reduces the development of pancreatic fistulas following PD. Two hundred thirty-eight patients were randomized to either receive a pancreatic stent (S) or no stent (NS), and stratified according to the texture of the pancreatic remnant (soft/normal versus hard). Four patients were excluded from the study; in three instances due to a pancreatic duct that was too small to cannulate and in the other instance because a total pancreatectomy was performed. Patients who randomized to the S group had a 6-cm-long segment of a plastic pediatric feeding tube used to stent the pancreaticojejunostomy anastomosis. In patients with a soft pancreas, 57 randomized to the S group and 56 randomized to the NS group. In patients with a hard pancreas, 58 randomized to the S group and 63 randomized to the NS group. The S and NS groups for the entire study population, as well as for the subgroup of high-risk patients with soft pancreata, were similar as regard to demographics, past medical history, preoperative symptoms,

preoperative procedures, and intraoperative data. The pancreatic fistula rate for the entire study population was 9.4%. The fistula rates in the S and NS subgroups with hard pancreata were similar, at 1.7% and 4.8% (P = 0.4), respectively. The fistula rates in the S and NS subgroups with soft pancreata were also similar, at 21.1% and 10.7% (P = 0.1), respectively. A nonstatistically significant increase in the pancreatic fistula rate in the S group persisted after adjusting for the operating surgeon and technical details of the operation (e.g., anastomotic technique, anastomotic orientation, pancreatic duct size, and number of intra-abdominal drains placed). In patients with soft pancreata, 63% percent of the pancreatic fistulas in stented patients required adjustment to the clinical pathway (including two deaths), compared to 47% of the pancreatic fistulas in patients in the NS group (P = 0.3). Internal pancreatic duct stenting does not decrease the frequency or the severity of postoperative pancreatic fistulas.

12. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. Knaebel HP, Diener MK, Wente MN et al. Br J Surg. 2005;92:539-46.

BACKGROUND: Appropriate closure of the pancreatic remnant after distal pancreatectomy is still debated. A variety of procedures have been recommended to reduce the frequency of pancreatic fistula. This review quantitatively compares the available techniques. METHODS: Original articles and abstracts published up to the end of June 2004 were searched without language restriction in the Cochrane Controlled Trials Register, Medline and Embase. Three reviewers independently assessed each study's eligibility and quality, and extracted the data. A random effects model was performed using weighted odds ratios. RESULTS: Only ten of 262 articles could be included, two randomized clinical trials and eight observational studies. Reported postoperative morbidity varied from

13.3 to 64 per cent. The primary outcome measure, pancreatic fistula rate, occurred within the range 0-60.9 per cent. Meta-analysis of the six studies comparing stapler versus hand-sutured closure showed a non-significant combined odds ratio for occurrence of a pancreatic fistula of 0.66 (95 per cent confidence interval 0.35 to 1.26, P = 0.21) in favour of stapler closure. CONCLUSIONS: The quality and quantity of information extracted from the available trials are insufficient to enable any firm conclusion to be drawn on the optimal surgical technique of pancreatic stump closure; there is a trend in favour of the stapling technique.

13. Management of pancreatic fistulas after pancreaticoduodenectomy: results in 437 consecutive patients. Kazanjian KK, Hines OJ, Eibl G et al. Arch Surg. 2005;140:849-54; discussion 854-6.

HYPOTHESIS: Pancreatic fistula (PF), a common and potentially lethal complication of pancreaticoduodenectomy, can be managed nonoperatively in most cases. DESIGN: Retrospective case series. SETTING: Major academic medical and pancreatic surgery center. PATIENTS: A total of 437 consecutive patients who underwent pancreaticoduodenectomy for various diagnoses between January 1, 1988, and August 31, 2004. INTERVENTIONS: Conservative management of PF with an intraoperatively placed closed-suction drain near the pancreaticojejunostomy anastomosis, computed tomography-guided percutaneous drainage, and surgery. MAIN OUTCOME MEASURES: Incidence of PF after pancreaticoduodenectomy and patient outcomes. RESULTS: Fifty-five patients (12.6%) developed a PF, which was most common after resections for ampullary tumors (21.1%) and cystic neoplasms (31.3%), and uncommon after resection for pancreatic cancer (6.5%). The mean number of complications (excluding PF) was greater in the PF group

(PF, 1.24; no PF, 0.54; P<.001), but these did not prolong hospital stay (PF, 15.2 days; no PF, 13.7 days; P = .20). Biliary fistula, sepsis, reoperation, and late biliary stricture were more common in patients with PF (P<.05), but mortality rate and long-term survival in patients with either pancreatic or ampullary cancer were unaffected by the presence of PF (P>.40). Fifty-two patients (94.5%) had successful conservative management of their PF with prolonged tube drainage; 4 also required CT-guided percutaneous drainage. Three patients (5.5%) underwent reoperation and 1 died. CONCLUSIONS: Pancreatic fistula is a common problem after pancreaticoduodenectomy. It is associated with increased morbidity, but it does not affect the mortality rate. More than 90% of PF cases can be managed nonoperatively without significantly prolonging hospital stay.

14. Implications and management of pancreatic fistulas following pancreaticoduodenectomy: the Massachusetts General Hospital experience. Veillette G, Dominguez I, Ferrone C et al. Arch Surg. 2008 ;143:476-81.

OBJECTIVE: To describe the management and impact of pancreatic fistulas in a high-volume center. DESIGN: Retrospective case series. SETTING: Tertiary academic center. PATIENTS: Five hundred eighty-one consecutive patients who underwent pancreaticoduodenectomy from January 2001 through June 2006. MAIN OUTCOME MEASURES: Development of a pancreatic fistula (defined as > 30 mL of amylase-rich fluid from drains on or after postoperative day 7, or discharge with surgical drains in place, regardless of amount); the need for additional interventions or total parenteral nutrition; other morbidity; and mortality. RESULTS: Seventy-five patients (12.9%) developed a pancreatic fistula. Fistulas were managed with gradual withdrawal of surgical drains. This allowed for patient discharge and eventual closure at a mean of 18 days in 38.7% of cases; these were classified

as low-impact fistulas. The remaining 46 patients (61.3%) had an associated abscess, required percutaneous drainage or total parenteral nutrition, or developed bleeding; these were classified as high-impact fistulas and closed a mean of 35 days after surgery. Standard 30-day in-hospital mortality was 1.9% for all pancreaticoduodenectomies and 6.7% for those who developed a pancreatic fistula. The overall fistula-related mortality was 9.3% (7 patients), all but 1 of which was related to major hemorrhage. CONCLUSIONS: More than one-third of pancreatic fistulas are clinically insignificant (low impact). The remaining 60% of fistulas have a high clinical impact and nearly an 8-fold increase in overall mortality.

15. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Wente MN, Veit JA, Bassi C et al. Surgery. 2007 ;142:20-5.

BACKGROUND: Postoperative hemorrhage is one of the most severe complications after pancreatic surgery. Due to the lack of an internationally accepted, universal definition of postpancreatectomy hemorrhage (PPH), the incidences reported in the literature vary considerably, even in reports from randomized controlled trials. Because of these variations in the definition of what constitutes a PPH, the incidences of its occurrence are not comparable. METHODS: The International Study Group of Pancreatic Surgery (ISGPS) developed an objective, generally applicable definition of PPH based on a literature review and consensus clinical experience. RESULTS: Postpancreatectomy hemorrhage is defined by 3 parameters: onset, location, and severity. The onset is either early (< or =24 hours after the end of the index operation) or late (>24 hours). The location is either intraluminal or extraluminal. The severity of bleeding may be either mild or severe. Three different grades of PPH (grades A, B, and C) are defined according to the time of onset, site of bleeding,

severity, and clinical impact. CONCLUSIONS: An objective, universally accepted definition and clinical grading of PPH is important for the appropriate management and use of interventions in PPH. Such a definition also would allow comparisons of results from future clinical trials. Such standardized definitions are necessary to compare, in a nonpartisan manner, the outcomes of studies and the evaluation of novel operative treatment modalities in pancreatic surgery.

16. Management of delayed postoperative hemorrhage after pancreaticoduodenectomy: a meta-analysis. Limongelli P, Khorsandi SE, Pai M et al. Arch Surg. 2008 ;143:1001-7; discussion 1007

OBJECTIVE: To determine whether interventional radiology (IR) or laparotomy (LAP) is the best management of delayed postoperative hemorrhage (DPH) after pancreaticoduodenectomy. Data Source We undertook an electronic search of MEDLINE and selected for analysis only original articles published between January 1, 1990, and December 31, 2007. STUDY SELECTION: Two of us independently selected studies reporting on clinical presentation and incidence of postoperative DPH and the following outcomes: complete hemostasis, morbidity, and mortality. DATA EXTRACTION: Two of us independently performed data extraction. Data were entered and analyzed by means of dedicated software from The Cochrane Collaboration. A random-effects meta-analytical technique was used for analysis. DATA SYNTHESIS: One hundred sixty-three cases of DPH after pancreaticoduodenectomy were identified from the literature. The incidence of DPH after pancreaticoduodenectomy was 3.9%. Seventy-seven patients (47.2%) underwent LAP; 73 (44.8%), IR; and 13 (8%), conservative treatment. On meta-analysis comparing LAP vs IR for DPH, no significant difference was found between the 2 treatment options for complete hemostasis (73% vs 76%;

P = .23), mortality (43% vs 20%; P = .14), or morbidity (77% vs 35%; P = .06). CONCLUSIONS: This meta-analysis, although based on data from small case series, is unable to demonstrate any significant difference between LAP and IR in the management of DPH after pancreaticoduodenectomy. The management of this life-threatening complication is difficult, and the appropriate treatment pathway ultimately will be decided by the clinical status of the patient and the institution preference.

17. Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Yekebas EF, Wolfram L, Cataldegirmen G et al. Ann Surg. 2007;246:269-80.

BACKGROUND: To analyze clinical courses and outcome of postpancreatectomy hemorrhage (PPH) after major pancreatic surgery. SUMMARY BACKGROUND DATA: Although PPH is the most life-threatening complication following pancreatic surgery, standardized rules for its management do not exist. METHODS: Between 1992 and 2006, 1524 patients operated on for pancreatic diseases were included in a prospective database. A risk stratification of PPH according to the following parameters was performed: severity of PPH classified as mild (drop of hemoglobin concentration <3 g/dL) or severe (>3 g/dL), time of PPH occurrence (early, first to fifth postoperative day; late, after sixth day), coincident pancreatic fistula, intraluminal or extraluminal bleeding manifestation, and presence of "complex" vascular pathologies (erosions, pseudoaneurysms). Success rates of interventional endoscopy and angiography in preventing relaparotomy were analyzed as well as PPH-related overall outcome. RESULTS: Prevalence of PPH was 5.7% (n = 87) distributed almost equally among patients suffering from malignancies, borderline tumors, and focal pancreatitis (n = 47) and from chronic pancreatitis (n = 40). PPH-related overall mortality of 16% (n = 14) was

closely associated with 1) the occurrence of pancreatic fistula (13 of 14); 2) vascular pathologies, ie, erosions and pseudoaneurysms (12 of 14); 3) delayed PPH occurrence (14 of 14); and 4) underlying disease with lethal PPH found only in patients with soft texture of the pancreatic remnant, while no patient with chronic pancreatitis died. Conversely, primary severity of PPH (mild vs. severe) and the kind of index operation (Whipple resection, pylorus-preserving partial pancreaticoduodenectomy, organ-preserving procedures) had no influence on outcome of PPH. Endoscopy was successful in 3 from 15 patients (20%), who had intraluminal PPH within the first or second postoperative day. "True," early extraluminal PPH had uniformly to be treated by relaparotomy. Seventeen patients had "false," early extraluminal PPH due to primarily intraluminal bleeding site from the pancreaticoenteric anastomosis with secondary disruption of the anastomosis. From 43 patients subjected to angiography, 25 underwent interventional coiling with a success rate of 80% (n = 20). Overall, relaparotomy was performed in 60 patients among whom 33 underwent surgery as first-line treatment, while 27 were relaparotomied as rescue treatment after failure of interventional endoscopy or radiology. CONCLUSION: Prognosis of PPH depends mainly on the presence of preceding pancreatic fistula. Decision making as to the indication for nonsurgical interventions should consider time of onset, presence of pancreatic fistula, vascular pathologies, and the underlying disease.

18. Delayed massive hemorrhage after pancreatic and biliary surgery: embolization or surgery? de Castro SM, Kuhlmann KF, Busch OR et al. Ann Surg. 2005;241:85-91.

OBJECTIVE: To analyze the management of delayed massive hemorrhage (DMH) after major pancreatic and biliary surgery. SUMMARY BACKGROUND DATA: Despite a decreased mortality rate for pancreatic and biliary surgery, DMH is still

an important cause of postoperative mortality. The aim of the present study was to analyze the management of DMH after pancreatic and biliary surgery, and specifically to assess the role of embolization and surgical intervention. METHODS: The study group (SG) consisted of 1010 patients from 1994 to 2002 who underwent pancreatic or biliary surgery (cholecystectomy excluded). Patients from a previous study (1983-1993, n = 686) were used as a historical control group (HCG). RESULTS: The incidence of DMH (SG 2.3% vs. HCG 3.2%) declined somewhat but did not differ significantly between both periods. The number of patients with a septic complication (SG 74% vs. HCG 50%) and a sentinel bleed (SG 78% vs. HCG 100%) before the onset of DMH did not differ significantly. Embolization (SG 2 of 2 patients vs. HCG 0 of 2 patients) was not used frequently. Successful outcome after surgical intervention (SG 14 of 16 patients vs. HCG 8 of 14 patients) and the surgical procedures performed to obtain hemostasis were comparable and overall mortality (SG 22% vs. HCG 29%) was comparable. CONCLUSIONS: The incidence of DMH declined somewhat from 3.2% to 2.3% over the past years. Most patients present with septic complications and a sentinel bleed before onset of DMH. Despite general acceptance of embolization in our unit, it was used infrequently in patients with DMH. Aggressive surgical intervention was the treatment of choice in patients with DMH after pancreatic or biliary surgery.

19. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Wente MN, Bassi C, Dervenis C et al. Surgery. 2007;142:761-8.

BACKGROUND: Delayed gastric emptying (DGE) is one of the most common complications after pancreatic resection. In the literature, the reported incidence of DGE after pancreatic surgery varies considerably between different surgical centers,

primarily because an internationally accepted consensus definition of DGE is not available. Several surgical centers use a different definition of DGE. Hence, a valid comparison of different study reports and operative techniques is not possible. METHODS: After a literature review on DGE after pancreatic resection, the International Study Group of Pancreatic Surgery (ISGPS) developed an objective and generally applicable definition with grades of DGE based primarily on severity and clinical impact. RESULTS: DGE represents the inability to return to a standard diet by the end of the first postoperative week and includes prolonged nasogastric intubation of the patient. Three different grades (A, B, and C) were defined based on the impact on the clinical course and on postoperative management. CONCLUSION: The proposed definition, which includes a clinical grading of DGE, should allow objective and accurate comparison of the results of future clinical trials and will facilitate the objective evaluation of novel interventions and surgical modalities in the field of pancreatic surgery.

20. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Tani M, Terasawa H, Kawai M et al. Ann Surg. 2006;243:316-20.

OBJECTIVE: To determine if an antecolic or a retrocolic duodenojejunostomy during pylorus-preserving pancreaticoduodenectomy (PpPD) was associated with the least incidence of delayed gastric emptying (DGE), in a prospective, randomized, controlled trial. SUMMARY BACKGROUND DATA: The pathogenesis of DGE after PpPD has been speculated to be related to factors such as inflammation, ischemia, gastric atony, motilin levels, and type of surgical procedure. Previous retrospective studies have shown a lower incidence of DGE after antecolic duodenojejunostomy. A prospective trial is needed.

METHODS: Forty patients were enrolled in this trial between May 2002 and April 2004. Just before duodenojejunostomy during PpPD, the patients were randomly assigned to undergo either an antecolic or a retrocolic duodenojejunostomy. RESULTS: DGE occurred in 5% of patients with the antecolic route for duodenojejunostomy versus 50% with the retrocolic route (P = 0.0014). Those with the antecolic route had a significantly shorter duration of postoperative nasogastric tube drainage than did those with the retrocolic route (4.2 days versus 18.9 days, respectively, P = 0.047). By postoperative day 14, all patients with the antecolic route could take solid foods, while only 55% (11 of 20) of the patients with the retrocolic route could take solid foods (P = 0.0007). The length of stay in the hospital was 28 days for the antecolic group versus 48 days for the retrocolic group (P = 0.018). CONCLUSIONS: Antecolic reconstruction for duodenojejunostomy during PpPD decreases postoperative morbidity and length of hospital stay by decreasing DGE. Our data suggest that PpPD with antecolic duodenojejunostomy is a safer operation.

21. Pancreaticoduodenectomy (classic Whipple) versus pylorus-preserving pancreaticoduodenectomy (pp Whipple) for surgical treatment of periampullary and pancreatic carcinoma. Diener MK, Heukaufer C, Schwarzer G et al. Cochrane Database Syst Rev. 2008 16;:CD006053

The standard treatment for resectable pancreatic tumours is either a classic Whipple operation or a pylorus-preserving pancreaticoduodenectomy but it is still unclear which of the two procedures is more favourable in terms of survival, mortality, complications, perioperative factors and quality of life. OBJECTIVES: The objective of this systematic review is to compare the effectiveness of each technique. SEARCH STRATEGY: A search was conducted to identify all published

and unpublished randomised controlled trials. Trials were identified by searching the following electronic databases - The Cochrane Library, MEDLINE, EMBASE and Current Contents. Reference lists from trials selected by electronic searching were hand-searched to identify further relevant trials. SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing the classical Whipple (CW) with the pylorus-preserving pancreaticoduodenectomy (PPW) were considered eligible if patients with periampullary or pancreatic carcinoma were included. DATA COLLECTION AND ANALYSIS: Two authors independently extracted data for included studies. A random-effects model was used for pooling data from the different trials. Binary outcomes were compared using odds ratios, continuous outcomes were pooled using weighted mean differences and hazard ratios were used to for the meta-analysis of survival data. The methodological quality of included studies was evaluated independently by two authors according to quality standards and by using a questionnaire that covers different aspects of quality. MAIN RESULTS: 1235 abstracts were retrieved and checked for eligibility and seven RCTs were finally included. The critical appraisal revealed vast heterogeneity with respect to methodological quality and outcome parameters. The comparison of overall in-hospital mortality (odds ratio 0.49; 95% CI 0.17 to 1.40; P=0.18), overall survival (hazard ratio 0.84; 95% CI 0.61 to 1.16; P=0.29) and morbidity showed no significant difference. However, operating time (weighted mean difference -68.26 min; 95% CI -105.70 to -30.83; P=0.0004) and intra-operative blood loss (weighted mean difference -0.76 ml; 95% CI -0.96 to -0.56; P<0.00001) were significantly reduced in the PPW group. AUTHORS' CONCLUSIONS: There is no evidence of relevant differences in mortality, morbidity and survival between the PPW and the CW. Given obvious clinical and methodological inter-study heterogeneity, future efforts have to be undertaken to perform high quality RCTs of complex surgical interventions on the basis of well defined outcome.

22. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Yeo CJ, Cameron JL, Lillemoe KD et al. Ann Surg. 2002;236:355-66; discussion 366-8.

OBJECTIVE: To evaluate, in a prospective, randomized single-institution trial, the end points of operative morbidity, operative mortality, and survival in patients undergoing standard versus radical (extended) pancreaticoduodenectomy. SUMMARY BACKGROUND DATA: Numerous retrospective reports and a few prospective randomized trials have suggested that the performance of an extended lymphadenectomy in association with a pancreaticoduodenal resection may improve survival for patients with pancreatic and other periampullary adenocarcinomas. METHODS: Between April 1996 and June 2001, 299 patients with periampullary adenocarcinoma were enrolled in a prospective, randomized single-institution trial. After intraoperative verification (by frozen section) of margin-negative resected periampullary adenocarcinoma, patients were randomized to either a standard pancreaticoduodenectomy (removing only the peripancreatic lymph nodes en bloc with the specimen) or a radical (extended) pancreaticoduodenectomy (standard resection plus distal gastrectomy and retroperitoneal lymphadenectomy). All pathology specimens were reviewed, fully categorized, and staged. The postoperative morbidity, mortality, and survival data were analyzed. RESULTS: Of the 299 patients randomized, 5 (1.7%) were subsequently excluded because their final pathology failed to reveal periampullary adenocarcinoma, leaving 294 patients for analysis (146 standard vs. 148 radical). The two groups were statistically similar with regard to age (median 67 years) and gender (54% male). All the patients in the radical group underwent distal gastric resection, while 86% of the patients in the standard

group underwent pylorus preservation (<.0001). The mean operative time in the radical group was 6.4 hours, compared to 5.9 hours in the standard group (=.002). There were no significant differences between the two groups with respect to intraoperative blood loss, transfusion requirements (median zero units), location of primary tumor (57% pancreatic, 22% ampullary, 17% distal bile duct, 3% duodenal), mean tumor size (2.6 cm), positive lymph node status (74%), or positive margin status on final permanent section (10%). The mean total number of lymph nodes resected was significantly higher in the radical group. Of the 148 patients in the radical group, only 15% (n = 22) had metastatic adenocarcinoma in the resected retroperitoneal lymph nodes, and none had retroperitoneal nodes as the only site of lymph node involvement. One patient in the radical group with negative pancreaticoduodenectomy specimen lymph nodes had a micrometastasis to one perigastric lymph node. There were six perioperative deaths (4%) in the standard group versus three perioperative deaths (2%) in the radical group (= NS). The overall complication rates were 29% for the standard group versus 43% for the radical group (=.01), with patients in the radical group having significantly higher rates of early delayed gastric emptying and pancreatic fistula and a significantly longer mean postoperative stay. With a mean patient follow-up of 24 months, there were no significant differences in 1-, 3-, or 5-year and median survival when comparing the standard and radical groups. CONCLUSIONS: Radical (extended) pancreaticoduodenectomy can be performed with similar mortality but some increased morbidity compared to standard pancreaticoduodenectomy. The data to date fail to indicate that a survival benefit is derived from the addition of a distal gastrectomy and retroperitoneal lymphadenectomy to a pylorus-preserving pancreaticoduodenectomy.

Section — V

Colorectal Surgery

Contributors

PJ Shukla

SV Shrikhande

AT Jadhav

MD Patel

Evidence Based Guidelines for The Management of Colorectal Anastomotic Dehisence

Risk Factors

Patient-specific risk factors include LOE 2

Malnutrition >5 kg weight loss LOE 2

Steroids LOE 2

Smoking LOE 2

Tobacco LOE 2

Leukocytosis LOE 2

Cardiovascular disease LOE 2

Alcohol use LOE 2

American Society of Anesthesiologists (ASA) score > 3 LOE 2

Low anastomosis (< 6 cm from anal verge).Ileo rectal and ileocolic both have increased risk. LOE 2

Suboptimal anastomotic blood supply LOE 2

Operative time > 2 hours LOE 2

Bowel obstruction LOE 2

Perioperative blood transfusion LOE 2

Intra-operative septic conditions, not conducive to primary anastomosis LOE 2

Gender (male) LOE 2

Obesity LOE 2

Use of drains for Intraperitoneal Anastomosis LOE 2

Mechanical Bowel Preparation LOE 1

Anastomotic technique: Stapled versus Hand-Sewn Anastomosis LOE 1

Laparoscopic versus Open LOE 1

Role of Proximal Diversion LOE 2

Intraoperative testing of the integrity of the anastomosis LOE 2

Influence of caseload and surgical specialty LOE 3

Neoadjuvant therapy LOE 3

Endostents and Transanal endoscopic vacuum devices LOE5

Fibrin glue to seal the anastomoses LOE5

Buttress the staple line with bovine pericardial strips LOE5

Anastomotic dehiscence is one of the most dreaded complications of operations of the large intestine. Breakdown of an anastomosis results in increased morbidity and mortality and adversely affects length of stay, cost, and cancer recurrence. Reported rates of anastomotic dehiscence vary between 1% and 30%, although experienced colorectal surgeons often quote 3% to 6% as an acceptable overall leakage rate (Chambers WM, et al. 2004).

Definition

In 1991, the United Kingdom Surgical Infection Study Group proposed the definition as a "leak of luminal contents from a surgical join between two hollow viscera." These contents can exit through wounds or drains, or collect at the anastomotic site (Peel AL, et al. 1991).

Risk Factors

Patient-specific risk factors include

Malnutrition >5 kg weight loss

Steroids

Smoking

Tobacco

Leukocytosis

Cardiovascular disease

Alcohol use

American Society of Anesthesiologists (ASA) score > 3.

(391 patients Konishi T, et al. 2006, Makela JT, et al. 2003**,** 1417 patients multi variate analysis Choi HK, et al. 2006, Sorensen LT, et al. 1999 - Level of Evidence 2).

Recto sigmoid Resections compared to colonic resections. (1834 Patients Branagan G, et al. 2005 – LOE 2).

Intraoperative Risk Factors

Low anastomosis (< 6 cm from anal verge). Ileo rectal and ileocolic both have increased risk. (Hyman N, et al. 2007 – LOE 2).

Suboptimal anastomotic blood supply

Operative time > 2 hours

Bowel obstruction

Perioperative blood transfusion

Intra-operative septic conditions, not conducive to primary anastomosis.

Risk Factors for Low Rectal Anastomosis

Gender (male) (541 patients Lipska MA, et al. 2006 –LOE 2) and Obesity (defined as 20% heavier than ideal body weight) compared with a 15% leak rate in non-obese patients (Rullier E, et al. 1998- LOE 2).

A new identified risk factor for anastomotic leak is Bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor receptor Because the half-life of the drug is 20 days, and wound-healing complications have been documented up to 56 days after treatment, it is advisable to delay operation for three half-lives, or 60 days, after the last treatment (Heinzerling JH, et al. 2006, Saif MW, et al. 2007 – LOE 4).

Laser Doppler flow measurements in colorectal anastomoses found substantially decreased anastomotic blood flow after dissection in end to end anastomoses when compared with side to end anastomoses. This method can be considered in difficult cases, where adequate blood supply to the proximal limb might be in doubt (Boyle NH, et al. 2000 – LOE 5).

There is no data to support routine use of drains when Intraperitoneal Anastomosis (IP) is performed (317 patients Merad F, et al.1998 – LOE 2).

Mechanical Bowel Preparation

There is no convincing evidence that mechanical bowel preparation is associated with reduced rates of anastomotic leakage after elective colorectal surgery. On the contrary, there is evidence that this intervention may be associated with an increased rate of anastomotic leakage and wound complications. It is not possible to b conclude on the latter issue because of the clinical heterogeneity of trial inclusion criteria, methodological inadequacies in trial (in particular, poor reporting of concealment and allocation), potential performance biases, and failure of intention-to-treat analyses. Nevertheless, the dogma that mechanical bowel preparation is necessary before elective colorectal surgery should be reconsidered (Cochrane data base systematic review. 2005 – LOE 1).

Anastomotic technique: Stapled versus Hand-Sewn Anastomosis

In order for an anastomosis to heal properly, three critical factors must be present: no tension, adequate blood supply, and an inverted anastomosis.

There is no difference in leak rates between stapled and hand-sewn anastomoses (Cochrane meta-analysis 2001 – LOE 1).

Cochrane meta-analysis 2001 also showed that the leak rates were no different between hand sewn and stapled anastomosis even for low anastomosis (< 6cm).

Laparoscopic versus Open

There were no differences in the anastomotic leak rate between the two groups (Review of 52 articles Patankar SK, et al. 2003**,** Jayne DG, et al. UK MRC CLASICC Trial 2007, 872 patients COST trial 2004 **–** LOE 1).

Role of Proximal Diversion

There appears to be a paucity of statistically significant data to support the concept that proximal diversion abates the incidence of leaks compared with those patients not diverted. It should be recognized that proximal protective diversion does not prevent leaks, but reduces the severity of complications even in higher-risk patients (234 patients Matthiessen P, et al. 2007 – LOE 2).

Intraoperative testing of the integrity of the anastomosis

There are several methods to test the integrity of an anastomosis at the time of operation.

1 Air insuffalation - After completion of the anastomosis, the pelvis is filled with saline and the proximal bowel is manually occluded. Air is then insufflated through the

rectum, and if air bubbles are noted, an incomplete anastomosis is present.

2. Betadine Test - Distend the rectum with Betadine-tinged saline and look for extravasation.

In either case, repair of the anastomotic defect should be attempted and the anastomosis then retested. Even if the repair is convincingly complete a protective diverting colostomy / ileostomy may be added (Beard JD et al. 1990 - LOE 2)

Age and other co-morbidities like diabetes, obesity are consider by us for a protective diversion stoma (LOE 5).

Influence of caseload and surgical specialty

The data has provided evidence that improved outcomes across the board like increased sphincter preservation decreased post operative complications and improved long-term survival following colonic cancer surgery is seen with increase in hospital caseload and surgeon's specialization. There is no evidence of a relationship for rectal cancer surgery, possibly owing to methodological artifacts however no study has reported an inverse relation (Iverson LH, et al. 2007 Review article – LOE 2).

Surgical Training and Outcome

There was no difference in anastomotic leaks rates, operative mortality or survival between unsupervised trainees, supervised trainees and consultants when case-mix adjustment was applied for all types of colorectal cancer surgeries. Borowski DW, et al showed that there is considerable underused training capacity available (LOE 2).

Neoadjuvant therapy

Neoadjuvant chemoradiation therapy was not found to be significantly associated with leakage after tumor-specific

mesorectal excision for rectal cancer (230 patients review Martel G, et al. 2008 – LOE 2).

Local wound complications rates are higher after radiotherapy (38 patients Aritoukh DY, et al. 2007 – LOE 3).

When do leaks occur?

Anastomotic leaks are detected anywhere from 3 to 45 days postoperatively. There appear to be two peaks when the diagnosis is made. When leaks occur clinically, the median postoperative day of diagnosis is 7 days; when made radiographically, the median postoperative day of leakage is 16. Close follow-up must be carried out during the first 40 days after operation, as late leaks can occur anywhere during this time frame. This is relevant to overall outcomes, because there is increased morbidity due to excessive fibrosis and inflammation resulting in stenosis when there is a delay in treating anastomotic leaks (LOE 5).

Management of anastomotic leaks in an era of expanding technology

Patients with anastomotic leaks most often require volume resuscitation and should all be started on broad spectrum antibiotics.

Once an anastomotic leak has been recognized, prompt management should be individualized to accommodate patient's needs.

Available strategies

- Observation and bowel rest
- Percutaneous drainage
- Surgical revision, diversion, or drainage
- Colonic stenting

With a small degree of contamination, right-sided colonic leaks can often be re-anastomosed and drained.

With more extensive contamination, resection with ileostomy and mucous fistula or creation of a Hartman's pouch should be used.

Management of left-colon leaks depends on the level of the anastomosis.

Intraperitoneal leaks should be resected with the ends brought out as ostomies, if possible.

Extremely low anastomotic leaks should be extensively drained with proximal complete diversion with either an ileostomy or colostomy (Alves A, et al. 1999**.** Alberts JC, et al. 2003 – LOE 2).

A new classification system has been reported from Tata Memorial aiding management of leaks following anterior resections (LOE 5).

Table for management of anastomotic leaks following anterior resection

Dehiscence	% of circumference	Peritonitis	Management
Minor	< 10 %	Localized	Conservative
Minor	< 10 %	Generalized	Surgical
Major	> 10 %	Localized	Surgical without disconnection
Major	> 10 %	Generalized	Anastomotic disconnection

Newer approaches

Endostents and Transanal endoscopic vacuum devices.

The latter device is placed through the lumen of the colon into the abscess cavity to decompress the cavity and help generate granulation tissue. This approach is hampered by the need for the sponge system to be changed every 48 to 72 hours and by

the excessively long duration of treatment with a mean of 34 days with 11 endoscopic sessions per patient (Scileppi T, et al. 2005, Weidenhagen R, et al. 2008- LOE 5).

Anastomotic leakage had an independent negative association with overall survival and cancer-specific survival (2235 patients McArdle CS, et al. 2005- LOE 2).

One area of current intense investigation is preventing anastomotic dehiscence. There have been several animal and human studies done with different types of buttressing material to strengthen anastomoses.

Intraluminal tubes that are meant to aid in suturing and protecting an intracorporeal anastomosis are newer methods being tried.

Fibrin glue to seal the anastomoses.

Buttress the staple line with bovine pericardial strips

(Yo LS, et al. 2006. Nguyen NT, et al. 2004 – LOE 5).

Conclusion

Mortality rates for colorectal resections report a wide range from 0% to 32 %. (Konishi T, et al. 2006).

Proven patient-specific risk factors include alcohol and tobacco use, patients with diverticular disease, ASA score 3, steroid use, and weight loss and malnutrition (LOE-2).

Intra operative factors that can affect the leakage rate include the duration of the surgical procedure, adequate blood supply to prevent ischemia, and intra operative testing of left-sided anastomosis (LOE -2).

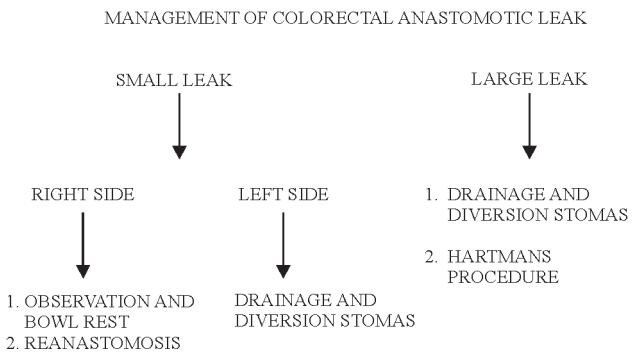
Laparoscopic colon resections have been proved to have a similar leak rate when compared with open colon resections (LOE -2).

Stapled and hand sewn anastomoses also have equal complication rates (LOE-2).

Proximal diversion of high-risk anastomoses does not alter the anastomotic leak rate, but it does decrease the sequelae of a leak (LOE -2).

There is not enough definitive data to prove whether wrapping the omentum around an anastomosis, leaving drains around low rectal anastomoses, or using preoperative bowel preparations have a substantial effect on leak rates.

The two proved risks associated with low rectal anastomoses include male patients and obesity (LOE -2).



1. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study.

Buch NC, Gervaz P, Secic M, et al. Int J Colorectal Disease 2008; 23:265-270. Epub 2007

BACKGROUND: Anastomotic dehiscence is the most severe surgical complication after large bowel resection. This study was designed to assess the incidence, to observe the consequences, and to identify the risk factors associated with anastomotic leakage after colorectal surgery. MATERIALS AND METHODS: All procedures involving anastomoses of the colon or the rectum, which were performed between November 2002 and February 2006 in a single institution, were prospectively entered into a computerized database. RESULTS: One thousand eighteen colorectal resections and 811 anastomoses were performed over this 40-month period. The most frequent procedures were sigmoid (276) and right colectomies (217). The overall anastomotic leak rate was 3.8%. The mortality rate associated with anastomotic leak was 12.9%. In univariate analysis, the following parameters were associated with an increased risk for anastomotic dehiscence: (1) ASA score >or= 3 ($p = 0.004$), (2) prolonged (>3 h) operative time ($p = 0.02$), (3) rectal location of the disease ($p < 0.001$), (4) and a body mass index > 25 ($p = 0.04$). In multivariate analysis, ASA score >or= 3 (OR = 2.5; 95% CI 1.5-4.3, $p < 0.001$), operative time > 3 h [OR = 3.0; 95% CI 1.1-8.0, $p = 0.02$), and rectal location of the disease (OR = 3.75; 95% CI 1.5-9.0 (vs left colon), $p = 0.003$; OR = 7.69; 95% CI 2.2-27.3 (vs right colon), $p = 0.001$] were factors significantly associated with a higher risk of anastomotic dehiscence. CONCLUSIONS: Three risk factors for anastomotic leak have been identified, one is patient-related (ASA score), one is disease-related (rectal location), the third being surgery-related (prolonged operative time). These factors

should be considered in perioperative decision-making regarding defunctioning stoma formation.

2. Defunctioning loop ileostomy with low anterior resection for distal rectal cancer: should we make an ileostomy as a routine procedure? A prospective randomized study.

Chude GG, Rayate NV, Patris V, et al.
Hepatogastroenterology 2008;55:1562-567

BACKGROUND/AIMS: Anastomotic leakage is a major problem in colorectal surgery particularly in low rectal cancer. The defunctioning loop ileostomy was introduced as a technique to create a manageable stoma that would divert the fecal stream from a more distal anastomosis in order to reduce the consequences of any anastomotic leakage. Therefore, the use of a defunctioning stoma has been suggested, but limited data exist to clearly determine the necessity of routine diversion. This study was designed to evaluate early morbidity, mortality and hospital stay in patients undergoing lower rectal cancer surgery concerned with or without loop ileostomy. METHODOLOGY: This is a prospective randomized study that was performed between May 2001 and March 2008. There were 256 patients who underwent elective low anterior resection and stapler anastomosis. They were divided into two groups. Group A consisted of 120 patients who underwent straight anastomosis without ileostomy and group B consisted of 136 patients who underwent straight anastomosis with loop ileostomy. Data regarding patient demographics, underlying pathology, anastomotic problems, and ileostomy-related problems were gathered. The patients were all monitored closely after surgery for an anastomotic leak and all stoma-related complications were recorded. Inclusion criteria consisted of biopsy proven adenocarcinoma of the rectum located at < or = 5 cm above the anal verge, age > or = 22

years, and informed consent. Exclusion criteria included age more than 90 years, associated co morbid conditions Stage IV with disease spread to liver and peritoneum. RESULTS: Indications for surgery were lower rectal cancer (n=256). Mean age 55.5 years (range 22-90 years) and a male: female ratio of 1.1:1. All patients were undergoing elective surgery for lower rectal cancer. In our study 12 patients in group A developed anastomotic leak, two of them were re-explored for anastomotic leak and Hartman's colostomy was carried out. There were two deaths in Group A. In group B anastomotic leak was seen in three patients. In all three, anastomotic healing took place at a later period of time on the 18th, 20th, and 25th postoperative day respectively without any additional morbidity and mortality. Ileostomy-related problems were minor and limited to the stoma and complaints requiring stoma nurse evaluation (n=8), dehydration requiring outpatient care (n=3), bleeding at the stoma closure site (n=l). No stoma site hernias have been identified so far. CONCLUSIONS: The use of defunctioning loop ileostomy in all patients undergoing lower rectal surgery with stapler anastomosis is beneficial and safe. Defunctioning loop ileostomy use has resulted in no anastomotic leak rate and considerable low morbidity. So according to our study, we strongly recommend defunctioning loop ileostomy as a routine procedure in patients undergoing lower rectal cancer surgery.

3. "Spontaneous," delayed colon and rectal anastomotic complications associated with bevacizumab therapy.

August DA, Serrano D, Poplin E, et al. J Surg Oncol. 2008; 97:180-185

Bevacizumab, a humanized monoclonal antibody used to treat recurrent and metastatic colorectal cancer, targets the vascular endothelial growth factor (VEGF) molecule. It is hypothesized that bevacizumab works by both depriving tumors of the

neovascularity they require to grow, and by improving local delivery of chemotherapy through alterations of tumor vasculature permeability and Starling forces. Complications of bevacizumab treatment include bowel ischemia and perforation, but to date, these complications have only rarely been described as occurring at the site of presumably healed anastomoses following surgery. We report two cases of delayed, "spontaneous" low anterior colorectal anastomotic dehiscence and one right colon anastomotic colocutaneous fistula associated with bevacizumab therapy. After seeing three patients with complications arising from apparently healed low anterior colorectal or right colon anastomoses following initiation of bevacizumab therapy for treatment of metastatic colorectal cancer, we reviewed the experience of The Cancer Institute of New Jersey (CINJ) with use of bevacizumab in approximately 50 patients between April 2004 and December 2006. The three index cases had been treated surgically at CINJ but received chemotherapy elsewhere. None of the 50 patients receiving bevacizumab at CINJ who had previous colon or rectal anastomoses were identified as having this complication. The medical records of the three index cases were reviewed and analyzed. Additionally, a Medline search was performed to identify other reports documenting similar cases. Two reports of related cases were found in the literature. In two of our index cases who underwent low anterior anastomoses, the patients had received preoperative pelvic irradiation before their initial low anterior resection. In one of the two cases, the initial resection was complicated by an anastomotic leak requiring proximal diversion and then subsequent stoma takedown. In both cases, the dehiscence occurred more than 1 year after anastomosis, and became evident 1-10 months following initiation of bevacizumab treatment. In the third index case, a colocutaneous fistula arising from the anastomotic site presented 5 months following right colon resection and 3 months after starting adjuvant

systemic therapy with FOLFOX (5-fluorouracil (5-FU), leucovorin, and oxaliplatin) and bevacizumab. Delayed colorectal anastomotic complications may occur in association with bevacizumab therapy. Contributing factors may include anastomotic leak at the time of the original operation and history of anastomotic irradiation. Clinicians treating patients who receive bevacizumab following colectomy for colorectal cancer should be aware of this possible life-threatening complication. These findings may also be relevant to the design of trials of the use of bevacizumab for the postoperative adjuvant treatment of patients with colorectal cancer.

4. Neodajuvant therapy and anastomotic leak after tumour-specific mesorectal excision for rectal cancer.

Martel G, Al-Suhaibani Y, Moloo H, et al. Dis Colon Rectum 2008;51:1195-201. Epub 2008.

PURPOSE: This study was designed to evaluate whether neoadjuvant therapy is a risk factor for anastomotic leakage after rectal cancer surgery. METHODS: A retrospective review of 220 patients who underwent tumor-specific mesorectal excision for rectal cancer from 2000 to 2005 was performed. Risk factors for leak were identified by using a multivariable regression model. RESULTS: A total of 54 patients received neoadjuvant chemoradiation therapy and surgery, whereas 166 received surgery alone. No difference in clinically significant leaks was observed between the two groups (5.6 vs. 6.6 percent, P = 1). A diverting ileostomy was performed in 26.4 percent of patients who received neoadjuvant therapy compared with 9.7 percent for surgery alone (P = 0.0021). Neoadjuvant patients were more likely to have ultralow anastomoses (17.6 vs. 2.5 percent, P < 0.0001). On multivariate analysis, smoking (odds ratio, 6.37 (1.8, 22.2), P = 0.004), difficult anastomosis (odds ratio, 7.66 (1.8, 31.5), P = 0.0048), and low level of anastomosis (<or=4 cm from the verge; odds

ratio, 5.28 (1.05, 26.6), P = 0.044) were independently associated with anastomotic leakage.

CONCLUSIONS: Significant predictors of anastomotic leak include smoking, difficult anastomosis, and level of anastomosis (<or=4 cm). Neoadjuvant chemoradiation therapy was not found to be significantly associated with leakage after tumor-specific mesorectal excision for rectal cancer.

Complications of Stomas

- Loop ileostomy or loop colostomy LOE 1
- Laparoscopic stoma creation for fecal diversion is safe, feasible and effective LOE 4

Stoma is an artificial opening made in the bowel to divert feaces and flatus to the exterior, where it can be collected in an external appliance.

Indications for loop / defunctioning stoma

- After anterior resection
- Malignancy associated obstruction
- Defunctioning after bowel injury (colon/rectum)
- Diverticular disease
- Non healing perineal wounds
- Uncontrolled bowel function after spinal injury

Types

Colostomy - end
- loop - transverse
- sigmoid

Ileostomy - end
- loop

Features of ileostomy

- spouting (3 cm above the skin)

Advantages
- easier to deliver loop of ileum
- better vascularity
- less odour

Disadvantages
- fluid content
- more skin irritation
- increased chances of electrolyte imbalance

Features of colostomy

- flush to skin

Advantages
- solid contents and easier to manage
- less skin irritation
- less electrolyte imbalance

Disadvantages
- odour
- relatively poor vascularity

Stoma complications

Early
- skin irritation
- infection / abscess
- ischemia / necrosis
- retraction
- mucosal bleed

Late
- hernia
- fistula formation
- prolapse
- stenosis
- malignant change / stoma site recurrence.

Complications are reported in 30-60% of stomas.

Loop colostomy is associated with increased chances of prolapse (0 – 42%), wound infection and wound complications.

Chances of pre and post closure obstruction were more in ileostomy patients (0-10%), as were chances of high output stoma (2.6-71%).

Prolapse and hernia are associated with poor nutritional status, poor surgical technique, emergency surgery, and early complications like wound infection, fistula, ischemia or necrosis also predispose to prolapse and hernia.

Incidence rates vary widely among studies, and this reflects wide variations in definitions, techniques and even teaching methodologies.

Stoma site varices associated with portal hypertension have also been reported.

Factors associated with increased stoma complications

- increasing age
- emergency surgery
- nature of disease (malignant)
- diabetes (late skin irritation)
- body mass index- higer BMI associated with increased early skin excoriation and retraction
- improper surgical technique

Prevention of complications

Preoperative counselling

By a trained stoma clinic nurse and should include psychosocial support, information regarding stoma formation, appliances available and its handling, stoma management and support groups.

Stoma site marking

The site should be away from bony prominences, skin crease and scars to ensure proper fitting of appliance and to decrease chances of skin irritation.

The marking should be both, in sitting and supine positions, and should be visible to the patient in the sitting position.

The stoma should be sited within the rectus abdominis muscle to avoid prolapse.

Operative procedure and techinical considerations to avoid complications

Adequate sized skin incision taken at marked site and is deepened till the sheath to accomodate two fingers; an excessively large stoma size predisposes to prolapse.

Care should be taken to avoid "coring in" and dead space creation in subcutaneous space to decrease infections and abscess formation.

The muscle is split along its length and retracted. Division of muscle should be avoided.

A well perfused end segment or loop of bowel should be delivered into the site without traction on the bowel or blood vessels. In case of end stomas, the end segment of bowel should be closed with fine sutures or staples before delivering to avoid accidental spillage of bowel contents and subsequent infections.

Mesenteric vessels may be ligated, taking care to preserve the arcade, to provide adequate, tension free length and thus avoid traction to the actual stoma.

The bowel is approximated to the sheath with fine sutures on a round body needle. This step ensures decreases chances of stoma prolapse and herniation.

Management of complications

Most stoma complications can be managed conservatively.

10-20% of stomas require surgical interventions.

Isolated stoma site recurrence of malignancy warrants wide excision with creation of stoma at a new site away from the earlier one.

Management of prolapse

They can be managed conservatively with change to appropriate stomal appliance or binder with plastic ring over stoma device to keep the hernia reduced.

Surgical intervention can be through a local approach or intraperitoneal approach.

Local procedures involve excision including mucocutaneous junction, refashioning the delivered bowel and then maturing the stoma with or without use of mesh. Care should be taken so that excess of skin is not excised and stomal opening should not be large; else chances of recurrence are high.

Some reports have suggested cutting through the mucosa leaving a rim of mucosa on the mucocutaneous junction to avoid this problem.

A modified Delorme's procedure with excision of mucosa of prolapsed segment, leaving behind the seromuscular layer, and then taking pleating sutures has also been suggested.

In the intraperitoneal approach, the bowel is reposited under anesthesia and the facial opening may be plicated to required size, with or without use of mesh to reinforce. The bowel is then approximated to the abdominal wall with 2-3 sutures.

Management of peristomal hernia

Conservative management is similar to that of a prolapse. Surgical intervention should be considered only for

troublesome symptoms since chances of re-occurrence are high.

Surgery involves either relocating it at another site with primary closure of the hernial site with or without a meshplasty. This carries a lower chance of recurrence but involves formation of a new stoma with all associated consequences. Another approach is to repair the defect intraperitoneally with plication of the fascial sheath with or without mesh reinforcement. The underlay method has been preferred in some studies. The placement of a mesh adjacent to bowel carries inherent problems of bowel erosion.

Loop ileostomy or loop colostomy?

The available evidence for decompression of colorectal anastomosis, either use of loop ileostomy or loop colostomy, could not be clarified. So far, the results in terms of occurrence of postoperative stoma prolapse and other complications support the choice of loop ileostomy as a technique for fecal diversion for colorectal anastomosis, but large scale RCT's are needed to verify this.

In the Cochrane analysis (2007) evaluating ileostomy versus colostomy for defunctioning after colorectal anastomosis, the rates of complications for ileostomy compared with colostomy were wound infection (8% and 14%), prolapse (2% and 19%), retraction (4% and 1%), peristomal hernia (3% and 2%), fistula (3% and 4%), skin irritation (13% and 21%) respectively. The post stoma closure complications were, leak (4% and 2%), post closure obstruction (5% and 4%), incisional hernia (0% and 10%) respectively for ileostomy and colostomy (Level of Evidence i.e. LOE 1).

According to a recent study by Harris DA, ileostomy patients reported a better quality of life and loop ileostomy had lower complication rates over loop colostomy for defunctioning of colorectal anastomosis, but these results did not reach statistical

significance and no conclusion could be drawn regarding superiority of one form of stoma over the other.

Laproscopy and stoma

Laproscopic stoma creation is a feasible option and also helps as a stepping stone for learning laproscopic colorectal surgery. In a study published in 2005 by Liu et al., the advantages of laparoscopic stoma creation were low morbidity (approx 11%) and reoperation rates. Furthermore, there was no procedure-related mortality; they concluded that laparoscopic stoma creation for fecal diversion is safe, feasible and effective (LOE 4).

Laparoscopy is also useful in management of complication like prolapse and hernia repair.

References

1. Complications and mortality following stoma formation.

Harris DA, Egbeare D, Jones S, et al. Ann R Coll Surg Engl 2005;87:427–31.

INTRODUCTION: As stoma formation is thought to be declining, we performed a study to evaluate the rate of stoma formation and the impact on stoma complication rates, together with risk factors for complications. PATIENTS AND METHODS: Stoma incidence, individual complications and mortality rates were retrieved from a stoma nurse database of 345 stomas created over an 8-year period. RESULTS: Stoma formation increased over the study period, although the incidence of complications declined. Stoma complications were more frequently seen in emergency surgery. A significant association between stoma complications and mortality was identified. CONCLUSIONS: Age of patient, urgency of surgery and diagnosis were associated with high levels of

morbidity and mortality. Stomas are often formed in frail patients unsuitable for anastomosis formation, which may explain the high mortality in ostomy patients.

2. Complications of abdominal stoma surgery.

Shellito PC. Dis Colon Rectum 1998;41:1562–572.

PURPOSE: This study was undertaken to review and summarize the complications of ileostomy and colostomy creation and subsequent closure. METHODS: The English-language medical literature for at least the past 15 years was reviewed comprehensively. RESULTS: Complications of surgery for the creation of end, loop, and "end loop" stomas are presented. Technical factors, which might influence complication rates, are discussed. Optimal management of ostomy complications is presented, especially for peristomal hernias. Similarly, techniques and complications for stoma closure are analyzed. CONCLUSIONS: Stoma creation is not a trivial undertaking; careful surgical technique minimizes complications (which are relatively frequent), and promotes good ostomy function. Peristomal hernias are difficult to cure permanently. The morbidity of ileostomy and colostomy closure is also appreciable.

3. Incidence of complications of the stoma and peristomal skin among individuals with colostomy, ileostomy, and urostomy: a systematic review.

Salvadalena G. J Wound Ostomy Continence Nurs. 2008;35:596-607.

The objectives of this systematic review were to assess the incidence of complications of the stoma and peristomal skin, synthesize possible reasons for variability in results, and make recommendations for future research. Twenty-one studies published in English between January 1990 and August 2007, with a prospective design that reported the number of

complications of the stoma or peristomal skin among participants with colostomy, ileostomy, or urostomy, were identified. The types of complications most commonly reported were retraction, hernia, prolapse, peristomal skin problems, and necrosis. Incidence rates varied widely among studies, even when the same types of complications were measured. Inadequate reporting of attrition, the number of participants at each phase of analysis, and missing data were common problems. Differences among study durations, the absence of definitions of complications, and failure to describe how complications were evaluated contributed to variability in reported complication rates. More studies are needed that use a prospective design, consistent operational definitions, and valid and reliable measurement methods. These recommendations will help increase the availability of standardized data to make comparisons among studies possible.

4. Ileostomy or colostomy for temporary decompression of colorectal anastomosis.

Güenaga KF, Lustosa SA, Saad SS et al. Cochrane Database Syst Rev. 2007 24;:CD004647.

BACKGROUND: The use of loop ileostomy or loop transverse colostomy represents an important issue in colorectal surgery. Despite a slight preference for a loop ileostomy as a temporary stoma, the best form for temporary decompression of colorectal anastomosis still remains controversial. OBJECTIVES: To assess the evidence in the use of loop ileostomy compared with loop transverse colostomy for temporary decompression of colorectal anastomosis, comparing the safety and effectiveness. SEARCH STRATEGY: We identified randomised controlled trials from MEDLINE, EMBASE, Lilacs, and the Cochrane Central Register of Controlled Trials. Further, by hand-searching relevant medical journals and proceedings from major gastroenterological congresses. We

did not limit the seaches regarding date and language. SELECTION CRITERIA: We assessed all randomised clinical trials, that met the objectives and reported major outcomes: 1. Mortality; 2. Wound infection; 3. Time of formation of stoma; 4. Time of closure of stoma; 5. Time interval between formation and closure of stoma; 6. Stoma prolapse; 7. Stoma retraction; 8. Parastomal hernia; 9. Parastomal fistula; 10. Stenosis; 11. Necrosis; 12. Skin irritation; 13. Ileus; 14. Bowel leakage; 15. Reoperation; 16. Patient adaptation; 17. Length of hospital stay; 18. Colorectal anastomotic dehiscence; 19. Incisional hernia; 20. Postoperative bowel obstruction. DATA COLLECTION AND ANALYSIS: Details of the randomisation, blinding, whether an intention-to-treat analysis was done, and the number of patients lost to follow-up was recorded. For data analysis the relative risk and risk difference were used with corresponding 95% confidence interval; fixed effect was used for all outcomes unless incisional hernia (random effect model). Statistical heterogeneity in the results of the meta-analysis was assessed by inspection of graphical presentation (funnel plot) and by calculating a test of heterogeneity. MAIN RESULTS: Five trials were included with 334 patients: 168 to loop ileostomy group and 166 to loop transverse colostomy group. The continuous outcomes could not be measured because of the lack of the data. The outcomes stoma prolapse had statistical significant difference: p=0.00001, but with statistical heterogeneity, p=0,001. When the sensitive analysis was applied excluding the trials that included emergencies surgeries, the result had a discreet difference: p = 0.02 and Test for heterogeneity: chi-square = 0.78, df = 2, p = 0.68, I(2)=0%. AUTHORS' CONCLUSIONS: The best available evidence for decompression of colorectal anastomosis, either use of loop ileostomy or loop colostomy, could not be clarified from this review. So far, the results in terms of occurrence of postoperative stoma prolapse support the choice of loop ileostomy as a technique for fecal diversion

for colorectal anastomosis, but large scale RCT's is needed to verify this.

5. A prospective audit of stomas—analysis of risk factors and complications and their management.

Arumugam PJ, Bevan L, Macdonald L et al. Colorectal Dis. 2003;5:49-52.

AIM: To prospectively audit stomas and to determine the nature and rate of complications and their relationship with various risk factors and their management. MATERIALS AND METHODS: The study was performed prospectively on 97 consecutive patients who had stomas formed between January 2000 to August 2000. Patients were followed up for one year. Risk factors including age, body mass index (BMI), preoperative siting, contour of the abdominal wall, smoking, grade of operating surgeon, emergency or elective procedure, diabetes, type of stoma and suture material used were noted. The type of surgery, and indications for surgery were also recorded. The complications were documented by two qualified stoma nurses and a photographic record taken. Statistical analysis comprising both univariate and multivariate methods, was performed by SPSS 10. RESULTS: The mean age was 65 years (standard deviation 16.01, range 16-99) and mean body mass index was 24.5 (standard deviation 4.66, range 15-37). Forty-nine of 97 (50.5%) stomas developed one or more complications. Twenty-three patients experienced retraction, 18 had stomas sited in a skin crease, 16 had early and 12 had late skin excoriation, 12 had detachments and a further 12 had parastomal hernia. Eleven further stoma complications were noted including prolapse, necrosis, ischaemia and sloughing. None of the risk factors achieved statistical significance when analysed against the overall complication rate. However, when the risk factors were analysed against individual complications using univariate logistic regression, a high body mass index was associated

with more retractions (P = 0.003), early skin excoriation (P = 0.036) and poor siting (stoma in crease) occurred more commonly in emergencies (P = 0.022). Diabetes was associated with late skin excoriation (P = 0.02). Multivariate logistic regressions confirmed an independent association of body mass index, diabetes and emergency surgery with complications. Forty-five of 49 patients who had complications needed some conservative management such as a convexity appliance. Four patients needed refashioning. CONCLUSION: Body mass index, diabetes and emergency surgery were the significant risk factors identified in our study. Overall complications compare favourably with other series. We found that preoperative siting by stoma nurses and the grade of operating surgeon did not affect the outcome.

6. Temporary Ileostomy Versus Temporary Colostomy: A Meta-analysis of Complications.

Lertsithichai P, Rattanapichart P. Asian J Surg. 2004;27:202-210; discussion 211-12.

OBJECTIVE: To compare the complications of temporary diverting ileostomy with those of temporary colostomy for patients with colorectal diseases. METHODS: Two independent researchers conducted a systematic search for randomized controlled trials (RCTs) comparing temporary ileostomy with temporary colostomy in MEDLINE, the Cochrane database, evidence-based medicine reviews and the American College of Physicians journal club, as well as relevant reference lists in journal articles. Five RCTs were found and included in this meta-analysis. All complications were abstracted and compared between groups. All complications were also assessed using tests of statistical heterogeneity, pooling of risk ratios using Mantel-Haenszel fixed effects and DerSimonian and Laird random effects. Clinical heterogeneity was investigated by examining the

methodology and selection of patients described in each trial. RESULTS: Temporary colostomy was significantly more likely to cause stoma complications in colorectal cancer patients undergoing elective resections, and also more likely to cause infectious and wound complications. Temporary ileostomy tended to cause more post-closure surgical complications. CONCLUSIONS: There is not yet a strong case for the superiority of one temporary diverting stoma over another for all colorectal patients. In this regard, a large, well-conducted RCT is still needed.

7. Stoma formation for fecal diversion: a plea for the laparoscopic approach.

Liu J, Bruch HP, Farke S et al. Tech Coloproctol. 2005; 9:9-14; discussion 14

BACKGROUND: The aim of this study was to assess the results of laparoscopic stoma creation for fecal diversion, specifically focussing on feasibility, safety, and efficacy, as well as indications and techniques. METHODS: Within a 10-year-period, all patients requiring laparoscopic stoma creation were evaluated prospectively. Patients' profiles and indications, procedures and results of operation, conversion, morbidity, mortality and short-term complications (stoma-related, laparoscopy-associated) were analyzed. RESULTS: A total of 80 patients (39 males, 41 females) with a mean age of 55.5 years (range, 17-91) underwent laparoscopic stoma creation. Most common indications were unresectable advanced colorectal cancer (n=20), pelvic malignant cancer (e. g. ovarian, cervix and prostate cancer, n=16), and perianal Crohn's disease with complex fistulas (n=16). Only in one female patient with pelvic malignant disease was the procedure converted to laparotomy due to obesity (conversion rate, 1.3%). 79 patients underwent laparoscopic stoma creation (completion rate, 98.7%) including loop ileostomy (n=30),

loop sigmoid colostomy (n=40) and end sigmoid colostomy (n=9). Postoperative complications were documented in 9 patients (overall morbidity rate, 11.4%), including 4 minor complications treated conservatively (2 cases of prolonged atonia and 1 case each of pneumonia and urinary tract infection) and 5 major complications requiring reoperation (reoperation rate, 6.3%): one parastomal abscess (drainage), one stoma retraction following rod dislocation (laparoscopic stoma recreation), small bowel obstruction in two patients (small bowel resection), one port-site hernia (fascial closure), and hemorrhage (managed by re-laparoscopy). Mean operation time was 74 min (range, 30-245 min). Mean blood loss volume was 80 ml (range, 30-400 ml). Patients were discharged from hospital after a mean of 10.3 days (range, 3-47). Within a 1-year follow-up, no further stoma complications were documented. CONCLUSIONS: The advantages of laparoscopic stoma creation are low morbidity and reoperation rates, and no procedure-related mortality; our results suggest that laparoscopic stoma creation for fecal diversion is safe, feasible and effective. Therefore, at our institution, laparoscopic stoma creation is the method of choice for fecal diversion.

8. Laparoscopic parastomal hernia repair is feasible and safe: early results of a prospective clinical study including 55 consecutive patients.

Hansson BM, de Hingh IH, Bleichrodt RP. Surg Endosc. 2007 ;21:989-93.

BACKGROUND: Parastomal herniation is a common complication, and its operative treatment is notoriously difficult. Recently, the authors have described a laparoscopic technique for closure and reinforcement of the hernia with a hand-made "funnel-shaped" Gore-Tex Dual Mesh. Potentially this technique combines the advantages of a mesh repair with

those of minimal invasive surgery. METHODS: In 2002, a multicenter trial of this new technique was started in The Netherlands. To date, 55 consecutive patients (27 men; median age, 63 years) with a symptomatic primary (n = 45) or recurrent (n = 10) parastomal hernia have undergone elective surgery using this technique. The demographic, perioperative, and early follow-up data prospectively collected for these patients are presented in this report. RESULTS: Of the 55 procedures, 47 (85.5%) could be completed laparoscopically (median operation time, 120 min). Conversion to laparotomy was indicated because of dense adhesions prohibiting safe dissection (n = 4) or bowel injury (n = 4). No in-hospital mortality occurred. Postoperative recovery was uneventful for 47 patients (85%), who had a median hospital stay of 4 days. Surgical and nonsurgical complications occurred, respectively, for four patients each (7.2%). Full-thickness enterotomy appeared to be the most troublesome complication. After 6 weeks, when all the patients were reexamined, one recurrence was noted. CONCLUSION: Maximal efforts should be undertaken to prevent perioperative full-thickness enterotomy. Because this was achieved for the vast majority of patients, it is concluded that laparoscopic parastomal hernia repair is feasible and safe. Although a longer follow-up period is needed for definitive conclusions to be drawn regarding the recurrence rate, early follow-up evaluation shows very promising results.

Section — VI

Gynaecological Oncology

Contributors

HB Tongaonkar

RA Kerkar

A Maheshwari

T Jose

Complications of Ovarian Cancer Surgery

- Aggressive cytoreductive surgery for ovarian cancer LOE 2
- Retroperitoneal approach in pelvic tumor resection LOE 3
- Retrograde hysterectomy in pelvic tumor resection LOE 4
- Pelvic and para-aortic lymphadenectomy in ovarian cancer surgery LOE 1
- Role of bowel surgery in ovarian cancer cytoreduction LOE 3
- Risk factors for anastomotic leak after rectosigmoid resectin in ovarian cancer LOE 3
- Splenectomy as part of cytoreductive ovarian cancer surgery LOE 3
- Complications of diaphargmatic tumor resection and diaphragmatic peritonectomy in ovarian cancer surgery LOE 3
- Role of hepatic resection in metastic ovarian carcinoma LOE 3

Surgery for Ovarian Carcinoma

Tumor reductive surgery is the foundation of primary treatment, since the amount of postoperative residual disease is the only prognostic factor that the physician can influence. To achieve a goal of limited residual disease, apart from resection of pelvic mass, several different procedures including retroperitoneal lymphadenectomy, intensive stripping of pelvic or abdominal peritoneum , diaphragm peritoneum stripping or resection , recto-sigmoidectomy, other bowel resection/s, splenectomy, or liver resection may be required to be undertaken. These procedures carry the risk of complications and morbidity.[1,2]

Complications of Pelvic Tumor Resection

Ovarian cancer commonly spreads along the peritoneal surfaces in the abdomen without respecting organ boundaries and commonly involves the internal genitalia, bowel , omentum and soft tissues in contiguity, with loss of normal surgical planes, forming an abdominopelvic mass. Pelvic tumor resections therefore can be very tedious and complicated.

Complications of Pelvic Tumor Resections

- Injury to pelvic viscera – Urinary bladder, Ureters, and Bowel.
- Injury to pelvic and retroperitoneal blood vessels – leading to per operative hemorrhage.
- Post operative pelvic and deep vein thrombosis.
- Post operative sepsis.
- Urinary and Bowel fistulas – Recto-vaginal fistula, Vesico-vaginal fistulas, Uretero-vaginal fistulas.
- Intestinal Obstructions in the late post operative period.

Prevention of Complications

- Retroperitoneal Approach : The essential principle of removal of pelvic tumor is to enter the retro peritoneum laterally by incising the peritoneum on the psoas muscle lateral to the infundibulopelvic ligament and colon thus preventing injuries to the Iliac vessels, ureters and obturator nerve so that surgeon can gain control over infundibulopelvic ligament and uterine pedicles supplying the tumor mass. With vital structures identified and protected and with the blood supply under control, the tumor and the pelvic viscera can be mobilized medially and removed.[3]
- Delineation Of Anatomy Of Pelvis : Identification of the ureters, the pelvic blood vessels and the round and infundibulopelvic ligaments not only prevent injuries to these structures but also guide in reconstructing the distorted anatomy and proceeding with the dissection safely.
- Development of Avascular Planes in the Pelvis : Development of paravesical, para rectal, prerectal, vesico-uterine and vesico-cervical spaces provide avascular planes for dissection thus preventing excessive bleeding and injury to important structures in the pelvis.
- Retrograde Hysterectomy: When the posterior cul-de-sac is completely obliterated by the tumor 'Hudson's method' of retrograde hysterectomy may be employed where the ureters are dissected out entirely in the parametrium and the vagina is entered anteriorly. By circumscribing the vagina and severing the uterosacral ligaments without entering the posterior cul de sac entire pelvic mass can be lifted out of the pelvis thus facilitating the removal of the cul- de-sac and removal the tumor from the surface of the rectum. If the rectum is involved removal of a segment may be required along with the tumor.[4]

Prevention of Urinary tract injuries

- o Pre operative ureteric stenting : rarely required.
- o Intra operative cystoscopy and methylene blue test for recognition of injuries.
- o Prolonged bladder drainage in case of injury to urinary tract repaired during surgery.
- o Careful ureteric handling and dissections – to avoid devascularization injury to ureter.
- o Proper intraoperative identification and repair of ureteric and bladder injuries.
- - **Thromboprophylaxis and Early ambulation** – to prevent DVT and other thrombotic complications.
- - **Broad spectrum antibiotic cover** – in view of the diverse flora of the female genital tract.

Prevention of Complications of Omentectomy

Omentectomy forms an essential part of staging and cytoreduction because, after pelvis omentum is the second most frequently involved site in ovarian cancer. The complications of omentectomy include:-

- - Bleeding from omental vessels, short gastric vessels
- - Injury to transverse colon
- - Injuries to :-
    - o Stomach
    - o Spleen
    - o Tail of Pancreas

These injuries may be prevented by the following surgical principles:-

- - Adequate incision to provide exposure till the splenic flexure when the disease in the omentum extends to the splenic flexure.

- Dissection to begin from the inferior aspect of the transverse colon along the definite plane that exists between the colon and the omentum thus exposing the lesser sac. The rest of omentum is then ligated from the greater curvature of the stomach.
- Careful ligation of the vessels supplying the omentum – Gastroepiploic and small gastric vessels from the gstroepiploic arcade.
- Splenectomy or repair of the splenic injury in case of injury to the capsule or splenic blood vessels.
- Nasogastric drainage in the post operative period to prevent distension of the stomach thereby disrupting ligated blood vessels along the greater curvature to cause bleeding.

Lymphadenectomy in Ovarian Cancers

Retroperitoneal lymph node dissection (RPLND) and pelvic lymph node dissection has been shown to improve 5-year progression-free survival for patients with optimally debulked advanced ovarian carcinoma.[5] The ability to perform an extensive RPLND is an important skill in the surgical armamentarium of the gynecologic oncologist. However these procedures put the patient at risk for certain complications.[6]

Complications of Lymphadenectomy

- Obturator nerve injury
- Vascular injury causing hemorrhage
- Ureteric Injury
- Duodenal Injury
- Lymphorrhoea and Lymphocoele
- Thrombotic episodes
- Pulmonary embolism

- Prolonged ileus
- Prolonged fever

Prevention of complications

- Adequate exposure
- Definition of boundaries of dissection and identification of vital structures.
- Meticulous hemostasis – use of cautery and hemaclips during dissection.
- Surgiclips to occlude lymphatic channels.
- Split and Roll technique of dissection – Aorta and IVC exposed , lumbar branches and tributaries split (ligated) and vessels rolled medially and laterally to complete clearance.
- Thromboprophylaxis in the post op period.
- Drainage of lymphorrhoea and lymphocoele.

Rectosigmoid Resection

In advanced ovarian cancers recto-sigmoid resection (RSR), either alone or en bloc with hysterectomy and bilateral salpingooophorectomy, is often necessary to achieve complete clearance of pelvic disease.

The options available after rectosigmoid resection are:-

- Primary anastomosis with or without diverting stoma.
- Colostomy with Hartman's procedure.

Complications of Rectosigmoid Resection

The most important complications are:-

- Anastomotic leaks after primary anastomosis.
- Stoma complications.
- Defaecatory dysfunction – due to very short residual sigmoid colon.

Anastomotic leak after RSR for ovarian cancer is a devastating and life-threatening complication. The leak rate reported in the colorectal literature varies from 2.8 to 23% , whereas it ranges from 0.8 to 3.2% in the gynecologic oncology literature. Recent publications indicate the mortality rate after an anastomotic leak ranges from 7.3 to 16%.[7]

Preoperative and Intraoperative Risk Factors for Anastomotic Leak.[8]

- Unprepared Bowel
- Long operating times (>120 Mins)
- Previous pelvic irradiation
- Short distance of the anastomosis to the anal verge (< 7cm)
- Low serum albumin level (< 3.0 g/dL)

Distance from the anal verge seems to be the most reproducible and important risk factor.

Prevention of Anastomotic Leaks after Rectosigmoid Resection

- Preoperative bowel preparation in all cases of Ca ovary.
- Avoiding primary anastomosis in cases at high risk for anastamotic leaks.
- Meticulous use of diversion colostomy after primary anastomosis.
- Use of contemporary stapling devices, such as the End to End (EEA) stapler.

Large Bowel Resection

Colon resection is central to ovarian cancer cytoreduction due to its frequency of involvement (over 50% in some recent series). Omentectomy en bloc with transverse colectomy is a straightforward operation. Due to its location in the pelvis, it is not surprising that the ileocecum is the second most frequent

portion of bowel to become extensively involved with ovarian cancer. In view of the haphazard and often widespread intraabdominal distribution of ovarian cancer metastasis, it is not surprising that multiple bowel segments may become involved in a single patient.[9]

Complications of Colon Resections

- Injury to viscera – Ureters, Spleen, Liver and Duodenum.
- Post operative bleeding – Secondary hemorrhage.
- Infections :
  - Non specific infections.
  - Infections secondary to anastamotic dehiscence.
- Cardio respiratory Complications : atelectasis, aspiration pneumonia and pulmonary embolism.
- Abdominal Complications
  - Post operative Ileus
  - Fascial dehiscence
  - Anastamotic breakdown - Clinical leaks occur in 1–2% of all colonic resections, but sub clinical leaks are more frequent and may be seen incidentally on contrast studies in otherwise asymptomatic patients.
- Short Bowel Syndrome

Prevention of Complications

- Adequate upper abdominal exposure during surgery.
- Meticulous hemostasis and following the principles of anastamosis.
- Adequate preoperative bowel preparation.
- Adequate post operative pain relief.
- Early post operative ambulation and chest physiotherapy.
- Carefully monitored fluid and electrolyte balance.

- Early detection of anastamotic leaks and timely management.

Splenectomy

For optimal cytoreductive results, splenectomy may be required when disease involves the hilum, capsule, or parenchyma of the spleen. In patients with extensive omental involvement extending into the splenic hilum, spleen may have to be removed en bloc with the omentum. The spleen or splenic vessels can be traumatized intraoperatively, when the spleen may require removal.[10]

Complications of splenectomy

- Pleural effusions – Left sided.
- Pneumonia – Left lower lobe atelectasis.
- Traumatic injury to the pancreatic tail and pancreatic fistula.
- Postoperative sepsis.
- Thrombosis of splenic , hepatic and superior mesenteric veins.
- OPSI (Overwhelming Post Splenectomy Infection).
- Transient reactive thrombocytosis in the immediate postoperative period.

Prevention of Complications

- Vaccinations: The importance of appropriate vaccination in the splenectomized patient merits special attention. Pneumococcus is the major pathogen in postsplenectomy sepsis, accounting for 50% to 90% of all infections. If there is known splenic parenchymal involvement preoperatively and a splenectomy is anticipated, patients should receive the pneumococcal vaccine (Pneumovax), H influenzae vaccine (if available), and meningococcal vaccinations approximately 10 to 14 days before surgery

to maximize immunity. Patients who do not receive the vaccine preoperatively should receive the appropriate vaccinations in the immediate postoperative period.

- Closed suction drainage for traumatic injury to the pancreatic tail.
- Anti Platelet agents : Acetyl salicylic acid to prevent thrombotic complications.
- Early recognition of OPSI and aggressive treatment.

Diaphragmatic Peritonectomy and Resection

Bulky diaphragmatic disease is a factor precluding optimal cytoreduction, second only to portal triad disease. . A major source of inability to achieve optimal surgical debulking is the inability to remove significant disease from the hemi diaphragm.

Diaphragmatic Peritonectomy (DP) is a relatively simple procedure and greatly facilitated by hepatic mobilization. Adoption of this technique has the potential to improve maximal cytoreduction rates and patient outcomes. It should be noted that these patients appear to be more prone to the development of post-operative pleural effusions. While no prophylactic intervention is necessary, due vigilance is required to assess these patients for shortness of breath and the possible need for thoracentesis.[11]

Diaphragmatic resections (DR) might be required in cases of disease involving the diaphragm in depth.. Adequate exposure of the hemi diaphragm is the single most critical variable in safe resection of disease in the right hemi diaphragm. For those lesions which penetrate the diaphragm, attempts at destruction with either electrocautery or CUSA (Caritron Ultrasonic Surgical Aspirator) carries a high risk of either perforation of the diaphragm or leaving residual disease. The lesion is grasped with long Allis clamps to evert the diaphragm and sharp resection is performed. The anesthesiology team is informed

of the large defect and resultant pneumothorax. The pleura and lung are carefully inspected and meticulous hemostasis secured to avoid hemothorax in the postoperative period. The diaphragmatic defect is then closed with monofilament delayed absorbable sutures in an interrupted horizontal mattress fashion. The diaphragm is inspected for leaks and for obvious evidence of significant residual pneumothorax; a post- or intra-operative chest radiograph is performed on all cases and any significant pneumothorax managed with a chest tube. DR as part of cytoreductive surgery for ovarian cancer carries risks comparable to other radical debulking procedures.[12]

Hepatic Resection

Hepatic metastases occur in about 10 % cases of advanced ovarian cancer. One-half of the hepatic parenchymal metastases from peritoneal seeding require anatomic resection, which must be performed by a hepatobiliary surgeon; and the other half required non-anatomic resection, which could be resected by an experienced gynecologic oncologist. Measures aimed at preserving hepatic parenchyma, without compromising the integrity of the resection, have a significant influence on operative morbidity and mortality.[12]

Complications of Hepatic Resection

- Intra operative hemorrhage
- Inadvertent injury to aberrant vascular and billiary structures
- Persistent bile drainage
- Sepsis
- Post operative liver failure and jaundice
- Metabolic derangements – hypokalaemia, hypo-phosphatemia, hypokalaemia and hypoalbimunemia.
- Coagulopathies – due to blood loss, dilution factors and inadequate liver functions

- Pulmonary complications – atelectasis, effusions, consolidations and pneumonia.
- Thrombophlebitis

Prevention of Complications

- Adherence to the ‘ Principles of Liver Resection’ (Quattlebaum and Quattlebaum 1967)
    - Adequate exposure
    - Complete mobilization
    - Hilar control of vascular and billiary structures
        - Extra hepatic portal dissection and transaction.
        - Intrahepatic vascular inflow control.
        - Hepatotomy method (Posterior Method).
        - Transection method (Anterior Method).
    - Atraumatic division of liver substance
        - Finger fracture method.
        - Cavitron Ultrasonic Surgical Aspirator(CUSA).
        - Argon beam coagulation.
    - Avoidance of mattress sutures
    - Adequate drainage.
- Use of haemostatic agents during surgery - Oxidized regenerated cellulose (Surgicel), Purified Gelatin (Gelfoam) etc.
- Anatomical segmental resections rather than nonanatomical wedge resections whenever feasible
- Use of Intraoperative ultrasound.
- Intensive post operative care – to prevent pulmonary, infective and metabolic complications.

Role of Surgeon in Complications

The operative technique and experience of the operating surgeon are the main factors associated with the rate of complications. The surgeon must be strongly familiar with anatomic variations that can yield complications . The appropriate management of such complications done quickly and completely considerably reduces the morbidity and mortality. Homesley et al [14] reported that operating time, postoperative stay, estimated blood loss and postoperative complications were increased significantly between the surgeons depending on their subspeciality training. Ovarian cancer specialists, usually gynecologic oncologists, are much more likely to accurately assess the stage of the disease, and optimally cytoreduce the tumor with acceptable complication rates and thus most likely to impact survival.[15]

References

1. Winter WE, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage A epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2008;26:83–9.
2. Bristow RE, Tomacruz RS, Armstrong DK. et al., Montz FJ.Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248–59.
3. Benedetti-Panici P, Maneschi F, Scambia G. et al. The pelvic retroperitoneal approach in the treatment of advanced ovarian carcinoma: Obstet Gynecol.1996; 87:532-8.
4. Hudson CN. Surgical treatment of ovarian cancer. Gynecol Oncol, 1973;1;370-375
5. Panici PB, Maggioni A, Hacker N, et al. Systematic aortic and pelvic lymphadenectomy versus resection of

bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. J Natl Cancer Inst 2005;97:560–5.

6. Zorlu CG, Mendlcolu D, Smsek T, et al. Pelvic and Paraaortic Lymphadenectomy as a Staging and Therapeutic Procedure: Mortality and Morbidity. T Klin J Gynecol Obst .2000; 10:36-9.

7. Juretzka MM , Barakat RR. Pelvic cytoreduction with rectosigmoid resection Gynecologic Oncology 2007; 104 : S40–4.

8. Richardson DL, Mariani A, et al. Risk factors for anastomotic leak after recto-sigmoid resection for ovarian cancer. Gynecologic Oncology 2006; 103: 667–72.

9. Cai HB, Zhou YF, Chen HZ, et al. The Role of Bowel Surgery with Cytoreduction for Epithelial Ovarian Cancer. Clinical Oncology. 2007; 19: 757-62.

10. Magtibay PM, Adams PB, Silverman MB, et al. Splenectomy as part of cytoreductive surgery in ovarian cancer. Gynecologic Oncology 2006; 102: 369–74.

11. Dowdy SC, Loewen RT, Aletti G, et al. Assessment of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma. Gynecologic Oncology. 2008;109:303–7.

12. Cliby W, Dowdy S C, Feitoza SS, et al. Diaphragm resection for ovarian cancer: technique and short-term complications. Gynecologic Oncology. 2004; 94: 655–60.

13. Lim MC, Kang S, Lee KS, et al. The clinical significance of hepatic parenchymal metastasis in patients with primary epithelial ovarian cancer. Gynecologic Oncology. 2009;112: 28–34.

14. Homesley HD, Kadar N, Barrett RJ, et al. Selective pelvic and periaortic lymphadenectomy does not increase mobidity in surgical staging of endometrial carcinoma. Am J Obstet Gynecol 167:1225-30.

15. Eisenkop SM, Spirtos NM, Montag TW, et al.The impact of subspeciality training on the management of advanced ovarian cancer. Gynecol Oncol. 1992 ;47(2):203-9.

1. Tumor Residual After Surgical Cytoreduction in Prediction of Clinical Outcome in Stage IV Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study.

Winter WE, Maxwell GL, Tian C et al. J Clin Onco.; 2008; 26:83-89.

Purpose: To identify factors predictive of poor prognosis in a similarly treated population of women with stage IV epithelial ovarian cancer (EOC). **Patients and Methods**: A retrospective review of 360 patients with International Federation of Gynecology and Obstetrics stage IV EOC who underwent primary surgery followed by six cycles of intravenous platinum/ paclitaxel was performed. A proportional hazards model was used to assess the association of potential prognostic factors with progression-free survival (PFS) and overall survival (OS). **Results**:The median PFS and OS for this group of stage IV ovarian cancer patients was 12 and 29 months, respectively. Multivariate regression analysis revealed that histology, malignant pleural effusion, intraparenchymal liver metastasis, and residual tumor size were significant prognostic variables. Whereas patients with microscopic residual disease had the best outcome, patients with 0.1 to 1.0 cm residual disease and patients with 1.1 to 5.0 cm residual disease had similar PFS and OS Patients with a residual size more than 5 cm had a diminished PFS and OS when compared with all other groups. Median OS for microscopic, 0.1 to 5.0 cm, and

more than 5.0 cm residual disease was 64, 30, and 19 months, respectively. **Conclusion** : Patients with more than 5 cm residual disease have the shortest PFS and OS, whereas patients with 0.1 to 1.0 and 1.1 to 5.0 cm have similar outcome. These findings suggest that ultraradical cytoreductive procedures might be targeted for selected patients in whom microscopic residual disease is achievable. Patients with less than 5.0 cm of disease initially and significant disease and/or comorbidities precluding microscopic cytoreduction may be considered for alternative therapeutic options other than primary cytoreduction.

2. Aggressive surgical strategies in advanced ovarian cancer: A monocentric study of 203 stage IIIC and IV patients.

Colombo PE , Mourregot A, Fabbro M, et al. EJSO 2008: 1-9 (Accepted online 8 January 2008)

Aims: The standard treatment for advanced ovarian cancer consists of cytoreductive surgery associated with a platinum/paclitaxel-based chemotherapy. Nevertheless, there is still the question as to the extent and timing of the surgical debulking. The aim of this study was to evaluate the place of surgery in the therapeutic sequence. **Patients and methods**: We reviewed data from all consecutive patients with stage IIIC and IV epithelial ovarian cancer, operated on at our institution between 1990 and 2005. Patients were divided into 2 groups, according to the position of surgery in the therapeutic sequence. Patients in group 1 received initial debulking surgery. Group 2 consisted of patients having received their first debulking after initial chemotherapy. **Results**: Two hundred and three patients were identified and frequently underwent aggressive surgery, in particular, digestive surgery with bowel resections. Perioperative mortality and morbidity rates were low (2% and 14%, respectively) and there was no difference between the

groups. Overall survival in group 1 for patients with complete cytoreduction (residual disease (RD) ¼ 0), optimal surgery (RD < 1 cm) or sub-optimal surgery (RD > 1 cm) was 50%, 30% and 14%, respectively. In group 2, overall survival following complete surgery was 30%, and no long-term survival was observed when surgery was not complete at the time of interval surgery. Survival was worse for patients who had received more than 4 cycles of neoadjuvant chemotherapy. **Conclusion**: This study confirms the importance of surgery in the prognosis of advanced ovarian cancer. Only the patient subgroup that underwent complete initial or interval surgery was associated with a prolonged remission. Optimal surgery with a controlled morbidity can be achieved in many cases, even if bowel resection is needed, at the time of primary debulking. In the interval cytoreductive surgery subgroup, the response to initial chemotherapy and surgery was found to be essential for prognosis.

3. The pelvic retroperitoneal approach in the treatment of advanced ovarian carcinoma.

Benedetti-Panici P, Maneschi F, Scambia G et al. Obstet Gynecol.1996; 87:532-8.

Objective: To evaluate the feasibility, complications, and clinical role of pelvic cytoreduction using the retroperitoneal approach in the treatment of advanced ovarian cancer. **Methods**: We studied 66 women with previously untreated advanced ovarian cancer who underwent pelvic retroperitoneal surgery. The possibility of achieving extrapelvic cytoreduction (residual disease less than 2 cm), involvement of the Douglas cul-de-sac or vesicouterine fold, or the presence of a frozen pelvis were indications for the retroperitoneal approach. Operative time, blood loss and transfusions, perioperative complications, and postoperative stay were analyzed prospectively. The performance status of each patient was

assessed preoperatively and postoperatively. **Results**: The pelvic retroperitoneal approach was used in 66 of 147 (45%) consecutive patients who underwent primary surgery with intent of cytoreduction. This approach was necessary in 60 of 94 (64%) patients with residual tumor less than 0.5 cm and contributed to achieving such a minimal residual disease in 36 of 38 (95%) stage IIB-IIIB and 58 of 109 (53%) IIIC-IV patients. Severe morbidity, but with no long-term sequelae, occurred in six (9%) patients. Before surgery, only ten (15%) of these patients had a performance status grade 0-1, 21 (32%) had grade 2, and 35 (53%) grade 3-4. After surgery, these figures were 52 (79%), 14 (21%), and 0, respectively. The 5-year survival rate was 37%, with a median survival and follow up time of 27 months (range 4-98) and 43 months, respectively. **Conclusion**: If the proper technique is used, complete pelvic cytoreduction is always feasible and morbidity is acceptable. In our series, it was necessary to approach the pelvis retroperitoneally in 64% of optimally cytoreduced patients, which suggests that this technique has an important clinical role in the treatment of patients with advanced ovarian cancer.

4. Pelvic and Paraaortic Lymphadenectomy As a Staging and Therapeutic Procedure: Mortality and Morbidity

Zorlu CG, Mendlcolu D, Smsek T et al. T Klin J Gynecol Obst 2000, 10:36-39

Objective: To assess the complications occurred due to pelvic and paraaortic lymphadenectomy

Study Design: A retrospective review of 41 patients with gynecologic malignancies who underwent pelvic and paraaortic lymphadenectomy along with various types of hysterectomy was performed for intraoperative, early postoperative and late postoperative complications. **Results**: Vascular injuries occurred in two patients (4.8%): one internal

iliac artery (2.4%) and one vena cava inferior (2.4%). Two patients experienced tromboembolic complications (4.8%). One pelvic lymphocele (2.4%) was diagnosed postoperatively. Obturator nerve injury occurred in one case (2.4%). In nine patients (21.9%), minor complications such as wound infection, prolonged ileus and prolonged fever were observed. **Conclusion**: We conclude that lymphadenectomy procedure can be performed with low morbidity in all gynecologic malignancies by means of proper surgical technique and wide experience.

5. The Role of Bowel Surgery with Cytoreduction for Epithelial Ovarian Cancer

Cai HB, Zhou YF, Chen HZ et al. Clinical Oncology 2007; 19: 757-762

Aims: To assess the efficiency and morbidity associated with bowel resection with the initial cytoreduction procedurefor advanced ovarian cancer. **Materials and methods**: A review was carried of 95 patients with ovarian cancer who underwent cytoreductive surgery between 2000 and 2003. The relationship between dichotomised preoperative, intra-operative and postoperative outcome variables were tested using SPSS software. KaplaneMeier curves were generated to compare survival. Cox proportional hazards regression was used to determine the independent significance of factors after cytoreductive surgery. **Results**: In patients in whom bowel resection was carried out, the largest residual tumour mass was !1 cm in 66.67% of patients, compared with 45.28% of patients undergoing surgery without bowel resection (P[0.038). The median survival in the optimally debulked patients was 50.38 months compared with 37.15 months in the patients who had suboptimal cytoreduction (P[0.0021). The median survival in patients undergoing bowel resection was 50.70 months compared with 44.62 months in the patients who had cytoreduction without bowel resection (P[0.2176).

Multivariate analysis showed that optimal cytoreduction (P[0.005) was found to be independently prognostic for overall survival. Major adverse events, such as ileus, intestinal fistulae, urinary tract fistulae, were not significantly different between groups. **Conclusion**: Bowel resection is a worthwhile endeavour in selected patients with advanced ovarian cancer to increase therapeutic efficiency. The surgical morbidity rate from these procedures is not serious and seems acceptable.

6. Risk factors for anastomotic leak after recto-sigmoid resection for ovarian cancer.

Richardson DL, Mariani A, Cliby WA et al. Gynecologic Oncology 2006; 103:667–72

Objectives. Anastomotic leak after recto-sigmoid (RS) resection for ovarian cancer (OC) is a life-threatening complication. Selection of patients for protective diverting stomas has been based on observations from the colorectal literature. Our objective was to identify primary risk factors for anastomotic leak in OC patients undergoing RS resection to better determine who would most benefit from protective diversion. **Methods**. All patients with OC or primary peritoneal cancer who underwent a debulking procedure with RS resection between January 1999 and December 2004 were included. Retrospective chart review including review of operative notes, pathology reports, and medical records including follow-up visits was done. Cases with inadequate postoperative follow-up, primary end colostomies, or diverting stomas were excluded. **Results**. 177 patients form our study cohort. There were a total of 12/177 anastomotic leaks (6.8%). The mean time to diagnosis of anastomotic leak was 19 days (range 4–32). The leak rate for primary debulking operations was 8.7% (10/115), whereas the leak rate in secondary debulking procedures was 3.2% (2/62) (NS, P = 0.22). In univariate analysis, only perioperative serum albumin was significantly associated with an increased risk of anastomotic

leak (mean 3.4 g/dL vs. 2.4 g/dL, P = 0.002). Based on serum albumin, the leak rate was 6/29 (21%) for levels <3.0 g/dL and 2/58 (3.4%) for patients with albumin greater than or equal to 3.0 g/dL (OR 7.3, 95% CI 1.37–38.87). **Conclusions**. Low serum albumin is associated with an increased risk of anastomotic leak after RS resection for OC. Patients with a low albumin level may benefit from a protective diverting colostomy/ileostomy.

7. Splenectomy as part of cytoreductive surgery in ovarian cancer

Magtibay PM, Adams PB, Silverman MB et al.
Gynecologic Oncology 2006; 102: 369–74

Objective. Epithelial ovarian carcinoma with extensive upper abdominal disease may require splenectomy for optimal tumor cytoreduction. We describe patients who required splenectomy during tumor reduction procedures for primary or recurrent epithelial ovarian carcinoma. **Methods**. Data were abstracted from records of 112 patients who underwent splenectomy as part of primary or secondary cytoreductive surgery. Results. Of 112 patients, 66 had primary and 46 had secondary cytoreduction. Some patients also required bowel resection (50%), formal lymphadenectomy (31%), or urinary tract resection (5%). The most common indications for splenectomy were direct metastatic involvement (46%), facilitation of an en bloc resection of perisplenic disease (41%), and intraoperative trauma (13%). Histologically, 65% had hilar involvement; 52%, capsular involvement; and 16%, parenchymal metastases. Short-term complications included wound infections (7), pneumonias (5), thromboembolic events (9), and sepsis (5). Sepsis was associated with an anastomotic bowel leak in 1 patient, with fungal infections in 2 patients (1 pneumonia and 1 pelvic abscess), and with no identifiable infectious source in 2. Two patients required reoperation for bleeding: 1 for diffuse intraabdominal bleeding, including the

splenic bed, and 1 for pelvic sidewall bleeding. The perioperative mortality rate at splenectomy was 5%: 3 from sepsis (1 anastomotic leak, 2 pneumonias), 2 from pulmonary embolism, and 1 for which the precise cause of death was not ascertainable. The primary cytoreduction group had a median survival of 1.8 years, with an estimated 2-year survival rate of 46%. The median survival in the secondary debulking group was 1.7 years, with an estimated 2-year survival of 42%. **Conclusions**. In patients with clinically significant upper abdominal disease, splenectomy as part of primary or secondary cytoreductive surgery is associated with modest morbidity and mortality. The risk–benefit ratio of aggressive surgical cytoreduction must be considered.

8. Diaphragm resection for ovarian cancer: technique and short-term complications

Cliby W, Dowdy S C, Feitoza SS et al. Gynecologic Oncology. 2004; 94: 655–60

Objective. Diaphragm resection (DR) is occasionally necessary to achieve optimal cytoreductive surgery in ovarian carcinoma (OC). In a recent survey of the SGO membership, bulky diaphragm disease was one of the most common justifications for suboptimal debulking (Gynecol. Oncol. 82 (2001) 489). The aim of this study was to assess postoperative complications of DR in OC. **Methods**. Retrospective chart review of all patients with OC who underwent DR from January 1988 through December 2001 at Mayo Clinic. **Results**. We identified 41 women who underwent DR for OC. DR was performed during debulking for recurrent disease in 85%. Most patients (95%) underwent associated radical debulking procedures including bowel resection (51%), hepatic resection (27%), and splenectomy (17%). Full-thickness diaphragmatic lesions were present in 85% of specimens. Residual disease was classified as no gross residual in 80% of cases and b1 cm in 10%. Postoperative complications requiring treatment

occurred in eight cases: pneumothorax (two cases, definitely attributable to DR); symptomatic pleural effusion (four cases, possibly attributable to DR); one case each of subphrenic abscess and gastro-pleural fistula (most likely unrelated to DR). **Conclusions**. (1) DR as part of cytoreductive surgery for ovarian cancer carries comparable risks to other radical debulking procedures. (2) The majority of complications are expected outcomes after entrance into the pleural cavity and generally manageable with chest tube. (3) DR is a useful adjunct to other radical debulking procedures and can eliminate isolated bulky diaphragmatic disease as an obstacle to optimal cytoreductive surgery for patients with ovarian cancer.

9. Assessment of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma

Dowdy SC, Loewen RT, Aletti G et al. Gynecologic Oncology. 2008;109:303–7

Objective. To describe the technique of diaphragmatic peritonectomy (DP) for ovarian cancer cytoreduction and to assess associated morbidity. **Methods**. Retrospective review yielded 56 patients who underwent DP as part of a cytoreductive procedure for primary or recurrent ovarian cancer between 1988 and 2004. Patients who underwent diaphragmatic resection, removal of diaphragmatic implants with CUSA, cautery, curette, or finger fracture, and patients with pseudomyxoma were excluded from analysis. **Results**. DP was performed as a component of primary or secondary cytoreduction in 37 (66%) and 19 (34%) patients, respectively. Extended procedures including bowel resection, hepatic resection, splenectomy, or radical hysterectomy were performed with DP in 47 patients (82%). Resection of all diseaseN1 cm was achieved in 95% (microscopic residuum in 43%). For those undergoing primary cytoreduction, median survival was 59 months and 5-year survival was 49% with

median follow-up of 34 months. When performed for recurrent ovarian carcinoma, 5- year survival was 16% and median survival was 23 months. No intra-operative complications could be specifically attributed to DP. Post-operative complications included a 30% rate of pleural effusion which was associated with entry into the pleural space during DP (pb0.0001); thoracentesis was required in 12.5%. **Conclusions**. Diaphragmatic metastases are a common obstacle to optimal cytoreduction for patients with ovarian cancer. When necessary, utilizing DP in concert with other extended procedures to obtain maximal cytoreduction is associated with excellent survival. It should be recognized that DP is associated with an increased incidence of post-operative pleural effusion, particularly when the pleural space is entered.

10. The clinical significance of hepatic parenchymal metastasis in patients with primary epithelial ovarian cancer

Lim MC, Kang S, Lee KS et al. Gynecologic Oncology. 2009;112: 28–34

Objective. The objective of this study was to determine the clinical significance of hepatic parenchymal metastasis on survival in patients with advanced epithelial ovarian cancer. **Methods**. We conducted a retrospective review of ovarian cancer patients with stages IIIc and IV hepatic parenchymal metastasis who were treated at the National Cancer Center in Korea between January 2001 and January 2008. Hepatic metastases were divided into unresectable, hematogenous parenchymal metastasis and resectable, parenchymal metastasis from peritoneal seeding. **Results**. One hundred twenty patients were identified, 113 of whom were included in the study. The stage IIIc group in cluded 97 patients, and the group with stage IV disease and hepatic parenchymal metastasis included 16 patients. Of the 16 patients with hepatic

parenchymal metastasis, 2 patients had unresectable, hematogenous parenchymal metastasis with a poor prognosis compared to the patients with resectable, hepatic parenchymal metastasis from peritoneal seeding. Fourteen patients with hepatic parenchymal metastases from peritoneal seeding underwent complete resection without complications as follows: wedge resection (n=7), segmentectomy (n=5), and he mi-hepatectomy (n=2). Age, tumor grade, histology, serum CA-125 level, and the rate of optimal debulking were similar in patients with stage IIIc disease and patients with stage IV disease who had resectable, hepatic parenchymal metastasis from peritoneal seeding. The 5-year progression free survival rate and the 5-year overall survival rate for patients with stage IIIc disease and patients with stage IV disease and hepatic parenchymal metastasis from peritoneal seeding were 25 and 23% (p=0.8063), and 55 and 51% (p=0.5671), respectively. **Conclusion**. Our findings suggest that complete hepatic resection should be attempted for patients with hepatic parenchymal metastasis from peritoneal seeding.

Radical Hysterectomy in Gynaecological Oncology

Introduction

Radical hysterectomy (RH) with bilateral pelvic lymphadenectomy is the current surgical standard of care for the management of operable cervical (FIGO Stages IA2-IIA) and Stage II endometrial cancer. It involves the en bloc removal of the uterus with cervix, a cuff of vagina and supporting parametrium as well as the pelvic lymph nodes. The procedure involves an extensive dissection of the pelvic retroperitoneum and is associated with a potential risk of significant intra-operative complications as well as medium and long term morbidity.

Although intra-operative complications of RH are acceptably low in high-volume centres, longer term morbidity related to partial surgical denervation of the pelvic floor continues to be a problem. Since the 5-year survival rates in node-negative disease are uniformly in excess of 85-90%, a significant number of women are likely to survive in the long term with the disabling morbidity of surgery. Quality of life issues are therefore becoming highly relevant in the management of this disease.

Types of Radical Hysterectomy

Radical hysterectomy (RH) as it is performed today has evolved from the "Meig's Operation" (1) which included pelvic lymphadenectomy and was thus an improvement over the earlier classical publications of Clark (2) and Wertheims (3).

The Piver-Rutledge classification of hysterectomy (4) (TABLE I) based on the extent of the resected parametrium is widely accepted. This is relevant to any discussion of complications associated with RH as there is evidence to suggest that complication rates and morbidity are directly linked to the amount of parametrial tissue resected in the surgical specimen (5-8).

TABLE I The Piver – Rutledge Classification

Type	Description
I	Extrafascial hysterectomy
II	Modified radical hysterectomy Resection of the medial half of the uterosacral and cardinal ligaments Division of the uterine vessels just medial to the ureter
III	Radical resection of the entire parametrium i.e. uterosacral-cardinal ligament complex from the pelvic sidewall. Radical resection of the upper third of the vagina and paravaginal tissues. Division of the uterine vessels at their origin from the internal iliac artery.
IV	Resection of all periureteric tissues including the superior vesical artery Division of the ureter from the pubovesical ligament Resection of the upper three-fourths of the vagina
V	Extended radical hysterectomy with associated resection of bladder and/or terminal ureters or bowel Synonymous with pelvic exenterative surgery

Complications of Radical Hysterectomy

Complication rates after RH are acceptably low in high volume centres (9) and are reported to range between 1.1-7.4% (10-11). Table II summarises the known complications of RH

TABLE II Complications of Radical Hysterectomy

Intra-operative	Haemorrhage
	Injury to the lower urinary tract
	Injury to the rectum
	Neurological injuries
Early Post-operative	Reactionary haemorrhage
	Febrile morbidity
	Sepsis
	Lymphocysts
	Venous thromboembolism
	Urinary fistulae
Delayed	Pelvic floor dysfunction
	Psycho-sexual morbidity

(A) Intra-operative Complications

Haemorrhage

Blood loss during RH is expected to vary between 400-1500 mls. (6, 10). Significant haemorrhage is most likely to occur during pelvic sidewall dissection, dissection in the depths of the pararectal spaces, ureteric canal and vesicovaginal ligaments and during resection of the uterosacral-cardinal ligament complex.

The most vulnerable vessels are the internal iliac vein, accessory obturator vessels, obturator venous plexus and venous radicals in the parametrial/paravaginal tissues and the vesicovaginal ligament.

Arterial haemorrhage is easy to identify and control with clips, clamps, or ligatures. Difficulties arise in controlling hemorrhage from lacerations of deep pelvic veins that are fragile, tortuous, distended, sometimes hidden or retracted from view, and sometimes held open by attachment of the vein wall to surrounding tissue. Pressure tamponade is the most effective procedure to control such haemorrhage followed by careful occlusion of the bleeding vessels.

Injury to the lower urinary tract

Improvements in surgical technique have largely contributed to a reduction in the risk of lower urinary tract injury during RH and resultant urinary fistula rates have reduced from 5-15% in the mid-twentieth century to less than 1% (6, 12).

Bladder injury

Inadvertent cystotomy is reported to occur in less than 1% of cases (13). It may occur during mobilization of the bladder flap and caudal dissection of the bladder from the anterior vaginal wall. A primary two-layered closure using a fine atraumatic delayed absorbable suture followed by continuous bladder drainage for 15-21 days is usually associated with a good outcome. Juxta-trigonal cystotomy close to the uretero-vesical junction however additionally mandates the placement of a ureteric stent to reduce the possibility of subsequent ureteric stricture.

Ureteric injury

Injury to the pelvic ureter is reported to occur in 0.6-1.7% of cases (13). The usual site is the lower third in the vicinity of the ureteric canal and injuries can include partial/complete transection, ligation, crush or electrothermal damage and devascularisation with subsequent ischaemic necrosis due to disruption of the ureteric blood supply as a result of surgical disruption of the peri-ureteric sheath. Devascularisation injury

is currently believed to be responsible for the vast majority of post-RH ureterovaginal fistulae

Several workers have described innovative techniques aimed at reducing the rate of ureteric complications (14-17). Given a normal non-irradiated ureter, the incidence of ureteric injury and consequent fistulae, stenosis and stricture can be reduced to less than 1% with meticulous surgical technique and judicious use of electrosurgical energy during ureteric dissection to minimize disruption of the peri-ureteric sheath.

Should ureteric injury occur it should be treated depending upon the site, extent and nature of the injury. Primary repair i.e. uretero-ureterostomy or neoureterocystostomy, with placement of an appropriate ureteric stent should be performed as indicated.

Injury to the rectum

Rectal injury with subsequent rectovaginal fistula formation is a very rare complication of RH in appropriately selected cases. Rectal injury should be closed primarily with or without a covering transverse colostomy depending upon the site, extent and nature of the injury.

Neurological injuries

Neurological injury is reported to occur in approximately 1% of patients (18). The majority involve the genitofemoral and obturator nerves although injuries of the ilioinguinal, iliohypogastric, lateral femoral cutaneous and pudendal nerves have also been described.

A thorough knowledge of surgical anatomy, meticulous surgical technique, careful placement of retractors, and careful patient positioning will help to prevent most nerve injuries. Most of these injuries are not associated with serious or permanent disability, however, injury to the obturator nerve can lead to adductor weakness and lower extremity instability.

(B) Early Post-operative Complications

Reactionary Haemorrhage

Reactionary haemorrhage is a rare complication of RH. It can however occur in those cases associated with significant intra-operative bleeding which has not been effectively controlled at the completion of surgery and/or if there is associated consumptive coagulopathy.

It is rare to identify a specific source of the bleeding at re-laparotomy and these emergencies are best managed by packing the pelvis with multiple gauze packs, one end being exteriorized through the open vagina. Pelvic packs should be advanced within 24 to 48 hours and removed shortly thereafter to avoid infection.

In certain cases of postoperative hemorrhage, selective embolization using interventional radiology techniques can prevent re-operation

Febrile morbidity

Post-RH fever, presenting more than 24 hrs after surgery is generally due to UTI (10-16%), wound sepsis (4-6%) and only rarely due to pelvic peritonitis (7).

The increased risk of UTI is probably secondary to continuous catheterization as also due to transient alterations in ureteric function that are well described after RH. These include transient hydroureter and reduced peristaltic activity which usually resolve spontaneously within 1 month after surgery.

Sepsis

Serious pelvic sepsis i.e. peritonitis and abscess are rare. Prophylactic use of broad-spectrum antibiotics with both aerobic and anaerobic coverage is therefore recommended.

Pelvic Lymphocysts

Pelvic lymphocyst formation is a well-recognized complication of pelvic lymphadenectomy, the reported incidence varying between 4-30% and largely depending upon the mode of ascertainment. The majority are small, asymptomatic and of no clinical significance. Large lymphocysts can however lead to lymphoedema, DVT, ureteric obstruction, pain and secondary infection (19-20).

The traditional belief that closed suction drainage of the retroperitoneum reduced the risk of pelvic infection, fistula, and lymphocyst formation has been challenged and disproved (21-23). It is now accepted that this practice does not influence the incidence of these complications.

Small asymptomatic lymphocysts need not be treated. Symptomatic lymphocysts and those that cause obstructive uropathy should be aspirated. Ultrasound or CT-directed needle aspiration is recommended. Sclerosis of recurrent lymphocysts by intra-cystic image-guided injection of a solution of Tetracycline or Povidone-iodine has been reported (24). Open surgical drainage is rarely necessary.

Venous Thrombosis and Embolism (VTE)

DVT and PE are reported to occur in 0-17% cases after RH. It is now accepted that all patients undergoing RH should receive prophylactic anticoagulation with either unfractionated or Low Molecular Weight Heparin beginning prior to surgery and continuing in the immediate post-operative period until full ambulation (25-26). Intermittent pneumatic calf compression during surgery and ideally, continuing until complete ambulation discharge from hospital is a useful adjunct.

The American Society of Clinical Oncology VTE Guideline Panel has recently recommended the following (27):

- All hospitalized cancer patients should be considered for VTE prophylaxis unless contraindicated

- Routine prophylaxis of ambulatory patients is not recommended
- All patients undergoing radical surgery for cancer should receive pharmacologic thromboprophylaxis
- LMWH is the preferred agent for both, the initial and continuing treatment of patients with established VTE
- The impact of anticoagulants on patient survival requires further study and cannot be recommended at present

Approximately 3% to 5% of patients with occult venous thrombosis of the lower extremities develop pulmonary emboli. Established DVT merits aggressive treatment with full anticoagulation to prevent pulmonary embolism (PE). However, the decision about how soon after radical surgery it is safe to fully anticoagulate a patient may be difficult. PE after full anticoagulation is rare. IVC filters may be considered in patients with recurrent PE.

Urinary Fistulae

In the absence of prior pelvic irradiation, vesicovaginal or ureterovaginal fistulae (VVF, UVF), are uncommon complications. VVFs occur in less than 1% and UVFs in approximately 2% of patients (28). Nearly one third of urinary tract fistulas following surgery heal spontaneously, as compared with none if adjuvant radiation therapy is given (29-31). Adjuvant radiotherapy with/without concurrent chemotherapy significantly increases the risk of urinary fistulae post-RH (32-33).

Most urinary fistulae present within 2-3 weeks of surgery. IVU-cystogram and cystoscopy will facilitate identification of the site and extent of most urinary fistulae. Contrast-enhanced CT scans/MRI scans are also helpful as adjunct investigations (34).

Small VVFs are best managed with continuous indwelling catheter drainage of the bladder in anticipation of spontaneous healing, which occurs in the vast majority of such cases. Definitive repair if indicated should be undertaken 4-6 weeks after surgery. UVFs should be initially managed with the placement of a Double-J ureteric stent, which may be the only treatment required for some small UVFs. Definitive surgical repair is required in the remaining.

Routine intra-operative placement of ureteric stents is not indicated as there is no evidence that such a practice reduces the risk of intra-operative ureteric injury and/or subsequent fistula formation (35).

(C) Delayed Complications

Pelvic Floor Dysfunction

The syndrome of pelvic floor dysfunction (PFD) accounts for most of the long-term morbidity of RH It includes a range of distressing symptoms associated with the lower urinary and GI tracts (TABLE A) which can significantly impact quality of life and are reported to occur in 20% of patients after RH (36).

TABLE A Pelvic Floor Dysfunction

Bladder	Sensory loss
	Storage dysfunction
	Voiding dysfunction
	Urinary incontinence
Rectum	Rectal tenesmus
	Fecal incontinence

Mechanism

PFD is thought to result from a partial denervation of the autonomic nerve supply of the pelvic viscera during the dissection of the uterosacral-cardinal ligament complex and

resection of the vaginal cuff (37). Data from cadaveric (38) and immunohistochemical (39) studies suggest that the inferior hypogastric plexus and pelvic autonomic nerves and ganglia ramify within the uterosacral-cardinal ligament complex with the greatest nerve fibre density at its origin at the pelvic sidewall and that a significantly greater number of nerves are disrupted during radical as compared to conservative parametrial resection.

Surgical disruption of these autonomic nerves during RH may occur at the following stages (40):

- Superior hypogastric plexus
  - o Dissection of para-aortic and presacral area
- Hypogastric nerve
  - o Rectouterine/uterosacral ligament resection
- Inferior hypogastric plexus (proximal)
  - o Dissection/resection of the cardinal ligament complex
- Inferior hypogastric plexus (distal)
  - o Division of vesicovaginal ligaments, paravaginal tissue and vaginal cuff resection

There is some evidence to suggest that the radicality of the parametrial resection during RH is associated with both, the incidence and the severity of PFD following surgery (5-8). More recently it has been suggested that the radicality of the vaginal cuff and paravaginal tissue resection is significantly associated with the incidence and severity of post-RH PFD (41).

Bladder dysfunction

Bladder dysfunction represents the major long-term morbidity associated with RH. Varying degrees of lower urinary tract dysfunction occur in 50-85% of women after RH (42-43). Although some degree of spontaneous recovery is usual within

6-12 months of surgery, clinically significant storage and voiding dysfunction persists in more than 30% of patients with approximately 15-16% being severely disabled by this problem (44).

Urodynamic studies objectively evaluating post-RH urethrovesical function (41, 44-50) appear to suggest that there are two phases of post-RH bladder dysfunction:

- Initial hypertonic phase
    - Small capacity, spastic bladder.
    - Due to parasympathetic dominance (51-52) and/or increased detrusor tone secondary to surgical trauma and prolonged catheter drainage (53).
    - Associated sympathetic loss leading to low bladder compliance, involuntary detrusor contractility and relaxation of the bladder neck and proximal urethra
    - Typically manifests as de novo detrusor instability and dyssynergia and stress urinary incontinence (42, 54).
    - Usually transient with spontaneous return to normal function after 8-12 weeks (55).
- Later hypotonic phase
    - Large capacity, overdistended bladder
    - Leads to acute or chronic urinary retention with overflow and recurrent UTI
    - Largely due to overdistension of the bladder in the early post-operative phase due to inappropriate bladder management

Voiding difficulties post-RH are either due to loss of bladder sensation, inability to initiate or maintain adequate detrusor contractions or an inability to initiate urethral relaxation. This has been confirmed by the demonstration of an increase in maximal voiding pressure along with a decrease in the maximum urinary flow rate during voiding (43).

Genuine stress urinary incontinence post-RH is possibly due to anatomical disruption of the supports of the bladder neck following parametrial and vaginal cuff resection or due to pelvic or pudendal nerve damage during surgery (50, 56).

Incidence data pertaining to post-RH urinary dysfunction should however be interpreted with caution:

- High incidence of clinically inapparent ("occult"), urodynamically detectable urinary dysfunction in patients with cervical cancer as also in apparently healthy asymptomatic women (57).
- Incidence of post-RH dysfunction is higher in those with pre-operative urinary dysfunction (50).

While accepting the inevitability of some degree of bladder dysfunction post-RH, appropriate management of the bladder in the first few weeks after surgery helps to minimize the risk of longer-term morbidity by avoiding overdistension (45). Optimal duration of bladder drainage with self-retaining catheters, suprapubic versus transurethral drainage, the value of intermittent self-catheterization, and the value of routine post-operative cystometry have all been debated.

Most gynaecological oncologists prefer continuous suprapubic or transurethral catheter drainage for 5 to 7 days post-surgery. Immediate post-void residual should be checked (Ultrasound scans for residual urine may be used). If the post-void residual is less than 50 to 75 mls. and the volume of spontaneously voided urine is greater than the post-void residual, the patient may be discharged. Patients with unacceptably large post-void residuals are best managed with prolonged indwelling catheter drainage for several weeks before attempting removal.

Patients presenting with acute retention of urine are best managed with continuous indwelling catheter drainage, sometimes for several weeks, Urinary tract infections are

common and must be looked for and treated with appropriate antibiotics.

In patients with persistent bladder hypotonia and storage disorders, intermittent self-catheterisation (ISC), Crede maneuver (suprapubic pressure) and the Valsalva maneuver (abdominal straining) have all been shown to be of benefit (58).

Anorectal dysfunction

Acute or chronic anorectal dysfunction following RH, though well described, is much less frequent than bladder dysfunction. This is characterized by difficulty with bowel evacuation, loss of defecatory urge and constipation.

Anorectal dysfunction is possibly secondary to a partial denervation of the inferior hypogastric and consequently the rectal plexus of pelvic nerves during rectal mobilization and dissection of the uterosacral ligaments and pudendal nerve injury during pararectal dissection (59).

Recent studies using anal manometry before and after RH have confirmed varying degrees of impairment of rectal sensory perception as well as abnormalities of the internal anal sphincter (59-60). Dietary fiber modifications and/or laxatives are usually beneficial.

Psychosexual morbidity

RH can lead to a number of psychosexual problems as listed below (61):

- Reduced libido
- Reduced sexual satisfaction
- Problems with orgasm
- Dyspareunia

These are largely related to vaginal foreshortening and reduced lubrication compounded by the effects of surgical menopause

if the ovaries have also been removed at the time of surgery. Many of these problems appear to resolve spontaneously with time although reduced libido has been shown to persist for as long as two years after surgery.

Radical Hysterectomy: Recent Innovations

In recent years, nerve-sparing, laparoscopic and robotic radical hysterectomies are gaining popularity on the premise that such procedures are likely to be associated with lesser morbidity without compromising the oncological outcome.

Laparoscopic and Robotic Radical Hysterectomy

Total Laparoscopic Radical Hysterectomy (TLRH), Laparoscopically-Assisted Radical Vaginal Hysterectomy (LARVH) and the Robotic Radical Hysterectomy (RRH) are techniques that are being increasingly evaluated for the surgical management of selected patients with operable cervical and endometrial cancers. It is widely believed that such procedures may provide less morbid alternatives to conventional radical hysterectomy without compromising oncological outcomes.

Although there are no published randomised trials to-date, there are studies comparing morbidity and outcomes using appropriately matched controls (62-69). The following conclusions can be drawn based on the available data:

- TLRH and LARVH are both associated with a reduction in intra-operative blood loss, post-operative analgesia requirements, wound complications, DVT, febrile/ infectious morbidity, earlier ambulation and reduced hospital stay.
- No significant differences in the lymph node harvests and other surgico-pathological parameters i.e. length of resected parametrium, vaginal cuff (70-71).
- Longer OR time (270-300 mins v/s 180-240 mins) and higher incidence of intra-operative complications

(1.5-8% v/s 1-2%) with the laparoscopic procedures particularly cystotomy and ureteric injury. There is evidence that both, OR time as well as complication rates reduce with an increase in surgical experience and numbers of procedures performed (62, 65, 72-73).

- No significant difference in the incidence of long-term bladder dysfunction.

Published data on RRH, albeit preliminary, appear to suggest that it is equivalent to the TLRH. Proponents of RRH argue that the intuitive nature of the robotic approach, magnification, dexterity, and flexibility combined with significant reduction in surgeon's fatigue offered by the robotic system make it a more appealing alternative to the TLRH (67, 69).

Nerve Sparing Radical Hysterectomy (NSRH)

The technique of nerve-sparing radical hysterectomy (NSRH) was initially described by Okabayashi (74) and later refined by other surgeons (75-80) in Japan and by Hockel and others (81-84) in Europe NSRH was developed in an attempt to reduce the urological morbidity associated with conventional RH.

There are subtle variations in the surgical approach and dissection techniques amongst various authors (82, 84-86). The basic surgical principle is to try and preserve the autonomic pelvic nerves of the hypogastric plexus within the uterosacral-cardinal ligament plexus as also the nerves within the vesicouterine ligament thereby reducing the risk of partial denervation of the bladder.

There are no randomized trials to-date comparing NSRH with conventional RH. There is however data to suggest that bilateral nerve-sparing is superior to unilateral nerve-sparing with respect to return of normal bladder function (79) and that Type III NSRH is comparable to Type II NSRH and

superior to conventional Type III RH in terms of early bladder dysfunction (87).

Conclusion

RH remains the current surgical standard of care for operable cervical and selected patients with endometrial cancer. Although intra-operative and immediate post-operative complication rates have been reduced to acceptable levels, long term morbidity related to the lower urinary tract remains a major cause for concern. It remains to be seen if recent technical modifications of the conventional RH will significantly impact the longer-term morbidity of this procedure. There is therefore a need for appropriate randomized trials prospectively comparing the newer modifications against the standard procedure before these techniques can be incorporated into the standard surgical management of this disease.

References

1 Meigs JV, Radical hysterectomy with bilateral pelvic lymph node dissections; a report of 100 patients operated five or more years ago. American Journal of Obstetrics and Gynecology 1951; 62: 854-870

2 Clark JG, A more radical method of performing hysterectomy for cancer of the uterus Johns Hopkins Medical Bulletin 1895; 6: 120-124

3 Wertheim E, The extended abdominal operation for carcinoma uteri American Journal of Obstetrics 1912; 66: 169-232

4 Piver MS, Rutledge F, Smith JP, Five classes of extended hysterectomy for women with cervical cancer Obstet Gynecol 1974; 44: 265-272

5 Ralph G, Tamussino K, Lichtenegger W, Urological complications after radical abdominal hysterectomy for

cervical cancer Ballieres Clin Obstet Gynecol 1988; 2: 943-952

6 Landoni F, Maneo A, Cormio G, Perego P, et al. Caruso O Class II versus Class III radical hysterectomy in Stage IB-IIA cervical cancer A prospective randomized study Gynecol Oncol 2001; 80: 3-12

7 Magrina JF, Goodrich M, Weaver A, et al. Modified radical hysterectomy: morbidity and mortality Gynecol Oncol 1995; 59: 277-282

8 Ralph G, Winter R, Michelitsch L, Tamussino K Radicality of the parametrial resection and dysfunction of the lower urinary tract after radical hysterectomy Eur J Gynaecol Oncol 1991; 12: 27-30

9 Covens A, Rosen B, Gibbons A, et al. Differences in the morbidity of radical hysterectomy between gynecological oncologists. Gynecol Oncol 1993; 51: 39-45

10 Kenter GG, Ansink AC, Heintz AP et al. Carcinoma of the uterine cervix Stage I and IIA: results of surgical treatment: Complications, recurrence and survival. European Journal of Surgical Oncology 1989; 15: 55-60

11 Lee YN, Wang KL, Lin MH et al. Radical hysterectomy with pelvic lymph node dissection for treatment of cervical cancer: a clinical review of 954 cases. Gynecol Oncol 1989; 32: 135-142

12 Magrina JF, Goodrich M, Weaver A et al. Modified radical hysterectomy: morbidity and mortality. Gynecol Oncol 1995; 59: 277-282

13 Kindermann G, Deus-Thiede G, Postoperative urological complications after radical hysterectomy for cervical cancer. Ballieres Clin Obstet Gynecol 1988; 2: 933-941

14 Novak F, Procedure for the reduction of uretero-vaginal fistulas after Wertheim's operation. Am J Obstet Gynecol 1956; 72: 506-510

15 Green TH Jr., Ureteral suspension for prevention of ureteral complications following radical hysterectomy. Obstet Gynecol 1966; 28: 1-11

16 Symmonds RE and Pratt JH, Prevention of fistula and lymphocysts in radical hysterectomy. Obstet Gynecol 1961; 17: 57-64

17 Patsner B and Hackett DO. Use of the omental J-flap for prevention of post-operative complications following radical abdominal hysterectomy: Report of 140 cases and literature review. Gynecol Oncol 1996; 65: 405-407

18 Hoffman MS, Roberts WS and Cavanagh D, Neuropathies associated with radical pelvic surgery for gynecologic cancer. Gynecol Oncol 1988; 31: 462-466

19 Ilancherian A, Monaghan JM, Pelvic lymphocyst – a 10 year experience. Gynecol Oncol 1988; 29: 333-336

20 Conte M, Panici PB, Guarglia L et al. Pelvic lymphocele following radical para-aortic and pelvic lymphadenectomy for cervical carcinoma: incidence rate and percutaneous management. Obstet Gynecol 1990; 76: 268-271

21 Jensen Jk, Lucci JA 3rd, DiSaia PJ et al. To drain or not to drain: a retrospective study of closed-suction drainage following radical hysterectomy with pelvic lymphadenectomy. Gynecol Oncol 1993; 51(1): 46-49

22 Lopes ADB, Hall JR, Monaghan JM. Drainage following radical hysterectomy with pelvic lymphadenectomy: dogma or need? Obstet Gynecol 1995; 86(6): 960-963

23 Franchi M, Trimbos JB, Zanaboni F et al. Randomised trial of drains or no drains following radical hysterectomy and pelvic lymph node dissection: A European

Organisation for Research and Treatment of Cancer – Gynecological Cancer group (EORTC-GCG) study in 234 patients. Eur J Cancer 2007; 43: 1265-1268

24 Mann WJ Jr, Orr JW Jr, Shingleton HM, et al. Perioperative influences on infectious morbidity in radical hysterectomy. Gynecol Oncol 1981; 11: 207–212.

25 Clarke-Pearson DL, Synan IS, Dodge R et al A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. Am J Obstet Gynecol 1993; 168: 1146-1153

26 Fishman A, Altaras M, Klein Z et al Low molecular heparin (Enoxaparin) as an alternative treatment for acute deep venous thrombosis in gynecologic oncology patients. Eur J Gynecol Oncol 1996; 17: 365-367

27 Lyman GH, Khorana AA, Falanga A et al J Clin Oncol 2007; 25(34): 5490-5505

28 Shingleton HM, Orr JW Jr, eds. Cancer of the cervix. Philadelphia: JB Lippincott, 1995

29 Wertheim's radical hysterectomy 1921-1986: changes in urologic complications. Arch Gynecol Obstet 1988; 241(4): 249-253

30 Likic-Ladevic I, Kadija S, Ladevic N et al Urological complications after radical hysterectomy: incidence rates and predisposing factors. Vojnosanit Pregl 2007; 64(6): 381-384

31 Bai SW, Huh EH, Jung da J et al Urinary tract injuries during pelvic surgery: incidence rates and predisposing factors. Int Urogynecol J Pelvic Floor Dysfunct 2006; 17(4): 360-364

32 Sartori E, Zanaqnolo V Complications following radical hysterectomy for cervical carcinoma. Recenti Prog Med 2003; 94(12): 562-567

33 Landoni F, Maneo A, Colombo A et al. Randomised study of radical surgery versus radiotherapy for Stage Ib-IIa cervical cancer. Lancet 1997; 350(9077): 535-540

34 Demos TC, Churchill R, Flisak ME et al. The radiological diagnosis of complications following gynecologic surgery: radiography, computed tomography, sonography and scintigraphy. Crit Rev Diagn Imaging 1984; 22(1): 43-94

35 Schimpf MO, Gottenger EE, Wagner JR. Universal ureteral stent placement at hysterectomy to identify ureteral injury: a decision analysis. Brit J Obstet Gynaecol 2008; 115(9): 1151-1158

36 Bergmark K, Avall-Lundqvist E, Dickman P et al. Patient rating of distressful symptoms after treatment for early cervical cancer. Acta Obstet Gynaecol Scand 2002; 81: 443-450

37 Tamussino K, Winter R, Lang PFJ. The cardinal ligament: surgical anatomy and resection. CME J Gynecol Oncol 1997; 6: 265-271

38 Trimbos JB, Mass CP, Deruiter MC et al. A nerve-sparing hysterectomy: guidelines and feasibility in Western patients. Int J Gynecol Cancer 2001; 11: 180-188

39 Butler-Manuel SA, Buttery LDK, A'Hern RP et al. Pelvic nerve plexus trauma at radical hysterectomy and simple hysterectomy Cancer 2000; 89: 834-841

40 Hockel M. Basic neuroanatomy and neurophysiology of urethrovesical function with special reference to extended hysterectomy CME J Gynecol Oncol 2002; 7: 32-35

41 Zullo MA, Manci N, Angioli R et al. Vesical dysfunctions after radical hysterectomy for cervical cancer: A critical review. Crit Rev Oncol Hematol 2003; 48: 287-293

42 Low JA, Mauger GM, Carmichael JA. The effect of Wertheim hysterectomy on bladder and urethral function. Am J Obstet Gynecol 1981; 139: 826-834

43 Scotti RJ, Bergman A, Bhatia NN et al. Urodynamic changes in urethrovesical function after radical hysterectomy. Obstet Gynecol 1986; 68: 111-120

44 Naik R, Mayne C, Nwabinelli J et al. Prevalence and management of (non-fistulous) urinary incontinence in women following radical hysterectomy for early stage cervical cancer. Eur J Gynecol Oncol 2001; 22: 26-30

45 Bandy LC, Clark-Pearson DL, Soper JT et al. Long-term effects on bladder function following radical hysterectomy with or without post-operative radiation. Gynecol Oncol 1987; 26: 160-168

46 Ralph G, Tamussino, Lichtenegger W. Urodynamics following radical abdominal hysterectomy for cervical cancer Arch Gynecol Obstet 1988; 243: 215-220

47 Loran OB, Pushkar DU. Urethral instability after radical hysterectomy J Urol (Paris) 1992; 98: 210-212

48 Sekido N, Kawai K, Akaza H. Lower urinary tract dysfunction as persistent complication of radical hysterectomy Int J Urol 1997; 4: 259-264

49 Lin HH, Sheu BC, Lo MC et al. Abnormal urodynamic findings after radical hysterectomy or pelvic irradiation for cervical cancer. Int J Gynecol Obstet 1998; 63: 169-174

50 Chen GD, Lin LY, Wang PH et al. Urinary tract dysfunction after radical hysterectomy for cervical cancer. Gynecol Oncol 2002; 85: 292-297

51 Roman-Lopez JJ, Barclay D. Bladder dysfunction following Schauta hysterectomy. Am J Obstet Gynecol 1973; 115: 81-90

52 Glahn BE. The neurogenic factor in vesical dysfunction following radical hysterectomy for carcinoma of the cervix. Scand J Urol Nephrol 1970; 4(2): 107-116

53 Seski JC, Diokno AC. Bladder dysfunction after radical hysterectomy. Am J Obstet Gynecol 1977; 128: 643-651

54 Forney JP. The effect of radical hysterectomy on bladder physiology. Am J Obstet Gynecol 1980; 138: 374-382

55 DeGroat WC, Kawatani M. Reorganization of sympathetic preganglionic connections in cat bladder ganglia following parasympathetic denervation J Physiol 1989; 49: 431

56 Vervest HA, deJonge MK, Vervest TM et al. Micturition symptoms and urinary incontinence after non-radical hysterectomy Acta Obstet Gynecol Scand 1988; 67: 141

57 Lin HH, Yu HJ, Sheu BC et al. Importance of urodynamic study before radical hysterectomy for cervical cancer. 2001; 81(2): 270-272

58 Farquharson D, Shingleton HM, Soong SJ et al. The adverse effects of cervical cancer treatment on bladder function. Gynecol Oncol 1987; 27: 15-23

59 Sood A, Nygaard I, Shahin MS et al. Anorectal dysfunction after surgical treatment of cervical cancer. Am Coll Surg 2002; 4: 513-519

60 Barens W, Wagonner S, Delgado G et al. Manometric characterization of rectal dysfunction following radical hysterectomy. Gynecol Oncol 1991; 42: 116-119

61 Jensen PT, Groenvold M, Klee MC et al. Early-stage cervical carcinoma, radical hysterectomy and sexual function. A longitudinal study. Cancer 2004; 100: 97-106

62 H Xu, Y Chen, Y Li, Q Zha et al. Complications of laparoscopic radical hysterectomy and

lymphadenectomy for invasive cervical cancer: experience based on 317 procedures. Surg Endosc Volume 21, Number 6, June 2007

63 Lee CL, Huang KG, Jain S et al. Comparison of laparoscopic and conventional surgery in the treatment of early cervical cancer. J Am Assoc Gynecol Laparosc 2002; 9(4): 481-48

64 Steed H, Rosen B, Murphy J et al. A comparison of laparoscopically- assisted radical vaginal hysterectomy and radical abdominal hysterectomy in the treatment of cervical cancer. Gynecol Oncol 2004; 93: 588-593

65 Guangyi Li, Xiaojian Yan, Huilin Shang et al. A comparison of laparoscopically radical hysterectomy and pelvic lymphadenectomy and laparotomy in the treatment of IB-IIA cervical cancer. Gynecol Oncol 2007; 105: 176-180

66 Uccella S, Laterza R, Ciravolo G. A comparison of urinary complications following total laparoscopic radical hysterectomy and laparoscopic pelvic lymphadenectomy to open abdominal surgery. Gynecol Oncol, Vol. 107, Issue 1, Supplement 1, October 2007, Pages S147-S149

67 Nezhat FR, Datta MS et al. Robotic radical hysterectomy versus total laparoscopic radical hysterectomy with pelvic lymphadenectomy for treatment of early cervical cancer. JSLS. 2008; 12(3): 227-37

68 Frumovitz M, Dos Reis R, Sun C et al. Comparison of total laparoscopic and abdominal radical hysterectomy for patients with early-stage cervical cancer. Obstet Gynecol 2007; 110: 96–102

69 Ko E, Michael G, Berkowitz RS et al. Robotic versus open radical hysterectomy: A comparative study at a single institution. Gynecol Oncol 2008; 111: 425-430

70 Spritos NM, Eisenkop SM, Schlaerth JB et al. Laparoscopic radical hysterectomy (Type III) with aortic and pelvic lymphadenectomy in patients with Stage I cervical cancer. Surgical morbidity and intermediate follow-up. Am J Obstet Gynecol 2002; 187: 340-348

71 Lin YS. Preliminary results of laparoscopic modified radical hysterectomy in early invasive cervical cancer. J Am Assoc Gynecol Laparosc 2003; 10: 480-484

72 Hertel H, Kohler C, Michels W et al. Laparoscopically-assisted radical vaginal hysterectomy (LARVH): prospective evaluation of 200 patients with cervical cancer. Gynecol Oncol 2003; 90: 505-511

73 Sardi J, Vidauretta J, Bermudez A et al. Laparoscopically-assisted Schauta operation: Learning experience at the Gynecologic Oncology Unit, Buenos Aires University Hospital. Gynecol Oncol 1999; 75: 361-3

74 Okabayashi H. Radical hysterectomy for cancer of the cervix uteri, modification of the Takayama operation. Surg Gynecol Obstet 1921; 33: 35-41

75 Fujiwara T. Surgery for cervical cancer (in Japanese). Tokyo: Igakutoshyosyuppan; 1984

76 Sakomoto S, Takazawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for cervical cancer. Ballieres Clin Obstet Gynecol 1988; 2: 953-962

77 Yabuki K, Asamoto A, Hoshiba T et al. A new proposal for radical hysterectomy. Gynecol Oncol 1996; 62: 370-378

78 Yabuki K, Asamoto A, Hoshiba T et al. Radical hysterectomy: an anatomic evaluation of parametrial dissection. Gynecol Oncol 2000; 77: 155-163

79 Kato K, Suzuka K, Osaki T et al. Unilateral or bilateral nerve-sparing radical hysterectomy: a surgical technique

to preserve the pelvic autonomic nerves while increasing radicality. Int J Gynecol Cancer 2007; 17(5): 1172-1178

80 Fujii S, Takakura K, Matsumura N et al. Anatomic identification and functional outcomes of the nerve-sparing Okabayashi hysterectomy. Gynecol Oncol 2007; 1007: 4-13

81 Hockel M, Konerding MA, Heussel CP et al. Liposuction-assisted nerve-sparing extended radical hysterectomy: oncologic rationale, surgical anatomy: feasibility study. Am J Obstet Gynecol 1998; 178: 971-976

82 Possover M, Stober S, Plaul K et al. Identification and preservation of the motoric innervation of the bladder in radical hysterectomy Type III. Gynecol Oncol 2000; 79: 154-157

83 Trimbos JB, Mass CP, DeRuiter et al. A nerve-sparing radical hysterectomy; guidelines and feasibility in Western patients. Int J Gynecol Cancer 2001; 11(3): 180-186

84 Raspagliesi F, Ditto A, Fontanelli R, et al. Nerve-sparing radical hysterectomy: a surgical technique for preserving the autonomic hypogastric nerve. Gynecol Oncol 2004; 93: 307–314.

85 Possover M, Quakernack J, Chiantera V. The LANN technique to reduce postoperative functional morbidity in laparoscopic radical pelvic surgery. J Am Coll Surg 2005; 201: 913-917

86 Katahira H, Nikuraa Y, Kaihob H et al. Intraoperative electrical stimulation of the pelvic splanchnic nerves during nerve-sparing radical hysterectomy

87 Raspagliesi F, Ditto A, Fontanelli R, et al. Type II versus Type III nerve-sparing radical hysterectomy: comparison of lower urinary tract dysfunction. Gynecol Oncol 2006; 102(2): 256-262