



# **Guidelines for Urological Cancers Vol IX**

## **Part A**

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**Dedicated to  
all our patients at  
The Tata Memorial Hospital**

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## Preface

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The Centre for Evidence Based Medicine (EBM) defines EBM as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”. EBM has percolated into all fields and levels of medical practice and this has been particularly exemplified in current oncology practice. There is an increasing need to update our knowledge and be guided by EBM, especially in an era where there have been rapid developments and innovations in oncology.

Important innovations have been made in diagnostic methods and surgical management of various urological cancers especially renal and prostatic cancers. Minimally invasive surgery and robotic surgery have been embraced by uro oncologists the world over. Major progress has also been made in the treatment paradigms of cancers of the urinary bladder, testes and prostate. The role of neoadjuvant and adjuvant treatment in urological oncology continues to be redefined. Targeted therapy has revolutionized the way we treat several solid cancers and inroads have been made in renal cancers too with anti VEGF drugs and mTOR inhibitors.

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Separating evidence from opinions is especially difficult in this era of information overload; the EBM meeting and guidelines book on urological cancers is planned to do precisely this. As always, in addition to collating the best available evidence, the meeting and book also highlight areas where strong evidence is lacking. Exciting new research is ongoing in dendritic cell therapy for prostatic cancer, mini-transplant for renal cell carcinoma, Gemcitabine instillation for superficial bladder cancer, autologous transplant in refractory germ cell testicular tumors, chemotherapy for penile cancers and many other areas. I hope that in addition to updating practicing urologists, surgical, medical and radiation oncologists, this book and meeting serves as a stimulus for investigators to actively participate in clinical research. Controversies in management exist in a number of areas and we have a responsibility to address them by well conducted clinical trials.

A handwritten signature in black ink, appearing to read 'R. A. Badwe', with a horizontal line underneath it.

February, 2010  
Mumbai, India

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# Renal Cell Carcinoma

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## **Epidemiology:**

Renal cell carcinoma (RCC) is the third most common and the most lethal of all genitourinary malignancies. (1-3). It accounts for 1.5% of all malignancies in India. Annually there are approximately 209000 new cases and 102000 deaths secondary to RCC in the world. There has been a steady rise in the incidence of RCC at the rate of 2.3 -4.3% annually over the past 30 years (4-6), partly due to a general increase in life expectancy and increased detection consequent upon the widespread use of abdominal imaging. This has been associated with an increased detection of localized incidentally detected tumours and an improved 5 year survival rates (1, 7, 8). However, despite this increasing incidence, the mortality from RCC has decreased only marginally.

The peak incidence of RCC is in the 7<sup>th</sup> decade (1); and there is a male preponderance in the ratio of 1.5:1. RCCs are extremely uncommon in children and constitute 2.3-6.6% of all childhood renal tumours. In children, the mean age at diagnosis is 8-9 years with an equal incidence in both sexes (9, 10). RCCs in children are more likely to

be of papillary histology, often have locally advanced high grade features, and can have unfavorable histological variants. Hence, aggressive surgery is recommended for RCC in children and young adults (9,11,12).

### **Aetiology:**

The exact etiology of RCC remains unclear. A number of environmental, hormonal, cellular and genetic factors have been studied for their association with RCC.

- I. Obesity and smoking appear to be risk factors, with relative risks of 3.6 & 2.3 respectively (13-17).
- II. Chow et al (2000) found a significant correlation between hypertension and renal cell carcinoma (18).
- III. Endogenous genetic risk factors include hereditary familial forms of kidney cancer such as the Von Hippel-Lindau disease (VHL), familial papillary renal cell carcinoma (HPRCC), hereditary leiomyoma RCC (HLRCC), the Birt-Hogg-Dube Syndrome (BHD), and Tuberous Sclerosis (TS).
- IV. Other genetic alterations in clear cell R.C.C include frequent LOH of chromosomes 8p, 14q and 9p (p16) among others suggesting other unknown tumour suppressors may be important in renal cell tumourigenesis.
- V. The most common genetic events associated with papillary R.C.C are trisomy of chromosomes 7 and 17 and loss of Y.
- VI. Analgesic abuse, exposure to industrial solvents, antihypertensive medication, cadmium exposure, long term exposure to petroleum, tar and pitch products. (Evidence of association inconsistent and effect probably low).
- VII. Patients of ESRD on long term dialysis.

## **Pathogenesis:**

The majority of RCCs are sporadic and only 4% are estimated to be familial. Most RCCs are unilateral and unifocal. Bilateral RCCs are uncommon (2-4%) in sporadic forms but much more common in familial forms. Multicentricity is seen in 10-20% of patients, mainly with familial forms or papillary histology. Specific genotyping alterations have been associated with different histological subtypes of RCC:

1. Mutations in the VHL gene (a tumour suppressor gene) are responsible for most cases of conventional (clear cell) carcinoma. The VHL gene has been mapped to 3p25 and contains three exons with 852 coding nucleotides. Somatic mutations of the VHL gene are seen in approximately 50-75% of cases of sporadic clear cell renal carcinoma and are mostly point mutations, hypermethylation or rearrangement of the gene. RCC develops in about 50% patients with VHL disease and is associated with early age of presentation and bilateral or multifocal involvement.
2. Other genetic alterations in clear cell RCC are LOH of chromosomes 8p, 14q, 9p suggesting possible role of tumour –suppressors in the tumourigenesis.
3. Papillary RCC: Trisomy of chromosomes 7, 17 and loss of Y chromosome in male patients.
4. Chromophobe RCC: Multiple chromosome losses and hyperploidy. Associated with Brit – Hogg – Dube syndrome.

## **Pathology:**

RCC originates from the renal tubular epithelium, as evidenced by electron microscopy (19) and immunohistochemical analysis (20). RCCs form a fibrous

pseudocapsule when they grow and are usually not infiltrative except the collecting duct carcinomas. Renal cell carcinoma has a number of distinct subtypes, each with a unique genetic basis and tumour biology (21). On the basis of distinct histological and infrastructural features, RCCs are now classified into the following histological subtypes (21, 22):

- I. Conventional clear cell - 70%
- II. Papillary, chromophobe
- III. Collecting duct (including medullary)
- IV. Unclassified (6%) those which cannot be a part of any of the above categories.

Though earlier RCC was thought to arise primarily from the proximal convoluted tubules, some histological subtypes like chromophobe and collecting duct RCC are derived from the more distal parts of the nephron (23, 24). Conventional clear cell RCCs are the commonest and have characteristic golden yellow appearance due to the abundance of lipids in the tumour cells. Cystic degeneration is seen in about 10-25% of RCCs and signifies a favourable biological behavior while calcification is seen in about 10-20% of RCCs (25,26). Papillary carcinoma (10-15%) may be multiple in up to 45% of cases (27-29) and have a variegated appearance with cystic and solid yellow and brown black areas. Microscopically, presence of foam cells in the stalks is a useful diagnostic feature. Chromophobe RCC (3-5%) may have a characteristic central scar on cut surface and may resemble an oncocytoma. Binucleate cells, nuclear border crumpling and perinuclear halo are important distinguishing microscopic features of chromophobe RCC. This subtype is usually associated with a favourable prognosis in most patients. Collecting

duct carcinomas are high grade cancers and are invariably associated with aggressive biological behaviour and poor outcome. Medullary carcinoma occurs almost exclusively in association with the sickle cell trait and closely resembles the collecting duct variety. Sarcomatoid change can occur in any histological type and is associated with poor prognosis.

Nuclear grading is done by using the Fuhrman criteria and is an independent prognostic parameter affecting survival (1, 30).

The methods of spread of RCC are –

- I. By direct invasion through the renal capsule into perinephric fat and adjacent visceral structures or in about 10% patients.
- II. By direct extension into the renal vein and inferior vena cava.
- III. Hematogenous – About 25-30% of patients have evidence of metastatic disease at presentation; the common metastatic sites being the lung, liver, bones. Other sites such as adrenal gland, brain, the opposite kidney, and subcutaneous tissue are frequent sites of disease spread.
- IV. Lymphatic – commonly to the hilar lymph nodes and further dissemination can be lymphatic or hematogeneous.

### **Diagnosis and Staging:**

Currently, more than 50% of RCCs are detected incidentally due to increased use of non-invasive imaging to evaluate a variety of non-specific symptom complexes (31). Incidentally detected RCCs are generally smaller and of lower stage than symptomatic RCCs. The classic triad of flank pain, gross haematuria and palpable

abdominal mass is now rare (6-10%), but when present, signifies an advanced stage of the disease (32-34).

The commonest symptoms associated with RCC are as follows:

- 1) Haematuria,
- 2) Flank pain or backache
- 3) Palpable mass in the abdomen or flank.
- 4) Symptoms due to metastatic disease (25-30% patients present with metastatic disease) such as bone pains, chronic cough, etc.
- 5) Non-reducing varicocele or bilateral lower extremity oedema, both of which suggest venous involvement.
- 6) Paraneoplastic syndromes (35) are seen in about 20-30% of patients with symptomatic RCC, such as:
  - a. hypertension due to increased rennin secretion,
  - b. cachexia,
  - c. weight loss,
  - d. pyrexia,
  - e. neuromyopathy,
  - f. amyloidosis,
  - g. elevated erythrocyte sedimentation rate,
  - h. anaemia,
  - i. non-metastatic hepatic dysfunction (3-20%) (Stauffer's syndrome).
  - j. hypercalcaemia,
  - k. polycythemia due to increased erythropoietin secretion etc.

Most of these are reversible after Nephrectomy but are usually not corrected by medical therapy.



## **Laboratory tests:**

Apart from routine hematological tests, biochemical investigations such as estimation of serum creatinine, erythrocyte sedimentation rate, alkaline phosphatase, LDH and serum calcium are advised. Estimation of renal function is especially important in patients having with tumour in solitary kidney or bilateral tumours as well as in patients with diabetes, chronic pyelonephritis, renovascular, stone or renal polycystic disease where the function of the contralateral kidney may be compromised. Preoperative hypercalcemia, anemia, and elevated ESR and few other abnormal laboratory values are independently associated with increased risk of cancer-specific death from clinically confined clear cell RCC (36).

## **Imaging:**

1. Ultrasonography - noninvasive, accurate, and relatively inexpensive and hence is usually the first investigation. It can differentiate between solid and cystic masses and also identify the need for further radiological investigations. (37).
2. CT scan – A high quality contrast enhanced spiral thin slice CT scan remains the single most important radiographic test for assessment of a renal mass. A solid mass with significant heterogenous post-contrast enhancement (due to characteristic high vascularity) less than of the normal renal parenchyma is virtually diagnostic of RCC (37-39), and any renal mass that enhances with contrast administration by more than 15 HU should be considered as RCC unless proved otherwise. CT also assesses primary tumour extension with extrarenal spread, venous involvement,

enlargement of locoregional lymph nodes, the adrenal and the liver, while also providing information about the function of contralateral kidney. CT can help rule out angiomyolipomas by demonstrating areas of negative CT attenuation indicative of the presence of fat in the tumour. (40)

3. Gadolinium contrast - enhanced MRI: It is useful in certain patients, e.g., those with renal insufficiency, allergy to iodinated contrast agents or those with probable venous extension. MRI has better sensitivity than CT scan in evaluating the presence and extent of venous extension, differentiating a tumour thrombus from a bland one and invasion of surrounding tissue and organs.
4. Venacavography - is indicated in presence of ambiguous MRI findings in cases with venous extension or in patients who cannot have MRI for some reason.
5. Doppler ultrasonography has limited sensitivity but a transoesophageal echocardiography is a useful tool for evaluating the cephalad extent of the thrombus.
6. Arteriography - Has a limited role and can be done prior to embolization.
7. Fine needle aspiration cytology/ biopsy (FNAC/ FNAB) is rarely indicated only when a renal abscess or infected cyst is suspected and when RCC must be differentiated from metastatic malignant disease or renal lymphoma (41, 42). FNAB has excellent accuracy for detecting malignant masses especially when combined with molecular analysis (43, 44) but has a suboptimal predictive value for detecting benign masses (44). Although the risk of complications is low, its impact on improving

diagnostic accuracy or influencing clinical management is limited.

It is still difficult at times to distinguish RCC, adenoma, and oncocytoma with current diagnostic techniques and approximately 10% to 30% of small, solid, CT-enhancing renal masses with features suggestive of RCC prove to be benign after surgical excision (45). Oncocytoma although being a benign tumour, is associated RCC in the same or the opposite kidney has been found in as many as 30% of patients (46).

### **Metastatic work up:**

This includes

1. X-ray chest or CT scan of the chest.
2. Isotope bone scans and targeted skeletal radiographs or scans, if indicated by clinical symptoms or raised serum alkaline phosphatase.
3. CT / MRI of brain is advised only if indicated by symptoms.
4. PET scan – investigational.

### **Staging:**

Currently, the AJCC TNM classification system (2002), is recommended due to better differentiation of different prognostic groups.

### **AJCC TNM Staging (2002)**

#### **Primary Tumour (T)**

- T<sub>x</sub> Primary tumour cannot be assessed  
T<sub>0</sub> No evidence of primary tumour  
T<sub>1</sub> Tumour 7cm or less in greatest dimension confined to the kidney

- T1a Tumour 4 cm or less in greatest dimension, confined to the kidney
- T1b Tumour more than 4 cm but not more than 7 cm in greatest dimension, confined to the kidney
- T<sub>2</sub> Tumour more than 7cm in greatest dimension, limited to the kidney
- T<sub>3</sub> Tumour extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
  - T<sub>3a</sub> Tumour directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
  - T<sub>3b</sub> Tumour grossly extends into the renal vein or its segmental branches, or vena cava below the diaphragm
  - T<sub>3c</sub> Tumour grossly extends into vena cava above diaphragm or invades the wall of the vena cava
- T<sub>4</sub> Tumour invades beyond Gerota's fascia

### **Regional Lymph Nodes (N)**

- N<sub>x</sub> Regional lymph nodes cannot be assessed
- N<sub>0</sub> No regional lymph node metastasis
- N<sub>1</sub> Metastasis in a single regional lymph node
- N<sub>2</sub> Metastasis in more than one regional lymph node

### **Distant Metastasis (M)**

- M<sub>x</sub> Distant metastasis cannot be assessed
- M<sub>0</sub> No distant metastasis
- M<sub>1</sub> Distant metastasis

The estimated 5-year survival rates for renal cell carcinoma is as follows: 96% for stage I, 82% for stage II, 64% for stage III and 23% for stage IV (47).

## **Prognostic factors:**

1. Pathological stage is probably the most important factor affecting outcome. Patients with systemic metastases are further assessed with performance status and classified in to risk groups.
2. Symptomatic presentation, poor performance status and weight loss of more than 10% body weight indicate poor prognosis.
3. Presence of para neoplastic signs.
4. Tumour size – Exact correlation is debatable.
5. Nuclear grade and histologic subtype - Sarcomatoid, collecting duct and medullary histology indicate a very poor prognosis.
6. Prognostic scoring systems - Kattan et al proposed a prognostic system incorporating symptoms, histology, tumour size and pathologic stage to predict probability of cancer free survival after nephrectomy in which they have incorporated tumour necrosis, tumour grade and vascular invasion to predict the outcome in patients with conventional RCC (48). Parker et al (2009) evaluated a biomarker panel (BioScore) to enhance prognostic algorithms for clear cell renal cell carcinoma (49).

## **Treatment:**

Surgery is the mainstay of treatment of localized RCC. Radical nephrectomy as described by Robson (1969) still remains the gold standard for patients with localized RCC and has a cure rate of 70-92% (50).

The principles of radical nephrectomy include –

1. Early ligation of renal artery and vein,,
2. Removal of kidney and ipsilateral adrenal gland surrounded by the Gerota's fascia

3. Regional lymphadenectomy from the crus of the diaphragm to the bifurcation of aorta or inferior vena cava.

The erstwhile dogma of routine adrenalectomy and classical lymphadenectomy is now being questioned. In patients without radiological abnormality of the adrenal gland, routine adrenalectomy is not indicated except in patients with T3-T4 disease, locally advanced tumours and upper pole tumours (51, 52). There remains a lack of consensus regarding the indications and extent of lymphadenectomy. Current evidence suggests that lymphadenectomy should be restricted to staging, as extended lymphadenectomy does not improve survival. Consequently, it is recommended to perform a hilar and immediate adjacent paraaortic or paracaval nodal dissection during a routine radical nephrectomy, for staging purpose. Numerous studies have identified risk factors for lymph node metastasis such as large tumour size >10 cm, T<sub>3</sub>-T<sub>4</sub> tumours, high tumour grade, sarcomatoid component and histological tumour necrosis (53, 54). If more than 2 factors are present the risk of lymph node metastasis is around 10% vs 0.6% when less than two factors are present. In the higher risk group a complete lymph node dissection may be warranted.

Radical nephrectomy can be done by following methods

1. Open.
2. Laparoscopic - transperitoneal, extraperitoneal or hand assisted.
3. Robotic.

Presently, there is no evidence favouring a specific surgical approach. In open approach, the choice of incision depends on the size and location of the tumour and the comfort of the surgeon. There is no impact of a specific incision on the final outcome.

Laparoscopic radical nephrectomy is indicated for localized renal cell carcinoma with tumour size <10 cm with no renal vein thrombus or lymph node metastases.

The surgical and oncological outcomes after laparoscopic surgery have been reported to be equivalent to those after open surgery, with equivalent cancer specific survival rates and post-operative morbidity rates. However, there have been no randomized trials comparing laparoscopic with the open radical nephrectomy. Nevertheless, at the present time, laparoscopic radical nephrectomy should be considered the standard of care for  $T_{1-2}N_0M_0$  tumours. Appropriate patient selection as well as experience and expertise of surgeon remain vital to success of laparoscopic radical nephrectomy.

### **Nephron sparing surgery (NSS):**

NSS was first described by Czerny in 1890 but later popularized by Vermooten in 1950. The absolute indication for NSS has been tumour in an anatomically or functionally solitary kidney where removal of the whole kidney would make the patient anephric with subsequent high risk of dialysis or transplant.

Relative indications for NSS are:

1. Patients with unilateral cancer and the contralateral functioning kidney affected by a condition that might threaten its future function such as renal artery stenosis, nephrosclerosis, hydronephrosis, diabetes, calculus disease, hypertension.
2. Hereditary forms of RCC with a high chance of developing a contralateral renal tumour.

NSS can be done in patients with unilateral localized RCC with normal contralateral kidney as an elective indication.

A number of centers have reported excellent cancer specific survivals of 90-100% following NSS (55-58). NSS can be safely offered to patients with tumours <4 cm in size, unilateral, unifocal and with low pathological tumour stage as recurrence – free and long term survival rates are similar to those reported with radical nephrectomy. The indications of NSS have been extended to include tumours up to 7 cm size and reports suggest no significant difference for tumour recurrence, cancer specific survival and renal function when compared to 4 cm size (59-65). There seems to be no difference in outcome irrespective of the tumour is polar or central/hilar in location. Another issue in NSS is the thickness of the tumour free margin. The thickness of negative margin does not correlate with recurrence so long as the resection margin is cancer free and even 1 mm margin all around has been reported to be adequate (66, 67).

Laparoscopic partial nephrectomy is an alternative in suitable patients in the hands of an experienced laparoscopic surgeon. Small, peripheral renal tumours are optimum indications for LPN. Although some centres have reported equivalent oncological outcomes after LPN, long term reliable data is yet not available from large studies. Besides, LPN is associated with longer warm ischemia time and increased intra and post operative complications and hence its use should be limited to high volume centres with surgeons experienced in laparoscopic surgery.

### **Ablative surgical procedures:**

May be used as alternatives to surgery.

Indications:

1. patients with small, incidental renal tumours,



2. patients with genetic predisposition to multiple tumours,
3. patients with tumours in solitary kidney or with bilateral tumours;
4. Elderly patients with significant co-morbidities who are not fit for an open surgical approach etc.

The various ablative techniques e.g. radiofrequency ablation (RFA), cyrotherapy, microwave and high-intensity focused ultrasonic ablation (HIFU) have been tried in patients with RCC. These can be instituted by open surgical route, by laparoscopic or even a percutaneous route.

The potential advantages of these procedures are that they are less morbid, can be done at outpatient procedures and can be offered to unfit patients. The main disadvantages of these procedures are that there is no tissue available for histological confirmation of the lesion and that there is no histological proof of completeness of ablation. This is indirectly assumed by a set CT criterion. In a recent population-based comparison of survival after nephrectomy vs nonsurgical management for small renal masses, these modalities have been found to be inferior to nephrectomy. (68) The Oncological outcomes and morbidity of these procedures have not been tested in clinical trials and hence these must be considered experimental at present.

### **Close observation or Active surveillance:**

In view of an extremely slow growth rate of small renal masses (0.01-0.86 cm/year in retrospective analysis from numerous studies), close observation of these masses is being investigated, especially once nearly one third to one fourth of these masses are benign on histological

examination. There may be a place for close observation with serial renal imaging in elderly or moribund patients who are poor risk for surgery or ablative procedures. This approach is not advocated for young, fit patients with small renal masses if radiological features suggest RCC.

Tumour thrombus extension to renal vein or inferior vena cava:

This is seen in 4-10% patients of RCC. Tumour thrombus should be suspected in patients with –

1. Lower extremity oedema,
2. Unilateral right sided varicocele or one which does not collapse on recumbency,
3. Dilated veins on anterior abdominal wall,
4. Non-functioning involved kidney,
5. Proteinuria,
6. Prior history of pulmonary embolism or a right atrial mass on imaging.

An accurate assessment of the presence and extent of thrombus especially its cephalad limit is mandatory for planning appropriate treatment. MRI is probably the best modality for accurate demonstration of the thrombus and for differentiating between a tumour thrombus and a bland thrombus by demonstrating post-contrast enhancement of the thrombus. Inferior venacavography is generally reserved for patients in whom the MRI findings are equivocal or in whom MRI is contraindicated. Transoesophageal ultrasonography and abdominal colour flow Doppler may also be employed to accurately assess the cephalad extent of thrombus. The venous thrombus extension is classified by its level as follows:

- I: adjacent to renal vein ostium
- II: extending up to lower border of liver (intrahepatic)
- III: involving intrahepatic portion of IVC but below the diaphragm
- IV: extending above the diaphragm

Presence and extent of tumour thrombus have no adverse impact on survival. Many types III/IV thrombi are however associated with advanced locoregional disease and hence have a poorer prognosis (69-71).

Excellent survivals of 40-70% at 5 years have been reported with complete excision of the primary tumour and its extension into the renal vein or IVC (72) and in the absence of metastatic disease, surgical excision of thrombus along with radical nephrectomy is recommended.

### **Adjuvant therapy:**

Presently, there is no evidence that any adjuvant treatment after radical or partial nephrectomy improves survival. The use of autologous tumour vaccine in adjuvant setting showed some advantage in progression free survival, but did not affect the overall survival. In patients with high risk factors and locally advanced disease undergoing radical nephrectomy targeted therapy agents are being investigated for their role in the adjuvant setting.

### **Surveillance following surgery for RCC:**

Follow up is necessary to monitor

1. Post-operative complications.
2. Renal function.
3. Local recurrence.

4. Recurrence in the contralateral kidney.
5. Development of metastases.

However, there are no evidence based surveillance guidelines. The patients may be classified into different risk groups according to one of the risk assignment systems based on clinicopathological factors and histological subtypes; and then the surveillance strategy may be individualized depending on the risk of relapse. Although early detection of relapse is desirable, actually only a small percentage of patients with relapse can be salvaged by curative therapy. One of the commonly employed follow up surveillance schemes is as follows:

*Low risk:* Clinical examination, X-ray chest, ultrasonography of abdomen every 6 months. CT scan not routinely advised.

*Intermediate risk:* Clinical examination, X-ray chest or CT thorax, CT abdomen every 6 months for 2 years and then annually upto 5 years.

*High risk:* Clinical examination, CT thorax and CT abdomen at 3 months, then every 6 months for 5 years and annually thereafter.

### **Local recurrence after radical nephrectomy or NSS:**

Local recurrence after radical nephrectomy is rare (1-4%) and seen in patients with node positive or locally advanced disease at presentation. (73-75). Nearly two thirds of these will have associated systemic disease. In documented absence of distant relapse, surgery may be offered to remove the disease. Patients not suitable for surgery may be managed with local radiation therapy or oral targeted therapy.

Relapse after NSS is also rare (1-10%) and is seen in patients with higher T stage. Recurrence may be seen at the same site or at a different site (due to multifocality of disease). If metastatic work up reveals no abnormality, either a repeat partial nephrectomy or a radical nephrectomy is recommended (76). In patients unsuitable for surgery, local ablative therapies may be tried.

Local recurrences after local ablative therapies are usually at the site of the original tumour and are suspected by persistent enhancement within the tumour bed or in rest of the kidney. Treatment can be re-ablative therapy or total nephrectomy.

### **Metastatic renal cell carcinoma:**

Approximately one third of patients with RCC present with metastatic disease and another 40-50% will develop distant metastases some time during their natural history (77). Majority of these patients will die of disease within 12-24 months if left untreated.

However, there is a small subset of patients (1-4%) with solitary metastasis, who may have a better biological behavior than those with multiple metastases. These may benefit with an aggressive therapeutic approach with intent of cure. Many centers have reported excellent survival rates of 33-60% five year survivals after complete excision of the primary renal tumour and the metastatic disease.

The following factors indicate a better prognosis: (78-80).

1. Lung only metastasis
2. Solitary vs. multiple sites of metastases (54% vs. 29% 5-year overall survival)

3. Metachronous metastases.
4. Long relapse-free interval – greater than 12 months (55% vs. 9% 5 year survival)
5. Complete resection of metastatic disease possible.
6. Good performance status
7. Age less than 60 years (49% vs. 35% 5-year overall survival).

Metastatectomy can also be considered in patients with residual metastatic lesions responding to immunotherapy or target therapy, provided the metastasis is resectable.

The aim of treatment in patients with multiple metastases is palliative. Patients with multiple metastases may be classified into different prognostic groups for prognostication and planning optimum therapy. (81)

Two prospective randomized trials have examined the value of cytoreductive nephrectomy prior to immunotherapy (82,83). The results of both these trials as well as their combined analysis have shown survival advantage in the nephrectomy arm (13.6 vs. 7.8 months) (84). In view of this, cytoreductive nephrectomy followed by systemic treatment should be considered in patients of metastatic RCC. Patients have to be properly selected as few will be unable to take systemic treatment due to post-operative complications or rapid disease progression. Patients most likely to benefit from cytoreductive nephrectomy are those with:

1. Good performance status with no/minimum co-morbidities.
2. Preferably lung only metastasis.
3. Absence of CNS or liver metastasis.
4. Easily resectable tumour with minimal morbidity.

5. Possibility of more than 75% tumour reduction with nephrectomy.

In some patients with unresectable disease, systemic / targeted therapy can be started and then assessed for nephrectomy. This may allow selection of better patients with biologically more responsive tumours, reserving aggressive treatment for the patients most likely to benefit from it. Pantuck et al in a retrospective analysis, recommended complete regional lymphadenectomy in patients undergoing cytoreductive nephrectomy for advanced disease and demonstrated a survival benefit in those undergoing lymphadenectomy in a retrospective analysis (85). The role of cytoreductive nephrectomy has not been studied in non-clear cell histology.

Radiotherapy may be given for selected patients with brain metastases or painful skeletal metastases, for symptomatic relief.

### **Systemic therapy for metastatic RCC:**

Hormonal therapy in the form of progestational agents (86,87) and chemotherapy (88) have not been found to be effective in RCC. In non-clear cell histology or in patients with sarcomatoid differentiation, chemotherapy may have a role and the preferred agents are doxorubicin and gemcitabine (89)

Immunotherapeutic approaches to RCC include treatment with alpha interferon (IFN- $\alpha$ ) or interleukin-2 (IL-2) or a combination of the two. Several trials have shown 10-15% partial response to IFN- $\alpha$  (90). The benefit to immunotherapy is limited to patients with good performance status, lung only metastasis, long metastasis free interval following nephrectomy and clear cell histology. High dose IL-2 has been shown to be

superior to conventional dose IL-2 and has given durable complete responses in some patients but its use is limited due to associated high toxicity.

Combination of immunotherapy and chemotherapy has not been shown to be beneficial.

Targeted therapy: Better understanding of the molecular pathways has led to the development of targeted agents with robust clinical effects. Vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKI) have shown efficacy in clear cell RCC.

1. Sunitinib - tyrosine kinase inhibitor (TKI) of VEGF receptor; Platelet derived growth factor, c-KIT and FLT-3. In a phase III double blind RCT comparing sunitinib with IFN- $\alpha$ , sunitinib achieved a longer progression free survival (11 months vs. 5 months) in low and intermediate risk patients. This difference was larger in patients who did not receive any post-study treatment (28.1 vs 14.1 months). The median overall survival was also longer in sunitinib arm (26.4 months vs. 21.8 months), as also the response rate (47% vs. 12%). In view of this, sunitinib is recommended as first line drug of choice in good and intermediate risk criteria patients.(91)
2. Sorafenib - oral multikinase inhibitor. It is recommended as second line therapy. A randomized trial comparing sorafenib with placebo demonstrated improved progression free survival (5.5 months vs. 2.8 months) with sorafenib in patients who had failed cytokine therapy. However, this effect was not seen in previously untreated patients.(92)
3. Bevacizumab + IFN – is also recommended as first line therapy in good and intermediate risk patients



with mRCC. This recommendation is based on the results of 2 RCTs – AVOREN and CALGB, both of which showed improved progression free survival with combination of bevacizumab and IFN-a vs. IFN-a alone.(93, 94)

4. Temsirolimus (m-TOR inhibitor) – is recommended in poor risk patients as a first line therapy, based on a RCT which showed improved progression-free and overall survival with temsirolimus as compared to IFN-a or a combination of the two.(95)
5. Everolimus – is an oral m-TOR inhibitor and used in patients of metastatic RCC refractory to sorafenib, sunitinib as well as cytokines (96). A recent phase III trial in patients who had failed previous anti VEGF-R treatment showed better progression free survival with everolimus as compared to placebo (4 months vs. 1.9 months).

Surgical resection of renal cell carcinoma after targeted therapy is feasible with low morbidity in most patients. However, significant complications can occur, raising concern for possible compromise of tissue and/or vascular integrity associated with surgery in this setting. In this group of patients, careful patient selection, preoperative patient optimization and meticulous perioperative care can lead to a better outcome. (97)

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# **Carcinoma of the Urinary Bladder**

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## **Introduction:**

Carcinoma of bladder is a heterogeneous disease which presents as superficial, muscle invasive or metastatic disease. These different presentations of bladder cancer have different clinical behaviour, management protocols and outcome. Bladder cancer is the commonest urological malignancy in India and the second most common genitourinary malignant disease in the USA, with an expected 69,000 newly diagnosed cases in 2008, and 14 000 deaths in the USA. Males are commonly affected (M: F= 2.4:1) and occurs mostly in the elderly (median age of presentation 60 to 70 years). In the SEER data, from 2002-2006, median age at diagnosis of urinary bladder cancer was 73 years and nearly 90% of the diagnosis is made in patients over the age of 55 years.

## **Aetiology: (level of evidence 3)**

*Cigarette smoking* is the single most important environmental etiological factor associated with bladder cancer and triples the risk of bladder cancer. The risk of bladder cancer directly relates to duration of smoking

and number of cigarettes smoked per day and an immediate reduction in the risk of bladder cancer is observed with cessation of smoking.

The other associated aetiological factors are:

### **A) Chemical exposure**

- Chemical agents: Exposure to aromatic amines as seen in workers of dye, rubber, leather industry, gas and tar manufacturing, industrial painting etc.  
( median latent period between exposure and disease is 18 year)
- Dietary habits: less fluid intake, fried meat & fat intake, Low vitamin A
- Drugs— phenacetin, cyclophosphamide, immunosuppressive.

### **B) Chronic irritation**

- Chronic urinary tract Infection, schistosomiasis, long term use of catheter, pelvic irradiation.

### **C) Genetic abnormality**

- 17p deletion, p53 expression; RB gene expression, 9q aberration.

## **Clinical presentations**

At presentation a majority (70%) are superficial (non-muscle invasive) tumours, 30% are invasive, of which about 5-10% are metastatic (5). Patients usually present with painless haematuria (80-90%) or with unexplained urinary frequency or irritative voiding symptoms. Lower urinary irritative and obstructive symptoms may be the sole presenting symptoms in the absence of haematuria. Pelvic pain and obstructive symptoms are seen in patients with advanced invasive disease.



The degree of haematuria does not correlate with the extent of disease – it may be gross or microscopic. Even a single episode of haematuria needs to be investigated from the point of view of bladder cancer, even if another potential cause for haematuria is found. All patients over 40 years old, smokers and those with exposure to industrial carcinogens with painless haematuria should be investigated with urinary cytology, cystoscopy and imaging (IVP or CT-scan) for urinary tract malignancy.

### **Investigations :**

The aims of investigations in bladder cancer are diagnosis and staging to guide therapy. The main factor that decides the treatment is the presence or absence of muscle invasion. The diagnostic and staging investigations in a case of bladder cancer are as follows:

- Routine haematological & biochemical investigations including renal chemistry.
- Freshly voided urine cytology of exfoliated cancer cells is particularly useful in the presence of a high-grade malignancy or CIS. Urine specimens for cytology should not be obtained from the first voided morning specimens. Positive cytology in the absence of any lesion on imaging may indicate a lesion anywhere in the urinary tract. Negative voided cytology does not necessarily exclude the presence of a low-grade bladder tumour. Overall urinary cytology examination is promising but with low sensitivity (sensitivity 40-60%, specificity 90%). However, in high grade tumors the sensitivity is high (~90%) (level of evidence 2a).
- Intravenous urogram is indicated in all patients with haematuria or cystoscopic evidence of bladder cancer. It is not a sensitive means of detecting

bladder cancer alone but useful in examining the upper urinary tracts for associated urothelial tumours. Retrograde pyelogram should be performed if the upper tracts are not adequately visualized on the intravenous urogram. The necessity to perform routine IVU at initial diagnosis is now questioned because of the low incidence of important findings obtained with this method (incidence of upper tract tumours is about 1.8%) and the easy availability of cross sectional imaging (see below) (Level of evidence 3).

- Ultrasonography of the abdomen and pelvis to document status of upper tracts and for associated upper tract urothelial tumours, besides demonstrating the bladder tumour. Combined with plain abdominal film, it can be as accurate as IVU in the diagnosis of the cause of haematuria.
- Cystoscopic examination of the bladder and pathological evaluation of the resected lesion form the cornerstone of diagnosis. During cystoscopy, the characteristics of bladder tumour(s) are noted and a biopsy from the bladder tumour taken. Bladder washings for cytology should be taken as studies have demonstrated superiority of bladder washing over voided urine cytology. The first treatment decision based on tumour stage is whether the patient has a superficial or muscle invasive bladder cancer. Transurethral resection of the bladder tumour (TURBT) is the most important test for judging the depth of tumour penetration. Inclusion of muscle in biopsy is essential. During resection, the following are recommended:
  1. Resect the tumour down to muscle and send superficial and deep components of the tumour separately to the pathologist

2. If the cancer is muscle invasive, complete debulking is preferable
  3. Biopsy of the base of the tumour
  4. Random biopsies from apparently uninvolved normal areas of bladder are indicated in the presence of positive cytology, in the absence of a tumour or in any non-papillary tumour. Random biopsies in a patient with a solitary papillary lesion are contraindicated due to the perceived hazard of implantation of tumour cells, low likelihood of detection of CIS (<2%) and absence of any additional information. Biopsies from the prostatic urethra are indicated in the case of bladder neck tumour, when bladder CIS is present or suspected, in the case of positive cytology without evidence of tumour in the bladder or when abnormalities of prostatic urethra are visible (level of evidence 3). The biopsy is taken using resection loop from the precolicula area.
- Bimanual examination under anaesthesia may be done in case of invasive tumours for local staging of the tumour. It may be performed both before and after the TUR. The presence of a palpable mass after TUR implies an extravesical disease. It can also indicate fixity to the pelvic side walls.
  - Urinary markers: Various tests for bladder tumour antigen, NMP 22, FDP etc are now available. These have a better sensitivity for detecting bladder cancer but the specificity is much lower. Sensitivity of nuclear matrix protein (NMP-22) and bladder tumour antigen (BTA) is 50-70%. Higher false positive tests can lead to unnecessary imaging and bladder biopsies. It is not clear whether these tests can offer additional information, which is useful for

decision making, treatment and prognosis of superficial bladder cancer.

- Fluorescence cystoscopy is a promising tool using violet light after intravesical instillation of a photosensitizer e.g. 5-aminolaevulinic acid or hexaminolaevulinate. Fluorescence-guided biopsy and resection are more sensitive than conventional procedures in detecting malignant tumour, particularly CIS (level of evidence 2a). If urinary cytology is persistently positive without any demonstrable bladder lesion, ALA installation and use of specific wavelengths yields higher positive biopsies. The technique is still evolving.
- Imaging: The purpose of imaging for staging is to assess extent of local tumour invasion, detect lymph node spread and to detect distant metastases. For invasive cancers, it is essential to document the extent of the disease by doing cross sectional imaging. Both computed tomography (CT) and MRI scans can be used for assessment of local invasion, but they are unable to detect microscopic invasion of perivesical fat (T3a). The aim of CT and MRI scanning is therefore to detect T3b disease or higher. Multidetector contrast enhanced CT scan has a lower sensitivity (89% vs 100%) and higher specificity (95% vs 73%) compared to MRI scanning for diagnosis of perivesical invasion, whereas the cancer-detection rate and overall accuracy for perivesical invasion are similar.
- Imaging is also used to assess the presence of pelvic and para-aortic lymphadenopathy and the possible presence of liver or adrenal metastases. However, it has limitations in recognizing minimal pelvic nodal disease or microscopic invasion of

adjacent organs. Pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short axis diameter should be regarded as enlarged on CT and MRI scans.

For optimal staging, either MRI with fast dynamic contrast enhancement or MDCT with contrast enhancement are recommended.

- Metastatic work up:

Chest radiographs are performed to rule out pulmonary metastases, however, CT scan is the most sensitive means of detecting pulmonary metastasis.

Isotope bone scan is done to detect bony metastasis and also useful as a baseline for future reference, particularly in patients with bone pains or increased alkaline phosphatase.

CT or MRI of brain is done if clinically indicated.

## **Natural History and pathology**

Bladder cancer is multicentric and asynchronous. Morphologically a majority (70%) are exophytic papillary tumor confined to mucosa (Ta) or invade submucosa (T1). About 50-70% of superficial tumours recur and 5-20% of them progress to invasive disease. Histopathologically, majority of bladder cancers are transitional cell carcinoma (90-95%). Pure squamous cell tumor with keratinisation (3%) occurs in schistosomia infestation and chronic irritation. Adenocarcinoma (2%) occurs in the embryonal remnants of urachus. Low grade tumours (G1) have high local recurrence rate but usually do not invade muscularis. High grade superficial tumours have high propensity to transform to invasive tumour. All invasive tumours are high grade.

## **Histological grading:**

### **1973 WHO grading**

Urothelial papilloma

Grade 1: well differentiated

Grade 2: moderately differentiated

Grade 3: poorly differentiated

### **2004 WHO ISUP grading**

Urothelial papilloma

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Low-grade papillary urothelial carcinoma

High-grade papillary urothelial carcinoma

The use of the 2004 WHO/ISUP grading is advocated, as this should result in a uniform diagnosis of tumours, which is better classified according to risk potential. However, until the 2004 WHO classification has been validated by more clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications

## **Staging:**

The 2002 UICC TNM system is widely accepted.

### **Primary tumour (T)**

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour

Ta Non-invasive papillary tumour

Tis In-situ flat tumour

T1 Tumour invades subepithelial connective tissue (lamina propria)

- T2 Tumour invades muscle
  - T2a Inner half (superficial muscle)
  - T2b Outer half (deep muscle)
- T3 Tumour invades perivesical tissues
  - T3a Microscopically
  - T3b Macroscopically (Extravesical mass)
- T4 Tumour invades adjacent structures e.g. prostate, uterus, vagina, pelvic wall, abdominal wall
  - T4a Tumour invades prostate, uterus or vagina
  - T4b ITumour invades pelvic wall, abdominal wall

### **Lymph nodes (N)**

- Nx Regional nodes cannot be assessed
- N0 No lymph node metastases
- N1 Metastasis to a single node 2cm or less in the greatest dimension
- N2 Metastasis to a single node >2cm but <5 cm in the greatest dimension or multiple lymph nodes, none >5 cm in the greatest dimension
- N3 Metastasis in a lymph node >5cm in the greatest dimension

### **Distant metastases (M)**

- Mx Distant metastases cannot be assessed
- M0 No evidence of distant metastases
- M1 Distant metastases present

## **Management of non-muscle invasive bladder cancer:**

The objective in managing non-muscle invasive bladder cancer is in the prevention and detection of recurrences and progression.

Transurethral resection of bladder tumour (TURBT): Transurethral resection of the bladder tumour(s) is the standard of care for superficial bladder cancers. Goal of TURBT in Ta/T1 bladder tumours is to make correct diagnosis and remove all visible lesions.

Small tumours (less than 1 cm) can be resected en bloc. Specimen should contain a part of the underlying bladder wall. Larger tumours should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and edges of the resection area. Cauterization should be avoided during resection to prevent tissue destruction.

Re-TURBT: There is a significant risk of understaging after initial resection of Ta/T1 tumours (level of evidence 1), with residual disease detected at second resection in 33-53% of patients. Nearly 20% T1 patients are upstaged to muscle invasive disease, the likelihood being more if the initial resection specimen contained no muscle tissue. Accurate staging of disease is important for optimum treatment and understaging may lead to inadequate treatment and poor outcome. Second TURBT should be considered if there is a suspicion of incomplete initial resection (multiple or large tumours present with no muscle invasion on pathology) and after diagnosis of high-grade non-muscle-invasive tumour. It has been shown that the second TURBT can increase recurrence-free and progression-free survival (level of evidence 2a). There is no consensus regarding the timing of the second TUR but is generally recommended 2–6 weeks after the initial TURBT and should always include resection of the primary tumour site.



### **Prognostic factors for recurrence and progression:**

Numerous prognostic factors have been shown to be associated with recurrence and progression of non muscle invasive bladder cancer viz.:

- high grade or poorly differentiated tumours (G3)
- co-existent CIS or dysplasia in random mucosal biopsies
- multiple or multicentric tumours
- multiple recurrences within a short period of time (rapidly recurrent tumours)
- lamina propria invasion (T1)
- tumour size more than 3 cm
- prostatic urethral involvement

Based on these prognostic factors, superficial bladder cancers can be divided into the following risk groups:

- Low risk : Single, Ta, G1, <3 cm in diameter
- High risk : T1, G3, multifocal or highly recurrent, CIS
- Intermediate risk : All other tumours, Ta-T1, G1-G2, >3 cm in diameter

The risk of recurrence and progression can be separately predicted in individual patients, using EORTC scoring system and risk tables, developed from a database of more than 2500 patients.

Despite an adequate transurethral resection, nearly 70-80% of patients will have relapse within the bladder while 20-25% will progress to muscle invasion. Bladder cancer with low risk of recurrence or progression can be managed by close surveillance and regular check cystoscopy, while those with high risk of relapse need intravesical chemotherapy or immunoprophylaxis.

Intravesical therapy is indicated in patients who are at high risk for tumour recurrence and progression. The aim of intravesical therapy is to reduce invasion and recurrence after initial TURBT.

### **A. Single post TURBT instillation:**

In a meta-analysis of 7 randomized trials, a single immediate instillation of chemotherapy after TURBT decreased recurrence rate by 12% and odds of recurrence by 39% in both single and multiple tumours (level of evidence 1a). Mitomycin C (MMC), epirubicin, and doxorubicin have all shown a comparable beneficial effect level of evidence 1b). The timing of the instillation is crucial and the single instillation is recommended within 24 hours (preferably within 6 hours) of TURBT and a delay increases in the relative risk of recurrence twofold (level of evidence 2a). The effect of single post-operative instillation is mainly seen in the first 2 years. A single immediate post-operative instillation of chemotherapy is recommended in all patients irrespective of the risk group, provided there is no perforation or bleeding.

Low risk group patients with papillary tumours require no further treatment as the recurrence rate in this group is very low after single instillation immediately after TURBT (level of evidence 1a). Intermediate and high-risk patients require a further 4-8 weeks course of intravesical therapy.

### **B. Additional adjuvant intravesical therapy:**

The need for further adjuvant chemotherapy or BCG immunotherapy largely depends on the risk of recurrence or progression. A meta-analysis of the MRC and EORTC data comparing intravesical chemotherapy to TURBT alone demonstrated that chemotherapy prevents

recurrence but not progression (level of evidence 1a). It is still controversial how long and how frequently intravesical chemotherapy instillations have to be given. From a systematic review of the literature of randomized clinical trials, which compared different schedules of intravesical chemotherapy, it can be seen that the ideal duration and intensity of the schedule remains undefined because of conflicting data. Four meta-analyses have confirmed that BCG after TURBT is superior to TURBT alone or TURBT and chemotherapy in preventing recurrences of TaT1 tumours (level of evidence 1a). The efficacy of intravesical chemotherapy in reducing the risk of recurrence was demonstrated in the primary as well as recurrent settings by 2 meta-analyses by Huntcharek in 2000 and 2001. To increase the efficacy of intravesical chemotherapy, optimized schedules have been tried. The studies demonstrated that adapting the urinary pH, decreasing the urine formation and excretion, buffering the intravesical solution and increasing the relative concentration of the drug in the instilled solution may lead to improvement in efficacy. (level of evidence 1a).

Bacillus Calmette-Guerin (BCG) is used as intravesical immunotherapy and has been shown to be effective in reducing tumour recurrence rate and presently is the only agent, which has been shown to reduce the progression rate to muscle invasion, reduce the need for cystectomy, increase the time to cystectomy and improve survival. In an EORTC meta-analysis, only patients receiving maintenance BCG were benefited (level of evidence 1a). Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression. The EORTC meta-analysis of nearly 5000 patients demonstrated that there is 27% reduction in rate of progression after intravesical BCG treatment in both

TaT1 and CIS disease (level of evidence 1a). In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the odds of progression was observed. The most optimal BCG maintenance schedule is not known. Although weekly instillations for 6 weeks are a commonly used schedule empirical schedule, a meta-analysis concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over MMC in preventing recurrence or progression (level of evidence 1a). Hence, in patients with intermediate and high risk patients, maintenance BCG is advised to achieve best results, provided patients can tolerate it. Various schedules of maintenance BCG have been described but to date, there is no optimum schedule based on high level of evidence. Most centres, however, follow the schedule described by Lamm.

The optimal dose of BCG is yet undefined. To reduce BCG toxicity, several authors have proposed dose reduction of BCG to one third to one fourth of the standard dose. The Spanish Oncology Group (CUETO) compared the standard dose with one third dose of BCG in a randomized trial and did not find any difference in efficacy, except in patients with high risk prognostic group.

### **Treatment of failure of intravesical therapy:**

Failure of intravesical chemotherapy: Patients with non muscle invasive recurrences after intravesical chemotherapy may benefit from intravesical BCG immunoprophylaxis.

Failure of intravesical BCG immunotherapy: The response to BCG is assessed at 6 months after TUR, since the disease status at this point of time has been shown to best correlate with subsequent progression and survival. Patients with BCG failure may be classified into:

BCG resistant, BCG refractory, BCG relapsing and BCG intolerant. This classification helps in identifying optimum treatment for patients in each subgroup.

Treatment with BCG is considered to have failed in case of:

- a. development of muscle invasive tumour
- b. presence of high grade non-muscle invasive tumour present at 3 and 6 months. In patients with such tumour at 3 months, an additional course of BCG is indicated and 50% of these patients respond to this additional course of BCG.
- c. Worsening of disease such as increased number of recurrences, higher stage or grade, appearance of CIS in spite of initial response to BCG

Various strategies have been recommended for treatment of BCG failure:

- a. Intravesical chemotherapy, especially device assisted one
- b. Newer intravesical chemotherapeutic agents such as gemcitabine
- c. Second line immunotherapeutic agents such as interferons with or without BCG
- d. Cystectomy

### **Cystectomy for non-muscle invasive bladder cancer:**

Despite intravesical adjuvant therapies, there is a substantial group of patients with initial high-grade stage T1 tumor who have progression and are at risk of dying from urothelial cancer. It is reasonable to propose immediate cystectomy to those patients who are at high

risk of progression (multiple recurrent high-grade tumours, high-grade T1 tumours, high-grade tumours with concomitant CIS). Cystectomy is advocated in patients with BCG failure and delaying cystectomy in these patients may lead to decreased disease specific survival.

### **Management of carcinoma-in-situ:**

Carcinoma-in-situ of bladder may exist alone (primary CIS) or in combination with a bladder tumour. Primary CIS confined to bladder is treated with intravesical BCG, with excellent complete response rates of 82-93% (level of evidence 2). Recurrence of primary CIS despite first course of BCG may be treated with a second course of BCG with response seen in 40-50% of patients.

CIS associated with an overt tumour is treated according to the merits of the tumour. Approximately 50% patients develop recurrent disease with muscle invasion or extravesical tumour (level of evidence 2), and 10-20% die of their disease within 5-7 years after an initial complete response. Non-responders or incomplete responders have a significant risk of tumour progression and cystectomy is recommended in such patients. Patients with an incomplete response at 9 months, recurrent tumours or extravesical disease also need cystectomy.

### **Follow up schedules in superficial tumours:**

Prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrences is critical and delay in diagnosis and therapy could compromise survival. Tumour recurrence in low-risk group is nearly always low stage and low grade and does not pose a threat to life. High risk patients may present as muscle invasive

disease on recurrence and need immediate diagnosis and treatment. The result of first cystoscopy after TUR at 3 months is an important prognostic factor for recurrence and progression (level of evidence 1a) and hence cystoscopy at 3 months post-TUR is recommended in all patients.

1. Patients with low risk of recurrence/progression: Cystoscopy at 3 month post-TURBT. If negative, following cystoscopy is advised at 9 month and consequently yearly for 5 yr. First cystoscopy finding (at 3 months) is significant prognostic factor for recurrence and for progression
2. Patients with high risk of progression: Cystoscopy and urinary cytology at 3 month post-TURBT. If negative, following cystoscopies and cytologies should be repeated every 3 mo for a period of 2 yr, every 4 months in the third year, every 6 month thereafter until 5 yr, and yearly thereafter. A yearly exploration of the upper tract is recommended
3. Intermediate risk: should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to individual factors.

Cytological surveillance should accompany every cystoscopic examination. During cystoscopy, directed biopsy should be taken if there is any suspicious area. The risk of upper tract urothelial cancer in bladder cancer is about 4%. Intravenous urogram is therefore recommended at least once in two years, or in the presence of positive cytology and negative cystscopy. Ultrasonography is recommended once a year. The role of urinary markers like NMP22, urine cytology or multitarget FISH study on exfoliated urine cells to replace cystoscopic evaluation or to postpone it is under

evaluation but till the time the results of these studies are available, cystoscopic evaluation remains the gold standard for follow up in a patient with superficial bladder cancer.

## **Management of Muscle-Invasive Bladder Cancer:**

Approximately 30% of newly diagnosed bladder cancers have muscle invasion. Besides, 20-25% of superficial bladder cancers progress to muscle invasion some time during their natural history. Approximately 30% of patients diagnosed with muscle-invasive bladder cancer have undetected metastasis at the time of treatment of the primary tumour, while 25% of patients submitted to radical cystectomy present with lymph node involvement at the time of surgery.

### **A. Surgery**

Radical cystectomy is the preferred treatment for invasive bladder cancers in patients whose medical condition allows major surgical procedure (Level of evidence 2a). Pelvic lymphadenectomy is routinely performed as part of radical cystectomy for bladder cancers; however, there is lack of consensus on the intent (therapeutic or staging/prognostic) and extent of lymph node dissection. There is evidence from retrospective studies that extended lymphadenectomy improves outcome in patients with tumours confined to the bladder. However, no controlled studies support extended lymphadenectomy as curative treatment. Thus limited or regional lymph node dissection is the recommended standard surgical method (Level of evidence 3). Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as beneficial for overall



survival in retrospective studies In the presence of gross nodal disease; 5-year survival rates are poor.

Radical cystectomy is recommended for non-transitional cell carcinomas, which generally respond less to radiation and chemotherapy. However, despite an adequate surgery, approximately 50% patients will develop metastatic disease within 2 years, emphasizing the need for augmenting treatment in these patients. The 5-year survival rates after radical cystectomy alone in T2, T3a, T3b and T4 disease are 63%, 57%, 31% and 18% respectively. Partial cystectomy may be indicated in only selected patients with 1) Transitional cell tumour 2) solitary muscle invasive tumour location at dome, 3) no extravesical spread 4) random mucosal biopsies are negative and 5) intra-operative frozen section surgical margins negative.

Laparoscopic or robot assisted radical cystectomy may be an option for the future. Current data, however, is insufficient to support its routine use at present.

Urethrectomy has been recommended if the tumour involves the bladder neck in women or the prostatic urethra in men. A positive urethral cut margin at the end of cystectomy also signifies the need for urethrectomy. Extensive involvement of the prostate also necessitates urethrectomy. Recently, there is a trend towards preservation of urethra to make orthotopic neobladder possible as well as preservation of intrapelvic autonomic nerves to improve potency and continence. Urethrectomy may be done at the time of cystectomy or subsequently as a separate procedure. Contra-indications to orthotopic neobladder include prostatic urethral involvement, positive urethral margins, multiple bladder tumours or multicentric involvement of the urinary tract.

Urinary diversion or reconstruction: The various options available are incontinent conduit with an external stoma, continent catheterizable reservoirs with an abdominal stoma and bladder substitution (neobladder) procedures. The type of urinary diversion does not affect oncological outcome (Level of evidence 3). Orthotopic neobladder is the reconstruction of choice undergoing radical cystectomy and is recommended in suitable male and female patients. However, the advantage of orthotopic neobladder over other diversions in terms of quality of life remains a matter of debate. Terminal ileum and colon are the intestinal segments of choice for urinary diversion. The morbidity of orthotopic neobladder reconstruction is appreciable in terms of major complications and reoperation rates. The contra-indications to orthotopic neobladder include prostatic urethral involvement, positive urethral margins, multiple bladder tumours or multicentric involvement of the urinary tract (i.e in the presence of significant risk of urethral recurrence). Orthotopic neobladder reconstruction should be advised to suitable patients after cystectomy for organ-confined muscle-invasive bladder tumour. While discussing this option with the patient, the morbidity must be addressed. The longer recovery period after orthotopic neobladder may delay the subsequent adjuvant therapy in patients with locally advanced disease and in these patients, this option may not be advisable.

## **B. Definitive radiation therapy alone:**

External beam radiation therapy should only be considered a therapeutic option when the patient is unfit for cystectomy for a multimodality bladder sparing approach (level of evidence 3). Based on available data, a Cochrane analysis has demonstrated that radical

cystectomy has an overall survival benefit over radiation therapy alone.

### **C. Chemotherapy alone:**

Chemotherapy alone is not recommended as primary therapy of muscle invasive bladder cancer, despite nearly 30% patients achieving CR following chemotherapy.

### **D. Pre-operative Radiotherapy**

Pre-operative radiotherapy for operable muscle-invasive bladder cancer, using a dose of 45 to 50 Gy in fractions of 1.8 to 2 Gy has been used for down-staging after 4 to 6 weeks (Level of evidence 2). It does not significantly increase toxicity after surgery and may result in a decrease in local recurrence of muscle-invasive bladder cancer (Level of evidence 3). Pre-operative radiotherapy in above dose for operable muscle-invasive bladder cancer does not increase survival and cannot be recommended as standard practice as the data may not be applicable to modern surgical and radiotherapeutic procedures (Level of evidence 2).

### **E. Multimodality treatment and Bladder preservation approaches:**

The use of organ-preservation therapy for bladder cancer is a valid alternative to radical cystectomy in selected patients (Level of evidence 3). Contemporary protocols utilize a combination of aggressive TUR, concurrent radiation and chemotherapy, and often adjuvant chemotherapy. These approaches require close coordination among all disciplines involved. Application of systemic chemotherapy, most commonly CMV or M-VAC aims at eradication of micrometastases. Cisplatin based chemotherapy in combination with radiation therapy, following TUR-BT, results in a CR of 60-80%. For

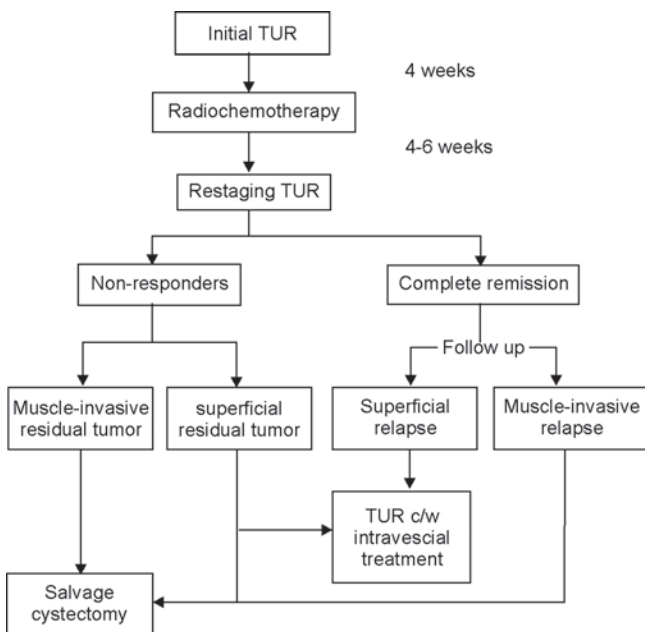
preventing poor outcome in non-responders, early cystectomy is recommended in individuals who do not achieve complete response following combination treatment. This will allow about 40-45% patients to survive with an intact bladder at 4-5 years. Successful long-term survival rates have been observed in select non-randomized trials with this approach. Approximately 50% of patients with bladder preservation treatment are expected to survive with their intact bladder and rest need salvage cystectomy due to loco-regional recurrence. Non-invasive relapses may be treated with TUR followed by intravesical therapy. In view of the high local recurrence rate, a long-term follow up with cystoscopy, exfoliative urine cytology and other investigations to rule out disseminated disease is warranted. Although it has not been compared with radical surgery in randomized controlled trials, from historical series, 5 years control rate of 24-45% with a 5 years overall survival of 26-40% is achieved with radiotherapy for muscle invasive bladder cancer. In the best hands, overall survival rates with bladder preservation are comparable to radical cystectomy (Level of evidence 3).

Clinical criteria helpful in determining patients for bladder preservation include such variables a small tumour size (<5 cm), early stage, a visibly and microscopically complete TURBT, absence of CIS, ureteral obstruction and hydronephrosis and no evidence of pelvic lymph node metastases. On multivariate analysis, the completeness of TURBT has been found to be one of the strongest prognostic factors for overall survival.

With standard fractionation (1.8-2 Gy/fraction), the total radiation dose is typically in the range of 45-50 Gy to treat the pelvic lymph nodes and between 55 and 70 Gy to the bladder. There is a suggestion of a dose response

relationship and retrospective analyses have suggested improved local control with doses greater than 55-60 Gy (Level of evidence 3). Prophylactic irradiation of pelvic nodes is debated with no consensus on its utility. Use of altered fractionation has been reported to induce a higher local control rate but this modality is still investigational.

Overall, the available data indicate that differences in local control between different radiation fractionation schedules are more related to the total dose than to the fractionation regimens. A reduction in overall treatment time and large fraction sizes should be avoided, especially when radiotherapy is combined with concomitant chemotherapy. New treatment techniques, such as image-guided and intensity-modulated



radiotherapy, may allow dose escalation with the expectation to further improve tumour response and long-term local control.

It is important to understand that despite a complete response to multimodality bladder preservation strategies, the bladder remains a potential source of recurrence and hence, lifelong monitoring of disease status – both in the bladder and extravesical is recommended.

## **F. Neoadjuvant Chemotherapy before radical cystectomy:**

Although radical cystectomy is the standard treatment for patients with muscle invasive bladder cancer, it leads to long-term cure in only 50% of patients. In order to improve these results, use of neoadjuvant chemotherapy has been explored. The rationale for chemotherapy prior to cystectomy or radical radiation therapy is based on the intent to treat micrometastatic disease that is present at diagnosis. There is level 1 evidence of a survival benefit conferred by neoadjuvant chemotherapy administered before definitive local treatment (surgery or radiotherapy). A recent IPD meta-analysis of 3005 patients from 11 randomized trials found that neoadjuvant chemotherapy decreased the risk of death by 14%, improved the absolute disease-specific survival by 9%, and improved overall survival by 5% at 5 years ( $p = 0.003$ ). This advantage in survival was seen for all muscle-invasive tumours, and only patients who received a cisplatin containing regimen benefited. While the available data support the use of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) or CMV (cisplatin, methotrexate, vinblastine) as neoadjuvant chemotherapy, these regimens are less frequently used because phase 3 data in the metastatic setting suggested that a less

toxic regimen of gemcitabine and cisplatin (GC) has similar efficacy to M-VAC. The efficacy of the GC combination in the neoadjuvant setting, however, has not yet been proven, suggesting that M-VAC or CMV should still be used, based purely on the available data.

Neoadjuvant chemotherapy is not recommended in patients with poor performance score and impaired renal function.

## **G. Adjuvant therapy**

Till date, there have been five published randomized trials of adjuvant chemotherapy and one meta-analysis, with updated individual patient data from six trials and a total of only 491 patients for survival analysis. Neither randomized trials nor the meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy (Level of evidence 1a). The commonest regimens used are MVAC/CMV or CISCA. Although not convincingly shown to improve survival, it may be useful in patients with pT3-4 and/or N+ patients.

Adjuvant postoperative radiotherapy has been studied in retrospective series have shown improved loco-regional control (particularly for squamous cell carcinomas), but no survival benefit. Toxicity has been a concern with postoperative RT but with modern techniques like IMRT, this can be addressed adequately. Adjuvant RT may be useful in subgroup of patients with LN + ve and close/ positive margin of resection (Level of evidence 3).

## **Chemotherapy for Metastatic Bladder Cancer**

Approximately 5-10% of bladder cancers are metastatic at presentation and another 40% of patients will develop metastatic disease during their clinical course, typically

appearing in lymph nodes, lung, liver or bone. Chemotherapy is the standard therapy for patients with metastatic bladder cancer. Urothelial carcinoma is a chemosensitive tumour. Performance status and presence or absence of visceral metastases are important prognostic factors for survival. Patients with lymph node metastases only, good PS, and adequate renal function may be the best candidates for chemotherapy, with about 15% long-term survival. Methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (M-VAC) and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months respectively (Level of evidence 1b). Single-agent chemotherapy provides low response rates of typically short duration. Combination M-VAC chemotherapy is superior to single agent chemotherapy (Level of evidence 1b). Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival (Level of evidence: 2a). Either MVAC or CMV has been considered standard combination for metastatic bladder cancer. In an international randomized trial, M-VAC was compared with gemcitabine & cisplatin (GC). Both the arms were found to be equivalent in terms of response rates, time to treatment failure, time to progressive disease and overall survival. GC appeared to have reduced toxicity profile as compared to M-VAC, making GC a new standard chemotherapeutic option in patients with metastatic bladder cancer (Level of evidence 1b). There is insufficient data to provide a recommendation on standard second-line chemotherapy. Therefore, second-line therapy should be provided within a clinical trial setting. Single agents or paclitaxel/gemcitabine, if the patient has a good PS, may be considered. Quality of life issues are very important considerations while deciding further chemotherapy.



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# Urothelial Tumors of Upper Urinary Tract

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## **INTRODUCTION:**

Upper urinary tract transitional cell carcinoma (TCC) refers to malignant changes of the transitional epithelial cells lining the urinary tract from the renal calyces to the ureteral orifice. Although over 60,000 new cases of bladder cancer are diagnosed annually in the US, upper-tract TCC is much less common, accounting for approximately 5% of urothelial malignancies, and less than 10% of all renal tumors. (1). Ureteral tumors are even more uncommon, occurring with one quarter the frequency of renal pelvis TCC's. The frequency of upper-tract TCC is increasing over the last 2 decades. Fortunately, this has been associated with a slight improvement in the overall and disease-specific survival of patients with upper tract malignant neoplasms. (2)

## **ETIOLOGY:**

Proposed etiologies for developing upper-tract TCC are similar to that of bladder cancer and include environmental factors (cigarette smoking), occupational

exposures (aniline dyes), and treatment with anti-inflammatory (phenacetin) or chemotherapeutic (cyclophosphamide, ifosfamide) agents and heredity may play a part in the development of TCC (Balkan nephropathy, Lynch syndrome type II, etc). (3,4,5) Men are about twice as likely to develop upper tract tumors as are women. In addition, whites are about twice as likely as African Americans to develop upper tract tumors (6).

## **PATHOPHYSIOLOGY:**

### **Types of upper urinary tract tumors**

TCC is the most common histology accounting for greater than 90% of upper urinary tract urothelial tumors. Morphologically, TCC of the renal pelvis and ureter, like bladder TCC, can be papillary or solid and associated with carcinoma *in situ*.

Squamous cell carcinoma comprises 1-7% of upper tract urothelial tumors.

Adenocarcinoma accounts for less than 1% of upper tract tumors.

Inverted papilloma is an unusual lesion that is generally considered a benign histologic lesion.

### **Molecular mechanisms**

Studies have proved that losses of *p53*, *p19*, and *p16* tumor suppressor genes are associated with low-grade cancers, while a loss of tumor suppressor gene *RB1* has been associated with higher-grade, more aggressive tumors.(7)

Tumor microsatellite instability (MSI) has been studied as a favorable prognostic indicator for upper tract tumors,

particularly in younger patients with T2 or T3/N0 disease.  
(8)

### **Patterns of spread**

1. Contiguous spread – renal parenchyma. Also, approximately 30%-75% of patients with upper tract urothelial tumors develop bladder tumors at some point during their cancer course.
2. Lymphatic spread – First station area from crus of diaphragm to bifurcation of aorta.
3. Hematogenous spread to liver, lung, bone, etc.

### **Distribution of upper tract transitional cell carcinoma**

- Renal pelvis - 58%
- Ureter - 35% (73% of which are located in the distal ureter)
- Ipsilateral renal pelvis and ureter - 7%
- Bilateral involvement - 2-5%

### **Presentation**

1. Gross or microscopic hematuria
2. Flank pain and dysuria
3. Constitutional symptoms - Weight loss, anorexia, and flank mass, or bone pain are symptoms of advanced disease.

### **INVESTIGATIONS:**

Patients should undergo routine tests and some specific investigations. These include

**Urinalysis** is done to look for microscopic haematuria and rule out urinary tract infection.

**Urine cytology** - Higher grade tumors including carcinoma in situ tend to shed more tumor cells and hence can be picked up by cytopathology with a sensitivity of almost 80% whereas for well-differentiated tumors the accuracy rate is only 10% to 40%.(9,10)

## **Imaging studies:**

### **1. Intravenous pyelography (IVP)**

IVP may show a radiolucent filling defect that is characteristically irregular and in continuity with the wall of the collecting system.

### **2. CT scan/CT - IVU scan:**

CT scan usually shows a centrally located, minimally enhancing, hypovascular, irregular filling defect. More recently, CT urography has been performed to obtain a three-dimensional image of the upper tracts. With CT urography, the sensitivity for detecting upper tract malignant disease has been reported to approach 100%, with a specificity of 60% and a negative predictive value of 100% (11)

### **3. MRI/ MR Urography:**

MRI scan provides the information regarding the extent of invasion, an associated mass lesion outside the collecting system, and the presence of lymph node or distant metastases, and is especially useful in patients in which a contrast CT is contraindicated.

### **4. Cystoscopy and Retrograde Ureteropyelography:**

Cystoscopy is mandatory to rule out coexistent bladder lesions. It is also essential for postoperative surveillance to monitor the bladder tumor development. RGU allows better visualization of the collecting system than excretory

urography and is preferable in patients with azotemia and/or contrast allergy. Overall, retrograde urography is more than 75% accurate in establishing a diagnosis of urothelial cancer. Uretero-pyeloscopy is used increasingly for the diagnosis of upper tract urothelial tumors. Biopsy forceps or cytology brushings can be used to collect tissue. It may also help in collecting urine sample from either ureter/renal system separately. This procedure yields an accuracy of 86% in diagnosing renal pelvis tumors and 90% in diagnosing ureteral tumors.

### **5. Role of PET Scan:**

In urothelial cancer, the role of PET is still being defined, but it has a high positive predictive value and can be used for problem solving in patients with indeterminate findings on conventional imaging (12)

## **CLINICAL STAGING**

Clinical staging is same as for TCC bladder. Routine staging includes chest radiograph and/or thoracoabdominal CT. Radionuclide bone scan is recommended in symptomatic patients or those having advanced disease.

## **TREATMENT:**

The management of urothelial carcinoma can be divided into

1. Standard radical nephroureterectomy.
2. Conservative techniques:
  - Nephron sparing surgery for renal pelvis tumors: pyelotomy and tumor ablation and partial nephrectomy.
  - Segmental ureterectomy.

### 3. Minimally invasive approaches:

- Endoscopic procedures.
- Laproscopic approach.
- Combination approach.

### **Radical Nephroureterectomy**

Radical nephroureterectomy with excision of an ipsilateral bladder cuff is the gold-standard therapy for patients with a normal contralateral kidney (13) particularly in cases of high-grade, invasive tumors or low–moderate-grade lesions that are large, bulky, or multifocal. The entire kidney, along with all the perinephric fat and Gerota's fascia, with the ipsilateral adrenal gland and the whole of ureter, including the intramural portion and the ureteral orifice with a cuff of bladder is removed. Nephroureterectomy can be performed by an open, laparoscopic, or hand-assisted laparoscopic technique. Ipsilateral adrenalectomy is generally unnecessary unless the tumor is a superior lesion with suspected direct adrenal invasion. (14)

#### Management of the Distal Ureteric lesion.

The entire distal ureter including the intramural portion and ipsilateral ureteral orifice must be removed regardless of the surgical modality for extirpation of the kidney and upper ureter. Either open or laparoscopic techniques could be used for this surgery. (15)

#### **Open technique.**

The *intravesical method* involves creating an anterior cystotomy and circumscribing one cm cuff of the bladder surrounding the ipsilateral ureter.

The *extravesical technique* involves dissection of the ureter through the detrusor hiatus to ensure a complete dissection of the intramural portion of the ureter. With



gentle traction on the ureter, a right angle clamp or an endoscopic gastrointestinal anastomosis (GIA) stapler can be used to transect the ureter with a cuff of bladder.

### **Transurethral resection of the ureteral orifice: 'pluck' technique.**

Endoscopic resection of the ureteral orifice and the intramural ureter is done till perivesical fat is seen so as to achieve complete detachment of the ureter from the bladder, allowing for it to be 'plucked' during the antegrade dissection. Potential complications associated with this technique include fluid and electrolyte disturbances, pelvic or peritoneal seeding of tumor cells from bladder extravasation, and failure to adequately address tumors of the intramural ureter. (16,17)

### **Intussusception (stripping) technique.**

A ureteral catheter is inserted at the start of the procedure, and the ureter is dissected as distally as possible during the nephrectomy portion of the operation. The ureter is ligated and transected with the ureteral catheter secured to the proximal portion of the distal ureter. The patient is repositioned in the lithotomy position, and the distal ureter is intussuscepted into the bladder by traction on the ureteral catheter. A resectoscope is then used to excise the bladder cuff, thus releasing the distal ureter.

## **Segmental Resection**

### **Nephron-sparing Surgery for Renal Pelvis Tumors**

Historically, open nephron-sparing surgery for upper-tract TCC was used in patients with a large renal pelvis tumor in a solitary kidney or synchronous bilateral tumors. With the advances in endourologic techniques, the conservative management of renal pelvis tumors is

further supplanted. . A flank incision is used for kidney exposure, followed by a pyelotomy and excision or resection of the renal pelvis tumor. The base of the lesion is cauterized, the pyelotomy defect is repaired, and postoperative drainage is accomplished by ureteral stenting or via a percutaneous nephrostomy tube.

The cumulative risk of tumor recurrence within the ipsilateral renal pelvis following pyelotomy or partial nephrectomy ranges from 7% to 70%. (18, 19)The high recurrence rates are secondary to the inherent field change defect observed with upper tract TCC.

### **Partial Ureterectomy**

Distal ureterectomy with reimplantation is a reasonable alternative for patients with high-grade, invasive, or bulky tumors of the distal ureter that are not amenable to endoscopic ablation. Distal ureterectomy is also being done with both the laparoscopic and robotic techniques with promising results. (20, 21)

Segmental ureterectomy of the proximal or mid-ureter with primary ureterostomy is rarely indicated. Exceptions to this would be proximal tumors not amenable to endoscopic ablation in a functional solitary kidney.

Mazeman et al found that the local recurrence rates after subtotal ureterectomy are similar to that of radical nephroureterectomy in patients with solitary ureteral lesions. (22)

### **Endoscopic procedures:**

The basic principles for treatment of transitional cell carcinoma of the upper urinary tract are similar to those for the bladder counterpart. Tumors of the upper urinary tract can be approached in a retrograde or antegrade fashion. The approach chosen depends largely on the

tumor location and size. In general, a retrograde ureteroscopic approach is used for low-volume ureteral and renal tumors. With the improvement in the endoscopic instruments (flexible scopes, etc), tumor biopsy and ablation by various energy sources (electrocautery, neodymium:yttrium-aluminum-garnet (Nd:YAG) or holmium:YAG are possible even through the smallest instruments.

### **Percutaneous Management:**

#### *Advantages*

- Preferred for larger tumors of the renal pelvis and proximal ureter.
- Better visualization of the renal pelvis.
- Superior access to the lower pole calyces, as well as to renal units with complicated calyceal anatomy.

#### *Disadvantages:*

- Violation of urothelial integrity with reports of tumor seeding of nonurothelial surfaces around the kidney or in the nephrostomy tract.
- Bleeding, infection, electrolyte abnormalities, adjacent organ injury, and pleural injury.

### **Adjuvant Topical Therapy:**

Adjuvant topical immunotherapy or chemotherapy can be used to reduce recurrence rates. The same agents used to treat urothelial carcinoma of the bladder can be used to treat tumors of the upper tracts. The most common agents instilled are BCG or mitomycin-C.

### **Role of Lymphadenectomy**

There are no definitive data supporting the use of lymph node dissection. However since the TCC bladder data has shown that the number of positive lymph nodes

removed and the lymph node density are important prognostic variables in patients undergoing cystectomy, therapeutic regional lymphadenectomy is advisable in TCC upper tract. (23) Extent of this dissection is from crus of diaphragm to the aortic bifurcation.

### **Role of Chemotherapy**

Urothelial tumors of the upper urinary tract are chemosensitive tumors. (3, 24, 25)

Neo adjuvant chemotherapy: The advantage of chemotherapy in the neoadjuvant setting includes eradication of subclinical metastatic disease, better tolerability before surgical extirpation, and the ability to deliver higher doses than in the adjuvant setting.(3) Studies have presented compelling data for the use of neoadjuvant platinum-based chemotherapy regimens before radical cystectomy.(26, 27) Regimens comprised of gemcitabine and cisplatin that provide a similar survival advantage to methotrexate–vinblastine–doxorubicin–cisplatin (MVAC), with a better safety profile and tolerability, increase the attractiveness of neoadjuvant chemotherapy.(28)

### **Adjuvant chemotherapy**

The role of adjuvant chemotherapy is poorly defined with no randomized studies for bladder TCC available for comparison. Consensus opinion is that patients with pT3 disease or worse or pathologic lymph node involvement would be likely to benefit from adjuvant chemotherapy (3)

### **Role of radiotherapy:**

Various studies have proved that adjuvant radiation for high-stage disease does not decrease local relapse or protect against a high rate of distant failure.

## **Bladder Cancer Following Upper-tract TCC**

Transitional epithelial cells line the whole urinary tract; consequently, it has been suggested that in cases of TCC the entire urothelium is at risk of developing subsequent tumors. Bladder tumors reportedly occur in 15–50% of patients following upper-tract TCC. (29, 30, 31) Hence, close surveillance with cystoscopy and cytology following surgical management of upper-tract TCC is essential.

### **Surveillance and Follow up:**

The recommended follow-up for patients treated for upper-tract TCC should consist of interval history and physical examination, urinary cytology, and surveillance cystoscopy every 3 months for the first 2 years after treatment, every 6 months for the next 2 years, and yearly thereafter if the patient is free from disease recurrence.(25, 32)

## **Squamous Cell Cancers**

Squamous cell cancers make up 0.7% to 7% of upper tract cancers (Babaian and Johnson, 1980; Blacker et al, 1985). Squamous cancers are frequently associated with a condition of chronic inflammation, stone disease, infection or with analgesic abuse (Stewart et al, 1999). These tumors occur six times more frequently in the renal pelvis than in the ureter and are generally moderately to poorly differentiated and more likely to be invasive at the time of presentation, however distant metastasis is infrequent. Squamous cell cancers occur as pure SCC or TCC with squamoid differentiation. The presenting symptoms are painless gross hematuria, frequency-urgency, and sometimes obstructive urinary symptoms. Treatment is essentially surgical-radical nephroureterectomy. Addition of RT either in neoadjuvant or adjuvant setting improves the survival. Although distant

metastasis is infrequent (8-10%), the prognosis is grave and most patients die after failure of even loco-regional control.

### **Adenocarcinoma**

Adenocarcinomas account for less than 1% of all renal pelvic tumors and are typically associated with long-term obstruction, inflammation, or urinary calculi (Stein et al, 1988; Spires et al, 1993). The process is assumed to begin with an urothelial metaplasia resulting from a reaction to chronic irritation, leading to dedifferentiation, dysplasia and, in the end, to a squamous cell carcinoma or adenocarcinoma. The relevant medical histories include chronic episodes of pyelonephritis or nephrolithiasis. These tumors typically present at advanced stage and display a poor prognosis.

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## Testicular Germ Cell Tumours

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### **Incidence:**

Testicular cancer forms about 1% of all malignancies in males in India. Germ cell tumors comprise of 95 % of malignant tumors arising from testis. These tumors predominantly affect young males in the prime of their life. Besides, the disease as well as the treatment can affect the fertility of these patients and affect their quality of life. Testicular tumors are the models of the success of multimodality approach to cancer, boasting of high cure rates even in the presence of metastatic disease. About 40% of all testicular tumors are pure seminomas. 2-3% percent of the patients present as bilateral tumors. Other histological varieties like yolk sac tumor (endodermal sinus tumour), teratoma, embryonal carcinoma etc are considered together for management due to similar biological behaviour and natural history and are collectively called “non-seminomatous germ cell tumors of testis” (NSGCT).

## **Predisposing factors:**

### **Cryptorchidism**

Germ cell tumors (GCT) can develop in an inguinal cryptorchid testis in approximately 2% of cases. Another 5%-10% of cases will develop in the normally descended testis. If orchiopexy is to reduce the likelihood of GCT, it should be performed prior to puberty. If the cryptorchid testis is inguinal, hormonally functioning, and easily examined, surveillance is recommended. If the cryptorchid testis is abdominal, nonfunctioning and not amenable to orchiopexy, orchiectomy is recommended.

### **Klinefelter Syndrome**

Klinefelter syndrome is diagnosed by a 47, XXY karyotype and is characterized by testicular atrophy, absence of spermatogenesis, a eunuchoid habitus, and gynecomastia,. Patients with Klinefelter syndrome are at increased risk for mediastinal GCT.

## **Other Risk Factors for Testicular Cancer:**

Family history

Presence of tumour or testicular intraepithelial neoplasia (IIN) in contralateral testis

Altered intrauterine hormonal environment

Low fertility

Abnormal sperm analysis

Immunosuppression

Histological classification: GCT is classified into two major subgroups: seminoma and nonseminoma. The classification of the World Health Organization, derived from Mostofi and Sesterhenn's adaptation of the Dixon/Moore classification, is the system most commonly used in western as well as asian countries.

## **World Health Organization Histologic Classification of Testis Tumors**

### **Germ cell tumors (intratubular germ cell neoplasia, unclassified)**

- A. Tumors of one histological type (pure forms)
  - Seminoma
  - Seminoma with syncytiotrophoblastic cells
  - Spermatocytic seminoma
  - Spermatocytic seminoma with sarcoma
  - Embryonal carcinoma
  - Yolk sac tumors
  - Trophoblastic tumors
    - Choriocarcinoma
    - Trophoblastic neoplasms other than choriocarcinoma
      - Monophasic choriocarcinoma
  - Placental site trophoblastic tumors
  - Teratoma
    - Dermoid cyst
    - Monodermal teratoma
    - Teratoma with somatic type malignancies
- B. Tumors of more than one histologic type (mixed forms)
  - Mixed embryonal carcinoma and teratoma
  - Mixed teratoma and seminoma
  - Choriocarcinoma and teratoma/embryonal carcinoma

### **Others**

Intratubular Germ-Cell Neoplasia

IGCN is the precursor lesion of most types of GCTs. Abnormal germ cells within the seminal tubules are found

adjacent to invasive germ-cell tumors. Although initially termed carcinoma in situ (CIS), these cells are not of epithelial origin and are better termed intratubular germ-cell neoplasia or testicular intraepithelial neoplasia (TIN).

IGCN is found adjacent to testicular germ-cell tumors in over 95% of cases. It is also found in all clinical groups known to be at high risk for testicular cancer development: Cryptorchidism (2% to 4%), infertility (1%), ambiguous genitalia (25%), and contralateral testes of patients with testicular cancer (5%).

ICGN is characterized by seminiferous tubules showing decreased spermatogenesis in which the normal constituents of the tubules are replaced by abnormal germ cells with the appearance of seminoma cells. These cells stain strongly for placental alkaline phosphatase (PLAP), whereas normal germ cells are negative.

IGCN has a 50% risk of developing into an invasive germ-cell tumor within 5 years. That risk probably approaches 100% by 8 years. There is strong evidence that IGCN is a precursor lesion of all types of germ-cell tumors except spermatocytic seminoma and infantile testicular tumors.

## **Seminoma**

### **Classical Type**

Seminoma is the most frequent germ-cell tumor, comprising over 50% of all germ-cell neoplasms. Serum level of human chorionic gonadotropin (HCG) is elevated in 15% to 30% of men at presentation, related to the presence of syncytiotrophoblastic cells. These may be identified in 7% of tumors on routine hematoxylin and eosin sections or by immunoperoxidase stains in 24%. Serum alpha-fetoprotein is not elevated in pure seminoma.

Grossly, seminoma is a soft tan-colored diffused multinodular mass. Focal necrosis is sometimes present. A prominent lymphocytic infiltrate is commonly seen within the fibrous stroma. Over 90% of seminomas will stain positive for placental alkaline phosphatase. (PLAP).

### **Spermatocytic Seminoma**

Spermatocytic seminoma is a rare variant seen generally in older men. Its relationship to other GCTs is not clear because it is not associated with ITGCN or bilaterality, it does not express placental alkaline phosphatase (PLAP) and it has not been shown to have the same genetic abnormalities as other GCTs. Metastatic potential is minimal.

## **Nonseminomatous Germ-Cell Tumours**

### **Embryonal Carcinoma**

Pure embryonal carcinoma makes up about 3% of all testicular germ-cell tumours and is a component of almost 50% of mixed germ-cell tumours. Over 80% of these tumours occur between the ages of 15 and 34 years.

Grossly, the tumour often exhibits a large area of hemorrhage and necrosis. Almost all embryonal carcinomas are PLAP positive and alpha-fetoprotein and HCG-positive cells are present in 33% and 21%, respectively.

### **Yolk Sac (Endodermal Sinus Tumour)**

Pure yolk sac tumour makes up <2% of testicular tumors in adults but forms a component of 40% of mixed germ-cell tumours. It makes up 60% of germ-cell tumours in children. Eighty percent of pure yolk sac tumours occur

in the first 2 years of life. It is associated with elevated serum levels of alpha-fetoprotein. Grossly, yolk sac tumours contain cystic spaces containing a gelatinous material. There is a variable amount of hemorrhage and necrosis. Microscopically, Schiller-Duval bodies are a characteristic feature.

### **Teratoma**

Pure teratoma makes up 5% of all testicular germ-cell tumours. Teratomatous component may be seen in about 50% of mixed germ-cell tumours. In pure teratoma serum HCG and alpha-fetoprotein are normal. Mature teratoma consists of mature well-differentiated somatic tissues. Despite their benign appearance, metastases can occur. Immature teratoma contains immature elements in addition to varying amounts of well-differentiated tissue. Both mature and immature teratomas have a similar behavior. Teratoma with malignant transformation results from the development of a somatic carcinoma or sarcoma within the teratoma.

### **Choriocarcinoma**

Pure choriocarcinoma is the rarest type of germ-cell tumour, accounting for less than 0.05% of lesions but present in about 4% of mixed germ-cell tumours. It is a highly aggressive neoplasm and often presents with metastatic disease, the primary lesion being occult. The serum HCG is elevated.

### **Mixed Germ-Cell Tumors**

Mixed germ-cell tumors account for up to 50% of germ-cell tumours. Any of the above elements can be present in combination. Serum markers are elevated depending on the proportion of different elements present within.



## **Clinical presentation and patterns of spread:**

A testicular tumour usually presents as a painless scrotal swelling, heaviness, tenderness and loss of testicular sensation. Contrary to common belief, pain is a presenting feature in as many as 46% of cases (due to torsion, infection, bleeding or infarction).

Involvement of retroperitoneal lymph nodes may produce back pain or abdominal swelling. Widely disseminated parenchymal disease in lungs, liver, bone, or brain is uncommon but, if present, may produce systemic symptoms. Gynecomastia is a rare presentation of embryonal carcinoma and may be seen in association with the very uncommon sex cord-stromal tumors. Occasionally, patients present with metastatic germ-cell malignancies diagnosed by biopsy or elevated levels of serum tumor markers without evidence of a palpable mass in the testis. Occult primary disease in the testis is often detected by testicular ultrasound. If there is no evidence of a primary tumor in the testis, a diagnosis of an extratesticular germ-cell tumor, usually mediastinal, retroperitoneal, or pineal, may be made.

Some of the uncommon presentations of GCTs are hematemesis due to lymph node eroding duodenum, spinal cord compression due to paraspinal mass or painless swelling in the neck.

The pattern of spread in NSGCT is distinct from that seen in Seminomas. In NSGCT, 60% of cases will present with extensive disease. The spread is usually to the retroperitoneal lymph nodes first and then hematogenously to other parts. The exception is pure choriocarcinoma – which rapidly spreads to lungs, brain and other soft tissues early in the disease. Pattern of

retroperitoneal lymph nodal involvement in germ cell tumors has important treatment implications. Donohue et al have shown that a right sided primary will usually involve the interaortocaval, precaval and preaortic nodes. The left testicular mass will involve the left paraaortic, preaortic and interaortocaval nodes. Suprahilar LN involvement is uncommon and external iliac/ obturator nodes are only rarely the sites of metastasis.

### **Pretreatment Evaluation:**

When an intratesticular mass is identified, further evaluation includes the following.

- Serum tumour markers: AFP, b HCG, LDH. Pure seminomas do not produce any tumor markers (90% cases, 10% may have mildly raised b-HCG). Pure choriocarcinomas produce only b-HCG. Embryonal and yolk sac tumors usually have elevated AFP alone. NSGCTs will usually show elevation of both b-HCG and AFP. Elevated tumor markers are used to support the diagnosis, assess prognosis, indicate residual tumor following orchidectomy, evaluate response to chemotherapy and detect early relapse. Elevated values of b-HCG, AFP and LDH should be followed up closely so as to determine accurate staging.

AFP is increased in 50-70% of patients with NSGCT and a rise in b-HCG is seen in 40-60% patients with NSGCT. About 90% of NSGCT present with a rise in one or two of the markers. Upto 30% of seminomas can present or develop an elevated b-HCG level during the course of the disease. LDH is a less specific marker and its level may be elevated in 80% of patients with advanced testicular cancer.

- Imaging of the testis: Ultrasound of the testicular mass performed mostly to define the lesion though, it is not mandatory when the diagnosis is obvious on physical examination. It can determine whether the mass is intratesticular or extratesticular and helps to monitor the status of contralateral testis in high risk patients. It may be useful to identify small non-palpable tumour in patients with metastatic disease.
- X-ray chest
- Abdominopelvic CT scan or MRI: Have a sensitivity of 70-80% in determination of retroperitoneal and mediastinal lymph nodes.
- Chest CT may be indicated only if abdominal CT scan confirms retroperitoneal adenopathy or the chest X ray is abnormal. This is especially important in patients with NSGCT.
- Open inguinal biopsy of the contralateral testis is not routinely performed , but can be considered if cryptorchid testis or atrophic testis is present.(Biopsy to be considered if suspicious intratesticular mass or macrocalcification but not microcalcification)
- CBC, Biochemistry including renal chemistry and liver function tests.
- MRI Brain and bone scan if clinically indicated or in patients of NSGCT with extensive widespread lung metastases.
- Patients should be counseled for sperm banking and same should be done before any therapeutic intervention. (See appendix I)

## **Role of PET scan as an imaging modality**

Studies comparing FDG PET with CT in primary staging of GCT show that FDG PET is useful for detecting viable tumor in lesions that are visible on CT and may prevent false-positive diagnosis on CT in clinical stage II disease .However, FDG PET does not improve staging in patients with clinical stage I disease because, similar to CT, it is poor at detecting small-volume (i.e. subcentimeter) disease [1-2] Furthermore, FDG PET is not able to identify mature teratoma. Presently, there is not sufficient evidence to support the use of FDG-PET scan in staging and hence not recommended in the primary staging of testicular GCT [3] (Level III). It however has a role in characterization of post-chemotherapy residual mass in patients with seminoma and may direct therapy (intervention vs. observation).

## **Primary (Initial) Treatment :**

### **High Inguinal Radical Orchiectomy.**

The diagnosis of testicular germ cell tumour is based on the histology of the testicular mass removed by inguinal orchiectomy. A thorough histopathological review including histological subtype, tumor size and extent, presence or absence of lymphatic or vascular emboli, tumor necrosis etc. is essential. In cases of disseminated disease and life-threatening metastases, it may be recommended to start chemotherapy upfront and orchiectomy may be done after stabilization of the clinical status of the patient.

Orchiectomy is not required in patients with extragonadal GCT with normal testicular examination (clinical and sonographical).

Patients sometimes present with scrotal orchidectomy being done if malignancy is not suspected and especially if a patient presents to a non-oncological centre. In such circumstances, aggressive local therapy (resection of inguinal portion of spermatic cord and hemi-scrotectomy) will ensure that the survival of the patient is not compromised.

**Testis-sparing surgery:** This is not routinely recommended in patients with normal contralateral testis. However, in synchronous bilateral tumours, metachronous contralateral tumours or in patients with a tumour in a solitary testis, testis-preserving surgery may be indicated when the tumour volume is less than 30% of the total testicular volume and the tumour is completely removed. There is a high risk of associated Tin and many patients require local radiation therapy (20 Gy) to control primary disease. This option may be carried out after thorough consultation with the patient.

### **Post Primary Treatment Work-up:**

- Post primary treatment markers: AFP, beta HCG and LDH (Markers used for risk classification are post orchidectomy).

Staging: (Post Primary Surgery) UICC Staging & Classification of Testis Tumours 2002

Staging shall be done by the TNM system and the prognostic group assignment is done as per the International Germ Cell Consensus Classification.

pT Primary tumour

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

pTis Intratubular germ cell neoplasia

pT1 Tumour limited to the testis and epididymis

- No vascular/lymphatic invasion
- May invade the tunica albuginea
- No invasion of the tunica vaginalis
- pT2 Tumour limited to the testis and epididymis
  - Vascular/lymphatic invasion or tumour extending through the tunica albuginea with involvement of the tunica vaginalis
- pT3 Tumour invades the spermatic cord with or without vascular/lymphatic invasion
- pT4 Tumour invades the spermatic cord with or without vascular/lymphatic invasion
- pT4 Tumour invades the scrotum with or without vascular/lymphatic invasion
- N Regional nodes: Clinical
- NX Nodes not assessed
- N0 No regional lymph node metastasis
- N1 Lymph node mass or multiple lymph node masses <2 cm in greatest dimension
- N2 Lymph node mass or multiple lymph node masses >2 cm but <5 cm in greatest dimension
- N3 Lymph node mass >5 cm in greatest dimension
- pN0 No evidence of tumor in lymph nodes
- pN1 Lymph node mass < 2 cm in greatest dimension  
5 nodes positive
- pN2 Lymph node mass >2 cm but <5 cm in greatest dimension  
>5 nodes positive  
Evidence of extranodal extension of tumor
- pN3 Lymph node mass >5 cm in greatest dimension
- M Distant metastases
- M0 No evidence of distant metastases
- M1 Distant metastases
- M1a Nonregional nodal or pulmonary metastases
- M2b Nonpulmonary visceral metastases
- S: Serum tumour markers

<b>S</b>	<b>LDH</b>		<b>hCG† (mIU/mL)</b>		<b>AFP (ng/mL)</b>
SX	Not assessed		Not assessed		Not assessed
S0	?N	and	Normal	and	Normal
S1	<1.5 x N	and	<5,000	and	<1,000
S2	1.5-10 x N	or	5,000-50,000	or	1,000-10,000
S3	>10 x N	or	> 50,000	or	> 10,000

N = upper limit of normal for the LDH assay

### Stage Grouping

<b>Stage grouping</b>	<b>T</b>	<b>N</b>	<b>M</b>	<b>S</b>
Stage 0	PT is	N0	Mo	S0
Stage I	T1-T4	N0	Mo	Sx
Stage IA	T1	N0	Mo	So
Stage IB	T2-4	N0	Mo	So
Stage IS	Any T	N0	Mo	S1-S3
Stage II	Any T	Any N	Mo	SX
Stage IIA	Any T	N1	Mo	S0-S1
Stage IIB	Any T	N2	Mo	S0-S1
Stage IIC	Any T	N3	Mo	S0-S1
Stage III	Any T	Any N	M1	Sx
Stage IIIA	Any T	Any N	M1a	S0-S1
Stage IIIB	Any T	Any N	M0-M1a	S2
Stage IIIC	Any T	Any N	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S

### International Germ Cell Consensus Classification for Seminoma:

In 1997, IGCCCC defined a staging system for metastatic disease based on some independent clinical prognostic factors. This system has now been incorporated into the

TNM classification and categorizes patients into good, intermediate and poor prognostic groups.

**Good Risk (90%)**

- Normal alpha fetoprotein, any b-HCG, any LDH
- Any primary site and
- No non-pulmonary visceral metastases present

**Intermediate Risk: (10%)**

- Non-pulmonary visceral metastases present
- Any primary site and
- Normal alpha fetoprotein, any b-HCG, any LDH

Seminomas are never included in the Poor prognostic group, irrespective of stage.

**International Consensus Advanced Germ Cell Tumor Prognosis Classification Scheme (NSGCT)**

**Good Risk**

- Testicular or retroperitoneal primary tumor.
- No non-pulmonary visceral metastases present
- Post orchiectomy AFP <1000 ng/ml and b-hCG <5000 IU/l and LDH <1.5 X upper limit of normal (ULN)

**Intermediate Prognosis:**

- Testicular or retroperitoneal primary tumour.
- No non-pulmonary visceral metastases present.
- AFP 1000-10000 ng/ml or hCG 5000-50000 IU/l or LDH 1.5-10 X ULN



**Poor prognosis:**

- Mediastinal primary site
- Non-pulmonary visceral metastases present.
- AFP >10000 ng/ml or b-hCG >50000 IU/l or LDH 10 X ULN

**Management of Seminoma:****Stage I:**

The DFS and OAS for Stage I seminoma testis is 95-99% at 10 years with excellent salvage rates even at relapses [4]. About 15-20% patients with stage I seminoma have subclinical metastatic disease, usually in the retroperitoneum and will relapse after orchidectomy alone.

Options of treatment for stage I seminoma are as follows:

1. Prophylactic (adjuvant) radiation therapy (5)
2. Adjuvant chemotherapy (6,7)
3. Surveillance

There is no role of retroperitoneal lymph node dissection in stage I seminoma.

**Prophylactic (Adjuvant) Para-aortic +/-Pelvic Nodes Radiation:** Around 15-20% of the patients under surveillance will relapse if they do not receive adjuvant radiotherapy post orchidectomy [8]. External beam radiation therapy to para-aortic area either alone or with ipsilateral iliac nodal region (hockey stick field) to a dose of 20-25Gy with 6-15 MV photons @1.5 -1.8 Gy/# in 2-3 weeks, from lower border of D10 vertebra (retrocrural nodes) to lower border of L5 vertebra (with shielding of contralateral testis) is recommended with a relapse rate of 1-3%[5,8-9]. In patients with undisturbed lymphatic drainage, para-aortic radiation therapy alone has been

shown to be adequate but with slightly higher rate (2% vs 0%) in the iliac region as compared to the traditional hockey stick field. A RCT conducted by MRC comparing 20 Gy to 30 Gy paraaortic radiation therapy in stage I seminoma showed equivalence of both doses in terms of recurrence rate. Most relapses after radiation therapy are outside the radiation field. If previous scrotal surgery, field of radiation therapy to be extended to include ipsilateral inguinal nodes (dog-leg radiotherapy). [Level I]

Presently, there is no evidence suggest the necessity of prophylactic mediastinal radiation therapy in patients with stage I seminoma.

The main disadvantage of radiation therapy is the gastrointestinal toxicity and risk of second malignancy in the radiated field.

**Adjuvant chemotherapy:** A single dose of carboplatin has also been recommended as an alternative to radiotherapy or surveillance in patients with stage I seminoma. In the MRC TE 19 study, which compared one cycle of carboplatin (AUC 7) to adjuvant radiotherapy, there was no significant difference in the recurrence rate, time to recurrence and survival rate after a median follow up of 4 years[6][Level 1]. Updated results of the same study were reported in ASCO 2008 annual meeting which confirmed non inferiority of single agent carboplatin AUC 7 as compared to radiotherapy with reduced risk of 2<sup>nd</sup> GCT in carboplatin arm with lesser toxicity.[7] [Level I]. Two courses of adjuvant carboplatin seem to reduce the relapse rate further to 1-3% but long term results of these studies are awaited.

**Surveillance:** This option is considered in select cases of T1, T2 disease with committed for long-term follow up [Level II]. It is a recommended option for horse shoe

kidney, patients suffering from inflammatory bowel disease and prior abdominal radiation. [Level I]

Surveillance policy has been evaluated in several randomized studies. A meta-analysis of 4 studies showed an actuarial 5 years relapse free rate of 82.3%. A large single institutional study from Princess Margaret Hospital, Canada with more than 1500 patients reported an overall relapse rate of 16.8%, with most relapses in the retroperitoneum. The overall cancer specific survival with surveillance reported from major centres is 97-100%. The main drawback of surveillance strategy is the need for more intensive follow up with repeated imaging studies for a prolonged period of time since about 20% of relapses in seminoma occur beyond 4 years after orchidectomy. This translates into cost escalation and need for strict compliance to surveillance schedule.

**Risk based approach:** Patients with stage I seminoma may be divided into high and low risk groups depending on the presence or absence of poor prognostic factors eg tumour size >4 cm and rete testis invasion. Low risk patients (risk of relapse 12%) may be kept on surveillance while the high risk patients (risk of relapse 32%) may be treated with radiation therapy or chemotherapy.

Post-treatment follow up: Strict follow up is mandatory. For patients not undergoing radiation therapy, more intense follow up is required. This is done with history, physical examination, serial tumor markers every 3-4 months for first 3 years, 6 months for next 3 years and annually thereafter. CT scan abdomen + pelvis is recommended, for first 3 years for patients who had received RT whereas in patients on surveillance, it is required at every visit. X ray chest is advised every alternate visit for upto 10 years for those who are under surveillance or have received single agent carboplatin.

## **Treatment of metastatic seminoma:**

### **Low volume metastatic disease (II A/B)**

Treatment options:

- Radical Radiation Therapy
- Chemotherapy

**Radical Radiation Therapy** : Radical radiation therapy to Para-aortic and ipsilateral pelvic region (dog-leg) to a dose of 30-40 Gy @1.5-1.8 Gy/# in 3-4 weeks with reducing fields, with a boost to the involved site [10-11]. The role of prophylactic mediastinal irradiation is not clear. [Level I]. This gives excellent relapse free survival of 95% and 89% at 5 years and most relapses can be successfully salvaged with chemotherapy.

**Chemotherapy**: In patients of stage IIB seminoma not willing for radiation therapy or in those where it is contraindicated, 3 cycles of BEP or 4 cycles of cisplatin and etoposide [EP] is an alternative. (See appendix II)

### **Advanced metastatic seminoma: Stage IIC-III:**

This group can be divided into good risk or intermediate risk depending upon the absence or presence of non pulmonary visceral metastases respectively.

For good risk seminomas, 3 cycles of bleomycin, etoposide and cisplatin (BEP) regimen or 4 cycles of EP are recommended. Four cycles of BEP should be given for the patients with intermediate risk group. [12-15] [Level I].

Following chemotherapy, tumor markers and imaging studies are repeated to assess the response. Patients are then stratified according to the presence or absence of mass and the status of tumor markers. If complete

response, no further treatment required. If there is a residual mass, a PET-CT scan is recommended to assess the viability of the tumor [16]. To reduce false positive rates, PET is typically done after 6 weeks of chemotherapy. No further treatment is recommended in PET negative patients; however, these patients need to be observed closely. If the PET scan is positive, biopsy is recommended followed by surgical excision or radiotherapy to a dose of 30 – 40 Gy @ 1.8 Gy / # in 3-4 weeks [17-18].[Level II].

If the PET scan is not available, the evaluation should be done by CT scan. Residual mass of the size 3cm or more can be treated by surgery [Category 2B] or radiation [Level II].Surgery in metastatic seminoma post-chemotherapy is extremely difficult and morbid due to extensive fibrosis in the treated area. Patients with mass less than 3 cm should be observed. (See appendix III)

### **Management of stage INSGCT:**

If untreated, 30% of stage I NSGCT will relapse.

Following high orchiectomy, the treatment options include:

**Surveillance:** Based on availability of accurate tumour markers for monitoring of disease status and effective chemotherapy for salvage of relapse, surveillance protocols have been studied in stage I NSGCT. The relapse rates are approximately 30% - 80% of them occurring in the first year, 12% in the second, 6% in the third and 1% each in the fourth and the fifth year. About 60% of the relapses are in the retroperitoneum. Although has the potential to avoid major surgery with its morbidity, it requires a very intensive follow up with tumour markers, X-ray chest and CT scan abdomen at very frequent

intervals. Thus it requires excellent compliance from the patients which may not be possible in India. Besides, there is an anxiety about the nearly 30% chance of relapse, some of which may be advanced and unsalvageable if the patient does not comply with the surveillance schedule.

**Nerve sparing retroperitoneal lymph node dissection:** This is usually the preferred option since it identifies the high risk patients with occult retroperitoneal lymph node metastases (approximately 30%) who will need chemotherapy, has a very low (<2%) chance of relapse in the retroperitoneum and a very high cure rate. It preserves antegrade ejaculation in more than 90% of patients. Extensive follow up with CT scan as in surveillance is not mandatory which brings down the cost and patient anxiety is allayed. [Level I] (See appendix IV). A laparoscopic RPLND may become a suitable alternative to open nerve sparing RPLND in future but cannot be presently recommended as the standard of care.

**Chemotherapy:** Several studies using 2 course of BEP chemotherapy as the primary treatment for high risk stage I NSGCT have reported a relapse rate of only 2.7% at a median follow up of 8 years, with very little long-term toxicity and with little adverse impact on fertility or sexual activity. However, the concern about primary chemotherapy is the emergence of chemoresistant relapse and possibility of slow growing retroperitoneal teratomas necessitating intensive monitoring of retroperitoneum in the follow up period. This has considerable cost implications.

**Risk based treatment:** Various prognostic factors in the primary affecting risk of relapse have been identified viz.

presence of vascular invasion, predominance of embryonal carcinoma, absence of yolk sac elements or >T2 disease. Patients with no risk factors may be offered surveillance while those with high risk factors may be offered nerve sparing RPLND or chemotherapy. Patients with vascular invasion should be offered chemotherapy.

### **Management of clinical stage I with persistently elevated serum tumour markers (CS1S):**

These patients should be followed up with serial serum tumour markers if the marker levels are falling at the expected rate as per their half life values. If the marker levels remain persistently high or increase during follow up, the patient certainly has residual disease. Ultrasound examination of the contralateral testis must be done to rule out another primary lesion there. The treatment of these patients is controversial – they may be treated with RPLND or primary chemotherapy. Nearly 87% patients undergoing RPLND for CS1S disease have metastatic retroperitoneal nodes. Patients with associated vascular invasion may be treated with 4 cycles of EP or 3 cycles of BEP. [19-20]

### **Management of low volume metastatic NSGCT (II A/B)**

This group of patients is divided as per tumour marker levels. Patients with persistent elevation of tumour marker levels are treated with chemotherapy with 3-4 cycles of BEP followed by open nerve sparing RPLND for residual mass, if any. [Level I] Patients not willing for chemotherapy may be given the option of primary RPLND and 2 cycles of adjuvant chemotherapy in case of metastatic disease. [Level II] The cure rates with either approach are about 98% but the spectrum of toxicity is different.

Patients with negative tumour markers probably have metastatic differentiated teratoma or pure embryonal carcinoma and may be treated with either open nerve sparing RPLND or surveillance.

### **Management of advanced metastatic NSGCT (Stage IIC-III):**

Good risk (IIC and IIIA): Primary chemotherapy with 3 cycles of BEP or 4 cycles of EP is recommended [21-22]. [Level I] This group can be expected to have more than 90% chance of responding to chemotherapy [23] and more than 85% will be long term survivors. Hence the focus in this subset is to reduce toxicity. [Level II].

For the patients in the intermediate prognosis group (IIB), the cure rate is approximately 80% with chemotherapy with 4 cycles of BEP. [Level I]

For patients in poor prognosis group (IIIC), 4 cycles of BEP are recommended although the durable responses are seen in less than half the patients and 5 year progression free survival is only 45-50%. [Level I].

For patients with brain metastases, primary chemotherapy and consolidation radiotherapy is the standard of care. Surgical intervention is recommended in selected cases with solitary residual lesions depending on the status of the systemic relapse, site of metastasis and histology of the primary tumour. Certain sites of metastasis confer a distinct disadvantage in patients with NSGCT. These include liver, bone and brain. Metastasis to any of these sites reduces the 3-year OS rates significantly.

In patients of extragonadal GCTs, as in mediastinal GCT, which are considered as high risk, treatment essentially consists of 4 cycles of BEP chemotherapy followed by the excision of residual disease.



### **Post chemotherapy management:**

Response to primary chemotherapy is assessed 2-3 weeks after completion of the planned course of chemotherapy. Clinical evaluation, CT scan of the abdomen + pelvis, X-ray or CT scan of chest and serum biomarkers estimation are advised for evaluation of response. In patients with complete response (clinical, radiological and serological), surgery is not recommended and patients are kept under surveillance.

In patients with residual masses, decision regarding adjuvant surgery is based on whether the tumor markers remain elevated or have normalized. In patients with normal post-chemotherapy markers and any residual mass > 1 cm in size, complete surgical resection is warranted to document the histology of the residual mass and for disease control. All areas of residual disease need to be resected, since histology may be divergent at different metastatic sites. Complete resections should be done aggressively for retroperitoneal and pulmonary masses. If technically feasible, nerve sparing RPLND should be done. If necrotic tissue or teratoma is encountered, then no further therapy is warranted.

In the 15 % of patients who have viable residual disease, 2 cycles of chemotherapy as EP or VeIP [vinblastine, ifosfamide and cisplatin] or TIP [paclitaxel, ifosfamide and cisplatin] are recommended. [Level III] (See appendix II).

### **Systemic salvage treatment for relapsed or refractory disease: Salvage chemotherapy:**

Standard salvage chemotherapy regimen after first line chemotherapy consists of either 4 cycles of VeIP or 4 cycles of TIP. Conventionally dosed salvage regimens may achieve long term remission in 15-40% of patients.

Increasing the number of chemotherapy agents does not improve the response rates but increases toxicity. The prognostic indicators of response to salvage therapy are location and histology of the primary tumour, response to first line treatment, duration of remission and levels of tumour markers at relapse.

In good risk patients, a RCT failed to show advantage of high dose salvage regimen over the conventionally dosed one and hence the latter is recommended in these patients. Patients treated with VeIP regimen will have 50% CR rate and 25% durable CR rate. Those treated with TIP regimen have 70 % CR rates and 63 % durable CR rates. [25] [Level III]

In poor risk patients, early intensification of dose followed by autologous stem cell transplantation is the preferred option. [Level II] Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease. [26]

Another second line palliative therapy for intensively pretreated cisplatin resistant or refractory germ cell tumor is the use of GEMOX (gemcitabine and oxaliplatin).[27-28] . This combination is safe and can offer long term survival in select group of patients. [Level II]. Rarely, patient with metastatic disease with elevated tumor marker levels at a solitary site can be offered surgical resection with curative intent.[29]

Residual tumours after salvage chemotherapy should be resected after normalization or plateauing of markers. In case the markers are elevated during the course of salvage chemotherapy, the prognosis is extremely poor and resection of residual disease (desperation surgery)

should be considered if complete resection of all tumour seems feasible. With this approach, about 25% long term survivals may be achieved.

## **Appendix I.**

### **Sperm Banking**

In patients with testicular cancer, overall condition of the patient and the sperm quality may be poor even before start of therapy. Many patients have to start chemotherapy immediately or soon enough to limit the number of ejaculates to one or two samples. Even in these instances, it is reasonable to make every effort to bank sperm since recent progress in andrology laboratories and the use of assisted reproductive techniques, particularly the technique of intracytoplasmic sperm injection (ICSI) allows the successful freezing and future use of a very limited amount of sperm. Oncologists should make every effort to discuss sperm banking with appropriate patients.

## **Appendix II: Chemotherapy regimens:**

### **BEP (1<sup>st</sup> line) Repeat cycle every 21 days**

Bleomycin: 30 U IV on days 2, 9, and 16

Etoposide: 100 mg/m<sup>2</sup> IV on days 1–5

Cisplatin: 20 mg/m<sup>2</sup> IV on days 1–5

### **EP (1<sup>st</sup> line) Repeat cycle every 21 days**

Etoposide: 100 mg/m<sup>2</sup> IV on days 1–5

Cisplatin: 20 mg/m<sup>2</sup> IV on days 1–5

### **VelP (salvage regimen) Repeat cycle every 21 days**

Vinblastine: 0.11 mg/kg IV on days 1 and 2

Ifosfamide: 1,200 mg/m<sup>2</sup> IV on days 1–5

Cisplatin: 20 mg/m<sup>2</sup> IV on days 1–5  
Mesna: 400 mg/m<sup>2</sup> IV, given 15 minutes before first ifosfamide dose, then 1,200 mg/m<sup>2</sup>/day IV continuous infusion for 5 days

**VIP (salvage regimen) Repeat cycle every 21 days**

Etoposide (VP-16): 75 mg/m<sup>2</sup> IV on days 1–5  
Ifosfamide: 1,200 mg/m<sup>2</sup> IV on days 1–5  
Cisplatin: 20 mg/m<sup>2</sup> IV on days 1–5  
Mesna: 400 mg/m<sup>2</sup> IV, given 15 minutes before first ifosfamide dose, then 1,200 mg/m<sup>2</sup>/day IV continuous infusion for 5 days

**TIP regimen (Salvage regimen)**

Repeat cycle every 21 days  
Paclitaxel 250mg /m<sup>2</sup> 24 hour infusion Day 1  
Ifosfamide 1500 mg/m<sup>2</sup> Day 2 to day 5  
Mesna 500 mg/m<sup>2</sup> just before Ifosfamide and at 4 and 8 hours Day2 to day 5.  
Cisplatin 25 mg/m<sup>2</sup> Day2 to day 5

## **Appendix III: Follow up**

### **Seminoma**

History, physical examination and chest X ray  
AFP,  $\beta$  HCG and LDH  
Every 2 months for 1 year.  
Every 3 months for 2<sup>nd</sup> year.  
Every 4 months for 3<sup>rd</sup> year.  
Every 6 months for 4th year.  
Abdominopelvic CT 4 months post surgery, and subsequently as and when indicated.

## **NSGCT**

IA and IB tumors

<b>Year</b>	<b>Months between visits, tumor markers, and chest X rays</b>	<b>Months between abdominopelvic CT</b>
1	1-2	2-3
2	2	3-4
3	3	4
4	4	6
5	6	12
6+	12	12

Surveillance after complete response to RPLND and chemotherapy.

<b>Year</b>	<b>Months between visits, tumor markers, and chest X rays</b>	<b>Months between abdominopelvic CT</b>
1	2-3	6
2	2-3	6-12
3	4	12
4	4	12
5	6	12
6+	12	As clinically indicated.

## **Appendix IV: Retroperitoneal Lymph Node Dissection (RPLND)**

RPLND provides critical staging information and must always be performed with a curative intent. Adequate exposure for RPLND can be achieved through either a

thoracoabdominal or a transabdominal approach. The bilateral infra hilar RPLND template has replaced the supra hilar dissection and is the standard against which therapeutic alternatives are judged. (See Figure 1). A bilateral infra hilar RPLND includes the precaval, retrocaval, paracaval, interaortocaval, retroaortic, preaortic, para-aortic, and common iliac lymph nodes bilaterally. Since the gonadal vessel itself or the adjacent tissue may harbor disease, the ipsilateral gonadal vein and surrounding fibroadipose tissue from its insertion to the internal ring must be completely excised to minimize the possibility of a late paracolic recurrence. The procedure is associated with a mortality rate of less than 1%, and major complications such as hemorrhage, ureteral injury, bowel obstruction, pulmonary embolus, and wound dehiscence are rare. Minor complications include lymphocele, atelectasis, wound infection, and prolonged ileus.

Modified RPLND templates maximize rates of ejaculation by limiting dissection in areas thought to be at reduced risk of metastatic spread based on surgical mapping studies. These templates do not identify specific nerve fibers, but should include resection of all interaortocaval and ipsilateral lymph nodes between the level of the renal vessels and the bifurcation of the common iliac artery. This approach minimizes contralateral dissection, thereby reducing trauma to the hypogastric plexus and contralateral postganglionic sympathetic fibers. Preservation of antegrade ejaculation with this approach ranges from 50% to 80%.

Nerve-sparing techniques can be used in the primary or postchemotherapy setting. In a nerve-sparing RPLND, both sympathetic chains, the postganglionic sympathetic fibers, and hypogastric plexus are prospectively

identified, dissected, and preserved. With prospective nerve-sparing techniques, antegrade ejaculation is preserved in over 95% of all patients. Therefore, the original value of templates to prevent loss of ejaculatory function is diminished. Whatever the approach, margins of resection should not be compromised in an attempt to preserve ejaculation.

## **Standard modified bilateral retroperitoneal lymph node dissection.**

**Photograph from Devita Text Book of Cancer 2008.**  
UROLOGICAL CANCERS

Testicular Germs Cell Tumors

EBM

- 1. Albers P, Bender H, Positron emission tomography in the clinical staging of patients with Stage I and II testicular germ cell tumors. Urology. 1999 Apr; 53(4):808-11.**

**OBJECTIVES:** To evaluate the accuracy of fluorodeoxyglucose positron emission tomography (PET) compared with computed tomography (CT) staging in patients with Stage I and II testicular germ cell tumors (GCTs). **METHODS:** From January 1995 to July 1997, in 37 patients with clinical Stage (CS) I (n = 25) and CS II (n = 12) GCT (24 nonseminomas, 13 seminomas), PET and CT were compared in the initial staging. After PET, the patients with nonseminomatous GCT were staged surgically by retroperitoneal lymph node dissection and the patients with seminomatous GCT were followed up clinically. **RESULTS:** Correct staging by PET was achieved in 34 of 37 patients compared with correct CT staging in 29 of 37 patients. Of 10 metastatic lesions, 7 and 4 were detected by PET and CT, respectively. PET did not show false-positive signals. PET was unable to

detect vital cancer with a maximal diameter less than 0.5 cm or teratoma at any size. **CONCLUSIONS:** PET was useful for detecting viable tumor in lesions that are visible on CT scan and, thus, it may omit false-positive CS II lesions. However, PET was not able to identify mature teratoma. In this study, PET did not improve the staging in patients with CS I tumor.

**2. Spermon JR, De Geus-Oei LF, The role of (18)fluoro-2-deoxyglucose positron emission tomography in initial staging and re-staging after chemotherapy for testicular germ cell tumours. BJU Int. 2002 Apr;89(6):549-56.**

**OBJECTIVE:** To investigate the role of 18fluoro-2-deoxyglucose positron emission tomography (FDG-PET) in the initial staging of clinical stage I and II nonseminomatous germ cell tumours (NSGCTs) and in re-staging (non)seminomatous GCTs after chemotherapy. **PATIENTS AND METHODS:** FDG-PET studies were undertaken in 50 patients. FDG uptake was interpreted visually and when possible the standardized uptake value was determined. A FDG-PET scan was taken in five patients with clinical stage I and in seven with stage II NSGCT. The scans were validated by histology. Stage I patients underwent a retroperitoneal lymph node dissection because of vascular invasion in the primary tumour. Thirty-eight scans were taken after completing chemotherapy (28 NSGCTs and 10 seminomatous GCTs), and validated by histology or clinical follow-up. **RESULTS:** In stage I NSGCT, FDG-PET staging was equivalent to computed tomography (CT) staging. One small lesion, consisting of mature teratoma, was missed by both FDG-PET and CT. In stage II NSGCT, FDG-PET missed two lesions (mature teratoma and retroperitoneal mass with a small



component of embryonal cell carcinoma) whereas CT correctly classified all. In 20 of 28 patients with NSGCT, histology was obtained after chemotherapy. In one of three patients with viable tumorous residual mass the FDG-PET scan was clearly positive; in four of 12 with mature teratoma and inflammation components retroperitoneally, the FDG-PET was also positive. In contrast, eight patients with solitary mature teratoma had a negative PET result. In four of five patients with necrosis after chemotherapy the PET result was correctly negative. All eight patients on surveillance had a negative PET scan and were free of disease at median (range) of 14 (8-18) months. Interestingly, of the 12 patients with a correct negative PET result, 11 had no mature teratoma in their primary tumour. Nine of 10 patients with SGCT were correctly staged. Two FDG-PET studies showed increased uptake; in one, a viable seminomatous mass was found and in the other there was inflammation in the residual mass. In all other patients the FDG-PET scan correctly predicted absence of viability in the residual mass. **CONCLUSIONS:** In primary staging, FDG-PET has no benefit over CT. In re-staging, a negative FDG-PET result predicts fibrotic residual mass in seminomatous GCT. Moreover, it could be useful to predict fibrotic residual mass in NSGCT in those patients with no teratoma component in their primary tumour.

**3. Krege S, Beyer J, Souchon R, Eur Urol. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. 2008 Mar;53(3):478-96.**

**OBJECTIVES:** The first consensus report presented by the European Germ Cell Cancer Consensus Group

(EGCCCG) in the year 2004 has found widespread approval by many colleagues throughout the world. In November 2006, the group met a second time under the auspices of the Department of Urology of the Amsterdam Medical Center, Amsterdam, The Netherlands. METHODS: Medical oncologists, urological surgeons, radiation oncologists as well as pathologists from several European countries reviewed and discussed the data that had emerged since the 2002 conference, and incorporated the new data into updated and revised guidelines. As for the first meeting, the methodology of evidence-based medicine (EBM) was applied. The results of the discussion were compiled by the writing committee. All participants have agreed to this final update. RESULTS: The first part of the consensus paper describes the clinical presentation of the primary tumor, its treatment, the importance and treatment of testicular intraepithelial neoplasia (TIN), histological classification, staging and prognostic factors, and treatment of stage I seminoma and non-seminoma. CONCLUSIONS: Whereas the vast majority of the recommendations made in 2004 remain valid 3 yr later, refinements in the treatment of early- and advanced-stage testicular cancer have emerged from clinical trials. Despite technical improvements, expert clinical skills will continue to be one of the major determinants for the prognosis of patients with germ cell cancer. In addition, the particular needs of testicular cancer survivors have been acknowledged.

**4. *Padraig Warde, Lena Specht. Prognostic Factors for Relapse in Stage I Seminomas Managed by Surveillance: A Pooled Analysis: J Clin Oncol 2002; 20:4448-4452.***

Purpose: Several management options are available to patients with stage I seminoma, including adjuvant

radiotherapy, surveillance, and adjuvant chemotherapy. We performed a pooled analysis of patients from the four largest surveillance studies to better delineate prognostic factors associated with disease progression. Patients and Methods : Individual patient data were obtained from each center (Princess Margaret Hospital, Danish Testicular Cancer Study Group, Royal Marsden Hospital, and Royal London Hospital) for 638 patients. Tumor characteristics (size, histologic subtype, invasion of rete testis, and tumor invasion into small vessels [SVI]) as well as age at diagnosis were analyzed for prognostic importance for relapse. Results: With a median follow-up of 7.0 years (range, 0.02 to 17.5 years), 121 relapses were observed for an actuarial 5-year relapse-free rate (RFR) of 82.3%. On univariate analysis, tumor size (RFR: < 4 cm, 87%; > 4 cm, 76%; P\_.003), rete testis invasion (RFR: 86% [absent] v 77% [present], P\_.003), and the presence of SVI (RFR: 86% [absent] v 77% [present], P\_.038) were predictive of relapse. On multivariate analysis, tumor size (< 4 cm v > 4 cm, hazard ratio 2.0; 95% confidence interval [CI], 1.3 to 3.2) and invasion of the rete testis (hazard ratio 1.7; 95% CI, 1.1 to 2.6) remained as important predictors for relapse. Conclusion: We have identified size of primary tumor and rete testis invasion as important prognostic factors for relapse in patients with stage I seminoma managed with surveillance. This information will allow patients and clinicians to choose management based on a more accurate assessment of an individual patient's risk of relapse. In addition, it will allow clinicians to tailor follow-up protocols based on risk of occult disease.

**5. Jones WG, Fossa SD. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical**

**Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol. 2005 Feb 20; 23(6):1200-8.**

**PURPOSE:** To assess the possibility of reducing radiotherapy doses without compromising efficacy in the management of patients with stage I seminoma.

**PATIENTS AND METHODS:** Patients were randomly assigned 20 Gy/10 fractions over 2 weeks or 30 Gy/15 fractions during 3 weeks after orchidectomy. They completed a symptom diary card during treatment and quality-of-life forms pre- and post-treatment. The trial was powered to exclude absolute differences in 2-year relapse rates of 3% to 4% ( $\alpha = .05$  [one sided]; 90% power).

**RESULTS:** From 1995 to 1998, 625 patients were randomly assigned to treatment. Four weeks after starting radiotherapy, significantly more patients receiving 30 Gy reported moderate or severe lethargy (20% v 5%) and an inability to carry out their normal work (46% v 28%). However, by 12 weeks, levels in both groups were similar. With a median follow-up of 61 months, 10 and 11 relapses, respectively, have been reported in the 30- and 20-Gy groups (hazard ratio, 1.11; 90% CI, 0.54 to 2.28). The absolute difference in 2-year relapse rates is 0.7%; the lower 90% confidence limit is 2.9%. Only one patient has died from seminoma (allocated to the 20-Gy treatment group).

**CONCLUSION:** Treatment with 20 Gy in 10 fractions is unlikely to produce relapse rates more than 3% higher than for standard 30 Gy radiation therapy, and data on an additional 469 patients randomly assigned in a subsequent trial support and strengthen these results.

Reductions in morbidity enable patients to return to work more rapidly. Prolonged follow-up is required before any inference can be made about any impact of allocated treatment on new primary cancer diagnoses.

**6. Oliver RT, Mason MD. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomized trial, MRC TE19 collaborators and the EORTC 30982 collaborators. Lancet. 2005 Jul 23-29; 366(9482):293-300.**

**BACKGROUND:** Adjuvant radiotherapy is effective treatment for stage I seminoma, but is associated with a risk of late non-germ-cell cancer and cardiovascular events. After good results in initial studies with one injection of carboplatin, we undertook a large randomised trial to compare the approaches of radiotherapy with chemotherapy in seminoma treatment.

**METHODS:** Between 1996 and 2001, 1477 patients from 70 hospitals in 14 countries were randomly assigned to receive radiotherapy (para-aortic strip or dog-leg field; n=904) or one injection of carboplatin (n=573; dose based on the formula  $7 \times [\text{glomerular filtration rate} + 25]$  mg), at two trial centres in the UK and Belgium. The primary outcome measure was the relapse-free rate, with the trial powered to exclude absolute differences in 2-year rates of more than 3%. Analysis was by intention to treat and per protocol. This trial has been assigned the International Standard Randomised Controlled Trial Number ISRCTN27163214.

**FINDINGS:** 885 and 560 patients received radiotherapy and carboplatin, respectively. With a median follow-up of 4 years (IQR 3.0-4.9), relapse-free survival rates for radiotherapy and carboplatin were similar (96.7% [95%

CI 95.3-97.7] vs 97.7% [96.0-98.6] at 2 years; 95.9% [94.4-97.1] vs 94.8% [92.5-96.4] at 3 years, respectively; hazard ratio 1.28 [90% CI 0.85-1.93],  $p=0.32$ ). At 2 years' follow-up, the absolute differences in relapse-free rates (radiotherapy-chemotherapy) were -1.0% (90% CI -2.5 to 0.5) by direct comparison of proportions, and 0.9% (-0.5 to 3.0) by a hazard-ratio-based approach. Patients given carboplatin were less lethargic and less likely to take time off work than those given radiotherapy. New, second primary testicular germ-cell tumours were reported in ten patients allocated irradiation (all after para-aortic strip field) and two allocated carboplatin (5-year event rate 1.96% [95% CI 1.0-3.8] vs 0.54% [0.1-2.1],  $p=0.04$ ). One seminoma-related death occurred after radiotherapy and none after carboplatin.

**INTERPRETATION:** This trial has shown the non-inferiority of carboplatin to radiotherapy in the treatment of stage I seminoma. Although the absence of disease-related deaths and preliminary data indicating fewer second primary testicular germ-cell tumours favour carboplatin use, these findings need to be confirmed beyond 4 years' follow-up.

**7. R. T. Oliver, G. M. Mead Radiotherapy versus carboplatin for stage I seminoma: Updated analysis of the MRC/EORTC randomized trial (ISRCTN27163214). J Clin Oncol 2005; 23:1200-1208.**

**Background:** At ASCO 2004 we reported a randomised trial (MRC TE19, EORTC 30982) comparing 1 course carboplatin (C) at AUCx7 with adjuvant radiotherapy (RT) for stage I seminoma. With median follow-up (FU) of 4 yrs, C was shown to be non-inferior for relapse free rate (1° outcome) and there was a reduction in contralateral testicular germ cell cancers (GCT). Because late relapses

and 2<sup>nd</sup> GCT can occur beyond 5 and 10 yrs we have continued FU of these patients (pts). We report the updated results, and further analysis of C dose and outcome in relation to method of assessing renal function. Methods: The 1<sup>o</sup> randomisation was RT versus one injection of C dosed at 7x (GFR+25) based on EDTA (n=357) and 90% of this dose if based on creatinine clearance (n=202). The trial was powered to exclude absolute differences in the 2 yr relapse-free rates (RFR) of > 3%. RFR were determined by the Kaplan-Meier method, and hazard ratios (HR) from the Cox regression model; HR>1 favors RT. Results: Between 1996-2001, 1,447 pts were randomised in a 3:5 ratio (C=573, RT=904). Median FU is now 6.5 yrs with documented minimum 5 yr FU on 1,148 pts. RFRs at 5 yrs are 95% (C) and 96% (RT) (HR 1.25, 90% CI 0.83, 1.89); an increase in 5yr RFR of >3.6% can be excluded with 95% confidence. Only one death from seminoma (RT) has been reported. There was a significant difference in the rate of new GCTs (2 on C vs 15 on RT), giving a HR of 0.22 (95% CI 0.05, 0.95 p=0.03). High levels of pre-treatment FSH (>12 iu/L) were associated with an increased risk of developing a 2nd GCT (HR: 8.57 (95% CI 1.82 - 40.38)). Analysing the variation in dose received in the C group, showed that those who received at least 99% of the 7AUC dose (n=347) ignoring GFR method had 5 yr RFR of 96.1% (95% CI 93.4-97.7) compared with 92.6% (88.0-95.5) in those who received lower doses (n=212, HR: 0.51 (0.24 - 1.07) p=0.08)). Analysis of the available data on pathological risk factors demonstrated that larger tumours (>4cm) had poorer RFR (HR: 3.68 (1.49 - 9.13)). Conclusions: With prolonged FU this trial confirms the non-inferiority of single dose C (AUC7) vs RT in terms of RFR but with a reduced risk of 2<sup>nd</sup> GCT in the C arm. The observation on the impact of C dosage, though not significant in its own right,

**8. John P. Logue, Margaret A. Harris Short course para-aortic radiation for Stage I Seminoma of the testis. Int. J Radiat Oncol Biol Phys. 2003; 57:1304-1309.**

Purpose : To determine the outcome in men with Stage I seminoma treated with low-dose para-aortic radiation. Methods and Materials: Between January 1988 and December 2000, 431 men with Stage I seminoma were treated with para-aortic radiation to a midplane dose of 20 Gy in 8 fractions over 10 days. Results: At a median follow-up of 62 months, 15 patients (3.5%) had relapsed, with a median time to relapse of 13 months (range: 9 to 39 months). Nine patients had pelvic nodal relapse; in addition, 1 patient had para-aortic involvement, and 2 had distant disease. Four had metastatic disease only (mediastinum 2, lung 2). One patient had scrotal recurrence, and 1 was treated for progressive rise in human chorionic gonadotrophin without identifiable disease. Initial treatment at relapse was chemotherapy (12), radiation (2), and surgery (1). One patient died from progressive disease. Thirteen men (3%) have developed second malignancies, including 7 contralateral testicular tumors, 5 solid malignancies, and 1 leukemia. The overall 5-year survival was 98%, and the estimated recurrence-free survival at 5 years was 96.3%. On log-rank univariate analysis, lymphovascular invasion, involvement of the tunica, and a preoperative human chorionic gonadotrophin level of greater than 5 were found to be of prognostic significance for recurrence. Conclusions : These data support short-duration, limited-field radiation as an optimal safe and effective protocol in the management of Stage I seminoma patients.



**9. Fossa S.D., Horwich A. Optimal Planning Target Volume for Stage I Testicular Seminoma: A Medical Research Council Randomized Trial, J Clin Oncol. 1999; 17; 1146 - 1154.**

Purpose : To compare relapse rates and toxicity associated with para-aortic (PA) strip or PA and ipsilateral iliac lymph node irradiation (dogleg [DL] field) (30 Gy/15 fractions/3 weeks) for stage I testicular seminoma. Patients and Methods: Between July 1989 and May 1993, 478 men with testicular seminoma stage I (T1 to T3; no ipsilateral inguinoscrotal operation before orchiectomy) were randomized (PA, 236 patients; DL, 242 patients). Results: Median follow-up time is 4.5 years. Eighteen relapses, nine in each treatment group, have occurred 4 to 35 months after radiotherapy; among these, four were pelvic relapses, all occurring after PA radiotherapy. However, the 95% confidence interval (CI) for the difference in pelvic relapse rates excludes differences of more than 4%. The 3-year relapse-free survival was 96% (95% CI, 94% to 99%) after PA radiotherapy and 96.6% (95% CI, 94% to 99%) after DL (difference, 0.6%; 95% confidence limits, 23.4%, 14.6%). One patient (PA field) has died from seminoma. Survival at 3 years was 99.3% for PA and 100% for DL radiotherapy. Acute toxicity (nausea, vomiting, leukopenia) was less frequent and less pronounced in patients in the PA arm. Within the first 18 months of follow-up, the sperm counts were significantly higher after PA than after DL irradiation. Conclusion: In patients with testicular seminoma stage I (T1 to T3) and with undisturbed lymphatic drainage, adjuvant radiotherapy confined to the PA lymph nodes is associated with reduced hematologic, gastrointestinal, and gonadal toxicity, but with a higher risk of pelvic recurrence, compared with DL radiotherapy. The recurrence rate is low with either treatment. PA

radiotherapy is recommended as standard treatment in these patients.

**10. Schmidberger H, Bamberg M. Treatment options in early-stage testicular seminoma. Review of the literature with initial results of a prospective multicenter study on radiotherapy of clinical-stage I, IIA and IIB seminomas. *Strahlenther Onkol.* 1995 Mar; 171(3):125-39.**

**BACKGROUND:** Testicular seminoma in the early stages is treated with orchiectomy and radiotherapy to the retroperitoneal nodes. Despite the high cure rates of this treatment, there is an ongoing controversy concerning the extent of the radiation fields and the radiation doses to be given in the clinical stages I, IIA and IIB. In the following literature review, these controversial issues are discussed. Recent reports emphasize, that the irradiation of the paraaortic nodes seems to be adequate in stage I disease. The “wait and see” strategy avoids an overtreatment in 80% of the patients in stage I. The application of 1 or 2 cycles of carboplatinum chemotherapy induced comparable results to adjuvant radiotherapy. In the stages IIA and IIB radiotherapy to the paraaortal and ipsilateral iliacal nodes, with a prescribed dose of 30 Gy and 36 Gy respectively, has been the standard treatment. The treatment of the upper contralateral iliacal nodes has been a matter of controversy.

**PATIENTS AND METHODS:** Four hundred and ninety-one patients in stage I testicular seminoma received adjuvant paraaortic irradiation with a total dose of 26 Gy. Forty-one patients in stage IIA, and 19 patients in stage IIB received 30 Gy or 36 Gy respectively to the paraaortic and ipsilateral iliacal nodes.

**RESULTS :** Paraaortic radiotherapy in stage I disease was associated with low acute side effects and a disease-free survival in 97.1% of the patients after a median observation of 13 months. In stage IIA the disease-free survival was 100%, in stage IIB 94.7%.

**CONCLUSIONS :** The literature review and preliminary results of the reported ongoing trial are indicating that paraaortic irradiation in stage I and paraaortic with ipsilateral iliacal irradiation in stages IIA and IIB seem to be a sufficient treatment in early stage testicular seminoma with low treatment associated morbidity.

**11. P Warde, M Gospodarowicz. Management of stage II seminoma : J Clin Oncol. 1998; 16:290-294.**

**PURPOSE :** To assess the results of treatment, patterns of failure, and prognostic factors for relapse in a contemporary cohort of patients with stage II seminoma.

**MATERIALS AND METHODS :** From January 1981 and December 1993, 99 patients (median age, 35 years) with stage II seminoma (IIA, 41; IIB, 28; IIC, 24; IID, six) were managed at our institution. Eighty were treated with radiation therapy (RT) and 19 with chemotherapy (ChT).

**RESULTS :** With a median follow-up of 6.7 years, the five-year overall actuarial survival was 94%, the 5-year cause-specific survival was 94%, and the 5-year relapse-free rate was 83%. Sixteen (20%) of the 80 patients treated with RT relapsed (median time to relapse, 9 months). Relapse occurred outside the irradiated area in all but two patients. Distant relapse sites included the supraclavicular fossa, bone (four patients, three with spinal cord compression), and lung/mediastinum. All 19 patients treated primarily with ChT achieved disease control and none has relapsed. The relapse rate at 5

years for patients with stage IIA to IIB was 11% (seven of 64), and 56% (nine of 16) for those with stage IIC to IID disease ( $P < .0001$ ). No patient with IIC or IID disease treated with ChT relapsed as compared with 56% of patients treated with RT (0 of 14 v nine of 16,  $P = .002$ ).

**CONCLUSION :** Radiation therapy is highly effective in patients with stage IIA or IIB seminoma (89% were relapse free). In stage IIC or IID disease, although local control with RT is excellent, a 50% risk of distant relapse is unacceptable, and not all patients who relapse can be salvaged. Chemotherapy should clearly be the primary treatment in patients with stage IIC or IID seminoma.

**12. de Wit R, Roberts JT, Wilkinson PM. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol. 2001 Mar 15; 19(6):1629-40.**

**PURPOSE:** To test the equivalence of three versus four cycles of bleomycin, etoposide, and cisplatin (BEP) and of the 5-day schedule versus 3 days per cycle in good-prognosis germ cell cancer.

**PATIENTS AND METHODS:** The study was designed as a 2 x 2 factorial trial. The aim was to rule out a 5% decrease in the 2-year progression-free survival (PFS) rate. The study included the assessment of patient quality of life. A cycle of BEP consisted of etoposide 500 mg/m<sup>2</sup>, administered at either 100 mg/m<sup>2</sup> days 1 through 5 or 165 mg/m<sup>2</sup> days 1 through 3, cisplatin 100 mg/

m(2), administered at either 20 mg/m(2) days 1 through 5 or 50 mg/m(2) days 1 and 2. Bleomycin 30 mg was administered on days 1, 8, and 15 during cycles 1 through 3. The randomization procedure allowed some investigators to participate only in the comparison of three versus four cycles.

**RESULTS:** From March 1995 until April 1998, 812 patients were randomly assigned to receive three or four cycles: of these, 681 were also randomly assigned to the 5-day or the 3-day schedule. Histology, marker values, and disease extent are well balanced in the treatment arms of the two comparisons. The projected 2-year PFS is 90.4% on three cycles and 89.4% on four cycles. The difference in PFS between three and four cycles is -1.0% (80% confidence limit [CL], -3.8%, +1.8%). Equivalence for three versus four cycles is claimed because both the upper and lower bounds of the 80% CL are less than 5%. In the 5- versus 3-day comparison, the projected 2-year PFS is 88.8% and 89.7%, respectively (difference, -0.9%, (80% CL, -4.1%, +2.2%). Hence, equivalence is claimed in this comparison also. Frequencies of hematologic and nonhematologic toxicities were essentially similar. Quality of life was maintained better in patients receiving three cycles; no differences were detected between 3 and 5 days of treatment.

**CONCLUSION:** We conclude that three cycles of BEP, with etoposide at 500 mg/m(2), is sufficient therapy in good-prognosis germ cell cancer and that the administration of the chemotherapy in 3 days has no detrimental effect on the effectiveness of the BEP regimen.

**13. Loehrer PJ Sr, Johnson D Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial: J Clin Oncol. 1995 Feb;13(2):470-6.**

**PURPOSE:** This prospective, randomized trial was designed to determine if three cycles of cisplatin plus etoposide (PVP16) can produce therapeutic results comparable to three cycles of cisplatin, etoposide, and bleomycin (PVP16B) in patients with disseminated germ cell tumors.

**PATIENTS AND METHODS:** One hundred seventy-eight patients with minimal- or moderate-stage disease (Indiana staging system) were randomized to receive cisplatin (20 mg/m<sup>2</sup> on days 1 to 5) plus etoposide (100 mg/m<sup>2</sup> on days 1 to 5) with or without weekly bleomycin (30 IU/wk for 9 consecutive weeks). Following three cycles of chemotherapy over 9 weeks, patients with residual radiographic disease underwent surgical resection. If persistent carcinoma was noted, two additional 3-week courses of chemotherapy were administered.

**RESULTS:** One hundred seventy-one patients were fully assessable for response and survival. The two treatment groups were similar with respect to patient characteristics. The toxicities were comparable between the two arms. No clinically significant incidence of pulmonary toxicity occurred with PVP16B. Overall, 81 of 86 patients (94%) who received PVP16B and 75 of 85 patients (88%) who received PVP16 achieved a disease-free status with chemotherapy and/or surgery. However, greater numbers of treatment failures, including persistent carcinoma in postchemotherapy resected residual disease and relapses from complete remission,

occurred on the arm without bleomycin (overall adverse outcome,  $P = .004$ ). The failure-free (86% v 69%;  $P = .01$ ) and overall survival (95% v 86%;  $P = .01$ ) rates were inferior on the PVP16 arm.

**CONCLUSION:** Bleomycin is an essential component of PVP16B therapy in patients who receive three cycles of treatment for minimal- or moderate-stage disseminated germ cell tumors.

**14. Bajorin DF, Sarosdy MF. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol. 1993 Apr; 11(4):598-606.**

**PURPOSE:** This multicenter, randomized phase III clinical trial evaluated the efficacy of etoposide plus carboplatin (EC) versus etoposide plus cisplatin (EP) in good-risk germ cell tumor (GCT) patients.

**PATIENTS AND METHODS:** Between October 1986 and December 1990, 270 patients with good-risk GCTs were randomized to receive four cycles of either EP or EC. The etoposide dose in all patients was 100 mg/m<sup>2</sup> on days 1 through 5. EP patients received cisplatin at 20 mg/m<sup>2</sup> on days 1 through 5 and therapy was recycled at 21-day intervals. For EC patients, the carboplatin dose was 500 mg/m<sup>2</sup> on day 1 of each cycle and the EC recycling interval was 28 days.

**RESULTS:** Two hundred sixty-five patients were assessable: 131 patients treated with EC and 134 treated with EP. One hundred fifteen of 131 assessable patients (88%) treated with EC achieved a complete response (CR) versus 121 of 134 patients (90%) treated with EP ( $P = .32$ ). Sixteen patients (12%) treated with EC relapsed from CR versus four patients (3%) treated with EP.

Therefore, 32 patients (24%) who received carboplatin experienced an event (incomplete response [IR] or relapse) compared with 17 of 134 patients (13%) who received cisplatin ( $P = .02$ ). At a median follow-up of 22.4 months, event-free and relapse-free survival were inferior for patients treated with EC ( $P = .02$  and  $P = .005$ , respectively). No difference in overall survival was evident ( $P = .52$ ).

**CONCLUSION:** Two-drug therapy with EC using this dose and schedule was inferior to therapy with EP. Cisplatin remains as the standard platinum analog in the treatment of patients with good-risk GCTs. Carboplatin should be restricted to investigational trials in GCT.

**15. Kondagunta GV, Bacik J. Etoposide and cisplatin chemotherapy for metastatic good-risk germ cell tumors: J Clin Oncol. 2005 Dec 20;23(36):9290-4.**

**PURPOSE:** To assess response, overall survival, and relapse-free survival of patients with good-risk metastatic germ cell tumor (GCT) by International Germ Cell Consensus Classification Group (IGCCCG) criteria treated with four cycles of etoposide and cisplatin (EP).

**PATIENTS AND METHODS:** Two hundred eighty-nine patients with IGCCCG good-risk GCT were treated with four cycles of EP. EP consisted of four cycles of etoposide 100 mg/m<sup>2</sup> and cisplatin 20 mg/m<sup>2</sup> on days 1 to 5 every 21 days. **RESULTS:** Two hundred eighty-two of 289 patients (98%) achieved a complete response; 269 (93%) responded to chemotherapy alone and 13 (5%) responded to chemotherapy plus surgical resection of viable disease (GCT other than mature teratoma). Seventeen (6%) experienced relapse, and nine (3%) died as a result of disease at a median follow-up of 7.7 years



(range, 0.4 to 21.1 years). Sixty-two of 204 patients (30%) with nonseminoma had findings of teratoma or viable GCT at postchemotherapy surgery.

**CONCLUSION:** Four cycles of EP is a highly effective therapy for patients with good-risk GCT, with a high cure rate, low relapse rate, and little evidence of late relapse. Postchemotherapy surgery resection of residual disease remains an important aspect of treatment for these patients. Four cycles of EP is acceptable as a standard regimen for the treatment of good-risk metastatic GCT, and serves as an alternative to three cycles of bleomycin and etoposide before cisplatin.

**16. Becherer A, De Santis M. FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals: Eur J Radiol. 2005 May;54(2):284-8.**

**AIM:** In advanced seminoma the management of residuals after completion of chemotherapy is controversial. Some centres routinely perform surgery for lesions  $>$  or  $=$ 3 cm diameter, others recommend surgery solely if the residual fail to shrink or show even growth. This study prospectively investigates whether FDG PET can improve the prediction of viable tumour in post-chemotherapy seminoma residuals.

**MATERIALS AND METHODS:** After an expansion of a previous study population, 54 patients from eight centres with metastatic seminoma and a CT-documented mass after chemotherapy were included in the study. Six patients were excluded from evaluation because of protocol violations. After PET, the patients underwent either surgery or were followed clinically. On follow-up the lesions were considered to be non-viable when there was unequivocal shrinking, or when the lesion remained

morphologically stable for at least 24 months. Any lesion growth was assumed to be malignant. PET results were compared to CT discrimination (< or > or =3 cm) of the residual masses.

**RESULTS:** Fifty-two PET scans were evaluable. After adequate chemotherapy, there were 74 CT-documented residual masses ranging in size from 1 to 11 cm (median, 2.2 cm). Their dignities were confirmed histologically in 13 lesions, or by follow-up CT in 61 lesions. Four of forty-seven lesions <3 cm and 11/27 lesions > or =3 cm were viable. PET was true positive in one lesion <3 cm and in 11 lesions > or =3 cm, false negative in three lesions <3 cm, and true negative in 59 lesions (43 lesions <3 cm). No PET scan was false positive. In detecting viability the sensitivity and specificity was 73% (95% CI, 44-88), and 73% (59-83), respectively, for CT (< or > or =3 cm); and 80% (51-95), and 100% (93-100), respectively, for PET (specificity, P < 0.001).

**CONCLUSION:** In post-chemotherapy seminoma residuals, a positive PET is highly predictive for the presence of viable tumour. The specificity of PET is significantly higher than that of CT when using a > or =3 cm cut-off. A negative PET scan is excellent for the exclusion of disease in lesions > or =3 cm, with a somewhat higher sensitivity than CT (n.s.). PET can contribute to the management of residual seminoma lesions, especially in terms of avoiding unnecessary additional treatment for patients with lesions > or =3 cm.

**17. HS Puc, R Heelan. Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center: J Clin Oncol. 1998; 14:454-460.**

**PURPOSE :** Guidelines for management of postchemotherapy residual mass in patients with advanced seminoma remain controversial. We sought to characterize independent prognostic factor(s) for persistence of tumor to identify patients with a high risk of residual carcinoma.

**PATIENTS AND METHODS :** One hundred four patients with advanced seminoma were assessed. All had achieved a complete response or partial response with normal markers to induction cisplatin-based chemotherapy and had radiographs available for review. Selected prechemotherapy and postchemotherapy characteristics were compared for patients who had either germ cell tumor histology at surgery or relapsed at the assessed site (defined as site failure) versus those who had only necrosis or fibrosis found at surgery and did not relapse at the assessed site (defined as site nonfailure).

**RESULTS :** At a median follow-up time of 47 months (range, 5 to 153), 94 patients (90%) were designated as site nonfailures and 10 (10%) as site failures. Site failure correlated only with size of the residual mass (< 3 cm or normal v > or = 3 cm;  $P=.0006$ ). Two of 74 patients (3%) with residual masses less than 3 cm were considered site failures, compared with eight of 30 (27%) with residual masses > or = 3 cm.

**CONCLUSION :** Patients with advanced seminoma who have normal radiographs or residual masses less than 3 cm after chemotherapy can be observed without further intervention. The following three options exist for patients with a residual mass > or = 3 cm: observation, radiotherapy, or surgical intervention. We prefer the latter to define response, resect viable tumor when possible, and direct further treatment.

**18. BR Mason and JH Kearsley. Radiotherapy for stage II testicular seminoma: the prognostic influence of tumor bulk: J Clin Oncol. 1988;6(12):1856-62.**

Forty-nine consecutive patients with stage 2 testicular seminoma were treated with primary radiotherapy from 1968 to 1985. Overall diseases-free survival (DFS) for patients with 36 months minimum follow-up was 82% at 3 years. This figure did not decline further with time. Infradiaphragmatic bulk disease was found to be a significant prognostic factor for local and distant relapse as well as for ultimate survival. Patients with either stage 2A or 2B disease (infradiaphragmatic bulk less than or equal to 10 cm size) had a 3-year DFS of 89% compared with a 64% 3-year DFS rate for patients with stage 2C disease (infradiaphragmatic bulk greater than or equal to 10 cm size). The (local plus distant) relapse rate was 4.0% for patients with stage 2A disease, 16.7% for patients with stage 2B disease, and 33.3% for patients with stage 2C disease. The majority of distant relapses were multifocal and prophylactic mediastinal irradiation did not appear to influence either relapse rate nor overall survival. Of seven patients who relapsed, four died of progressive malignancy, two deaths were related to salvage chemotherapy, and only one patient is alive and well following successful chemotherapeutic salvage. On the basis of our experience, we recommend radiotherapy with the use of modern imaging techniques as initial treatment for patients with retroperitoneal masses less than 10 cm size. Aggressive cisplatin-based chemotherapy should be seriously considered for patients with retroperitoneal masses greater than or equal to 10 cm size, or for patients who relapse following radiotherapy.

19. Davis BE, Herr HW. The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy :J Urol. 1994 Jul;152(1):111-3.

Management of patients with nonseminomatous germ cell tumors of the testis who have persistently elevated serum tumor marker levels (alpha-fetoprotein and/or human chorionic gonadotropin) following orchiectomy and no clinical evidence of disease is controversial. We reviewed our experience with 15 such patients at our cancer center between March 1977 and November 1991. Group 1 (11 patients) underwent initial retroperitoneal lymph node dissection and group 2 (4 patients) received primary chemotherapy. All group 1 patients required subsequent chemotherapy for retroperitoneal disease or persistent marker elevation, whereas only 1 of the 4 who received primary chemotherapy required later surgery. We conclude that tumor marker elevation in this setting is usually indicative of systemic tumor, which is best treated primarily by initial chemotherapy.

**20. Culine S, Theodore C. Primary chemotherapy in patients with nonseminomatous germ cell tumors of the testis and biological disease only after orchiectomy: J Urol. 1996 Apr;155(4):1296-8.**

Purpose: We assessed the efficacy of primary chemotherapy in patients with nonseminomatous germ cell tumors of the testis and elevated serum tumor markers as the only evidence of disease after orchiectomy. Materials and Methods: We analyzed the outcome of 20 patients with biological disease only who received cisplatin-based (16) or carboplatin-based (4) chemotherapy as primary treatment following orchiectomy. Results: Serum tumor markers returned to

normal levels in all 20 patients. One patient required subsequent surgery for recurrent retroperitoneal mature teratoma. Two patients experienced a relapse with active disease, 1 of whom died of progressive germ cell tumor. Of the patients 19 remained free of disease 18 to 116 months after the end of treatment. Conclusions: Since results with primary retroperitoneal lymph node dissection suggest that elevated serum tumor markers usually reflect systemic metastases rather than retroperitoneal disease, primary chemotherapy seems to be the most appropriate strategy to consider in patients with biological disease only following orchiectomy.

**21. Horwich A, Sleijfer DT . Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer : a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial: J Clin Oncol. 1997 May;15(5):1844-52.**

**PURPOSE :** This prospective randomized multicenter trial was designed to evaluate the efficacy of carboplatin plus etoposide and bleomycin (CEB) versus cisplatin plus etoposide and bleomycin (BEP) in first-line chemotherapy of patients with good-risk nonseminomatous germ cell tumors.

**PATIENTS AND METHODS :** Between September 1989 and May 1993, a total of 598 patients with good-risk nonseminomatous germ cell tumors were randomized to receive four cycles of either BEP or CEB. In each cycle, the etoposide dose was 120 mg/m<sup>2</sup> on days 1, 2, and 3, and the bleomycin dose was 30 U on day 2. BEP patients received cisplatin at 20 mg/m<sup>2</sup>/d on days 1 to 5 or 50 mg/m<sup>2</sup> on days 1 and 2. For CEB patients, the

carboplatin dose was calculated from the glomerular filtration rate to achieve a serum concentration x time of 5 mg/mL x minutes. Chemotherapy was recycled at 21-day intervals to a total of four cycles.

**RESULTS :** Of patients assessable for response, 253 of 268 (94.4%) of those allocated to receive BEP achieved a complete response, compared with 227 of 260 (87.3%) allocated to receive CEB (P=.009). There were 30 treatment failures in the 300 patients allocated to BEP and 79 in the 298 allocated to CEB (log-rank chi 2=26.9; P<.001), which led to failure-free rates at 1 year of 91% (95% confidence interval [CI], 88% to 94%) and 77% (95% CI, 72% to 82%), respectively. There were 10 deaths in patients allocated to BEP and 27 in patients allocated to CEB (log-rank chi 2=8.77; P=.003), which led to 3-year survival rates of 97% (95% CI, 95% to 99%) and 90% (95% CI, 86% to 94%), respectively.

**CONCLUSION :** With these drug doses and schedules, combination chemotherapy based on carboplatin was inferior to that based on cisplatin. This BEP regimen that contains moderate doses of etoposide and bleomycin is effective in the treatment of patients with good-prognosis metastatic nonseminoma.

**22. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group: *J Clin Oncol.* 1997 Feb;15(2):594-603.**

**PURPOSE :** Cisplatin-containing chemotherapy has dramatically improved the outlook for patients with metastatic germ cell tumors (GCT), and overall cure rates now exceed 80%. To make appropriate risk-based

decisions about therapy and to facilitate collaborative trials, a simple prognostic factor-based staging classification is required.

**MATERIALS :** Collaborative groups from 10 countries provided clinical data on patients with metastatic GCT treated with cisplatin-containing chemotherapy. Multivariate analyses of prognostic factors for progression and survival were performed and models were validated on an independent data set.

**RESULTS :** Data were available on 5,202 patients with nonseminomatous GCT (NSGCT) and 660 patients with seminoma. Median follow-up time was 5 years. For NSGCT the following independent adverse factors were identified: mediastinal primary site; degree of elevation of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactic dehydrogenase (LDH); and presence of nonpulmonary visceral metastases (NPVM), such as liver, bone, and brain. For seminoma, the predominant adverse feature was the presence of NPVM. Integration of these factors produced the following groupings: good prognosis, comprising 60% of GCT with a 91% (89% to 93%) 5-year survival rate; intermediate prognosis, comprising 26% of GCT with a 79% (75% to 83%) 5-year survival rate; and poor prognosis, comprising 14% of GCT (all with NSGCT) with a 48% (42% to 54%) 5-year survival rate.

**CONCLUSION :** An easily applicable, clinically based, prognostic classification for GCT has been agreed on between all the major clinical trial groups who are presently active worldwide. This should be used in clinical practice and in the design and reporting of clinical trials to aid international collaboration and understanding.



**23. Jones RH, Vasey PA. PART II: Testicular cancer management of advanced disease. *Lancet oncol* 2003;4:738-747.**

Up to 80% of metastatic germ-cell tumours are curable with conventional chemotherapy. The combination of cisplatin, bleomycin, and etoposide has become the gold standard in this disease. Patients can be divided into good, intermediate, and poor prognosis groups. For those patients with good prognostic features, cure rates reach 90% and attempts have been made to reduce toxic effects of treatment while maintaining efficacy. Patients that relapse require salvage treatment. This can involve the incorporation of drugs such as ifosfamide and taxol into conventional protocols or the use of high-dose chemotherapy with stem-cell transplants. Patients with poor prognosis disease are much more likely to fail conventional chemotherapy and are candidates for dose-intensive protocols or transplants as first-line treatment. Although the results obtained in treating metastatic germ-cell tumours are superior to those with other solid tumour types, there are still many areas that require further improvement.

**24. Motzer RJ, Geller NL. Salvage chemotherapy for patients with germ cell tumors. The Memorial Sloan-Kettering Cancer Center experience (1979-1989): *Cancer*. 1991 Mar 1;67(5):1305-10.**

Twenty-eight of 124 (23%) advanced germ cell tumor (GCT) patients who were treated on four successive platin-based induction regimens and who failed to achieve a durable complete response (CR) remain alive (median follow-up, 50 months). An analysis of prognostic factors for response and survival was conducted on the 94 patients who received salvage chemotherapy. Survival

and/or response to salvage therapy were significantly enhanced for patients with a prior CR to induction chemotherapy, treatment with a cisplatin-based salvage regimen, a testis primary site, a normal serum human chorionic gonadotropin level, a normal serum lactate dehydrogenase level, one site of metastasis, and an Indiana Class of 6 or less. Patients with a prior incomplete response (IR) had a particularly poor prognosis ( $P = 0.00007$ ) with only 4 of 52 (9%) patients alive (median follow-up, 37 months) compared with 15 of 42 (36%) patients with a prior best response of a CR (median follow-up, 35 months). The poor survival of patients who fail to achieve a durable CR to induction chemotherapy warrants the continued investigation of new salvage therapy. The identification of prognostic features may direct salvage therapy and aid in the interpretation of clinical trials of salvage regimens.

**25. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors: J Clin Oncol 2005;23:6549.**

**PURPOSE:** The efficacy of paclitaxel was evaluated in combination with ifosfamide and cisplatin as second-line chemotherapy for patients with relapsed testicular germ cell tumors (GCTs).

**PATIENTS AND METHODS:** Forty-six patients with progressive metastatic GCTs were treated with paclitaxel and ifosfamide plus cisplatin (TIP) as second-line therapy. Eligibility required that patients have both a testis primary tumor site and a prior complete response (CR) to a first-line chemotherapy program, which had been identified previously as favorable prognostic factors to conventional-dose salvage chemotherapy.

**RESULTS:** Thirty-two (70%) of 46 patients achieved a CR to treatment. Three patients (7%) who achieved a CR relapsed after TIP chemotherapy. Twenty-nine patients are continuously disease free at a median follow-up time of 69 months, resulting in a 63% durable CR rate and a 2-year progression-free survival rate of 65% (95% CI, 51% to 79%).

**CONCLUSION:** Four cycles of TIP as second-line therapy achieved a durable CR rate in a high proportion of patients with relapsed testicular GCT. The high CR rate emphasizes the importance of patient selection according to prognostic factors to achieve a favorable outcome to conventional-dose salvage therapy.

**26. Einhorn LH, Williams SD. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *New Engl J Med.* 2007 Jul 26;357(4):340-8.**

**BACKGROUND:** Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy.

**METHODS:** We conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer that had progressed after they received cisplatin-containing combination chemotherapy. We gave 173 patients two consecutive courses of high-dose chemotherapy consisting of 700 mg of carboplatin per square meter of body-surface area and 750 mg of etoposide per square meter, each for 3 consecutive days, and each followed by an infusion of autologous peripheral-blood hematopoietic stem cells; the other 11 patients received a single course of this treatment. In 110 patients, cytoreduction with one or two courses of vinblastine plus

ifosfamide plus cisplatin preceded the high-dose chemotherapy.

**RESULTS:** Of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months (range, 14 to 118). Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 were disease-free. A total of 98 of 144 patients who had platinum-sensitive disease were disease-free, and 26 of 35 patients with seminoma and 90 of 149 patients with nonseminomatous germ-cell tumors were disease-free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy.

**CONCLUSIONS:** Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.

**27. Pectasides D, Pectasides M. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study. Ann Oncol 2004;15:493-497.**

**BACKGROUND:** To investigate the efficacy and toxicity of the combination of gemcitabine and oxaliplatin (GEMOX) in patients with relapsed or cisplatin-refractory non-seminomatous germ cell tumors (NSGCT).

**PATIENTS AND METHODS:** Twenty-nine patients with relapsed or cisplatin-refractory NSGCT were treated with gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8 followed by

oxaliplatin 130 mg/m<sup>2</sup> on day 1 every 3 weeks for a maximum of six cycles. Twenty-four patients (83%) were considered refractory and five (17%) absolutely refractory to cisplatin.

**RESULTS:** Twenty-eight patients were assessable for response. Overall, nine patients (32%) achieved a favourable response (complete response, four; partial response, five). One of the complete responders relapsed after 7 months and went into disease-free status lasting for 11+ months after resection of lung metastases. The rest of the complete responders are continuously disease-free at 14+, 19+ and 28+ months with the study regimen plus or minus surgery. One of the complete responders had absolutely cisplatin-refractory disease and another one presented with a late relapse. Toxicity was primarily hematological and generally manageable: 62% of patients experienced grade 3/4 neutropenia, 10% neutropenic fever and 41% grade 3/4 thrombocytopenia. Non-hematological toxicity consisted mainly of nausea/vomiting. Three patients (10%) developed grade 3 neurotoxicity and discontinued treatment.

**CONCLUSIONS:** The combination of GEMOX is an active, moderately toxic and easily administered regimen in patients with relapsed or cisplatin-refractory NSGCT. The 14% long-term disease-free status accomplished in this heavily pretreated patient population is quite encouraging.

**28. De Giorgi U, Rosti G. Phase II study of oxaliplatin and gemcitabine salvage chemotherapy in patients with cisplatin-refractory nonseminomatous germ cell tumor: Eur Urol. 2006 Nov;50(5):1032-8; discussion 1038-9.**

**OBJECTIVE:** Cisplatin-refractory germ cell tumors (GCTs) represent a subset of germinal neoplasms with a poor prognosis. Conventional-dose chemotherapy induces objective response in 10-20% of these patients with rare durable complete remissions. We investigated the activity and tolerance of a chemotherapeutic regimen with oxaliplatin and gemcitabine.

**PATIENTS AND METHODS:** Treatment consisted of oxaliplatin 130 mg/m<sup>2</sup> day 1, and gemcitabine 1,250 mg/m<sup>2</sup>, days 1 and 8, every three weeks.

**RESULTS:** Eighteen patients were enrolled and were assessable for response and toxicity. Primary site was testis in twelve cases, retroperitoneum in four, and mediastinum in two. Seven patients (39%) were cisplatin-refractory, while eleven (61%) absolutely cisplatin-refractory. A median of three cycles (range, 1-6) per patient were given. One patient achieved a clinical complete remission, one a partial remission with negative marker in whom complete surgical resection of residual masses yielded mature teratoma only, and one a partial remission with positive marker in whom complete surgical resection of residual masses yielded viable tumor cells. These three cases were characterized by testicular primary embryonal carcinoma. They remained disease-free at 44+, 20+, and 18+ months of follow-up.

**CONCLUSION:** The oxaliplatin-gemcitabine combination is a safe and active standard-dose regimen for patients with cisplatin-refractory testicular primary GCT.

**29. Wood DP Jr, Herr HW. Surgical resection of solitary metastases after chemotherapy in patients with nonseminomatous germ cell tumors and elevated serum tumor markers. Cancer. 1992 Nov 1;70(9):2354-7.**

**BACKGROUND.** Chemorefractory metastatic germ cell tumors and elevated tumor markers generally indicate inoperable disease.

**METHODS.** Solitary metastases were resected in 15 patients who had a nonseminomatous germ cell tumor and an elevated alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) serum level after treatment with cisplatin-based chemotherapy. Patients underwent resection for a residual mass after chemotherapy or for a new solitary metastasis after achieving a complete response (CR) to salvage chemotherapy.

**RESULTS.** Seven patients were disease-free after surgical resection alone. All five patients with an elevated HCG level had a relapse after surgery compared with 3 of 10 patients with only an elevated AFP level. Only 4 of 10 patients with a retroperitoneal metastasis had a relapse after surgery compared with 4 of 5 patients with visceral disease. Eleven of 15 patients overall were disease-free after surgery and subsequent chemotherapy after a relapse.

**CONCLUSIONS.** Surgical resection of a solitary metastasis despite elevated serum tumor markers should be considered in patients who have not had a durable CR to cisplatin-based chemotherapy.

## Penile Cancer: Management Guidelines

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### **Epidemiology:**

Penile cancer is an uncommon malignancy and constitutes approximately 1% of all malignancies in males in India. It is commonly seen in the 5<sup>th</sup> and 6<sup>th</sup> decade [1, 2, 3] with 19% patients less than 40 years of age [6] and 7% less than 30 years [2,5,6]. A high incidence of penile cancer has been recorded in Barshi and Chennai registries. High incidence is seen in north eastern districts of Tamil Nadu and especially Villupuram had an AAR of 3.1/100,000 [4].

Penile cancer is more common in a population associated with poor socioeconomic status, across the world. Consequently, a high incidence rate is also seen in underdeveloped countries such as Uganda (2.8/100,000) and in certain areas of Brazil (1.5-3.7 / 100,000), whereas the incidence in developed countries is decreasing and varies from 0.3-1.8/ 100,000. The lowest reported incidence rate is in Israeli Jew community, that of 0.1/100,000 [7] and is probably due to the religious practice of neonatal circumcision among the Jews. A



report from Sweden has documented familial association of penile cancer. The risk of cancer in any familial proband (sibling, mother, or father) is 7.54. [8]. [L E 4]

### **Risk factors:**

The risk factors causal to invasive carcinoma have been brought out in several case control studies. Phimosis and chronic irritative and inflammatory conditions as well as high risk oncogenic HPV 16 and 18 are commonly associated with penile cancer. There is strong evidence that HPV 16 and 18 are associated with penile cancer in more than 50% cases as well as with penile carcinoma in situ, basaloid and verrucous lesions ( LE 2A). Penile Lichen sclerosis, also called as Balanitis Xerotica obliterans (BXO) is associated with penile cancer, particularly those not related to HPV strains [9]. [LE 3] Balanoposthitis of glans is the other chronic disease seen, but it is detected more in diabetics.

Some studies suggest that circumcision done in the neonatal period decreased the risk of penile cancer [10, 11].

Phimosis is a known risk factor (OR =11.4%; 95% CI 5.0 – 25.9). The old time view that smegma is or contains a carcinogen has been debunked [12]. [LE 3]

Cigarette smoking is associated with a risk of 4.5 fold increase in the risk of penile cancer (95% CI 2.0 – 10.1). Tseng et al. found that the incidence of penile cancer (CIS and invasive combined) among men who had ever smoked cigarettes was 2.4 times that of men who had never smoked (95% CI = 0.86 – 7.3) [13]. The rate was higher among current smokers (OR = 3.1; 95% CI = 0.93 – 11) than among ex-smokers (OR = 1.6; 95% CI = 0.44 – 6.9), and it was appreciably higher for men who

currently smoked more than 20 cigarettes per day (OR = 5.9; 95% CI = 1.4 – 24) than among men who smoked fewer than 20 cigarettes per day (OR = 1.2; 95% CI = 0.33 – 4.1).Hellberg et al found that smoking had a significant effect on the occurrence of penile cancer even when the amount of smoking was not considered [14].

It has also been noted that the male partners of women with cervical intraepithelial neoplasia have a significantly higher incidence of penile intraepithelial neoplasia [15]. Early age at first intercourse and multiple sexual partners are associated with 3-5 fold increased risk. However there is no consistent association of penile cancer with presence of cervical cancer in the wife or partner. In a recent study done by Lont et al, the 5 year survival has been better in those penile cancers with high risk HPV DNA positive(78% versus 93%;log rank test p=0.03), indicating a survival advantage [16]. HPV strains interact with the genomes altering the balance of oncogenes versus the tumor suppressor genes (Rb and P 53). There is an increased risk of penile cancer in persons who suffer from condyloma acuminata [17].

### **Pre malignant conditions:**

Erythroplasia of Queyrat, Bowen's disease and Bowenoid papulosis are histologically the same and are actually "intraepithelial neoplasia" or "carcinoma in situ" and can progress towards higher stages of disease. Cutaneous horn of penis, hyperkeratotic dysplasia, giant condyloma (Bushke Lowenstein), pseudoepitheliomatous Micaceous and Keratotic Balanitis, leukoplakia and Balanitis Xerotica Obliterans are the other pre malignant lesions less sporadically associated with penile cancer [18, 19].

## **Pathology:**

Penile cancer essentially metastasizes by lymphatic embolisation to inguinal lymph nodes, with a stepwise spread to pelvic and para aortic nodes. Distant metastases are rare. The occurrence of lymph node metastasis is dependent upon depth of invasion, tumour grade, lymphovascular embolisation, corporal involvement, and the growth pattern. (LE 2a). Pelvic lymph node metastases are common with involvement of 2 or more inguinal nodes (LE 2b) and bilateral involvement is common. The vast majority (95%) of penile malignancies are squamous cell carcinomas. Malignant melanomas and basal cell carcinomas are less common. Mesenchymal tumours and metastatic tumours of penis are rare [20].

The pathological variants of squamous carcinoma include classic squamous carcinoma, verrucous (papillary, warty, mixed), sarcomatoid, basaloid and adenosquamous. Higher histological grade, deeper anatomical infiltration (lamina, corpus spongiosum, corpora cavernosa etc), and vascular and perineural invasion are common findings in sarcomatoid, basaloid and adenosquamous carcinoma cases, correlating with a higher rate of nodal metastasis and mortality. These features are unusual in verrucous, papillary and warty carcinoma cases [21]. High grade tumors (basaloid and sarcomatoid) tend to be significantly associated with recurrent tumors, whereas low grade variants (papillary, warty and verrucous) are usually non-recurrent. The incidence of inguinal lymph node metastasis is higher in recurrent tumors (79% vs. 49%,  $P=0.0272$ ) [20]. Histological grade, depth of tumor infiltration, and perineural invasion (PNI) are considered important pathologic prognostic parameters in penile cancer, for

development of lymph node metastasis as well as for survival.

A Prognostic Index combining these 3 factors has been devised [22]. The Prognostic Index score (ranging from 2 to 7) consisted in the addition of numerical values given to histologic grade (1 to 3), deepest anatomic level involved by cancer (1 to 3), and presence of PNI (0 or 1). On logistic regression analysis evaluating various pathologic factors, prognostic Index scores were found as the best predictors of inguinal node metastasis and patients' survival. Inguinal node dissections might not be necessary for patients with low indices (2 and 3). Nodal dissections might be formally indicated for high-grade indexes (5 to 7). Patients with index 4 should be individually assessed for nodal dissection. In a recent study, lymph node density proved to be a significantly better prognosticator of disease specific survival than the current TNM nodal staging system in patients with penile cancer and nodal involvement [23]. Further independent validation is required to determine the clinical usefulness of lymph node density.

Pathology report: The final pathology report of the primary carcinoma is based on information obtained from resected specimens and should contain the following information

- 1) Histological type and subtype;
- 2) Tumor site;
- 3) Size (in cm);
- 4) Pattern of growth;
- 5) Histological grade (1-3);
- 6) Anatomic levels of invasion;
- 7) Depth of invasion (in mm);

- 8) Vascular invasion;
- 9) Perineural invasion;
- 10) Margins of resection;
- 11) Associated precancerous lesions;
- 12) Other lesions associated (lichen sclerosus, dermatitides, etc).

## **Diagnosis:**

Correct histological diagnosis and staging are essential for appropriate treatment of penile cancer. [24].

**Primary tumour:** Physical examination should precede histological confirmation and is often sufficient for staging and planning therapy. Primary lesion needs to be described with respect to the site, size, morphology (papillary, flat, ulcerative or nodular), number, and invasion of corpora, invasion of urethra, etc and the extent of induration in shaft of penis. An adequate biopsy from the representative area to confirm histological diagnosis is mandatory before proceeding to treatment. MRI gives good resolution and interpretation of soft tissues and in combination with alprostadil induced artificial erection is helpful in gauging the depth of corporal invasion. However, it is rarely required and is expensive.

**Inguinal nodes:** Careful clinical examination of the inguinal lymph nodes is recommended. The note should be made of the size, number, laterality, consistency and fixity to skin and underlying tissues as well as presence of oedema of leg or scrotum.

- (a) In patients with non-palpable nodes, routine imaging or histological evaluation is not recommended. Inguinal ultrasound with a guided biopsy/ FNA if required has been recommended by some but the

evidence to its efficacy is lacking. Sentinel node biopsy has been reported to have false negative rates of about 25% and hence is not recommended [26]. Recently, dynamic sentinel node biopsy using isosulfan blue or 99m-Tc-colloid sulphur has been reported, with a sensitivity of 85-90% and specificity of 100%. This new procedure, although validated in a prospective study, has not been tested in randomized trials and hence is not incorporated in routine clinical practice [27, 28]. It is advisable to perform a surgical staging with prophylactic groin node dissection in presence of adverse prognostic factors [29].

- (b) In patients with palpable nodes, a note should be made of the size, number, laterality, consistency of the nodes and fixity to skin and/or underlying tissues, as well as presence of oedema of the lower extremity or scrotum. Approximately 50% of patients with palpable nodes at diagnosis will be negative for metastasis whereas almost 100% patients with such nodes at follow up will be positive [30] {LE2A}. Hence, it is recommended that regional nodes should be evaluated 4-6 weeks after treatment of the primary lesion and after a course of antibiotics.

Histological confirmation of malignancy in enlarged palpable nodes needs to be done with fine needle aspiration cytology or an appropriate biopsy procedure.

Distant metastases: Imaging techniques are used to detect the locoregional spread and the distant metastases. In patients with palpable or USG detected nodes a CECT abdomen and pelvis is done to find status of pelvic and retroperitoneal nodes. Although lung metastases are rare, an X ray chest is recommended. Bone scan should be considered only in symptomatic

patients. 18F-FDG PET/CT is of value in the penile cancer staging and its implementation might lead to an increase in diagnostic efficacy and hence to more precise and stage-appropriate therapeutic regimens [32] {LE 3b}.

Classification & Staging: The 2002 UICC Tumor, Node, and Metastasis (TNM) classification is as follows [33].

### **T - Primary tumour**

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Ta Non-invasive verrucous carcinoma

T1 Tumor invades subepithelial connective tissue

T2 Tumor invades corpus spongiosum or cavernosum

T3 Tumor invades urethra or prostate

T4 Tumor invades other adjacent structures

### **N - Regional lymph nodes**

NX Regional lymph nodes cannot be assessed

N0 No evidence of lymph node metastasis

N1 Metastasis in a single inguinal lymph node

N2 Metastasis in multiple or bilateral superficial lymph nodes

N3 Metastasis in deep inguinal or pelvic lymph nodes, unilateral or bilateral

### **M - Distant metastases**

MX Distant metastases cannot be assessed

M0 No evidence of distant metastases

M1 Distant metastases

The increasing stage corresponds with the overall cancer morbidity and mortality [35].

## **Treatment of primary:**

The modality of treating the primary site depends upon the T stage.

Penile intraepithelial neoplasia (Tis): Penis preserving strategies recommended (LE 3). This may be achieved by one of the following depending on the experience and personal preference of the treating clinician:

- \* Wide surgical excision
- \* Laser excision
- \* Moh's surgery
- \* Topical 5-fluorouracil cream
- \* Cryotherapy
- \* Photodynamic therapy
- \* Topical 5% imiquimod therapy

Ta G1-2 lesions may also be treated with these conservative techniques [36, 37, 38, 39, and 40].

A wide local excision with circumcision may be done for T1G1 tumors in the coronal sulcus and foreskin; tumor free margin required here is 3-4 mm [41] {LE 2a}. T1 lesions in glans can be treated with CO2 laser or glans resurfacing [42].

In patients with T1 G2-3, who are willing to follow on time, a penis preserving approach in the form of either laser excision with reconstruction or glansectomy [43] {LE 2A}. Glansectomy has the lowest recurrence rate of 2%. Other modalities such as external radiation therapy, interstitial brachytherapy, laser therapy and wide excision have comparable recurrences of around 15-25% [44]. In view of this, intraoperative careful pathological assessment of negative surgical margins is essential to reduce the local recurrence rate and a meticulous follow up is



recommended to detect local relapses early for successful salvage (LE 2b). In general, local relapse does not impact upon survival (LE 3). In patients who are unlikely to comply with regular follow up, partial penectomy is recommended.

Patients with local relapse after conservative surgery may be treated with repeat conservative surgery in cases of small, non-infiltrating relapse (LE 2b). However, a salvage partial or total penectomy is recommended if the relapse is large or deeply infiltrating.

In T1G3 or T2 lesions of glans either a partial or total glansectomy is done [45]{LE 2a}. In corporal T2 lesions, a partial amputation or a total penectomy should be done depending on the involvement of the shaft length [25]. Earlier a margin free of 2 cm was recommended but now a surgical margin of 5-10 mm is considered safe [46]. Partial penectomy is recommended when after adequate excision of the primary, the residual stump is adequate for upright micturition without scrotal soiling and for sexual intercourse.

In T3 lesions either a partial amputation or total penectomy is recommended.

Tumors infiltrating other organs generally have a poorer prognosis and may be treated with palliative care. A urethral neo meatal stenosis is seen in about 7-10 % of patients post surgery.

### **Treatment of Lymph nodes:**

Patients with non-palpable nodes need to be classified into various risk groups based on predictive and prognostic factors identified in uni- and multivariate analyses in numerous studies and also adopted by EAU in its guidelines in 2004 [47, 48].

1. Low risk patients: Tis, TaG1-2, T1G1: Risk of occult lymph node metastases low (<15%)
  - a. Surveillance strategy recommended
  - b. If patient unreliable for surveillance: prophylactic modified inguinal lymphadenectomy LE 2a
2. Intermediate risk patients: T1G2: Risk of occult lymph node metastases 30-35%
  - a. Absence of vascular or lymphatic invasion and superficial growth pattern: Surveillance
  - b. Presence of vascular or lymphatic invasion and /or infiltrative growth pattern: prophylactic modified inguinal lymphadenectomy
  - c. Uncompliant patient: prophylactic modified inguinal lymphadenectomy
  - d. Dynamic sentinel node biopsy may be most applicable in this category in the future, if found to be consistently reliable and may replace dependence on high risk features LE 2a
3. High risk patients: T2 or more and/or G3: Risk of occult lymph node metastases high (>60%)
  - a. Radical inguinal lymphadenectomy recommended
  - b. Prophylactic modified inguinal lymphadenectomy, with extension to complete lymphadenectomy if nodes positive on frozen section examination.
  - c. Improvement in this context was attempted by Ficarra et al, 2006 who formatted nomograms and by Kroon et al (2005) who applied the technique of dynamic sentinel node biopsy [49, 50].

In all categories, pelvic lymphadenectomy recommended as per criteria mentioned in the section on palpable nodes.

In patients with histologically proven positive inguinal lymph nodes, a complete bilateral radical inguinal and pelvic lymphadenectomy is highly effective and is strongly recommended (LE 2a).

The incidence of positive pelvic lymph-nodes in patients with inguinal disease ranges from 15-35%. The number of positive inguinal lymph nodes and extra capsular extent of metastatic disease are important pathological predictors of pelvic node involvement in patients with positive inguinal nodes [51] {LE2a}. The rate of pelvic node positivity in 2 and > 2 inguinal node positive patients is 23% and 56%. The latter is also associated with one or more inguinal node with extra capsular extension [52]. Pelvic lymphadenectomy is recommended when the risk of pelvic lymph node involvement is high (2 or more positive nodes, extranodal extension, grade III tumours etc.) The pelvic lymph node metastases are often microscopic and pelvic lymphadenectomy in such cases may lead to cure in 14-50% of patients (LE 2b). If there is no involvement of inguinal nodes, pelvic lymphadenectomy is not warranted.

If there are no palpable nodes in the contralateral groin, modified inguinal lymphadenectomy may be considered and may be extended to a complete lymphadenectomy if the nodes are metastatic on frozen section examination.

Video endoscopic inguinal and pelvic lymph node dissection (VEIL) has been described. However the reliability of this technique has yet to be established. [53]{LE 4}.

Inguinal lymphadenectomy is associated with significant morbidity which includes lymphorrhoea, wound infection, skin necrosis, wound dehiscence, lymphoedema and lymphocele in approximately 30% of patients. Good skin handling and proper skin flaps is the secret to prevent or reduce the above. Rotation and pedicle based flaps should be used as a primary cover in appropriate cases.

Inguinopelvic lymphadenectomy may be done at the time of surgery for the primary tumour or as an interval procedure 2-3 weeks after surgery for the primary. There is no difference in the oncological outcome as well as morbidity with the 2 approaches.

Adjuvant chemotherapy – taxane based is recommended in patients with pN2-3 patients, those with 2 or more positive nodes and in those with extranodal extension of disease.[54] {LE2a}. The results of phase II trials suggest that adjuvant chemotherapy is beneficial in these patients. Very little data is available for use and efficacy of adjuvant radiation therapy (LE 3).

In patients with relapsed groin nodes wide excision of the nodal area should be done.

Patients with fixed inguinal node mass or clinically palpable pelvic nodes may be offered neoadjuvant chemotherapy and in case of good response (25-60% partial or complete responses), complete radical surgery is recommended (LE 2b). Pre-operative radiation therapy may also be tried instead of chemotherapy (LE 3) – however, the morbidity of lymphadenectomy after radiation therapy is substantial.

### **Role of Radiation therapy:**

External beam radiotherapy (EBRT) and Brachytherapy (BRT) are both used in the primary treatment of T1-2

penile cancers <4 cm in size. They can be used separately or together. EBRT is delivered by megavoltage telecobalt gamma rays or 6MV photons from Linear accelerators. The different types of BRT used are external isotope mould, low dose rate BRT, pulse dose rate BRT or high dose BRT [55]. The type of radiotherapy best suited for a patient depends upon the tumor location, size, thickness and its proximity to the urethra. In well selected patients with T1-2 tumors, (lesser than 4 cm) organ preservation can be achieved with primary tumor RT {LE 2A}. But there are no prospective or randomized trials within the radiation modalities. EBRT has universal applicability and can be used in all RT departments, whereas BRT needs expertise. A variety of fractionation schedules have been described in the literature with variable results. At the Tata Memorial Hospital we traditionally use a hypo fractionated accelerated regimen of 54Gy in 18 daily fractions over 3 weeks. This provides excellent local control in early cancers without any symptomatic late sequelae. However, the acute radiation muco-cutaneous reaction over the glans and penile shaft heals after a median period of 6 weeks. The main advantage of the accelerated 3-4 weeks regimen over the more protracted 6 weeks regimen is that it allows the completion of radiotherapy before the onset of the inevitable brisk radiation reaction.

The local control rates reported for EBRT and BRT are 60% and 70 to 90% respectively.[56,57,58]. The radiated patients have higher local failure rates, but salvage surgery can regain local control [59]. Certain iatrogenic complications are attributed to the high doses of radiation needed to achieve local control. These include glans necrosis (10-20%), urethral stenosis (20-35%) and late fibrosis and can lead to loss of function [60]. The actuarial

penile preservation rate after BRT was 87% at 5 years [60]. All these patients need a close follow up as some radiation related changes are difficult to be differentiated from recurrence. In metastatic disease, palliative local EBRT (40-50GY) has been described.

There is no role of prophylactic RT in clinically N0 patients of penile cancer as RT fails to prevent metastatic lymph nodes [61], there are related severe complications [62] and further even the fibrotic change makes the follow up difficult.

Adjuvant radiation therapy may improve local control in patients with extensive nodal metastases and /or extra nodal spread, but severe side effects may occur.

### **Role of Chemotherapy:**

In spite of improvement in awareness leading to early diagnosis, patients present with unresectable disease in the form of local disease extension and/or fixed ilio-inguinal nodes encasing vessels. These patients have a dismal prognosis, with an estimated 3-years survival of less than 10% [63,64]. Neoadjuvant chemotherapy can help achieve downsizing of initially inoperable lymph node masses and primary lesions, to make them suitable for surgery. Many chemotherapeutic agents have been used over the years. Some of those found effective having a best response rate of 20% [64] are 5-FU, methotrexate, ifosfamide, cisplatin, paclitaxel and docetaxel. A better response is seen with combination agents, ranging from 25 to 72% with a complete response of 17% [64]. Until this era of combination therapy, cisplatin (CDDP) and 5 FU have represented the standard therapy for this disease. A combination of taxanes with CDDP and 5 FU has been used as this has demonstrated a benefit in squamous cancers in the head and neck region [65].

Corral et al have reported promising results with BMP (Bleomycin, Methotrexate, Cisplatin), with median survival of 34 months in responders [66]. In patients with multiple, bilateral or unilateral pelvic nodes or those with extranodal spread, adjuvant chemotherapy with 3 drugs is recommended. Patients chosen for chemotherapy have to be assessed well as in most instances they will be elderly patients.

Patients with juxtaregional lymph node metastases or those with distant metastases may be offered palliative chemotherapy.

### **Follow up:**

In penile cancer, follow up helps to assess the results of surgery, complications associated with it, and note early or late, local and loco-regional recurrences. If we can detect recurrence early, the chances of cure are greater. It also helps patients treated with penile conservation techniques with an opportunity to discuss their sexual problems. In follow up, patients are evaluated with a thorough physical examination, appropriate imaging of abdomen and pelvis in selected patients, and X-ray chest. The need for any other investigation is dictated by symptoms or the results of these primary tests. Leitje et al (2008) found that 74.3% of all recurrences, 66.4% of local recurrences, 86.1% of regional recurrences and 100% of distant recurrences occur during the first 2 years and that 92.2% of all recurrences occurred in the first 5 years [67]. Oncologists should keep in mind that patients require an intensive follow up for first 2 years; every 3 months and a less intensive follow up from 3-5 years; at every 6 months. Kroon et al (2005), also documented occurrence of late local recurrences but found it reasonable to stop the follow up at 5 years, provided patient would report back if needed later [68].

Management of local relapse: Local recurrences are more seen in patients with penile preserving therapies. However, they do not impact upon survival. They may be treated with re-penile preserving surgery if feasible or with salvage partial or total penectomy in other cases. Patients should be taught and encouraged to do penile self examination.

Management of inguinal nodal relapse in the follow up period: It is mandatory to get histological confirmation of metastasis in the palpable inguinal node by fine needle aspiration cytology or by an appropriate biopsy procedure.

In patients with short relapse free interval, a complete bilateral inguinopelvic lymphadenectomy is recommended, as the risk of occult metastases in contralateral groin is significant.

In patients with long (>2 years) relapse free interval, a unilateral lymphadenectomy on the involved side is recommended and the contralateral side may be kept under surveillance since in these patients, the risk of occult contralateral node metastasis is only about 10%. However, if the involved side has more than 1 metastatic node or there is evidence of extranodal extension, a modified prophylactic groin dissection should be done on the contralateral side, since the risk of occult metastases on the contralateral side is approximately 30%.

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## Carcinoma Prostate

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**Introduction and Epidemiology:** The prostate cancer is the most common male malignancy. One in six American men will be diagnosed with prostate cancer during his lifetime, usually at the age of over 60 years. In Europe, the annual incidence rates were 214 per 1000 men in 2005. The established risk factors include race, age, and family history. About 15% of male cancers are prostate cancers in developed countries compared to 4% of male cancers in developing countries. At the Tata Memorial Hospital, prostate cancer constitutes only 2.4% of all cancers in males.

There are three well-established risk factors: increasing age, ethnical origin and heredity. If one first-line relative has prostate cancer, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases 5- to 11-fold. Patients with hereditary prostate cancer usually have an onset 6-7 years prior to spontaneous cases, but do not differ in other ways. Factors such as food consumption like saturated/animal fat, red meat, pattern of sexual behavior, alcohol consumption,

exposure to ultraviolet radiation and occupational exposure have all been discussed as being of etiological importance.

**Staging of prostate cancer:** TNM 2002 Staging (*AJCC Cancer Staging Manual. 6<sup>th</sup>ed. New York, NY: Springer, 2002, 309-316*)

The primary extension assessment of prostate cancer is usually made by digital rectal examination (DRE), prostate-specific antigen (PSA) measurement and bone scan, supplemented with computed tomography (CT) or magnetic resonance imaging (MRI) and chest X-ray in specific situations.

### **Primary Tumor (T)**

- Tx Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Clinically in-apparent tumor not palpable nor visible by imaging
  - T1a Tumor incidental histologic finding in <5% of tissue resected
  - T1b Tumor incidental histologic finding in >5% of tissue resected
  - T1c Tumor identified by needle biopsy (because of elevated PSA)
- T2 Tumor confined within prostate\*
  - T2a involves one half of 1 lobe or less
  - T2b Tumor involves more than one half of 1 lobe but not both lobes
  - T2c Tumor involves both lobes
- T3 extends through the prostate capsule\*\*
  - T3a Extracapsular extension (unilateral or bilateral)
  - T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

### **Regional lymph nodes (N)<sup>\$</sup>**

Nx Regional lymph nodes were not assessed

No No regional lymph node metastasis

N1 Metastasis in regional lymph node (s)

### **Distant Metastasis (M)**

Mx Distant metastasis cannot be assessed (not evaluated by any modality)

Mo No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s) with or without bone disease

*\* Tumor found in 1 or both lobes by needle biopsy, but not palpable or reliably visible by imaging is classified as T1c.*

*\*\* Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.*

*\$ Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups (laterality does not affect the N classification): pelvic (not otherwise specified [NOS]), hypogastric, obturator, iliac (i.e., internal, external, or NOS), and sacral (lateral, presacral, promontory [e.g., Gerota], or NOS). Distant lymph nodes are outside the confines of the true pelvis.*

### **Histopathologic grade (G)**

- GX: Grade cannot be assessed
- G1: Well differentiated (slight anaplasia) (GS of 2–4)

- G2: Moderately differentiated (moderate anaplasia) (GS of 5–6)
- G3-4: Poorly differentiated or undifferentiated (marked anaplasia) (GS of 7–10)

**Histology:** More than 95% of primary prostate cancers are adenocarcinomas and remaining 5% constitutes of other histologies like transitional cell carcinoma, sarcoma, lymphoma etc.

### **Diagnosis and staging methods:**

The main diagnostic tools used to look for evidence of prostate cancer include DRE, serum concentration of PSA and trans-rectal ultrasonography (TRUS) apart from getting a histological confirmation of prostate cancer. The local stage of the disease (organ confined vs. non-organ confined) is the most important factor which decides therapy as well as prognosis.

1. **Digital Rectal Examination (DRE):** It is a simple and cost effective method having a positive predictive value (from 21% to 53%). It is a good staging method with a sensitivity of 52% and specificity of 80%. It can, however, underestimate (common) or overestimate the actual pathological stage. [1] (*level of evidence: 2a*)
2. **Prostate Specific Antigen (PSA):** The normal values of PSA are <4 ng/ml. The appropriate threshold PSA level for detection of cancer of the prostate is 4.0 ng/ml. As yet, there is no long-term data to help determine the optimal PSA threshold value for detecting non-palpable, but clinically significant, Prostate Cancer (*level of evidence: 3*). Clinically significant cancers are detected by PSA testing. If the PSA level is high, biopsy of the

prostate may be recommended. Some men with prostate cancer have PSA results less than 10. About 25% of men with cancer will have a normal or low PSA. Therefore a combination of PSA & DRE as complementary investigations to guide biopsy is recommended. **(level of evidence 3, Grade B Recommendation)**

PSA estimation can also help as a guide to stage of prostate cancer. Serum PSA <10 ng/ml indicates a low risk of peri-prostatic spread and metastases. An increased risk of peri-prostatic spread, seminal vesicle involvement and even distant metastases exists when serum PSA >20 ng/ml. As a general guide, PSA >10 ng/ml indicates capsular penetration in more than 50% patients while PSA >50 ng/ml is usually associated with metastatic disease.

PSA is prostate specific and not cancer specific and may be raised in non-cancerous conditions like BPH, prostatitis, tuberculosis etc, especially when the PSA is in the normal or borderline zone of 4-10 ng/ml. A ratio of free to total PSA of <0.1 is most likely associated with prostate cancer, and with higher percentages with benign prostatic hypertrophy [2] **(level of evidence: 2a)**. A ratio of < 0.15 was associated with a higher Gleason score and poorer prognosis PSA density is calculated by dividing the serum PSA concentration by the volume of the prostate gland measured by TRUS. A higher PSA density is associated with malignancy.

3. **Trans-rectal Ultrasound (TRUS)** gives excellent resolution for detection of prostatic nodules. It gives

about 60% sensitivity for differentiation between organ confined disease and extraprostatic extension. In the absence of MRI, it can be used for local staging of prostate cancer. TRUS is useful in performing tissue biopsies, prostate volume assessment, PSA density calculation and in prostate brachytherapy. Limitations of this imaging modality include the difficulty in characterizing the integrity of prostatic capsule and visualizing early extracapsular extension or seminal vesicle involvement. (**Grade C recommendation**)

4. **Computed Tomography** is done mainly to document the retroperitoneal or pelvic lymphadenopathy, especially in patients with high risk of nodal metastasis i. e. T3, T4 disease, PSA > 20 ng/ml, high Gleason score etc and may identify advanced disease. Routine preoperative CT scanning may not always be justified in patients with a PSA <25 ng/mL. Although the histologic incidence of positive pelvic lymph nodes is substantial when PSA levels exceed 25 ng/mL, however the sensitivity of CT for detecting positive nodes is only approximately 30% to 35% even at these levels.
5. **MR Imaging** currently offers the most accurate and complete assessment of local disease and its spread. MRI with endo-rectal coil and MR spectroscopy (higher choline-citrate ratio) can give an excellent delineation of the prostate gland. It has a reported accuracy of 85-90% for differentiating between organ-confined disease and extraprostatic spread. It gives excellent information about seminal vesicles involvement and retroperitoneal

lymphadenopathy. MRI is clearly superior to CT in defining the prostate apex, neurovascular bundles, and anterior rectal wall. Comparing prostate volumes defined by MRI and CT there is 32% increase in prostate volume when defined by non-contrast CT scan.

When compared with DRE and TRUS prostate biopsy findings, endo-rectal MRI contributes significant incremental value for local staging [3], particularly in the pre-operative identification of extra capsular extension (ECE) and seminal vesicle invasion (SVI). MR spectroscopic imaging (MRSI) allows for the assessment of tumor metabolism by displaying the relative concentrations of citrate, choline, creatinine and polyamines. Differences in the concentrations of these chemical metabolites between normal and malignant prostate tissues allow for better tumor localization within the peripheral zone, increasing the accuracy of ECE detection. Furthermore, correlations have been demonstrated between the metabolic signal pattern and a pathological Gleason score, suggesting the potential for a non-invasive assessment of aggressiveness [4]. **(Grade C recommendation)**

6. **Isotope Bone Scan:** The present evidence suggests that it may not be mandatory to perform an isotope bone scan if the PSA is less than 20 ng/ml and there is absence of bone pain, since the positive yield in such cases is extremely low (1%). **(Grade B recommendations)**
7. **Prostatic biopsy:** Trans-rectal ultrasonography (TRUS) guided biopsy of the prostate is the most widely accepted method to diagnose prostate



cancer. The indications for prostate biopsy include an abnormal digital rectal examination (DRE) or serum prostate specific antigen (PSA) level. Sextant biopsy is no longer considered adequate. At a glandular volume of 30-40 mL, at least eight cores should be sampled. More than 12 cores are not significantly more conclusive [5] (**level of evidence: 1a**). Seminal Vesicle and transition zone biopsies are not routinely recommended, as the yield is low and moreover, it does not add significantly to the combination of clinical staging, PSA and Gleason score. A minimum of 10 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volumes. (**Grade B recommendation**)

## Pathology:

Histological diagnosis of prostate cancer is mandatory before starting therapy, even if there is overriding evidence of advanced carcinoma of the prostate.

- Targeted, sextant or extended biopsies may be done, usually by the trans-rectal route and the biopsies should be separately labeled and sent to the pathologist.
- The biopsy specimens should be reported as per the published standard reporting guidelines for reporting prostatic specimens.
- Extensive sampling of all biopsy cores or TUR chips will yield a higher proportion of unsuspected cancers than restricted sampling.
- Before processing, record the number of cores per vial and length of each core. There is a significant correlation between the length of prostate biopsy

tissue on the histological slide and the detection rate of [6].

- The number of cores involved by tumor and the percentage of each core involved may influence treatment and should be carefully recorded.
- Gleason Score: Five distinct patterns of growth from well to poorly differentiated has been described in the original Gleason scale [7]. Pattern 1 tumors are the most differentiated, with discrete glandular formation, whereas pattern 5 lesions are the most undifferentiated, with loss of the glandular architecture. The final Gleason score is the sum of the grades of the most common, and second most common growth patterns; the Gleason score can range from 2 (1 + 1) to 10 (5 + 5). Among patients with Gleason score 7, primary Gleason grade 4 indicates a likelihood of higher tumor stage and higher probability of PSA recurrence than does primary pattern 3. Some investigators have advocated that the percentage of Gleason 4/5 tumor be reported more precisely as the percentage of high grade is not adequately described by conventional Gleason sums [8]. Where more than two patterns are present, and the worst grade is neither the predominant nor the secondary grade, the predominant and highest grade should be chosen to arrive at a score (e.g, 60%, grade 3; 35%, grade 4; 5%, grade 5 is scored as 3+ 5 = 8).

## **Histopathology of radical prostatectomy Specimen:**

The histo-pathological examination of radical prostatectomy (RP) specimens aims to provide

information about the actual pathological stage, grade and surgical margin status of the prostate cancer. The weight and dimensions of the specimen are recorded before embedding it for histological processing. It is generally recommended that RP specimens are totally embedded to enable the best assessment of location, multifocality and heterogeneity of the cancer. However, for cost-efficiency purposes, partial embedding using a standard method may also be considered, particularly for large-sized prostates (> 60 g).

The pathology report provides essential information on the prognostic characteristics relevant for making clinical decisions. The report should include:

- typing (> 95% represent conventional (acinic) adenocarcinomas)
  - grading according to the Gleason score and presence of HG PIN
  - (sub) staging and surgical margin status of the tumour
  - if appropriate, location and extent of extra-prostatic extension, sidedness of extra-prostatic extension or seminal vesicle invasion, location and extent of positive surgical margins
  - additional information may be provided on multifocality, diameter of the dominant tumor and the zonal location (transition zone, peripheral zone, anterior horn) of the dominant tumor.
  - Regional lymph nodes
8. ***Pelvic lymph node dissection:*** This remains the most accurate method of assessing nodal metastasis. However, patients with low risk disease (PSA < 10ng/ml, Gleason's score < 7 and stage

T1c disease) have less than 5% chance of having positive lymph nodes. As such, only high-risk patients with stage T3c, PSA>20ng/dl or Gleason>8 or node-positive disease should be recommended for pelvic lymph nodes dissection before definitive treatment for localized prostate cancer. Based on pathologic findings in prostatectomy specimens, the probability of lymph node involvement can be estimated by Roach's formula i.e  $\text{Nodes+} = \frac{2}{3} \text{PSA} + (\text{Gleason score} - 6) \times 10$ , If more than 15% than pelvic irradiation for nodes or laparoscopic pelvic node dissection is warranted (**level of evidence: 1b**). When deciding on pelvic lymph node dissection, extended lymphadenectomy should be considered, despite its disadvantages: it requires surgical experience; it is time-consuming; and it often leads to more complications than the limited procedures [9].

9. **PET scan:** PET scanning is being increasingly used to detect recurrences post treatment. Methionine PET of the prostate with short dynamic scanning and multicore biopsy is a useful method to ensure a high detection rate of prostate cancer in patients with increased PSA and repeat negative biopsies. [10]

## **Treatment Guidelines:**

### **Management of high grade prostatic intraepithelial neoplasia (PIN)**

The presence of high grade PIN on biopsy is in itself not an indication for treatment but requires careful follow-up and early re-biopsy to rule out invasive cancer. With the increase in prostatic biopsies in recent years, the presence of PIN is being more frequently reported. Although high grade PIN indicates a higher predisposition to the development of invasive cancer, the natural history of PIN is uncertain and hence the evidence at the present time does not warrant early treatment of high grade PIN.

### **Management of invasive prostatic adenocarcinoma**

After initial work-up of DRE, S. PSA, TRUS and biopsy with GS score, invasive prostate carcinoma depending on the recurrence risk has been divided into:

- 1) Localized prostate cancer (T1 – T3a N0)**
  - Low risk (cT1-T2a and Gleason score 2-6 and PSA < 10)
  - Intermediate risk (cT2b-T2c or Gleason score = 7 or PSA 10-20)
  - High Risk (cT3a or Gleason score 8-10 or PSA > 20)
- 2) Locally advanced disease (T3b-T4 N0)**
- 3) Metastatic disease: Any T, N+ or Any T, Any N & distant metastasis (M+)**

## 1) Treatment of localized prostate cancer (T1 – T3a N0):

Depending on the risk the options include

- Active Surveillance
- Radical prostatectomy +/-Pelvic lymph node dissection +/-Adj RT / HT
- Radical radiotherapy in the form of either
  - \* External beam: 3D Conformal / IMRT or
  - \* Brachytherapy Permanent seeds or HDR Interstitial

All patients considered fit for radical therapy must be counseled regarding the above options. The choice of treatment should be made on the basis of clinical efficacy (there is no evidence of superiority of one modality over the other), biological behaviour, morbidity of treatment, age and life expectancy of the patient and finally patient's own perceptions and choice.

**Active Surveillance (AS)** assumes that the risk posed by a given cancer can be assessed with some degree of certainty and that delayed treatment will be as curative as immediate treatment. With active surveillance, we attempt to avoid over-treatment in the majority of patients, but also to administer curative therapy to selected cases. AS is beneficial in patients with low-volume, low-grade prostatic carcinoma and elderly patients or medical comorbidities with limited life expectancy and comply for regular follow up. Most series have shown a 80-90% 10-year survival rates after excluding deaths from inter-current diseases (*level of evidence: 2a*). Follow-up assessment includes 6 monthly consultations with routine DRE and serum PSA with repeat imaging and biopsy 12 to 18 months after the baseline evaluation, then every 2

to 3 years. The goal is to detect progression of the cancer while cure is still possible. Prostatic biopsy and bone scans may be done as indicated. In patients with low grade tumors selected for surveillance, the rate of development of metastases during surveillance is 2.1%/year as opposed to 14% with high grade tumors [11]. Only data from non-mature randomized clinical trials of AS with follow-up < 10 years are currently available. A multicentre clinical trial of AS versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025.

**Radical prostatectomy (RP)** : RP which involves removal of the entire prostate gland between the urethra and the bladder, with resection of both seminal vesicles is recommended at most centres for the management of organ confined prostate cancer in men with life expectancy of >10 years. Besides being curative due to complete removal of cancer, it gives a more accurate pathological staging and allows better planning for adjuvant therapy. Currently, radical prostatectomy is the only treatment for localized disease that has shown a cancer-specific survival benefit when compared with conservative management in a prospective, randomized trial [12]. The retropubic approach is more commonly performed, as it enables simultaneous pelvic lymph node assessment to be carried out which is an advantage over the perineal approach.

In the past 5-10 years, several centres have acquired considerable experience with laparoscopic radical prostatectomy. More recently, the robotic-assisted laparoscopic RP has been developed. It is likely that laparoscopic, robot-assisted and perineal prostatectomies have lower morbidity than the retropubic

operation, but randomized studies are as yet unavailable. Functional and short-term oncological outcomes of laparoscopic and robot-assisted RP with the open technique in high-volume centres seem comparable. However, long-term oncological outcomes are still unavailable [13].

Although the risk of disease progression of untreated T1a Prostate Cancer after five years is only 5%, these cancers can progress in about 50% of cases after 10-13 years [14]. Thus, in younger patients with a life-expectancy of 15 years or more, the chance of disease progression is real. An RP may be offered when the Gleason score is > 6. In contrast, most patients with T1b tumours are expected to show disease progression after five years, and aggressive treatment is often warranted [14]. Patients with T1b lesions are offered RP when they have a life expectancy of 10 years or more. For patients with T1c tumours, RP should be advocated, bearing in mind that significant tumors will be found in most of these individuals. T2a patients with a 10-year life expectancy should be offered RP since 35-55% of them will have disease progression after five years if not treated. An extended pelvic lymph node dissection is not necessary in low-risk, localized Prostate Cancer, as the risk for positive lymph nodes does not exceed 7% [15].

RP is one of the recommended standard treatments for patients with intermediate-risk Prostate Cancer and a life expectancy of more than 10 years. The prognosis is excellent when the tumor is confined to the prostate based on pathological examination. As a rule of thumb, an elective pelvic lymph nodal dissection should be performed if the estimated risk for positive lymph nodes exceeds 7% [15] (*level of evidence 1b*).



There is no consensus regarding the optimal treatment of men with high-risk localized disease. Surgical treatment of clinical stage T3 has traditionally been discouraged, mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse [16]. RP for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable (**level of evidence: 3**). Increased overall surgical experience must contribute to a decreased operative morbidity and to better functional results after RP for clinical T3 cancer [17]. An elective pelvic lymph nodal dissection should be performed in all high-risk cases, as the estimated risk for positive lymph nodes will be in the range 15-40% [15].

In cases of positive lymph nodes at final histopathology, adjuvant ADT may be considered. Messing et al. examined the role of immediate ADT Vs observation in patients with positive lymph nodes found at initial surgery. At a median follow-up of 11.9 years, those receiving immediate ADT had a significant improvement in OS over those managed with observation [18].

*Neo-adjuvant HT followed by RP:* As prostate cancer is an androgen-dependent tumor, neo-adjuvant hormonal therapy (NHT) is an appealing concept. Following is the summary of the findings from Cochrane review [19] (**level of evidence: 1a**)

- Neo-adjuvant hormonal therapy before RP does not provide a significant OS advantage over prostatectomy alone.
- Neo-adjuvant hormonal therapy before RP does not provide a significant advantage in disease-free survival over prostatectomy alone.

- Neo-adjuvant hormonal therapy before RP does substantially improve local pathological variables such as organ-confined rates, pathological down-staging, positive surgical margins and rate of lymph node involvement.
- Adjuvant hormonal therapy following RP shows no survival advantage at 10 years.

**Complications of RP:** The mortality rate is 0-1.5%; urinary fistulas are seen in 1.2-4% of patients; and urinary incontinence persists after one year in 7.7%. In men undergoing prostatectomy, the rates of post-operative and late urinary complications are significantly reduced if the procedure is performed in a high-volume hospital and by a surgeon who performs a large number of such procedures. Erectile dysfunction used to occur in nearly all patients, but nerve-sparing techniques can be applied in early-stage disease [20]. Patients who benefit from nerve-sparing RP may have a higher chance of local disease recurrence and should therefore be selected carefully. [21]

**Radical Radiotherapy (RT):** There are no randomized studies comparing radical prostatectomy with either external beam therapy or brachytherapy for localized prostate cancer, but the National Institutes of Health (NIH) consensus set up in 1988 remains available: external irradiation offers the same long-term survival results as surgery; moreover, external irradiation provides a quality of life at least as good as that provided by surgery. Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard and, at the beginning of the third millennium, intensity modulated radiotherapy (IMRT), an optimized form of 3D-CRT, is gradually gaining ground in centres of excellence. [22] (*level of evidence : 2*) In addition to

external irradiation, there has been continued and growing interest in trans-perineal low dose or high dose brachytherapy.

Whatever the technique, the choice of treatment after the appropriate assessment of tumor extension must be based on a multidisciplinary approach taking account of:

- Tumor Node Metastasis (TNM-2002) classification
- Gleason score defined on a sufficient number of core biopsies (at least 12)
- Baseline prostate-specific antigen (PSA)
- Age of the patient
- Co-morbidities, life expectancy and quality of life

For patients with low risk localized disease retrospective, non-randomized studies have shown that biochemical disease-free survival is significantly higher with a radiation dose  $> 72$  Gy compared with  $< 72$  Gy ( $p = 0.04$ ). Also, two randomized trials focusing on clinical stages T1-3 N0 M0 paved the way for dose escalation:

- The MD Anderson study compared 78 Gy with 70 Gy conventional radiotherapy (n =305 T1-3 pts & pre-treatment PSA level of more than 10 ng/mL. With a median follow-up of 8.7 years, showed a significant increase in freedom from biochemical and/or clinical failure for low-risk patients ( $p = 0.04$ ) [23].
- The PROG 95-09 evaluated 393 T1b-T2b patients, of whom 75% had a Gleason score  $< 6$  and a PSA  $< 15$  ng/mL. Patients were randomized to receive an initial boost to the prostate alone, using conformal protons of either 19.8 Gy or 28.8 Gy, and

then 50.4 Gy to a larger volume. With a median follow-up of 5.5 years, there was a significant increase in five-year freedom from biochemical failure ( $p < 0.001$ ) in favour of low-risk patients, who were given a higher dose (79.2 Gy), compared with those receiving a conventional dose (70.2 Gy) [24].

Hence in daily practice, a minimum dose of 70 - 74 Gy is recommended for low risk group (external with / without brachytherapy). (**level of evidence : 2**)

For intermediate risk localized disease, many non-randomized studies have shown dose escalation to have a significant impact on five-year survival without biochemical relapse for patients classified as  $cT_1 - cT_3$ , with a dose ranging from 76-81 Gy. Randomized trials (Dutch : 68 Gy Vs 78 Gy) showed a significant increase in five-year freedom from clinical or biochemical failure for patients in an intermediate-risk group [25] and French study (70 Gy Vs 80 Gy) has shown a better five-year biological outcome in intermediate-risk patients so far.[26]

Hence in daily practice, a minimum dose of 74 - 76 Gy is recommended for Int risk group (external with / without brachytherapy). (**level of evidence : 2**)

For high risk group, external irradiation with dose escalation is mandatory since it improves the five-year biochemical disease-free survival, as shown in several phase III randomized trials namely, Dutch study (68 Gy Vs 78 Gy) [25], MRC study (64 Gy Vs 74 Gy with neo-adjuvant HT) [27], PROG 95-09 study (79.2 Gy Vs 70.2 Gy) [24], and MD Anderson study [23]. EORTC trial 22991, comparing 3D-CRT +/- IMRT with a choice of three levels of dose (70 Gy, 74 Gy and 78 Gy), with or

without six months of neo-adjuvant and concomitant hormonal therapy, was closed in April 2008 after recruiting 800 patients, and its results are awaited [28].

In daily practice, a combination of external irradiation with short-term androgen deprivation is recommended, based on the results of a phase III randomized trial. This trial, which included 206 patients with a PSA of at least 10 ng/mL (maximum 40 ng/mL), a Gleason score of at least 7 (range 5-10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with six months of ADT. After a median follow-up of 7.6 years, intermediate- or high-risk patients without moderate or severe co-morbidity randomized to receive 3D-CRT plus ADT had a 13% improvement in overall survival rate ( $p < 0.001$ ) [29]. **(level of evidence : 1b)**

Further, meta-analysis of data obtained exclusively from RCT's provides evidence that high dose RT is superior to conventional dose RT in terms of preventing biochemical failure in low-, intermediate-, and high-risk prostate cancer patients, high dose RT should be offered to all patients regardless of their risk status. Between the doses of 70 and 80 Gy, there was a significant increase in the 5-year Biochemical control rate of 14%, 17.8%, and 19.2% in low-, intermediate, and high-risk patients, respectively. [30, 31] **(Level of evidence :1a Grade A recommendation)**

Hence in daily practice, a minimum dose of 74 - 80 Gy is recommended for high risk group with a component of newer highly conformal radiation techniques (external with / without brachytherapy). **(level of evidence : 1a)**

*Prophylactic irradiation of pelvic lymph nodes in high-risk localized prostate cancer*

Invasion of the pelvic lymph nodes is a poor prognostic factor and mandates systemic medical treatment because radiotherapy alone is insufficient. Prophylactic whole pelvis irradiation has been abandoned since randomized trials failed to show that patients benefited from prophylactic irradiation of the pelvic lymph nodes in high-risk cases (46-50 Gy) [32 – 36]. Studies demonstrated that patients with a risk of LN involvement of 15% to 35% benefited the most from pelvic nodal RT, whereas those with a risk of less than 15% or more than 35% (higher distant metastasis) did not benefit from pelvic nodal RT [37] (*level of evidence 2b ; Grade B recommendations*).

**Interstitial brachytherapy:** Tumors, which can be completely encompassed by the implant high-dose volume may be treated with brachytherapy alone. Ideal patients for permanent interstitial implantation as monotherapy are those with favorable risk prognostic features who have a high likelihood of organ-confined disease. This group includes those with PSA levels 10 ng/mL or less, Gleason scores less than 6-7, and clinical stages T1b- T2a, and prostate volume of < 50 cm<sup>3</sup> and good International Prostatic Symptom Score (IPSS) [38]. It is not recommended for patients with locally advanced disease. (*level of evidence : 2b*)

Combination of brachytherapy and EBRT is generally considered a more suitable treatment option than implantation alone for patients with intermediate and high-risk patients with localized prostate cancer. Usually ultrasound guided implantation with <sup>125</sup>I seeds or <sup>103</sup>Pd implants is done. In general, 45 to 50 Gy of EBRT is delivered using conventional or conformal-based techniques to the prostate and peri-prostatic tissues. If a low-dose-rate boost is used, the brachytherapy

prescription dose has been 90-100 Gy for  $^{103}\text{Pd}$  implants and 110 Gy for  $^{125}\text{I}$  implants. For HDR brachytherapy approach patients undergo trans-perineal placement of after-loading catheters in the prostate under ultrasound guidance. After CT-based treatment planning, several high-dose fractions, ranging from 4 to 6 Gy each, are administered during an interval of 24 to 36 hours using  $^{192}\text{Ir}$ . This treatment is followed by supplemental EBRT directed to the prostate and peri-prostatic tissues to a dose of 45 to 50.4 Gy using conventional fractionation. Advantage with HDR being the radiation oncologist and physicist can more easily optimize the delivery of RT to the prostate, reducing the potential for under-dosage, reduces radiation exposure to the radiation oncologist and others involved in the procedure compared with permanent interstitial implantation, radiobiologically more efficacious in terms of tumor cell kill for patients with increased tumor bulk or adverse prognostic features compared with low-dose-rate boosts such as  $^{125}\text{I}$  or  $^{103}\text{Pd}$ . Results of permanent implants have been reported from different institutions, with a median follow-up ranging between 36 and 120 months. Recurrence-free survival after five and 10 years was reported to range from 71-93% and from 65-85%, respectively [39].

*Dose escalation with HDR brachy vs Radioactive seeds.* The combination of external beam radiotherapy with HDR appeared to give better biochemical control and better overall survival as compared to external beam radiotherapy alone. Though the biochemical control rates with radioactive seeds was comparable to that of HDR brachytherapy, the overall survival was better with HDR brachytherapy. [30] **(Level of evidence: 1a, Grade A recommendations)**

*Brachytherapy Related Toxicity:* Patients must be informed about the potential late genitourinary or gastrointestinal toxicity that may occur, as well as the impact of irradiation on erectile function. Radiotherapy affects erectile function to a lesser degree than surgery according to retrospective surveys of patients. A recent meta-analysis has shown that the one-year rate of probability for maintaining erectile function was 0.76 after brachytherapy, 0.60 after brachytherapy plus external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing radical prostatectomy, and 0.25 after standard radical prostatectomy. When studies with more than two years of follow-up were selected (i.e. excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches [40].

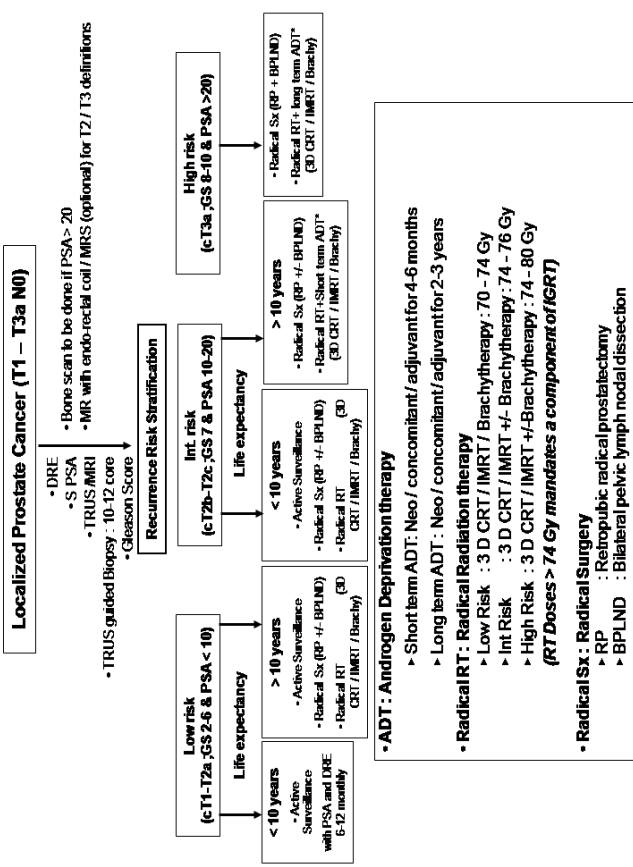
*Post operative Adjuvant therapy:* The Early Prostate Cancer Program randomized trial of adjuvant bicalutamide Vs no adjuvant treatment in patients with localized prostate cancer managed by radical prostatectomy, radiation therapy or surveillance demonstrated a significant reduction in the risk of recurrence and progression. These results need to be confirmed in other trials before incorporating into routine clinical practice.

Extracapsular invasion (pT3) is associated with a risk of local recurrence, which can be as high as 30%. In a multifactorial analysis, the predictors of biochemical relapse are:

- PSA level ( $p = 0.005$ )
- Gleason score of the surgical specimen ( $p = 0.002$ )
- Positive surgical margins ( $p < 0.001$ )



Three prospective randomized trials have assessed the role of immediate post-operative radiotherapy. The EORTC study 22911, with a target sample size of 1005 patients, compared immediate post-operative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 after retropubic radical prostatectomy. Immediate post-operative radiotherapy proved to be well tolerated, with a risk of grade 3-4 urinary toxicity of less than 3.5%, without significant differences regarding the rate of incontinence and/or stricture of anastomosis. The study concludes that immediate post-operative radiotherapy after surgery significantly improves five-year clinical or biological survival: 72.2% vs 51.8% ( $p < 0.0001$ ) [41]. However, the EORTC study has not yet demonstrated improved metastasis-free and cancer-specific survival in this cohort of patients. The most suitable candidates for immediate radiation therapy might be those with multifocal positive surgical margins and a Gleason score  $> 7$ . The conclusions of the ARO trial 96-02 – based on a cohort of 385 patients – echoed those of EORTC since after a median follow-up of 54 months, biochemical progression-free survival was significantly improved in the radiotherapy group: 72% vs 54% ( $p = 0.0015$ ) [42]. In the same way, the SWOG 8794 trial randomised 425 pT3 patients, and the updated results [43], with a median follow-up of 11.5 years, show that adjuvant radiation significantly improved metastasis-free survival, with a 15-year metastasis-free survival of 46% vs 38% ( $p = 0.036$ ) and a 15-year overall survival of 47% vs 37% ( $p = 0.053$ ). Thus, for patients classified as T1-2 N0 (or T3 N0 with selected prognostic factors), pT3 pN0 with a high risk of local failure after radical prostatectomy due to capsular rupture, positive margins and/or invasion of the seminal vesicles, who present with a PSA level of  $< 0.1$  ng/mL



**• ADT : Androgen Deprivation therapy**

- ▶ Short term ADT: Neo / concomitant/ adjuvant for 4-6 months
- ▶ Long term ADT : Neo / concomitant/ adjuvant for 2-3 years

**• Radical RT : Radical Radiation therapy**

- ▶ Low Risk : 3 D CRT / IMRT / Brachytherapy : 70 – 74 Gy
- ▶ Int Risk : 3 D CRT / IMRT +/- Brachytherapy : 74 – 76 Gy
- ▶ High Risk : 3 D CRT / IMRT +/- Brachytherapy : 74 – 80 Gy
- (RT Doses > 74 Gy mandates a component of IGRT)**

**• Radical Sx : Radical Surgery**

- ▶ RP : Retropubic radical prostatectomy
- ▶ BPLND : Bilateral pelvic lymph nodal dissection

one month after surgery, two options can be offered within the frame of an informed consent:

- *either* an immediate radiotherapy to the surgical bed [44] upon recovery of urinary function (**level of evidence:1**)
- *or* clinical and biological monitoring followed by salvage radiotherapy when the PSA exceeds 0.5 ng/ mL [45]; 1.0 ng/mL seems to be a breakpoint above which the likelihood of local control is significantly reduced. (**level of evidence:3**)

**2) Treatment of locally advanced Prostate Cancer (T3b-T4):** The incidence of locally advanced prostate cancer has declined as a result of individual or mass screening. Pelvic lymph node irradiation is optional for N0 patients, but the results of radiotherapy alone are very poor. Because of the hormonal dependence of prostate cancer, ADT has been combined with external irradiation.

Treatment options include,

- Neo-adjuvant hormone therapy followed by Radical radiation therapy
- Neo-adjuvant hormone therapy followed by Radical prostatectomy
- Hormonal therapy alone
- Watchful waiting - Elderly patients with limited life expectancy

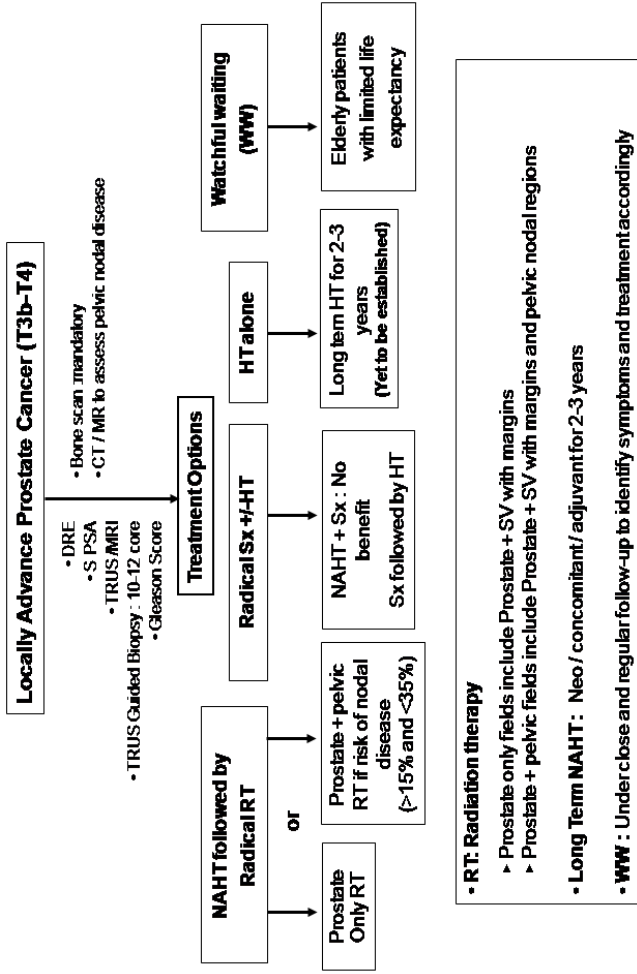
*Neo-adjuvant and adjuvant hormone therapy followed by Radiation therapy:* This treatment option should be considered for patients with locally advanced disease who are to be treated with a local therapy.

Neoadjuvant and concomitant HT [46], concomitant and long term adjuvant HT [47], long term adjuvant HT [48] approaches have shown significant benefit in terms of progression free survival and overall survival. Also, neo-adjuvant, concomitant and long term Adj HT shows better outcome as shown by RTOG 92-02 trial [49]. The RTOG 92-02 trial closed in 1995 after accruing 1554 patients. Statistically significant improvements were observed in actuarial biochemical freedom from disease (bNED) control, distant metastatic failure, local control, and disease-free survival in patients receiving long-term ADT (LDAT) (before, during, and two years after radiotherapy), compared with short-term androgen deprivation (STAD) (two months before and during radiotherapy). With a median follow-up of 5.8 years, the LTAD treatment arm showed significant improvement over the STAD arm in all efficacy end-points except five-year overall survival, which was 80% Vs 78.5% ( $p = 0.73$ ), respectively. In a subset of patients that was not part of the original study design, with Gleason score 8-10 tumors, the LTAD arm showed significantly better overall survival after five years than the STAD arm, with 81% vs 70.7% ( $p = 0.04$ ) [49]. **(level of evidence:1b)**

*Neo-adjuvant hormone therapy followed by radical prostatectomy:* Neo-adjuvant hormone therapy followed by radical prostatectomy has been attempted. This approach, though technically feasible in patients with minimal peri-prostatic spread, causes downsizing of the tumor, higher resectability and reduction in positive surgical margins. Efficacy of hormone therapy when used as neo-adjuvant with prostatectomy has no improvement in overall, disease-specific survival or biochemical free survival despite improvements in outcomes such as margin free positive status **(level of evidence: 1b)**.

*Hormonal therapy Alone:* ADT upfront is beneficial in terms of cancer specific survival. ADT alone still needs to be tested. Further results of CAB alone Vs CAB +RT have shown benefit with addition of RT while other trials results are awaited [50, 51]. **(level of evidence:1b)**

*Watchful waiting (WW)* is offered to asymptomatic patients with well or moderately differentiated cancer and a short life expectancy (level of evidence: 3) or PSA < 50 ng/mL and PSA doubling time > 12 months (level of evidence: 1) In a recent prospective randomized clinical phase III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0 prostate cancer were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic disease progression or occurrence of serious complications. After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% CI, 1.05-1.48; non-inferiority  $p > 0.1$ ) favoring immediate treatment, seemingly due to fewer deaths of non-prostatic cancer causes ( $p = 0.06$ ). The time from randomization to progression of hormone refractory disease did not differ significantly, nor did prostate cancer-specific survival. The median time to the start of deferred treatment after study entry was seven years. In this group, 126 patients (25.6%) died without ever needing treatment (44% of the deaths in this arm). The conclusion drawn from this study is that immediate ADT resulted in a modest but statistically significant increase in overall survival but no significant difference in prostate cancer mortality or symptom free survival. Furthermore, the authors identified significant risk factors associated with a significantly worse outcome: in both arms, patients with a baseline PSA > 50 ng/mL were at a > 3.5-fold higher risk of dying of prostate cancer than



patients with a baseline PSA d" 8 ng/mL. If the baseline PSA was between 8 ng/mL and 50 ng/ mL, the risk of death was approximately 7.5-fold higher in patients with a PSA doubling time < 12 months than in patients with a PSA doubling time > 12 months. However, when early and delayed treatments were compared in a large randomized trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormone therapy was demonstrated [52], comparable with the results of the Lundgren et al. study mentioned above [53] (*level of evidence: 1b*).

### 3) Treatment of Metastatic Disease:

3a) Metastatic nodal (N+) disease

3b) Distant Metastatic (M+) disease

3a) Metastatic nodal (N+) disease:

Treatment Options include:

- Hormanet therapy
- Watchful waiting (WW)
- Surgery
- Radiation therapy

**Hormonal therapy:** is the mainstay of treatment in the form of long term hormonal therapy followed by local therapy, with radiation therapy preferred.

**WW:** The literature reporting on deferred treatment for locally advanced Prostate Cancer is sparse. There are no randomized studies that compare more aggressive treatments, such as radiotherapy or surgery, with or without hormones. Most patients whose disease progresses after deferred treatment of locally advanced Prostate Cancer will be candidates for hormone therapy.

**Surgery:** Lymph node-positive (N+) disease will mostly be followed by systemic disease progression, and all patients with significant N+ disease will ultimately fail treatment. Nevertheless, the combination of RP and simultaneous hormonal treatment has been shown to achieve a 10-year CSS rate of 80% [54]. However, it is questionable whether or not these results could also have been obtained with hormonal treatment alone. Most urologists are reluctant to perform RP for clinical N+ disease, or will cancel surgery if a frozen section shows lymph node invasion.

**Radiation therapy:** Patients with a pelvic lymph node involvement lower than the iliac regional nodes, younger than 80 years old with WHO performance status 0-1 and no severe co-morbidity may be candidates for external beam irradiation plus immediate long-term hormonal manipulation. The RTOG 85-31 randomised phase III trial has shown, with a median follow-up of 6.5 years, that 95 patients out of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better five and nine-year progression-free survival (PSA < 1.5 ng/mL), with 54% and 10% respectively versus 33% and 4% with radiation alone and hormonal manipulation instituted at the time of relapse ( $p < 0.0001$ ). Multivariate analysis revealed this combination as having a statistically significant impact on overall survival, disease-specific failure, metastatic failure and biochemical control [55]. (*level of evidence : 1b*)

### **3b) Distant Metastatic (M+) Disease:**

Immediate hormone therapy is indicated in all patients with metastatic prostate cancer and should be offered



early to all patients with metastatic disease (symptomatic and asymptomatic) [56] (**level of evidence:1**). The response rate to hormone therapy in patients with metastatic disease is 85%, with median duration of response of 18 months and median survival of 36 months. In M1 cases, the median OS ranges between 28 and 53 months; only 7% of patients with metastatic cancer treated with hormonal therapy are reported to live 10 years or more [57]. Survival is likely to depend on the PSA level at diagnosis, the Gleason score, the volume of metastatic disease, and the presence of bony symptoms.

Treatment of osseous metastases:

### 1. **Surgical Intervention**

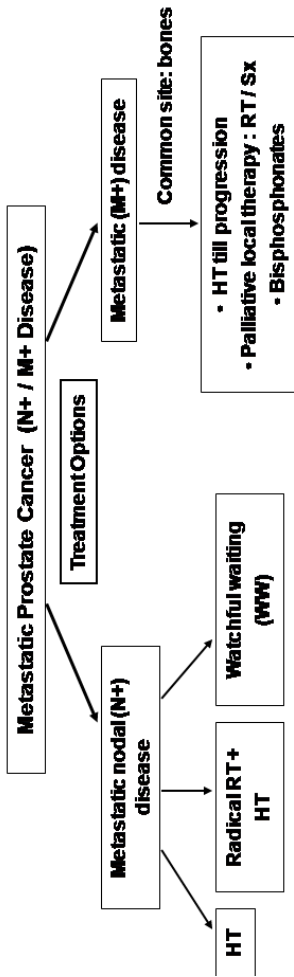
- Pathological fracture of weight bearing bones in patients with reasonable life-expectancy
- Decompressive surgery in spinal cord compression

### 2. **Radiation therapy**

- External beam radiation therapy for painful or unstable skeletal metastases: A single fraction of 8 Gy will relieve pain in over 70% of patients [58,59] (**Level of evidence: 1b**). Fractionated RT for bone metastases may be considered in patients with spinal cord compression or bone-only disease.
- Hemibody radiation in patients with multiple symptomatic skeletal metastases (8 Gy for UHBI & 6 Gy for LHBI).
- Systemic radionuclide therapy : Radioisotopes like Strontium89 and Samarium153 may improve bone pains in upto 70% patients

3. **Bisphosphonates (Zoledronic Acid):** Has been shown to reduce bone pains and skeletal-related events including fractures in randomized trials. **(Grade A recommendation)** Recently, bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in HRPC to provide effective treatment of skeletal complications and to reduce pain or provide total pain relief. In the largest single phase III trial, 643 patients who had HRPC with bone metastases were randomized to receive zoledronic acid, 8 mg or 4 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with only 4 mg of zoledronic acid had fewer skeletal related events compared to the placebo group (44% vs 33%,  $p = 0.021$ ) and fewer pathological fractures (13.1% vs 22.1%,  $p = 0.015$ ). Furthermore, the time to first skeletal-related event was longer in the zoledronate group, so improving QoL. Patients were initially randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg because of toxicity. [60] Currently, bisphosphonates could be proposed to patients with HRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear, but at present is every 3 weeks or less. The toxicity, e.g. jaw necrosis, of these drugs, especially amino bisphosphonate, must always be kept in mind.

In summary, pain due to osseous metastases is one of the most debilitating complications of prostate cancer. Bisphosphonates have been highly effective with a response rate of 70-80% in small, open trials, which, associated with a low frequency of side-effects, makes



- HT : Long term hormonal therapy
- Radical RT
  - ▶ To include Prostate + SV with margins and pelvic nodal regions
- Palliative local therapy: RT / Sx
  - ▶ RT : To painful sites (8 Gy / 1# or 30 Gy/10#)
  - ▶ Sx: Decompressive surgery or fixation of pathological fracture
- Bisphosphonates: : Zoledronic acid infusion every 3 weekly for 12-15 months

bisphosphonates an ideal medication for palliative therapy. Bisphosphonates should be considered early in the management of symptomatic bone metastasis. **(Grade A recommendation)** Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur (i.e. palliative external beam radiation, cortisone, analgesics and antiemetics).

**Hormonal therapy:** Androgen deprivation can be achieved either by suppressing the secretion of testicular androgens by means of surgical or medical castration, or by inhibiting the action of the circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens. Alternatively, these two modalities can be combined to achieve what is commonly known as complete (or maximal or total) androgen blockade (CAB).

*Bilateral orchiectomy*, either total or by means of a subcapsular technique (i.e. with preservation of tunica albuginea and epididymis), is a simple and virtually complication-free surgical procedure that can easily be performed under local anaesthesia. It is the quickest way to achieve a castration level, which is usually obtained in less than 12 hours. The main drawback of orchiectomy is that it may have a negative psychological effect: some men consider it to be an unacceptable assault on their manhood. In addition, it is irreversible and does not allow for intermittent treatment. The use of bilateral orchiectomy has declined recently, which can be attributed to the effects of stage migration towards earlier disease, and the introduction of equally effective pharmacological modalities of castration.

*Long-acting LHRH agonists* (buserelin, goserelin, leuprorelin and triptorelin) have been used in advanced Prostate Cancer for more than 15 years and are currently the predominant forms of ADT [61]. They are synthetic analogues of LHRH, generally delivered as depot injections on a one-, two-, three-, or six-monthly basis, that interfere with the hypothalamic-pituitary-gonadal axis. They initially stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release, and consequently elevate testosterone production (known as 'testosterone surge' or 'flare up' phenomenon), which begins within approximately two or three days of the first injection and lasts through approximately the first week of therapy.

In a recent meta-analysis evaluating single-therapy ADT for advanced Prostate Cancer, LHRH agonists were shown to have comparable efficacy to orchiectomy and DES [62] (**level of evidence: 1a**). This observation questions the clinical impact of changing the castrate testosterone level definition from 50 ng/dL to 20 ng/dL. In addition, although only based on an indirect comparison, all seemed equally effective whatever their formulation [62] (**level of evidence: 3**).

Today, LHRH agonists have become the 'standard of care' in hormonal therapy because they avoid the physical and psychological discomfort associated with orchiectomy, and lack the potential cardiotoxicity associated with DES. However, the main concerns associated with the administration of LHRH agonists are the potentially detrimental effects associated with the 'flare phenomenon' in advanced disease, namely increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and

fatal cardiovascular events due to hyper-coagulation status. A recent review addressing these issues concluded that clinical flare needs to be distinguished from the more common biochemical flare (i.e. increasing levels of PSA), and even from asymptomatic radiographic evidence of progression, and that patients at risk for clinical flare are overwhelmingly those with high volume, symptomatic, bony disease, accounting for only 4-10% of M1 patients.

*Anti-androgens* compete with testosterone and DHT for binding sites on their receptors in the prostate cell nucleus, thus promoting apoptosis and inhibiting Prostate Cancer growth. These orally administered compounds are classified according to their chemical structure as steroidal (e.g. cyproterone acetate [CPA], megestrol acetate and medroxyprogesterone acetate) and non-steroidal or pure (e.g. nilutamide, flutamide and bicalutamide). Both classes compete with androgens at the receptor level, but while this is the sole action of non-steroidal anti-androgens, steroidal anti-androgens additionally have progestational properties with central inhibition of the pituitary gland. As a consequence, non-steroidal anti-androgens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

As primary monotherapy, bicalutamide 150 mg/day has been compared with medical or surgical castration in two large prospective randomised trials with identical study designs, including a total of 1435 patients with locally advanced M0 or M1 Prostate Cancer [63]. A pooled analysis showed:

- In M1 patients, an improvement in OS with castration, although the difference in median

survival between the groups was only six weeks; a further post hoc analysis showed a survival benefit only for patients with higher PSA levels (> 400 ng/mL) at study entry.

- In M0 patients (N = 480), no significant difference was noted in OS based on the Kaplan Meier test, with median survival being 63.5 months in the bicalutamide arm compared with 69.9 months in the castration one.

### **Intermittent Vs Continuous Androgen Deprivation Therapy**

For reasons that as yet remain unclear, long-term CAB, which stimulates prostate cell apoptosis, fails to eliminate the entire malignant cell population, so that after a variable period (averaging 24 months) the tumor inevitably relapses, being characterized by an androgen-independent state of growth. Experimental data indicate that androgen-independent progression may begin early after the administration of hormonal therapy, coinciding with the cessation of androgen-induced differentiation of stem cells. It is therefore theoretically possible that if androgen deprivation is stopped prior to the progression of androgen-independent cells, any subsequent tumour growth would then be solely sustained by the proliferation of androgen-dependent stem cells, which should be susceptible once again to androgen withdrawal. In this way, cyclical ADT would delay the emergence of the androgen-independent clone. Thus, intermittent ADT may result in two other benefits: namely the preservation of QoL in the off-therapy periods and the reduction of cost. Several phase II trials have demonstrated the feasibility of intermittent androgen blockade (IAB) in metastatic or biochemically recurrent disease, with PSA response rates

and symptom improvement similar to that of CAB, but phase III prospective, randomized controlled trials are still underway, and data on survival endpoints and QoL are not mature. Preliminary results of clinical phase III trials have demonstrated not significantly different efficacy for intermittent vs continuous ADT in men with PSA progression following radical prostatectomy and in advanced metastatic prostate cancer [64,65, 66].

The South West Oncology Group (SWOG) trial 9346 randomized 1134 men with stage D2 Prostate Cancer to intermittent and continuous ADT after seven months' induction ADT with PSA reduction < 4 ng/mL. No significant differences with regard to survival in a very preliminary analysis were identified between treatment groups [62]. A PSA reduction to < 0.2 ng/mL, < 4 ng/mL and > 4 ng/mL was identified as a significant prognostic factor with regard to survival, achieving 13 months, 44 months and 75 months, respectively. In some other trials, 75 patients were considered for IAD if they had achieved PSA serum levels < 4 ng/mL or at least 90% reduction of pre-treatment levels after 9 months of ADT [65]. Patients went on when PSA values rose > 20 ng/mL at which the 9-month cycle of ADT was repeated. 86% of the men are alive at a median of 134 months, with a median survival of 95 months from the initial ADT cycle. A 100% and 70% survival at 5 years was calculated for those presenting with locally advanced disease and metastases at initial presentation, respectively. (*level of evidence:2*)

**Follow-up Protocol:** PSA measurement, disease-specific history and DRE are recommended at the following intervals: 3, 6 and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually. (*Grade B recommendation*) The purpose of the first



clinic visit is mainly to detect treatment-related complications and to assist patients in coping with the new situation. Tumor or patient characteristics may allow alterations to this schedule. After initiation of hormonal treatment, it is recommended that patients be followed-up at three and six months. These guidelines must be individualized, and each patient should be told to contact his physician in the event of troublesome symptoms.

### **Management of biochemical relapses after radical local therapy:**

#### *PSA monitoring after radical prostatectomy*

PSA is expected to be undetectable within 3 weeks after a successful radical prostatectomy [67]. A persistently elevated PSA level means that PSA-producing tissue remains in the body. In patients treated with radical prostatectomy, this is generally thought to be residual cancer due to either micro-metastases that were not detected or undetectable beforehand, or residual disease in the pelvis possibly due to positive surgical margins. A rapidly increasing PSA level (high PSA velocity, short PSA doubling time) indicates distant metastases, while a later and slowly increasing concentration of PSA is most likely to indicate local disease recurrence. The time to PSA recurrence and tumor differentiation are also important predictive factors distinguishing between local and systemic recurrence [68 69]. Both local treatment failure and distant metastases have been shown to occur with undetectable PSA levels. This is very rare and occurs almost only in patients with unfavourable pathology (undifferentiated tumors) [70 71]. This means that, in patients with a relatively favorable pathology (< pT3, pN0, Gleason score < 8), PSA measurement, together with the disease-specific history, could stand as the single test in follow-up after radical prostatectomy

### *PSA monitoring after radiation therapy*

The PSA level falls slowly after radiotherapy compared with radical prostatectomy. The optimal cut-off value for a favourable PSA nadir after radiotherapy is somewhat controversial. Achieving a PSA nadir of less than 0.5 ng/mL seems to be associated with a favourable outcome [72]. The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. A PSA rising more than 2 ng/mL above the nadir PSA is the current definition of biochemical failure after radiotherapy. Also, after radiotherapy, the PSA doubling time has been shown to correlate to the site of recurrence; patients with local recurrence had a doubling time of 13 months compared to 3 months for those with distant failure [73].

### *PSA Failure Definitions:*

The level of PSA at which to define treatment failure differs between radical prostatectomy cases and radiation treated cases. Following radical retropubic prostatectomy, two consecutive values of 0.2 ng/mL or greater appear to represent an international consensus defining recurrent cancer [74, 75]. At the 2006 RTOG-ASTRO Consensus conference a new definition of radiation failure was established with as the main aim to establish a better correlation between the definition and clinical outcome. The new definition of radiation failure is a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value) [76]. This definition is applicable for patients treated with or without hormonal therapy.

With regard to further management once PSA relapse has been diagnosed, it is of major importance to determine whether the recurrence has developed at local or distant sites. About 50% of patients who underwent

radical retropubic prostatectomy will have local disease, and the remainder will have either distant disease alone, or distant and local disease.

Important parameters to help differentiate between local or distant relapse include:

- Timing of the PSA increase after surgery
- PSA velocity
- PSA doubling time (PSADT)
- Pathohistological stage
- Gleason score of the prostatectomy specimen

PSA elevations developing within the first two years following surgery are associated with distant recurrences. It has been shown that a median PSADT of 4.3 months is associated with distant relapse, whereas a median PSADT of 11.7 months predicts local failure. According to a recent study, PSA velocity of  $< 0.75$  ng/mL/y was observed in 94% of patients with local recurrence, whereas 56% of patients with distant metastases demonstrated a PSA velocity of  $> 0.75$  ng/mL/y.

With radiotherapy, any continuously rising PSA following a nadir after radiation is an indicator for local recurrence, systemic metastatic spread or a combination of both. However, due to the well known PSA bounce phenomenon, biochemical recurrence is defined by three consecutive PSA rises above the nadir level according to ASTRO guidelines. After radiotherapy, a late and slowly rising PSA is a sign of local failure only.

**Local recurrence is defined by:**

- a prostatic biopsy demonstrating malignant cells 18 months or longer after initial radiotherapy

- plus an associated rise in PSA
- plus no evidence of metastatic spread documented by computed tomography (CT) or magnetic resonance imaging (MRI) and bone scintigraphy.

Following radical prostatectomy,

- CT scans of the pelvis and abdomen are of low sensitivity and specificity in patients with PSA levels < 20 ng/mL or a PSA velocity of < 20 ng/mL/y
- Endorectal MRI or PET scans may help to detect local recurrences if PSA is > 1-2.0 ng/mL, but is not yet routine clinical practice
- If available, a capromab pendetide scan shows a diagnostic yield of 60-80% independent of the PSA serum level

*Treatment of PSA only failures:* The timing and mode of treatment of PSA-only recurrence after radical prostatectomy or radiation therapy remains controversial. After radical retropubic prostatectomy observation, radiation therapy to the prostatic bed, (complete) androgen blockade, intermittent androgen deprivation (IAD), a combination of anti-androgens with 5 alpha reductase inhibitors, and even early chemo-hormonal approaches are therapeutic options. The same therapeutic options may be applied for PSA recurrences following radiation therapy. In addition, salvage prostatectomy, cryotherapy and brachytherapy might be indicated in carefully selected patients. (**Grade B recommendation**)

## **Hormone Refractory Prostate Cancer (HRPC)**

## Definition of HRPC

- Serum castration levels of testosterone (testosterone < 50 ng/dL, or < 1.7 nmol/L)
- Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with a PSA > 2 ng/mL
- Anti-androgen withdrawal for at least 4 weeks\*
- PSA progression, despite secondary hormonal manipulations\*
- Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using the RECIST criteria\*\* and with nodes  $\geq 2$  cm in diameter

[\* *Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for HRPC.*

\*\* *(From Therasse et al., 2000).]*

## Androgen deprivation in androgen-independent Prostate Cancer

The existence of androgen-independent Prostate Cancer demonstrates that disease progression occurs despite castration. The castration levels of testosterone must therefore be documented and a serum testosterone level < 50 ng/mL (1.7 nmol/L) should be documented at initial relapse on hormonal therapy [77]. The overall effect of continued testicular androgen suppression in HRPC is minimal. Two recent trials have challenged these data by showing only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies. However, in the absence of prospective data, the modest potential benefits outweigh the minimal risk of treatment and androgen suppression should be

continued indefinitely in these patients. (**Grade C recommendation**)

For the patient with progressive disease after androgen deprivation, there are many therapeutic options. They include anti-androgen withdrawal, addition of anti-androgens, anti-androgen replacement, oestrogenic compounds, adrenolytic agents and novel approaches [78].

*Androgen withdrawal* should be systematically considered as a first-line modality in relapsing patients, even if its efficacy is limited (**level of evidence: 2**). Approximately one-third of patients respond to anti-androgen withdrawal, as indicated by a > 50% PSA decrease, for a median duration of approximately 4 months.

*Switching to an alternative anti-androgen therapy:* There has been recent interest in another simple modality: the alternative anti-androgen therapy. After CAB in 232 progressing patients (76% being M1b), a withdrawal effect was observed in 31 men (15.1%). A second line hormonal treatment was performed by giving an alternative non-steroidal drug (i.e. initial flutamide was replaced by bicalutamide and vice versa). An overall > 50% decline in PSA was observed in 83 men (35.8%), irrespective of any previous withdrawal effect, and lasting more than 6 months. The higher the PSA at the start of second-line therapy, the shorter the efficacy. Aminoglutethimide, ketoconazole and corticosteroids act mainly via this mechanism to produce a PSA response in about 25% of patients for about 4 months [79]. However, the simultaneous addition of ketoconazole to anti-androgen withdrawal, produced a significantly increased PSA response (32% Vs 11%) and a longer

time to PSA progression (8.6 Vs 5.9 months) compared to anti-androgen withdrawal alone [80].

*Oestrogens:* Recently, DES [81] achieved a positive PSA response between 24% and 80%, with an overall estimated survival of 63% at 2 years. However, even at low doses of DES, about one-third (31%) of patients developed deep venous thrombosis and 7% experienced myocardial infarction.

*Cytotoxic Chemotherapy in HRPC:* Several proven chemotherapeutic options are available for metastatic disease in HRPC. Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient. **(Grade C recommendation)** A significant improvement in median survival of about 2 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy [82, 83] **(Grade A recommendation)**. Currently, the only indication for chemotherapy in HRPC non-metastatic patients is inside clinical trials and patients should be advised to participate. A recent phase III trial in HRPC patients confirmed the potential interest of thalidomide compared to placebo in non-metastatic patients with a progression-free survival of 15 months versus 9.6 months ( $p = 0.0002$ ) [84]. In the CALGB 9182 study, 244 patients with symptomatic metastatic HRPC were randomized to receive either mitoxantrone + hydrocortisone, 12 mg/m<sup>2</sup> every 3 weeks, or hydrocortisone alone. No differences were observed with regard to survival, PSA response, and median time to progression. However, the QoL was significantly improved in the combination arm.

Encouraging results have been seen with alternative treatments evaluated in prospective clinical phase II trials, including pegylated doxorubicin, vinorelbine, a

combination of paclitaxel, carboplatin and estramustine, a combination of vinblastine, doxorubicin and radionuclides, and a combination of docetaxel and mitoxantrone. The lack of representative randomised phase III trials and unknown long-term efficacy are major problems associated with all these studies.

**Salvage CT:** Since all patients who receive docetaxel-based chemotherapy for HRPC will progress within 6 to 8 months, there have been many clinical trials investigating the role of salvage chemotherapy. The results suggest the most appropriate approaches are intermittent docetaxel CT (**Grade B recommendation**), molecular-targeted therapy like thalidomide [85] and second-line satraplatin. Many new drugs, such as gefitinib, bevacuzimab (phase III trial CALB 90401), oblimersen (phase III trial EORTC 30021), and also a vaccine, G-Vax , are being tested in phase III trials.

Palliative treatment options should be offered depending on the symptoms as described in previous section.

Hormone-refractory prostate cancer is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers.

**Screening and Early detection of Prostate Cancer:** Population or mass screening is defined as the examination of asymptomatic men (at risk). It usually takes place as part of a trial or study and is initiated by the screener. In contrast, early detection or opportunistic screening comprises individual case findings, which are initiated by the person being screened (patient) and/or his physician. The primary endpoint of both types of screening has two aspects:



1. *Reduction in mortality from Prostate Cancer.* The goal is not to detect more and more carcinomas, nor is survival the endpoint because survival is strongly influenced by lead-time from diagnosis.
2. The quality of life is important as expressed by quality-of-life adjusted gain in life years (QUALYs).

Prostate cancer mortality trends range widely from country to country. Decreased mortality rates due to prostate cancer have occurred in the USA, Austria, UK and France, while in Sweden, the 5-year survival rate has increased from 1960 to 1988, probably due to increased diagnostic activity and greater detection of non-lethal tumors. However, this trend was not confirmed in a similar study from the Netherlands. The reduced mortality seen recently in the USA is often attributed to the widely adopted aggressive screening policy, but there is still no absolute proof that prostate-specific antigen (PSA) screening reduces mortality due to Prostate Cancer (**level of evidence: 2**).

Prospective, preferably population-based, randomized trials are needed to properly evaluate the efficacy of Prostate cancer screening. Two large trials are underway, the PLCO (Prostate, Lung, Colorectal and Ovary) trial in the USA [86] and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe [87]. The main endpoint of these trials is difference in prostate cancer mortality.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) [*median follow-up of 9 years in 2009*] and the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) [*follow-up ay 10 years in 2009*] Cancer Screening Trial recently reported on the mortality benefit of prostate-specific antigen screening. However,

the decline in mortality rates are quite small compared with the large number of men diagnosed and treated for prostate cancer. Both studies mention the need for further investigations that assess the relationship between prostate cancer screening, treatment, and quality of life. This is especially important if results continue to show little impact on mortality and increasing stress placed on the patient through over-diagnosis and over-treatment. Both studies would require at-least 13 years follow-up for final estimates to generate level of evidence: 1b. [88]

Thus, there is currently no evidence for introducing widespread, population-based, screening programmes for early prostate cancer detection in all men in a given population (**level of evidence: 2**). A less controversial programme, which is also recommended by most guidelines, is using PSA with digital rectal examination (DRE) as an aid to early diagnosis (**level of evidence: 3**).

The decision to undergo early PSA testing should be a shared decision between the patient and his physician. PSA testing and digital rectal examination should be offered from the age of 45 years to men with a life expectancy of at least 10 years. The most recent research suggests further PSA testing is unnecessary in men >75 years and a PSA level < ng/mL at their first screening visit. This is because these men have a very low risk of dying from prostate cancer.

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