MANUAL OF UROLOGIC MALIGNANCIES

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PREFACE

Urologic malignancies account for about 20% of all cancers in men and <3% in women in India. A standard treatment approach is the key for appropriate management. While guidelines exist for the standard management of germ cell tumors, consensus for other urologic malignancies is evolving. Recently, availability of targeted therapy and small molecules has led to paradigm shift in the management of metastatic renal cell cancer. A clinician needs to be aware about adverse reactions and also dose modifications needed to reduce toxicity of these molecules in certain subsets of patients. Unavailability of handy information, prompted us to compile this information in this manual which we hope will be useful to busy residents and physicians involved in the care of such patients. A number of colleagues have helped in this effort; Lipika Goel, a fellow from Harvard Medical School inspired us to work on this, later Ranjit Sahoo, Venkatraman Radhakrishnan and Gaurav Prakash helped to put this information together. We have made an effort to give information on our current practice at AIIMS and also at other centres. Some data particularly on targeted therapy in renal cell cancer has been taken from other sources. Mr Yogesh Kumar and Mrs. Sheeja Siyad from K L Wig Centre for Medical Education and Technology (CMET) have helped immensely in editing of the manual. Many colleagues in Medical Oncology, Radiation Oncology and Urology (Ganesh Bakshi, TMH, Mumbai) also reviewed the data / information. We would welcome suggestions and comments (lalitaiims@yahoo.com) on content of this manual.

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Incidence of Urologic Malignancies in India: Age adjusted incidence rate (Per 100,000 populations)

Population based Registries	Kidney Cancer		Urinary Bladder Cancer		Prostate Cancer
	Males	Females	Males	Females	Males
Delhi	2.5	0.9	6.8	1.7	10.9
Mumbai	2.3	1.0	3.9	1.1	7.5
Bangalore	1.8	1.2	3.5	1.0	8.9
Thiruvanthapuram	1.7	0.6	3.7	0.6	7.2
Kolkata	1.7	0.9	4.3	0.9	6.3
Ahmedabad urban	1.6	0.6	2.1	0.5	3.4
Pune	1.6	0.8	2.9	0.8	7.5
Kollam	1.5	0.2	3.1	0.4	4.1
Chennai	1.3	0.8	3.0	0.7	4.6
Nagpur	1.2	0.4	2.1	0.7	3.5
Dibrugarh District	1.1	0.1	2.8	0.3	2.4
Bhopal	1.1	0.7	1.8	0.3	5.1
Imphal West District	1.0	0.8	3.7	0.8	3.4
Manipur State (MR)	1.0	0.3	1.9	0.5	1.2
Aurangabad	1.0	0.3	1.1	0.8	2.5
MR excluding Imphal West	1.0	0.2	1.4	0.4	0.8
Kamrup urban District	1.0	1.3	3.3	0.8	8.5
Barshi Rural	1.0	0.0	0.9	0.0	2.3
Cachar District	0.8	0.1	1.9	0.2	1.6
Ahmedabad Rural	0.6	0.6	1.1	0.3	1.5
MZ-excluding Aizawl	0.6	0.1	0.8	0.9	1.6
Sikkim State	0.5	0.2	1.6	0.9	1.6
Mizoram State (MZ)	0.5	0.2	1.4	1.1	2.2
Barshi Expanded	0.4	0.3	0.6	0.2	1.5
Aizwal District	0.2	0.5	2.5	1.5	3.2

Source: National Cancer Registry Programme: Three Year Report of Population based Cancer Registries: 2006-2008, Indian Council of Medical Research, November 2010.

1 RENAL CELL CARCINOMA (RCC)

1.1 Investigations

- Physical examination
- Complete hemogram
- Liver and renal functions , serum calcium, serum LDH
- Urine analysis
- Chest X-ray P/A view
- US abdomen and pelvis
- CT scan abdomen & Pelvis
- Bone scan if the patient has skeletal symptoms or raised serum alkaline phosphatase
- CT scan/MRI head – if focal neurological deficit is present.
- Urine cytology – If urothelial carcinoma suspected (e.g. central mass)
- Percutaneous biopsy – There is small but unacceptable risk of seeding of needle tracts and converting a curable tumor into an incurable tumor. If a renal mass cannot be confirmed as benign by CT scan, excision is usually indicated.

1.2 Salient Points

1.2.1 INTRODUCTION

- Malignant neoplasm of the kidney arising from the epithelium of the renal tubules.
- Incidence: 15-22/100,000/Yr, 2% of all malignant tumors,
- In India : Males: 1.2/100,000, Females : 0.5/ 100,000
- Indians living in western countries have higher incidence
- M:F = 2:1
- Age peak: 50 to 70 years
- India : mean age – 52 years

1.2.2 RISK FACTORS

- Smoking: two times increased risk compared to non-smokers ; 30% cases in men and 24% cases in women are directly related to smoking
- Obesity
- Hypertension
- Chronic hemodialysis (patients on long term dialysis)
- Ionizing radiation,
- Occupational exposure to cadmium, trichloroethylene, oven workers
- Nephropathy associated with analgesic abuse (renal pelvis)

1.2.3 HEREDITARY FORMS

- Von Hippel Lindau syndrome (VHL) : 35% of these cases are multifocal and B/L
- Hereditary clear cell/ papillary/ chromophilic RCC
- Tuberous sclerosis
- RCC with hereditary cystic kidney disease

1.2.4 MOLECULAR GENETIC ABNORMALITIES

- Chromosomal aberration : del 3p- (VHL gene), t (3;8)(FHIT gene) and t(3;11)
- In 80% of sporadic RCC: VHL gene aberration (on chromosome 3p25). VHL gene mutation leads to dysregulation of hypoxia inducible factors (HIF) with simultaneous overexpression of VEGF. Later causes angiogenesis, which leads to increased tumor vascularization and increased risk of metastasis.

1.2.5 METASTATIC SPREAD

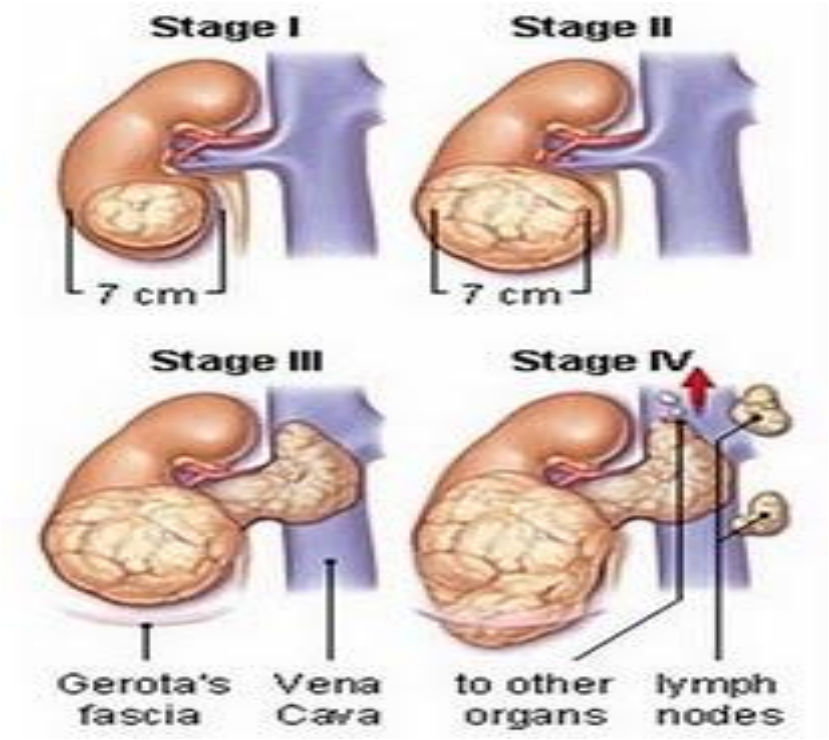
- 30% of cases have distant metastasis at diagnosis
- Tumor < 3cm in diameter- usually without metastasis
- Hematogenous metastasis - Lung, liver, bone, CNS
- Lymphatic : to pelvic and para-aortic lymph nodes
- Local : to regional lymph nodes: para-aortic, paracaval, renal hilar lymph nodes

1.2.6 METASTATIC PATTERN

Site	Incidence
Lung and mediastinum	55%
Regional lymph nodes	34%
Liver	33%
Bone	32%
Adrenal gland	19%
Contralateral kidney	11%
CNS	6%

1.2.7 TNM STAGING

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 7cm in greatest dimension limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor > 7cm in greatest dimension limited to the kidney
T3	Tumor extends into major veins or invades the adrenal gland or perinephric tissues, but not beyond Gerota's fascia.
T3a	Tumor invades the adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3b	Tumor grossly extends into renal vein (s) or vena cava below the diaphragm
T3c	Tumor grossly extends into renal vein(s) or vena cava above the diaphragm
T4	Tumor invades beyond Gerota's fascia, infiltration of neighbouring organs
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastasis
Distant Metastasis (M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis



1.2.8 STAGE GROUPING

	T	N	M	Frequency*
Stage I	T1	N0	M0	40-45%
Stage II	T2	N0	M0	10-20%
Stage III	T1 T2 T3a T3a T3b T3b T3c T3c	N1 N1 N0 N1 N0 N1 N0 N1	M0 M0 M0 M0 M0 M0 M0 M0	20%
Stage IV	T4 T4 Any T Any T	N0 N1 N2 Any M	M0 M0 M0 M1	20-30%

*From the AJCC (American Joint Commission on Cancer Staging) Manual International data.

1.2.9 HISTOLOGIC CLASSIFICATION[1]

- More than 95% of cases are derived from tubular cells
- Renal cell carcinoma (usually adenocarcinomas of the renal parenchyma): 95%

Type	Frequency
Clear cell type	75%
Papillary types 1 & 2	15%,

- Chromophobe, collecting duct and miscellaneous histologic types make up the remainder.

Others: nephroblastomas, sarcomas, lymphomas, hemangiopericytoma, angiomyolipomas : rare
Transitional Cell Tumors are usually tumors of renal pelvis.

- Renal parenchymal tumors comprise ~80% of renal tumors

1.2.10 CLINICAL PRESENTATION

- No early symptoms
- Classical triad of hematuria, flank pain, palpable abdominal mass: 10%
- In advanced stage: hematuria 60%, flank pain-40%, palpable abdominal mass- 45%,
- Weight loss 35%, Anemia- 20%, varicocele, edema of leg (due to invasion of renal vein or IVC)
- 60% of RCCs are diagnosed incidentally through US examination.

1.2.11 PARANEOPLASTIC SYNDROMES

Due to tumor associated cytokine or hormone production

- Fever, thrombocytosis, raised ESR (Interleukins-IL6),

[1] Cheville JC, Lohse CM, Zincke H, et al. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol* 2003; 27: 612.

- Hypertension (renin), erythrocytosis (erythropoietin)
- Hypercalcemia (PTH)
- Amyloidosis
- Stauffer's syndrome : (focal liver necrosis, enzyme increase, fever, weight loss)
- Non-metastatic elevation of serum alkaline phosphatase (SAP)

1.2.12 DIFFERENTIAL DIAGNOSIS

- Renal cyst, angiomyolipoma, nephroblastoma, renal sarcoma

1.3 Prognostic Factors – MSKCC Scoring System

Poor-prognosis patients are defined as those having ≥ 3 more factors: these are predictors of short survival:

- Serum LDH > 1.5 times the upper limit of normal
- Hemoglobin (g/dl) : < lower limit of normal
- Corrected serum Calcium > 10 mg/dL (2.5 mmol/L)
- Interval less than a year from original diagnosis to start of systemic therapy
- Karnofsky Performance Score ≤ 70
- ≥ 2 sites of organ metastasis

1.4 Overall Survival

Histological Subtype	5 Year Cancer-Specific Survival[1]
Clear Cell Type	68.9%
Papillary (Chromophilic type)	87.4%
Chromophobe type	86.7%

1.5 Spontaneous course of metastatic disease

Spontaneous remission	0.3%
One year survival	25%
Three year survival	4%
Five year survival	2%

1.6 Treatment

1.6.1 EARLY DISEASE: T1 OR T2, N0 [STAGE I & II DISEASE]

- Surgery is the treatment of choice.
- Currently, there is no role for neoadjuvant or adjuvant chemotherapy or radiation.

Surgery

- Radical nephrectomy – Includes *en bloc* resection of kidney, Gerota's fascia and perinephric fat.
- Ipsilateral adrenalectomy is performed for large, upper pole tumors or if the adrenal is abnormal on CT scan. Adrenal gland may be left, if uninvolved and tumor is not high risk.
- Regional lymph node dissection is optional. It can be omitted in tumors less than 5 cm in size where CT shows no abnormality[2]. For larger tumors, lymph node dissection should be done, especially in tumors which are large, have more necrosis and CT scan shows lymph node enlargement. In such cases, LND should be complete.

Partial nephrectomy (nephron-sparing surgery)

- Indications: if radical nephrectomy would lead to the immediate need for dialysis (i.e. bilateral RCC, RCC in a solitary kidney) and
- In patients at risk for future insults to the non-diseased kidney or patients with small (< 4cm) tumors that are clearly localized.

1.6.2 LOCALLY ADVANCED DISEASE: T3 OR T4, N1 OR N2

- Surgery is the main treatment.
- Currently, there is no role for neo-adjuvant or adjuvant chemotherapy or radiation.

[2] Blom JHM, van Poppel H, Maréchal JM et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur. Urol*. 2009;55:28-34.

Surgery:

- Radical or partial nephrectomy
- Thrombectomy – May be done if tumor thrombus is present and if technically possible (determined by superior extension of tumor thrombus)
- Renal artery embolization – May be used to shrink large tumors or diminish the extent of IVC thrombus
- Resection of invasive tumor – May be necessary, if tumor invades adjacent organs such as liver, pancreas, or colon, which can sometimes happen in the absence of metastatic disease (T4N0M0 or T4N1M0).

1.6.3 METASTATIC DISEASE: ANY T, ANY N, M_1

1.6.3.1 Solitary metastasis

- Present in 3% of cases
- **If resectable:** radical nephrectomy with resection of metastases.

  5-year survival: 35% to 60%. Radiation is often delivered after surgery.

- Not Resectable

  For patients with a solitary metastatic site that cannot be resected, radiation can provide symptomatic relief in 66% of patients and cause objective tumor regression in 50% of patients.

- Nephrectomy for local palliation

1.6.3.2 Multiple metastases

Options include:

- Targeted therapies
- High dose IL-2
- Cytoreductive nephrectomy + Targeted/Interleukin therapy

If fractional percentage of tumor volume (FPTV) <90%, patient can be started on targeted therapy, assess response followed by consolidation surgery (nephrectomy with complete lymph node dissection)[3]

For Clear cell RCC

- With good performance status: Molecular targeted therapy OR high dose IL-2
- With poor performance status: targeted therapy

For non-clear cell RCC and poor prognosis: consider Temsirolimus. If this is not available, consider other molecular targeted therapies.

1.7 Immunotherapy

1.7.1 INTERLEUKIN-2 (IL-2)

- High dose intravenous IL-2 : an overall response rate of 21% , CR - 5%
- Low dose Intravenous IL-2[4] : overall response rate – 13%
- The median duration of response is reported at 54 months.[5]
- Low dose subcutaneous regimens: similar survival rates to high dose IV IL-2 but inferior overall response rates.

1.7.2 INTERFERON-α (IFN-α)

- Response rates: 14%.[6]
- Median duration of response is 6 months but rarely exceeds 2 years.

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[3] Pierorazio PM, McKiernan JM, McCann TR, *et al.*Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumor volume removed. *BJU Int.* 2007;100: 755-9.

[4] Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol* 2003;21: 3127-32.

[5] Fisher RI, Rosenberg SA, Fyfe G. Long term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6:Suppl 1: S55-S57.

[6] Small EJ, Motzer RJ. Interferon for renal cell carcinoma. In: Belldegrun A, Ritchie AWS, Figlin RA, Oliver RTD,Vaughan ED,eds. *Renal and adrenal tumors.* New York: Oxford University Press,2003:381-7.

1.8 Molecular-targeted therapy

1.8.1 SUNITINIB

- Small-molecule, oral, multi-targeted tyrosine kinase inhibitor of
- (i) VEGF 2, (ii) PDGFR-β, (iii) SRC kinase, (iv) FGFR-1
- Response rate: PR = 40-43%, CR = 0-1%
- Progression-free survival: in responders = 14.8 months
  in stable disease = 7.9 months
- Dose: 50mg/day x 4 weeks, then 2 weeks off

1.8.2 SORAFENIB

- Small-molecule, oral, multi-targeted TKI and VEGF inhibitor
- Progression free survival -5.5 months
- Dose: 400 mg BD (for advanced RCC)

1.8.3 PAZOPANIB

- Small molecule, oral, multitargeted TKI and VEGF-R inhibitor
- Progression-free survival 9.2 months [7]
- Dose: 800 mg daily once , one hour before food

1.8.4 TEMSIROLIMUS

- Mammalian target of rapamycin kinase (mTOR) inhibitor
- Median overall survival - 10.9 months[8]
- Dose: 25 mg infused over a 30-60 minute period, once a week.

[7] Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. *J Clin Oncol.* 2010; 28(6): 1061-8.
[8] Hudes G, Carducci M, Tomczak P, et al. The Global ARCC Trial. Temsirolimus, Interferon Alfa, or Both for advanced renal cell carcinoma. *N Engl J Med* 2007;356: 2271-2281.

1.8.5 EVEROLIMUS

- Oral mTOR inhibitor
- Dose : 10mg/day,
- Progression-free survival : 4 months (in sunitinib and sorafenib failure cases)

1.8.6 BEVACIZUMAB

- VEGF inhibitor
- Progression-free survival : 10.2 months (in previously untreated metastatic RCC) [9]

1.9 Cytoreductive nephrectomy in metastatic RCC

- Radical nephrectomy in the setting of metastatic disease has also been shown to cause tumor regression.
- In a study of radical nephrectomy plus interferon compared to interferon alone, a statistically significant survival benefit was seen in favor of the nephrectomy arm (17 months versus 7 months)[10].

1.10 Non-myeloablative Allogeneic stem cell transplantation

- From an HLA-identical sibling: has shown promise in treatment of metastatic clear cell RCC, possibly due to its potent graft- versus-tumor effect.

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[9] Escudier B, Pluzanska A, Koralewski P, et al. AVOREN trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A Randomised Double-Blind phase III trial. *Lancet* 2007; 370(9605): 2103-11.

[10]Mickisch GH, Garin A, van Poppel H *et al*. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. *Lancet* 2001;358:966-970.

- Limitations : severe graft-versus-host disease
- Currently experimental

1.11 Follow up

Follow up in RCC is based on risk, stage and tumor grade.

1.11.1 FOR PATIENTS TREATED WITH CURATIVE INTENT

- Every 3 months for first 2 years,
- Then every 6 months till 5 years,
- Then once a year
- US abdomen and pelvis and Chest X ray on each visit

1.11.2 FOR PATIENTS TREATED WITH PALLIATIVE APPROACH

- Symptom based approach

1.12 NCCN [a] guidelines

For treatment of relapsed or stage IV RCC that is medically or surgically unresectable

	First-Line Therapy[b]	Subsequent Therapy[e]
Predominantly Clear Cell Histology	Clinical Trial OR Sunitinib (category 1) OR Temsirolimus (category 1 for poor-prognosis[c] patients, category 2B for selected patients and other risk groups) OR Bevacizumab + IFN(category 1) OR Pazopanib (category 1) OR High Dose IL-2 for selected patients OR Sorafenib for selected patients And Best Supportive Care[d]	Clinical Trial Or Everolimus (category 1 following tyrosine kinase inhibitor[f]) Or Sorafenib (category 1 following cytokine therapy and category 2A following other tyrosine kinase inhibitor[f]) Or Sunitinib (category 1 following cytokine therapy and category 2A following other tyrosine kinase inhibitor[f]) Or Pazopanib (category 1 following cytokine therapy and category 3 following other tyrosine kinase inhibitor[f]) Or Temsirolumus (category 2A following cytokine therapy and category 2B following other tyrosine kinase inhibitor[f]) Or Bevacizumab (category 2B) Or IFN or IL-2 (category 2B) And

		Best Supportive Care[d]
Non-Clear Cell Histology	Clinical trial (preferred) OR Temsirolimus (category 1 for poor prognosis patients, category 2A for other risk groups) OR Sorafenib OR Sunitinib OR Pazopanib (category 3) OR Chemotherapy (category 3): gemcitabine or capecitabine or floxuride or 5-FU or doxorubicin (in sarcomatoid type only) And Best Supportive Care[d]	No Subsequent Therapies Listed

1.12.1 NCCN CATEGORY OF EVIDENCE AND CONSENSUS

Category 1	The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.
Category 2A	The recommendation is based on lower-level evidence and there is uniform NCCN consensus.
Category 2B	The recommendation is based on lower-level evidence and there is non-uniform NCCN consensus (but no major disagreement).
Category 3	The recommendation is based on any level of evidence but reflects major disagreement.
*All recommendations are category 2A unless otherwise noted.	

[a] National Comprehensive Cancer Network
[b] Category 1 recommendations are listed in order of FDA approval
[c] Poor prognosis patients, defined as those with ≥ 3 factors predictors of short survival
[d] Best supportive care can include palliative Radiation, metastasectomy, or bisphosphonates for bony metastases
[e] Tyrosine kinase inhibitors with category 1 designation are listed in order of FDA approval
[f] For example, sorafenib, sunitinib, or pazopanib

1.13 Immunotherapy regimens

IL-2	Multiple possible dosing regimens including: • High dose: 600,000 IU/kg IV. bolus every 8 h for a total of 14 doses over 5 days. Repeat every 2 weeks • 18MU/m^2/d continuous IV infusion x 5d Repeat every 3 wk for 2 induction cycles and 4 maintenance cycles
IFN-A-2A	Multiple possible dosing regimens including: • 3 million IU/m^2 SC. for 3x/week x 1 week • 6 million IU/m^2 SC. for 3x/week x 1 week • 18 million IU/m^2 SC. for 3x/week x 1 week • 6 million IU/m^2 SC. for 3x/week without dose escalation • 9 million IU/m^2 SC. for 3x/week without dose escalation
IFN α-2B	Dose 3x/week Week 1: 5MU, 5MU, 10MU Weeks 2-11: 10MU 3x/week

1.14 Molecular targeted therapy regimens

Sorafenib	400mg p.o. BD (comes in 200mg tablets) (Should be reduced to 400mg. OD, if dose reduction is needed)
Sunitinib	50mg p.o. OD x 4wk (comes in 12.5, 25, and 50mg tablets) Repeat cycle every 6 wk Dose should be reduced to 37.5mg OD and then to 25mg OD, if dose reduction is needed 37.5mg p.o. OD (given daily without breaks in treatment)
Temsirolimus	25 mg IV infused over 30–60 minutes once per week
Bevacizumab + IFN	Bevacizumab – 10 mg/kg every 2 weeks IFN α-2A – 9 million IU/m^2 SC for 3x/week
Pazopanib	800 mg PO once daily

1.15 Side effects of therapy

1.15.1 IL-2

- Flu-like symptoms (fever, chills, headache, muscle aches and pains, malaise), flushing,

- Skin rash, nausea, vomiting, hypotension, diarrhea, anemia, thrombocytopenia, mental status changes, tachycardia, oliguria, hepatotoxicity, edema.
- Capillary leak syndrome is a rare side effect which is characterized by hypotension, hypoalbuminemia without albuminuria and generalized edema.

1.15.2 INTERFERON-ALFA

Flu-like symptoms (fever, chills, headache, muscle aches and pains, malaise), fatigue, diarrhea, nausea, vomiting, abdominal pain, joint aches, back pain, dizziness, anorexia, congestion, tachycardia, confusion, myelosuppression, hepatotoxicity, hypertriglyceridemia, rash, alopecia, edema, cough, dyspnea

1.15.3 SORAFENIB AND SUNITINIB

Side Effect	Sorafenib (all grades)	Sunitinib (all grades)
Fatigue	37%	74%
Diarrhea	43%	55%
Nausea	23%	54%
Rash/Desquamation	40%	40%
Hand-foot syndrome[b]	30%	21%[c]
Alopecia	27%	-
Pruritis	19%	-
Hypertension	17%	28%

[b]Hand-Foot Syndrome - (Palmar-plantar erythrodysesthesia) – skin rash, swelling, redness, pain and/or peeling of the skin on the palms and soles. Usually mild, starting 5-6 weeks after start of drug. May require dose reductions.

1.15.4 TEMSIROLIMUS

- Fatigue, rash, stomatitis, peripheral edema, anemia, lymphopenia, hyperglycemia, hyperlipidemia

1.15.5 BEVACIZUMAB

- Fatigue, abdominal pain, nausea, vomiting, diarrhea, poor appetite, leucopenia,
- Proteinuria, alopecia, headache, hypertension, gastrointestinal perforation.

1.16 Dose modifications for Sorafenib and Sunitinib

1.16.1 SORAFENIB

1.16.1.1 Renal and hepatic impairment

No dose adjustment is required on the basis of kidney function, although sorafenib has not been studied in hemodialysis patients.

No dose adjustment is required for Childs Pugh A or B hepatic impairment (hepatocellular carcinoma patients); Sorafenib has not been studied in patients with Childs-Pugh C hepatic impairment.

1.16.1.2 CYP3A4 inducers

Concomitant use of strong CYP3A4 inducers may decrease sorafenib plasma concentrations, so a Sorafenib dose increase may be considered in this setting with close monitoring.

1.16.1.3 Skin toxicity

In 3rd occurrence of Grade 3 toxicity or 4th occurrence of Grade 4 toxicity discontinue Sorafenib. In other grades of skin toxicities, Sorafenib is interrupted until toxicity resolves to grade 0 or 1.

Table - Hand-Foot Syndrome According to Grade of Severity*

Grade	
I	Minimal skin changes or dermatitis and no pain Dysesthesia, paresthesia, painless swelling, erythema, discomfort of hands or feet No interference with patient's activities of daily living
II	Skin changes, such as blisters, peeling, bleeding, or edema, with some pain
III	Ulcerative dermatitis or skin changes with pain Interferes with activities of daily living

* La Couture ME, et al. *The Oncologist*. 2008;13: 1001-1011

Table - Sorafenib Dosage Modifications for Skin Toxicity

Skin Toxicity	Occurrence	Modification
Grade 1	Any	Continue Sorafenib; give topical therapy for symptomatic relief
Grade 2	1st	Continue Sorafenib; give topical therapy for symptomatic relief; reassess in 7 days
	2nd or 3rd	Hold Sorafenib until skin toxicity has resolved to grade ≤ 1; when restarting therapy, decrease dosage to 400 mg daily or every other day
	4th	Discontinue Sorafenib
Grade 3	1st or 2nd	Hold Sorafenib until skin toxicity has resolved to grade ≤ 1; when restarting therapy, decrease dosage to 400 mg daily or every other day
	3rd	Discontinue Sorafenib

Ref : Sorafenib package insert

1.16.2 SUNITINIB

1.16.2.1 Renal and hepatic impairment

No dose adjustments are necessary for renal or hepatic impairment, but it the drug should be discontinued in the setting of hepatic failure.

1.16.2.2 CYP3A4 inhibitors and inducers

- Dose increase or reduction of 12.5 mg increments is recommended based on individual safety and tolerability.
- Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. A dose reduction for Sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor.
- CYP3A4 inducers such as Rifampin may decrease Sunitinib plasma concentrations. A dose increase for Sunitinib to a maximum of 87.5 mg daily should be considered if Sunitinib must be co-administered with a CYP3A4 inducer.

1.16.2.3 Cardiac

- Discontinue, if CHF develops.
- In patients without clinical evidence of CHF but in whom left ventricular ejection fraction (LVEF) is < 50% and is reduced from baseline by more than 20%, interruption of therapy and/or dosage reduction is recommended.
- If severe hypertension occurs, temporary interruption of therapy is recommended until the blood pressure is controlled.

1.16.2.4 Hematologic

- Temporarily hold Sunitinib in patients with grade 3 or 4 hematologic toxicity (excluding lymphopenia). When manifestations resolve or decrease in intensity to grade 2 or less.
- Patients who originally experience grade 3 hematologic toxicity can resume Sunitinib therapy at the same dosage.
- Patients who originally experience grade 4 hematologic toxicity can resume therapy at 1 dose level lower than the previous dosage.

- Patients who experience grade 3 or 4 lymphopenia can continue therapy without interruption.

1.16.3 PAZOPANIB

- Grades 1 and 2: Diarrhoea (52%), hypertension (40%), hair color change (depigmentation) (38%) , nausea (26%), anorexia (22%), vomiting (21%)
- Grades 3 and 4: hypertension (4%), diarrhea (4%).
- Toxicity is higher in cytokine pre-treated patients compared to treatment-naïve patients.

1.16.3.1 Renal and hepatic impairment

- No dose adjustments are necessary for renal impairment,
- For baseline moderate hepatic impairment- dose 200 mg/day
- For severe hepatic impairment : Pazopanib should not be given.

1.16.3.2 CYP3A4 inhibitors and inducers

- Strong CYP3A4 inhibitors such as Ketoconazole , Clarithromycin may increase Pazopanib plasma concentrations. A dose reduction is necessary.
- CYP3A4 inducers such as Rifampin may decrease Pazopanib plasma concentrations. Co-administration not recommended.

1.16.3.3 Cardiac

- Monitor EKG and electrolytes in patients prone for QT interval prolongation.

1.16.3.4 GIT

- Use with caution in patients with GI perforation and fistula

2 URINARY BLADDER CANCER

2.1 Investigations

- History and physical examination
- Complete blood counts
- Renal and Liver Functions
- Urine R/ E
- Chest X-ray
- Urine for malignant cytology (x 3 samples)
- Cystoscopy with EUA and TURBT if possible
- MRI/CT (with contrast) of abdomen and pelvis (if tumor > 5 cm, broad based, presence of hydroureteronephrosis)
- Bone Scan (if bone pains, localized tenderness or raised serum alkaline phosphatase)

2.2 Risk Factors

- Cigarette Smoking
- Polycyclic aromatic hydrocarbons
- Drugs: Cyclophosphamide
- *Schistosomia haematobium* infection (mostly SqCC)

2.3 AJCC 2009 TNM Staging

Primary Tumor (T)	
Tis	Carcinoma in situ
Ta	Noninvasive papillary tumor
T1	Tumor invades lamina propria, but not beyond
T2	Tumor invades the muscularis propria
pT2a	Tumor invades superficial muscle (inner half)
pT2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical tissue)
T4	Tumor invades any of the following: prostatic stroma, uterus, vagina, pelvis,

	or abdominal wall
T4a	Tumor invades prostate, uterus, vagina
T4b	Tumor invades pelvic or abdominal wall
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node in primary drainage region
N2	Metastasis in multiple lymph nodes in primary drainage region
N3	Common iliac lymph node involvement
Distant Metastasis (M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

2.3.1 STAGE GROUPING

Stage	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage 1	T1	N0	M0
Stage 2	T2a	N0	M0
	T2b	N0	M0
Stage 3	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage 4	T4b	N0	M0
	Any T	N1,2 or 3	M0
	Any T	Any N	M1

2.4 Histopathology

- 95% of UB cancers are transitional cell carcinoma

1973 WHO grading	2004 WHO Grading
Urothelial Papilloma	Urothelial Papilloma

Grade 1: Well differentiated	Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Grade 2: Moderately differentiated	Low-grade papillary Urothelial ca.
Grade 3: Poorly differentiated	High-grade papillary Urothelial ca.

The pathological report should specify the grade, the depth of tumor invasion and whether muscle tissue is present in the specimen.

2.5 Prognosis

Pathologic Stage	Disease-Specific Survival (%)	Overall Survival (%)
pTa, Tis, T1 with high risk of progression	82	
Organ confined, negative nodes (pT2,N0)	73	49
Non-organ confined (pT3,4a or pN1 N2)	33	23
Lymph node-positive (any T, pN1 N2)	28-34	21

Ref. De Vita: Cancer Principles and Practice of Oncology, 8th edition, page 1363

2.6 Treatment

- Superficial Bladder Cancer (Non muscle invasive bladder cancer Ta, Tis, T1) Trans-urethral resection +/- intravesical therapy
- Patients should undergo repeated cystoscopy after 3 months (risk of recurrence is common)

Stage	Recurrence at			Rate of progression to muscle invasion %
	1 year (%)	3 year (%)	5 year (%)	
Ta G1	25	50	65	Rare
Ta G 2, 3	35	65	85	20
Tis Focal	25	50	65	20
Tis Multi-centric	50	75	100	50-80
T1	50	80	90	50

Ref. The Washington Manual of Oncology, 2nd edition, p 218

2.6.1 INDICATIONS FOR INTRAVESICAL THERAPY

- Ta, Grade 3 (High grade) disease
- 2 or more recurrences in a year
- Tumor involving more than 40% of bladder surface
- Diffuse Tis (Carcinoma in situ)

- T1 disease

2.6.2 DRUGS FOR INTRAVESICAL THERAPY

- BCG (most commonly used)

Other options include:

- Interferon alpha
- Mitomycin C
- Thiotepa
- Doxorubicin

2.7 Advanced Stage Disease (Muscle-invasive): T2-T4a,No-Nx,Mo

Radical surgery and urinary diversion.

- Radical cystoprostatectomy is the preferred curative treatment for localized bladder neoplasms.
- Radical cystoprostatectomy includes removal of regional lymph nodes, the extent of which is either standard or extended. In general, more than 12 nodes need to be detected in HPE. All lymph node group packets should be labeled separately and sent to the pathologist.
- Radical cystoprostatectomy in both sexes may not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution.
- Types of urinary diversions:
- Continent- Orthotopic (neobladder) and non-orthotopic (abdominal). Non-orthotopic includes continent pouch/ ureterosigmoidostomy, rectal bladders.
- Non-continent- Ileal conduit is preferred. Other conduits: colonic and jejunal. Terminal ileum and colon are the intestinal segments of choice for urinary diversion.
- The type of urinary diversion does not affect oncological outcome.

2.7.1 CONTRAINDICATIONS FOR ORTHOTOPIC BLADDER SUBSTITUTION

- Positive margins at the level of urethral dissection,
- Positive margins anywhere on the bladder specimen (in both sexes),
- Primary tumor is located at the bladder neck or in the urethra (in women), or
- If tumor extensively infiltrates the prostate.

2.7.2 ADJUVANT CHEMOTHERAPY

- Role of adjuvant chemotherapy is under evaluation. Cisplatin-based chemotherapy has been found most effective (GC/MVAC).
- Adjuvant chemotherapy is not indicated in low-risk disease (no benefit)
    - T2 or less (if pT_3-T_4 then consider for adjuvant chemotherapy)
    - Low grade tumor
    - No nodal involvement
    - No lymphovascular invasion
- Beneficial in:
    - T2 with segmental cystectomy or bladder sparing following TURBT
    - T3 or high grade primary tumor
    - Lymph node involvement
    - Lymphovascular involvement

2.7.3 NEOADJUVANT CHEMOTHERAPY

2.7.3.1 Indications

- Muscle invasive bladder cancer. If upfront surgery is difficult to perform due to larger size/ difficult anatomical location.
- Regional lymph node enlargement

2.7.3.2 Contraindications

- Patients with impaired performance status – 3 to 4
- Impaired renal function

2.7.3.3 Rationale

- To treat micro-metastatic disease at presentation and down stage tumor to increase success of cystectomy.
- Pathologic CR with Cisplatin-based NACT: 14-38%.

A meta-analysis[11] of all completed randomized trials of neoadjuvant chemotherapy for invasive bladder cancer, comprising 2,688 patients, showed that cisplatinum based combination chemotherapy regimens improve the 5-year survival by 5% and reduces the risk of death by 13%.

In another meta-analysis by Winquist et al[12], pT0 status (pathologic CR) was the only factor independently predictive of overall survival in multivariate analyses of four trials (786 patients).

2.7.4 PALLIATIVE CYSTECTOMY FOR MUSCLE-INVASIVE BLADDER CANCER

- Primary radical cystectomy in T4b bladder cancer is not a curative option.
- If there are symptoms, radical cystectomy may be a therapeutic/palliative option.
- Palliative cystectomy can be simple cystectomy only to take care of symptoms. Salvage cystectomy is done if primary radiotherapy fails.
- Intestinal or non-intestinal forms of urinary diversion can be used with or without palliative cystectomy.
- Neo-adjuvant radiotherapy in Muscle-Invasive Bladder Cancer: survival benefit of pre-operative radiotherapy for operable muscle-invasive bladder cancer has not been confirmed.

Bladder Preservation

- Suitable only for patients with disease confined to bladder (T2).
- Tri-modality therapy using chemotherapy, radiation and transurethral resection of tumor is recommended.
- One third of the patients entering a potential bladder-preserving protocol with trimodality therapy will require radical cystectomy. Thus, bladder conservation is reserved for those patients who have a clinical CR to concurrent chemotherapy and radiation.

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[11] Raghavan D, Quinn D, Skinner DG, et al. Surgery and adjunctive chemotherapy for invasive bladder cancer. *Surg Onc* 2002; 11:55.

[12] Winquist E, Waldron T, Segal R, et al. Neoadjuvant chemotherapy in transitional cell carcinoma of the bladder: A systematic review and meta-analysis. *J Urol* 2004; 171:561.

- Prompt cystectomy is recommended for those patients whose tumors respond only incompletely or who subsequently develop an invasive tumor.
- Radiation (RT) is given at a dose of 45 GY in 25 fractions over 5 weeks.
- Cisplatin is given @40 mg/m2 on every week for 5 weeks.
- Repeat cystoscopy is advised at the end of therapy and if no residual tumor is identified than additional 25 Gy may be given with 2 more weekly doses of Cisplatin.
- Concurrent CT + RT (CCRT):
- RT : 40 Gy (25#) = 1 week, CT : weekly CDDP 40 mg/m2 x 6 doses

2.8 Metastatic Disease

- Prognostic Factors:
- **Performance status** and the **absence of visceral metastases** are two important independent prognostic factors for survival.

2.9 Chemotherapy

- Choice of chemotherapy regimen in this setting partially depends on the presence or absence of medical co-morbidities.

2.9.1 INDICATIONS

- Good performance status
- Normal renal function
- Renal dysfunction is not uncommon in patients of metastatic urinary bladder cancer due to obstructive uropathy. Such patients are not fit for most commonly used CDDP based regimen and combination of Taxane + carboplatin may be a preferred regimen.
- No benefit of chemotherapy in patients with
    - Poor performance status
    - Multiple visceral metastasis

- Patients with poor PS and multiple visceral metastases usually do not tolerate combination chemotherapy and in such setting single agent chemotherapy with palliative intent or best supportive care is the best option.

2.9.2 RESULTS

- Median survival of up to 14 months, with long-term disease-free survival reported in
- about 15% of patients with nodal disease and good performance status following cisplatin based combination chemotherapy.

2.9.3 OPTIONS

- Cisplatin / Paclitaxel
- Cisplatin/ Docetaxel
- Gemcitabine / Cisplatin
- Gemcitabine / Paclitaxel
- Although Carboplatin has good activity in bladder cancer but seems to be inferior to Cisplatin therefore Cisplatin should not be replaced with Carboplatin.
- Radiation therapy may be used for symptom relief

2.10 Chemotherapy Schedule

First Line:

- Gemcitabine and Cisplatinum or MVAC
- Both GC and MVAC have comparable efficacies but toxicity profile of GC is much more favourable
- Patients unfit for Cisplatin: use Carboplatin combination chemotherapy or single agents (Gemcitabine, Paclitaxel)

Second Line:

- Paclitaxel/Gemcitabine with or without Cisplatin

2.11 Follow-up

- Every three months for first two years then once in 6 months
- Urine cytology
- Liver and kidney function tests
- Chest X-ray, USG abdomen and pelvis/CT abdomen and pelvis once in 6 months for first 3 years
- Cystoscopy for early stage tumors and for those who have undergone partial cystectomy.

2.12 Cancer of Renal Pelvis and Ureter

- Rare
- 90% are transitional cell and 10 % are squamous cell carcinoma on histopathology.
- Staging workup : similar to urinary bladder cancer
- Standard therapy: Radical excision of the kidney and the ipsilateral ureter and cuff of bladder with complete lymph node dissection from diaphragm to aortic bifurcation and if necessary to include pelvic lymph nodes.
- Evaluation of the total remaining renal function prior to a proposed nephrectomy is indicated using isotope renal scanning.
- The place of radiation and chemotherapy, however, has yet to be established
- Patients with pT2-T4, nodal involvement should be considered for adjuvant chemotherapy as above
- Prognosis is poor compared to bladder cancer

2.13 Non urothelial/Non Transitional Bladder Cancer

- Less than 10% (mixed histology, adenocarcinoma, squamous and small cell)
- Staging and work-up similar to transitional bladder cancer
- No data supporting use of adjuvant chemotherapy
- Urachal tumors will require removal of urachal remnant

2.14 Radiation Schedule at IRCH

2.14.1 INDICATIONS FOR RADIOTHERAPY

T1N0M0 : Radiotherapy not indicated

T2, T3, N1

Options:

- Radical Cystectomy OR
- Maximal TURBT+ CTRT

T4a

- Radical Cystectomy + PORT or
- CTRT or RT alone

PORT after Radical Cystectomy

- Positive /close margins
- Node positive
- Upstaged to T4

T4b, N2, N3, M1 : Palliative RT

Newer options include IMRT and IGRT.

2.14.2 RT DOSE

- Radical RT: 45 Gy /25 # /5 wks to pelvis + Boost 15 Gy/7#
- Post-operative RT: 45Gy/25 #/5 weeks+ Boost 10 Gy

2.15 Common Chemotherapy Agents

2.15.1 CISPLATIN

- Mechanism: DNA alkylator
- Metabolism: widely distributed in the body. Plasma half-life: 3 days. Native drug (30%) and metabolites excreted in urine

Toxicity

- Common: severe nausea and vomiting, hypokalemia and mild myelosuppression.
- Cumulative renal insufficiency - 5% with and 25% to 45% without hydration measures. Increased by concurrent administration of nephrotoxic drugs, such as aminoglycoside antibiotics, or Methotrexate.
- Peripheral sensory neuropathy develops after the administration of cumulative dose of > 200 mg/m2
- Ototoxicity with tinnitus and high-frequency hearing loss occurs in 5% of patients, at the dose of more than 100 mg/m2
- Dose modification. Renal function must return to normal before Cisplatin can be given. Cisplatin should not be given if creatinine clearance is less than 40 mL/minute.
- Cisplatin is relatively contraindicated in patients with documented hearing impairment.

2.15.2 GEMCITABINE

- Mechanism : Antimetabolite. Cell-phase specific, primarily killing cells in S phase and also blocking the progression of cells through the G1-phase to S-phase.
- Metabolism: Nearly entirely excreted in urine as active drug and metabolites

Toxicity

- Dose-limiting: Myelosuppression
- Common.
- Fever with flulike symptoms (40%);
- Nausea, vomiting, diarrhea, stomatitis;
- Macular or maculopapular rash;
- Transient transaminase elevations;
- Mild proteinuria and hematuria.

2.15.3 PACLITAXEL

- Mechanism : antimicrotubule agent, prevents depolymerization

- Metabolism : Nearly totally protein bound and distributed well to body fluids (including effusions) with a plasma half-life of about 5 hours

Toxicity

- Dose-limiting toxicity: Neutropenia
- Hypersensitivity reactions
- Cardiotoxicity (bradyarrythmias)
- Mild to moderate myelosuppression
- Peripheral neuropathy
- Muscle cramps/myalgias

2.16 Chemotherapy Protocols

2.16.1 GEMCITABINE/CISPLATINUM

- Indications (First Line)
- Neoadjuvant: 3 cycles
- Adjuvant: 6 cycles
- Not indicated in low-risk disease (T2 or less, no nodal involvement and no lymphovascular invasion)
- Palliative: 6 cycles
- Anti-emetics: before each chemotherapy
    - Inj Emeset 8mg IV
    - Inj Dexamethasone 8 mg IV
- Day 1
    - Gemcitabine 1250mg/m2 Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
- Day 2
    - Sodium chloride 0.9% 1000ml Intravenous infusion over 1 hour
    - Sodium chloride 0.9% 500ml Intravenous infusion over 30 minutes
    - Mannitol 10% 100ml intravenous infusion over 10 minutes
- Cisplatin 70mg/m2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes (split and give over days 1 & 2)

Sodium chloride 0.9% + 20mmol magnesium sulphate + 20 mmol potassium chloride 1000ml intravenous infusion over 2 hours

- Day 8
    - Gemcitabine 1250mg/m2 Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
- Frequency & duration: every 21 days for a maximum of 6 cycles

Notes:

- BSA should be calculated at the beginning of each cycle.
- Blood counts (Hb, TLC, and platelets), Blood urea, serum creatinine and LFTs must be done prior to Day 1 of each cycle.
- The GFR prior to the first treatment should routinely be > 60 ml/minute. Then prior to each cycle, GFR should be estimated. The dose of Cisplatin should be modified as per guidelines.
- Gemcitabine/Carboplatin (when Cisplatin is contraindicated)

2.16.2 MVAC PROTOCOL (FIRST LINE)

- Schedule:

    Methotrexate 30mg/m2 IV bolus Day 1, 15, 22

    Vinblastine 3mg/m2 (max 10mg) IV bolus Day 2, 15, 22

    Doxorubicin 30mg/m2 IV bolus Day 2 (normal MUGA/ECHO)

    Cisplatin 70mg/m2 IV over 4 hrs Day 2 (with adequate hydration, MgSO4 and mannitol as described in GC protocol)

- Interval between cycles: Repeat Day 28
- Number of cycles:

    Neoadjuvant: 3 cycles

    Adjuvant: 4 cycles

    Metastatic: 6 cycles

- Tests before starting course of chemo: CBC and serum chemistry

- Renal modification of Cisplatinum as described above, doses of other drugs also to be modified according to CBC/Biochem.
- MVAC has equal efficacy to Gemcitabine and Cisplatin but has greater toxicity

2.16.3 2ND LINE CHEMOTHERAPY

- Paclitaxel/Gemcitabine/Cisplatinum
- Paclitaxel/Gemcitabine/Carboplatinum

2.16.4 GEMCITABINE AND CISPLATIN: DOSE MODIFICATIONS

Blood counts

For Gemcitabine day 1 of each cycle

Absolute neutrophil count (ANC)		Platelets (per cu mm)	Dose
More than or equal to 1000/cu mm	And	More than 100,000	100%
500 to 990/cu. mm.	or	75000 to 100,000	75%
Less than 500/ cu mm.	or	Less than 75,000	Delay*

Cisplatin also delayed

Dose modification on day 8 Gemcitabine of each cycle

Absolute neutrophil count (ANC)		Platelets (per cu mm)	Dose
More than or equal to 1000/cu mm	And	More than 100,000	100%
500 to 990/cu mm	or	75000 to 100,000	75%
Less than 500/cu mm	or	Less than 75,000	omit

Renal dysfunction

Creatinine clearance (GFR) (ml/min)	Cisplatin dose	Gemcitabine dose Platelets (per cu mm)
More than or equal to 60	70 mg/m2 on day 1	100%
45-59	35 mg/m2 on day 1 and 2 OR days 1 and 8	100%
Less than 45	Delay	Delay/Omit

3 PROSTATE CANCER

3.1 Investigations

- Physical Examination including Digital Rectal Exam (DRE)
- Serum PSA (prostate specific antigen)
- Complete hemogram
- Liver Function tests, Alkaline Phosphatase, Renal Function Tests, Calcium/ Phosphate
- Urine routine examination and urine culture
- Transrectal ultrasound-guided needle biopsy of prostate
- X ray : Lumbar spine and Pelvis A/P view,
- Bone scan
- Bone marrow biopsy (If anemia or thrombocytopenia present, to rule out BM involvement)
- CT scan abdomen if patient is high-risk or symptomatic.
- MRI spine, in presence of back pain or neurologic deficits, to look for vertebral metastases and cord compression

3.2 Staging

Primary Tumor (T)

Clinical

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically unapparent tumor, neither palpable nor visible by imaging
T1a	Tumor incidental histological finding in ≤ 5% of tissue resected
T1b	Tumor incidental histological finding in > 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumor confined within prostate
T2a	Tumor involves ≤ 50% of one lobe
T2b	Tumor involves > 50% of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades the 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

Pathologic (pT)

pT2	Organ confined
pT2a	Unilateral, involving ≤ ½ of the lobe or less
pT2b	Unilateral, involving > ½ of one lobe but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension
pT3b	Seminal Vesicle invasion
pT4	Invasion of bladder or rectum

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in regional lymph nodes

Pathologic

pNX	Regional lymph nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)

Distant Metastases (M)

MX	Distant metastasis cannot be assessed (not evaluated by any modality)
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

3.3 Histologic Grade

- GX: cannot assess grade
- G1: the tumor closely resembles normal tissue , well differentiated(Gleason 2–4)
- G2: moderately differentiated with moderate anaplasia (Gleason 5–6)
- G3–4: Poorly differentiated / undifferentiated , marked anaplasia (Gleason 7–10)
- Gleason 3+3: tumor is low grade (favorable prognosis)
- Gleason 3+4 / 3+5: tumor is mostly low grade with some high grade
- Gleason 4+3 / 5+3: tumor is mostly high grade with some low grade
- Gleason 4+4 / 4+5 / 5+4 / 5+5: tumor is all high grade

Staging				
	T	N	M	G
Stage I	T1a	N0	M0	G1
Stage II	T1a T1b T1c T1 T2	N0 N0 N0 N0 N0	M0 M0 M0 M0 M0	G2, 3, 4 Any G Any G Any G Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4 Any T Any T	N0 N1 Any N	M0 M0 M1	Any G Any G Any G

3.4 Risk factors

Low-Risk	High-Risk
PSA level <10ng/mL Gleason score ≤ 6 at diagnosis	PSA level>10ng/mL Free-to-total PSA ratio of <20% PSA velocity > 0.75 ng/mL/year Gleason score 7-10 at diagnosis PSA level increase by >2.0ng/mL in the year prior to diagnosis

3.5 10 year Survival Rates (According to AJCC staging)

- Stage I 85%
- Stage II 72%
- Stage III 55%
- Stage IV 30%

Ref.Berger DP, *et al*.(eds) *Concise Manual of Hematology and Oncology* Springer, 2009, p.675.

3.6 Treatment

3.6.1 INCIDENTAL TUMOR (PT1A,PN0,M0,G1)

Surgery: TUR followed by observation, exclude presence of metastasis

3.6.2 LOCALIZED DISEASE

Stage I and II

- Radical prostatectomy – Options include
  - Radical retropubic prostatectomy via midline lower-abdominal incision and
  - Laparoscopic radical prostatectomy with or without robotic assistance.
  - Pelvic lymphadenectomy should be considered for staging of high risk patients.
- Surgery: Contra-indications:
  - Age >75 years,
  - Life expectancy <10 years
- Radiation - Options include :
  - External beam radiation
  - Brachytherapy, and
  - Intensity modulated radiation therapy (IMRT).
  - 3DCRT
  - IGRT
- **Active surveillance** – May be considered in compliant men with low risk disease. Repeat baseline evaluation – digital rectal exam (DRE), free and total PSA, prostate imaging (preferably endorectal MRI), transrectal US-guided biopsy of prostate.

If studies confirm low-risk disease and patient chooses active surveillance,

- Repeat DRE and PSA levels every 6 months indefinitely;
- Repeat imaging and biopsy 12 to 18 months after the baseline evaluation then every 2 to 3 years.

3.6.3 LOCALLY ADVANCED DISEASE

Stage III

Surgery +/- neoadjuvant hormonal therapy – Neoadjuvant hormonal therapy has been shown to decrease the rate of positive surgical margins, but it has not been shown to affect overall survival.

Radiation (external beam (XRT) or brachytherapy) +/- hormonal therapy – The combination of hormonal therapy and XRT has been shown to improve progression free survival compared to radiation alone, but the data on the overall survival benefit of combination therapy over radiation alone is conflicting.

Immediate versus delayed hormonal blockade – Immediate hormonal blockade has been shown to improve quality of life (decreased incidence of cord compression, ureteral obstruction, and pathologic fractures) more than delayed hormonal therapy but studies regarding overall survival benefit are conflicting.

3.6.4 METASTATIC DISEASE

Stage IV: Hormone sensitive disease

First line:

- Medical castration with androgen deprivation therapy

OR

- Surgical castration: bilateral orchiectomy (more cost effective)

Both are equally effective. Response rate 80%,

FOR MEDICAL CASTRATION

Start gonadotropin-releasing hormone (GnRH) agonist such as

- Leuprolide acetate (Leupron) : IM injection : 30 mg q 4 months or 22.5mg q 3 months or 7.5 mg q once a month

- Goserelin (Zoladex): subcutaneous depot injection: 10.6 mg q 3 months or 3.6 mg q 1 month.

Two weeks prior to GnRH agonist, start an androgen receptor antagonist (flutamide 250 mg thrice a day or bicalutamide 50-150 mg/day) to prevent transient testosterone flare phenomenon, and continue for 1 month.

- Degarelix acetate (trade name Firmagon) is a new GnRh antagonist. This drug has got fast and profound suppression of testosterone and is valuable where fast control of diseases is needed. It is also used to prevent flare phenomenon which happens with GnRH agonists. It is given subcutaneously. The common side effects include pain at injection site, hot flushes, weight gain and increase in transaminases and GGTP.

3.6.5 PROGRESSIVE DISEASE DURING HORMONE THERAPY

Often indicated by:

- An asymptomatic rise in PSA and less commonly by
- Symptomatic urinary tract obstruction or
- Bone pain- new lesion on bone scan or new bone pain in existing lesion.
- After orchiectomy or monotherapy with LHRH agonists: addition of antiandrogen especially *if testosterone level identified*.
- After combined androgen blockade: discontinue antiandrogen (possibility of antiandrogen withdrawl response in 25% of cases) then possibly change to alternative antiandrogen e.g. from flutamide to bicalutamide.
- Treatment attempt with ketoconazole 200 mg thrice a day can be considered (blockade of testicular and adrenal androgen synthesis + hydrocortisone (5-10% of circulating androgens are produced by the adrenal glands).
- Other agents with endocrine activity: diethylstilbestrol (DES), Stilbestrol, Tetrasodium Fosfosterol (Honvan), Chlorotriansiene (TACE) and Megesterol acetate may be considered as an alternative in case of failure of initial hormone therapy. Whether any of these drugs confers prolonged survival is uncertain.
- Screening – Screening for and intervention to prevent/treat diabetes and cardiovascular disease is recommended for all patients receiving androgen deprivation therapy (ADT).

3.6.6 HORMONE REFRACTORY DISEASE

Treat with:

- Docetaxel plus prednisone (first line)
- Or other docetaxel regimen
- Or Mitoxantrone plus steroids (QOL benefit, but no proven survival benefit)
- Palliative RT or radionuclide for symptomatic bone metastasis
- Bisphosphonates for bone metastases
- After failure or relapse post-first-line therapy, consider biopsy of metastatic lesion.
- If biopsy is positive for neuroendocrine features (with or without small cell features), consider Cisplatin/Etoposide or Carboplatin/Etoposide or Docetaxel-based regimen.
- If biopsy is negative for neuroendocrine features (with or without small cell features), consider options under "hormone refractory" disease.
- Abiraterone acetate (trade name Zytiga) an orally administered CYP17A1 inhibitor was approved in April 2011.

3.7 Increasing PSA after prostatectomy or radiation

Asymptomatic increase in PSA is a common problem.

- Risk-Assessment – Determine the likelihood of the rising PSA being a sign of treatment failure.
- *High risk factors* include seminal vesicle involvement, Gleason score >6, PSA >10. PSA doubling time of <6 months is also highly predictive of disease progression.
- Local Control – Post-surgery (radical prostatectomy) radiation may provide local control, but no survival benefit has been demonstrated, and radiation-related complications may be higher.
- Post-radiation - salvage surgery is generally not attempted due to higher surgical complication rates. Most men are given medical therapy (given under "Hormone Sensitive Disease" above).

3.8 Follow Up

For patients with early stage disease treated with curative intent

- Initially every 3 months for first 2 years
- Then every 6 months till 5 years
- Then annually

For patients with palliative situation: symptom based approach

3.9 Hormone therapy

GnRH Agonists

Leuprolide (Leupron)	30mg q 4 months IM OR 22.5mg q 3 months IM OR 7.5mg q 1 month IM
Goserelin (Zoladex)	Subcutaneous depot injection into the abdominal wall 10.6mg q 3 months SC OR 3.6mg q 1 month SC

Androgen Receptor Antagonists – Start 2 weeks prior to GnRH agonist

Bicalutamide (Casodex)	50mg OD PO x 1 month
Nilutamide	150mg OD PO x 1 month
Flutamide	250mg x3 PO x 1 month

3.10 Chemotherapy

Docetaxel/ Prednisone	Docetaxel 75 mg/m^2 IV on day 1 Prednisone 5-10 mg PO daily day 1 to 21 Repeat cycle every 21 d for up to total of 10 cycles
Docetaxel	Docetaxel 75 mg/m^2 IV Repeat cycle every 21 d
Docetaxel/ Estramustine	Docetaxel 35 mg/m^2 IV on day 2 of weeks 1 and 2 Estramustine 280 mg/m2 PO days 1 to 5, and days 7 to 11 Dexamethasone 4 mg PO b.i.d. on days 1-3 of weeks 1 and 2 (for premedication) Repeat cycle every 21d
Mitoxantrone/ Prednisone	Mitoxantrone 12mg/m^2 IV on day 1 Prednisone 5 mg PO b.i.d. Repeat cycle every 3 weeks
Estramustine/ Etoposide	Estramustine 15mg/kg/d PO in 4 divided doses x 21d Etoposide 50mg/m^2/d PO in 2 divided doses x 21d

	Repeat cycle every 28 days
Paclitaxel	Paclitaxel 135-170 mg/m^2 IV on day 1 Repeat cycle every 3 weeks
Paclitaxel/ Estramustine (PE)	Paclitaxel 120mg/m^2 CIVI over 96h Repeat paclitaxel every 21 d Estramustine 600 mg/m^2/d PO in 2-3 divided doses continuously starting 24 h before first paclitaxel Repeat cycle every 21 d
Paclitaxel/ Estramustine/ Carboplatin (TEC)	Estramustine 10mg/kg/d in divided doses 5d per wk (start 48h before chemotherapy) Paclitaxel 60-100 mg/m^2 IV weekly Carboplatin AUC 6 IV every 4 wks

3.11 Supportive care

Bisphosphonates

Zoledronic Acid (for CrCl > 30mL/min) Analgesics	4mg IV q 3-4 weeks (for 6-9 months then at 3 monthly interval) For adequate pain control

3.12 Treatment complications

3.12.1 SURGERY (RADICAL PROSTATOVESICULECTOMY):

- Incontinence – 8-11%
- Impotence – more pronounced in patients over 70 years old and less pronounced in patients under 50 years old. Can be treated with Sildenafil, Verdanafil, Tadalafil, and non-pharmacologic techniques.
- Bleeding requiring blood transfusion – Blood transfusion rate is reported at 1-2% for laparoscopic prostatectomy compared to 5-10% for open radical prostatovesiculectomy.
- DVT risk – 1-3%
- Rectal injury risk - < 1%
- Pulmonary embolism and wound infection

3.12.2 RADIATION

- Impotency - 30% to 70% cases
- Rectal symptoms including pain, tenesmus, and diarrhea

- Bladder symptoms including cystitis, hematuria, incontinence,

3.12.3 HORMONE DEPRIVATION THERAPY AND ANTIANDROGENS

- Decreased total and free testosterone leads to hypogonadism, impotence, decreased libido, decreased muscle mass, increased adipose tissue, osteoporosis
- Increase in estrogen to testosterone ratio may cause hot flashes, sweats, and gynecomastia
- Endocrine changes may lead to metabolic syndrome with hyperglycemia, hyperinsulinemia and insulin resistance and dyslipidemia.

3.13 Side effects of chemotherapy

3.13.1 DOCETAXEL

- Allergic reaction (less common with premedication with dexamethasone)
- Musculoskeletal and bone and joint pain and stiffness
- Treatment – Cap. Proxyvon 1 cap thrice a day x 3 to 5 days)
- Fatigue (50%), alopecia (40%), nausea or vomiting (40%), diarrhea (33%)
- BM suppression with a short-lived neutropenia (33%) (peak time day 8 to12), febrile neutropenia (3%)
- Nail changes and sensory neuropathy (33%)
- Fluid retention, especially in the form of pedal edema (20%)
- Alteration in taste and anorexia (20%)
- Excessive tearing (10%)
- Liver damage (administer with caution if LFTs deranged or bilirubin high)

3.13.2 MITOXANTRONE

- Nausea, vomiting,
- Myelosuppression, fever,
- Hepatotoxicity,
- Alopecia, back pain,
- Blue-green urine

3.13.3 CISPLATIN

- Nausea, vomiting,
- Renal toxicity
- Ototoxicity
- Peripheral neuropathy

3.13.4 ETOPOSIDE

- Nausea, vomiting, loss of appetite, diarrhoea,
- Alopecia, back pain,
- Myelosuppression,
- Blue or purple discoloration of skin

4 GCT OF TESTIS

4.1 Investigations

- Complete blood counts
- Renal and Liver Function Tests, Calcium, Phosphate, Uric acid, Na/K
- Serum Markers : Alfa fetoprotein (AFP) , β-HCG, LDH
- Chest X-ray
- CT scan Abdomen/Pelvis
- CT Chest [if abnormal Chest X-ray or CT Abdomen shows RPLN Enlargement]
- Testicular ultrasound
- Brain MRI [if clinically indicated]
- Bone Scan [if clinically indicated]
- Open inguinal Biopsy of contra lateral testis if suspicious ultrasound, cryptorchid testis, or marked atrophy
- Pulmonary function tests (in patients with h/o chronic pulmonary pathology e.g. COPD)
- Sperm banking (patients need to be counseled, if they are unmarried or if married, not yet completed family)

4.2 Salient Points

4.2.1 RISK FACTORS

- Mal / undescended testis, often bilateral, (40 times higher risk)
- Cryptorchidism (risk increased by 10% to 40%, 60% of these are seminoma)
- Family history: 4-10 times higher risk, if father or brother are affected.
- After contra lateral testicular tumor
- Orchitis, trauma, ionizing radiation
- **Genetic defect:** Inv 12p in >80% of tumours. Dupl. 12 p in 20%
- **Age:** commonest malignancy between 20-40 years age group.

4.2.2 DIFFERENTIAL DIAGNOSIS

- Hematoma
- Hydrocele,
- Varicocele,
- Spermatocele,
- Epididymitis,
- Orchitis,
- Inguinal hernia,

4.3 Histology

Histologic subtype		% of all GCTs	Peak Age (Years)
Seminoma		40	25–45
	Classic and anaplastic	35	25–45
	Spermatocytic	5	Average 65
Nonseminoma		60	15–35
	Malignant teratoma	20-25	20–30
	Embryonal Carcinoma	15-20	
	Mixed	8	
	Choriocarcinoma (pure)	<1	
	Yolk sac tumor (pure)	3	
	Differentiated teratoma (mature)	3	

Ref : Abell Textbook of Clinical Oncology

4.4 Serum Markers

Histology	B-HCG [<5MIU/ML, t1/2=18-36 hrs]	AFP [<15ng/ml, t1/2=5-7 days]	LDH
Seminoma	±, 10% +ve, usually <100 IU/mL	-	+
Teratoma	±	+	+
Embryonal	±	+	+
Yolk sac tumors	-	++	+
Choriocarcinoma	++	-	+

During the initial 7-10 days after chemotherapy tumor marker levels may increase, which is usually followed by an exponential drop.

4.5 Staging

TNM classification

Primary Tumor (T)	
The extent of primary tumor is usually classified after radical orchiectomy, and for this reason, a pathologic stage is assigned.	
pTX	Primary tumor cannot be assessed (if no radical orchiectomy then TX is used)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT0	No evidence of primary tumor (e.g., histological scar in testis)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades the spermatic cord with/without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2cm or less in greatest dimension; or multiple lymph nodes, none more than 2cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2cm but not more than 5cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non regional nodal or pulmonary metastasis
M1b	Distant metastasis other than to non regional lymph nodes and lungs

Serum	Tumor Markers (S)
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 times N and β-hCG (mIu/ml) <5,000 and AFP (ng/ml) <1,000ng/ml
S2	LDH 1.5–10 times N or hCG (mIu/ml) 5,000–50,000 or AFP (ng/ml) 1,000–10,000 ng/ml
S3	LDH >10 times N or hCG (mIu/ml) >50,000 or AFP (ng/ml) >10,000 ng/ml

(N indicates the upper limit of normal for the LDH assay.)

4.6 Stage Grouping

0	pTis	N0	M0	S0,SX
I	pT1–4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	T2-4	N0	M0	S0
IS	Any T	N0	M0	S1-3
II	Any pT/T	N1-3	M0	SX
IIA	Any pT/T	N1	M0	S0-1
IIB	Any pT/T	N2	M0	S0-1
IIC	Any pT/T	N3	M0	S0-1
III	Any pT/T	Any N	M1	Sx
IIIA	Any pT/T	Any N	M1-1a	S0-1
IIIB	Any pT/T	N1-3	M0-1a	S2
IIIC	Any pT/T	N1-3	M0-1a M1b	S3 Any S

4.7 Risk stratification

Risk category/Type	NSGCT	Seminoma
GOOD	Testis/RP primary & No Non-Pulmonary Visceral Metastases & S1	Any primary & No Non-Pulmonary Visceral Metastases & Any S
INTERMEDIATE	Testis/RP primary, No Non-Pulmonary Visceral Metastases.	Any primary & Non-Pulmonary Visceral Metastases & Any S
POOR	Mediastinal primary or Non-Pulmonary Visceral Metastases or S3	-

NPVM=Non Pulmonary Visceral Metastases

4.8 5 Year Survival

Histology	Risk Category	5 yr PFS [%]	5yr OS [%]
NSGCT	Good	86	90
	Intermediate	67	72
	Poor (High risk)	41	48
Seminoma	Good	82	86
	Intermediate	75	85

4.9 Treatment: Seminomatous GCT

Treatment is based upon (i) Histologic subtype- seminomatous or nonseminomatous (ii) Stage of disease

4.9.1 SEMINOMA STAGE IA, IB

- Orchiectomy followed by close follow up (active surveillance)
- **Follow Up schedule:** Physical examination, serum LDH , and β- HCG, if raised initially on each visit

Schedule	Interval
Every 3-4 months	Up to 3 years
Every 6 months	4-7 years
Every 1 year	8-10 years

- CT Scan Whole abdomen: once in 6 months for 3 years then yearly till 5 years
- Chest X-Ray once in 6 months for 3 years then SOS (if indicated)
- For patients where active surveillance is not possible consider
- **Adjuvant chemotherapy** with single agent Carboplatin [AUC=7 for 1/2 Cycles (category 1)]

  OR

- **Adjuvant Radiation therapy** (20-30 Gy) [Category 1] to the infradiaphragmatic area, including the para-aortic lymph nodes and in some cases the ipsilateral ileo-inguinal nodes.

4.9.2 SEMINOMA: STAGE IS

- Orchiectomy followed by adjuvant radiation therapy

(20-30 Gy, administered to the infradiaphragmatic area, including para-aortic lymph nodes, with or without ipsilateral ileo-inguinal nodes).

4.9.3 SEMINOMA STAGE IIA AND IIB

- Orchiectomy followed by adjuvant chemotherapy
- Chemotherapy: Four cycles of etoposide and cisplatin (EP).
- Alternative to chemotherapy:

  Radiation therapy: 35-40 Gy to the infradiaphragmatic area, including the para-aortic and ipsilateral iliac lymph nodes. Mediastinal irradiation is not recommended.

4.9.4 SEMINOMA STAGE IIC AND III

- Good risk: 4 cycles of EP OR 3 cycles of BEP chemotherapy
- Intermediate risk: 4 cycles of BEP
- Non pulmonary visceral metastasis): Re-assess for response 4 weeks after above treatment
- **Residual mass with normal markers**: Do PET scan 6 weeks after the last course of chemotherapy
    - If the PET scan is negative - ONLY FOLLOW UP.
    - If PET scan is positive: Do biopsy: If positive - then salvage chemotherapy or radiation therapy OR surgical excision, if feasible.
    - If a PET scan cannot be done and (i) the residual mass is 3 cm or less in size, follow up is advised
    - If the mass is larger than 3 cm in size, consider radiation therapy or surgery (if feasible) or chemotherapy.
- Progressive disease with a growing mass or rising marker levels: salvage chemotherapy

4.10 Follow up plan

- Physical examination: Once in 3-4 months up to 3 years, then once in 6 months till 5 years then once a year indefinitely.
- Chest X-Ray and marker (serum LDH and β HCG, wherever elevated) – Once in 3-4 months up to 3 years, then once in 6 months till 5 years then once a year indefinitely.
- CT abdomen & Pelvis: Once in 6 months up to 3 years, then once a year till 5 years.

4.11 Treatment of Relapse: Seminomatous GCT

STAGE	RELAPSE RISK	TREATMENT
Stage I	4%	BEP x 4 cycles
Stage II A	9%	BEP x 4 cycles
Stage II B	16%	BEP x 4 cycles
Stage IIC	5%	VIP x 2-4 cycles, consider HDCT
Stage III	25%	VIP x 2-4 cycles, consider HDCT

4.12 Treatment: Nonseminomatous GCT

4.12.1 STAGE IA/B, IIA/B:

Primary radical inguinal orchiectomy followed by 3 cycles of BEP chemotherapy

(For IIB – we prefer 4 cycles).

4.12.2 STAGE IIC, IIIA, IIIB, IIIC

Stage	Risk category	Cure rate	Management
IIC,IIIA	Good	95%	4 cycles of BEP
IIIB	Intermediate	70%	4 cycles of BEP
IIIC	Poor	50%	4 cycles of BEP or. Enrollment in clinical trials is preferred.

Brain metastases: Risk: 10% in Pts with advanced disease

Primary chemotherapy plus radiation. Surgery, if single lesion.

If single metastasis: Good prognosis

Long term survival: 35%

In patients with primary cerebral metastases- 30-40%

Metastases occurring during the treatment or in relapsed patients – 2 to 5%.

4.12.3 RESPONSE ASSESSMENT

- 4 weeks after last cycle of chemotherapy and is done by –
- Physical examination,
- Serum tumour markers and
- CT scan of abdomen and pelvis.
- Complete response: follow up
- **If Residual disease +ve** on CT scan, but markers are normal : surgery to resect all the residual disease
- If the resection specimen shows only necrotic tissue or teratoma : follow up
- If residual disease present e.g. embryonal, yolk sac, choriocarcinoma, or seminoma elements are present, the patient should receive 2 cycles of salvage chemotherapy using EP, or TIP, or VIP, or VeIP.
- Patients who do not have a complete response to chemotherapy and/or whose disease cannot be resected - should receive salvage chemotherapy.

4.13 Recurrent disease and salvage treatment

Patients who do not have a complete response to first-line therapy, or whose disease recurs after complete response, are categorized into favorable and unfavorable prognostic groups.

Variables	Favourable	Unfavourable
Primary	Testis	Non testis
Volume	Low	High
Markers	Low	High
Response to 1ST line Chemotherapy	CR	Incomplete Response
Management	VeIP/TIP	Clinical Trial [preferred] or VeIP/TIP

4.13.1 CHEMOTHERAPY REGIMES

Regimen	Schedule		Treatment Interval
BEP	Bleomycin 10 IU/m2	IV day 1-3	21 days
	Etoposide 100 mg/m2	IV day 1-5	
	Cisplatin 20mg/m2	IV day 1-5	
EP	Etoposide 100 mg/m2	IV day 1-5	21 days
	Cisplatin 20 mg/m2	IV day 1-5	
VIP	Etoposide 100 mg/m^2	IV days 1-5	21 days
	Ifosfamide 1.2 gm/m^2	IV days 1-5	
	Mesna [60% of Ifosfamide]	IV days 1-5	
	Cisplatin 20mg/m^2	IV days 1-5	
TIP	Paclitaxel 250 mg/ m^2	IV days 1-3	21 days
	Ifosfamide 1500 mg/m^2	IV days 2-5	
	Cisplatin 20 mg/m^2	IV days 1-5	
VeIP	Inj Vinblastine 0.11mg/kg	IV days 1- 2	21 days
	Ifosfamide 1.2 gm/m^2	IV days 1-5	
	Mesna [60% of Ifos]	IV days 1-5	
	Cisplatin 20mg/m2	IV day 1-5	
Gemox	Gemcitabine 1000mg/m^2	IV days 1, 8	21 days
	Oxaliplatin 130 mg/m^2	IV days 1	

Occasional patient especially with yolk sac tumor with platinum refractory disease may respond to Actinomycin D containing salvage chemotherapy.

High-dose chemotherapy and stem cell rescue:

CR rate is 5-10% in Cisplatin-refractory testicular cancers.

Patients with Cisplatin-sensitive disease have much better responses; more than 60% of these patients can have long term outcome following high dose chemotherapy.

5 EXTRAGONADAL GERM CELL TUMOUR (E-GCT)

5.1 Investigations

- Physical examination, palpation of testis, and neurological examination for intra-cranial extragonadal GCT
- Complete blood counts
- Liver and renal functions tests,
- Serum tumor markers: AFP, β-HCG, LDH
- Chest X ray PA view
- Abdominal and testicular ultrasound (obligatory, especially with retroperitoneal germ cell tumors).
- CT scan of chest and whole abdomen
- MRI brain and spinal cord (mandatory with intracranial tumors)
- PET scan (as part of clinical study)
- Histopathology
- Bone marrow biopsy with touch preparation and cytogenetics (for mediastinal GCT)

5.2 Salient Points

- Extragonadal germ cell tumors are located in mediastinum, retroperitoneum, pineal region, coccygeal region, and rarely in prostate, liver, esophagus, stomach.
- Frequency
    - Adults-5-10% of all GCT cases are extra-gonadal.
    - Pediatric age group-82% of GCTs are extra-gonadal.
- Peak age:20-40 years;
- M: F = 12:1 (exception: benign teratoma: male:female = 1:1)

5.2.1 GENETIC PREDISPOSITION

- Frequent detection of isochromosome 12p
- Non-seminomatous mediastinal GCTs - increased incidence in patients with Klinefelter's syndrome (47, XXY in 20% of cases).
- Predisposition for hematological neoplasia (in approximately 20% of cases), e.g. acute leukemia
- (AML, FAB M7), myelodysplastic syndrome, malignant histiocytosis: isochromosome- 12p present in leukemic blasts.
- Retroperitoneal germ cell tumors: increased risk of carcinoma in situ (CIS) testicular carcinoma (40%).

5.2.2 HISTOLOGY

- Extragonadal GCTs are histologically similar to gonadal GCTs.
- Differentiation between pure seminomas and non-seminomatous tumors has therapeutic and prognostic relevance.
- Approximately 20% of all germ cell tumors are mixed tumors.

5.2.2.1 Benign

- Mature teratomas (potentially malignant, if containing> 50% immature tissue)

5.2.2.2 Malignant

- Seminomas (intracranial seminomas = "germinomas"), 20-24%
- Non-seminomatous (immature teratoma, embryonic carcinoma, teratocarcinoma, choriocarcinoma, yolk sac tumor).
- Mixed tumors (including seminoma-containing tumors).
- Uni or bilateral testicular carcinoma in situ (CIS, synonym: TIN, testicular intraepithelial neoplasia) occurs in 33% of all cases of extragonadal germ cell tumors. As patients with extragonadal tumors are treated with platinum-based therapy (curative for TIN)
- Testicular biopsy is not necessary in case of normal ultrasound finding.

5.2.3 LOCATION

	Children (≤ 15 years of age)	Adults (>15 years of age)
Coccygeal region	27%	Rare
Intracranial	15%	2-10%
Retroperitoneum	4%	20-30%
Mediastinum	3%	50-70%

- Teratomas are often already present at birth; peak age for highly malignant non-seminomatous tumors: 1-5 years; seminomas occur mainly in children < 7 years.
- Origin of mediastinal and retroperitoneal malignant germ cell tumors is often non-seminomatous (76 %).
- Seminomas frequently occur intracranially (65%, "germinomas"); peak age: 20-30 years.

5.3 Symptoms

5.3.1 MEDIASTINAL GERM CELL TUMORS

Symptoms only in late stages:

Cough, chest pain, dyspnea, and superior vena cava syndrome;

50% of mediastinal tumors are diagnosed incidentally

5.3.2 RETROPERITONEAL GERM CELL TUMORS

Symptoms often only in late stages:

Abdominal pressure, flank pain/backache, organ displacement symptoms (constipation, dysfunctional voiding, abdominal distension): often incidental diagnosis.

5.3.3 PINEAL TUMORS

Signs of increased intracranial pressure: headaches, reduced visual field, ataxia, lethargy, nausea;

Parinaud's syndrome (vertical gaze palsy, nystagmus, diplopia.)

Signs of pituitary failure (e.g., diabetes insipidus) with invasive tumors or suprasellar location.

5.3.4 COCCYGEAL REGION

Pain, sciatica, rectal compression, compression of the urinary bladder, voiding and defecation disorders

5.3.5 GENERAL SYMPTOMS

Fever, night sweats, weight loss, anorexia, reduced performance) with malignant and rapidly progressive tumors, gynecomastia if β-HCG increased.

5.4 Differential diagnosis

- Anterior mediastinum
    - Thymoma,
    - Lymphomas,
    - Mesenchymal tumors,
    - Endocrine tumors,
    - Cysts
- Retroperitoneal tumors
    - Tumours of the adrenal glands,
    - Mesenchymal tumours,
    - Lymphomas,
    - Lymph node metastatases
- Most primary retroperitoneal germ cell tumours manifest themselves along the midline; in contrast, lymph node metastases to the left or the right are indicative of an occult primary ipsilateral tumor.
- Pineal region
    - Glioma,
    - Pineoblastoma,
    - Pineocytoma,
    - Cysts

5.5 Prognosis

- The prognostic classification of testicular germ cell tumors does not apply to extragonadal tumors.
- Extragonadal seminomatous tumors: carry a favorable prognosis similar to testicular seminomas.
- Extragonadal non-seminomatous germ cell tumors carry a poor prognosis compared to testicular non-seminomatous tumors.
- The prognostic score of Hartmann is used.

Prognotic Score for extragonadal non-seminomatous GCTs (Hartmann 2002)

Prognostic factors	**Score**
Mediastinal tumor	2
Raised β-HCG	1
Metastasis to lung	1
Metastasis to liver	1
CNS Metastasis	2

Prognostic score	5 year survival
Intermediate low (0-1)	52%
Intermediate high (2-3)	47%
Poor (>3)	11%

5.6 Treatment

5.6.1 MEDIASTINAL / RETROPERITONEAL GERM CELL TUMORS

5.6.1.1 Seminomatous Extragonadal Germ Cell Tumors

Retroperitoneal location : tumors ≤ 5 cm

- Chemotherapy: Four cycles of etoposide and cisplatin (EP) or 3 cycles of BEP followed by re-assessment
- Alternative to chemotherapy: Radiation therapy: 35-40 Gy to the infra-diaphragmatic area, including the para-aortic and ipsilateral iliac lymph nodes.

Retroperitoneal tumors >5cm

- Chemotherapy : Four cycles of of BEP followed by re-assessment 4 weeks after chemotherapy
- Residual mass with normal markers
- Do PET scan 6 weeks after the last course of chemotherapy
- If the PET scan is negative - ONLY FOLLOW UP.
- If PET scan is positive: Do biopsy. If positive - then radiation therapy OR surgical excision, if feasible or salvage chemotherapy.
- **If a PET scan cannot be done** and the residual mass is 3 cm or less in size, follow up is advised
- If the mass is larger than 3 cm in size, consider radiation therapy or surgery (if feasible)
- Progressive disease with a growing mass or rising marker levels: salvage chemotherapy

Mediastinal location. BEP Chemotherapy: Four cycles followed by re-assessment. Four weeks after chemotherapy followed by surgical resection of residual tumor tissue.

5.6.1.2 Non-seminomatous Extragonadal Germ Cell Tumors

- Treatment like high-risk testicular tumors: BEP x 4 cycles: followed by reassessment.
- Consider: early intensification with high-dose chemotherapy and stem cell transplantation and resection of residual tumor (esp. with mediastinal tumors) → 5-year survival 75%

5.6.1.3 Teratomas

- Primary surgery
- With large tumors: neoadjuvant chemotherapy to reduce tumour size followed by resection with curative intent.

5.6.2 TREATMENT OF BENIGN TERATOMAS

- Tumour resection;
- Chemotherapy and radiotherapy not indicated.

5.6.3 TREATMENT OF INTRACRANIAL GERM CELL TUMORS

Treatment according to existing pediatric protocols (e.g. SIOP CNS GCT 96)

Germinomas (intracranial seminomas)

- Radiotherapy, 24 Gy to craniospinal+ 16 Gy tumor bed OR
- 2 cycles of VIP protocol + 40 Gy local radiotherapy

Non-germinomas (yolk sac tumors, choriocarcinomas, embryonic carcinomas)

- 4 cycles of VIP protocol , possibly resection of residual tumor followed by radiotherapy

Teratomas: primary surgery; with large tumors, neoadjuvant chemotherapy followed by surgery.

5.7 Chemotherapy Protocols

Regimen	Schedule	Treatment Interval
BEP	Bleomycin 10 IU/m2 IV day 1-3	21 days
	Etoposide 100 mg/m2 IV day 1-5	
	Cisplatin 20mg/m2 IV day 1-5	
VIP	Etoposide 100 mg/m^2 IV day 1-5	21 days
	Ifosfamide 1.2 gm/m^2 IV day 1-5	
	Mesna [60% of Ifosfamide] IV day 1-5	
	Cisplatin 20mg/m^2 IV day 1-5	

5.8 Follow up

- Patients treated with curative intent should be closely monitored including physical examination, tumor marker assays, and imaging.
- In palliative situation: symptom-based approach.

References

Bokemeyer C, Nichols CR, Droz JP et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol* 2002; 20:1864-73.

Hartmann JT, Nichols CR, Droz JP et al. Prognostic variables for response and outcome in patients with extra gonadal germ-cell tumors, *Ann Oncol* 2002:13:1017-28.

6 PENILE CANCER

6.1 Investigations

- Physical Examination
- Complete hemogram
- Liver and renal functions, calcium, serum LDH
- Urine analysis
- Chest X-ray
- US abdomen and pelvis including inguinal region
- CT scan abdomen & pelvis
- Bone scan / skeletal survey (in patients with bone pains)
- Cystourethroscopy
- Histology: Obligatory: biopsy for histological analysis

6.2 Risk Factors

- Age
- Smoking
- Chronic irritation (e.g., phimosis), poor hygiene, smegma retention.
- Sexual promiscuity, recurrent balanoposthitis.
- HPV infection: particularly with genotypes 16 and 18 (rarely 31,35, and 39); HPV detected in 27-71% of patients with penile cancer
- PUVA therapy.
- Occupational risk (chimney sweeper).

6.3 Precancerous Lesions

A number of penile lesions have the potential of malignant transformation. The exact role of these lesions in the development of penile cancer is uncertain.

- Balanitis xerotica obliterans, balanitis plasmacellularis of Zoon
- Erythroplakia of Queyrat
- Leukoplakia
- Bowen's disease

- Buschke-Lowenstein giant condyloma (verrucous carcinoma)

6.4 Clinical Presentation

- Incidence: 1-2 cases/100,000 men/year; after 50 years of age:
- Exophytic masses of the penis (47%)
- Pain, ulcers (35%)
- Inflammatory changes of the penis (17%)
- Burning or stabbing sensation under the prepuce
- Enlarged inguinal lymph nodes. 20-60% of men have palpable lymph nodes → 50% are nodal metastases, and 50% infective involvement
- In some cases: weight loss, fatigue
- Late symptoms: bleeding, urethral fistula or obstruction, weight loss, fatigue.

6.5 Histology subtypes

Type	Frequency (%)
Squamous cell carcinoma	>93
Basal cell carcinoma	4
Carcinoma in situ	1
Melanoma	1
Sarcoma	1
Malignant hemangioendothelioma	rare
Kaposi's sarcoma (especially in HIV patients)	rare
Metastases	rare

6.6 Staging

6.6.1 TNM

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Non invasive verrucous carcinoma
T1	Tumor invades sub epithelial connective tissue
T2	Tumor invade corpus spongiosum
T3	Tumor invades urethra or prostate
T4	Tumor invades contiguous structures

N	Regional Lymph nodes involved
NX	Regional Lymph nodes cannot be assessed
N0	No regional lymph node metastasiss
N1	Metastasis to a single superficial inguinal lymph node
N2	Metastasis to multiple or bilateral superficial inguinal lymph nodes
N3	Metastasis to deep iliac or pelvic lymph nodes
M	Distant Metastasis
MX	Distant Metastasis cannot be assessed
M0	No metastasis
M1	Metastasis present

6.6.2 AJCC STAGING (2002)

Stage	TNM classification		
0	Tis-a	N0	M0
I	T1	N0	M0
II	T1	N0	M0
	T2	N0-1	M0
III	T1-2	N2	M0
	T3	N0-2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

6.6.3 STAGING ACCORDING TO JACKSON

Stage 0 (A)	Tumor limited to glans / prepuce
Stage I (B)	Tumor invades shaft of penis
Stage III (C)	Tumor with operable inguinal lymph nodes
Stage IV (D)	Tumor invades contiguous structures, inoperable inguinal lymph nodes or distant metastasis.

6.7 Prognostic Factors

Most important prognostic factor is: clinical tumor stage at presentation which includes -

Size, depth of infiltration, and involvement of regional lymph nodes

5 year survival:

- With positive inguinal nodes = 27%

- With negative inguinal nodes = 66%

6.8 Treatment

6.8.1 CARCINOMA IN SITU

Options:

- Local surgical excision,
- Laser treatment,
- Topical 5-FU,
- Cryotherapy, and
- Radiotherapy.

6.8.2 INVASIVE PENILE CARCINOMA

6.8.2.1 Surgery is the standard approach

- Radical surgical resection: Local tumor stage and involvement of regional lymph nodes determine extent of resection
- Stage T1 (localized): Wide excision with a free proximal margin of 2 cm

  Smaller margins result in local relapse rates of up to 32%.

- Stage T2-3: Total penectomy.
- Stage T4: Wide en bloc resection of the primary lesion and any involved sections of the abdominal wall as well as bilateral inguinal lymphadenectomy.

6.8.2.2 Role of Inguinal lymph node dissection

- T1, T2 tumor without palpable inguinal lymph nodes : wait and watch .
- T1, T2 with persistent lymph node enlargement after 4-6 weeks of adequate antibiotic treatment : Bilateral inguinal lymphadenectomy : should be performed.
- In locally advanced stages (T3, 4): “prophylactic” bilateral lymph node dissection (but probably does improve overall survival).

- Only 20% of men with occult lymph node metastases come under treatment with curative intent (cure rate approx. 88%), while 80% of men probably do not benefit from prophylactic lymphadenectomy (no lymph node metastasis).
- The procedure related mortality rate is < 1% and complications such as lymph edema, pulmonary embolism, infection, etc. may occur.
- Modified inguinal lymphadenectomy and selective lymphadenectomy can be carried out in certain patients.
- Sentinel lymph node biopsy: No definite evidence yet for its value.

6.8.2.3 Radiotherapy

- In earlier stages:as an organ-preserving form of treatment. Local relapse rate: approx. 10-20%.
- In locally nonresectable tumors or relapses, and in cases where lymphadenectomy is impossible: palliative percutaneous radiotherapy should be considered.

6.8.2.4 Adjuvant treatment

No definite evidence yet for role of adjuvant radiotherapy or chemotherapy following surgical resection.

6.8.2.5 Conservative (non-surgical) approach

- Neoadjuvant chemotherapy,
- Radio-chemotherapy, or
- Intra-arterial chemotherapy.

6.9 Treatment of Relapsed and Advanced Disease

- Local relapse: More after organ preserving treatment;
  Salvage therapy: complete penectomy and, if necessary, total anterior exenteration.
- Consider prophylactic or therapeutic bilateral inguinal lymphadenectomy.

6.10 Treatment of Metastatic Disease

- A combination of local therapy and systemic chemotherapy.
- Active drugs alone or in combination.
    - Bleomycin,
    - MTX,
    - 5-FU,
    - Cisplatin, and Cyclophosphamide
- Others e.g. Ifosfamide, Docetaxel, Paclitaxel, Gemcitabine, or Vinorelbine; these have not yet been tested in randomized studies in penile cancer.
- CMB regimen
    - Inj. Cisplatin 75mg/m2 D1
    - Inj. Methotrexate 25 mg/m2 IV bolus D 1 & 8
    - Inj. Bleomycin 10 u/m2 IV D1 & 8

Reference:

Castellsague X, Bosch FX, Munoz N, et al. Male circumcision, penile human papilloma virus infection, and cervical cancer in female partners. *N Engl J Med* 2002; 346:1105-12.

7 ADRENOCORTICAL CARCINOMA

7.1 Evaluation

- Medical history and physical examination
- Performance status
- Complete hemogram, Peripheral Smear
- Routine chemistry (LFT, RFT, Calcium, Phosphate, Uric Acid)
- Serum cholesterol and serum triglycerides
- ECG and Echocardiography
- X-ray chest PA view
- CECT Chest if indicated
- CECT Abdomen/Pelvis
- Bone scan: if symptoms suggestive of bone involvement.
- Endocrine evaluation

7.1.1 ENDOCRINE SCREENING

- Serum cortisol (Basal, Overnight Dexamethasone Suppression Test)
- Serum dehydroepiandrosterone sulfate (DHEA-S)
- Plasma adrenocorticotropic hormone (ACTH) [After serum cortisol screening if indicated]

Screening recommended at the time of starting treatment and at 3 and 6 months

7.2 TNM Staging

Tumor (T)	
T1	Tumor 5 cm or less in size; invasion absent
T2	Tumor greater than 5 cm in size; invasion absent
T3	Tumor outside adrenal in fat
T4	Tumor grossly invading adjacent organs
Lymph nodes (N)	

N0	No positive lymph nodes
N1	Positive lymph nodes
Metastases (M)	
M0	No distant metastases
M1	Distant metastases

Stage	TNM Classification
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1, N1, M0 T2, N1, M0 T3, N0, M0
Stage IV	T3, N1, M0 T4, any N, M0 Any T, any N, M1

7.3 Treatment options according to stage

- **Stage I.** Complete surgical removal of the tumor.
- **Stage II.** Same as for Stage I.
- **Stage III.** Complete surgical removal of tumor with removal of lymph node tissues in the area. For patients unable to undergo complete resection, drug therapy with mitotane.
- **Stage IV.** Chemotherapy

Mitotane EDP Regimen for Adrenocortical Carcinoma:

- IV Etoposide 100 mg/m2 on Day 5,6, and 7
- IV Doxorubicin 20 mg/m2 on Days 1 and 8
- IV Cisplatin 40 mg/m2 on Days 2 and 9.

4 weekly cycles

Maximum 6 cycles.

Hemogram is to be done between 12th and the 15th day from the start of EDP administration.

Physical examination and hematologic profile is done before each course of chemotherapy.

Mitotane:

- Administered orally (Tablet)
- Starting dose: 1 g/day
- Progressive dose increments up to 4 g/day (or the maximum tolerated dose)
- Given in divided doses.
- If tolerated, continuously administered concomitantly with chemotherapy and during the rest period between successive cycles, and afterwards until a diagnosis of progression or the onset of severe toxicity.

All patients: concomitant administration of hydrocortisone or dexamethasone to prevent adrenal insufficiency.

[*Ref*: Berruti A et al. *Cancer*. 1998;83:2194–2200.]

8 APPENDICES

8.1 How to Determine Creatinine Clearance?

The creatinine clearance is calculated by the Cockcroft–Gault formula which takes into account age, weight, and serum creatinine.

$$\text{For Males Creatinine Clearance (ml/mt)} = \frac{(140 - \text{Age}) \text{ weight in Kg}}{72 \text{ x serum creatinine}}$$

$$\text{For Females Creatinine Clearance (ml/mt)} = \frac{(140 - \text{Age}) \text{ weight in Kg}}{72 \text{ x serum creatinine}} \times 0.85$$

(Ref : Cockcroft DW and Gault MH. *Nephron* 1976;16:31-34.)

The creatinine clearance can also be determined from a timed urine collection.

$$\text{Creatinine clearance} = \frac{\text{urine creatinine}}{\text{serum creatinine}} \times \frac{\text{urine volume}}{\text{time}}$$

8.2 How to Determine Drug Dose?

- Drug doses are calculated according to body surface area (BSA, mg/m2)
- BSA is determined by using a nomogram scale or by using a BSA calculator
- Once the BSA is determined, multiply the BSA by the amount of drug specified in the regimen to find the total dose of drug to be administered.
- For obese patients, ideal body weight as opposed to actual body weight may be used to calculate BSA. It is important to refer to IBW table to determine IBW on the individual's actual height. Once the IBW is determined, add one third of the IBW to the IBW, which is then used to determine the BSA. For example a patient's height is 160 cm and her body weight is 100 kg. IBW for this height should be 60 kg. So 60 + 20 (one third of IBW) = 80kg should be used to calculate her BSA.

8.3 Area Under Curve (AUC)

- The AUC refers to the area under the drug concentration x time curve, and it provides a measure of total drug exposure. It is expressed in concentration x units (mg/ml x min).
- A formula for quantifying exposure to Carboplatin based on dose and renal function was developed by Calvert et al (Calvert AH et al. *J Clin Oncol* 1989;7:1748-56.)
- Carboplatin dose (mg) = target AUC (mg/ml x min) x [GFR (ml/min) + 25]
- It is important to note that the **total dose is in mg and not mg/m^2**. Target AUC is usually between 5 and 7 mg/ml/min for previously untreated patients. In previously treated patients, lower AUC generally 5 (between 4 and 6 mg/ml/min) is recommended. AUC > 7 is generally not associated with improved response rates.

8.4 Guidelines for Common Chemotherapy Drugs based on Renal Function

Drug	Recommended dose
Bleomycin	No dose reduction if Cr Cl >60 ml/min
	Reduce dose by 25% if Cr Cl 10-60 ml/min
	Reduce dose by 50% if Cr Cl <10 ml/min
Cisplatin	No dose reduction necessary if creatinine clearance is >60 ml/min
	Reduce dose by 50% if creatinine clearance 30 to 60 ml/min
	Omit, if creatinine clearance <30 ml/min
Carboplatin	No dose reduction if Cr Cl >60 ml/min
	AUC dose is modified according to creatinine clearance
Cyclophosphamide	No dose reduction if Cr Cl >50 ml/min
	Reduce dose by 25% if Cr Cl 10 to 50 ml/min
	Reduce dose by 50% if Cr Cl <10 ml/min
DTIC (Dacarbazine)	No formal guidelines available, however, dose reduction may be necessary in presence of severe renal dysfunction.
Docetaxel	No dose reduction necessary
Doxorubicin	No dose reduction necessary
Liposomal doxorubicin	No dose reduction necessary
Etoposide(VP-16)	No dose reduction necessary if Cr Cl >50 ml/min
	Reduce dose by 25% if Cr Cl 10 to 50 ml/min
	Reduce dose by 50% if Cr Cl <10 ml/min
5 Flourouracil	No dose reduction is necessary
Gemcitabine	No dose reduction necessary
Ifosphamide	Dose reduction necessary in presence of severe renal failure
Leucovorin	No dose reduction necessary
Melphalan	No dose reduction necessary but use caution in presence of severe renal failure
Methotrexate	No dose reduction necessary if Cr Cl >60 ml/min
	Reduce dose by 50% if Cr Cl 30-60 ml/min
	Omit if Cr Cl <30 ml/min
Paclitaxel	No dose reduction necessary
Topotecan	No dose reduction necessary if Cr Cl >60 ml/min
	Reduce dose by 50% if Cr Cl 10-60 ml/min
	Omit if Cr Cl <10 ml/min
Actinomycin-D	Not available. However use with caution in presence of renal dysfunction.
Vinblastine	No dose reduction necessary
Vincristine	No dose reduction necessary
Vinorelbine	No dose reduction necessary

Guidelines on targeted therapy (e.g. Sunitinib, Sorafenib, Pazopanib, etc. refer to page nos. 16 to 18).

8.5 Guidelines for Chemotherapy Dosage based on Hepatic Function

Drug	Recommended dose reduction
Altretamine (hexamethylmelamine0	No dose reduction is necessary
Amifostine	No dose reduction is necessary
Bleomycin	No dose reduction is necessary
Carboplatin	No dose reduction is necessary
Cisplatin	No dose reduction is necessary
Cyclophosphamide	Reduce by 25% if bilirubin 3.0-5.0 mg% Or SGOT>180IU/dl
Dacarbazine (DTIC)	No dose reduction necessary
Docetaxel	Omit, if bilirubin >1.5 mg%, SGOT>60 IU, alk Phos >2.5 times of upper limit of normal
Doxorubicin	Reduce dose by 50% if bilirubin 1.5 to 3.0 mg% Reduce dose by 75% if bilirubin 3.1-5.0 mg% Omit, if bilirubin >5.0 mg%
Liposomal doxorubicin	Reduce dose by 50% if bilirubin 1.5 to 3.0 mg% Reduce dose by 75% if bilirubin 3.1-5.0 mg% Omit, if bilirubin >5.0 mg%
Etoposide (VP-16)	Reduce dose by 50% if bilirubin 1.5 to 3.0 mg% Or SGOT 60-180 IU/dl Omit, if bilirubin >3 mg%, SGOT >180 IU/dl
5-Flourouracil	Omit , if bilirubin >5 mg%
Gemcitabine	No dose reduction is necessary
Ifosfamide	No dose reduction is necessary
Leucovorin	No dose reduction is necessary
Melphalan	No dose reduction is necessary
Megesterol acetate	No dose reduction is necessary
Mesna	No dose reduction is necessary
Methotrexate	Reduce dose by 25% if bilirubin 3.1to 5.0 mg/dl Or SGOT >180 IU/dl Omit, if bilirubin >5 mg%.
Mitoxantrone	Reduce dose by 25% if bilirubin >3mg%
Paclitaxel	No formal recommendation for dose reduction if bilirubin 1.5 to 3.0 mg% or SGOT 60-180 IU/dl. Omit if bilirubin >5mg/dl or SGOT >180 IU/dl
Tamoxifen	No dose reduction necessary
Thiotepa	No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary

Vinblastine	No dose reduction if bilirubin<1.5 mg/dl, and SGOT <60 IU/ml. Reduce dose by 50% if bilirubin 1.5 to 3.0 mg/dl And SGOT 60-180 IU/dl Omit, if bilirubin >3 mg% and SGOT >180 IU/ml.
Vincristine	No dose reduction if bilirubin<1.5 mg/dl, and SGOT <60 IU/ml. Reduce dose by 50% if bilirubin 1.5 to 3.0 mg/dl And SGOT 60-180 IU/dl Omit, if bilirubin >3 mg% and SGOT >180 IU/ml.
Vinorelbine	No dose reduction if bilirubin<2 mg/dl, Reduce dose by 50% if bilirubin 2.0 to 3.0 mg/dl Reduce dose by 75% if bilirubin 3.1 to 5.0 mg% Omit, if bilirubin >5.0 mg%

8.6 ECOG Performance Status

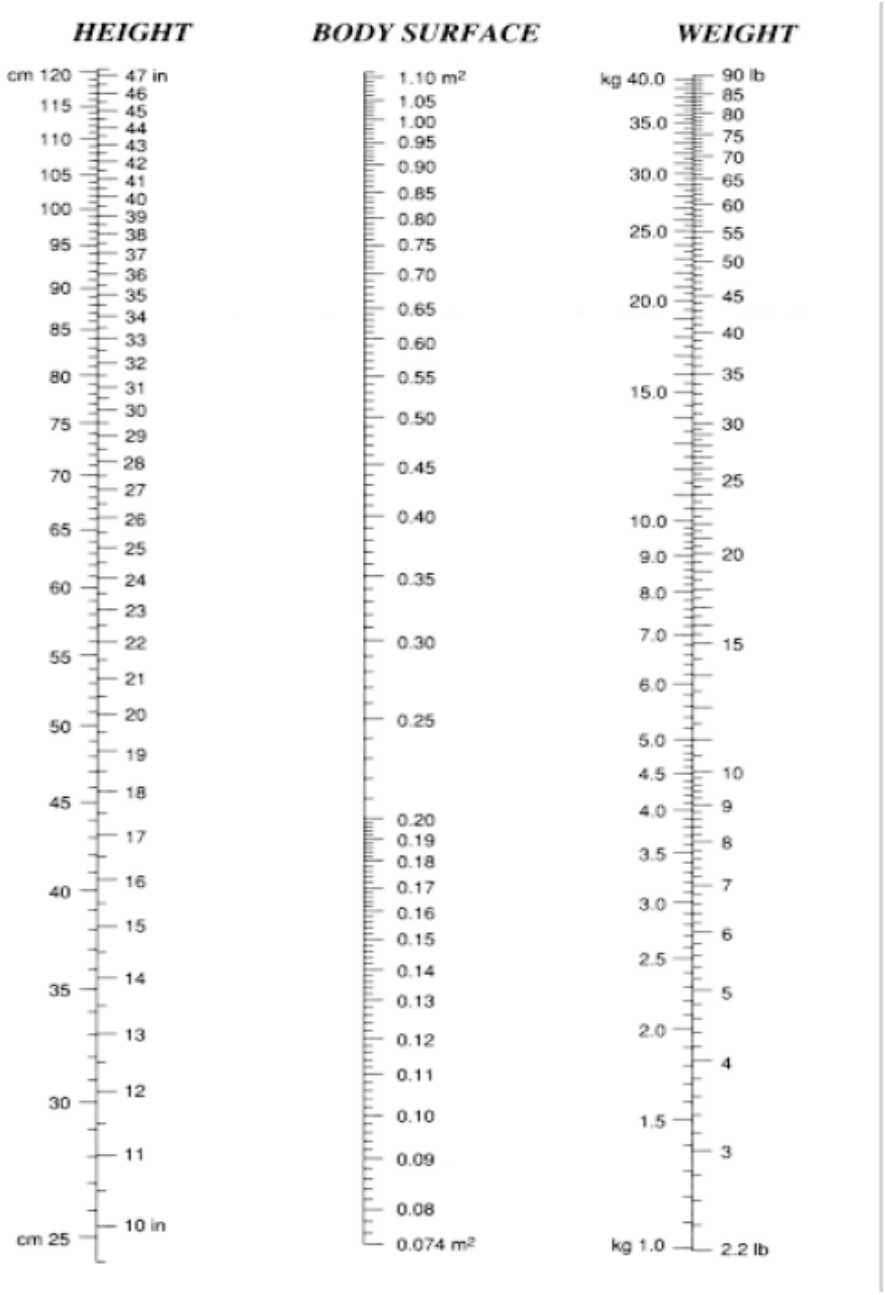
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Ref : Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.

8.7 Karnofsky Performance Scale

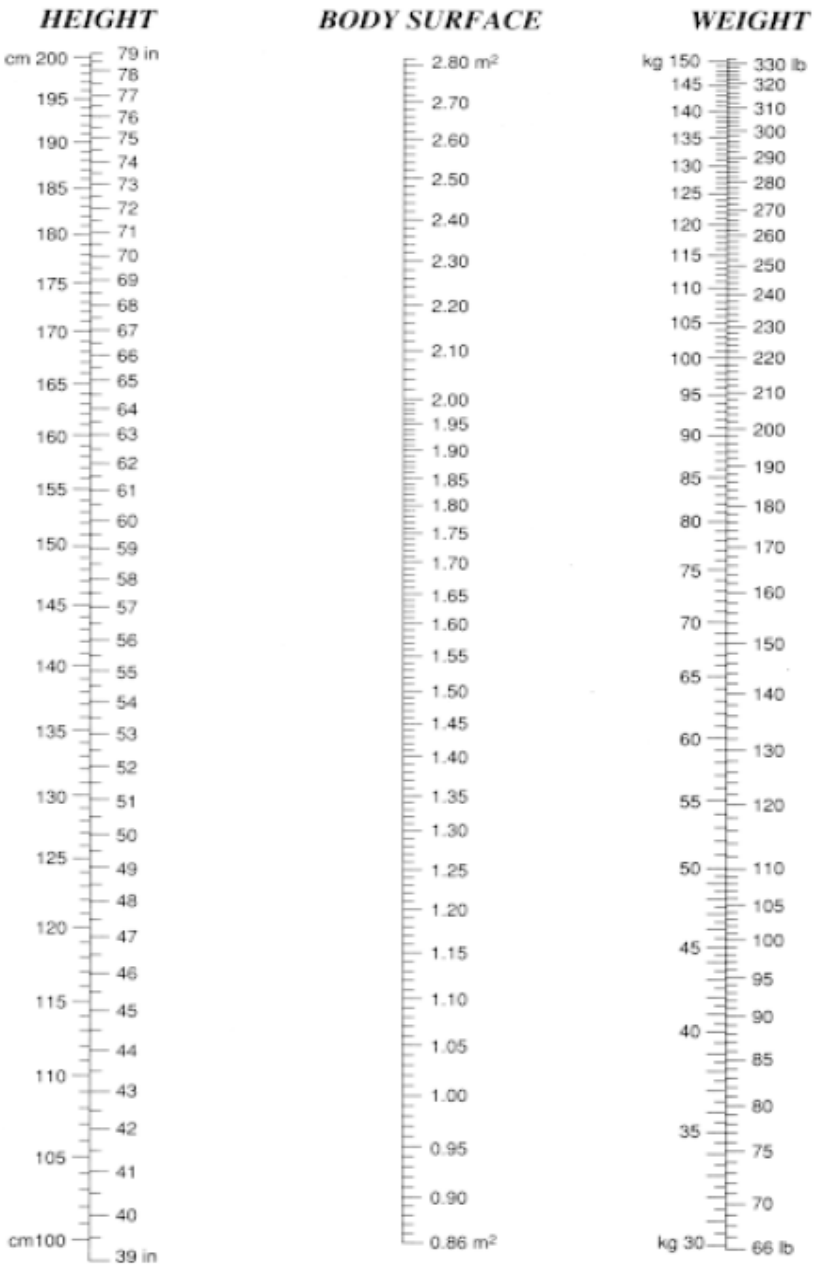
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

8.8 Nomogram for calculating Body Surface Area: Children



A straight edge is placed from the patient's height in the left column to his/her weight in the right column and this intersect on the body surface area column indicates the body surface area.

8.9 Nomogram for calculating Body Surface Area: Adults



From the formula of Du Bois and Du Bois, Archives of Internal Medicine. 17:863, 1916.

A straight edge is placed from the patient's height in the left column to his/her weight in the right column and the intersect on the body surface area column indicates the body surface area.