Guidelines for Management of Urological Cancers

Vol. XVII (Part B)

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Preface

Tata Memorial Centre has been at the forefront of the cause of Evidence Based Medicine (EBM) in cancer care in India. The EBM conference, an annual feature is now in its 18th year. This year we focus on three themes; Uro-Oncology -A decade of transformation, Contemporary Management in Neuro-Oncology, and Palliative Medicine - Current Concepts and Controversies.

The management of urological malignancies has undergone a sea change in the last decade. The previous TMH-EBM on urological cancers was held in 2010 when some of today's commonly used and well-established terms in like "RARP", "SBRT", "Chemo-hormonal therapy" "Abiraterone" "PSMA PET-CT" were still in their infancy. We aim to provide an update on the current standard of management of urological cancers, with an emphasis on situations that are relevant to the Indian healthcare scenario. The meeting will offer a highly educational program consisting of invited lectures, debates, and discussions involving renowned international and national

faculty members, each expert in the field. As per tradition, we present you the "EBM book", nectar of the best available evidence, gleaned from the literature, summarised in a focussed and succinct manner. The book is also available on our official website. Clinicians and students from across the country face the increasingly difficult task of keeping up with the evidence available and choose from multiple effective treatments that can be expensive and potentially toxic. We hope this meeting, as it lives on with the EBM books, helps them get updated on the knowledge and evidence, find inspiration to excel and make a positive difference to every patient they treat.

Prof R A Badwe
Director,
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Mumbai

CHAPTER 1

Prostate Cancer

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1. INTRODUCTION & EPIDEMIOLOGY

Prostate cancer is the second common cancer amongst men worldwide and the fifth most common cancer overall, as also the sixth leading cause of death in men. In India, the data about incidence is not robust as there are a handful of population-based registries and it is not a notifiable disease.

Wide variations in the age adjusted incidence rates (AAR) of prostate cancer is seen in different parts of the world and in India the rates are only one tenth of that seen in the western countries. AAR ranges from 0.8 – 10.9 in India, with the highest in metropolitan cities such as Delhi (10.9), Bangalore (8.9), Mumbai (7.5), Pune (7.5) and in some of the north eastern regional registries including eastern India – Kolkata. The possible reasons for observing varied incidence rates might be due to large differences in dietary practices and social evils like tobacco and alcohol

consumption among Indian population across the country. This incidence is higher than some Asian countries but much lower than the western countries.

As per Globocan 2018 – Prostate cancer was ranked 16th overall in India, with 2.2% of new cancer cases and responsible for 2.2% of the cancer deaths. National Cancer Registry report published in 2016, reported increasing trends of ca prostate Delhi, Mumbai, Chennai, Bangalore and Bhopal registries (National Cancer Registry report, ICMR 2016). There was a change in the incidence rate of age group of ≥65 years by 11.9%, 80%, 126.1%, and 88%, respectively, in Mumbai, Chennai, Barshi, and Bengaluru registries in the period of 2008–2012 as compared to the period of 1988–1992.

2. SYMPTOMS

In localised disease, especially early, there are no symptoms. Many other patients will have lower urinary tract symptoms as seen in benign urinary conditions. With advanced disease, patients can present with urinary obstruction, haematuria, hematospermia, perineal pain, back ache and other bony pains, and sometimes with neurological deficits secondary to vertebral metastasis.

3. DIAGNOSIS AND STAGING METHODS:

The main diagnostic work up for prostate cancer detection includes DRE, assessing serum concentration of Prostate Specific Antigen (PSA) and trans-rectal ultrasonography (TRUS) apart from getting a histological confirmation of prostate cancer.

3.1 Digital Rectal Examination (DRE):

It is a simple and cost-effective method, having a positive predictive value (PPV) from 21% to 53%. AJCC 8th edition recommends DRE for T staging, although its sensitivity is 52% and specificity is 80%. Hence, it may not be accurate and is also subject to variability with different clinicians. Hard nodule on DRE warrants a biopsy irrespective of serum PSA.

3.2 Prostate Specific Antigen (PSA):

The normal values of Serum PSA are <4 ng/ml. As of yet, there is no long-term data to help determine the optimal PSA threshold value for detecting non-palpable, but clinically significant prostate cancer. Probably, age specific PSA in different populations are important in this respect. If the PSA level is high, biopsy of the prostate may be recommended. About 25% of men with cancer will have a normal or low PSA. Therefore, a combination of PSA & DRE, seem to be a better guide for recommending a biopsy.

PSA is prostate specific and not cancer specific and may be raised in non-cancerous conditions like BPH, prostatitis, tuberculosis etc. A ratio of free to total PSA of <0.1 is most likely associated with prostate cancer, and higher values suggest benign conditions. Ratio of < 0.15 has been associated with a higher Gleason score and poorer prognosis. Other PSA indices include PSA velocity and PSA density. PSA density is calculated by dividing the serum PSA concentration by the volume of the prostate gland measured by TRUS. A higher PSA density [PSA > 0.15 ng/mL/cc] is associated with malignancy.

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

3.3 Trans-rectal Ultrasound (TRUS):

TRUS provides more accurate local staging than DRE. Most of the cancer lesions are hypoechoic but lack of hypoechoic focus does not exclude proceeding with biopsy, because 39% of all cancers are isoechoic and up to 1% of tumors may be hyperechoic on TRUS.

TRUS is also used for biopsy of prostate, measuring PSA density and as a guide in cryosurgery, high intensity focused ultrasound and brachytherapy. Use of 3D TRUS, microbubbles and intra venous contrast may improve cancer visualization.

3.4 Computed Tomography (CT):

It is done mainly to assess nodal invasion by using LN diameter and morphology. Usually, LNs with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are considered malignant. CT sensitivity is less than 40%. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade group < 4 cancer, PSA < 20 ng/mL, or localised disease. It is not a very accurate investigation for local staging.

3.5 MR Imaging

T2-weighted imaging MRI is the most useful imaging for local assessment and treatment planning. At 1.5T (Tesla), MRI has low sensitivity for detecting extra prostatic extension of carcinoma or seminal vesical invasion (SVI). An endorectal coil improves staging accuracy at 1.5T with accuracy of 77-83% combined endorectal and external coils vs. 59-68% for external coil alone.

1.5T MRI with better software or 3 T MRI has now evolved to give prostatic images with a greater diagnostic accuracy using dynamic contrast enhancement (DCE), spectroscopy and diffusion weighted imaging (DWI). Along with T2 weighted imaging, the above techniques are collectively termed multi parametric MRI (mpMRI).

In mp MRI, together all these variables have a better sensitivity in diagnosing cancer. These advancements improve biopsy yield and overall diagnostic accuracy in prostate cancer. MRI gives a better information about local staging and regional nodal involvement, as well as the visualised skeletal system. T2 weighted images identify the cancer suspicious areas within the prostate. DWI has good sensitivity and specificity for peripheral as well as central lesions of prostate. Areas having low apparent diffusion coefficient (ADC) values are potentially cancerous. DWI is useful in MRI targeted biopsies done in prior biopsy negative elevated PSA patients. DCE MRI detects vascular perfusion and cancerous areas might have angiogenesis with neo vascularization. MRI also has a good sensitivity for higher Gleason grades thus leading to detection of clinically relevant cancers.

PROMIS study concluded that mp-MRI is a highly sensitive test (93%) for the detection of clinically significant cancer. It should ideally be performed prior to the biopsy. Also, it can prevent biopsies in 27% of men and diagnosis of 5% fewer clinically insignificant cancer

PRECISION study gives evidence for doing mpMRI before prostate biopsy in biopsy naïve men. It also highlights the importance of MRI targeted biopsy.

In men currently advised to have a repeat prostate biopsy, prostate mpMRI could be used to safely avoid a repeat biopsy in 14%. In current times, wherever available, for prostate cancer local imaging, mpMRI is the standard.

3.6 Bone imaging:

The axial skeleton is involved in 85% of prostate cancer (PCa) metastasis. Elevated skeletal alkaline phosphatase (ALP) indicates bone metastasis in 70% of cases significantly correlated with extent of bone disease.

99Tc-MDP bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. Its diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score .BS positivity rate is extremely low (< 1%) in low-risk patients and increases with advances stages of prostatic cancer (stage >T3, PSA > 20 and Gleason score e" 8. BS should be considered in any symptomatic patients, independent of PSA level, Gleason score or clinical stage.

18F-sodiumfluoride PET or PET/CT has better sensitivity than BS. Diffusion-weighted whole-body and axial MRI are more sensitive and specific than combined bone scan,

targeted radiography and abdominopelvic CT. Choice of bone evaluation scan is therefore preferred on the basis of availability and cost. In the fast-changing scenario, for bone imaging, many clinicians are using PSMA PET CT.

3.7 Prostate specific membrane antigen/PSMA-PET: Full Body Imaging.

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein naturally found on prostate epithelial cells, renal tubular cells, celiac ganglia and salivary glands. Due to its selective overexpression, PSMA is a reliable tissue marker for staging and restaging of carcinoma prostate. Increase in PSMA expression correlates with tumour grade, disease progression and cancer relapse.

The sensitivity (66% vs 44%) and specificity (99% vs 85%) of PET is higher as compared to cross-sectional imaging. 68Ga-PSMA-11 PET demonstrated 84% to 92% positive predictive value at 75% overall detection rate in patients with biochemically recurrent prostate cancer and median PSA of 2.1 ng/mL. Detection rates of 15-58%, 25-73% and 69-100%, 71-100% have been reported for PSA ranges of 0.2-0.5 ng/mL, 0.5-1 ng/mL, 1-2 ng/mL and > 2 ng/mL, respectively.

Even though not included in guidelines, PSMA-PET/CT is rapidly emerging as an essential tool for imaging prostate cancer. Its superior sensitivity and specificity for detecting locoregional lymph-node metastasis (often <10 mm), distant visceral and bone metastasis has positioned it as the 'one stop test' in advanced cancer prostate and in near future it may replace bone scan and stand-alone CT

completely. Current evidence suggests PSMA PET to be the ideal investigative modality for pre-treatment staging of intermediate, high risk and locally advanced prostate cancer and for biochemical recurrence.

The newer application of PSMA PET SCAN:

1. PSMA PET/CT and PSMA PET/MRI guided Biopsy.
2. PSMA PET/CT Directed Surgery and Radiotherapy.
3. Monitoring treatment response.
4. PET CT guided Theranostic Pair therapy with 17Lu-PSMA or 225Ac-PSMA.

3.8 Prostatic biopsy:

The indications for prostate biopsy include an abnormal digital rectal examination (DRE) or/ and raised PSA level. Prostatic biopsy can be TRUS guided, MRI guided and MRI-TRUS fusion biopsy. Local anaesthesia prior to biopsy using Ultrasound (periprostatic block) is given. Antibiotics prior to biopsy are given either oral or intravenous. Quinolones are the drugs of choice. Low-dose aspirin can be continued however other anti coagulant should be stopped 7 days prior to biopsy.

A transrectal approach is used for most prostate biopsies, although biopsy done through perineal approach can give a better yield of apical as well as other areas. Cancer detection rates are yet comparable with both approaches. The standard today is 10 to 12 core biopsies, with > 12 cores not being significantly more conclusive. The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30-43% and depends on the number of cores sampled during earlier biopsies.

Complications of biopsy include hematospermia, haematuria, rectal bleeding, prostatitis, epididymitis, urinary retention, rarely sepsis which may be managed conservatively and rarely need surgical interventions.

3.8.1 Pathology:

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

- Targeted, guided and / or extended biopsies may be done, usually by the trans-rectal route and the biopsies should be separately labelled and sent to the pathologist.
- The biopsy specimens should be reported as per the published standard reporting guidelines for reporting prostatic biopsy specimens.
- Extensive sampling of TUR chips will yield a higher proportion of unsuspected cancers than restricted sampling.

A diagnosis of atypical small acinar proliferation is given when quantitatively or qualitatively the focus of suspected cancer is too minimal. This diagnosis is usually dealt with either an immediate re-biopsy or a rebiopsy definitely within six months

Mandatory elements to be reported for a carcinoma-positive prostate biopsy in each core are:

a) Histological type of prostate carcinoma; (Conventional, ductal, small cell etc).

b) Gleason score = Primary pattern + worst pattern (both added to give the final score) (per biopsy site and global).

c) Percentage of tumor in the core. If GS =3+4 =7, then percentage of pattern 4 should be mentioned as it may help in choosing patients for active surveillance if % pattern 4 is miniscule

d) If present: EPE, seminal vesicle invasion, LVI, intraductal carcinoma/cribriform pattern, peri-neural invasion.

e) ISUP Grade Group: As per the ISUP 2016 classification. Grade Group 1 now includes pure GS 6 cases. The GS 7 has been split up into two Grade groups: Grade group 2 (3+4=7) and Grade group 3(4+3=7) with important prognostic difference. Grade group 4 includes all combinations which yield a GS of 8 and Grade group 5 encompasses GS 9and GS10.

f) Gleason Score: The 2005 International Society of Urological Pathology (ISUP) modified Gleason score (GS) of biopsy-detected cancer comprises the Gleason grade of the most extensive (primary) pattern, plus the second commonest (secondary) pattern, if two are present. If only one pattern is present, it needs to be doubled to yield the GS. For three grades, the biopsy GS comprises the most common grade plus the highest grade, irrespective of its extent. Tertiary grade is not reported in a prostatic biopsy. When a carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 3 glands should not be incorporated in the GS. A GS < 5 should never be given on a core biopsy. In addition to reporting of the carcinoma, features for each biopsy, an overall (or global) GS

based on the carcinoma-positive biopsies can be provided. The global GS takes under consideration the extent of every grade from all prostate biopsies.

The 2016 ISUP endorsed group grading system limits the number of PCa grades, ranging them from 1 to 5 in order to:

I. Align the PCa grading with the grading of other carcinomas;
II. Eliminate the anomaly that the most highly differentiated PCas have a GS 6;
III. To define further the clinically highly significant distinction between GS 7(3+4) and 7(4+3) PCa which have different prognosis.

3.8.2 Histopathology of radical prostatectomy Specimen:

The histo-pathological examination of radical prostatectomy (RP) specimens aims to provide information about the actual pathological stage, grade and surgical margin status of the prostate cancer. The weight and dimensions of the specimen are recorded before embedding it for histological processing. It is generally recommended that RP specimens are totally embedded to enable the assessment of location, multifocality and heterogeneity of the cancer. Another reason for this is that prostate cancer is not usually visible grossly. For cost-efficiency purposes, partial embedding can also be considered, particularly for large-sized prostates (> 60 g).

The pathology report provides essential information on the prognostic characteristics which are clinically relevant. The report should include:

a) Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma. GS, tertiary grade is to be reported. Tertiary grade or the minor grade component is usually a grade 5 component which is < 5% of tumor in an RP specimen

b) Grading according to ISUP grade (or not applicable if therapy-related changes).

c) Tumour (sub)staging and surgical margin status: location and extent of EPE, presence of bladder neck invasion, laterality of EPE or seminal vesicle invasion, location, extent and GS at positive surgical margins are important.

d) Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.

4. RISK STRATIFICATION:

European Association of Urology (EAU) Risk Stratification:

Definition		T stage	PSA	Gleason (ISUP Group Grade)
Localised	Low	cT1-T2a	< 10 ng/mL	< 7 (Group Grade 1)
	Inter-mediate	cT2b	10 -20 ng/mL	7 (Group Grade 2/3)
	High	cT2c	> 20 ng/mL	>7 (Group Grade 4/5
Locally Advanced		cT3 -T4 or N+	Any PSA	Any Gleason

5. STAGING OF PROSTATE CANCER:

TNM 2017 Staging

T - Primary Tumour (stage based on digital rectal examination [DRE] only)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Clinically inapparent tumour that is not palpable

T1a Tumour incidental histological finding in 5% or less of tissue resected

T1b Tumour incidental histological finding in more than 5% of tissue resected

T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])

T2 Tumour that is palpable and confined within the prostate

T2a Tumour involves one half of one lobe or less

T2b Tumour involves more than half of one lobe, but not both lobes

T2c Tumour involves both lobes

T3 Tumour extends through the prostatic capsule

T3a Extracapsular extension (unilateral or bilateral)

T3b Tumour invades seminal vesicle(s)

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

N - Regional (pelvic) Lymph Nodes[£]

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M - Distant Metastasis¥

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s)

£ Metastasis no larger than 0.2 cm can be designated pNmi.

¥ When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

AJCC 8th edition Pathological staging

T category	T criteria
pT2	Organ confined
pT3	Extra prostatic extension
pT3a	Extra prostatic extension (Unilateral or bilateral) or microscopic invasion of bladder neck
pT3b	Tumor invades seminal vesicle(s)
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles (SV)such as external sphincter, rectum, bladder, levator muscles, and /or pelvic wall
Note:	There is no pathological T1 classification.
Note:	Positive surgical margin should be indicated by R1 descriptor indicating residual microscopic disease.

AJCC Prognostic Groups

Group	T	N	M (ng/mL)	PSA Group	Grade
Stage I	cT1a-c	N0	M0	<10	1
	cT2a	N0	M0	<10	1
	pT2	N0	M0	< 10	1
Stage IIA	cT1a-c	N0	M0	>10 < 20	1
	cT2a	N0	M0	>10 < 20	1
	pT2	N0	M0	>10 < 20	1
	cT2b	N0	M0	< 20	1
	cT2c	N0	M0	< 20	1
Stage IIB	T1-2	N0	M0	< 20	2
Stage IIC	T1-2	N0	M0	< 20	3
	T1-2	N0	M0	< 20	4
Stage IIIA	T1-2	N0	M0	> 20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

6. TREATMENT :

6.1 Management of high grade prostatic intraepithelial neoplasia (PIN):

The presence of high-grade PIN on biopsy is in itself not an indication for treatment but requires careful follow-up and sometimes early re-biopsy to rule out invasive cancer.

For patients diagnosed with unifocal HGPIN on extended initial core sampling, in the absence of other clinical indicators of cancer, a repeat biopsy within the first year is not necessary. In view of lack of larger studies and potential medicolegal issues, a repeat biopsy should be requested at 3 years. HGPIN on greater than or equal to two cores is associated with a sufficiently high risk of subsequent cancer thereby warranting a rebiopsy within a year.

6.2 Management of invasive prostatic adenocarcinoma

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

a) Localized prostate cancer (T1 – T2 N0) – further stratified by EAU risk stratification.
   - Low risk (cT1-T2a and Gleason score 2-6 and PSA < 10)
   - Intermediate risk (cT2b or Gleason score = 7 or PSA 10-20)
   - High Risk (cT2c or Gleason score 8-10 or PSA > 20)

b) Locally advanced disease (T3-T4 or N +)

c) Metastatic disease: Any T, Any N & distant metastasis (M+)

6.2.1 Treatment of localized prostate cancer:

Depending on the risk the options include

Active Surveillance – only in selected patients. [low and few intermediate risk ca p]

Radical prostatectomy +/-Pelvic lymph node dissection +/- Adjuvant RT / HT

Radical radiotherapy in the form of either External beam: 3D Conformal / IMRT or Brachytherapy Permanent seeds or HDR Interstitial

All patients considered fit for radical therapy must be counselled regarding the above options. The choice of treatment should be made on the basis of clinical efficacy (there is no evidence of superiority of one modality over the other), biological behaviour, morbidity of treatment, age and life expectancy of the patient and finally patient's own perceptions and choice. Assessment of life expectancy is most critical in decision making & management of prostate cancer. These tables can be found in WHO guidelines. Usually, patients with a life expectancy less than 10 years, based on comorbidities, and / or to far internal risk are not offered active treatments. These would go for watchful waiting with due counselling.

Active Surveillance with Selective Delayed Intervention (AS)

AS is to delay curative local therapy until the natural history and threat posed by the cancer can be more accurately assessed and that delayed treatment intends to be as curative as immediate treatment. This selects cases better for therapy and avoids overtreatment in majority. If selected well, nearly 2/3rd patients on AS may be able to avoid definitive treatment.

At ten years' follow-up in the ProtecT study, where 60% had a low risk disease, a benefit for metastases free and

PFS, but neither cancer-specific nor OS, for RP compared to AM and RT was observed. In the SPCG-4 study, death from any cause and distant metastases were significantly reduced in low-risk PCa at eighteen years for RP compared with WW. Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.

The risk of progression seems to accelerate over time, hence frequent, regular and detailed evaluation of the status of cancer is required as long as patients are healthy and young enough to be a candidate for definitive therapy. A complete evaluation at baseline includes DRE, free and total PSA, imaging study of the prostate (preferably MRI with spectroscopy), and ultrasound-guided systematic needle biopsy.

TABLE of —- Normal and extended criteria for AS,	
Criteria for Active Surveillance	
Normal Criteria	1. ISUP grade 1 2. < 2-3 positive cores with < 50% cancer involvement in every positive core 3. Clinical T1c or T2a 4. PSA < 10 ng/mL 5. PSA density < 0.15 ng/mL/cc
Extended Criteria	1. Clinical stage T2 2. Up to 60% maximum core involvement 3. Up to 4 positive cores

The monitoring in AS includes a 6 monthly follow up with DRE and PSA indefinitely, with repeat imaging and biopsy 12 to 18 months after the baseline evaluation, then every 2 to 3 years, are recommended. Any evidence of progression (i.e. symptomatic or increasing Gleason grade or increasing number and extent of cores involved) would essentially exclude patient from AS and should prompt a conversion to potentially curative therapies. MRI & US fusion biopsies may increase the yield of the high grade (GS>7) cancers during follow up.

RADICAL PROSTATECTOMY (RP)

RP is recommended only for patients with clinically localized cancer with a life expectancy of 10 or more years and without significant comorbidities. Although the risk of recurrence after RP rises with higher clinical stage, Gleason grade, and serum PSA level, no absolute cut off values exclude a patient as a candidate for RP.

The goals of modern RP are to achieve “Pentafecta” – namely continence, potency, biochemical recurrence-free survival, no postoperative complication and negative surgical margins. The described approaches are either a suprapubic incision (open RP) or using a minimally invasive (laparoscopic or robot-assisted laparoscopic) approach. The key steps in this surgical procedure are ligation of the dorsal vein complex and anterior periprostatic veins, identification and control of the small branches from the neurovascular bundles to the prostate postero laterally.

A recent Cochrane review comparing either Robotic Radical Prostatectomy (RARP) or Laproscopic RP (LRP) vs. open radical prostatectomy (ORP) included two RCTs and found no significant differences between the comparisons for oncological, urinary function and sexual function outcomes, although RARP and LRP both resulted in statistically significant improvements in duration of hospital stay and blood transfusion rates over open RP . Therefore, there is no recommendation of surgical approachof one over theother.

Bilateral extended pelvic lymph node dissection (eLND) should be done in any patient likely to have >5% probability of lymph node metastases (Roach Formula) which includes removal of the nodes overlying the external iliac vessels, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes around the internal iliac artery. A frozen section of the lymph nodes is not routinely necessary.

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RARP vs. Watchful Wait (WW) in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71; 95% CI: 0.53-0.95), death from PCa (RR: 0.38; 95% CI: 0.23-0.62) and distant metastases (RR: 0.49; 95% CI: 0.32- 0.74) in intermediate-risk PCa at eighteen years were significantly reduced. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69 [95% CI: 0.49-0.98]), but not death from PCa (0.50; 95% CI: 0.21-1.21) at ten years. Hence offer RP to patients

with intermediate-risk disease and a life expectancy of > ten years.

TABLE of Oncological results of radical prostatectomy in organ-confined disease in RCTs			
Study	**Acronym**	**Risk Category**	**CSS**
Bill Axelson, et al, 2018	SPCG 4	Low and Intermediate risk	80.4 (at 23.5 yr.)
Wilt, et al, 2017	PIVOT	Low Intermediate Risk	95.9 91.5 (at 19.5 yr.)
Hamdy, et al, 2016	Protect	Low and Intermediate Risk	99 (at 10 yr.)

The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1%. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5%. In all other cases eLND can be omitted, which means accepting a low risk of missing positive nodes.

In High Risk disease, provided that the tumour is not fixed to the pelvic wall, or there is no invasion of the urethral sphincter, RP is a reasonable option as part of multimodal management. Patients with high risk disease (PSA > 20 ng/dl), RP should be considered in low volume disease, clinical localised disease (T2), Gleason score ≤7, young age, with obstructive features. Extended PLND should be performed in all high-risk PCa cases undergoing RP as the estimated risk for positive LNs is 15-40%. Offer RP to patients with high-risk localised PCa and a life expectancy of > ten years only as part of multi-modal therapy.

In men with localised cancer nerve-sparing RP can be done safely. Relative contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa or any ISUP grade > 3 on biopsy. Neuro vascular bundle (NVB) should be removed whenever there is doubt of residual disease.

Neoadjuvant androgen deprivation therapy before surgery:

Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of them using a 3-month period. The main findings were summarised in a Cochrane review. It is associated with a decreased rate of pT3 (downstaging), decreased positive margins, and a lower incidence of positive LNs. These benefits are greater with increased ADT duration (up to eight months). However, since neither the PSA relapse-free survival nor Cancer Specific Survival (CSS) were shown to improve, neoadjuvant ADT should not be considered as standard clinical practice.

Acute complications of surgery:

The mortality rate is 0.1 -0.2 %; urinary fistulas are seen in 1.2-4% of patients. Post-operative incontinence and Erectile Dysfunction (ED) are common problems following surgery for PCa.

A key consideration is whether these problems are reduced by using newer techniques such as RARP. The mean continence rates at twelve months were 89-100% for patients treated with RARP and 80-97% for patients treated with ORP. There is, as yet, no evidence from retrospective studies on differences in urinary incontinence at twelve

months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or ED outcomes.

Erectile dysfunction was observed in 70.4% after RARP and 74.7% after ORP [30]. High anterior release of the NVB is associated with significantly earlier recovery and return to baseline sexual function. In potent men undergoing high anterior release, 93% were potent 12 months after surgery and 70% reported a return to their baseline erectile function. The early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation remains controversial resulting in a lack of clear recommendations.

RADICAL RADIOTHERAPY

The modalities available include external beam radiotherapy (EBRT) using Photons or protons and Brachytherapy. EBRT planning with IMRT based planning is critical for safe dose escalation for optimal outcomes. Daily Image guided delivery (IGRT) is also proven to improve biochemical progression-free and clinical progression-free interval, and reduce rectal toxicity.

Evidence for dose escalation emerges from the trials of MD Anderson, PROG 95-09, MRC RT01, GETUG 06 and RTOG 0126 where doses 74-80Gy were used having a statistically significant improvement on 5 year BCR rates. A meta-analysis reveals dose escalation (74–80Gy) has an slightly increased risk of late GI toxicity compared to lower doses (64-70.2Gy).

The combination of RT with ADT (Neoadjuvant / Adjuvant hormone therapy) has been proven to be superior to RT

alone from multiple randomized trials in improving overall survival. Based on robust evidence intermediate risk cancer requires a shorter duration of ADT for 4-6 months before and during EBRT. The NCCN guidelines keeps ADT optional for Low risk and Favourable intermediate group when using dose escalated EBRT schedules (T1-T2c and GS 3+4/7 or group 2, PSA <20 and percentage biopsy core positive <50%). Three RCTs namely GICOR, DART01 and EORTC 22991 showed that the benefits of ADT are independent of dose escalation.

Moderate Hypofractionation (HFX)

Different fractionation schedules have been tested in prostate cancer EBRT. Hypofractionation and SBRT have the advantage of decreased treatment time and acceptable toxicity profiles with positive financial and logistic implications.

The sensitivity to fractionation of irradiated tissue, is characterized by a radiobiological parameter called the ±/² ratio. The ±/² ratio of adenocarcinoma prostate is low, in the range of 1.5 - 3Gy. The ±/² ratio of the adjacent rectum and bladder is greater than that of prostate cancer (about 5) implying that hypofractionation may further improve the therapeutic ratio of EBRT.

Type	**Fraction Size**
Conventional	1.8 – 2Gy
Moderate Hypofractionation	2.4 – 3.4Gy
Ultrahypofractionation/SBRT	≥ 5Gy

A meta-analysis of 25 studies including >14,000 patients concluded that hypofractionation could be more effective than conventional fractionation with the added advantage of being more convenient for the patient and cheaper for the health care system.

Study	N	Median FU (yrs)	Study Arms	Technique Groups	Risk	ADT	Outcome	Toxicity
CHHiP	3216	5.2	CRT - 74Gy/37#, HFX - 60Gy/20#, 57Gy/19#	IMRT IGRT optional (53% use)	15% LR, 73% IR, 12% HR	97%	HFX non inferior	NS
HYPRO	820	5	CRT - 78Gy/39#, HFX - 64.6Gy/ 19#	IMRT, IGRT	26% IR, 74% HR	67%	Not signi-ficant	Favours CRT
PROFIT	608	6	CRT - 78Gy/39#, HFX – 60Gy/20#	3D CRT or IMRT, IGRT	All IR	None	HFX non inferior	NS
RTOG 0415	1115	5.8	CRT - 73.8Gy/ 41# HFX – 70Gy/28#	3D CRT or IMRT, IGRT	All LR	None	HFX non inferior	NS

The CHHiP Trial consolidates the role of Moderate Hypofractionation as the new standard of care in the treatment of Prostate Cancer in the UK.

The AUA/ASTRO/ASCO group recommend that clinicians should consider moderate HFX for localized prostate cancer patient (of any risk category) as the accumulated data is sufficiently robust to justify routine use in clinical practice.

Extreme Hypofractionation / SBRT

Katz et al demonstrated that SBRT to a dose of 35-36.25Gy treated with Cyber knife in five daily fractions is effective for early low-risk prostate cancer, with acceptably toxicity. There appears to be no benefit to escalation beyond 35Gy. The 10 year BDFS appears to be higher than with standard IMRT. Kishan et al recently published pooled individual patient data analysis of 2142 patients of low and intermediate risk treated with doses ranging from 33-40Gy in 4-5 fractions resulting in 7-year biochemical control ranging 4.5-10.2% and severe GU and GI toxicity of 2.4% and 0.4% respectively.

Data from the Scandinavian RCT, HYPO-RT-PC trial for the intermediate risk group also proves the non-inferiority of SBRT (5-year control 83.7% vs 83.8%). The recently published PACE B study substantiated the claim that further shortening of treatment does not increase either acute GI or GU toxicity. Data in intermediate/high risk group is emerging with ongoing trials (NRG GU 005, PACE, HEAT, PRIME).

The recommendation for use of SBRT in low risk and intermediate risk is graded as “conditional” in the literature reflecting only moderate-quality evidence. IGRT is strongly recommended.

Rectal Spacers

It is a novel technique to minimize the toxicity to the anterior rectum from dose escalation. They are inserted in the interface between the posterior part of the prostate and the anterior part of the rectum. Spacers have been shown to significantly reduced the dose to the rectum from

V30-82 Gy, with the greatest difference observed at higher rectal doses (V65 to V82) and decreasing rectal toxicity as well as improving quality of life. Spacers may be used in patients undergoing SBRT or brachytherapy.

Brachytherapy

It is an alternate form of radiotherapy where sealed sources are placed inside or next to the area requiring treatment.

- LDR (Low dose rate brachytherapy)

Use of permanently implanted seeds of I-125, Pd 103 or Cs-131. Treatment delivery is usually over weeks and months.

Eligibility Criteria

1. Stage cT1b-T2a N0, M0; ISUP grade 1 with ≤ 50% of biopsy cores involved
2. ISUP grade 2 with ≤ 33% of biopsy cores involved with cancer; initial PSA ≤ 10 ng/mL; prostate volume < 50 cm3; an International Prostatic Symptom Score (IPSS) ≤ 12 and maximal flow rate > 15 mL/min on urinary flow tests.

- HDR (High dose rate brachytherapy)

Use of temporarily introduced radioactive source. Ir 192 is introduced through implanted needles and catheters. Treatment delivery is within minutes. It can be delivered in single or multiple fractions. It can also be combined with EBRT. Fractionated HDR brachytherapy may be offered to patients with low and intermediate prostate cancer with evidences showing 5-year control > 90% and

grade 3 toxicities < 5%. (Hauswald H et al, IJROBP 2016, Zamboglou N et al, IJROBP 2013). Brachytherapy has been used in high risk disease (ASCENDE-RT Trial) compared to dose escalated EBRT (46Gy) and LDR brachytherapy to EBRT (78Gy) in intermediate and high risk patients showing 5 and 7 years PFS (89% and 86% vs 84% and 75% respectively) increase at the cost of late Grade 3+ urinary toxicity (18% vs 8%).

6.2.2 Treatment of locally advanced prostate cancer – (T3-T4 or N +, any PSA, any GS)

No standard treatment can be defined in the absence of level 1 evidence. But a local treatment combined with a systemic one provides the best outcome, provided the patient is ready and fit enough to receive both. The optimal local treatment is still a matter of debate. Randomised controlled trials are only available for EBRT. There are no head on trials of RP vs RT as the local therapy.

SURGERY

Surgery for locally advanced disease as part of a multimodal therapy has been reported. However, the comparative oncological effectiveness of RP as part of a multimodality treatment strategy vs. upfront EBRT with ADT for locally advanced PCa remains unknown, although a prospective phase III RCT (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally advanced (T3) disease is currently recruiting. Data from retrospective case series demonstrated over 60% CSS at fifteen years and over 75% OS at ten years. Also, many report a down gradation in GS

and a much radical RP with wide margins, so as to have a complete treatment with RP alone.

In case of suspected positive LNs during RP (initially considered cN0), the procedure should not be abandoned since RP may have a survival benefit in these patients. There is no role of intraoperative frozen analysis of lymph nodes the evidence of RP for cN+ patients are very limited. Moschini et al. compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at preoperative staging. cN+ was not a significant predictor of CSS. An eLND should be done if a RP is planned.

RADIOTHERAPY

Combined local and systemic therapy provide the best results for locally advanced prostate cancer. It is widely accepted from multiple RCTs (RTOG 85-31, RTOG 94-13, RTOG 86-10, RTOG 92-02, EORTC 2961, EORTC 22863, TROG 96-01, PRO7) that the use of long term ADT (2-3 years) combined with RT has better OS than ADT alone or RT alone. (TROG 03.04 RADAR is one study indicating 18 months of ADT may be sufficient as opposed to long term ADT).

In high risk node negative prostate cancer, prophylactic lymph node irradiation is still a matter of debate as trials have shown inconsistent and conflicting results due to poor design and patient selection (RTOG 94-13, GETUG 01). A randomised trial from Tata Memorial Hospital, India (PoP RT, Radiother Oncol Jan 2020) showed higher urinary toxicity with pelvic RT compared to prostate alone RT. The failure outcomes from this trial and a larger RTOG trial (RTOG 0924) are awaited.

For high risk node positive disease, traditionally, ADT alone was indicated but presently, EBRT and long term ADT is an established standard treatment modality (STAMPEDE, PRO7)

Moderate Hypofractionation and SBRT have also been tried in high risk patients. Data comes from India with Mallick et al showing 4-year biochemical control of 77.5% and OS of 91% in the node positive group. The late grade 2+ toxicities were GI (13.1%) and GU (18%). Murthy et al showed the potential safety of SBRT in the high risk and node positive group with 94% biochemical control at a median follow up of 18 months. Late 3 GU and GI toxicity was 3% and 0% respectively.

The ongoing PRIME trial (NCT 03561961) from India is a noninferiority, multicentre, randomized trial in high risk &/or node positive prostate cancer with a hypothesis that SBRT is non inferior to moderate hypofractionation. The trial aims to establish a therapeutically efficacious and cost-efficient modality with an acceptable toxicity profile.

The FROGG group from Australia and New Zealand have recently published recommendations for radiotherapy in node positive prostate cancer.

Proton Therapy

Proton beam therapy is an alternate form of treatment delivery which uses heavy particles (1800 times heavier than photons). Protons have a different dose distribution property with the potential to avoid dose outside the target. The peak of energy delivery is referred to as BRAGG

PEAK. The peak can be made to spread out over the entire target area (spread out Bragg peak, SOBP) which maximizes high dose conformity while minimizing exit dose and sparing surrounding organs at risk like bladder and rectum. In spite of the dosimetric advantages and unique dose distribution properties, its high cost, restricted access and lack of level 1 evidence for a clear benefit make it an underused option for prostate cancer.

IMAGE GUIDED RADIOTHERAPY (IGRT)

IGRT is an essential component of IMRT that allows treatment verification and daily changes in target anatomy and position. IGRT is extremely important as the risk of geographical miss is well documented in high conformal RT. The surrounding normal structures like bladder and rectum are subject to variations during treatment and can account for toxicity. Appropriate IGRT can lead to reduction in PTV margins as well.[38] The recently published ESTRO ACROP consensus guideline on the use of IGRT for localized prostate cancer defines methods and procedures recommended for IGRT in daily practice. (Ghadjar P et al 2019).

COMPLICATIONS OF RT

a. Gastrointestinal - Acute toxicity - Proctitis (5-30%), Enteritis, Urgency, Tenesmus. Resolves within 3-8 weeks. Late toxicity - Persistent diarrhoea, rectal urgency or haematochezia. Incidence e" Grade 3 toxicity ranges from 1-5%.

b. Genitourinary - Acute toxicity - Frequency, Dysuria, Urgency due to cystitis, urethritis, or both. Resolves within 4 weeks. Late toxicity (uncommon) - Urethral strictures, Cystitis, Haematuria, Bladder contracture.

c. Sexual dysfunction - In contemporary series, 30-45% of men who are potent prior to RT become impotent after therapy, with the frequency increasing over time.

d. Insufficiency Fractures – Physiologic stress to weakened bone.

e. Secondary malignancy - Small increase in the incidence of bladder and rectal cancer, with the risk of death at 10 to 15 years being miniscule.

ADJUVANT THERAPY IN PRIMARY THERAPY

Indications for Adjuvant RT

1. Extra prostatic extension (pT3a)
2. Seminal Vesicle invasion (pT3b)
3. Margins positive (R1)
4. Invasion into bladder/rectum(pT4)

Three prospective trials have assessed the role

Study	N	Inclusion criteria	Rando-mization	Defi-nition of BCR PSA (ng/mL)	Median FU (yrs)	Bio-chemical PFS	OS
SWOG 8794	431	pT3 cN0 ± involved margins	60-64Gy vs Obser-vation	> 0.4	12.6	10yr 53% vs 30% (p<0.05)	10yr 74% vs 66% p=0.023
EORTC 22911	1005	pT3 ± involved margins pN0 pT2 involved margins pN0	60Gy vs Obser-vation	> 0.2	10.5	10yr 60.6% vs 41% (p<0.001)	10yr 81% vs. 77% NS
ARO 9602	388	pT3 (±involved margins) pN0 PSA post-RP undete-ctable	60Gy vs Obser-vation	> 0.05 + confir-mation	9.3	10yr 56% vs 35% (p=0.0001)	10yr 82% vs 86% NS

Abdollah et al addressed the role of Adjuvant RT and Adjuvant ADT in the pN1 scenario with the development of an algorithm and creation of five distinct groups with a statistically significant 8-year OS benefit in aRT + ADT compared to ADT alone (71% vs 64%, $p < 0.001$) demonstrated in Group 3 (pT3b/T4, GS 7-10 or positive margins with 1-2 positive pathological nodes).

PERSISTENT PSA AFTER RADICAL PROSTATECTOMY

Between 5 and 20% of men continue to have detectable or persistent PSA after RP. It is defined in the majority of studies as detectable post-RP PSA of > 0.1 ng/mL within four to eight weeks of surgery. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue. Persistent PSA after RP is associated with more advanced disease - such as positive surgical margins (PSM), pathologic stage > T3a, positive nodal status and/or pathologic ISUP grade group > 3.

Predictors of PSA persistence were higher BMI, higher pre-operative PSA and ISUP grade group > 3. In patients with PSA persistence, one and five-year BCR-free survival were 68% and 36%, compared to 95% and 72%, respectively, in men without PSA persistence. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively.

Appropriate imaging is needed in these cases, at around 6 weeks from RP, to guide next therapy. Standard imaging with bone scan and MRI has a low pick-up rate for men with a PSA below 2 ng/mL. PSMA PET CT would be the best investigation at this juncture. In case of no metastases, treatment options would be either ADT +/- salvage RT.

Management of only PSA recurrence after treatment with curative intent

Between 27% and 53% of all patients undergoing RP or RT develop a rising, PSA (PSA recurrence).

Post RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising. AUA guidelines accept a level of 0.2 ng/ml as failure.

After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir.

Based on the meta-analysis, proposal is to stratify patients into EAU Low-Risk BCR (PSA-DT > 1 year AND pathological ISUP grade < 4 for RP; interval to biochemical failure > eighteen months AND biopsy ISUP grade < 4 for RT) or EAU High-Risk BCR (PSA-DT < 1 year OR pathological ISUP grade 4-5 for RP, interval to biochemical failure < 18 months OR biopsy ISUP grade 4-5 for RT), since not all patients with BCR will have similar outcomes. The stratification into "EAU Low-Risk" or "EAU High-Risk" BCR has recently been validated in a European cohort.

The role of imaging in only PSA recurrence

In patients with BCR, imaging has the potential to play a role in detecting distant metastases and detecting and localising local recurrence. Early detection of metastases in a BCR setting is clinically highly relevant, either after RT or after RP. Many recent studies suggest that PSMA PET/CT is substantially more sensitive than abdominopelvic CT, bone scan and choline PET/CT in the detection of distant metastases in patients with BCR.

Local recurrence after RT prior to salvage treatment is confirmed by biopsy and, so far, mpMRI is the best technique to evaluate local recurrence and guide targeted biopsies.

Treatment of PSA-only recurrences

The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

SALVAGE RADIOTHERAPY (SRT)

PSA failure occurs in 15–40% of patients after RP. Salvage RT is usually combined with ADT.

Study	N groups	Risk FU (yrs)	Median	Randomization	Outcome
GETUG AFU16	369 RT + ADT 374 RT	GS ≤ 7 89%, GS ≥ 8 11% cN0	5.25	66Gy + GnRH analogue 6 months vs 66Gy	5yr PFS 80% p < 0.0001 5yr PFS 62%
RTOG 9601	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	13	64.8Gy + bicalutamide 24 months vs 64.8Gy + placebo	12yr DM 14% p=0.005 12yr DM 23% 12yr OS 76% p=0.04 12yr OS 71%

A recent update with a 112 month follows up for the GETUG-AFU 16 trial published in Lancet Oncol 2019, states salvage radiotherapy combined with short-term androgen suppression significantly reduced risk of biochemical or clinical progression and death compared with salvage radiotherapy alone confirming the efficacy of androgen suppression plus radiotherapy.

RTOG 0534 / SSPORT Trial is a 3-arm study comparing PBRT alone vs PBRT + STAD vs PLNRT + PBRT + STAD showing 5-year FFP of 71% vs 81% vs 87% respectively which is statistically significant. This is strong Level 1 evidence supporting PLNRT.

The optimal dose of SRT should range between 66-70Gy along with ADT.

ARTISTIC META-ANALYSIS

Across 3 trials (RADICALS, RAVES, GETUG AFU 17) 1,074 men were randomized to adjuvant radiotherapy and 1,077 to salvage radiotherapy. There is no evidence that ART improves EFS compared to eSRT with a 1% difference in EFS at 5 years. More than 60% of men randomized to eSRT in these trials are yet to start RT. The role for ART in some men from subgroup analyses yet needs to be determined.

Salvage radical prostatectomy for post RT recurrence.

Salvage RP though seems to be the best in this category, its use must be weighed against the possible enhanced adverse events compared to primary surgery because of the risk of RT fibrosis causing poor anastomosis and wound healing.

Its technically demanding with short-term and long-term complication rates exceeding those of standard RP. The risks of rectal injury, bladder neck contracture, urinary incontinence is higher than upfront RP. But with growing experience in this field and with the advent of robotic surgery, these complication rates may decrease in future.

6.2.3 Treatment of Metastatic Disease:

Median survival of patients with newly diagnosed metastases is approximately 42 months

Primary androgen deprivation therapy (ADT) has been the standard of care for over 50 years. There is no level 1 evidence in favour of a specific type of ADT, neither for orchiectomy nor for an LHRH analogue or antagonist. Exception is patients with impending spinal cord compression for whom either a bilateral orchidectomy or LHRH antagonists are the preferred options.

Based on a Cochrane SR comparing non-steroidal anti-androgen (NSAA) monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events.

ANDROGEN DEPRIVATION THERAPY:

Testosterone serves as the main stimulant for prostate cancer cell growth. Primary hormone therapy or androgen deprivation therapy (ADT) is the standard of care for advanced metastatic prostate cancer. ADT either stop testosterone from being produced from testis or directly block it from acting on prostate cancer cells. ADT can be considered in form of either bilateral orchiectomy (surgical castration) or with medical orchiectomy (medical castration).

Bilateral orchiectomy — Bilateral orchiectomy (surgical castration) rapidly reduces serum testosterone to castrate

levels. This is simple surgical and cost-effective process also.

Surgical castration is indicated when an early decrease in testosterone is required as in patients with impending spinal cord compression or in patients with urinary tract outlet obstruction.

Medical orchiectomy — Medical orchiectomy reduces production of testosterone through effects on the hypothalamic-pituitary axis. Gonadotropin-releasing hormone (GnRH) agonist or antagonist can be considered for medical castration. Antiandrogens (bicalutamide) is usually combined for 2 to 3 weeks with GnRH agonist to prevent the flare phenomenon, which can lead to initial worsening of disease specially in cases of spinal cord compression or urinary tract obstruction

Leuprolide, goserelin, buserelin, triptorelin are various types of GnRH agonist available for use.

GnRH antagonist (Degarelix) directly suppresses testosterone production and avoids the flare phenomenon seen with use of GnRH agonists. GnRH antagonist can be considered in place of GnRH agonist when a rapid fall in testosterone levels is desired as in cases of spinal cord compression.

ANDROGEN DEPRIVATION THERAPY ALONG WITH CHEMOTHERAPY IN HSPC SETTING:

Docetaxel and mHSPC

CHAARTED TRIAL: This trial randomized 790 patients with mHSPC to receive either ADT + docetaxel (75 mg/m2 every

3 weeks for six cycles) (ADT-DOCE) or ADT alone. The primary endpoint of study was overall survival (OS). Median overall survival was 13.6 months longer with ADT-DOCE than with ADT alone (57.6 months vs. 44.0 months; HR 0.61; 95%CI 0.47-0.80) after a median follow-up of 28.9 months. Other endpoint of study as median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the ADT-DOCE group, in comparison to 11.7 months in the ADT-alone group (HR 0.61, 95%CI 0.51-0.72). In a subgroup analysis of CHAARTED, early docetaxel treatment was associated with improved OS (51.2 vs 34.4 months; HR, 0.63; 95% CI, 0.50-0.79; P < .001) in patients with high-volume disease which was defined as presence of visceral metastases or ≥4 bone lesions, with >1 beyond the vertebral body or pelvis, whereas in patients with low-volume disease, no improvement in OS was seen (63.5 vs not reached; HR, 1.04; 95% CI, 0.70-1.55; P = .86) This trial established the benefit of Docetaxel along with ADT in mHSPC setting. In CHAARTED trial, the updated analysis was done and at a median follow-up 53.7 months showed a 28% risk reduction of death compared; the HR for OS was 0.72 (95%CI 0.59-0.89) which favoured docetaxel +ADT over ADT standard of care.

STAMPEDE DOCETAXEL TRIAL: STAMPEDE is a multi-arm, multi-stage design , in patients with high-risk, locally advanced or metastatic prostate cancer .Patients were randomized 2:1:1:1 to standard of care (SOC; ADT alone), SOC + zoledronic acid (SOC + ZA), SOC + docetaxel (ADT-DOCE), or SOC with both zoledronic acid and docetaxel (SOC + ZA + Doc). There were 2,962 patients randomized

between 2005 and 2013, including 1,817 (61%) men with M+ disease, 448 (15%) with N+/X M0, and 697 (24%) men who were N0M0. At the median follow-up of 43 months (IQR 30–60), there were 415 patients died in the control group, with a median OS of 71 months (IQR 32-not reached (NR)) for SOC, NR (IQR 32-NR) for SOC + ZA (HR 0.94, 95%CI 0.79–1.11), 81 months (41-NR) for ADT-DOCE (HR 0.78, 95%CI 0.66–0.93), and 76 months (IQR 39-NR) for SOC + ZA + Doc (HR 0.82, 95%CI 0.69–0.97). They concluded that Zoledronic acid showed no evidence of survival improvement and should not be part of standard of care for this population. Docetaxel chemotherapy, given at the time of long-term hormone therapy initiation in mHSPC patients, showed evidence of improved survival although at expense slight increase in adverse events especially haematological toxicities. An updated analysis of STAMPDE recently published, suggest that after median follow up of 6 year, among 1086 M1 patients, 362 (44%) had low and 468 (56%) high metastatic burden. There were 494 deaths on SOC. There is affirmative evidence of benefit of docetaxel over SOC on OS (HR= 0.81, 95% CI 0.69–0.95, P=0.009) with no evidence of heterogeneity of docetaxel effect between metastatic burden sub-groups (interaction P= 0.827). Evidence of benefit was found after analysing other outcomes for docetaxel over SOC in failure-free survival (HR=0.66, 95% CI 0.57–0.76, P<0.001) and progression-free survival (HR=0.69, 95% CI 0.59–0.81, P<0.001) with no evidence of heterogeneity of docetaxel effect. The clinically significant benefit in survival for upfront docetaxel persists even after longer follow-up, with no evidence that benefit differed by metastatic burden.

STAMPDE group concluded that the upfront docetaxel should be considered for metastatic hormone naïve prostate cancer patients regardless of metastatic burden.

Androgen deprivation therapy plus abiraterone:

LATITUDE TRIAL:

LATITUDE evaluated ADT+ abiraterone compared to ADT alone among men with high-risk mHSPC. High-risk was defined as least two of three criteria: (i) Gleason score ≥8, (ii) presence of ≥3 metastatic lesions on bone scan, or (iii) presence of measurable visceral lesions. Patients were randomized 1:1 to either ADT+ abiraterone (1000 mg abiraterone acetate + 5mg prednisone daily) (n=597) or ADT + placebo (n=602). Over a median follow-up of 30.4 months, patients treated with ADT-ABI had a 38% risk reduction of death (HR 0.62, 95%CI 0.51-0.76) compared to ADT + placebo. Median OS was not yet reached in the ADT-ABI arm, compared to 34.7 months in the ADT + placebo arm. There was also a 53% risk of reduction of radiographic progression or death for patients treated with ADT-ABI compared to ADT alone (HR 0.47, 95%CI 0.39-0.55). The study was unblinded at first analysis at results were presented. On longer median follow up (41 months) at the time of the second analysis there were 205 patients (34%) in the ADT-ABI arm and 70 patients (12%) in the ADT + placebo arm (of whom 57 patients (81%) had crossed over to ADT-ABI) who remained on treatment. updated OS results continued to favour ADT-ABI compared to ADT alone (NR vs 36.7 months; HR 0.638, 95%CI 0.538-0.758).

STAMPEDE ABI TRIAL:

STAMPEDE ABI study included patients with locally advanced or metastatic prostate cancer. These patients were then randomized 1:1 to SOC (ADT for ≥2 years, n=957) vs ADT-ABI (1000 mg abiraterone acetate + prednisone 5 mg daily, n=960). Primary outcomes were OS and failure-free survival (FFS). Over a median follow-up of 40 months, there was a 37% relative improvement in OS (HR 0.63, 95%CI 0.52-0.76) favouring ADT-ABI. ADT-ABI also demonstrated a 71% improvement in FFS (HR 0.29, 95%CI 0.25-0.34) as well as significantly decreasing SREs among the entire cohort (HR 0.46, 95%CI 0.37-0.58).

There are no large head to head trial comparing docetaxel versus abiraterone in HSPC setting. In a network meta-analysis which compared ADT-DOCE to ADT-ABI using data from GETUG, CHAARTED, LATITUDE, and the STAMPEDE trials. Overall, 6,067 patients were included: 1,181 (19.5%) patients who received ADT-DOCE, 1,557 (25.7%) patients who received ADT-ABI, and 3,329 (54.9%) patients who received ADT alone. The overall HR for OS was 0.75 (95%CI 0.63–0.91) for ADT-DOCE versus ADT alone and 0.63 (95%CI 0.55–0.72) for ADT-ABI versus ADT alone. The indirect comparison of ADT-ABI to ADT-DOCE demonstrated no statistically significant difference in OS between treatments (HR 0.84, 95%CI 0.67– 1.06) and the findings were similar among patients with metastatic disease. Both modalities have different and agent-specific side-effects. Mainly febrile neutropenia with docetaxel and cardiovascular events potentially related to mineralocorticoid-associated side-effects as well as hepatic

disorders with abiraterone and prednisolone. Both treatments require a strict follow-up policy. Currently, the choice between docetaxel or abiraterone acetate in mHSPC setting should be individualized on basis considering the patient's preference, cost of therapy, prognosis and comorbidities. Generally, patients with high-volume or de novo metastatic HSPC, docetaxel is preferred if patient is fit to receive the same, abiraterone acetate can be considered at a later point in treatment on subsequent progression of disease.

Androgen receptor inhibitors in mHSPC setting:

ENZAMET [ANZUP 1304]: This is a phase III randomized trial of standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer (mHSPC). Over span of three year 1125 patients were randomized to receive ADT plus either ENZA or NSAA (NSAA: bicalutamide, nilutamide, or flutamide) with or without docetaxel .After a median follow-up of 33 month, overall survival was significantly prolonged in the enzalutamide arm compared to the non-steroidal anti-androgen arm (HR 0.67, 95% CI 0.52-0.86). At 3 years, 36% NSAA vs 64% ENZA were still on their assigned study treatment. Serious adverse events within 30 days of study treatment occurred in 42% ENZA vs 34% NSAA. Enzalutamide significantly improved OS when added to SOC in mHSPC. The benefits were lower in those who planned to receive early docetaxel-based chemotherapy. Further follow up of this study is awaited.

TITAN: This was double-blind, phase 3 trial of 525 metastatic, castration-sensitive prostate cancer patient who received either apalutamide (240 mg per day) or placebo, added to ADT. Previous treatment for localized disease and previous docetaxel therapy were allowed. The primary end points were radiographic progression–free survival and overall survival. At the first interim analysis, overall survival at 24 months was greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P=0.005), radiographic progression–free survival at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001). The frequency of grade 3 or 4 adverse events was 42.2% in the apalutamide group and 40.8% in the placebo group; rash was more common in the apalutamide group. Based on the TITAN trial, apalutamide was approved for treatment of metastatic castration-sensitive prostate cancer in the United States in September 2019.

TREATMENT OF PRIMARY TUMOR IN NEWLY DIAGNOSED METASTATIC DISEASE

Metastatic prostate cancer is a clinically and genetically heterogeneous disease. Metastatic burden is classified according to the definition used in the CHAARTED trial. High Burden is defined as ≥4 bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both. All other assessable patients were considered to have low metastatic burden.

The HORRAD Study demonstrated a trend to benefit with ADT plus local radiotherapy in primary bone metastatic prostate cancer but no absolute OS was demonstrated. The STAMPEDE (H-Arm) study showed in a subgroup analysis that prostate radiotherapy (36Gy/6#/6 days and 55Gy/20#/4 weeks were the schedules used) showed improved failure free survival in patients with low metastatic burden at baseline.

METASTASIS DIRECTED THERAPY (MDT)

STOMP is the only Phase II study which enrolled 62 patients with a median follow up of 3 years and showed a median ADT free survival of 21 months for the MDT group vs 13 months for the surveillance group which was statistically insignificant but with no improvement in OS. The idea of MDT is to delay palliative morbid ADT and chemotherapy in this subset of patients.

CASTRATION RESISTANT PROSTATE CARCINOMA:

Definition of Castration-resistant prostate cancer:

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;

a. **Biochemical progression:** Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,

b. **Radiological progression:** The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [747].

Asymptomatic non-metastatic CRPC

This condition is commonly seen after definitive treatment of localized or locally advanced carcinoma prostate with ongoing ADT and testosterone level below castrate range (<50 ng/dl). One of the first clinical presentations of CRPC occurs in a patient with a rising PSA despite medical or surgical castration. This is typically seen as serially rising PSA and no radiologic evidence of metastatic prostate cancer on imaging. Apalutamide or enzalutamide can be considered along with continued androgen deprivation to patients with non-metastatic CRPC.

Apalutamide: In a phase 3 SPARTAN trial, 1,207 patients of non-metastatic CRPC with a PSA doubling time ≤10 months were randomized in a 2:1 ratio to receive apalutamide (240 mg per day) or placebo. At the time of planned primary analysis, median metastasis-free survival (MFS) was 40.5 months in the apalutamide group compared to 16.2 months in the placebo group (HR=0.28; 95% CI, 0.23 to 0.35; P<0.001), representing a 72% reduction in the risk of distant metastasis or death.

Enzalutamide: In a phase 3 study (PROSPER) 1,401 patients with M0 CRPC with a PSA doubling time ≤10 months and PSA ≥2ng/mL, were randomized (2:1) to enzalutamide 160 mg per day or placebo. In a planned interim analysis, 219 patients (23%) in the enzalutamide group had metastases or had died, as compared with 228 (49%) in the placebo group. Median MFS was approximately 22 months longer in the enzalutamide arm at 36.6 months compared to 14.7 months in the placebo group (HR=0.29; 95% CI 0.24 to 0.35; P<0.001).

Systemic therapy options in metastatic CRPC:

With approval of various drugs in CRPC, overall survival has improved over the years, all these therapies are given in along with continued ADT. These approaches include the following:

Pre-Docetaxel approved therapies:

Abiraterone

Abiraterone was evaluated in 1,088 chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients without visceral metastasis were randomised to abiraterone acetate or placebo, both combined with prednisone. Patients were stratified as per ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and radiographic PFS (rPFS) were the co-primary endpoints. After a median follow-up of 22.2 months, there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, $p < 0.001$) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70-0.93, $p = 0.0033$) [759]. Adverse events (AEs) related to excess mineralocorticoid activity and liver dysfunction were seen in abiraterone arm.

Enzalutamide:

In a randomised phase III trial (PREVAIL), 1717 chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients were randomized into enzalutamide and placebo. Only few patients with visceral metastases were eligible. Results of this trial showed a significant improvement in

both co-primary endpoints, rPFS (HR: 0.186; CI: 0.15-0.23, p < 0.0001), and OS (HR: 0.706; CI: 0.6-0.84, p < 0.001). A ≥50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension.

Sipuleucel-T: This an immunotherapy using activated autologous dendritic cells and was tested against 'placebo' in asymptomatic CRPC patients with slowly rising PSA. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 (p = 0.03). There was no effect on disease response or progression. Due to its high cost, logistic reasons and availability of other suitable alternative therapies, this is not routinely considered in day to day practice.

With the result of these two studies, abiraterone and enzalutamide are approved in chemo-naïve, asymptomatic or mildly symptomatic mCRPC patients before use of docetaxel.

Radium-223: In ALSYMPCIA trial of a bone-targeted Radium -223 an alpha emitter, was tested against placebo in over 900 men with bone-predominant, symptomatic CRPC without visceral disease and no previous exposure of docetaxel. Radium-223 improved overall survival (HR 0.70; 95% CI 0.58–0.83) and time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52–0.83). Main side effects Side-effects of radium-223 include myelosuppression, particularly thrombocytopenia, and diarrhoea.

Docetaxel:

In the landmark TAX-327 trial 1,006 men with mCRPC and good performance status randomized to receive 5mg prednisone twice daily and either docetaxel 75mg/M2 every three weeks; docetaxel 30mg/M2 weekly or; mitoxantrone 12mg/M2 weekly. Median survival in the docetaxel plus prednisone every three weeks group was 18.9 months compared to 16.5 months in the mitoxantrone group (HR for death: 0.75; p=0.009). Bone pain responses and QOL improvements were better in docetaxel patients (35% v. 22%; p=0.08) as compared to the mitoxantrone group. Updated results showed a similar median survival benefit for docetaxel every three weeks v. mitoxantrone, with three-year survival rates of 18.6% and 13.5%, respectively (p=0.005). The magnitude of benefit associated with docetaxel plus prednisone treatment for CRPC was independent of age, performance status or baseline PSA. With this result, the docetaxel three-weekly doses combined with prednisone 5 mg BID, up to minimum ten cycles became the standard first-line chemotherapy in mCRPC.

Second-line treatment for mCRPC (Post docetaxel progression):

Cabazitaxel: In a large prospective, randomised, phase III TROPIC trial Cabazitaxel plus prednisone was compared to mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy. Patients received a maximum of ten cycles of Cabazitaxel (25 mg/m2) or mitoxantrone (12 mg/m2) plus prednisone (10 mg/day). Overall survival was

significantly longer with Cabazitaxel (median: 15.1 vs. 12.7 months $p < 0.0001$). There was also improvement in PFS (median: 2.8 vs. 1.4 months, $p < 0.0001$), objective RECIST response (14.4% vs. 4.4%, $p < 0.005$), and PSA response rate (39.2% vs. 17.8%, $p < 0.0002$). Treatment-associated grade 3-4 AEs seen more frequently in the Cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, $p < 0.0002$). In an other study , 20 mg/m² Cabazitaxel was compared to 25 mg/m2 and it was concluded that 20 mg/m2 dose of Cabazitaxel was not inferior to 25 mg/m² in the second-line setting in terms of OS, but it is less toxic , hence , the lower dose is preferred and usually given along with prophylactic granulocyte colony-stimulating factor .

Abiraterone acetate after prior docetaxel:

In a phase III trial (COU-AA-301), 1,195 patients who had progression of disease over initial docetaxel received 1,000 mg abiraterone plus prednisone or placebo. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, $p < 0.0001$). The benefit was observed in all subgroups and all the secondary objectives favoured abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). Common Grade 3-4 AEs did not differ significantly between arms. As expected, mineralocorticoid-related side-effects (fluid retention, oedema and hypokalaemia) were more frequent in the abiraterone group, and majority of SAE were mainly Grade 1-2.

Enzalutamide post docetaxel: In AFFIRM phase III trial of 1,199 patients who had received prior docetaxel therapy,

received either enzalutamide 160 mg/day orally or placebo, and OS, the primary endpoint, favoured enzalutamide (18.4 months v 13.6 months). After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$). Enzalutamide benefited other secondary endpoint of study including PSA reduction, soft tissue response, QoL, time to PSA or objective progression. Side effects were similar in both groups with only difference in seizure which was seen in 0.6% patients in enzalutamide arm.

Sequencing of therapies in mCRPC: There is no consensus guidelines or head to head trials for sequencing of therapies in CRPC. Factors that can be considered in choosing the specific form of systemic therapy include the response to previous ADT (< 12 month versus > 12 months), site and extent of disease (visceral versus bone only disease), rate of disease progression, symptomatology, comorbidities and performance status, patients preference , availability of the modality, prior systemic treatments, side effects of the treatment , contraindications , social support and cost of the therapy . In nut shell, the sequencing of therapy in mCRPC needs to be individualized and one size does not fit all concept applies here also.

Treatment after docetaxel and one line of hormonal treatment for mCRPC: The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC was still open till the results of phase II CARD trial which is published recently. This was study of Cabazitaxel as third line therapy in metastatic castration-resistant

prostate cancer (mCRPC) after progression over docetaxel and one line of androgen directed therapy. The primary endpoint was radiographic progression-free survival (PFS). Secondary endpoints were overall survival, PFS and tumor response. Total of 255 patients underwent randomization. After a median follow-up of 9.2 months, imaging-based progression or death was reported in 95 of 129 patients (73.6%) in the Cabazitaxel group, as compared with 101 of 126 patients (80.2%) in the group that received an androgen-signalling–targeted inhibitor (hazard ratio, 0.54; 95% confidence interval [CI], 0.40 to 0.73; P<0.001). The median imaging-based progression-free survival was 8.0 months with Cabazitaxel and 3.7 months with the androgen-signalling–targeted inhibitor. The median overall survival was 13.6 months with Cabazitaxel and 11.0 months with the androgen-signalling–targeted inhibitor (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.89; P=0.008). Adverse events of grade 3 or higher occurred in 56.3% of patients receiving Cabazitaxel and in 52.4% of those receiving an androgen-signalling–targeted inhibitor. Study results concluded that Cabazitaxel significantly improved a number of clinical outcomes, as compared with the androgen-signalling–targeted inhibitor (abiraterone or enzalutamide), in patients with metastatic castration-resistant prostate cancer and should be considered as third line therapy in fit for receiving chemotherapy.

Molecular therapies in prostate cancer:

All men with metastatic prostate cancer preferably undergo germline testing for genes , which may influence the aggressiveness of the disease and/or treatment

options and includes :mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), and post meiotic segregation increased 2 (PMS2; for Lynch syndrome); BRCA1; BRCA2; ataxia telangiectasia mutated (ATM); PALB2; and checkpoint kinase 2 (CHEK2). Next-generation sequencing should also be used to test the prostate cancer for identification of somatic mutations.

In phase 2 trial (TOPARP-B) of metastatic castration-resistant prostate cancer who have progressed over two lines of taxane therapy and have DNA repair gene aberrations in biopsy sample received 400 mg or 300 mg olaparib twice daily continuously in 4-week cycles until disease progression or unacceptable toxicity. The primary endpoint of confirmed response was defined as a composite of all patients presenting with any of the following outcomes: radiological objective response as per RECIST, a decrease in prostate-specific antigen from baseline, or conversion of circulating tumour cell count. 161 patients had DDR gene aberrations, 98 of whom were randomly assigned and treated each dose level. Confirmed composite response was achieved in 25 (54·3%; 95% CI 39·0–69·1) of 46 evaluable patients in the 400 mg cohort, and 18 (39·1%; 25·1–54·6) of 46 evaluable patients in the 300 mg. this trial has confirmed that olaparib has antitumor activity against metastatic castration-resistant prostate cancer with DDR gene aberrations and also supports the need of genomic stratification of metastatic castration-resistant prostate for better treatment outcome.

Similarly, in a phase 3 study (PROfound) of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations. Patients were randomized 2:1 to olaparib (300 mg bid) or the physician's choice of enzalutamide (160 mg/day) or abiraterone (1000 mg/day + prednisone 5 mg BID). The primary endpoint was radiographic progression-free survival (rPFS). Two hundred forty-five randomized to Cohort A. Olaparib was associated with improved rPFS compared to enzalutamide/abiraterone among patients in Cohort A (HR 0.34, 95% CI 0.25-0.47), which was consistent across the majority of subgroups assessed. The interim results for overall survival (OS) demonstrated improved survival among patients in Cohort A (HR 0.64, 95% CI 0.43-0.97). The results of this study have shown the way for personalized therapy and need of molecular profiling of tumor in current era.

Pembrolizumab in men with heavily treated metastatic castration-resistant prostate cancer:

The MSI-H/dMMR phenotype was identified in 3.2% of prostate tumors in a study done at MSKCC. Anti–programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) treatment was given to 11 patients with MSI-H/dMMR castration-resistant prostate cancer. More than a 50% decline in prostate-specific antigen levels was observed in 6 (54.5%) patients out of these, 4 patients having radiographic responses also. Five of the 6 responders remained on treatment, with the longest ongoing response at the time of analysis being 89 weeks.

The MSI-H/dMMR molecular phenotype is rare but therapeutically can be targeted and can be somatically acquired during disease evolution. Pembrolizumab has been approved for use in any tumor with MSI-H/ dMMR deficient status on molecular testing.

Other options in mCRPC:

Lu 177 PSMA Therapy:

Patients who progressed on Docetaxel and one line of hormonal therapy with bony or visceral metastases or patients not fit for chemotherapy or not willing for chemotherapy and progressed over hormonal therapies and have PSMA avid lesion proven by PET can be considered for Lu177 PSMA therapy. Other option is actinium PSMA therapy .Patients treated with Lu-PSMA therapy has shown good symptomatic and radiological response in institutional experiences, although randomized trial is needed to exactly define the place of PSMA therapy in management of mCRPC.

Patients with progressive disease or not affording for newer therapies can be considered for other therapies including oral fosfestrol, low dose abiraterone with fatty meals, oral metronomic therapy with cyclophosphamide and low dose dexamethasone, ketoconazole, mitoxantrone, estramustine and weekly carboplatin and paclitaxel as per patients' general condition of patient, comorbidities and lab parameters.

Preventing skeletal-related events:

Bisphosphonates

Zoledronic acid has been investigated in mCRPC to reduce skeletal-related events (SRE). Out of 643 patients who had CRPC with Bone, metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for fifteen consecutive months, or placebo. After 24 months of follow-up, patients treated with 4 mg zoledronic acid had less skeletal-related events (SREs) compared to the placebo group (44 vs. 33%, p = 0.021) and also has reduced pathological fractures (13.1 vs. 22.1%, p = 0.015). The time to first SRE was also longer in the zoledronic acid group compared with placebo. Bisphosphonates have not shown any survival benefit in prospective studies.

RANK ligand inhibitors

Denosumab is fully human monoclonal antibody directed against RANKL which is mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months .HR: 0.85, p = 0.028) although this benefit did not translate into a statistically meaningfu survival difference (43.9 compared to 44.8 months, respectively) .The efficacy and safety of denosumab (n = 950) was compared with zoledronic acid (n = 951) in patients with metastatic CRPC in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs which was defined as pathological fracture, radiation or surgery to bone, or spinal cord compression of 20.7 vs. 17.1 months, respectively in favour of denosumab (HR: 0.82; p = 0.008).

Urinary N-telopeptide (NTX) and bone-specific alkaline phosphatase (BAP) which are the markers of bone turn over, were significantly lower in the denosumab arm compared with the zoledronic acid arm ($p < 0.0001$ for both).

These agents are associated with potential toxicity including osteonecrosis of the jaw and hypocalcaemia, should be prescribed with Vit D and calcium supplementation.

Patients should have a dental examination before starting therapy as the risk of osteonecrosis of jaw is increased by dental infection, history of trauma or dental surgery in past.

7. SCREENING AND EARLY DETECTION OF PROSTATE CANCER:

Currently, screening for PCa is one of the most controversial topics in the urology literature. Three larges prospective RCTs published data on screening in 2009 resulting in conflicting positions and policy papers. A comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction in the systematic screening group compared to a higher over-diagnosis with a marginal survival benefit, at best, in the opportunistic screening regimen.

A Cochrane review published in 2013 presents the main overview to date.

- Screening is associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).

- Screening is associated with detection of more localised disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80, 95% CI: 0.73-0.87).
- No Cancer specific survival benefit was observed (RR: 1.00, 95% CI: 0.86-1.17).
- No overall survival (OS) benefit was observed (RR: 1.00, 95% CI: 0.96-1.03).

An individualised risk-adapted strategy for early detection might be offered to a well-informed man with at least ten to fifteen years of life expectancy. It is important to carefully identify the patient taking into account the potential balances and harms involved.

Men at elevated risk of having PCa are those > 50 years or at age > 45 years with a family history of PCa (either paternal or maternal), or African-Americans. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years are also at increased risk of PCa metastasis or death from PCa several decades later.

A risk-adapted strategy can be considered, based on the initial PSA level. This could be every two years for those initially at risk, or postponed up to eight to ten years in those not at risk with an initial PSA < 1 ng/mL at 40 years and a PSA < 2 ng/mL at 60 years of age and a negative family history. New biological markers such as TMPRSS2-ERG fusion, PCA3 or kallikreins as incorporated in the Phi or 4Kscore tests have been shown to add sensitivity and specificity on top of PSA, potentially avoiding unnecessary biopsies and reducing overdiagnosis.

WHAT HAS CHANGED IN PROSTATE CANCER IN THE LAST DECADE

- Incidence of Prostate cancer seems to be increasing mpMRI has emerged as the standard for prostate cancer imaging and local staging
- PSMA-PET CECT is emerging as a one-stop test for the metastatic evaluation of advanced prostate cancer.
- ISUP/WHO 2016 Grade grouping classification is recommended for biopsy reporting of prostate cancer.
- Biopsy Gleason Score comprises the most common grade plus the highest grade
- The oncological safety of Active Surveillance in low and very low-risk disease is considered as an established option in selected intermediate-risk patients
- There are no significant differences in oncological, urinary function and sexual function outcomes when RARP as compared to open RP. RARP shows all benefits of MIS along with enhanced surgeon comfort and dexterity.
- The combination of RT with ADT is proven to be superior to RT alone in improving overall survival of intermediate-risk patients and in locally advanced prostate cancer.

- Moderate hypofractionation and Ultrafractionation/SBRT improves the therapeutic benefit of RT without increasing toxicity.
- In the post RP scenario, PSMA PET scan has an increasing role detection of disease recurrence, even for PSA values less than 0.5 ng/ml.
- Randomized trials show that salvage RT at PSA levels < 0.5 ng/ml is not inferior to adjuvant.
- Docetaxel, Abiraterone and Enzalutamide, all three are standard therapies in combination with ADT at mCSPC stage. Choice of drug should be tailored as per patient and tumor factors.
- Various RCTs have expanded the options available for mCSPC and mCRPC however the best sequencing of these drugs is still being evaluated.
- Zoledronic acid is known to reduce and delay SRE in mCRPC but doesn't offer survival benefit. Denosumab is superior to Zoledronic acid in reducing SRE and can be used in mCSPC/mCRPC.
- PSMA- radionuclide based therapy is being used in mCRPC stage with progressive disease. Lutetium and Actinium are used with some success.

SUGGESTED READING

1. Lalitha K, Suman G, Pruthvish S, Aleyamma M, Nandagudi M; Asian Pacifc Journal of Cancer Prevention, Vol 13, 2012, 6245-6250.

2. Budukh A, Bakshi G, Prakash G. Change in the ranking and increasing trend of the prostate cancer from the population-based cancer registries in India. Indian J Urol 2018; 34:235-6.)

3. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998;279(19): 1542-7.

4. Alonzi R, Padhani AR, Allen C. Dynamic contrast enhanced MRI in prostate cancer. Eur J Radiol 2007: 63:335–50.

5. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017; 389:815-822.

6. Kasivisvanathan, V., et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med, 2018. 378: 1767.

7. Gutzeit A, Doert A, Froehlich JM, et al. Comparison of diffusion-weighted whole body MRI and skeletal scintigraphy for the detection of bone metastases in patients with prostate or breast carcinoma. Skeletal Radiol 2010 Apr;39(4):333-43.

8. Wibmer AG, Burger IA, Sala E, Hricak H, Weber WA, Vargas HA. Molecular Imaging of Prostate Cancer. Radio Graphics. 2015 Nov 20;36(1):142–59.

9. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncol. 2019 Jun 1;5(6):856–63.

10. Sanli, Y., et al. Relationships between serum PSA levels, Gleason scores and results of 68Ga-PSMAPET/CT in patients with recurrent prostate cancer. Ann Nucl Med, 2017. 31: 709.

11. Campbell Walsh Textbook of Urology, WB Saunders, 10th edition Early Detection, Diagnosis, and Staging of Prostate Cancer 2363

12. Epstein, J.I., et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol, 2016. 40: 244.

13. Kane, C.J., et al. Variability in Outcomes for Patients with Intermediate-risk Prostate Cancer(Gleason Score 7, International Society of Urological Pathology Gleason Group 2-3) and Implications for Risk Stratification: A Systematic Review. Eur Urol Focus, 2017. 3: 487.

14. Brierley, J.D., et al., TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2017.

15. Hamdy, F.C., et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med, 2016. 375: 1415.

16 Ilic, D., et al. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Syst Rev, 2017. 9: CD009625.

17. Wilt, T.J., et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer.N Engl J Med, 2017. 377: 132.

18. Studer, U.E., et al. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol, 2008. 53: 941.

19. Passoni, N.M., et al. Prognosis of patients with pelvic lymph node (LN) metastasis after radical prostatectomy: value of extranodal extension and size of the largest LN metastasis. BJU Int, 2014. 114: 503.

20. Kumar, S., et al. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Cochrane Database Syst Rev, 2006: CD006019.

21. Ramsay, C., et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess, 2012. 16: 1.

22. Haglind, E., et al. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol, 2015. 68: 216.

23. Surgery Versus Radiotherapy for Locally Advanced Prostate Cancer (SPCG-15). 2014, U.S. National library of Medicine: NCT02102477.

24. Moschini, M., et al. Outcomes for Patients with Clinical Lymphadenopathy Treated with Radical Prostatectomy. Eur Urol, 2016. 69: 193.

25. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-1424.

26. Zaorsky NG, Keith SW, Shaikh T, Nguyen PL, Horwitz EM, Dicker AP, Den RB. Impact of radiation therapy dose escalation on prostate cancer outcomes and toxicities.

American Journal of Clinical Oncology. 2018 Apr 1;41(4):409-15.

27. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): A randomised, controlled, phase 3 trial. Lancet Oncol. 2015;16(3):320–7.

28. Morris, W.J., et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. Int J Radiat Oncol Biol Phys, 2017. 98: 275.

29. Morgan SC,et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. Journal of Clinical Oncology. 2018 Oct 11: JCO-18.

30 . Dearnaley D, Syndikus I, Mossop H, et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 17: 1047-1060, 2016.

31. Carrie C, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. The Lancet Oncology. 2019 Dec 1;20(12):1740-9.

32 . Kishan AU, Dang A, Katz AJ, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. JAMA Netw Open. 2019;2(2): e188006.

33. Pollack A, Karrison TG, Balogh AG, Low D, Bruner DW, Wefel JS, Gomella LG, Vigneault E, Michalski JM, Angyalfi S, Lukka H. Short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: the NRG Oncology/RTOG 0534 SPPORT trial. International Journal of Radiation Oncology• Biology• Physics. 2018 Dec 1;102(5):1605.

34 . Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, Ritchie AW, Attard G, Chowdhury S, Cross W, Dearnaley DP. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. The Lancet. 2018 Dec 1;392(10162):2353-66.

35. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, DeBruycker A, Lambert B, Delrue L, Bultijnck R, Claeys T, Goetghebeur E. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial.

36. Ghadjar P, Fiorino C, af Rosenschöld PM, Pinkawa M, Zilli T, van Der Heide UA. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. Radiotherapy and Oncology. 2019 Dec 1; 141:5-13.

37. Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, Koontz BF, Murphy DG, Nguyen PL, Nam RK. Pelvic complications after prostate cancer radiation therapy and their management: an international collaborative narrative review. European urology. 2019 Mar 1;75(3):464-76.

38 . Wiegel, T., et al. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of

the ARO 96-02 trial. Int J Radiat Oncol Biol Phys, 2015. 91: 288.

39. Moreira, D.M., et al. Definition and preoperative predictors of persistently elevated prostate-specific antigen after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. BJU Int, 2010. 105: 1541.

40. Toussi, A., et al. Standardizing the Definition of Biochemical Recurrence after Radical Prostatectomy-What Prostate Specific Antigen Cut Point Best Predicts a Durable Increase and Subsequent Systemic Progression? J Urol, 2016. 195: 1754.

41. Roach, M., 3rd, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys, 2006. 65: 965.

42. James, N.D., et al. Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol, 2015. 67: 1028.

43. Kunath, F., et al. Non-steroidal antiandrogen monotherapy compared with luteinising hormone releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev, 2014. 6: CD009266.

44. James, N.D., et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy.N Engl J Med, 2017. 377: 338.

45. Fizazi, K., et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med, 2017. 377: 352.

46. Sweeney, C.J., et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med, 2015. 373: 737.

47. Wallis, C.J.D., et al. Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naive Prostate Cancer: A Systematic Review and Network Meta-analysis. Eur Urol, 2018. 73: 834.

48. Boeve, L.M.S., et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol, 2018. S0302: 30658.

49. Hussain, M., et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer.N Engl J Med, 2018. 378: 2465.

50. Smith, M.R., et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer.N Engl J Med, 2018. 378: 1408.

51. Ryan, C.J., et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol, 2015. 16: 152.

52. Beer, T.M., et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med,2014. 371: 424

53. Tannock, I.F., et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med, 2004. 351: 1502.

54. Fizazi, K., et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer:final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol, 2012. 13: 983

55. Scher, H.I., et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med, 2012. 367: 1187.

56. Parker, C., et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med,2013. 369: 213.

57. Gillessen, S., et al. Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. Eur Urol, 2018. 73:

58. Saad, F., et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. J Natl Cancer Inst, 2002. 94: 1458.

59. Fizazi, K., et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet, 2011. 377: 813.

60. Andriole, G.L., et al. Mortality results from a randomized prostate-cancer screening trial.
N Engl J Med, 2009. 360: 1310.

CHAPTER 2

Bladder Cancer

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1. EPIDEMIOLOGY

Carcinoma of bladder is a heterogeneous disease which presents as non-muscle invasive, muscle-invasive or metastatic disease. These different presentations of bladder cancer have different clinical behaviour, management protocols and outcome. It is the 12th most common cancer worldwide, with an incidence of 5.7 cases per 100,000. Bladder cancer is more prevalent in developed countries. The incidence of bladder cancer shows high variations across countries. In India, the incidence is 1.5 cases per 100,000, being the 19th most common cancer. Mortality rate across the world is 1.9 per 100,000; whereas in India the mortality is 0.82 per 100,000. Non-invasive bladder cancer accounts for approximately three-fourths of all bladder cancers. Males are more commonly affected (M: F= 2.4:1). In the SEER data, from 2012-2016, the median age at diagnosis of urinary bladder cancer was 73 years, and nearly 90% of the diagnosis is made in patients over the age of 55 years.

2. AETIOLOGY:

2.1 Tobacco smoking

It is the single most important factor associated with bladder cancer and accounts for nearly 50% of all detected cases. The risk of bladder cancer directly relates to the duration of smoking and number of cigarettes smoked per day and an immediate reduction in the risk of bladder cancer is observed with the cessation of smoking.

2.2 Chemical exposure

Chemical agents: Exposure to aromatic amines as seen in workers of dye, rubber, leather industry, gas and tar manufacturing, industrial painting etc., which account for one-tenth of all detected cases (median latent period between exposure and disease is 18 year).

Dietary habits: less fluid intake, fried meat & fat intake, Low vitamin A, chlorination of drinking water

Drugs- phenacetin, cyclophosphamide, immunosuppressive.

2.3 Chronic irritation

Chronic urinary tract Infection, schistosomiasis, long term use of catheter, pelvic irradiation is associated with squamous cell carcinoma of the urinary bladder.

2.4 Genetic abnormality

17p deletion, p53 expression, RB gene expression, 9q aberration are known mutations leading to carcinogenesis. However, no significant genetic variation for bladder cancer has been detected.

2.5 Radiation Induced

Patients who have received external beam radiation to the pelvis are at an increased risk of secondary bladder cancer. Studies have indicated a relative risk of 2-4 in patients receiving EBRT for gynaecological malignancies. Radiation for prostate cancer is also known to be associated with risk of developing bladder cancer.

3. CLINICAL PRESENTATION:

Patients usually present with painless haematuria (80-90%) or with unexplained urinary frequency or irritative voiding symptoms. Lower urinary storage and obstructive symptoms may be the sole presenting symptoms in the absence of haematuria. These symptoms overlap with benign disorders, thus often delaying diagnosis. Pelvic pain and obstructive symptoms are seen in patients with advanced invasive disease.

Initial studies have reported that the extent of hematuria is related to the likelihood of malignancy. Some studies have stated the incidence of bladder cancer is 10-20% in patients presenting with gross hematuria, as compared with 2-5% incidence for those evaluated for microscopic hematuria. A single episode of haematuria should also be investigated, especially in patients over 40 years old, smokers and those with exposure to industrial carcinogens.

4. INVESTIGATIONS:

Investigations in bladder cancer are aimed at diagnosis and staging to guide therapy. The main factor that decides the treatment is the presence or absence of muscle invasion.

Evaluation for bladder cancer includes cystourethroscopy, urinary cytology, and evaluation of upper tracts as urothelial malignancy can be multifocal. The diagnostic and staging investigations in bladder cancer are as follows:

4.1 Urine analysis

Should be done on a freshly voided sample (except the first voided morning specimen). The analysis should include a gross and microscopic examination as well as a dipstick test for hematuria. Hematuria is not considered significant unless more than 3RBCs per high power field are present. In case of RBC lysis, dipstick analysis will be positive for blood (myoglobin), while the microscopic examination may be negative. These patients should be carefully evaluated.

4.2 Urine cytology

Urine cytology is commonly used as an adjunct to cystoscopy. Urine sample for cytology should be processed early, as cells degrade after 10- 15 minutes at room temperature. Contamination with cervical, vaginal or endometrial cells may lead to misinterpretation. Positive cytology in the absence of any lesion on cystoscopy or imaging may indicate a lesion anywhere in the urinary tract and may need screening of upper tract. Negative voided cytology does not exclude the presence of a low-grade bladder cancer. The sensitivity of urine cytology is poor, especially with low-grade tumors. Meta-analysis of 1255 patients has demonstrated sensitivity for grade 1, 2, and 3 tumors of 12, 26, and 64 percent, respectively. The

specificity of urine cytology is >98% in most of these studies.

Paris system for reporting urinary cytology diagnostic criteria, 2016, has been developed to standardise reporting of urinary cytology, which emphasises the identification of urothelial carcinoma, which is clinically more significant and relevant. The categories in this are as follows:

- non-diagnostic/unsatisfactory
- negative for high-grade urothelial carcinoma (NHGUC)
- atypical urothelial cells (AUC)
- suspicious for high-grade urothelial carcinoma (SHGUC)
- high-grade urothelial carcinoma (HGUC)
- low-grade urothelial neoplasia (LGUN)

Urinary markers:

Since the sensitivity of urine cytology is low, urinary markers have been developed as a non-invasive technique to supplement cystoscopy. They are based on the detection of DNA, RNA, and expression of tumour related proteins. The sensitivity of urinary markers ranges from 50 – 80% and the specificity ranges from 70 – 90% (lower than cytology). Markers include NMP 22, BTA -STRAK, UroVysion FISH test, FDP.

It is not clear whether these tests can offer additional information, or if they are useful for decision making, especially with the high cost involved.

4.3 Cystoscopy

Rigid or flexible (preferably) white light cystoscopy is the gold standard for the initial diagnosis of bladder cancer and gives the following information.

Bimanual examination under anaesthesia may be done in case of invasive tumours for local staging of the tumour. After transurethral resection, the presence of a palpable mass implies an extravesical disease or fixity to the pelvic sidewalls. The size, stalk, and configuration of cancer can be predictive of muscle invasion. All macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy should be described. One should use a bladder diagram to describe the findings. In general, low-grade, non-invasive tumours are papillary with a narrow stalk. A sessile, solid or nodular pattern is seen more frequently in high-grade tumours. Carcinoma in situ (CIS) is a high-grade, non-invasive tumour, which can appear as a flat velvety lesion and can arise in patches. CIS sometimes involves large parts of the urothelial lining.

Principles of Cystoscopy + TURBT:

1. Any visible tumour or suspicious lesion, seen at the initial (diagnostic) cystoscopy should be either biopsied or transurethrally resected down to muscle, and superficial and deep components of the tumour should be sent separately to the pathologist to determine the histology and depth of invasion.
2. In patients who present with a positive urine cytology and whose initial cystoscopy showed no visible

tumour (or suspicious lesion) within the bladder, a biopsy of apparently normal-appearing urothelial, prostatic urethra, and selective catheterisation of the ureters/renal pelvis with urine specimens for cytology from the upper tract should be performed.

3. Random biopsies in a patient with a solitary papillary lesion are contraindicated due to the perceived hazard of implantation of tumour cells, low likelihood of detection of CIS (<2%) and absence of any additional information.

Table 1: Indication of Prostatic urethral biopsies.	
1.	Bladder neck tumour,
2.	Bladder CIS is present or suspected,
3.	Positive cytology without evidence of tumour in the bladder or
4.	Abnormalities of prostatic urethra are visible

Enhanced Cystoscopy

New technologies in the form of fluorescence cystoscopy (PDD) or narrow-band imaging (NBI) focus on improving the detection of small or flat lesions. NBI is less well studied; thus guidelines statements focus on PDD.

Fluorescence cystoscopy (Blue light cystoscopy).

Cystoscopy with porphyrin dye such as hexaminolevulinate (HLA) or 5- amino levulinic acid (5-ALA) have better identification of tumors.Both small papillary tumors and almost one third more cases of CIS overlooked on white light cystoscopy (WLC) are identified. A meta-analysis of

HLA with Blue Light cystoscopy was showed improved detection rates of HGTa, T1, and CIS, leading to decreased recurrence rates at 12 months (34.5% vs 45.4% BLC vs WLC).

Randomised trials have confirmed that fluorescence cystoscopy detects more tumors (both papillary and CIS) than white-light cystoscopy, and this improves the tumour identification resulting in better patient outcome. AUA and NICE recommend enhanced cystoscopy be offered at the time of TURBT.

EAU recommends PDD-guided biopsies in the setting of positive cytology but negative cystoscopy, while NCCN does not recommend routine use of PDD-enhanced cystoscopy citing lack of evidence regarding reduced progression.

Table 2: Advantages of PDD (Blue light cystoscopy)	
1.	Improves detection rate (particularly CIS)
2.	Helps to identify tumors not seen on WLC when cytology is positive
3.	Reduces residual disease after TUR
4.	Decreases recurrence
5.	Possibly decreases progression

Narrow Band Imaging:

NBI is an optical enhancement technology that narrows the bandwidth of the light into 415 and 540 nm and thereby increases the visibility of microvascular structures in the mucosal surface, which are abundant in urothelial

tumors. The vascular structures appear dark brown or green against a pink of white mucosal background. 28% of CIS lesions that were missed with WLC were detected by NBI. A recent meta-analysis of 8 studies demonstrated that the sensitivity and specificity of NBI and WL were 94% versus 85% and 85% versus 87%, respectively.

Microscopic imaging techniques:

High-resolution cross-sectional views of vesicular tissues provided by optical coherence tomography and confocal laser endomicroscopy resemble images obtained by histopathological examination. Therefore, these are referred to as 'optical biopsy'.

Molecular imaging:

Offers highly specific real-time visualisation of cancer cells and their differentiation from healthy tissue, by combining optical imaging with fluorescent labelling of elements such as antibodies.

Table 3: Disadvantages of enhanced cystoscopy	
1.	Inflammation and scarring lead to higher false-positive rate.
2.	Requirement of a special lens system
3.	Need to instil the photosensitiser one hour before cystoscopy
4.	Rigid rather than flexible cystoscopy, and
5.	Higher cost

4.4 Imaging

The purpose of imaging for staging is to assess the extent of local tumour invasion, detect lymph node spread and

to detect distant metastases. For invasive cancers, it is essential to document the extent of the disease by doing cross-sectional imaging. Both computed tomography (CT) and MRI scans can be used for assessment of local invasion, but they are unable to detect microscopic invasion of perivesical fat (T3a). The aim of CT and MRI scanning is, therefore to detect T3b disease or higher.

Imaging is also used to assess the presence of pelvic and para-aortic lymphadenopathy and the possible presence of liver or adrenal metastases. Pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short-axis diameter should be regarded as enlarged on CT and MRI scans.

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

CT

Multidetector contrast-enhanced CT scan has a lower sensitivity (89% vs 100%) and higher specificity (95% vs 73%) compared to MRI scanning for diagnosis of perivesical invasion, whereas the cancer-detection rate and overall accuracy for perivesical invasion are similar.

MRI

Gadolinium enhanced MRI is a reliable imaging technique for characterisation of bladder cancers. When compared to CT, it has superior soft-tissue resolution but a poorer spatial resolution. MRI may be used for detection of superficial, multiple tumors, extravesical extension and invasion.VIRADS scoring system has been suggested to

evaluate local invasion of bladder tumors.An ongoing randomised trial (BladderPath) is assessing if MRI can reliably predict muscle invasion and obviate the need for doing a TURBT.

PET CT

FDG PET CT has a limited role in patients with localised bladder cancer since FDG is excreted in urine. PET CT may have a role in detecting metastatic disease. In a study of 46 patients, the sensitivity for metastases to adrenal, bone, kidney, lymph node, and soft tissue were 80 percent or greater.

5. NATURAL HISTORY AND PATHOLOGY

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

Histological Grading

Bladder tumors are classified according to the World Health Organization (WHO) 2016 schema. Within the WHO

system, urothelial cancer is classified as either low grade or high grade based upon the degree of nuclear anaplasia and architectural abnormalities. With rare exceptions (such as nested or tubular variants), invasive urothelial carcinoma is high grade in its cytological features. The 2016 WHO system used the same classification as 2004, and is as follows:

Table 4: WHO Classification 2016
Urothelial tumors
Infiltrating urothelial carcinoma
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet ring cell/diffuse
Sarcomatoid
Giant cell
Poorly differentiated
Noninvasive urothelial lesions
Urothelial carcinoma in situ
Noninvasive papillary urothelial carcinoma, low grade
Noninvasive papillary urothelial carcinoma, high grade
Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma
Inverted urothelial papilloma
Urothelial proliferation of uncertain malignant potential
Urothelial dysplasia

(Contd...)

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Squamous cell neoplasms
Pure squamous cell carcinoma
Verrucous carcinoma
Squamous cell papilloma
Glandular neoplasms
Adenocarcinoma, NOS
Enteric
Mucinous
Mixed
Villous adenoma
Urachal carcinoma
Tumors of Müllerian type
Clear cell carcinoma
Endometrioid carcinoma
Neuroendocrine tumors
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Well-differentiated neuroendocrine tumor
Paraganglioma

6. STAGING:

The 8th edition of UICC TNM system was updated in 2017 and is mentioned below. Compared with the 2009 TNM classification, there have been no changes.

Table 5: UICC 2017 Staging of Bladder Cancer	
Urothelial tumors	
Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary tumour
Tis	In-situ flat tumour
T1	Tumour invades subepithelial connective tissue (lamina propria
T2	Tumour invades muscle
T2a	Inner half (superficial muscle)
T2b	Outer half (deep muscle)
T3	Tumour invades perivesical tissues
T3a	Microscopically
T3b	Macroscopically (Extravesical mass)
T4	Tumour invades adjacent structures, e.g. prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall, abdominal wall
Lymph nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No lymph node metastases
N1	Metastasis to a single node 2cm or less in the greatest dimension
N2	Metastasis to a single node >2cm but <5 cm in the greatest dimension or multiple lymph nodes, none >5 cm in the greatest dimension
N3	Metastasis in a lymph node >5cm in the greatest dimension

Distant metastases (M)	
Mx	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases present

7. MANAGEMENT OF NON-MUSCLE INVASIVE BLADDER CANCER:

Transurethral resection of bladder tumour (TURBT): Transurethral resection of the bladder tumour(s) is the standard of care for non-muscle invasive bladder cancers. The ultimate goal of TURBT in Ta/T1 bladder tumors is to make the correct diagnosis and remove all visible lesions. It is done under regional or general anaesthesia. Complete resection can be achieved by either piecemeal or en-bloc resection. Energy sources used are diathermy (monopolar or bipolar) or Laser (Thallium YAG or Holmium YAG). Piecemeal resection provides good information about the vertical and horizontal extent of the tumour. En-bloc resection provides high quality resected specimens with the presence of detrusor muscle in 96-100% of cases, and there is data to suggest that en-bloc resection has the potential to reduce the rates of residual disease on restaging TURBT.

Tumours which are very small (less than 1 cm) should be resected en-bloc containing a part of the underlying bladder wall. Larger tumors should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and edges of the resection area. During resection

cauterisation of tissue should be avoided to prevent its destruction. Sending a separate deep margin that includes the muscularis propria may improve decision making and help ensure complete resection.

Re-TURBT: There is a significant risk of under staging after initial resection of TaT1 tumors, with residual disease detected at second resection in 33-53% of patients. Nearly 20% of T1 patients are upstaged to muscle-invasive disease, the likelihood being more if the initial resection specimen contained no muscle tissue. Accurate staging of disease is important for optimum treatment and under staging may lead to inadequate treatment and poor outcome. It has been shown that the second TURBT can increase recurrence-free and progression-free survival. Though there is no consensus regarding the timing of the second TUR, it is generally recommended 2–6 weeks after the initial TURBT and should always include resection of the primary tumour site.

The risk of recurrence and progression can be separately predicted in individual patients, using EORTC scoring system and risk tables, developed from a database of more than 2500 patients. Despite an adequate transurethral resection, nearly 70- 80% of patients will have a relapse within the bladder while 20-25% will progress to muscle invasion.

Bladder cancer with low risk of recurrence or progression can be managed by close surveillance and regular check cystoscopy, while those with a high risk of relapse need intravesical chemotherapy or immunoprophylaxis.

Table 6: Recommendations for Performance of Re-TUR:	
1.	Incomplete initial resection
2.	High-risk (recurrent, multifocal, >3cm)
3.	HG pTa tumour (High-grade tumour)
4.	Any T1 tumour – resection to include detrusor muscle
5.	Detrusor muscle not sampled in the initial specimen - except TaG1 and primary CIS or
6.	Presence of LVI

Table 7: Prognostic factors for recurrence and progression:	
1.	High grade or poorly differentiated tumors (G3)
2.	Co-existent CIS or dysplasia in random mucosal biopsies
3.	Multiple or multicentric tumors
4.	Multiple recurrences within a short time (rapidly recurrent tumors)
5.	Lamina propria invasion (T1)
6.	Tumour size more than 3 cm
7.	Prostatic urethral involvement

Radical cystectomy for NMIBC: - The reasons to consider immediate RC for selected patients with NMIBC are a) the staging accuracy for T1 tumors by TURBT is low with 27-51% of patients being upstaged to muscle-invasive tumour at RC. b) some patients with NMIBC experience disease progression to muscle-invasive disease. c) patients who experience disease progression to muscle-invasive stage, have a worse prognosis than those who present with 'primary' muscle-invasive disease.

ADJUVANT THERAPY

Intravesical chemotherapy

A single immediate post-operative instillation (SI) of chemotherapy is recommended in all patients irrespective of the risk group, provided there is no perforation or bleeding. It acts by destroying circulating tumour cells after TURB, and by an ablative effect (chemo resection) on residual tumour cells at the resection site and on small overlooked tumours. Timing of the instillation is crucial and is recommended within 24 hours (preferable within 6 hours). Meta-analysis of seven RCTs support the use of single post-operative instillation as recurrence rate are decreased by 14%. As the recurrence rate is very low after single instillation immediately after TURBT in low risk group papillary tumours, no further treatment is advised.

Repeat chemotherapy instillations (with or without previous SI) improve recurrence-free survival in intermediate-risk patients. The length and frequency of repeat chemotherapy instillations is still controversial. Mitomycin C (MMC), epirubicin, pirarubicin and doxorubicin have all shown a comparable beneficial effect. Options for improving efficacy of intravesical chemotherapy include adjustment of pH, duration of instillation, drug concentration and device-assisted intravesical chemotherapy like microwave-induced hyperthermia, hyperthermic intravesical chemotherapy and electromotive drug administration.

Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC. The EORTC meta-analysis of nearly 5000 patients demonstrated that there is a 27% reduction in the rate of progression after intravesical BCG treatment in both TaT1 and CIS disease. The most optimal BCG maintenance schedule is not known. Weekly instillations for 6 weeks are a commonly used empirical schedule. Various schedules of maintenance BCG have been described but to date, there is no optimum schedule based on high level of evidence. Most centres, however, follow the schedule described by Lamm. The optimal dose of BCG is yet undefined. To reduce BCG toxicity, several authors have proposed dose reduction of BCG to one-third to one-fourth of the standard dose. The Spanish Oncology Group (CUETO) compared the standard dose with one-third dose of BCG in a randomized trial and did not find any difference in efficacy, except in patients with high-risk prognostic group.

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy. However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases.

Table 8: Cleveland Clinic Approach to Management of Bacillus Calmette-Guérin (BCG) Toxicity	
GRADE 1: MODERATE SYMPTOMS <48 HOURS Mild or moderate irritative voiding symptoms, mild hematuria, fever <38.5°C.	Symptomatic management Anticholinergics, topical antispasmodics (phenazopyridine), analgesics, nonsteroidal anti-inflammatory drugs.
GRADE 2: SEVERE SYMPTOMS AND/OR >48 HOURS Severe irritative voiding symptoms, hematuria, or symptoms lasting >48 hr	Consider dose reduction to one half to one third of dose when instillations resume. Administer isoniazid and rifampicin, 300 mg/day and 600 mg/day, orally until symptom resolution
GRADE 3: SERIOUS COMPLICATIONS (HEMO-DYNAMIC CHANGES, PERSISTENT HIGH-GRADE FEVER)	Isoniazid, 300 mg/day, and rifampicin, 600 mg/day, for 3-6 months depending on response.

Contraindications to Bacillus Calmette Guérin (BCG) Therapy:-

a) Absolute contraindications
   - Immunosuppressed and immunocompromised patients
   - Immediately after TURBT based on the risk of intravasation and septic death
   - Personal history of BCG sepsis.
   - Gross hematuria (intravasation risk)
   - Traumatic catheterization (intravasation risk)
   - Total incontinence (patient will not retain agent)

b) Relative contraindications
- Urinary tract infection (intravasation risk)
- Liver disease (precludes treatment with isoniazid if sepsis occurs)
- Personal history of tuberculosis (risk theorized but unknown)
- Poor overall performance status
- Advanced age

Table 9: Classification of BCG failures

Classification of BCG failures	Definition	Treatment
Adequate BCG treatment	Patient receiving at least five of six planned instillations of induction treatment and at least two of three planned instillations of maintenance treatment over 6 months	—
BCG Refractory	Persistent high-grade disease at 6 months after adequate BCG induction and maintenance treatment or any progression in stage at 3 months assessment (i.e. after induction BCG cycle	Radical cystectomy Bladder-preserving strategies in patients unsuitable for radical cystectomy

(Contd...)

(Contd...)

Classification of BCG failures	Definition	Treatment
BCG Relapsing 1. Early relapse: <12 months 2. Intermediate relapse: 12-24 months 3. Late relapse: >24 months	Recurrence of high-grade disease after a disease-free interval of ≥ 6 months after adequate BCG induction and maintenance treatment	Radical cystectomy Bladder-preserving strategies Repeat BCG course
BCG unresponsive	Include BCG relapsing and BCG refractory. BCG relapsing patients should have recurrence within 6 months of last BCG exposure. Highest risk of recurrence and progression	—
BCG intolerant	Disease persistent because the patient cannot receive adequate BCG owing to BCG toxicity	Radical cystectomy is recommended.

Treatment of BCG failure and recurrences after BCG:

BCG failures comprise patients with high or intermediate risk NMIBC who have received one induction and at least one maintenance course of intravesical BCG and show recurrence or progression of disease. Depending on the time to failure, BCG refractory, BCG early and BCG late

relapsing patients can be distinguished. Radical cystectomy is considered the standard-of-care for these patients.

Salvage therapeutic strategies for BCG failures unfit or unwilling to undergo surgery comprise intravesical chemotherapy, chemoradiation or chemohyperthermia.

Intravesical chemotherapy: - various agents used are valrubicin, gemcitabine and intravesical taxanes (docetaxel, paclitaxel). Valrubicin is the only approved option for BCG-refractory patients with CIS if cystectomy cannot be performed. Gemcitabine and Docetaxel has been used as salvage mono chemotherapy agent with 1-year disease-free response rates varying from 21 to 50% in various series. Combination chemotherapy regimens like intravesical gemcitabine followed by intravesical docetaxel with 6 weekly induction and monthly maintenance for 2 years has 1- and 2-years response rates of 54 and 34%, respectively. Similar response rates were reported with combination of intravesical gemcitabine with mitomycin C (MMC) but response rates significantly decline after 2–5 years.

Chemohyperthermia: - It includes delivery of hyperthermic intravesical chemotherapy (HIVEC) with temperatures of 41-44ºC. The hypothesized mechanism is that there is a direct cytotoxic effect and hyperthermia enhances penetration of chemotherapeutic agent into the bladder wall with hyperthermia. In NMIBC, chemo-hyperthermia is combined with instillation of MMC, which displays greater toxicity under increased temperature, thereby enhancing its effects. Hyperthermia can be applied to the bladder with different modalities and different

devices (Synergo, Combat, Unithermia), among which the Synergo system is based on radiofrequency-induced hyperthermia, is the most frequently used. Reported recurrence-free rates for chemohyperthermia vary between 40 and 60% after 2 years; however, data on long-term outcomes are missing.

Immune checkpoint blockade: - The preliminary results of single arm KEYNOTE-057 phase II trial (NCT02625961), in which the anti-PD-1 antibody pembrolizumab is tested in patients unresponsive to BCG who are considered ineligible for or have refused to undergo radical cystectomy. After a median follow up of 15.8 months, the complete response rate was 40.2%, with a median CR duration of 12.7 months. 36.6% of patients developed recurrent NMIBC after having a complete response and no patients progressed to muscle-invasive disease/ metastatic disease. A phase 3 study evaluating pembrolizumab in high risk non-muscle invasive bladder cancer that is persistent after BCG induction (KEYNOTE 676) is underway. Several trials are currently ongoing with anti-PD-L1 antibody atezolizumab, alone or in combination with BCG and nivolumab an IDO-1 inhibitor or BCG (CheckMate 9UT, NCT03519256), or durvalumab (NCT02901548).

Mycobacterium phlei cell wall nucleic acid complex (MCNA): - It is an immunotherapeutic agent derived from M. phlei that has been used in BCG-refractory or BCG-relapsing patients. Recently, in a single-arm phase III trial with 129 BCG failure patients treated with induction and maintenance MCNA, recurrence-free survival rates of 25% after 12 months and 19% after 24 months were reported.

Viral gene therapies, and targeted therapies are currently tested in several clinical trials in patients after BCG failure. Interim results are encouraging and selected approaches might be added to the physician's armamentarium for bladder-sparing options after BCG failure in the future.

Table 10: Treatment recommendations in NMIBC

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS	One immediate instillation of intravesical chemo-therapy after TURB
Intermediate-risk tumours	Solitary low-grade Ta > 3cm, Multifocal low-grade Ta, Recurrence within 1 year of low grade Ta, High grade Ta ≥ 3cm, Low grade T1	In patients with previous low recurrence rate (≥ 1 recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus three-weekly instillations at 3, 6 and 12 months), or insti-llations of chemo-therapy (the optimal schedule is not known)

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Risk category	Definition	Treatment recommendation
		for a maximum of 1 year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present)	Intravesical full-dose BCG instillations for 1 to 3 years or radical cystectomy.
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for 1 to 3 years.

8. MANAGEMENT OF MUSCLE-INVASIVE BLADDER CANCER:

Approximately 30% of newly diagnosed bladder cancers have muscle invasion. Besides, 20-25% of superficial bladder cancers progress to muscle invasion sometime during their natural history. Approximately 30% of patients diagnosed with muscle-invasive bladder cancer have undetected metastasis at the time of treatment of the primary tumour, while 25% of patients submitted to radical cystectomy present with lymph node involvement at the time of surgery. The intent of treatment in MIBC is curative, with options including both, radical surgery, as well as bladder preservation techniques. Both approaches have comparable oncological outcomes and toxicities when performed at high volume centres. The decision of treatment is made with the patient after explaining the procedure and costs.

Surgery

Radical cystectomy is the preferred treatment for invasive bladder cancers in patients whose medical condition allows the major surgical procedure.

Indications are 1) Patients with MIBC T2-T4a, N0-Nx, M0; 2) High risk, very high risk and recurrent non-muscle-invasive tumors; 3) BCG-refractory, BCG-relapsing and BCG-unresponsive, T1G3 tumors; 4) Extensive papillary disease that cannot be controlled with TURBT and intravesical therapy alone.

RC should be performed within 90 days of diagnosis. Delay in radical cystectomy (RC) for > 3 months increases the risk of progression and cancer-specific mortality.

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs. Do not offer sexual-preserving cystectomy to men and women as standard therapy for muscle-invasive bladder cancer. Patients are selected based on a) organ-confined disease; b) absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.

Four main types of sexual-preserving techniques have been described: a) Prostate sparing cystectomy: part of or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles. b) Capsule sparing cystectomy: the capsule or peripheral part of the prostate is preserved with adenoma (including prostatic urethra) removed by TURP or en bloc with the bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved. c) Seminal sparing cystectomy: seminal vesicles, vas deferens and neurovascular bundles are preserved. d) Nerve-sparing cystectomy: the neurovascular bundles are the only tissue left in place. Data regarding pelvic organ-preserving radical cystectomy for female patients remain immature. These techniques involve preserving the neurovascular bundle, vagina, uterus or variations of any of the stated techniques. The evidence base suggests that

these procedures may yield better sexual outcomes than standard cystectomy without compromising oncological outcomes. However, the overall quality of the evidence was moderate, and hence if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored.

Pelvic lymphadenectomy is routinely performed as part of radical cystectomy for bladder cancers, however, there is a lack of consensus on the intent (therapeutic or staging/ prognostic) and extent of lymph node dissection. At present, limited or regional lymph node dissection is the recommended standard surgical method. A recent prospective randomised phase III study comparing extended versus limited lymph node dissection failed to show a significant advantage of extended lymph node dissection over limited dissection in RFS, CSS, and OS. No difference in outcome was reported between extended and super-extended LND in various studies. Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status as well as beneficial for overall survival in retrospective studies in the presence of gross nodal disease. Submitting separate nodal packets instead of en bloc has shown significantly increased total LN yield, but did not result in an increased number of positive LNs.Till further evidence is generated, limited lymph node dissection is the standard of care.

Table 11: Extent of lymph node dissection in bladder cancer:	
Type of Lymph Node Dissection	**Definition**
Limited	Lateral boundary: External iliac vein Medial boundary: Obturator nerve (Perivesical tissue and lymphatic tissue in obturator fossa)
Standard	Superiorly: bifurcation of the common iliac artery Inferiorly: circumflex iliac vein Medially: Internal iliac vessels Laterally: Genitofemoral nerve Floor: obturator fossa
Extended	Proximal boundary: crossing of ureter / common iliac artery. Rest landmarks as standard template
Super extended	Proximal boundary: origin of IMA. Rest landmarks as standard template

Radical cystectomy is recommended for non-transitional cell carcinomas, which generally respond less to radiation and chemotherapy. However, despite adequate surgery, approximately 50% of patients will develop metastatic disease within 2 years, emphasising the need for augmenting treatment in these patients. The 5-year survival rates after radical cystectomy alone in T2, T3a, T3b and T4 disease are 63%, 57%, 31% and 18% respectively.

Partial cystectomy is very rarely indicated in muscle-invasive urothelial cancer. Patients, who are not fit for radical cystectomy with solitary muscle-invasive tumour at the dome, with no extravesical spread and negative

random mucosal biopsies and intra-operative surgical margins negative on frozen section can be considered for partial cystectomy.

Urethrectomy:

Urethrectomy may be done at the time of cystectomy or subsequently as a separate procedure if the tumour involves the bladder neck in women or the prostatic urethra in men, or if the urethral cut margin is positive at the end of cystectomy, or in cases of extensive prostatic involvement.

Urinary diversion or reconstruction:

The type of urinary diversion does not affect the oncological outcome. The advantage of orthotropic neobladder over other diversions in terms of quality of life remains a matter of debate. Terminal ileum and colon are the intestinal segments of choice for urinary diversion. The morbidity of orthotropic neobladder reconstruction is appreciable in terms of major complications and reoperation rates. Orthotropic neobladder reconstruction should be advised to suitable patients after cystectomy for organ-confined muscle-invasive bladder tumour. While discussing this option with the patient, the morbidity must be addressed.

The various options available are

1. Incontinent conduit with an external stoma,
2. Continent catheterizable reservoirs with an abdominal stoma and
3. bladder substitution (neobladder) procedures.

Ideal characteristics of a urinary reservoir are Low-pressure system; Stores a functional amount of urine (~500 mL); Reliable, complete continence; Complete voluntary control of voiding; No absorption of urinary waste products by the reservoir wall.

Conduits: - Constructed using either colon or ileum. Ileal conduits have become the 'gold standard' for incontinent diversion and indeed remain the procedure of choice for patients with contraindications to continent diversion. Ileal conduits are relatively easy and quick to create, minimising the rate of postoperative complications. Typically, the terminal 10–15 cm of ileum is preserved to maintain adequate absorption of bile salts, vitamin B12, and fat-soluble vitamins.

Continent Urinary Diversion requiring CIC: - Reservoirs differ based upon the type of valve mechanism constructed, the type of catheterisable stoma created, and the exact segment of intestine used. Various types are 1) Continent Urinary Diversion requiring CIC are Continent Ileal reservoir (Kock Pouch); Double T pouch; Mainz pouch; Indiana Pouch; Right colon pouch with intussuscepted terminal ileum (UCLA pouch, Duke pouch, Le Bag); Penn pouch; Gastric pouch. 2) Variations of uretero-sigmoidostomy are Ileal caecal sigmoidostomy; rectal bladder; sigmoid hemikok surgery with proximal colonic intussusception; Sigma rectum pouch (Mainz II)

Table 12: Oncological principles of orthotropic neobladder reconstruction:	
1.	Patient must have a healthy urethra and adequate external sphincter function to maintain continence
2.	Bowel segment should be detubularized and reconstructed into a spherical shape.
3.	Ultimate storage volume should be at least 300 to 500 mL at low pressure

Table 13: Classification of Urinary diversion	
Classification	**Type of Urinary diversion**
1. Orthotopic	Orthotropic bladder substitution a. Studder neobladder b. Hautmann neobladder c. Mainz neobladder
2. Heterotopic	
a. Continent	1. Cutaneous (Catheterizable stoma on the abdominal wall) Types: a. Right colonic pouch (Indiana pouch, Florida pouch, Miami pouch, Penn pouch) b. Ileal pouches (Koch ouch, Mainz pouch)
b. Non-Continent	a. Ileal conduit/colonic conduit/ jejunal conduit b. Cutaneous ureterostomy
c. Diversion to GIT	a. Uretero-sigmoidostomy/rectal bladder

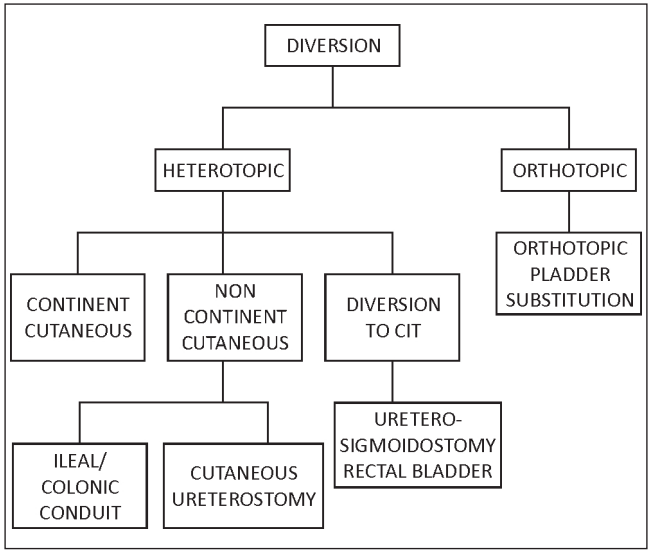

Table 14: Contra-indications to orthotropic neobladder:	
1.	Prostatic stromal involvement
2.	Positive urethral margins
3.	Multiple bladder tumors or multicentric involvement of the urinary tract

Table 15: Management of neobladder morbidity (30-64%).	
Complications	**Management**
Immediate complications:	
Post-operative nausea and vomiting	1. Anti-emetic agent (decrease opioids) 2. Nasogastric intubation
Post-operative ileus	1. Chewing gum 2. Nasogastric intubation 3. Avoid fluid excess and hypovolemia
Ureteral catheter obstruction	1. Inject 5cc saline in the ureteral catheter or 2. Increase volume infusion to increase diuresis
Urinary infection	1. No ureteral catheter removal and check the 3 drainages (ureters and neobladder) 2. Antibiotics
Uretero-ileal Anastomotic leak	1. Check drainages 2. Watchful waiting
Anaemia	1. Iron supplements
Late complications: Incontinence	1. Urine analysis 2. USG (post void residue) 3. Physiotherapy
Retention	1. Drainage 2. Self catheterization education

(Contd...)

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Complications	Management
Pyelonephritis	1. Antibiotics 2. Renal drainage (nephrostomy if necessary)
Pulmonary embolism	Heparin therapy
Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy), reimplantation
Compressive lymphocele	Surgery (marsupialization)
Ileal anastomosis leakage	Ileostomy, as soon as possible

Enhanced Recovery After Surgery (ERAS) Pathway Outcomes:

The ERAS study group was formed in 2001 with an emphasis on improving and standardizing perioperative care. In the setting of radical cystectomy, ERAS has shown benefit in reducing the incidence of postoperative gastrointestinal complications and also shortens the length of hospital stay. So, continuous modifications of the ERAS pathway will help us in refining patient care and improve postoperative outcomes.

Minimally Invasive Surgery for Bladder cancer:

RARC is gaining wide acceptance as a minimally invasive technique. Various series comparing open with robotic-assisted radical cystectomy have shown lower estimated blood loss, lower blood transfusion, long operative time with similar oncologic outcomes, increased cost, decreased

length of hospital stay and similar perioperative complications.

The randomized open versus robotic cystectomy (RAZOR) trial represented the first multicentric phase 3 study comparing the oncologic outcomes of robotic assisted (RARC with extracorporeal diversion) and open radical cystectomy (ORC) for bladder cancer. The updated analysis shows estimated PFS at 36 months was 68.4% and 65.4% in the robotic and open groups respectively (p=0.600). OS at 36 months was 73.9 % and 68.5% for the robotic and open group respectively (p=0.334). This analysis shows no difference in recurrence, 3-year PFS and 3-year OS between RARC and ORC. It provides important prospective data on the oncologic and functional efficacy of RARC. Ongoing randomised trials are comparing Open Radical Cystectomy to Robotic Radical Cystectomy with intracorporeal diversion. International Robotic Cystectomy Consortium database review showed ten-year recurrence-free, disease specific and overall survival rates were 59%, 65% and 35%, respectively.

Neoadjuvant chemotherapy

Although radical cystectomy is the standard treatment for patients with muscle-invasive bladder cancer, it leads to long-term cure in only 50% of patients. To improve these results, use of neoadjuvant chemotherapy (NACT) has been explored. The rationale for chemotherapy before cystectomy or radical radiation therapy is based on the intent to treat micrometastatic disease that is present at diagnosis.

Three metanalyses established survival benefit with NACT. In a metanalysis published in 2005 which included 3005 patients from 11 randomised trials, it was found that neoadjuvant chemotherapy decreased the risk of death by 14%, improved the absolute disease-specific survival by 9%, and improved overall survival by 5% at 5 years ($p = 0.003$).

The most recent meta-analysis published in 2016 included four additional randomised trials and used the updated results from the Nordic I, Nordic II, and BA06 30894 trials, consisting of information for 427 new patients and updated information for 1,596 patients. The results of this analysis confirmed the previously published data and showed an 18 % survival benefit with 8% absolute improvement in survival at five years

Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit, the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA (E) C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin and methotrexate (CM), cisplatin/adriamycin, and cisplatin/5-fluorouracil (5-FU)

Gemcitabine/cisplatin (GC) have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) in retrospective series and pooled data analyses, but have not been used in randomised controlled trials (RCTs).

A metanalysis of 13 retrospective studies was performed to compare MVAC with GC, There was no significant difference in pathological complete response between

MVAC and GC (PCR-25.7%), However, GC was associated with a significant reduced OS as compared to MVAC (HR-1.26), but after excluding carboplatin data, the OS difference was not statistically significant.

Modified dose-dense MVAC (ddMVAC) demonstrated high rates of pathologic complete remission in two small single-arm phase II studies. Moreover, a large cross-sectional analysis showed higher rates of downstaging and pathological complete response for ddMVAC.

In conclusion, in patients with the muscle-invasive disease with good PS and adequate renal function, cisplatin-based neoadjuvant chemotherapy improves overall survival. Dose-dense MVAC with primary GCSF is preferred regimen; however cisplatin and gemcitabine are other suitable alternative.

It is unclear if patients with non-urothelial carcinoma histology can also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumors had improved OS and lower rates of non-organ-confined disease when receiving NAC. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ confined disease were found, but no statistically significant impact on OS. Patients with SCC did not benefit from NAC

Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS. But there are still no tools available to select patients who have a higher probability of benefitting from NACT.

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

Currently, immunotherapy with checkpoint inhibitors is tested in phase II and III trials. Initial results are promising.

Adjuvant Chemotherapy

Role of adjuvant chemotherapy is still debatable in the context of radical cystectomy. Neither randomised trials nor the meta-analysis has provided sufficient data to support the routine use of adjuvant chemotherapy. It should be considered in patients with high-risk muscle-invasive bladder cancers who have not received neoadjuvant chemotherapy. High-risk cancers include T3-4 and/or node-positive disease. Preferred chemotherapy is cisplatin-based combination chemotherapy. The commonest regimens used are MVAC/CMV or CISCA.

Adjuvant chemotherapy after RC is useful in patients with pT3-4 and/or N+ patients who have not received neoadjuvant chemotherapy. An individual patient data meta-analysis of survival data from six RCTs of adjuvant chemotherapy conducted in 2005 including 491 patients failed to show convincing OS benefit from adjuvant chemotherapy. The commonest regimens used are MVAC/CMV or CISCA.

In 2014, this meta-analysis was updated with an additional three studies resulting in the inclusion of 945 patients from nine trials. None of the trials had fully accrued, and individual patient data were not used in the analysis. None of the included trial showed significant OS benefit. In two

of the trials Gem –cisplatin or Gem/pacli –cisplatin was used.

This Metaanalysis showed a trend toward OS benefit. The effect was stronger for DFS and when stratified for the ratio of nodal positivity. So, the positive role of adjuvant chemotherapy has been strengthened, however, still with a poor level of evidence.

Currently, immunotherapy in adjuvant setting with checkpoint inhibitors is being tested in trials.

Adjuvant Radiotherapy

Locoregional recurrence is strongly related to overall survival, and it may occur in as much as 43% of post-radical cystectomy patients. Most such failures occur in the pelvis, especially in extravesical disease. T3 disease and margin positivity post cystectomy are independent significant risk factors for failure. Radiation Therapy may be considered as an important modality to improve locoregional control in such patients. Whether adjuvant radiation is tolerable is doubtful due to the significant gastro-intestinal toxicities described in early studies. However, with the use of modern radiation techniques, adequate doses can be safely delivered to the target volume with sparing organs at risk. Prospective studies have demonstrated improved disease-free survival in patients receiving adjuvant radiation. These studies have also increased toxicities. Multiple trials are going on to assess the role of adjuvant radiation in advanced post cystectomy patients, including an ongoing randomised trial in India, which aims to evaluate the role of adjuvant radiation in post-cystectomy

patients in improving locoregional control. The aim is to treat the cystectomy bed and pelvic nodes to a dose of 50.4 Gy in 28 fractions.

Bladder Preservation

Bladder preservation strategy is a valid option for patients with invasive cancer, with outcomes comparable to cystectomy.

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

It may also be an option for patients refusing radical surgery, or those medically unfit.

A) Trimodality treatment

Trimodality treatment is the gold standard in bladder preservation, incorporates the use of maximal safe TURBT followed by radiation therapy with concurrent radio-sensitizing chemotherapy. The aim is to preserve the bladder without compromising oncological outcomes and maintaining the quality of life. There has been no completed randomised phase III trial comparing surgery versus trimodality treatment. Even comparison of prospective series poses a challenge because of differences in patient selection, and that cystectomized patients have

a pathological staging, which is not possible in patients with bladder preservation. A recently published meta-analysis of 9000 patients showed no difference in oncological outcomes between radical surgery and trimodality treatment. 5 year overall survival rates are 55% while 10 year OS rates have been 39%. Salvage cystectomy rates have varied among different published studies, ranging from 8% to 32.5%.

TURBT

Maximal safe TURBT is considered as an important component of trimodality treatment of bladder cancer. On multivariate analysis, the completeness of TURBT is one of the strongest prognostic factors for overall survival. Multi-stage TURBT can be performed if the resection is not complete.

Radiotherapy

Treatment includes radiation to the intact bladder with margins to a total dose of 60-64Gy at 2-Gy equivalent. The benefit of prophylactic irradiation of pelvic nodes is debatable, with the aim to deliver 50Gy (2-Gy equivalent dose), which may be considered with IMRT technique to reduce toxicities. Treatment planning can be done with three-dimensional conformal radiotherapy or, more recently, image-guided adaptive radiotherapy has been widely accepted. Plan of the day is a technique wherein different PTVs are generated for the bladder, and multiple plans are made. Treatment involves daily choice of plan, adapting for the bladder filling for the particular day (plan of the day). This technique allows more sparing of

surrounding normal tissues and daily image guidance provides accurate delivery of radiation.

Dose escalation is being tried in patients with bladder cancer. An ongoing study in UK is assessing the feasibility and long term side effects of dose escalation. A recently published study from India has shown no change in outcomes with dose escalation.

Concurrent Chemotherapy

BC2001, a multicenter phase 3 randomised study established the role of chemoradiotherapy over radiotherapy alone in patients post TURBT. It showed a 13% improvement in two-year locoregional DFS with addition of chemotherapy (5FU and mitomycin) to radiation, with a trend towards improvement in overall survival and a reduction in rate of cystectomy.

Two randomised trials have supported the use of concurrent chemotherapy along with radiation. Cisplatin-based chemotherapy is the preferred combination with radiotherapy. Patients unfit for cisplatin may receive a combination of 5FU with mitomycin, or a single agent Paclitaxel or gemcitabine. Carboplatin has not proven to be effective in bladder cancer patients, and should not be substituted for cisplatin.

Neoadjuvant/Adjuvant Chemotherapy

The intention for adding Neoadjuvant chemotherapy to trimodality treatment is to eradicate distant micrometastasis. There is no prospective data supporting the role of neoadjuvant or adjuvant chemotherapy in

bladder preservation (or in patients with metastatic regional nodes). The data is extrapolated from patients undergoing radical cystectomy.

Relapse

Patients with relapse on FU, persistent muscle-invasive disease are offered cystectomy. To prevent poor outcome in non-responders, cystectomy is recommended in individuals who do not achieve complete response following combination treatment. This will allow about 40-45% patients to survive with an intact bladder at 4-5 years. Survival rates post salvage cystectomy has been comparable to upfront cystectomy. Successful long-term survival rates have been observed in select non-randomized trials with this approach. Approximately 50% of patients with bladder preservation treatment are expected to survive with their intact bladder and rest need salvage cystectomy due to loco-regional recurrence. Non-invasive relapses may be treated with TUR followed by intravesical therapy.

Follow up

In view of the high local recurrence rate, a long-term follow up with cystoscopy, exfoliative urine cytology and other investigations to rule out the disseminated disease is warranted. It is important to understand that despite a complete response to multimodality bladder preservation strategies, the bladder remains a potential source of recurrence and hence, lifelong monitoring of disease status – both in the bladder and extravesical is recommended.

Other techniques

i. TURBT alone

TURBT is not a curative option in muscle-invasive bladder cancers but may be offered to patients who are unfit for radical treatment, those with limited superficial muscle-invasive tumors.

ii. Definitive RT alone

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

iii. Chemotherapy alone

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

9. METASTATIC BLADDER CANCER

Approximately 5-10% of bladder cancers are metastatic at presentation, and another 40% of patients will develop metastatic disease during their clinical course, typically appearing in lymph nodes, lung, liver or bone.

Chemotherapy is the standard therapy for patients with metastatic bladder cancer. Urothelial carcinoma is a chemosensitive tumour. Performance status and presence

or absences of visceral metastases are important prognostic factors for survival. Patients with lymph node metastases only, good PS, and adequate renal function may be the best candidates for chemotherapy, with about 15% long-term survival. For patients with platinum-refractory disease, liver metastasis, PS > 1 and low haemoglobin (< 10 g/dL) are negative prognostic factors.

Cisplatin-containing combination chemotherapy has been the standard of care. Methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (M-VAC) and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 months respectively (Level of evidence 1b). Single-agent chemotherapy provides low response rates of typically short duration. Combination M-VAC chemotherapy is superior to single-agent chemotherapy (Level of evidence 1b). Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival (Level of evidence: 2a). In an international cisplatin-based trial, M-VAC was compared with gemcitabine &cisplatin (GC). Both the arms were found to be equivalent in terms of response rates, time to treatment failure, time to progressive disease and overall survival. GC appeared to have reduced toxicity profile as compared to M-VAC, making GC a new standard chemotherapeutic option in patients with metastatic bladder cancer (Level of evidence 1b). DD-MVAC has shown to have similar median survival with lesser toxicity as compared to standard dose MVAC. Paclitaxel, cisplatin and gemcitabine is an additional option for first-line treatment of UC showing similar toxicity, higher response rate and a non –significant improvement in OS over Gemcitabine and cisplatin.

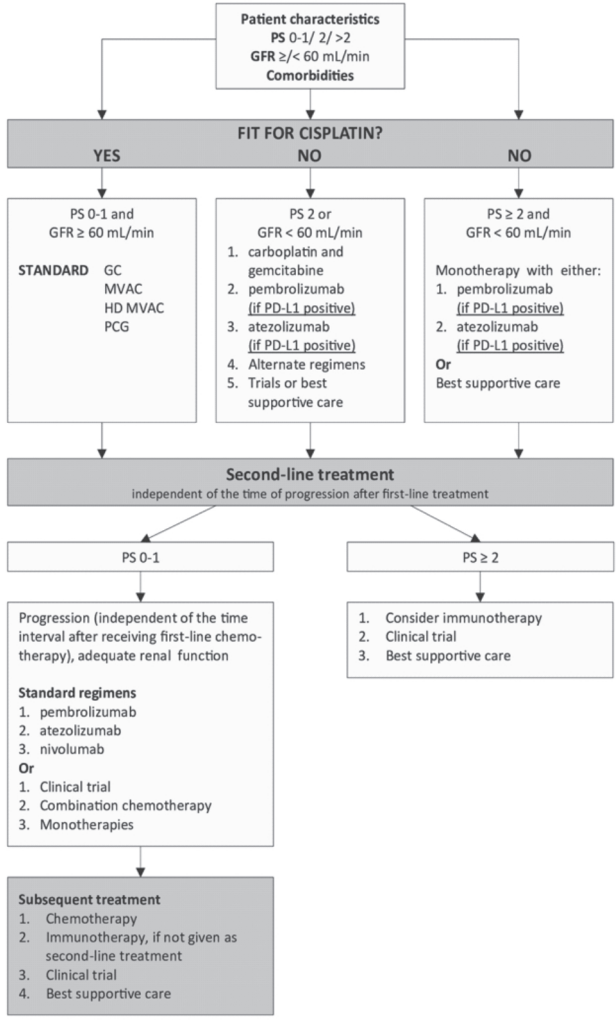
Up to 50% of patients are ineligible for cisplatin-containing chemotherapy. Chemotherapy with Gemcitabine–carboplatin, vinflunine-gemcitabine/Vinflunine-Carboplatin or Gemcitabine –paclitaxel can be used in patients ineligible for cisplatin. Immunotherapy with either pembrolizumab or atezolizumab is also an option in patients ineligible for cisplatin based therapy having PD-L1 positive tumors .

Zoledronic acid or denosumab should be offered for supportive treatment in case of bone metastases.

Second line Therapy.

Pembrolizumab is the preferred choice in patients progressing during or after platinum-based combination chemotherapy for metastatic disease, irrespective of PD-L1 status. Nivolumab and atezolizumab showed improved ORR in a phase II study and can be offered in platinum refractory setting.

Patients in whom immunotherapy is not feasible should ideally be treated in clinical trial. There is insufficient data to provide a recommendation on standard second-line chemotherapy. Various active agent like taxanes, gemcitabine, Vinflunine or paclitaxel/ gemcitabine, if the patient has a good PS, may be considered. Quality of life issues are very important considerations while deciding further chemotherapy.


Patient characteristics
PS 0-1/ 2/ >2
GFR ≥/< 60 mL/min
Comorbidities
FIT FOR CISPLATIN?
YES
NO
NO
PS 0-1 and
GFR ≥ 60 mL/min
STANDARD GC
MVAC
HD MVAC
PCG
PS 2 or
GFR < 60 mL/min
1. carboplatin and gemcitabine
2. pembrolizumab (if PD-L1 positive)
3. atezolizumab (if PD-L1 positive)
4. Alternate regimens
5. Trials or best supportive care
PS ≥ 2 and
GFR < 60 mL/min
Monotherapy with either:
1. pembrolizumab (if PD-L1 positive)
2. atezolizumab (if PD-L1 positive)
Or
Best supportive care
Second-line treatment
independent of the time of progression after first-line treatment
PS 0-1
PS ≥ 2
Progression (independent of the time interval after receiving first-line chemotherapy), adequate renal function
Standard regimens
1. pembrolizumab
2. atezolizumab
3. nivolumab
Or
1. Clinical trial
2. Combination chemotherapy
3. Monotherapies
1. Consider immunotherapy
2. Clinical trial
3. Best supportive care
Subsequent treatment
1. Chemotherapy
2. Immunotherapy, if not given as second-line treatment
3. Clinical trial
4. Best supportive care

WHAT HAS CHANGED IN BLADDER CANCER IN THE LAST DECADE?

- Standardized system for reporting urine cytology – Paris System
- Evidence in favour of enhanced cystoscopy (PDD and NBI)
- Evolving role of MRI in pre TURBT imaging
- Revised WHO pathology classification
- Robust evidence defining role of restaging TURBT in high grade NMIBC
- Evolution of technique and evidence for enblock TURBT
- Growing evidence for alternate intravesical agents in patients with BCG failure
- Bladder Preservation (trimodality therapy) outcomes comparable to radical cystectomy in high volume centres
- Evolving role of adjuvant radiotherapy after radical cystectomy
- Evolving role of intravesical and systemic immunotherapy in both NMIBC and MIBC

SUGGESTED READING

1. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology 2003; 61:109.
2. Apolo AB, Riches J, Schöder H, et al. Clinical value of fluorine-18 2-fluoro-2-deoxy-Dglucose positron emission tomography/computed tomography in bladder cancer. J Clin Oncol 2010; 28:3973.
3. Chou R, Gore JL, Buckley D, et al. Urinary Biomarkers for Diagnosis of Bladder Cancer: A Systematic Review and Meta-analysis. Ann Intern Med 2015; 163:922
4. Zaghloul MS, Mohran TZ, Saber RA, et al. Postoperative radiotherapy in bladder cancer. J Egypt Nat Cancer Inst 2002;14:161– 8
5. P., Baumann, B.C., Eapen, L., Christodouleas, J., Bahl, A., Murthy, V., Efstathiou, J., Fonteyne, V., Ballas, L., Zaghloul, M., Roubaud, G., Orré, M., Larré, S., Risk factors for loco-regional recurrence after radical cystectomy of muscle-invasive bladder cancer: A systematic-review and framework for adjuvant radiotherapy, Cancer Treatment Reviews Cancer Treatment Reviews (2018)
6. Vashistha V, Wang H, Mazzone A, et al. Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. Int J Radiat Oncol Biol Phys 2017; 97:1002.
7. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477.
8. Sanjai K Addla, Purushotham Naidu, Satish B Maddineni, Noel W. Long term survival outcome following radical

cystectomy for TCC of the bladder – comparison between primary and salvage radical cystectomy. The Journal of Urology, 2009

9. Robert Huddart et al RAIDER:A randomised phase II trial of adaptive image guided standard or dose escalated tumour boost radiotherapy in the treatment of transitional cell carcinoma of the bladder

10. Hoskin P1, Rojas A, Saunders M et al. Accelerated radiotherapy, carbogen, and nicotinamide (ARCON) in the treatment of advanced bladder cancer: mature results of a Phase II nonrandomized study. Int J Radiat Oncol Biol Phys. 2009

11. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience. Eur Urol 2017; 71:952.

12. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol 2014; 32:3801.

13. Stein, J.P., et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J ClinOncol, 2001. 19: 666.

14. Grossman, H.B., et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med, 2003. 349: 859.

15. Griffiths, G., et al. International phase III trial assessing neoadjuvantcisplatin, methotrexate, and vinblastine

chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J ClinOncol, 2011. 29: 2171.

16. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomized controlled trial. International collaboration of trialists on behalf of the MRC Advanced Bladder Cancer Working party. Lancet, 1999.354: 533.
17. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration.EurUrol, 2005. 48: 202
18. Yin, M., et al. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. Oncologist, 2016. 21: 708
19. Necchi, A., et al. Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study. J ClinOncol, 2018: JCO1801148.
20. ABC Meta-analysis Coll. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. EurUrol, 2005. 48: 189.
21. Leow, J.J., et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. EurUrol, 2014. 66: 42.
22. Cognetti, F., et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol, 2012. 23: 695.

23. Paz-Ares, L.G., et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. J ClinOncol, 2010. vol. 28 no. 18_suppl.

24. Von der Maase, H., et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J ClinOncol, 2005. 23: 4602.

25. Bellmunt, J., et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J ClinOncol, 2012. 30: 1107.

26. O'Donnell, P.H., et al. Pembrolizumab (Pembro; MK-3475) for advanced urothelial cancer: Results of a phase IB study. J ClinOncol, 2015. 33: 296.

27. Balar, A.V., et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet, 2017.389: 67.

28. Bellmunt, J., et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma.N Engl J Med, 2017. 376: 1015.

29. Powles, T., et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomized controlled trial. Lancet, 2018.391: 748.

30. Sharma, P., et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol, 2017. 18: 312

31. LG Paz Ares, et al. Randomized phase III trial comparing adjuvant Paclitaxel/Gemcitabin/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. J ClinOncol, 2010. vol. 28 no. 18_suppl.

CHAPTER 3

Renal Cancer

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1. EPIDEMIOLOGY:

Globally, the incidence of Renal Cell Carcinoma (RCC) varies across different regions, with highest rate observed in Czech Republic and North America. In the United State, there are approximately 74,000 new Cases and almost 15,000 deaths from RCC every year. In European countries, there were approximately 84,000 new cases and 35,000 death due to kidney cancer in 2012. As per Globocon 2018, RCC contributes for 1.47 % of all malignancies, with a total of 15,454 new cases and 9911 deaths.

RCC is approximately 50 % more common in men compared to women. RCC occurs predominately in sixth to eighth decade of life with median age of diagnosis around 64 years of age, according to 2003 to 2007 National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) cancer statistics Review; it is unusual in population under 40 years age and rare in children.

In India, Agnihotri *et al*. investigated the spectrum of RCC with regards to the age of onset, stage at presentation, and survival in 617 patients between January 2000 and December 2012 in a tertiary care hospital in North India. The mean age at diagnosis was 56 (median 56, range: 14–91 years) years, which is much lower than most Western studies. A total of 30.03% of renal tumors presented in patients younger than 50 years of age.

In contrast to the Western countries, where more than 60% of the RCC patients present with tumors <4 cm size (T1a), only 10.4% of Indian patients present that early. Unlike in the West where the male-to-female ratio is 2:1, males were 4 times likely to present with renal tumors in our population. Another difference observed was the incidence of clear cell RCC. Contrary to most of the Western literature where clear cell RCC is present in around 85% of the patients, clear cell RCC in the current study was present only in 71.33% of the patients.

2. AETIOLOGY:

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

Risk Factor	Remark
Tobacco	relative risk of between 1.5 to 2.5
Obesity	Considered a major risk factor for RCC with increased relative risk of 1.07 for each additional unit increase in BMI.

Risk Factor	Remark
Hypertension	History of hypertension was associated with a 67% increased risk of kidney cancer, which might be due to hypertension-induced renal injury and inflammation or metabolic or functional changes in renal tubules that may increase susceptibility to carcinogens
Genetic factors	hereditary familial forms of kidney cancer such as the Von Hippel-Lindau disease (VHL), familial papillary renal cell carcinoma (HPRCC), hereditary leiomyoma RCC (HLRCC), Cowden syndrome, the Birt-Hogg-Dube Syndrome (BHD), and Tuberous Sclerosis (TS)
Analgesic abuse	Acetaminophen and Non-aspirin NSAIDs
cadmium exposure	—
Acquired renal cystic disease	5 to 50 times increased incidence is noted in patients with End-stage renal disease on dialysis

3. CLINICAL PRESENTATION:

Currently, more than 60% of RCCs are detected incidentally in the western world due to increased use of non-invasive imaging to evaluate a variety of non-specific symptom complexes. Incidentally detected RCCs are generally smaller and of lower stage than symptomatic RCCs. The classic triad of flank pain, gross haematuria and palpable abdominal mass is now rare (6-10%), but when present, signifies an advanced stage of the disease.

The commonest presentation associated with RCC are as follows:

1) Incidental presentation
2) Symptom of local disease
   - Hematuria
   - Flank pain
   - Abdominal mass
   - Perirenal hematoma
3) Obstruction of IVC
   - Bilateral lower limb edema
   - Non-reducing varicocele
4) Symptoms due to metastatic disease (25-30% patients present with metastatic disease) such as bone pains, chronic cough, weight loss, cervical lymphadenopathy etc.
5) Paraneoplastic syndromes are seen in about 10-20 % of patients with symptomatic RCC, such as:

Paraneoplastic syndrome	**Relative %**
Elevated erythrocyte sedimentation rate	55.6%
Hypertension due to increased renin secretion	37.5%
Anaemia	36.3%
Cachexia, weight loss	34.5%
Pyrexia	17.2%
Abnormal LFT	14.4%
Hypercalcemia	4.9%
Neuropathy	3.2%
Amyloidosis	2.0%
Polycythemia due to increased erythropoietin	

Staging:

Currently, the AJCC TNM classification system (2018) is used, which gives a better differentiation of different prognostic groups.

TNM Staging (2018)

Primary Tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Tumour 7cm or less in greatest dimension confined to the kidney

T1a Tumour 4 cm or less in greatest dimension, confined to the kidney

T1b Tumour more than 4 cm but not more than 7 cm in greatest dimension, confined to the kidney

T2 Tumour more than 7cm in greatest dimension limited to the kidney

T2a Tumour >7 cm but < 10 cm

T2b Tumour> 10 cm but limited to kidney

T3 Tumour extends into major veins or perinephric fat but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

T3a Tumour grossly extends into the renal vein, or its segmental branches or tumour invades to perirenal and/or renal sinus fat but not beyond Gerota's fascia

T3b, tumour grossly extends into vena cava below the diaphragm

T3c Tumour grossly extends into vena cava above diaphragm or invades the wall of the vena cava

T4 Tumour invades beyond Gerota's fascia (including contagious extension to adrenal gland)

Regional Lymph Nodes (N)

Nx Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis into regional lymph node

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

TNM stage Grouping

Stage I	**T1**	**N0**	**M0**
Stage II	**T2**	**N0**	**M0**
Stage III	**T1 or T2**	**N1**	**M0**
	T3 Any	**N**	**M0**
Stage IV	**T4 Any**	**N**	**M0**
	Any T	**Any N**	**M1**

4. PROGNOSTIC FACTORS:

Cancer specific survival in non- metastatic RCC include various histological, anatomical, clinical and molecular factors and integrative approach combining variety of factors appears to be most powerful.

4.1 **Histological factors:** Pathological stage (TNM staging) is probably the most important factor affecting outcome. Adequate sections of tumor and its relation with renal sinus fat, perinephric fat and pelvicalyceal system should be taken to accurately stage the tumor. It is recommended that conventional RCC be graded as per the ISUP nuclear grading system instead of Fuhrman's nuclear grade as it is prognostically more relevant. Conventional RCC forms the major proportion of RCC with approx 75-80%, followed by Papillary RCC in 10-15 % and chromophobe RCC and oncocytoma (benign) forming approx 3-4% tumors. Histologic subtype have prognostic importance as conventional RCC do worse in comparison to Papillary type 1 RCC. Chromophobe RCC has the best outcome if not associated with sarcomatoid features. Any histology with sarcomatoid component worsens the prognosis and needs to be reported on histology. In 2014 WHO Vancouver classification, there were a number of recommendations with regards to modifications to the 2004 World Health Organization (WHO) classification of renal tumors. Five distinct and novel epithelial malignancies were added to the classification. These are tubulocystic RCC, acquired cystic disease-associated RCC, clear cell (tubulo) papillary RCC, microphthalmia transcription factor family (MiTF) translocation RCC and hereditary leiomyomatosis RCC syndrome-associated RCC.

4.2 **Clinical Factors:** Symptomatic presentation, poor performance status and weight loss of more than 10%

body weight indicate poor prognosis. Presence of para neoplastic signs has poor outcomes.

4.3 Anatomical factors:

4.4 **Tumour size:** Exact correlation is debatable although size is part of TNM staging.

Venous involvement once thought to be a very poor prognostic sign, can now be salvaged with aggressive surgical management. Direct invasion of wall of vein involvement is more important than cephalad extension of tumor.

Involvement of perinephric fat have intermediate survival

Presence of lymph nodes and systemic metastasis has markedly decreased survival.

4.5 **Molecular factors:** Carbonic anhydrase IX(CA IX), vascular endothelial growth factor (VEGF), Hypoxia-induced factor(HIF), Ki 67, p53,p21,PTEN, CD44, E-cadherin, osteopontin, CXCR4 are investigational and of debatable value.

Prognostic scoring systems: Kattan et al proposed a prognostic system incorporating symptoms, histology, tumor size, necrosis, tumor grade and vascular invasion to predict the probability of cancer-free survival after nephrectomy in patients with conventional RCC. Parker et al (2009) evaluated a biomarker panel (Bioscore) to enhance prognostic algorithm of renal cell carcinoma. Recently, new nomograms with excellent predictive value have been designed.

Prognostic model and variables:

Prognostic model for localized RCC	TNM staging	ECOG PS	RCC related symptom	Furhman grade	Tumour necrosis	Tumour size
UISS	X	X		X		
SSIGN	X			X	X	X
Post operative Karakiewicz's nomogram	X		X	X		X

Prognostic model for metastatic RCC	Karno-fsky PS	RCC related symptoms	Delay b/w diagnosis and treatment	LDH	Correted calcium	Hemo-globin count	Neutro-phill	Platelet count
MSKCC	X		X	X	X	X		
IMDC	X	X			X	X	X	X

5. IMAGING:

- Most renal tumour are diagnosed incidentally by abdominal ultrasonography (USG) or computed tomography (CT) performed for other medical reasons.
- Renal masses are classified as solid or cystic based on imaging findings on USG/ CT Scan/ MRI.
- USG-Noninvasive, accurate, and relatively inexpensive. Usually, USG is the first investigation of choice. It can differentiate between solid and cystic masses and also identify the need for further radiological investigations.

I. CT scan – A high-quality contrast-enhanced spiral thin slice CT scan remains the single most important radiographic test for assessment of a renal mass. A solid mass with significant heterogeneous postcontrast enhancement (due to characteristic high vascularity) less than of the normal renal parenchyma is virtually diagnostic of RCC, and any renal mass that enhances with contrast administration by more than 15 HU should be considered as RCC unless proved otherwise. CT also assesses primary tumour extension with extrarenal spread, venous involvement, enlargement of locoregional lymph nodes, the adrenal and the liver, while also providing information about the function of contralateral kidney. CT can help rule out angiomyolipomas by demonstrating areas of negative CT attenuation (-20 HU) indicative of the presence of fat in the tumour.

II. MRI: It is useful in certain patients, e.g., those with renal insufficiency, allergy to iodinated contrast agents or those with probable venous extension. MRI has better sensitivity than CT scan in evaluating the presence and extent of venous extension, differentiating a tumour thrombus from a bland one and assessment of invasion of surrounding tissue and organs.

III. Venacavography - Indicated in the presence of ambiguous CT scan/MRI findings in cases with venous extension or in patients who cannot have CT scan / MRI for some reason.

IV. Doppler ultrasonography is a useful tool for evaluating the cephalad extent of the thrombus with limited sensitivity than transoesophageal echocardiography

V. Arteriography - has a limited role and can be done prior to embolization of hypervascular masses.

VI. Fine needle aspiration cytology/ biopsy (FNAC/ FNAB) is rarely indicated only when a renal abscess or infected cyst is suspected and when RCC must be differentiated from metastatic malignant disease or renal lymphoma. Other indications are before active surveillance (AS), RFA and Cryosurgery. FNAB has excellent accuracy for detecting malignant masses, especially when combined with molecular analysis but has a suboptimal predictive value for detecting benign masses. Although the risk of complications is low, its impact on improving diagnostic accuracy or influencing clinical management is limited.

It is still difficult at times to distinguish RCC, adenoma, and oncocytoma with current diagnostic techniques and approximately 10% to 30% of small, solid, CT-enhancing renal masses with features suggestive of RCC prove to be benign after surgical excision. Though oncocytoma is a benign tumour, it can be associated with RCC in the same or the opposite kidney in 30% of patients.

Metastatic workup:

This includes,

- X-ray chest or CT scan of the chest.

- CT / MRI of brain is advised only if indicated by symptoms.
- Isotope bone scans and targeted skeletal radiographs or scans, if indicated by clinical symptoms or raised serum alkaline phosphatase.
- FDG PET CECT: Combining the FDG-PET and CT systems is helpful for detecting extra-renal metastasis rather than renal lesions as extrarenal lesions are not obscured by urinary FDG activity. In a recent meta-analysis, pooled sensitivity and specificity were reported to be 79% and 90%, respectively for detection of metastatic disease. Accuracy of FDG PET/CT for localisation of small lesions, however, is lower than for larger lesions. In a study, the sensitivity of FDG PET/CT increased from 76% to 93% when lesion size increased from more than 1cm to more than 2cm. In addition, high grade tumors are localized more efficiently than low grade ones. FDG PET/CT is also a valuable tool to discriminate between malignant and a bland tumor thrombus, which may help in planning surgery. FDG PET/CT can detect distant metastases with higher accuracy than contrast enhanced CT. However, as per the literature, FDG PET/CT has not been widely utilised for primary staging of RCC.The hybrid PET/CT system has comparable sensitivity and specificity with PET in detecting extra-renal lesions of RCC.

6. TREATMENT:

Surgical management which includes radical and partial nephrectomy remains the mainstay of treatment of renal

masses. Ablation and active surveillance are emerging options that may be preferable in a subset of patients.

6.1 local therapy in rcc

Radical Nephrectomy:

Radical nephrectomy was first described by Robson in 1969. The principles of radical nephrectomy include –

1. Early ligation of renal artery and vein,,
2. Removal of kidney and ipsilateral adrenal gland surrounded by the Gerota's fascia
3. Regional lymphadenectomy from the crux of the diaphragm to the bifurcation of aorta or inferior vena cava.

The erstwhile dogma of routine adrenalectomy and classical lymphadenectomy is now being questioned.

Role of adrenalectomy: Multivariate analysis has shown that upper pole location of tumour is not predictive of adrenal involvement. Adrenalectomy should be done when there is either abnormal radiographic appearance of adrenal gland or suspecious intraoperative findings, with no regard for primary tumour size.

Lymph node dissection: Current evidence suggests that lymphadenectomy should be restricted to staging, as extended lymphadenectomy does not improve survival. Numerous studies have identified risk factors for lymph node metastasis such as large tumour size >10 cm, T3-T4 tumours, high tumour grade, sarcomatoid component and histological tumour necrosis. If more than 2 factors are present the risk of lymph node metastasis is around 10%

vs 0.6% when less than two factors are present. In the higher risk group, a complete lymph node dissection may be warranted.Another indication of lymph node dissection is in patients with hereditary kidney tumors in HLRCC and SDH, because these syndromes are associated with aggressive renal tumors that tend to spread through lymph nodes.

Radical nephrectomy can be done by following methods

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

Presently, there is no evidence favouring a specific surgical approach. In the open approach, choice of incision depends on size and location of tumor, presence of retroperitoneal nodes, IVC thrombus and the comfort of the surgeon. There is no impact of a specific incision on the final outcome. Laparoscopic radical nephrectomy is indicated for localized renal cell carcinoma with tumor size <10 cm with no renal vein thrombus and manageable lymph node metastases.

The surgical and oncological outcomes after laparoscopic surgery have been reported to be equivalent to those after open surgery, with equivalent cancer specific survival rates and postoperative morbidity rates.

Robotic radical nephrectomy is safe, feasible and effective for localized RCC. In a study comparing laparoscopic and robotic radical nephrectomy, both groups had comparable intra-operative, peri-operative, post-operative and

oncological outcomes except for longer operating time and increased cost for Robotic group. There are no additional benefits of Robotic RN over Laparoscopic RN for localized RCC.

Partial Nephrectomy:

Partial nephrectomy is the preferred method of choice for all renal masses in order to preserve renal function. The goal of partial nephrectomy is to completely remove the primary tumour while preserving the largest possible amount of healthy renal parenchyma. While in the past partial nephrectomy was reserved for specific tumors i.e. patients with RCC who have only one kidney (anatomically or functionally), in those with bilateral synchronous RCC, conditions that can impair renal function (for example, kidney stones, hypertension, diabetes and pyelonephritis) and tumor less than 4 cm, indications of partial nephrectomy have considerably widened to include most renal masses that can be safely and completely removed irrespective of size.In various metaanalyses oncological safety (CSS and RFS) of PN has been proven to be similar for RN. PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term potentially limits the incidence of cardiovascular disorders occurring because of chronic kidney disease.PN is the preferred surgical treatment option as it avoids further deterioration of kidney function, the latter being associated with a higher risk of development of ESRD and the need for haemodialysis.

Nephrometry scoring systems have been proposed to predict the complexity of the partial nephrectomy procedure and predict perioperative outcomes according to the anatomical and topographical tumour chara-

cteristics. The R.E.N.A.L. score, PADUA score and C- index nephrometry systems are still the most popular and most used tools to preoperatively classify tumours . Clinical studies demonstrated that such nephrometry systems were able to predict the risk of bleeding and post-operative complications in patients who underwent partial nephrectomy. Thus, they represent valid tools for counselling patients and selecting the ideal candidate for partial nephrectomy according to surgeon experience.

Renal Score

RENAL	1 Point	2 Points	3 Points
R (radius, maximal diameter) (cm)	≤ 4	> 4 but < 7	≥ 7
E (exophytic/ endophytic)	≥ 50 % exophytic	< 50% exophytic	Completely endophytic
N (nearness to collecting system/ renal sinus) (mm)	≥ 7	> 4 but < 7	≤ 4
A (anterior/posterior locator) Descriptor of "a," "p," or "x" assigned to describe mass location.	No points given.	No points given.	No points given.
L (location relative to polar lines)	Entirely below lower polar or above upper polar line	Mass crosses polar line 50% of mass is across polar line	Mass is entirely between polar lines or mass crosses axial midline

Studies have shown that contact surface area (CSA) between the tumor and normal renal parenchyma may have impact on preservation of parenchymal after excision of mass and predict functional outcomes after PN. CSA linked closely with both mass preserved and ipsilateral GFR. CSA associated with GFR preserved ipsilaterally for exophytic masses rather for endophytic ones.

Padua Score

SCORE	1 Point	2 Points	3 Points
R (radius, maximal diameter) (cm)	≤H 4	> 4 but < 7	≥H 7
E (exophytic/ endophytic)	eH 50 % exophytic	< 50% exophytic	Completely endophytic
Longitudinal (polar) location	Superior/ inferior	Middle	
Renal rim	Lateral	Medial	
Renal sinus	Not involved	Involved	
Urinary collectingsystem	Not involved	Dislocated/ infiltrated	

Partial nephrectomy can be done by following methods, i.e. Open, Laparoscopic (LPN) and Robotics (RAPN). Laparoscopic partial nephrectomy (LPN) and robot-assisted partial nephrectomy (RAPN) are the alternatives to classical open partial nephrectomy (OPN).Available meta-analyses have demonstrated that RAPN provides equivalent perioperative outcomes to LPN, but a significantly shorter warm ischaemia time. Moreover, RAPN seems to be significantly better than OPN in terms of perioperative

complications, estimated blood loss and hospital stay. Transfusion rate, ischaemia time, estimated glomerular filtration rate change and early cancer outcomes are similar between the two approaches.

Partial nephrectomy can involve simple enucleation i.e. entirely sparing the healthy parenchyma around the tumour. In enucleoresection, a thin layer of healthy parenchyma is removed.In polar or wedge resection, a wider excision of healthy parenchyma is performed. A minimal tumour-free surgical margin following partial nephrectomy seems appropriate to avoid the increased risk of local recurrence. Positive surgical margins have been reported in 1–6% of cases regardless of the type of surgical technique used. Patients with positive surgical margin should be kept on stringent follow up to look for local or distant progression. Re resection or radical nephrectomy is considered as overtreatment. Haematuria, perirenal haematoma and urinary fistulas are the most common complications of partial nephrectomy procedures.

Ablative Therapies:

Thermal ablation (Cryoablation / Radiofrequency ablation) is an appealing option for T1a tumors in patients who have contraindication to surgical extirpative therapies because of comorbidities or advanced age. Additionally, patients who have underlying renal insufficiency, solitary kidney, multiple tumours, or recurrent tumours in the nephrectomy bed may be considered for ablative therapies. These procedures are usually done percutanously but some patients may need laparoscopic

approach due to technical issues with tumor location and proximity to vital tissues. Tumor ablation is confirmed within 3 months by absence of tumor enhancement and tumor enlargement on contrast enhanced CT or MRI. AUA recommends cross sectional imaging at 3 and 6 months after ablation, then annually for 5 years.In patients with good radiological response to ablation, post RFA biopsy is not routinely advised.Also, these biopsies are difficult to interpret.

Cryoablation and Radiofrequency Ablation can be performed by either percutaneous or laparoscopic method. There is no significant difference in overall survival, CSS, PFS between laparoscopic and percutaneous technique. Complications occur in 8 to 29 % of patients which includes pain or paresthesia at site of port insertion(most common), injury to nearby viscera(pleural cavity, colon, spleen, liver), urinary obstruction, urinoma, hematoma and haemorrhage)

Cytoreductive nephrectomy.-

In patient with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic therapy is necessary. In patient with poor PS or poor IMDC risk group,small primaries and high metastatic volume and / or sarcomatoid tumour, cytoreductive nephrectomy is not recommended. Role and sequence of CN has been investigated by two RCTs – CARMENA and SURTIME. CARMENA trial showed that sunitinib alone is non inferior to immediate CN followed by sunitinib with regards to overall survival. Patient selection for CN should be done

carefully. SURTIME study revealed that sequencing of cytoreductive nephrectomy and sunitinib did not affect progression free survival but strong overall survival benefit was observed in favour of deferred cytoreductive nephrectomy approach.

6.2 Radiotherapy in RCC

Previously RCC was thought to be a radio resistant tumor. There is emerging data suggesting that the apparent radioresistance of RCC can be overcome with the use of higher dose per fraction treatments delivered by new high-precision RT methods such as SBRT. It can be an attractive approach in patients with complex renal lesions, in which complete tumor resection might otherwise be required but whose suitability for surgery is borderline.

Primary lesion

Based on a systematic review consisting of 10 (three prospective) studies with 126 inoperable RCC patients treated with SBRT, the local control rate obtained across all studies was 92.9% with grade >3 toxicities of 3.8%. More recent prospective trial and retrospective studies have continued to indicate high short-term and medium-term rates of local control that are typically >90% with low toxicity rates.

Based on above, SBRT can be considered for patients who are elderly and or medically inoperable or unwilling to undergo nephrectomy.

Metastasis

Palliative RT is an effective treatment for palliation of symptoms such as of bony pain, controlling the severity of neurological symptoms or to ameliorate haematuria using mainly SBRT. Response rates of >50% have been seen among patients with metastatic RCC receiving conventionally fractionated RT. The objective of SBRT should be to achieve maximum dose per fraction to target (7-15 Gy per fraction). Generally, 3-5 fraction schedules are used.Some examples of dose schedule described in the literature include 25-26Gy in single fraction, 42-45 Gy in 3 #, 44-48Gy in 4 #, 30-50Gy in 5#.

For cranial metastases from RCC, treated using stereotactic RT with dose of 20Gy in 5 fractions to 30Gy in 10 fractions versus 12 – 24 Gy single fraction of the surgical cavity after complete resection of brain oligometastases significantly lowered local recurrence compared with observation alone without the decline in cognitive function observed with whole-brain RT (WBRT).

Combining SBRT With Immunotherapy

Based on preclinical and phase 2 clinical data, a particularly promising approach is the combination of RT and immunotherapy to augment the local efficacy of RT as well as to allow for improved and more durable systemic responses with immunotherapy. RT plays an important role in the potentiation and modulation of tumor immunity.

Adjuvant and neoadjuvant radiotherapy

Post-operative radiotherapy (PORT) is not standard in RCC as shown in two negative 'old' randomized trials with several limitations in trial design and methodology. The role of adjuvant RT using modern technology & conventionally fractionated schedules is being revisited in select group of patients.

There is no standard role of neoadjuvant RT in patients with RCC. In the scenario of invasion of direct adjacent organ invasion and when complete resection may not be feasible, neoadjuvant irradiation can potentially downsize the tumor increasing the likelihood of an adequate surgical resection but may not improve the overall survival based on two prospective clinical trials.

6.3 Adjuvant systemic therapy in localized Renal cell carcinoma

There is a debate about the role of systemic therapy after curative surgery in localised RCC. Several RCTs of adjuvant sunitinib (S-TRAC, ASSURE), sorafenib (ASSURE) and pazopanib (PROTECT) have been reported. Only S-TRAC was positive for its primary end point, disease free survival (DFS) by independent review, but without any OS benefit. This difference in the results may be because of different inclusion criteria used in S–TRAC, ASSURE and PROTECT studies as in S-TRAC , T3 and positive patients were included whereas in other studies even T2 patients were included and in PROTECT study majority of patients received 600 mg of pazopinib.

In the S-TRAC trial, high-risk clear-cell renal-cell carcinoma patient were randomized to receive either sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The median duration of disease-free survival was 6.8 years in the sunitinib group and 5.6 years in the placebo group (hazard ratio 0.76; P = 0.03).Dose reductions, dose interruption, treatment discontinuation and grade3/4 adverse events more frequent in the sunitinib group.This result led to approval of sunitinib by the United States Food and Drug Administration (US FDA). The European Medicines Agency (EMA) has not approved adjuvant therapy with any of these drugs because of the imbalance between risk and clinical benefit.

A recent pooled analysis of S-TRAC, ASSURE and PROTECT did not reveal a statistically significant effect between adjuvant VEGFR-targeted therapy and an improved DFS or OS in patients with intermediate-/high-risk local or regional fully resected RCC.

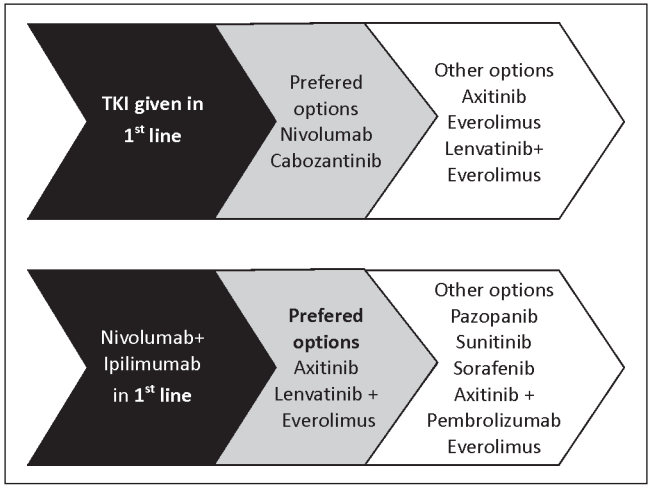
TREATMENT AS PER RISK STRATIFICATION

FIRST/FRONT LINE TREATMENT IN METASTATIC CLEAR CELL RCC

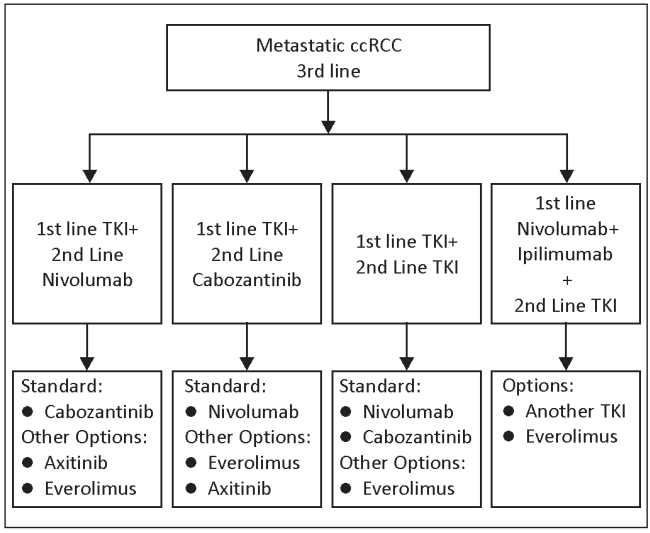
FAVOURABLE RISK		
Preferred/ standard regimens	**Other options**	**Useful in select cases**
Axitinib+ Pembrolizumab	Axitinib + Avelumab	Active surveillance
Sunitinib		High dose IL-2
Pazopanib		Bevacizumab +IFN Axitinib, Sorafenib
INTERMEDIATE RISK		
Nivolumab + Ipilimumab	Sunitinib	Axitinib
Axitinib+ Pembrolizumab	Pazopanib	High dose IL-2
Cabozantinib	Axitinib + Avelumab	Temsirolimus
POOR RISK		
Nivolumab + Ipilimumab	Sunitinib	Axitinib
Axitinib+ Pembrolizumab	Pazopanib	Temsirolimus
Cabozantinib	Axitinib + Avelumab	

TREATMENT OF METASTATIC cc RCC IN 2ND LINE AND BEYOND		
Preferred regimens	**Other recommended options**	**Useful in certain settings**
Nivolumab	Lenvatinib + Everolimus	Bevacizumab
Axitinib	Everolimus	Sorafenib
Cabozantinib	Pazopanib	IL-2 (in select patients)
	Sunitinib	Temsirolimus

TREATMENT OPTIONS IN SECOND LINE SETTING IN METASTATIC ccRCC



SEQUENCING OF THERAPY IN THIRD LINE SETTING IN METASTATIC ccRCC



7. SYSTEMIC THERAPY IN METASTATIC RENAL CELL CARCINOMA

It is imperative to risk stratify the patient with metastatic disease before planning systemic therapy

RISK STRATIFICATION

MSKCC PROGNOSTIC MODEL[1]*	IMDC (HENG'S) CRITERIA[2]**
Time from initial diagnosis to start of therapy < 1 year*	Less than 1 year from the time of diagnosis to systemic therapy
Karnofsky Performance status <80%	Karnofsky Performance status <80%
Corrected calcium greater than ULN	Corrected calcium greater than ULN
Serum Hemoglobin < Lower limit of normal	Serum Hemoglobin < Lower limit of normal
High lactate dehydrogenase (>1.5 x ULN)	Neutrophil > ULN Platelets > ULN
Prognostic risk groups	
Low-risk: No prognostic factors	Favourable-risk: No prognostic factors
Intermediate-risk: One or two prognostic factors	Intermediate- risk: One or two prognostic factors
Poor-risk: three or more prognostic factors	Poor-risk: three to six prognostic factors

* Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic model was derived from examining prognostic factors in patients with metastatic renal cell carcinoma (RCC) enrolled in clinical trials and treated with interferon-alfa as initial systemic therapy.

** International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model identified prognostic factors for patients treated with VEGF targeted agents. This model validated components of the MSKCC model with the addition of 2 new independent adverse prognostic factors -high platelet count and high absolute neutrophil count.

Table: Median OS estimates in first- and second-line RCC according to IMDC risk groups		
Risk group	**Median Overall Survival (months)**	
	First line	**Second line**
Favourable	43.2	35.3
Intermediate	22.5	16.6
Poor	7.8	5.4

SYSTEMIC THERAPY FOR METASTATIC RENAL CELL CARCINOMA

Tumor histology and risk stratification of patients is important in therapy selection. Since the interferon era, systemic therapy in metastatic RCC is based on risk stratification as it was noted by both the MSKCC and IMDC prognostic models that survival was much lower in the intermediate/ poor risk categories.

FIRST LINE THERAPY

Favourable risk group

In the favourable risk category, the anti-VEGF agents Sunitinib and pazopanib are standard of care. Both drugs have shown an improvement of PFS over IFN or placebo. In the trial that compared sunitinib to interferon alpha, sunitinib improved the progression-free survival significantly (11 months in the sunitinib group vs. 5 months in the interferon (IFN) alfa group, HR 0.42 ; P<0.001). Sunitinib was also associated with a higher objective response rate than interferon alfa (31% vs. 6%, P<0.001)

and significantly better quality of life than the patients in the IFN alfa group (P<0.001). The median overall survival was greater in the sunitinib group than in the IFN-alpha group (26.4 v 21.8 months, respectively; hazard ratio [HR] = 0.821; P=.051). Pazopanib was found to be non-inferior to Sunitinib (COMPARZ trial) with a better toxicity profile (PISCES trial). Both are recommended options in the first line setting in favourable risk patients.

In the recently published Keynote 426 trial, the median progression-free survival was 15.1 months in the pembrolizumab–axitinib group and 11.1 months in the sunitinib group (HR 0.69 ; P<0.001). The estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab–axitinib group and 78.3% in the sunitinib group (HR, 0.53; P<0.0001). The benefit of the Axitinib+ Pembrolizumab combination over Sunitinib in previously untreated patients with advanced RCC was seen across all IMDC risk groups (i.e. favourable, intermediate, and poor risk) and regardless of PD-L 1 expression, which makes it a promising treatment option in the first line setting.

Intermediate and poor risk groups

Evidence from the CheckMate 214 trial has made the combination of Nivolumab +ipilumumab the preferred regimen in these risk groups. The combination of Nivolumab +ipilumumab significantly improved the overall survival and objective response rates when compared to Sunitinib. The median progression free survival was also

longer (though not statistically significant). With extended follow-up (median follow-up 32·4 months) in intermediate/ poor-risk patients showed that nivolumab plus ipilimumab continued to be superior to sunitinib in terms of overall survival (median not reached vs 26·6 months; hazard ratio [HR] 0·66; p<0·0001), progression-free survival (median 8·2 months vs 8·3 months; HR 0·77, p=0·0014), and the proportion of patients achieving an objective response (42% vs 29%; p=0·0001).

This data has established nivolumab+ ipilimumab as the preferred first line therapy in intermediate and poor risk patients with metastatic, relapsed or medically unresectable RCC. Both the ESMO and NCCN guidelines recommend it as first line therapy in intermediate and poor risk RCC patients.

Since data from the Keynote 426 study showed the superiority of the axitinib+ pembrolizumab in the intermediate and poor risk groups as well, it is a treatment option in these patients.

Cabozantinib can also be considered for the treatment of intermediate/poor risk patients in the first line setting. The CABOSUN trial compared cabozantinib and sunitinib in intermediate/ poor risk patients with advanced RCC and patients treated with cabozantinib had a longer median PFS and higher ORR. Cabozantinib has been approved for first line therapy in poor/intermediate risk advanced RCC.

If the above agents are not available or not feasible, the anti VEGF TKIs (Sunitinib, Pazopanib) can also be considered for treatment in these risk groups.

SUBSEQUENT THERAPY FOR METASTATIC RCC (SECOND LINE AND BEYOND)

Anti VEGF and multikinase targeting TKIs

- ***Cabozantinib***

  The METEOR trial compared cabozantinib and everolimus in the second line setting in mRCC. Median overall survival was 21·4 months with cabozantinib and 16·5 months with everolimus (hazard ratio [HR] 0·66; p=0·00026). Cabozantinib treatment also improved the progression-free survival (HR 0·51; p<0·0001) and the objective response rate was 17% with cabozantinib vs 3% with everolimus (p<0·0001).This led to its approval by the FDA for the treatment of patients who have progressed after prior anti-angiogenic therapy.

- ***Axitinib***

  In the second line setting, axitinib improved PFS as compared to sorafenib in metastatic clear cell RCC who had progressive disease after one approved systemic therapy (AXIS trial, PFS 6.7 months vs 4.7months). The updated results showed a PFS of was 8·3 months with axitinib and 5·7 months with sorafenib (HR 0·656, 95% CI 0·552–0·779; one-sided p<0·0001). There was no OS benefit. The PFS was better than sorafenib in both patients treated with prior cytokine and prior sunitinib.

- ***Sorafenib***

  Sorafenib was evaluated for the treatment of RCC resistant to standard therapy (primarily cytokine therapy) in the TARGET trial. The median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio for disease progression in the sorafenib group, 0.44; P<0.01). The first interim analysis of overall survival in May 2005 showed that sorafenib reduced the risk of death, as compared with placebo (hazard ratio, 0.72; 95% CI, 0.54 to 0.94; P=0.02), although this benefit was not statistically significant probably due to crossover of patients to the sorafenib arm.Sorafenib is also safe and effective in second line therapy in patients who received prior sunitinib or bevacizumab.

- Pazopanib and Sunitinib both have activity in the second line setting. There is limited prospective data that suggests a lack of total cross resistance between TKIs (sorafenib followed by sunitinib or vice versa) hence sunitinib can be considered for second line therapy. Data from a phase 2 trial showed that pazopanib has activity in patients who have progressed after prior treatment with TKI or bevacizumab. Hence both drugs are treatment options in second line setting if immunotherapy or other second line TKIs are not feasible.

Immunotherapy

- ***Nivolumab***

  Nivolumab monotherapy is the preferred option for those who have disease progression with one or two regimens of antiangiogenic therapy. In the CheckMate 25 trial, the median overall survival was 25.0 months with nivolumab and 19.6 months with everolimus (HR 0.73; P=0.002). The objective response rate was greater with nivolumab than with everolimus (25% vs. 5%; odds ratio, 5.98; P<0.001). There were less grade3/4 adverse events with Nivolumab as compared to everolimus (19% vs37%) and the quality of life was better in the nivolumab arm. Since there is an overall survival benefit and better tolerance, nivolumab is preferred over everolimus in the second line setting after progression on anti angiogenic agent.

mTOR INHIBITORS

- ***Everolimus***

  In the RECORD -1 trial, everolimus was superior to placebo in patients with mRCC progressing on VEGF–TKI. The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (hazard ratio [HR], 0.33; P < .001) by independent central review and 5.5 months (everolimus) versus 1.9 months (placebo) (HR, 0.32; P < .001) by investigators. The survival corrected for crossover was 1.9-fold longer (95% confidence interval, 0.5-8.5) with everolimus compared with placebo only. Two recent phase 3

trials in the second line setting compared the efficacy of everolimus to nivolumab and cabozantinib. The CheckMate 025 trial showed superior OS with Nivolumab when compared to everolimus. The METEOR trial showed a significant improvement of both OS and PFS with cabozantinib when compared to everolimus.Hence nivolumab or cabozantinib is preferred over everolimus in eligible patients.

Combination therapy

- ***Lenvatinib+ everolimus***

  Lenvatinib is a multi-targeted TKI. A phase 2 trial compared lenvatinib plus everolimus, single-agent lenvatinib and single-agent everolimus. Lenvatinib plus everolimus significantly prolonged progression-free survival compared with everolimus alone (median 14·6 months *vs* 5·5 months; HR- 0·40; p=0·0005), but not compared with lenvatinib alone (7·4 months; HR 0·66; p=0·12). Single-agent lenvatinib also significantly prolonged progression-free survival compared with everolimus alone (HR 0·61; p=0·048). The median OS was also longer with the combination compared to everolimus alone. Grade 3-4 toxicities were higher with the lenvatinib + everolimus combination (71%) compared to everolimus (50%). The combination is a very effective option in the second line setting; however toxicity is significant.

SYSTEMIC THERAPY FOR RCC WITH NON CLEAR CELL HISTOLOGY

There is limited clinical data for systemic therapy for non-clear histological subtypes. Non clear cell histological subtypes are rare and are usually excluded from controlled phase III trials. Hence enrolment into speciûc clinical trials is strongly recommended. The current evidence is mainly based on data from expanded access trials, phase 2 trials, subgroup analyses from larger trials and retrospective analysis, which mainly focus on TKI or mTOR inhibitor testing. Overall, the most robust data exist for the use of sunitinib in patients with non-clear cell histology (most trials favoured sunitinib over the use of everolimus). In the ASPEN trial Sunitinib significantly increased progression-free survival compared with everolimus (8'"3 months vs 5'"6 months; hazard ratio 1'"41; p=0'"16), although heterogeneity of the treatment effect was noted based on histological subtypes and prognostic risk groups. Studies also suggest that these patients may beneût from treatment with everolimus, sorafenib, pazopanib or temsirolimus. However, in most of these studies, only patients with papillary and chromophobe tumours were enrolled.

HISTOLOGY	STANDARD/ PREFERRED REGIMEN	OTHER OPTIONS
Papillary RCC	Sunitinib Pazopanib	Everolimus Cabozantinib
Papillary RCC (select patients including those with HLRCC)	Bevacizumab + erlotinib	—
Papillary RCC with cMET mutation or amplification	Crizotinib/ cabozantinib	—
Chromophobe	—	Sunitinib Pazopanib Everolimus**
Collecting Duct/ medullary	Platinum based chemotherapy (Gemcitabine+ Cisplatin/ Carboplatin, Paclitaxel+ Carboplatin)	—
Sarcomatoid (predominant)	Nivolumab + Ipilimumab#	Sunitinib Pazopanib

* Crizotinib or other cMET inhibitors such as cabozantinib appear as an acceptable option instead of the usual VEGF TKIs.

** Some patients with chromophobe RCC may beneût from mTOR inhibitors since mutation on chromosome 7 was shown to lead to a loss of the folliculin gene with upregulation of mTOR

sarcomatoid tumours are very inûamed tumours, usually with poor-risk features and are sensitive to immune checkpoint inhibitors. Nivolumab/ipilimumab combination should be considered as a good option for these patients.

Regimens which may be useful under certain circumstances

- Axitinib
- Nivolumab
- Erlotinib
- Lenvatinib+ everolimus
- Bevacizumab + everolimus
- Temsirolimus(poor risk group)

Other agents used for the therapy in mRCC

- **Cytokines**

  IL-2 and IFN was the standard of care in metastatic RCC until the advent of targeted therapy. Historically intravenous bolus IL—2 was used to treat ccRCC which led to sustained responses in a small subset of patients. The durable complete remissions that occurred in 5-7% patients lead to US FDA approval in 1992. It is not used routinely any longer due to its toxicity and only a small fraction of very fit patients were eligible for this treatment.

  Interferon alpha as single or in combination with bevacizumab has been used in the treatment of mRCC. Single agent IFN is no longer used. The combination of bevacizumab plus IFN showed a significant improvement in PFS (10.2 vs 5.4 months, P<0.0001) and ORR (31% vs 13%, P<0.0001) when compared to IFN + placebo. The CALGB trial which compared IFN + bevacizumab vs IFN monotherapy showed improvement in PFS (8.5 vs 5.2 months) and

ORR (25.5% vs13.1%).The combination has significant toxicity and the contribution of IFN to the anti-tumor effect in this regimen is unclear.

- **mTOR inhibitors**

  Temsirolimus was tested in previously poor risk patients in the ARCC trial in patient with 3-6 adverse prognostic factors (which were specified). Patients who received temsirolimus alone had a significantly longer median overall survival than those treated with IFN alpha alone (10.9 months vs 7.3 months). However, the combination of temsirolimus +IFN alpha did not improve OS or PFS and significantly increased toxicity hence is not used. Temsirolimus is not recommended in first line setting as better agents with more favourable toxicity profiles are available, but may be considered under certain circumstances.

WHAT HAS CHANGED IN RENAL CELL CARCINOMA(RCC) IN THE LAST DECADE

- New variant histologies added to the classification
- Small renal mass considered a distinct entity
- Prognostic models and scoring systems in early and advanced RCC are in practice
- Renal Mass biopsy is considered safe, efficacious and is routinely performed when indicated
- Active Surveillance and ablative therapies are accepted options in management of small renal masses

- Evolving evidence in favour of SBRT in management of RCC
- Role and sequencing of cytoreductive nephrectomy is more defined
- Risk Categorization is a must before deciding systemic therapy for advanced RCC
- Multiple RCTs have brought TKI, Immunotherapy and a combination of two at the forefront of management of advanced RCC

SUGGESTED READING

1. Jayson, M., et al. Increased incidence of serendipitously discovered renal cell carcinoma. Urology, 1998. 51: 203.
2. Davidson AJ, Hartman DS, Choyke PL, Wagner BJ. Radiologic assessment of renal masses: implications for patient care. Radiology 1997;202: 297-305
3. Bosniak MA. Renal-cell carcinoma. N Engl J Med. 1997 Mar 13; 336(11):810.
4. Herts BR & Remer EM: Role of percutaneous biopsy in the evaluation of renal and adrenal mass. AUA Update Series 2000, Vol 19, Lesson 36.
5. Vasudevan A, Davies RJ, Shannon BA, Cohen RJ: Incidental renal tumours: the frequency of benign lesions and the role of preoperative core biopsy. BJU Int 2006, 97, 946-49.
6. Silver DA, Morash A and. Brenner P et al., Pathologic findings at the time of nephrectomy for renal mass. Ann Surg Oncol 1997, 4. 570–574.
7. Wang HY, Ding HJ, Chen JH, Chao CH, Lu YY, Lin WY, Kao CH. Meta-analysis of the diagnostic performance of [18F]FDG-PET and PET/CT in renal cell carcinoma. Cancer Imaging. 2012 Oct 26;12:464-74.

8. Agnihotri S et al. Renal cell carcinoma in India demonstrates early age of onset and a late stage of presentation. Indian J Med Res. 2014;140: 624-29

9. Pischon T, Lahmann PH, Boeing H, Tjønneland A, Halkjaer J, Overvad K et al: Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer. 2006 Feb 1;118(3):728-38

10. Patard JJ, Leray E, Rodriguez A, Rioux-Leclercq N, Guille F, Lobel B. Correlation between symptom gradation, tumour characteristics and survival in renal cell carcinoma . Eur Urol 2003; 44(2):226-32.

11. A Phase 3, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus Sunitinib Monotherapy in Subjects With Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma. 2015 p. NCT02231749.

12. Sabatino, M., *et al.* Serum vascular endothelial growth factor and fibronectin predict clinical response to high-dose interleukin-2 therapy. J Clin Oncol, 2009. 27: 2645.

13. Siva S, Kothari G, Muacevic A, et al. Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach. Nat Rev Urol 2017;14(9):549–63.

14. Kothari G, Foroudi F, Gill S, et al. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. Acta Oncol 2015;54(2):148–57.

15. C. Masini, P. Ciammella, G. Timon, et al. First results of safety profile of nivolumab (NIVO) in combination with stereotactic body radiotherapy (SBRT) in II and III line of patients. Annals of Oncology (2019) 30 (suppl_5)

16. Motzer RJ, Mazumdar M, Bacik J et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999; 17(8): 2530–2540

17. Heng D.Y.C., Xie W, Regan M, Warren M, Golshayan A.R, Sahi C, Eigl B.J, Ruether J.D, Cheng T, North S, et al. Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study. J Clin Oncol 27:5794-5799

18. Ko JJ, Xie W, Kroeger N et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol 2015; 16(3): 293–300.

19. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. 5 August 2019; Version 2.2020 Available at www.nccn.org

20. Escudier B, Porta C, Schmidinger M., Rioux-Leclercq N, Bex A, Khoo V, et al on behalf of the ESMO Guidelines Committee Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27 (Suppl 5): v58–v68.

21. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, OudardS, et al Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):115-24

22. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584-90

23. Motzer R.J, Hutson T.E, Cella D, Reeves J, Hawkins R, Guo J et al. Pazopanib versus Sunitinib Metastatic Renal-Cell Carcinoma.N Engl J Med 2013; 369:722-731.DOI: 10.1056/NEJMoa1303989

24. Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg C.N, Gschwend J.E, Giorgi U.D, Parikh O, Hawkins R et al. Randomized, Controlled, Double-Blind, Cross-Over Trial Assessing Treatment Preference for Pazopanib Versus Sunitinib in Patients With Metastatic Renal Cell Carcinoma: PISCES Study. J Clin Oncol 32:1412-1418.

25. Rini B.I.,Plimack E.R, Stus V., Gafanov R., R. Hawkins, D. Nosov, F. Pouliot, Alekseev B.,Soulières D,. Melichar B et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

26. Motzer RJ, Tannir NM, McDermott DF et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018; 378(14): 1277–1290.

27. Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, Walsh M, Olencki T, Picus J, Small EJ, Dakhil S, Feldman DR, Mangeshkar M et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer. 2018 May; 94:115-125. doi: 10.1016/j.ejca.2018.02.012

28. Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised,open-label, phase 3 trial. Lancet Oncol 2016; 17(7): 917–927.

29. Motzer R. J, Escudier B, Tomczak P, Hutson T.E, Michaelson M.D, Negrier S, Oudard S, Gore M.E, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013; 14: 552–62.

30. Escudier B, Eisen T, Stadler W.M, Szczyliket C et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. N Engl J Med 2007; 356:125-134.

31. Di Lorenzo G, Cartenì G, Autorino R, Bruni G, Tudini M, Rizzo M, Aieta M, Gonnella A, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol. 2009 Sep 20; 27 (27):4469-74.

32. Zimmermann K, Schmittel A, Steiner U, Asemissen A.M, Knoedler M, Thiel E, Miller K, Keilholz U. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. Oncology. 2009; 76(5):350-4.

33. Hainsworth J.D, Rubin M.S, Arrowsmith E.R, Khatcheressian J ,Crane E.J, Franco L.A ,et al. Pazopanib as Second-Line Treatment After Sunitinib or Bevacizumab in Patients With Advanced Renal Cell Carcinoma: A Sarah Cannon Oncology Research Consortium Phase II Trial.Clin Genitourin Cancer 2013;11:270-75

34. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373(19):1803–1813.

35. Motzer RJ, Escudier B, Oudard S, Hutson T.E, Porta C, Bracarda S, Grunwald V,. Thompson J.A, Figlin R.A, Hollaender N, et al. Phase 3 Trial of Everolimus for Metastatic Renal Cell Carcinoma: Final Results and Analysis of Prognostic Factors. Cancer 2010;116: 4256–65

36. Motzer RJ, Hutson TE, Glen H et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015; 16(15):1473-1482.

37. Armstrong AJ, Halabi S, Eisen T et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016; 17(3): 378–388.

38. Tannir NM, Jonasch E, Albiges L et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. Eur Urol 2016; 69(5): 866–874.

39. Koh Y, Lim HY, Ahn JH, Lee JL, Rha SY, Kim YJ, Kim TM, Lee SH. Phase II trial of everolimus for the treatment of non clear-cell renal cell carcinoma. Ann Oncol. 2013 Apr; 24(4):1026-31.

40. Jung KS, Lee SJ, Park SH, Lee JL, Lee SH, Lim JY, Kang JH, Lee S, et al. Pazopanib for the Treatment of Non-clear Cell Renal Cell Carcinoma: A Single-Arm, Open-Label, Multicenter, Phase II Study. Cancer Res Treat. 2018 Apr; 50(2):488-494. doi: 10.4143/crt.2016.584.

41. Prisciandaro M, Ratta R, Massari F, Fornarini G, Caponnetto S, Iacovelli R, De Giorgi U, Facchini G, Scagliarini S et al. Safety and Efficacy of Cabozantinib for Metastatic Non clear Renal Cell Carcinoma: Real-world Data From an Italian Managed Access Program. Am J Clin Oncol. 2019 Jan; 42(1):42-45.

42. N.M, Bossé D, Bilen M.A, Geynisman D.M, Balakrishnan A, Jain R.K, Bowman I.A, Zakharia Y, Narayan V, et al. Cabozantinib (Cabo) in advanced non-clear cell renal cell carcinoma (nccRCC): A retrospective multicenter analysis. J Clin Oncol. 2018; 36(15):4579

43. Schoffski P, Wozniak A, Escudier B et al. Crizotinib achieves long-lasting disease control in advanced papillary renal-cell carcinoma type 1 patients with MET mutations or amplification. EORTC 90101 CREATE trial. Eur J Cancer 2017; 87: 147–163.

44. Gordon MS, Hussey M, Nagle RB, Lara PN Jr, Mack PC, Dutcher J, Samlowski W, Clark JI, Quinn DI, Pan CX, Crawford D. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer:

SWOG S0317.J Clin Oncol. 2009 ;27(34):5788-93. doi: 10.1200/JCO.2008.18.8821

45. Voss MH, Molina AM, Chen YB, Woo KM, Chaim JL, Coskey DT, Redzematovic A, Wang P, Lee W, Selcuklu SD et al. Phase II Trial and Correlative Genomic Analysis of Everolimus Plus Bevacizumab in Advanced Non-Clear Cell Renal Cell Carcinoma. J Clin Oncol. 2016 Nov 10; 34(32):3846-3853. doi: 10.1200/JCO.2016.67.9084

46. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007; 370: 2103-11.

47. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol 2010; 28: 2137-43

48. Ravaud A, Motzer RJ, Pandha HS et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 2016; 375(23):2246–2254.

49. Haas NB, Manola J, Uzzo RG et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016; 387(10032): 2008.

50. Motzer RJ, Haas NB, Donskov F et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol 2017; 35(35):3916–3923.

51. Sun M, Marconi L, Eisen T et al. Adjuvant vascular endothelial growth factor-targeted therapy in renal cell carcinoma: a systematic review and pooled analysis. Eur Urol 2018; 74(5): 611–620.

CHAPTER 4

Testicular Cancer

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1. INCIDENCE:

Testicular cancer forms about 1% of all malignancies in males in India. Germ cell tumors (GCTs) comprise 95 % of malignant tumors arising from testis. These tumors predominantly affect young males. The disease as well as the treatment can affect the fertility of these patients and affect the quality of life. Testicular tumors are the models of the success of multimodality approach to cancer, boasting of high cure rates even in the presence of metastatic disease. About 40% of all testicular tumors are pure seminomas and rest are non seminomatous GCTs (NSGCTs). 2-3%percent of the patients at presentation have bilateral tumors.

2. PREDISPOSING FACTORS:

Cryptorchidism

Germ cell tumors (GCT) can develop in an inguinal cryptorchid testis in approximately 2% of cases. Another

5%-10% of cases will develop in the normally descended testis. Orchiopexy should be preferably done around 2 year of age to reduce the risk of development of second malignancy. If the cryptorchid testis is inguinal, hormonally functioning, and easily examined, surveillance is recommended. If the cryptorchid testis is abdominal, nonfunctioning and not amenable to orchiopexy, orchiectomy is recommended. Seminomas develop more commonly in cryptorchid testis compared to NSGCTs

Klinefelter Syndrome

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

Other Risk Factors for Testicular Cancer:

- Family history
- Presence of tumor or testicular intraepithelial neoplasia in the contralateral testis
- Altered intrauterine hormonal environment Low fertility
- Abnormal sperm analysis

Histological classification: GCT is classified into two major subgroups: seminoma and non-seminoma. The classification of the World Health Organization, derived mostly from Sesterhenn adaptation of the Dixon/ Moore classification of testicular cancer, is the system most commonly used.

3. WORLD HEALTH ORGANIZATION HISTOLOGIC CLASSIFICATION OF TESTIS TUMORS

The updated 2016 draft classification was discussed at an International Society of Urological Pathology Consultation on TesticularCancer. Major changes include a pathogenetically derived classification using germ cell neoplasia in situ (GCNIS) as a new name for the precursor lesion, and the distinction of prepubertal tumours (non-GCNIS derived) from postpubertal-type tumours (GCNIS derived.

Spermatocytic tumour is adopted as a replacement for spermatocytic seminoma, to avoid potential confusion with the unrelated usual seminoma. Currently, reporting of anaplasia (seminoma or spermatocytic tumour) or immaturity (teratoma) is not required, as these do not have demonstrable prognostic importance. In contrast, overgrowth of a teratomatous component (somatic-type malignancy) and sarcomatous change in spermatocytic tumour indicate more aggressive behaviour, and should be reported.

Germ cell Neoplasia in situ (GCNIS) derived tumors

Seminoma
Seminoma with syncytiotrophoblastic cells
Yolk sac tumors
Trophoblastic tumors Choriocarcinoma
Trophoblastic neoplasms other than Choriocarcinoma

Monophasic Choriocarcinoma Placental Site Trophoblastic tumors Teratoma

Dermoid cyst Monodermal Teratoma (post pubertal)

Choriocarcinoma and Teratoma/embryonal carcinoma

Non GCNIS (Germ cell Neoplasia in situ) derived tumors
Prepubertal Teratomas

Spermatocytic tumor (previously called spermatocytic seminoma)

Pediatric yolk sac tumors

GCNIS is found adjacent to testicular germ-cell tumor in over 95% of cases. It is also found in all clinical groups known to be at high risk for testicular cancer development: Cryptorchidism (2%to4%), infertility (1%), ambiguous genitalia (25%), and contralateral testes of patients with testicular cancer (5%).

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

GCNIS has a 50% risk of developing into an invasive germ-cell tumor within 5years. That risk probably approaches 100% by 8 years.

Seminoma

Classical Type

Seminoma is the most frequent germ-cell tumor, comprising over 50% of all germ-cell neoplasms. Serum

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

Grossly, seminoma is a soft tan-colored diffused multinodular mass. Focal necrosis is sometimes present. A prominent lymphocytic infiltrate is commonly seen within the fibrous stroma. Over 90% of seminomas will stain positive for placental alkaline phosphatase. (PLAP), CKit and D2-40.

Spermatocytic Tumor

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

Nonseminomatous Germ-Cell Tumors

Embryonal Carcinoma

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

Grossly, the tumor often exhibits a large area of hemorrhage and necrosis. Almost all embryonal

carcinomas are PLAP positive, and alpha-fetoprotein and HCG-positive cells are present in 33% and 21%, respectively.

Yolk Sac (Endodermal Sinus Tumor)

Pure yolk sac tumor makes up <2% of testicular tumors in adults and component of 40% of mixed germ- cell tumors. It makes up 60% of germ-cell tumors in children. Eighty percent of pure yolk sac tumors occur in the first 2 years of life. It is associated with elevated serum levels of alpha-fetoprotein. Grossly, yolk sac tumors contain cystic spaces containing a gelatinous material. There is a variable amount of hemorrhage and necrosis. Microscopically, Schiller-Duval bodies are a characteristic feature.

Teratoma

Pure teratoma makes up 5% of all testicular germ-cell tumors. Teratomatous component may be seen in about 50% of mixed germ-cell tumors. In pure teratoma serum, HCG and alpha-fetoprotein are normal. Mature teratoma consists of mature well-differentiated somatic tissues. It must be clearly understood that prepubertal teratomas are lmost always benign and post pubertal teratomas are malignant ebenthough they both show mature tissues. The reason is that post pubertal teratomas are derived from the precursor lesion GCNIS (derived) and have passed through a phase of malignancy/ premalignancy unlike prepubertal teratomas which are non GCNIS derived. Despite their benign appearance, metastases can occur in post pubertal teratoma. Immature teratoma contains immature elements in addition to varying amounts of well-differentiated tissue. Both mature and immature

teratomas have a similar behavior. Teratoma with malignant transformation results in the development of a somatic carcinoma or sarcoma within the teratoma.

Choriocarcinoma

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

Mixed Germ-Cell Tumors

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

4. CLINICAL PRESENTATION AND PATTERNS OF SPREAD:

A testicular tumor usually presents as pain less scrotal swelling, heaviness, tenderness and loss of testicular sensation. Contrary to common belief, pain is a presenting feature in approximately half the cases.

Involvement of retroperitoneal lymph nodes may produce back pain or abdominal swelling. Widely disseminated parenchymal disease in lungs, liver, bone, or brain is uncommon but, if present, may produce systemic symptoms. Gynecomastia is a rare presentation of choriocarcinoma and may be seen in association with the

very uncommon sex cord-stromal tumors. Occasionally, patients present with metastatic germ-cell malignancies diagnosed by biopsy or elevated levels of serum tumor markers without evidence of a palpable mass in the testis. Occult primary disease in the testis is often detected by testicular ultrasound. If there is no evidence of a primary tumor in the testis, a diagnosis of an extra-testicular germ-cell tumor, usually mediastinal, retroperitoneal, or pineal, can be considered.

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

The pattern of spread in NSGCT is distinct from that seen in Seminomas. In NSGCT, 60% of cases will present with extensive disease. The spread is usually to the retroperitoneal lymph nodes first and then hematogenously to other parts. The exception is pure choriocarcinoma–which rapidly spreads to lungs, brain and others of tissues early in the disease. Pattern of retroperitoneal lymph nodal involvement in germ cell tumors has important treatment implications. Right sided primary will usually involve the interaortocaval, precaval and pre-aortic nodes. The left testicular mass will involve the left paraaortic, preaortic and interaortocaval nodes. Suprahilar LN involvement is uncommon and external iliac/ obturator nodes are only rarely the sites of metastasis.

5. PRETREATMENT EVALUATION:

When an intra-testicular mass is identified, further evaluation includes the following.

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

  AFP is increased in 50-70% of patients with NSGCT and a rise in b-HCG is seen in 40-60% patients with NSGCT. LDH is a less specific marker, and its level may be elevated in 80% of patients with advanced testicular cancer.
- Imaging of the testis: Ultrasound of the testicular mass performed mostly to define the lesion. It can determine whether the mass is intra-testicular or extra-testicular and helps to monitor the status of contralateral testis in high risk patients. It may be useful to identify small non-palpable tumor in patients with metastatic disease.
- X-ray chest

- Abdominal pelvic CT scan or MRI: Have a sensitivity of 70-80% in the determination of retroperitoneal and mediastinal lymphnodes.
- Chest CT is indicated if abdominal CT scan confirms retroperitoneal adenopathy or the chest X-ray is abnormal.
- Open inguinal biopsy of the contralateral testis is not routinely performed but can be considered if cryptorchid testis or atrophic testis is present. (Biopsy to be considered if suspicious intra-testicular mass or micro calcification but not micro calcification)
- CBC, Biochemistry including renal chemistry and liver function tests.
- MRI Brain and bones can if clinically indicated or in patients of NSGCT with extensive wide spread lung metastases or in patients with very high b-HCG Suspected chorio Ca.
- Patients should be counseled for sperm banking if patients unmarried or family is not complete and same should be done before any therapeutic intervention

Role of PET scan as an imaging modality: FDG PET does not improve staging in patients with clinical stage I disease because, similar to CT, it is poor at detecting small-volume (i.e. sub centimeter) disease .Furthermore, FDG PET is not able to identify mature teratoma. Presently, there is not sufficient evidence to support the use of FDG-PET scan in staging and hence not recommended in the primary staging of testicular GCT (Level III). It however has a role in characterization of post-chemotherapy residual mass in patients with seminoma and may direct therapy (intervention vs observation).

6. PRIMARY (INITIAL) TREATMENT:

6.1 High Inguinal Radical Orchiectomy.

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

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

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

Testis-sparing surgery: This is not routinely recommended in patients with normal contra lateral testis. However, in synchronous bilateral tumors, metachronous contralateral tumors or in patients with a tumor in a solitary testis, testis-preserving surgery may be indicated when the tumor volume is less than 30% of the total testicular volume and

the tumor is completely removed. There is a high risk of associated many patients require local radiation therapy (20 Gy) to control primary disease. This option may be carried out after thorough consultation with the patient.

6.2 Post Primary Treatment Work-up:

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

Staging:

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

The pathologic classification of these primary tumors and lymph as per the 8th edition of AJCC published in 2017 is as follows: (Table 1 and Table 2)

Pathological T (pT)

Table 1: Pathologic staging (pT) of primary testicular tumors	
pT Category	**pT Criteria**
pTX	Primary tumor cannot be assessed
pTO	No evidence of primary tumor
pTis	Germ cell neoplasia in situ
pTI	Tumor limited to testis (including rete testis invasión) without lymphovascular invasion
pTla*	Tumor smaller than 3 cm in size
pT 1 b*	*Tumor 3 cm or larger in size*

(Contd...)

(Contd...)

pT Category	pT Criteria
pT2	Tumor limited to testis (including rete testis invasión) with lymphovascular invasión OR Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of túnica albugínea with or without lymphovascular invasión
pT3	Tumor invades spermatic cord with or without lymphovascular invasión
pT4	Tumor invades scrotum with or without lymphovascular invasión

**Subclassification of pTI applies only to puré seminoma.*

Table 2: Pathologic classification of lymph nodes (pN) in primary testis tumors

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pNO	No regional lymph node metastasis
pN 1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive. none larger than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or ‘ more than five nodes positive, none larger than 5 cm; or evidence of Extranodal extension of tumor
pN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

M	Stage
M0	No evidence of distant metastases
M1	Distant metastases
M1a	Non regional nodal or pulmonary metastases
M1b	Non pulmonary visceral metastases
S:	Serum tumor markers

S	LDH	hCG† (mIU/mL)	AFP (ng/mL)
SX	Not assessed	Not assessed	Not assessed
S0	N0	and Normal	and Normal
S1	<1.5 x N	and <5,000	and <1,000
S2	1.5-10 x N	or 5,000-50,000	or 1,000-10,000
S3	>10 x N	or >50,000	or > 10,000

N = upper limit of normal for the LDH assay

7. STAGE GROUPING

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

International Germ Cell Consensus Classification for Seminoma:

In1997, IGCCCC defined a staging system for metastatic disease based on some independent clinical prognostic factors. This system has now been incorporated into the

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

Good Risk (90%)

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

Intermediate Risk: (10%)

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

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

International Consensus Advanced Germ Cell Tumor Prognosis Classification for NSGCT:

Good Risk

- Testicular or retroperitoneal primary tumor.
- No non-pulmonary visceral metastases present
- Post orchiectomy AFP <1000 ng/ml and b-hCG

<5000 IU/l and LDH <1.5 X upper limit of normal (ULN)

Intermediate risk:

- Testicular or retroperitoneal primary tumor.
- No non-pulmonary visceral metastases present.
- AFP1000-10000ng/ml or b-hCG 5000-50000 IU/l or LDH 1.5-10 XULN

Poor risk:

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

8. MANAGEMENT OF SEMINOMA:

8.1 Stage I:

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

Options of treatment for stage I seminoma are as follows:

a) Prophylactic (adjuvant) radiation therapy
b) Adjuvant chemotherapy
c) Surveillance
d) Risk adapted treatment

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

Prophylactic (Adjuvant) Para-aortic+/-Pelvic Nodes Radiation: Around 15-20% of the patients under surveillance will relapse if they do not receive adjuvant radiotherapy post orchiectomy .External beam radiation therapy to para-aortic area either alone or with ipsilateral iliac nodal region (hockey stick field) to a dose of 20-25Gy with 6-15MV photons @1.5-1.8Gy/# in2-3 weeks, from lower border of D10 vertebra (retrocrural nodes) to lower border of L5 vertebra (with shielding of contralateral testis) is recommended with a relapse rate of 1-3%. In patients with undisturbed lymphatic drainage, para-aortic radiation therapy alone has been shown to be adequate but with slightly higher rate (2% vs 0%) in the iliac region as compared to the traditional hockey stick field. ARCT conducted by MRC comparing 20Gy to 30Gy paraaortic radiation therapy in stage I seminoma showed equt ivalence of both doses in terms of recurrence rate. Most relapses after radiation therapy are outside the radiation field. If previous scrotal surgery, field of radiation therapy to be extended to include ipsilateral inguinal nodes (dog-leg radiotherapy). [Level I]

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

The main disadvantage of radiation therapy is the gastrointestinal toxicity and risk of second malignancy in the radiated field although this data is with old radiotherapy techniques used in past.

Adjuvant chemotherapy: A single dose of carboplatin has also been recommended as an alternative to radiotherapy or surveillance in patients with stage I seminoma. In the MRC TE 19 study, which compared one cycle of carboplatin (AUC7) to adjuvant radiotherapy, there was no significant difference in the recurrence rate, time to recurrence and survival rate after a median follow up of 4 years (Level 1). Updated results of the same study were reported in ASCO2008 Annual meeting which confirmed non inferiority of single agent carboplatin AUC 7 as compared to radiotherapy with reduced risk of 2nd GCT in carboplatin arm with lesser toxicity [Level I]. Two courses of adjuvant carboplatin seem to reduce the relapse rate further to1-3%. Results show more negative impact of RT on QOL and well being with equivalent efficacy as chemotherapy.

Surveillance: This option is considered in select patients of T1,T2 disease with committed for long-term follow up [Level II]. This is recommended option for horse shoe kidney, patients suffering from inflammatory bowel disease and prior abdominal radiation. [Level I]

Surveillance policy has been evaluated in several randomized studies. A meta-analysis of 4 studies showed an actuarial 5 years relapse free rate of 82.3%. A large single institutional study from Princess Margaret Hospital, Canada with more than 1500 patients reported an overall relapse rate of 16.8%, with most relapses in the retroperitoneum. The overall cancer specific survival with surveillance reported from major centres is 97-100%. The main drawback of surveillance strategy is the need for more intensive follow up with repeated imaging studies

for a prolonged period of time since about 20% of relapses in seminoma occur beyond 4 years after Orchiectomy. This translates into cost escalation and need for strict compliance to surveillanceschedule.

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

Summary for treatment : Based on available evidence one to two cycle of Carboplatin (AUC-7) is preferred option and prophylactic abdominal radiotherapy is other option. Surveillance can also be considered if facilities are available and patient is compliant for same.

Post-treatment follow up: Strict follow up is mandatory. This is done with history, physical examination, serial tumor markers 6 months for first 3 years and annually thereafter. CT scan abdomen + pelvis is recommended, for first 3 years for patients who had received chemotherapy or RT whereas in patients on surveillance, it is required at every 6 monthly. X-Ray Chest not required, until clinically indicated.

8.2 Treatment of metastatic seminoma:

Low volume metastatic disease (II A/B)-

Treatment options:

- Radical Radiation Therapy
- Chemotherapy

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

Chemotherapy: Accumulating data on long term morbidity shows increased risk of cardiovascular events and increased risk of second malignancies following RT. Three cycle of BEP is an option in Stage IIa, and is the preferred treatment in stage IIb disease . 4 cycles of cisplatin and etoposide [EP] is a suitable alternative to 3 cycle of BEP .

8.3 Advanced metastatic seminoma: Stage IIC-III:

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

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

Following chemotherapy, tumor markers and imaging studies are repeated to assess the response. Patients are then stratified according to the presence or absence of mass and the status of tumor markers. If complete response, no further treatment is required. If there is a residual mass, a PET-CT scan is recommended to assess the viability of the tumor. To reduce false positive rates, PET is typically done after 8 to 10 weeks of chemotherapy. No further treatment is recommended in PET negative patients; however, these patients need to be observed closely. If the PET scan is positive, biopsy is recommended followed by surgical excision if technically feasible or salvage chemotherapy or radiotherapy to a dose of 30–40 Gy @1.8Gy/# in 3-4 weeks . [Level II].

If the PET scan is not available, the evaluation should be done by CT scan. Residual mass of the size 3cm or more can be treated by surgery [Category2B] or radiation [Level II]. Surgery in metastatic seminoma post-chemotherapy is extremely difficult and morbid due to extensive fibrosis in the treated area. Patients with mass less than 3cm should be observed. (See appendix III)

9. MANAGEMENT OF NSGCT:

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

Following high orchiectomy, the treatment options include:

9.1 Stage I NSGCT

Options

a) Surveillance
b) NSRPLND
c) Chemotherapy
d) Risk based treatment

Surveillance: Based on availability of accurate tumor markers for monitoring of disease status and effective chemotherapy for salvage of relapse, surveillance protocols have been studied in stage I NSGCT. The relapse rates are approximately 30% - 80% of them occurring in the first year, 12% in the second, 6% in the third and 1% each in the fourth and the fifth year. About 60% of there lapses are in the retro-peritoneum. Although surveillance has the potential to avoid major surgery with its morbidity, it requires a very intensive follow up with tumor markers, X-ray chest and CT scan abdomen at very frequent intervals. Thus it requires excellent compliance from the patients which may not be possible in India. Besides, there is an anxiety about the nearly 30% chance of relapse, some of which may be advanced and unsalvageable if the patient does not comply with the surveillance schedule.

Nerve sparing retroperitoneal lymph node dissection:

In view of high cancer specific survival rate surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic RPLND has diminished over time . In a RCT, one course of BEP showed a significantly lower recurrence rate as compared to surgery. If primary RPLND is done it identifies the high risk patients with occult retroperitoneal lymph node metastases (approximately 30%) who will need chemotherapy, has a very low (<2%) chance of relapse in the retroperitoneum and a very high cure rate. It preserves ante grade ejaculation in more than 90% of patients. Extensive follow up with CT scan as in surveillance is not mandatory which brings down the cost

and patient anxiety is allayed. [Level I] (See appendix IV). A laparoscopic RPLND may become a suitable alternative to open nerve sparing RPLND in future but cannot be presently recommended as the standard of care.

Chemotherapy: Historically, studies using 2 course of BEP chemotherapy as the primary treatment for high risk stage I NSGCT have reported are lapse rate of only 2.7% at a median follow up of 8 years, with very little long- term toxicity and with little adverse impact on fertility or sexual activity.

1 cycle of BEP was compared to RPLND in a RCT [B], 2 yrs recurrence free survival was 99.41% with chemotherapy, with 7% improvement over RPLND

A community based prospective study showed that after 8 yrs relapse rate was 2.3% with 1 cycle BEP and no relapses were seen after 3.3 years. Reduction from 2 to 1 cycle of BEP improves the risk benefit ratio of chemotherapy

However, the concern about primary chemotherapy is the emergence of chemo resistant relapse and possibility of slow growing retroperitoneal teratomas necessitating intensive monitoring of retroperitoneum in the follow up period.

Risk based treatment: Various prognostic factors in the primary affecting risk of relapse have been identified viz. presence of vascular invasion, predominance of embryonal carcinoma > 40 to50 % and >T2 disease.Among all these factors presence of lympho vasucular is the most important factor for decision making . Patients with no risk factors may be offered surveillance while those with high risk

factors may be offered nerves sparing RPLND or chemotherapy. Patients with vascular invasion should be offered chemotherapy with 1 cycle of BEP

9.2 Management of clinical stage I with persistently elevated serum tumor markers (CS1S):

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

9.3 Management of low volume metastatic NSGCT (IIA/B)

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

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

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

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

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

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

Recent data demonstrated that intensifying treatment in patients with early unfavorable tumor marker decline improves PFS but not OS, but further studies are required to validate this approach

For patients with brain metastases, primary chemotherapy and consolidation radiotherapy is the standard of care. Surgical intervention is recommended in selected cases with solitary residual lesions depending on the status of

the systemic relapse, site of metastasis and histology of the primary tumor. Certain sites of metastasis confer a distinct disadvantage in patients with NSGCT. These include liver, bone and brain. Metastasis to any of these sites reduces the 3-year OS rates significantly.

In patients of extra gonadal GCTs, as in mediastinal GCT, which are considered as high risk, treatment essentially consists of 4 cycles of BEP chemotherapy followed by the excision of residual disease. Other options include 4 cycle of VIP or TIP (cisplatin,ifosfamide and paclitaxel)

10. POST CHEMOTHERAPY MANAGEMENT:

Response to primary chemotherapy is assessed 3 to 4 weeks after completion of the planned course of chemotherapy. Clinical evaluation, CT scan of the abdomen + pelvis, X-ray or CT scan of chest and serum biomarkers estimation are advised for evaluation of response. In patients with complete response (clinical, radiological and serological), surgery is not recommended and patients are kept under surveillance.

In patients with residual masses, decision regarding adjuvant surgery is based on whether the tumor markers remain elevated or have normalized. In patients with normal post-chemotherapy markers and any residual mass > 1 cm in size, complete surgical resection is warranted to document the histology of the residual mass and for disease control. All residual disease need to be resected, since histology may be divergent at different metastatic sites. Complete resections should be done aggressively for retroperitoneal and pulmonary masses. If technically

feasible, nerve sparing RPLND should be done. If necrotic tissue or teratoma is encountered, then no further therapy is warranted.

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

11. SYSTEMIC SALVAGE TREATMENT FOR RELAPSED OR REFRACTORY DISEASE:

11.1 Salvage chemotherapy:

Standard salvage chemotherapy regimen after first line chemotherapy consists of either 4 cycles of VeIP or 4 cycles of TIP. Conventionally dosed salvage regimens may achieve long term remission in about 35 to 40 % of patients.

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

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

Testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue for 2 cycles (tandem transplant), even when this regimen is used as third-line or later therapy or in patients with platinum- refractory disease.

Role of salvage chemotherapy (TIP) vs tandem autologous transplant in first relapse is still unanswered. On going TIGER trial will give the answer to this question.

Another second line palliative therapy for intensively pretreated cisplatin resistant or refractory germ cell tumor is the use of GEMOX (gemcitabine and oxaliplatin). This combination is safe and can offer long term survival in select group of patients. [Level II]. Other chemotherapy options include gemcitabine and paclitaxel (Gem+Pacli) and gemcitabine, paclitaxel and oxalipaltin in combination. Rarely, patient with metastatic disease with elevated tumor marker levels at a solitary site can be offered surgical resection with curative intent (desperate RPLND or Surgery).

Residual tumors after salvage chemotherapy should be resected after normalization or plateauing of markers. In case the markers are elevated during the course of salvage chemotherapy, the prognosis is extremely poor and resection of residual disease should be considered if complete resection of all tumor seems feasible. With this approach, about 25% long term survivals may be achieved.

12. POST TREATMENT FOLLOW UP

Recommended minimal follow-up for non-seminoma stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumor markers ± doctor visit	4 times	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
CT (A+P)/ MRI A+P	2 times	At 24 months	Once at 36 months	Once at 60 months	

Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumor markers	4 times	4 times	2 times	2 times	Further ± doctor visit management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdomino-pelvic computed tomography (CT)/ magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

APPENDIX I

Sperm Banking

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

APPENDIX II

Chemotherapy regimens:

I. BEP (1st line) Repeat cycle every 21days Bleomycin: 30 U IV on days 2, 9, and Etoposide: 100 mg/m2 IV on days 1–5 Cisplatin: 20 mg/m2 IV on days1–5

EP (1st line) Repeat cycle every 21 days Etoposide: 100 mg/m2 IV on days 1–5 Cisplatin: 20 mg/m2 IV on days1–5

VeIP (salvage regimen) Repeat cycle every 21 days

Vinblastine: 0.11 mg/kg IV on days 1 and 2 Ifosfamide: 1,200 mg/m2 IV on days 1–5

Cisplatin: 20 mg/m2 IV on days 1–5

Mesna: 400 mg/m2 IV, given 15 minutes before first ifosfamide dose, then 1,200 mg/m2/day IV continuous infusion for 5 days

II. VIP (salvage regimen) Repeat cycle every 21 days
Etoposide (VP-16): 75 mg/m2 IV on days 1–5 Ifosfamide: 1,200 mg/m2 IV on days 1–5

Cisplatin: 20 mg/m2 IV on days 1–5

Mesna: 400 mg/m2 IV, given 15 minutes before first

ifosfamide dose, then 1,200 mg/m2/day IV continuous infusion for 5 days

III. TIP regimen (Salvage regimen)
Repeat cycle every 21 days

Paclitaxel 250mg /m2 24 hour infusion Day 1 or 175 mg/m2 over 3 hour infusion

Ifosfamide 1500 mg/m2 Day 2 to day 5

Mesna 500mg/m2 just before Ifosfamide and at 4 and 8 hours Day2 to day5.

Cisplatin 25 mg/m2 Day2 to day 5

APPENDIX III

Retroperitoneal Lymph Node Dissection (RPLND) Principles

RPLND provides critical staging information and must always be performed with a curative intent. Adequate exposure for RPLND can be achieved through either a thoraco-abdominal or a transabdominal approach. The bilateral infra hilar RPLND template has replaced the supra hilar dissection and is the standard against which therapeutic alternatives are judged. A bilateral infra hilar RPLND includes the pre-caval, retro-caval, paracaval, inter

aorto-caval, retro-aortic, pre-aortic, para-aortic, and common iliac lymph nodes bilaterally. Since the gonadal vessel itself or the adjacent tissue may harbor disease, the ipsilateral gonadal vein and surrounding fibro adipose tissue from its insertion to the internal ring must be completely excised to minimize the possibility of a late paracolic recurrence. The procedure is associated with a mortality rate of less than 1%, and major complications such as hemorrhage, ureteral injury, bowel obstruction, pulmonary embolus, and wound dehiscence are rare. Minor complications include lymphocele, atelectasis, wound infection, and prolonged ileus.

Modified RPLND templates maximize rates of ejaculation by limiting dissection in areas thought to be at reduced risk of metastatic spread based on surgical mapping studies. These templates do not identify specific nerve fibers, but should include resection of all inter aorto-caval and ipsilateral lymph nodes between the level of the renal vessels and the bifurcation of the common iliac artery. This approach minimizes contralateral dissection, thereby reducing trauma to the hypogastric plexus and contralateral postganglionic sympathetic fibers. Preservation of ante grade ejaculation with this approach ranges from 50% to80%.

Nerve-sparing technique scan be used in the primary or post chemotherapy setting. In a nerve-sparing RPLND, both sympathetic chains, the post ganglionic sympathetic fibers, and hypogastric plexus are prospectively identified, dissected, and preserved. With prospective nerve-sparing techniques, ante grade ejaculation is preserved in over 95%

of all patients. Therefore, the original value of templates to prevent loss of ejaculatory function is diminished. Whatever the approach, margins of resection should not be compromised in an attempt to preserve ejaculation.

WHAT HAS CHANGED IN TESTICULAR CANCER IN THE LAST DECADE

- Preferred treatment of stage I Seminoma is surveillance over Chemotherapy or Radiotherapy
- In High risk stage I NSGCT RCT has shown 1#BEP is comparable to 2#BEP
- Autologous versus second line chemotherapy in relapsed GCT results of RCT is ongoing.
- Safety of MRI over CT for repeated imaging during surveillance is under evaluation.
- miRNA biomarker has shown the potential to predict viable germ cell tumors in residual masses after chemotherapy in NSGCT
- The importance of Survivorship issues in testicular cancer is well recognized and being addressed in practice

SUGGESTED READING

1. Albers P, Bender H, Positron emission tomography in the clinical staging of patients with Stage I and II testicular germ cell tumors. Urology. 1999 Apr; 53(4):808-11.
2. Sperm on JR, De Geus-OeiL F, The role of (18) fluoro-2-deoxyglucose positron emission tomography in initial staging and re-staging after chemotherapy for testicular germ cell tumors. BJU Int. 2002Apr; 89 (6):549-56..

3. KregeS, Beyer J, SouchonR,EurUrol. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. 2008Mar; 53 (3):478-96.

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

5. Jones WG, Fossa SD. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on MedicalResearch Council Trial TE18, European Organization for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). JClinOncol. 2005 Feb 20; 23 (6):1200-

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

7. R. T. Oliver, G. M. Mead Radiotherapy versus carboplatin for stage I seminoma: Updated analysis of the MRC/EORTC randomized trial (ISRCTN27163214).JCiInOncol2005; 23:1200- 1208.

8. JohnP.Logue, MargaretA. Harris Shortcourse para-aortic radiation for Stage I Seminoma of the testis. Int. J RadiatOncolBiol Phys. 2003; 57:1304-1309.

9. FossaS.D.,HorwichA. Optimal Planning Target Volume for Stage I Testicular Seminoma: A Medical Research Council Randomized Trial, J ClinOncol. 1999; 17; 1146 -1154..

10. SchmidbergerH, Bamberg M. Treatment options in early-stage testicular seminoma. Review of the literature with initial results of a prospective multicenter study on

radiotherapy of clinical-stage I, IIA and IIB seminomas. StrahlentherOnkol. 1995 Mar; 171(3):12539.

11. P Warde, M Gospodarowicz. Management of stage II seminoma: JClinOncol.1998; 16:290- 294.
12. deWit R, RobertsJT, Wilkinson PM. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapyandofa3-or5-dayschedulein good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. JClinOncol. 2001 Mar 15; 19(6):1629-40.
13. LoehrerPJ Sr, Johnson D Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial: J ClinOncol. 1995 Feb; 13(2):470-6.
14. BajorinDF, SarosdyMF. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multi institutional study. JClinOncol. 1993 Apr; 11(4):598-606.
15. KondaguntaGV, BacikJ. Etoposide and cisplatin chemotherapy for metastatic good-risk germ cell tumors: J ClinOncol. 2005 Dec 20; 23(36):9290-4.
16. Becherer A, De Santis M. FDG PET is superior to CT in the prediction of viable tumor in post- chemotherapy seminoma residuals: EurJ Radiol. 2005May;54(2):284-8.
17. HS Puc, R Heelan. Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan- Kettering Cancer Center: J ClinOncol. 1998; 14:454-460.

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

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

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

21. Horwich A, SleijferDT. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic non seminomatous germ cell cancer: a Multi institutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial: JClinOncol. 1997May;15(5):1844-52.

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

23. JonesRH, VaseyPA. PARTII: Testicular cancer management of advanced disease. Lancet oncol2003;4:738-747.

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

25. KondaguntaGV, BacikJ, DonadioA, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors: J ClinOncol2005; 23:6549.

26. EinhornLH, Williams SD. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. New Engl J Med. 2007 Jul26;357(4):340-8.

27. Pectasides D, Pectasides M. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin- refractory germ cell tumors: a phase II study. Ann Oncol2004;15:493-497.

28. De Giorgi U, RostiG. Phase II study of oxaliplatinand gemcitabine salvage chemotherapy in patients with cisplatin- refractory non-seminomatous germ cell tumor: Eur Urol. 2006 Nov;50(5):1032-8; discussion 1038-9.

29. Wood DP Jr, Herr HW. Surgical resection of solitary metastases after chemotherapy in patients with non seminomatous germ cell tumors and elevated serum tumor markers. Cancer. 1992 Nov1; 70(9):2354-7.

30. Cullen M, Huddart R, Joffe J, Gardiner D, Maynard L, Hutton P, Mazhar D, Shamash J, Wheater M, White J, Goubar A, Porta N, Witts S, Lewis R, Hall E The 111 Study: A Single-arm, Phase 3 Trial Evaluating One Cycle of Bleomycin, Etoposide, and Cisplatin as Adjuvant Chemotherapy in High-risk, Stage 1 Nonseminomatous or Combined Germ Cell Tumours of the Testis.; 111 Trial Management Group.Eur Urol. 2019 Dec 19

31. Fankhauser CD, Grogg JB, Hayoz S, Wettstein MS, Dieckmann KP, Sulser T, Bode PK, Clarke NW, Beyer J, Hermanns T. Risk Factors and Treatment Outcomes of 1,375 Patients with Testicular Leydig Cell Tumors: Analysis of Published Case Series Data.J Urol. 2019 Dec 17

32. Rajpert-De Meyts E.Testicular germ cell cancer: recent developments in biology and clinical management. Andrology. 2019 Jul;7(4):391-393

33. Ruf CG, Borck S, Anheuser P, Matthies C, Nestler T, Zecha H, Isbarn H, Dieckmann KP.

34. Adjuvant carboplatin therapy in patients with clinical stage 1 testicular seminoma: is long-term morbidity increased?J Cancer Res Clin Oncol. 2019 Sep;145(9)

35. Corsi O, Rada G, Peña J.PET-CT for the management of testicular seminoma patients with post-chemotherapy residual masses.

Chapter 5

Penile Cancer

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1. EPIDEMIOLOGY

Penile cancer (PC) is an uncommon malignancy. It is seen most commonly in the 5th and 6th decade. In 3rd and 4th decade the incidence is < 7% and <14% respectively. In India, it accounts for approximately 1% of all male malignancies. Age-adjusted incidence is 0.7-2.3and 3/100,000 in urban and rural India respectively. High incidence is noted in Barshi, Chennai and Villupuram (3.1/100,000; Tamil Nadu) cancer registries. which have recorded up.

2. RISK FACTORS

PC arises from the epithelium of the prepuce or the glans. The risk factors with causal relation to invasive carcinoma have been brought out in several case-control studies. The highest risk factor is seen in those with Phimosis. The chronic infection associated with Phimosis is the factor leading to invasive cancer. The odd ratio mounts up to

11-16%. Smegma is not proven to be of carcinogenic potential. Other chronic infections like balanoposthitis are also associated with invasive carcinoma. Autoimmune conditions like Lichen sclerosis can also be attributed to the development of invasive carcinoma (not adverse histologigical features).

The treatment for psoriasis like psoralen and Ultraviolet A (UVA) phototherapy is also attributable factors. There is an exponential increase in the incidence with >250 treatments of UVA phototherapy. Smoking has been associated with a five-fold increase (CI 95% 2.0-10.1). Other lifestyle factors like multiple sexual partners, early age of first intercourse (3-5-fold increase) and unmarried cultures are associated with a higher incidence. Lower socioeconomic status and rural areas also have a higher incidence of penile cancers.

Circumcision

Neonatal circumcision has a protective effect with OR 0.41. The protective effect is weaker in circumcision without a history of phimosis, OR: 0.79. The lowest incidence of PC is seen in Israeli Jews (0.3/100,000/year) who routinely practice neonatal circumcision. The adult life circumcision does not have any protective effect. Also, circumcision does not seem to reduce the risk of PeIN (Penile intraepithelial neoplasia).

Human Papiloma Virus (Hpv) Infection

HPV infection is an important risk factor and viral DNA is identified in 70-100% of PeIN and 30-40% of invasive PC tissue samples. Commonest HPV subtypes: 16(72%), 6(9%)

and 18 (6%); multiple strains per sample are common. Rate of HPV-positivity differs between different histological subtypes. Commonly HPV associated subtypes are Basaloid (46%), papillary-basaloid, warty (39%), warty-basaloid (89%), clear cell, and lymphoepithelioma like carcinoma. Th ehistologies not known to be associated with HPV infection are usual squamous type, pseudohyperplastic, pseudo glandular, verrucous, papillary NOS, adenosquamous, sarcomatoid and carcinoma cuniculatum. The risk of PC is increased in patients with HPV & condyloma acuminate to 22.4% in verrucous squamous cell carcinoma and 6-66.3% in basaloid-warty types. HPV positivity is associated with better outcomes, where 5-year disease-specific survival is 93% vs 78% in negative. There is no definite association with cervical cancer and no general recommendation for vaccination is there currently.

Premalignant Conditions

PeIN or carcinoma in situ (CIS) are classified as Non-HPV-related (differentiated PeIN) and HPV related (undifferentiated PeIN). Other lesions which were previously called as Erythroplasia of Queyrat or Bowen's disease or Bowenoid papulosis are not used anymore as they have been renamed as PeIN. There are have reports that Lichen Sclerosis has a potential for sporadic conversion in invasive PC. Other premalignant lesions which have less common potential to convert into invasive carcinoma include Cutaneous horn of penis, Hyperkeratotic dysplasia, Giant condyloma (Bushke Lowenstein), Pseudo-epitheliomatous, Micaceous & Keratotic Balanitis, Leukoplakia and Balanitis Xerotica Obliterans.

3. PATHOLOGY

Squamous cell carcinoma (SCC) accounts for over 95% of penile malignancies. The table below shows the prognosis of various histologies and prognostic implication.

Table 1: Histological classification with prevalence

HISTOLOGY	% PREVALANCE
Good Prognosis	
Warty	7-10%
Papillary	5-15%
Verrucous	3-8%
pseudohyperplastic, carcinoma cuniculatum	<1%
Intermediate Prognosis	
Usual SCC	48-65%
Warty basaloid	9-14%
Mixed	9-10%
Poor Prognosis	
Sarcomatoid	1-3%
Clear cell	1-2%
Basaloid	4-10%
pseudoglandular, adenosquamous, mucoepidermoid	<1%

The Non-squamous type of malignant lesion is rare and include Melanocytic, mesenchymal, lymphomas, sarcomas & metastases. The penile metastases are frequently of prostatic, urothelial or colorectal origin.

4. GRADING

In penile cancer, grading has a prognostic significance. It is predictive of metastatic potential and hence it is included in TNM classification. However, grading is inherent with high inter-observer variation. It is recommended to use WHO specific grading.

Table 2: WHO Grading recommendations for penile SCC

Feature	Grade 1	Grade 2	Grade 3	Sarcomatoid
Cytological atypia	Mild	Moderate	Anaplasia	Sarcomatoid
Keratinisation	Usually abundant	Less prominent	May be present	Absent
Intercellular bridges	Prominent	Occasional	Few	Absent
Mitotic activity	Rare	Increased	Abundant	Abundant
Tumour margin	Pushing/ well	Infiltrative/ margin	Infiltrative/ margin	Infiltrative/ ill defined

Other poor prognostic factors include perineural invasion, lymph vascular invasion, greater depth of invasion, the extent of lymph node metastasis and extracapsular spread. The prognostic value of the involvement of distal urethra is controversial. The invasion of the more proximal urethra is usually seen in highly aggressive SCC and is associated with a poor prognosis.

5. DIAGNOSIS AND STAGING EVALUATION

Penile cancer can be cured in over 80% of cases if diagnosed early but it is a life-threatening disease when lymphatic metastasis occurs. Local treatment can be

mutilating and devastating for the patient's psychological well-being. Correct histological diagnosis and staging are essential for appropriate treatment of penile cancer.

5.1 Primary Tumour

Physical examination should precede histological confirmation. Usually presents as a clinically obvious lesion but it may be hidden under phimosis which may not be clinically evident. These patients might present upfront with inguinal node metastasis. Proper clinical examination is generally sufficient for local staging and planning therapy. The clinical description records must include Local site, size, morphology (papillary, flat, ulcerative or nodular), number, invasion of corpora, invasion of the urethra, the extent of induration in the shaft. Both groins should be assessed for lymph node status.

Ultrasound can be used for detecting the infiltration of the corpora. When coupled with Penile Doppler Ultrasound the staging accuracy increases drastically and has higher accuracy than an MRI in detecting corporal infiltration. Magnetic resonance imaging (MRI) with an artificially induced erection can also be used to exclude corporal invasion (sensitivity and specificity: 82.1% and 73.6%) and urethral invasion (sensitivity and specificity: 62.5% and 82.1%). The main disadvantage of using an MRI is the sustained erection which can be unpleasant to the patient.

Histopathological confirmation with the help of biopsy is mandatory. Confirmatory frozen section may be done before definitive surgical treatment. It is particularly helpful when there is a doubt regarding the nature of the lesion

(e.g. PeIN, metastasis or melanoma) or when when non-surgical treatment is planned with topical agents, radiotherapy or laser surgery. A punch biopsy is sufficient for superficial lesions while an excisional biopsy is generally preferable. When the size of biopsy is 0.1 cm then 91% times it is difficult to evaluate the depth of invasion. The grade may differ in up to 30% (mostly upgrading on a resected specimen) in these. The failure to detect cancer in 3.5% is seen. The vascular and lymphatic tumor emboli are detected in only 9-11%. Hence adequate tissue is recommended for optimal reporting.

5.2 Regional Lymph Nodes

Careful palpation of both groins must be included in initial physical examination.

If No Palpable Lymph Nodes (cN0)

25% likelihood for the micro-metastatic disease. Imaging is helpful in obese patients in whom palpation is unreliable. Otherwise imaging cannot detect micro-metastasis. The further management is guided by pathological risk factors of the primary tumor which include lymph vascular invasion, local stage and grade (predictive of lymphatic metastasis). Invasive lymph node staging is required in intermediate & high-risk patients. The existing literature and nomograms are not very accurate to guide regarding the management in N0 status.

Palpably Enlarged Lymph Nodes (cN+)

Highly indicative of lymph node metastases. During the physical examination, the total number of palpable nodes on each side and fixity to structures must be documented.

Fine-needle aspiration cytology also does not reliably exclude micro-metastatic disease and is not recommended. Prophylactic antibiotic course can delay and lead to delay management and disease progression.

In unreliable or doubtful clinical exam, ultrasonography with Inguinal Ultrasound (7.5 MHz) can be done. It detects abnormal, enlarged nodes with relatively high specificity using longitudinal/transverse diameter ratio and status of the lymph node hilum (absence). When inguinal nodes present, pelvic CT scan can be used to assess the pelvic lymph nodes. 18FDG-positron emission tomography (PET/CT) can detect lymph node metastases > 10 mm reliably with high sensitivity (88-100%) and specificity (98-100%) along with other sites of metastasis and may guide the plan of management. It is optional.

5.3 DISTANT METASTASIS

Patients with positive inguinal lymph nodes should be screened for distant metastasis. Abdominal and pelvic CT with chest X-ray is generally sufficient. Thoracic CT is more sensitive and can be done instead of chest X-ray. PET/CT is optional.

6. 2016 TNM CLINICAL AND PATHOLOGICAL CLASSIFICATION

The 2016 UICC TNM classification for penile cancer introduced some changes in comparison to previous editions. For penile cancer, unlike in other neoplasms, there is a subdivision of the T1 stage into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion and

grading. Corpora cavernosae involvement has been now included as pT3 stage (earlier edition staged it as pT2). Retroperitoneal lymph node metastases are classified as extra-regional nodal and, therefore, distant metastases.

Table 3: Penile Cancer staging TNM 2016 UICC

<table>
<tr><th colspan="2">T - Primary Tumour</th><th colspan="2">N - Regional Lymph Nodes</th></tr>
<tr><td>TX</td><td>Primary tumour cannot be assessed</td><td>Nx</td><td>Regional lymph nodes cannot be assessed</td></tr>
<tr><td>T0</td><td>No evidence of primary tumour</td><td>N0</td><td>No palpable or visibly enlarged inguinal lymph nodes</td></tr>
<tr><td>Tis</td><td>Carcinoma in situ</td><td>N1</td><td>Palpable mobile unilateral inguinal lymph node</td></tr>
<tr><td>Ta</td><td>Non-invasive verrucous carcinoma*</td><td>N2</td><td>Palpable mobile multiple or bilateral inguinal lymph nodes</td></tr>
<tr><td rowspan="2">T1</td><td rowspan="2">Tumour invades subepithelial connective tissue
T1a: Tumour invades subepithelial connective tissue without lympho-vascular invasion and is not poorly differentiated
T1b: Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated</td><td>N3</td><td>Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral</td></tr>
<tr><td colspan="2">M - Distant Metastasis</td></tr>
<tr><td>T2</td><td>Tumour invades corpus spongiosum with or without invasion of the urethra</td><td>M0</td><td>No distant metastasis</td></tr>
<tr><td>T3</td><td>Tumour invades corpus cavernosum with or without invasion of the urethra</td><td>M1</td><td>Distant metastasis</td></tr>
<tr><td>T4</td><td>Tumour invades other adjacent structures</td><td></td><td></td></tr>
</table>

pN - Regional Lymph Nodes		pM - Distant Metastasis	
pNX	Regional lymph nodes cannot be assessed	pM1	Distant metastasis microscopically confirmed
pN0	No regional lymph node metastasis	G - Histopathological Grading	
pN1	Metastasis in one or two inguinal lymph nodes	GX	Grade of differentiation cannot be assessed
pN2	Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes	G1	Well differentiated
		G2	Moderately differentiated
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral extranodal or extension of regional lymph node metastasis	G3	Poorly differentiated
		G4	Undifferentiated

7. TREATMENT

7.1 Primary Tumour

Patients should be counselled about all relevant treatment options. The modality of treating the primary site depends upon the T stage. The goal of treatment is maximal organ preservation without compromising oncological control. No RCT data are available for any of the organ preservation methods. All series suggest local recurrence has little influence on long-term survival, hence when feasible organ preservation should be attempted.

Advantage of surgical management is availability of adequate staging for the primary and nodes can be obtained. If surgical management is planned, then negative surgical margins must be obtained. If non-surgical management is planned, then histological diagnosis with

local staging must be obtained prior. Circumcision is advisable prior to any non-surgical methods intervention.

SUPERFICIAL NON-INVASIVE DISEASE (PeIN)

Non-surgical management includes topical chemotherapy with Imiquimod or 5-fluorouracil (5-FU). It is an effective first-line treatment. It is associated with significant inflammatory responses. The complete responses for PeIN is in the rates of 57% and for invasive cancer response rates are up to 74%. The disadvantage is the high persistence/ recurrence rates. Rx must be assessed by repeat biopsies over long-term surveillance. An insufficient response may signify underlying invasive disease. If topical treatment fails, it is not advisable to repeat it.

Laser treatment with Neodymium:yttrium-aluminium-garnet (Nd:YAG) laser or Carbon dioxide (CO2) laser can be offered. The advantage of CO2 laser is the enhanced photodynamic visualization. Rebiopsy for treatment control is mandatory.

The surgical management includes Glans resurfacing (total or partial) where complete removal of the glandular epithelium followed by reconstruction with a graft (split skin or buccal mucosa) is done. It can be a primary treatment for PeIN or a secondary option in case of failure of topical chemotherapy or laser therapy.

Invasive Disease Confined to The Glans (Category T1/T2)

General Principles

The treatment choice depends on the tumor size, histology, stage and grade, localization (especially relative to the

meatus) and patient preference. The foreskin tumors can be treated by 'radical circumcision' alone. The small and localized invasive lesions can be offered organ-sparing treatment. Small lesions can also be treated by laser therapy but in these cases, there is a risk of more invasive disease recurrence. For glans resurfacing Acetic acid, staining may be used to delineate abnormal areas.

The surgical options consist of local excision, partial glansectomy or total glansectomy with reconstruction. Local recurrences are more common with a partial amputation but it does not have any effect on overall survival. With respect to intraoperative margins, there is no clear evidence as to the required width of negative surgical margins. With organ preservation generally, 3-5mm can be considered as a safe maximum. A grade based differential approach can also be used where 3 mm for Grade 1, 5 mm for Grade 2 and 8 mm for Grade 3. Differentiated penile intraepithelial neoplasia, squamous hyperplasia and lichen sclerosis present at the surgical margins are frequent findings and are not relevant for cancer-specific survival.

External beam radiotherapy or brachytherapy are radiotherapeutic options which are available for organ preservation.

- Conservative, organ-sparing surgery improve quality of life (QoL).
- Local recurrence is more likely than after amputation surgery, but survival appears to be unaffected.
- Tumour grade, stage & lympho-vascular invasion are predictors of local recurrence. Treatment choice

depends on tumour size, histology, stage and grade, localisation (especially relative to the meatus) and patient preference.

- Small and localised invasive lesions should receive organ-sparing treatment.
- While using surgical intervention, negative surgical margins must be confirmed by histopathology. Treatment of the primary tumour and of the regional nodes can be done at the same time or as staged surgery. Ultimately, the modality of treatment of the primary depends on the T stage and compliance to follow up.
- Intra-operative frozen section & Margins (EAU guidelines) - A grade-based differentiated approach may also be used: 3 mm for grade one, 5 mm for grade two, and 8 mm for grade three.
- Surgical organ preserving treatments for T1/T2 diseases are laser treatment, Glans resurfacing, Moh's micrographic surgery and glansectomy. Alternatively, a partial penectomy may be performed. Results suggest that the local recurrence rates following penile preserving surgery are higher than with partial penectomy, although survival appears to be unaffected.
- Patients with local relapse after conservative surgery may be treated with repeat conservative surgery in cases of small, non-infiltrating relapse. However, a salvage partial or total penectomy is recommended if the relapse is large or deeply infiltrating.

Non Surgical Options

Laser Therapy

CO2 laser treatment: usually done in PeIN or T1 penile cancers. Combination with radiotherapy and chemotherapy has been shown to improve outcomes. Local recurrence seen for PeIN are 14% and 23% for T1 tumours. The secondary partial penectomy rate at ten years for PeIN & T1 are 3% and 10% respectively. The Inguinal nodal recurrence is 0-4%. No cancer-specific deaths were reported.

Nd: YAG laser treatment has been used as an alternative in many centers. The reported local recurrence ranges from 10-48% with inguinal nodal recurrence of 21%. The secondary partial penectomy rates are highly divergent between studies ranging from 4-45%. The cancer-specific mortality is reported between 2-9%. Potassium titanyl phosphate (KTP) laser has also been used in some patients.

Table 4: Laser treatment salient features

	CO2	**Nd:YAG**	**KTP**
Type	Gas	Solid-state	Solid-state
Wavelength	10.600nm	1064 nm	532 nm
Tissue penetration	0.1mm	3-4 mm	1-2 mm
Commonly used settings	Spot size1-5mm Power 5-10W Pulse cont or super pulse 100-200 Hz	Spot size1-5mm Power 40W Pulse 1 msec Pulse freq: 10-40 Hz	Fibre size: 400-600um Power 5-10W Pulse 10-2-ms Rep rate 2 Hz

Moh's micrographic surgery: is a historical technique, employed for the treatment of early penile cancers. The histological margins are taken geometrically around a conus of excision. The reported local and inguinal nodal recurrence rates are 32% and 8% respectively.

Glans resurfacing: is emerging as an oncological safe procedure where three studies have shown no cancer-specific deaths. The reported local recurrence rates are 0-6%. But, the nodal recurrence & complications rates are not reported.

Glansectomy: with circumcision for small lesions has a local recurrence of 2%. There are variable local recurrence rates reported in two large studies (7-8 % & 10-48%). The inguinal nodal and systemic recurrences rates are reported as 9-12.6% and 2.3% respectively.

Partial penectomy: Heterogeneous studies have been done in T1-T3 tumors with a follow up of 40-194 months. The local recurrence, cancer-specific mortality and 5 yr OS have been reported as 4-50%, 0-27% and 59-89% respectively.

- Treatment of T3 disease includes Glansectomy with distal corporectomy and reconstruction or partial amputation.
- Treatment of locally advanced T4 disease is Extensive partial amputation or total penectomy with perineal urethrostomy. For locally advanced and ulcerated cases, neoadjuvant chemotherapy may be an option. Otherwise, adjuvant chemotherapy or palliative radiotherapy are options.

- Partial penectomy is recommended when after adequate excision of the primary, the residual stump is adequate for upright micturition without scrotal soiling and for sexual intercourse.

Radiotherapy for primary tumor

Patient selection is of utmost importance for good outcomes. External beam or brachytherapy can be used separately or together. The type of radiotherapy best suited for a patient depends upon the tumour location, size, thickness and its proximity to the urethra. Radiotherapy is best suitable for T1-2 lesions and < 4 cm in diameter.

External radiotherapy has the advantage of universal applicability and can be used in all RT departments. Telecobalt gamma rays or 6MV photons from Linear accelerators can be used. A variety of fractionation schedules have been described, but the most commonly used prescription is 65-70Gy equivalent to primary (GTV) and 45-50.4 to high risk CTV. Specific complications of external beam radiotherapy include urethral stenosis (20-35%), Glans necrosis (10-20%) and Late fibrosis of the corpora cavernosa. At the Tata Memorial Hospital, we traditionally use hypofractionated accelerated regimen with 54Gy in 18 daily fractions over three weeks. The main advantage of a hypofractionated schedule is the completion of radiotherapy before the onset of the inevitable brisk radiation reaction. Usually, acute radiation mucocutaneous reaction over the glans and penile shaft heal after a median period of 6 weeks. Excellent local

control (60-70%) in early cancers without any late symptomatic sequelae have been reported.

Brachytherapy alone with equivalent dose can be tried. Different techniques of brachytherapy include external isotope mould, low dose rate, pulse dose rate or high dose. Brachytherapy offers the best results with Local control rates of 70-90%, Penile preservation rates of 70-80% and Overall penile conservation rates: 87% and 70% at five and ten years. The only limitation is the need for expertise in a penile brachytherapy procedure. The ABS & GEC-ESTRO consensus statement has reported good tumor control rates with acceptable morbidity and excellent functional organ preservation. Brachytherapy complications include Penile amputation for necrosis: 6.8%, Meatal stenosis: 6.6%, Dysuria: 5.3%, Pain with sexual intercourse: 2.6% Functional outcome are excellent with brachytherapy. In one report: 17⁄18 patients with normal erections before treatment maintained these after treatment.

The local recurrences after radiotherapy can be salvaged by surgery. In a surgery versus radiotherapy meta-analysis, 5-year OS, local control rates were 76 versus 73% and 84 versus 79% respectively. The organ preservation rate for brachytherapy were reported as 74%. The urethral neo meatal stenosis in post-surgery patients were reported to be 7-10%.

Invasive Disease Confined To The Glans With Or Without Urethral Involvement (T2)

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended. Partial amputation should be considered in patients unfit for reconstructive

surgery. Radiotherapy can also be given as an option in these patients.

Invading The Corpora Cavernosa And/Or Urethra (T3)

Standard Surgical Options include Glansectomy with distal corporectomy and reconstruction or Partial amputation with reconstruction.

Locally Advanced Disease Invading Adjacent Structures (T4)

These are the patients with poor prognosis. The standard advisable treatment is extensive partial amputation or total penectomy with perineal urethrostomy. In locally advanced and ulcerated cases, neoadjuvant chemotherapy may be an option. Otherwise, adjuvant chemotherapy, palliative chemotherapy or palliative radiotherapy are the options. Best supportive care may be offered when a patient is not suitable for any of the above options.

Local Recurrence After Organ-conserving Surgery

If there is no corpus cavernosum invasion, then a second organ-conserving procedure can be performed. In large or high-stage recurrence, partial or total amputation is required. Total phallic reconstruction may be offered. Best supportive care if not suitable for these options.

7.2 Lymph Nodes

Clinically Node-negative

Risk stratification for micro-metastatic inguinal lymph node depends on primary tumor stage, grade and

lymphovascular invasion. The overall classification is as below:

Table 5: risk stratification based on lymphnode involvement on histopathology

Risk Group	Description	Positive lymph nodes on histopathology
Low risk	pTa/pTis pT1 Well-differentiated G1 pT1	0%
Intermediate risk	pT1G2	25%
High risk	pT1G3 and all higher stage	42.2-100%

Management strategies include Bilateral lymphadenectomy versus radiotherapy versus surveillance with a 5-year OS of 74% vs 66% vs 63%.

Surveillance is only recommended in pTis/pTa tumours and appropriate caveats in low risk G1 pT1 tumors. Patients considering surveillance must be informed about this risk of opting for surveillance. Compliance is of paramount importance when surveillance is considered. If unreliable, then prophylactic modified inguinal lymphadenectomy must be offered. Early inguinal lymphadenectomy is superior for long-term patient survival when compared to lymphadenectomy at recurrence (90 vs 40%). Invasive nodal staging is recommended for pT1 tumours of intermediate and high-risk groups and all T2-T4 tumors. Fine-needle aspiration cytology is not recommended.

Standard Methods for histopathological diagnosis includes Dynamic sentinel-node biopsy (DSNB) which aims to detect affected sentinel nodes in both groins. Technetium-99m (99mTc) nano colloid is injected around the penile cancer site on the day before surgery often combined with patent blue. A Gamma-ray probe used intra-operatively to detect the sentinel nodes. A Meta-analysis of eighteen studies has shown a pooled sensitivity of 88% and improved to 90% with additional patent blue. The false-negative rate was 12-15%.

The 'sentinel' inguinal nodes are those first affected by lymphatic spread and appear to be located in the supero-medial zone followed by the central inguinal zones. This principle is exploited in invasive staging procedures. If lymph node metastasis is identified with any invasive staging procedure, an ipsilateral radical inguinal lymphadenectomy must be performed.

Modified inguinal lymphadenectomy (mILND) includes removal of medial superficial & central zone ILN bilaterally with preservation of greater saphenous vein. There is a lack of robust literature regarding the false-negative rate of mILND. Both methods may miss micro-metastatic disease, so if lymph node metastasis is found; then it is ideal to consider for Ipsilateral radical inguinal lymphadenectomy.

Superficial Inguinal Lymphadenectomy (SILD) - Performed via a 6-8 cm horizontal incision 1 cm inferior to the inguinal fold. In comparison with the MIL, this procedure involves excision of all the nodal basins superficial to the fascia lata from the adductor longus medially to the sartorius laterally. Like the MIL, the long saphenous vein is preserved.

Dynamic Sentinel Node Biopsy (DSNB) - Intradermal injection of radio-labelled Sulphur colloid on the day before surgery with lymphoscintigraphy and intradermal injection of patent blue dye just before surgery. A gamma probe is used during surgery to identify 'hot' nodes along with intra-op palpation of the inguinal region. All 'hot,' blue and palpable nodes are excised and submitted for frozen section examination. Serial sectioning and immune-histochemical staining of the nodes instead of routine paraffin sections. The role of ICG in detection of sentinel nodes is encouraging. DSNB has a significant learning curve and is promoted only in centers with a large volume of experience performing the procedure

Minimally Invasive Techniques - Video Endoscopic Inguinal Lymphadenectomy (VEIL) encompasses a laparoscopic performance of radical inguinal lymphadenectomy with the sacrifice of the great saphenous vein. A Robotic-Assisted VEIL (RAVEIL) has also been described. Because of a decrease in surgical morbidity, equivalent nodal yield, and comparable short-term oncologic outcomes, these endoscopic procedures have been widely accepted.

Management strategies based on risk assessment

- Low risk: Risk of occult lymph node metastases low and a surveillance strategy may be recommended if the patient can reliably follow up regularly. If the patient will not follow-up regularly, a prophylactic invasive staging procedure should be performed.
- Intermediate risk: A USG guided FNAC may be attempted if facilities are available. Positive FNAC warrants a complete ilio-inguinal lymph node dissection. Negative FNAC would require an invasive staging procedure (MILF/SILD/DSNB/VEIL).

High risk: Invasive staging procedure vs ilio-inguinal lymph node dissection.

Palpable Inguinal Nodes (CN1/CN2)

Uni/bilateral palpable inguinal lymph nodes (cN1/cN2) are highly suggestive of metastatic disease. Pelvic nodal staging includes CT or MRI. 18F-FDG-PET/CT can identify additional metastases. The dynamic sentinel-node biopsy is not indicated in clinically palpable nodes. If lymph nodes warrant surgical intervention, the pathologic assessment (by frozen section) and If positive then Radical inguinal lymphadenectomy can be performed. The notion that these may be inflammatory and so a trial of antibiotic treatment can be tried but generally not recommended. But it must be kept in mind that this principle is unfounded and it may be dangerous as it delays curative treatment. In clinically doubtful cases, US-guided fine-needle aspiration cytology may be an option.

Radical Inguinal Lymphadenectomy

The procedure involves clearing the superficial and deep inguinal nodal basins. Daseler's template is as follows - superiorly by a line joining the anterior superior iliac spine to the pubic tubercle, laterally a line 20 cm down perpendicular to the iliac spine, medially a line 15 cm down perpendicular to the pubic tubercle and inferiorly, a line joining these two points. It involves ligating the saphenous vein and baring the femoral vessels. Transposition of the Sartorius muscle is not recommended, and there is no benefit derived from using intraoperative fibrin glue.

It is a life-saving procedure and should not be underused for fear of associated morbidity. The transposition of the Sartorius muscle is not recommended. Also there is no benefit from using fibrin glue intraoperatively. Advanced cases may require reconstructive surgery for the wound closure.

There is associated significant morbidity of 25% with impaired lymph drainage from the legs and scrotum with increases by 50% with rising in body mass index (BMI). To minimize these complications techniques such as meticulous tissue handling, avoid electrocautery of lymphatic vessel walls (they do not contain smooth muscle) are recommended. Other strategies include, avoiding numerous metal clips as they may also cause post-operative problems, ligation of all lymphatic vessels while preserving the saphenous vein, improving postoperative measures to improve drainage like stockings, bandaging, inguinal pressure dressings or vacuum suction and prophylactic antibiotics.

The most commonly reported complications in recent series are wound infections (1.2-1.4%), skin necrosis (0.6-4.7%), lymphoedema (5-13.9%) and lymphocele formation (2.1-4%). Minimally-invasive surgical techniques (laparoscopic, robot-assisted) can be tried, but the evidence stems from small series only. It is suggested that they significantly reduce post-op morbidity except for the rate of lymphoceles.

Pelvic Lymphadenectomy

The indication for pelvic LND includes two or more positive ispilateral inguinal lymph node-positive (23% chance of

positive pelvic LN) and extracapsular lymph node extension in any node (56% chance of positive pelvic LN). Pelvic lymph node positivity is associated with a worse prognosis than only inguinal nodal metastasis with a five-year CSS of 71.0% vs 33.2%. It may be performed simultaneously with inguinal lymphadenectomy or as a secondary procedure. The unnecessary delay should be avoided when indicated bilateral pelvic dissection with a Midline suprapubic extra-peritoneal incision should be done.

Complications of surgery

- Wound infections
- Skin necrosis
- Lymphoedema
- Lymphocele formation

Complications may be as high as 25% in radical inguinal lymph node dissection, but this modality of therapy must not be underused for fear of associated morbidity. Post-operative problems arise due to impaired lymph drainage from the legs and scrotum and increase with increased body mass index (BMI). Advanced cases may require reconstructive surgery for wound closure. Morbidity may be minimized by

- Meticulous tissue handling
- Clip application and manual ligation of lymphatics as lymphatic vessel walls do not contain smooth muscle and are therefore not sealed by electrocautery
- Preserving the saphenous vein

- Implementing post-operative measures to improve lymphatic drainage such as the use of stockings, bandaging, inguinal pressure dressings or vacuum suction and prophylactic antibiotics

7.3 ADJUVANT TREATMENT

Radiation Therapy

In cN0 patients treated with radical radiotherapy, conventional radiotherapy portals for prophylactic groin have not been shown to be effective. It is also associated with local side effects and later difficult surgical salvage. With the advent of IMRT and CT based volume delineation and consistent immobilization along with image guided delivery, groin EBRT for cN0 may be used in T1/T2 intermediate or high-risk patients treated with radical brachytherapy. A prescription of 45-50.4 Gy equivalent conventional fractionation is suggested. In such situation, close monitoring is suggested for nodal recurrence and early surgical salvage.

In pN3 disease multimodal treatment can improve the patient outcomes. An improved loco-regional control also has an impact on survival. A dose of 45-54 Gy conventional fractionation radiotherapy is suggested to the bilateral groins. The ipsilateral pelvis is treated on the side of pN3 positivity. Concurrent chemotherapy with Cisplatin-based 40 mg/m2 weekly or equivalent is suggested whenever feasible. CT based contouring with IMRT planning, reproducible immobilization method and optimal IGRT should be performed to ensure good target coverage with the reduction in late side effects of post-surgical

radiotherapy. With the use of such techniques, DSS improved from 8 to 14.4 months (p=0.023). Studies have shown an OS decreased without adjuvant RT: HR: 1.7; 95% CI 1.01-2.92, p= 0.04 and DSS decreased without RT: HR 1.9; 95% CI, 1.09-3.36, p = 0.02.

Chemotherapy

Neoadjuvant chemotherapy can be considered in fixed or relapsed inguinal nodes and when complete surgical resection is unlikely. This allows for an early treatment of systemic disease and also the down-sizing of the inguinal lymph node metastases. In responders, complete surgical treatment is possible with a good clinical response. Commonly used Regimens are given in the table below.

Table 6: Commonly used NACT Regimen and response rates

Regimen	
TIP (Paclitaxel/ Ifosfamide and cisplatin	phase II trial with an objective response: 15/30 patients. 3 pCR. Estimated median time to progression (TTP: 8.1 months) and Median OS: 17.1 months
Bleomycin-vincristine-methotrexate (BVM) or bleomycin-metho-trexatecisplatin (BMP)	Treatment-related toxicity was unacceptable due to bleomycin-related mortality.
Cisplatin/5-FU (PF)	Response rate of 25-50% with more acceptable toxicity.
Irinotecan and cisplatin	3/26 patients of pathologically complete remissions (EORTC cancer study 30992).

(Contd...)

(Contd...)

Cisplatin and 5-FU plus a Taxane	Overall objective response rate: 44%; 14% pCR.
TPF with docetaxel	Objective response: 38.5% with Significant toxicity.

ADJUVANT CHEMOTHERAPY AFTER RADICAL LYMPHADENECTOMY

Can be considered in node-positive patients pN2-3. The evidence stems from a few small and heterogeneous series. Administration of the triple combination chemotherapy is suggested when feasible. Most commonly used regimens are given in the table below.

Table 7: Commonly used Adjuvant Chemotherapy Regimen and response rates

Regimen	
Vincristine, bleomycin, and methotrexate	Long-term (DFS) of 84% in 25 consecutive patients
Cisplatin /carboplatin plus paclitaxel	Ease of administration; Low toxicities
Cisplatin/5-FU (PF)	Lower toxicity and even better results compared to VBM
Cisplatin, 5-FU plus paclitaxel or docetaxel (TPF)	3-4 cycles after resection of pN2-3 disease. At 42 months, DFS: 52.6%; Good tolerability

Palliative Chemotherapy In Advanced And Relapsed Disease

Cisplatin/Carboplatin and taxane-based regimens are recommended. Independent prognostic factors include visceral metastases and 1 ECOG-performance status.

Oral metronomic chemotherapy agents also may be given.

Most commonly used regimens are

TIP:

- Paclitaxel: 175 mg/m2 iv over 3 hrs on D1
- Ifosamide 1200 mg/m2 iv over 2 hrs on D1-3
- Cisplatin 25 mg/m2 iv over 2 hrs on D1-3
- Repeat 3-4 weekly

5FU+Cisplatin

- Continuous infusion 5FU 800-1000 mg/m2 iv on Day 1-4 or D2-5
- Cisplatin 70-80 mg.m2 iv on D1
- Repeat 3-4 weekly

8. FOLLOW UP

Meticulous follow-up helps to assess the results and complications of the treatment. With Early or late, local and loco-regional recurrences chances of cure are greater in the first 2 years. First 2 years comprises of 74.3% of all recurrences, 66.4% of local recurrences, 86.1% of regional recurrences and 100% of distant recurrences. The first five years comprises of 92.2% of all recurrences. Penile conservation techniques increase the opportunity to

discuss their sexual problems. Patients should be taught and encouraged to do penile self-examination.

After local treatment with negative inguinal nodes, a thorough physical examination must be done on follow-up. Additional imaging has no proven benefit. USS groin may be done when groin cannot be assessed due to obesity. Histology from the glans should be obtained to confirm disease-free status following laser ablation or topical chemotherapy.

After potentially curative treatment for inguinal nodal metastases CT or MRI or PET CT imaging must be done for the detection of the systemic disease every 3 monthly for the first two years then 6 monthly till 5 years. Regular follow up can be stopped after five years, provided the patient understands the need to report any local changes immediately.

9. QUALITY OF LIFE

The consequences after penile cancer treatment include importantly sexual dysfunction. There is paucity in data for assessing sexual dysfunction and there is also heterogeneity in the available psychometric tools. Common tools used are Post-Operative International Index of Erectile Function (IIEF)-5,15, SF36 Health Survey and the Impact of Cancer questionnaire, Overall Sexual Functioning Questionnaire, Quality of Erection Questionnaire (QEQ), Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and Self-Esteem and Relationship (SEAR). Other problems include voiding problems, cosmetic penile appearance and lymphedema Care.

What has changed in Penile Cancer Over the Last Decade

1. The UICC TNM classification changes
2. Uncovering of association with HPV involvement
3. Emergence of FDG PET CECT for identifying metastatic disease in loco-regionally advanced cancer
4. Developments in surgical penile preservation and reconstruction strategies
5. Evolution of Dynamic sentinel node sampling
6. Improvement of radiotherapy technology in adjuvant setting
7. Increasing role of chemotherapy in adjuvant and metastatic setting.
8. More emphasis on quality of life score in survivors than ever before.

SUGGESTED READING

1. EUA guidelines and NCC Guideline on penile cancer 2019.
2. Chaux A, Netto GJ, Rodríguez IM, Barreto JE, Oertell J, Ocampos S, et al. Epidemiologic profile, sexual history, pathologic features, and human papillomavirus status of 103 patients with penile carcinoma. World J Urol. 2013;
3. Robinson R, Marconi L, MacPepple E, Hakenberg OW, Watkin N, Yuan Y, et al. Risks and Benefits of Adjuvant Radiotherapy After Inguinal Lymphadenectomy in Node-positive Penile Cancer: A Systematic Review by the European Association of Urology Penile Cancer Guidelines Panel. Vol. 74, European Urology. Elsevier B.V.; 2018. p. 76–83.

4. Hakenberg OW, Compérat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU guidelines on penile cancer: 2014 update. Eur Urol. 2015 Jan;67(1):142–50.

5. Ravi P, Pagliaro LC. Multimodal Therapy in the Management of Advanced Penile Cancer. Urol Clin North Am [Internet]. 2016 Nov;43(4):469–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27717433

6. Burnett AL. Penile preserving and reconstructive surgery in the management of penile cancer. Nat Rev Urol [Internet]. 2016 May;13(5):249–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27001013

7. Tward J. The case for nonsurgical therapy of nonmetastatic penile cancer. Nat Rev Urol [Internet]. 2018;15(9):574–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29950592

8. Fenner A. Penile cancer: Total glans resurfacing viable for all. Vol. 14, Nature Reviews Urology. Nature Publishing Group; 2017. p. 198.

9. Loughlin KR. Penile cancer sparing surgery: The balance between oncological cure and functional preservation. Urol Oncol [Internet]. 2018;36(4):153–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29306557

10. Downes MR. Review of in situ and invasive penile squamous cell carcinoma and associated non-neoplastic dermatological conditions. Vol. 68, Journal of Clinical Pathology. BMJ Publishing Group; 2015. p. 333–40.

11. Sanchez DF, Soares F, Alvarado-Cabrero I, Cañete S, Fernández-Nestosa MJ, Rodríguez IM, et al. Pathological factors, behavior, and histological prognostic risk groups in subtypes of penile squamous cell carcinomas (SCC). Semin Diagn Pathol. 2015 May;32(3):222–31.

12. Hölters S, Khalmurzaev O, Pryalukhin A, Loertzer P, Janssen M, Heinzelbecker J, et al. Challenging the prognostic impact of the new WHO and TNM classifications with special emphasis on HPV status in penile carcinoma. Virchows Arch. 2019 Aug;475(2):211–21.

13. Sanchez DF, Cañete S, Fernández-Nestosa MJ, Lezcano C, Rodríguez I, Barreto J, et al. HPV- and non-HPV-related subtypes of penile squamous cell carcinoma (SCC): Morphological features and differential diagnosis according to the new WHO classification (2015). Semin Diagn Pathol. 2015 May;32(3):198–221.

14. Cubilla AL, Velazquez EF, Amin MB, Epstein J, Berney DM, Corbishley CM. The World Health Organisation 2016 classification of penile carcinomas: a review and update from the International Society of Urological Pathology expert-driven recommendations. Vol. 72, Histopathology. Blackwell Publishing Ltd; 2018. p. 893–904.

15. Sahdev V, Albersen M, Christodoulidou M, Parnham A, Malone P, Nigam R, et al. Management of non-visualization following dynamic sentinel lymph node biopsy for squamous cell carcinoma of the penis. BJU Int. 2017 Apr;119(4):573–8.

16. Naumann CM, Colberg C, Jüptner M, Marx M, Zhao Y, Jiang P, et al. Evaluation of the diagnostic value of preoperative sentinel lymph node (SLN) imaging in penile carcinoma patients without palpable inguinal lymph nodes via single photon emission computed tomography/computed tomography (SPECT/CT) as compared to planar sci. Urol Oncol Semin Orig Investig. 2018 Mar;36(3):92.e17—92.e24.

17. O'Brien JS, Perera M, Manning T, Bozin M, Cabarkapa S, Chen E, et al. Penile Cancer: Contemporary Lymph Node Management. Vol. 197, Journal of Urology. Elsevier Inc.; 2017. p. 1387–95.

18. Leone A, Diorio GJ, Pettaway C, Master V, Spiess PE. Contemporary management of patients with penile cancer and lymph node metastasis. Vol. 14, Nature Reviews Urology. Nature Publishing Group; 2017. p. 335–47.

19. Crook J. Radiotherapy approaches for locally advanced penile cancer: Neoadjuvant and adjuvant. Vol. 27, Current Opinion in Urology. Lippincott Williams and Wilkins; 2017. p. 62–7.

20. Hakenberg OW, Compérat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU guidelines on penile cancer: 2014 update. Eur Urol. 2015 Jan;67(1):142–50.

21. Alkatout I, Naumann CM, Hedderich J, Hegele A, Bolenz C, Jünemann KP, et al. Squamous cell carcinoma of the penis: Predicting nodal metastases by histologic grade, pattern of invasion and clinical examination. Urol Oncol Semin Orig Investig. 2011;

22. Leijte JAP, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence Patterns of Squamous Cell Carcinoma of the Penis: Recommendations for Follow-Up Based on a Two-Centre Analysis of 700 Patients. Eur Urol. 2008;

23. de Crevoisier R, Slimane K, Sanfilippo N, Bossi A, Albano M, Dumas I, et al. Long-Term Results of Brachytherapy for Carcinoma of the Penis Confined to the Glans (N- or NX). Int J Radiat Oncol Biol Phys. 2009;

24. Azrif M, Logue JP, Swindell R, Cowan RA, Wylie JP, Livsey JE. External-beam Radiotherapy in T1-2 N0 Penile Carcinoma. Clin Oncol. 2006;

25. Kulkarni JN, Kamat MR. Prophylactic bilateral groin node dissection versus prophylactic radiotherapy and surveillance in patients with N0 and N(1-2A) carcinoma of the penis. Eur Urol. 1994;

26. Bermejo C, Busby JE, Spiess PE, Heller L, Pagliaro LC, Pettaway CA. Neoadjuvant Chemotherapy Followed by Aggressive Surgical Consolidation for Metastatic Penile Squamous Cell Carcinoma. J Urol. 2007;

27. Pizzocaro G, Nicolai N, Milani A. Taxanes in Combination with Cisplatin and Fluorouracil for Advanced Penile Cancer: Preliminary Results. Eur Urol. 2009;

28. Burt LM, Shrieve DC, Tward JD. Stage presentation, care patterns, and treatment outcomes for squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys. 2014;

29. Graafland NM, Moonen LMF, Van Boven HH, Van Werkhoven E, Kerst JM, Horenblas S. Inguinal recurrence following therapeutic lymphadenectomy for node positive penile carcinoma: Outcome and implications for management. J Urol. 2011;

30. Romero FR, Richter Pereira Dos Santos Romero K, De Mattos MAE, Camargo Garcia CR, De Carvalho Fernandes R, Cardenuto Perez MD. Sexual function after partial penectomy for penile cancer. Urology. 2005;

31. Sarin R, Norman AR, Steel GG, Horwich A. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys. 1997;

32. Noronha V, Patil V, Ostwal V, Tongaonkar H, Bakshi G, Prabhash K. Role of paclitaxel and platinum-based adjuvant chemotherapy in high-risk penile cancer. Urol Ann. 2012;

33. J.M. C, C. H-M, D.J. D, J.-J. M, A.A. M, M.J. R, et al. American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. Brachytherapy. 2013;

CHAPTER 6

Upper Tract Urothelial Cancer

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1. INTRODUCTION:

Upper tract urothelial carcinoma (UTUC) include the neoplasms arising from the lining of the urinary tract anywhere between the renal calyces to the distal ureter. UTUC share some similarities with urothelial carcinoma bladder; however, they tend to be rare and more advanced at the time of presentation. Radical Nephroureterectomy (RNU) with excision of the bladder cuff remains the gold standard treatment. Role of perioperative chemotherapy and nephron sparing approaches are area with evolving evidence.

2. INCIDENCE AND EPIDEMIOLOGY:

Tumors of the upper urinary tract are seen in men nearly twice as frequently as in women with the peak incidence at 75 to 79 years. Nearly all cases of urothelial carcinoma

are urinary bladder cancers, whereas UTUC accounts for just 5–10% of all urothelial malignancies. However, ~60% of UTUCs are invasive at diagnosis, compared with only 15–25% of bladder tumours. The most common location for this tumor is the renal pelvis. Ureteral tumors are located most commonly in the lower ureter and least commonly in the upper ureter. Incidence based on location is as follows: distal ureter in 70%, mid ureter in 25% and then proximal ureter in 5%. Concurrent bladder cancer is seen in 17% of UTUC cases. Recurrence of disease in the bladder occurs in 22-47% of the cases, whereas recurrence in the contralateral upper tract is found in 2-6%. Indian data on the epidemiology of this cancer is lacking.

Many environmental and genetic factors contribute to the development of UTUC.

Environmental factors:

The relative risk for developing UTUC among smokers was reported to be 2.5- to 7-fold higher than that for nonsmokers.

Balkan endemic nephropathy, a degenerative interstitial nephropathy, observed in individuals living in Balkan countries (i.e. Bulgaria, Greece, Romania, the former Yugoslavia), dietary exposure to aristolochic acid, derived from Aristolochia plants are the responsible carcinogen. A similar association with consumption of Chinese herbal products containing Aristolochia fangchi and Chinese herb nephropathy was postulated. Both diseases are associated with the development of UTUC. Surprisingly, the bladder cancer incidence is not affected. They are characterized

by a mutation of the p53 gene as a consequence of exposure to aristolochic acid.

Unusually high incidence of UTUC has been reported from the endemic area for "blackfoot disease", a type of vasculitis of southern Taiwan due to the arsenic-contaminated water. Phenacetin use with papillary necrosis has also been recognized as a risk factor for UTUC. Hence the use of phenacetin was progressively abandoned in the 1980s and replaced by acetaminophen.

Genetic factors:

Patients with HNPCC (Hereditary nonpolyposis colorectal carcinoma; Lynch syndrome) have abnormalities in DNA mismatch repair. These abnormalities are classically associated with colorectal and endometrial tumors. Approximately 22-fold increased relative risk of developing UTUC has been found in these patients.

3. CLINICAL PRESENTATION:

The common presenting features of UTUC are gross or microscopic hematuria (56-98%), flank pain (20-40%) and lumbar mass (10-20%). However, in about 15% of patients, UTUC is incidentally detected.

4. EVALUATION AND WORK-UP

A. Imaging:

i) Ultrasonography(USG): The sensitivity of detecting renal pelvis carcinoma using USG is moderate (82%) but can be as low as 12% for ureteric tumors.

However, USG can often identify secondary signs caused by ureteric tumors such as hydronephrosis and hydroureter.

ii) Computerized tomography (CT): Multiphasic CT-urography yields the highest diagnostic accuracy for UTUC with a sensitivity ranging from 67% to 100% and specificity of 93% to 99%. It can also detect urolithiasis and small renal masses; hence it has become the primary investigation for patients presenting with haematuria; however, flat ureteric lesions can be difficult to identify on CT unless there is associated wall thickening and peri-ureteric fat stranding.

iii) Magnetic Resonance Imaging (MRI): MRI is indicated in patients who cannot undergo CT due to contraindications related to radiation or iodinated contrast media. Reported sensitivity for this imaging modality is 75% after contrast administration for tumors < 2 cm. It is unreliable in detecting urolithiasis, which limits its use as the primary investigation for haematuria. As with CT, it can also miss flat or small tumours due to motion artefacts.

B. Endoscopy:

Clinicians should have a high index of suspicion for UTUC when cystoscopy is normal with positive urine cytology. In such a scenario, selective ureteric catheterization followed by barbotage or brushing is performed. The sensitivity of ureteral washing and brushing in detecting UTUC is 80% and 90% respectively. Additionally, Retrograde ureterography

(RGU) can help to identify any filling defects, often known as the "goblet sign". Selective collection of urine samples should be done before RGU, as high-osmolar contrast agents may alter the cytologic features.

Recent improvement in endoscopic technology, including better optics and finer flexible ureteroscopes with active deflection, is allowing routine visual surveillance of the entire urinary tract, and biopsy of the suspected lesions. The specificity of ureteroscopic-guided biopsy for determining tumour grade is between 75% and 92%. However, it is difficult to assess the depth of tumour invasion and further staging.

C. Tumor markers:

Urinary cytology for UTUC is generally less sensitive than it is for urothelial carcinoma of the bladder. However, ureteric washings improve the diagnostic yield. Fluorescence in situ hybridization (FISH) appears to be more sensitive than urinary cytology and have equal specificity in detecting UTUC. The Nuclear matrix protein (NMP22) test has higher sensitivity but lower specificity than urinary cytology.

D. Pathology:

The UTUCs can manifest as non-invasive papillary tumours, flat lesions (carcinoma in situ; CIS) and invasive carcinoma. On histologic examination, these lesions are similar to urothelial carcinoma of the bladder, but the relative thinness of the muscle layer

of the renal pelvis and ureter makes invasion through the muscle coat an earlier event. 2004 WHO grading distinguished three types of non-invasive neoplasms: papillary urothelial neoplasia of low malignant potential (PUNLMP), low-grade carcinomas, and high-grade carcinomas. This classification excludes urothelial papillomas, which are completely benign.

Reported variants of urothelial carcinoma are squamous cell, glandular, sarcomatoid, micropapillary, neuroendocrine & lymphoepithelial and can be seen in as high as 25% of UTUCs. These variants are considered to be relatively aggressive tumors.

The TNM classification 2017 is the presently used standard staging system. Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue (pT3b).

E. Genetic counselling:

HNPCC (Lynch syndrome) must be suspected in patients of upper tract urothelial carcinoma with younger age at presentation, either a person or family history of HNPCC spectrum of disorders. These patients subsequently should undergo germline DNA sequencing to confirm the diagnosis. Once HNPCC syndrome is diagnosed, the key to management is good surveillance to prevent disease recurrence as well as a screening of first-degree relatives for the HNPCC spectrum of diseases.

Table I - TNM classification 2017 for upper tract urothelial cell carcinoma:	
T -	**Primary tumour:**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N -	**Regional lymph nodes:**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M -	**Distant metastasis**
M0	No distant metastasis
M1	Distant metastasis

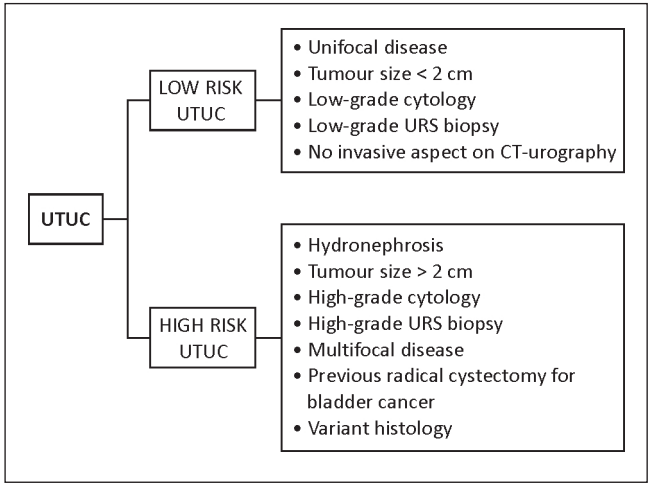
TNM = Tumour, Node, Metastasis (classification)

5. PRINCIPLES OF MANAGEMENT

The treatment of upper tract urothelial tumors has undergone significant changes recently. Various perioperative prognostic factors have been identified to guide therapy and predict survival outcomes. Previously treatment recommendations were based on practical limitations in follow-up and detection of local disease recurrence. Technologic improvements in imaging and endoscopic visualization of the urinary tract have not only allowed earlier and accurate diagnosis but also improved follow-up.

Treatment is primarily based on the risk stratification of the tumor. Treatment of low-risk non-invasive UTUC consists of conservative nephron-sparing surgery (e.g. endoscopic treatments, segmental resection) and adjuvant topical therapies (e.g., mitomycin C). Retrograde ureteroscopy and ureteropyeloscopy are preferred when tumor size, number, location and access allow complete tumor ablation. The percutaneous antegrade approach is chosen when the location and tumour characteristics do not allow complete ablation through a retrograde approach. Treatment of localized high-risk disease is radical nephroureterectomy. As most upper tract urothelial tumors are not large or bulky, laparoscopic surgery is preferred, at least for the renal portion of radical nephroureterectomy. A variety of approaches with various combinations of laparoscopic, open, robotic and sometimes endoscopic techniques are used for distal ureterectomy with bladder cuff excision. A comprehensive number of studies have examined the role of perioperative

chemotherapy for UTUC, and it appears to have benefit in overall survival and disease-free survival for cisplatin-based chemotherapy. Radiotherapy has no role as adjuvant treatment alone or as an adjunct to chemotherapy.



Risk stratification of upper urinary tract urothelial carcinoma

6. SURGICAL MANAGEMENT

Radical nephroureterectomy

Radical Nephroureterectomy (RNU) is the gold standard treatment for UTUC as it meets all conditions required for successful oncological surgery: excision of the entire tumor with an adequate surgical margin, control of local recurrence, and evaluation/control of the anatomical

spread of the tumor. Resection of the distal most intramural extent of the ureter, including its orifice, and a small circumferential cuff of bladder has been deemed beneficial because it is the part of the urinary tract at considerable risk of tumor recurrence. Various techniques have been described for resection of the distal ureter and bladder cuff excision. Except for ureteral stripping, these techniques are equivalent for excision of the bladder cuff.

Guidelines Recommends RNU if any of the following are present:

- Suspicious imaging findings suggesting infiltrating UTUC.
- High-grade tumor, as demonstrated by urinary cytology and/or biopsy.
- Multifocality with two functional kidneys.
- Large tumors (i.e. > 2cm).
- Variant histology.

Techniques for Resection of the Distal Ureter and Bladder Cuff Excision

1. Open Technique
2. Transurethral Resection of the Ureteral Orifice "Pluck" technique
3. Intussusception (Stripping) Technique
4. Transvesical Ligation and Detachment Technique
5. Total Laparoscopic technique

Adrenalectomy:

Ipsilateral adrenalectomy is performed with RNU if there is adrenal metastasis or direct invasion by renal pelvic tumors. Huang et al evaluated the role of adrenalectomy with localized UTUC treated by nephroureterectomy. There was no significant difference in 5-year survival, metastasis-free survival, or cancer-free survival between the two groups.

Lymphadenectomy:

Lymph node metastases and extranodal extension are proven to be powerful predictors of survival outcomes in UTUC. Lymph node dissection (LND) during RNU helps in optimal tumour staging; however its therapeutic role still remains a subject of debate.

Standard template of regional lymphadenectomy for renal pelvis and proximal or middle ureteral tumors includes the ipsilateral renal hilar nodes and the adjacent para-aortic or paracaval nodes. For distal ureteral tumors, pelvic nodes are dissected.

Kondo and Tanabe proposed an extended lymphadenectomy template based on the tumor location. For tumors of the renal pelvis this includes ipsilateral hilar, paracaval, retrocaval, and interaortocaval nodes up to the level of the inferior mesenteric artery for right-sided tumors, and ipsilateral hilar and para-aortic nodes up to the level of the inferior mesenteric artery for left-sided tumors. For tumors of the upper two thirds of the ureter, the distal border of dissection is extended to the level of aortic bifurcation. The template for lower third of the

ureteric tumors include ipsilateral obturator, internal, external, and common iliac, and presacral nodes.

Multiple series reported that oncologic outcomes for patients with pN0 are better than pNx, and worse for pN+ compared with pNx groups. . Lymph node dissection seems to be needless in cases of TaT1 UTUC; as Lymph node retrieval is reported in just 2.2% of T1 vs. 16 % of pT2–4 tumours. In summary, as in bladder cancer, lymphadenectomy appears to have prognostic and therapeutic value in patients with invasive disease (T2 to T4), and extended lymphadenectomy is beneficial for accurate staging.

Open vs Laparoscopic vs Robotic assisted RNU:

Open RNU with bladder cuff excision and extended lymph node dissection is the gold standard procedure for high-risk UTUC, regardless of the tumour location.

Recent meta-analysis by Liu et al on the efficacy and safety of laparoscopic RNU and open RNU for the treatment of UTUC reported that laparoscopic RNU was associated with longer operation time, shorter hospital stay and less blood loss. The occurrence of complications was similar between laparoscopic and open procedures. Most importantly, there was no significant difference in survival outcomes. Few cases of retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported. However, adhering to the strict oncological principles, Laparoscopic RNU is safe in experienced hands.Robot-assisted RNU has

demonstrated promising early results. Both single and double docking configurations are feasible depending on site of disease, generation of Robot and surgeon expertise. Even though intermediate outcomes and analyses have shown oncological equivalency when compared to other approaches, long term reports are still lacking.

Several precautions are recommended to lower the risk of tumour spillage during minimal invasive surgery, such as avoiding entering the urinary tract or direct contact between instruments and the tumour, avoiding morcellation of the tumour, use an endobag to retrieve en bloc specimen of Nephroureterectomy specimen with the bladder cuff. Outcomes of minimally invasive procedures are relatively poorer for invasive or large (T3/T4 and/or N+/M+) tumours when compared to an open approach. In summary, open, laparoscopic and robotic approaches have shown equivalent efficacy and safety in T1–2/N0 disease.

Adjuvant bladder instillation:

The rate of bladder recurrence after RNU for UTUC is 22–47%. Randomized trials and a metanalysis have shown that one post-operative dose of intravesical therapy (mitomycin C) shortly after surgery reduces the chance of bladder tumor recurrence.

Conservative surgery:

The conservative treatment for UTUC includes various segmental resections via endoscopic, open, or laparoscopic techniques.

Indications to Consider Conservative Management of UTUC

- Unifocal tumor
- Tumor size less than 2 cm
- Cytology or biopsy proven low grade
- Non- infiltrative lesion on CTU
- Patient understanding of close follow-up
- Inadequate renal reserve (chronic renal impairment or solitary kidney)
- Risk of bilateral disease (e.g. genetic, balkan nephropathy)
- Significant comorbidity
- Palliation

The conservative management of UTUC are as follows:

- Ureteroscopic management
- Percutaneous approach
- Ureteroureterostomy with wide margins indicated for:
  - Ta low grade tumors of the upper two third ureter that precludes its removal by endoscopic means.
  - high-grade or invasive tumors when preservation of renal function is imperative.
- Distal ureterectomy and neocystostomy with wide margins is indicated in tumours in the distal ureter that cannot be removed completely by endoscopic measure.

Ureteroscopic management :

Initially used for diagnostic purposes, ureteroscopy (URS) is now a common therapeutic modality. A flexible ureteroscope deflection angle of up to 270 degrees can be used for tumours difficult to access in the upper ureter or in the renal pelvis. Holmium or neodymium:yttrium-aluminium-garnet lasers are most frequently used for tumour ablation.

Advantages of the Ureteroscopic approach include:

- Preservation of renal function
- Reduced morbidity
- Shorter hospital stay
- Avoiding over-treatment for low grade non-invasive disease

Disadvantages of the Ureteroscopic approach include:

- Inability to treat larger tumours in one session
- Difficulty accessing upper ureteric or lower calyx tumours
- Under-staging tumours

Risks of Ureteroscopic Treatment include:

- Ureteric perforation or avulsion causing extraluminal tumour spillage.

- Ureteric strictures
- Residual disease.
- Subsequent tumour upstaging and progression requiring RNU

The outcomes of the ureteroscopic approach are dependent on the grade of the disease. The DSS outcomes for Grade 1 disease in suitable candidates when treated endoscopically were similar to those of laparoscopic nephroureterectomy.

Percutaneous management

Percutaneous access to the collecting system is used to treat larger tumours in the renal pelvis or proximal ureter and tumours not accessible via the retrograde ureteroscopic approach. Also, in patients who have had a previous cystectomy for bladder carcinoma with urinary diversion with upper tract recurrence.

Although more invasive, the outcomes of percutaneous surgery are similar to ureteroscopic treatment. The percutaneous approach is being used less frequently now with technological advances and the development of flexible ureteroscopes with increased active deflection.

Advantages of the Percutaneous approach include:

- Better visualisation
- Access to any location in the collecting system
- Treatment of large tumours in one session

- Deeper biopsies for accurate staging.
- Adjuvant treatment can be administered through the nephrostomy tube left in the collecting system at the end of the procedure.
- The same tract can be used for repeated procedures

Complications & Risks of the Percutaneous approach include:

- Bleeding requiring blood transfusions
- Obstruction of the pelvi-ureteric junction from stricture
- Surrounding organ and pleural injury.
- Risk of tumour cell seeding along the tract due to the disruption of the collecting system to gain entry.

Adjuvant therapy following endoscopic treatment:

Mitomycin-C (MMC) and bacillus Calmette-Guérin (BCG) is administered intravesically to patients with non-muscle invasive bladder urothelial carcinoma to prevent disease recurrence and progression. One might, therefore, expect similar results in the context of UTUC. However, given the lack of randomised controlled trials, there is limited evidence supporting the use of those agents.

Adjuvant topical therapy such as MMC and BCG can be delivered retrogradely through a ureteric catheter following ureteroscopic tumour ablation, anterogradely through a nephrostomy tube or by reflux up an indwelling ureteric stent. It is difficult to isolate the agents in the

upper urinary tract and there is currently no clear guidance regarding the dosage, frequency of instillation or instillation time in the management of UTUCs.

Mitomycin gel:

OLYMPUS (Optimized DeLivery of Mitomycin for Primary UTUC Study) is a pivotal, open-label, single-arm phase III clinical trial of UGN-101 (investigational formulation of mitomycin gel) in patients with endoscopically unresectable, low-grade upper tract urothelial cancer. The trial enrolled 71 patients at clinical sites across the United States and Israel. Participants were treated with six weekly instillations of mitomycin gel administered via a standard catheter. Four to six weeks following the last instillation, patients underwent a primary disease evaluation to determine response mitomycin and who achieved a complete response were then followed for up to 12 months to determine the durability of disease control. Results showed that instillation of mitomycin gel, produced a 60% (41 of 71 patients) complete response. Among the patients who achieved a complete response, three have relapsed during follow-up and two of these patients were considered unresectable. The authors concluded that a minimally invasive chemoablation approach utilizing mitomycin gel in this population results in a high rate of initial disease eradication, obviating the need for kidney removal in nearly half of treated individuals. A follow-up to ascertain the durability of complete response in this population is ongoing.

7. MEDICAL MANAGEMENT

Neoadjuvant chemotherapy :

RATIONALE OF NEOADJUVANT CHEMOTHERAPY

1. Able to tolerate chemotherapy with two functioning kidneys prior to RNU.
2. Pathological downstaging gives clinicians important prognostication information.
3. Level I evidence from urothelial carcinoma of the bladder recommending neoadjuvant chemotherapy prior to radical cystectomy.

Disadvantages of Neoadjuvant Chemotherapy

1. A delay to definitive surgical management, particularly in chemo resistant disease.
2. Increase in perioperative morbidity.
3. Overtreatment in patients who may simply have low-risk disease.

There are phase 2 trials assessing the role of different neoadjuvant chemotherapeutic regimens evaluating high-grade UTUC, with early results showing 60%–75% pathological downstaging rates. A recent retrospective study found that the patients who underwent neoadjuvant chemo-therapy had significantly longer 5-year overall survival (44% vs 29%) compared who had surgery alone, with an adjusted hazard ratio (HR) of 0.47 (95% CI 0.22 to 0.99, p=0.047).

Adjuvant chemotherapy :

The evidence supporting adjuvant chemotherapy comes from a meta-analysis of nine retrospective cohort studies, showing an overall survival benefit favouring the former, with an HR of 0.43 (95% CI 0.21 to 0.89, p=0.023) and a disease-free survival benefit with a pooled HR of 0.49 (95% CI 0.24 to 0.99, p=0.048). If any adjuvant chemotherapy is being considered for patients with UTUC the regimen of choice should be cisplatin-based. In terms of what specific cisplatin-based regimen is recommended, a recent multi-institutional study found that those who received adjuvant meth-otrexate, vinblastine, doxorubicin, cisplatin had favourable recurrence-free survival rates compared with those who received gemcitabine and cisplatin (71.4% vs 48.2%, p=0.022).

POUT is a phase III Randomized Trial of Peri-Operative Chemotherapy Versus Surveillance in Upper Tract Urothelial Cancer which addressed whether adjuvant chemotherapy improves disease-free survival (DFS) for patients with histologically confirmed pT2-T4 N0-3 M0 UTUC. There were 129 patients randomized to surveillance and 131 to chemotherapy at 57 UK centres. After a median follow-up of 17.6 months, a significant difference in DFS (HR 0.49, CI 0.31-0.76, p=0.001) favoring the chemotherapy arm was observed. At 2-years, this translated to a difference of 17% absolute difference in recurrence-free survival. Recruitment to the trial was terminated early because of efficacy favouring the chemotherapy arm.

Advantages of Adjuvant Chemotherapy include:

- The availability of accurate postoperative pathological staging in order not to overtreat non-invasive disease.
- Eradication of any subclinical micro metastases in order to maximise a patient's survival.

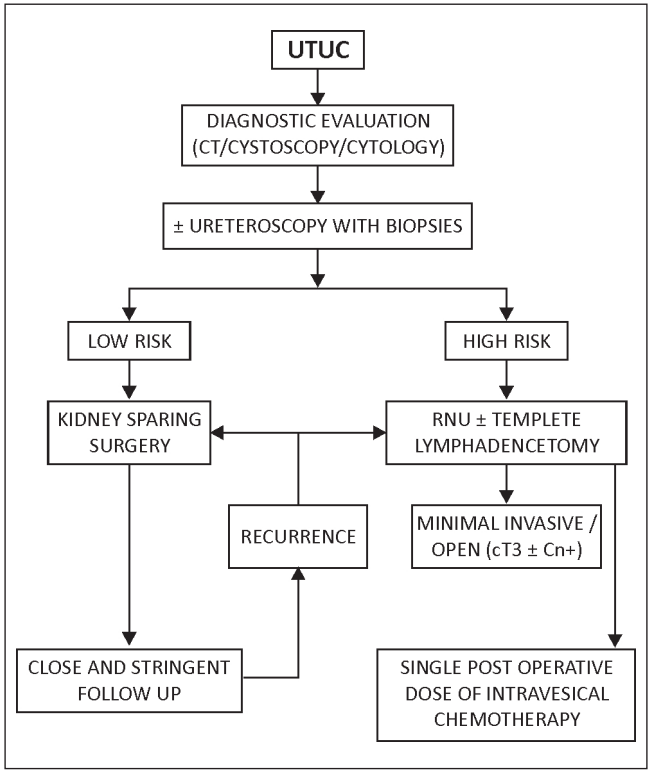
Disadvantages of Adjuvant Chemotherapy include:

- Subjecting patients to potentially nephrotoxic chemotherapy after removal of one kidney

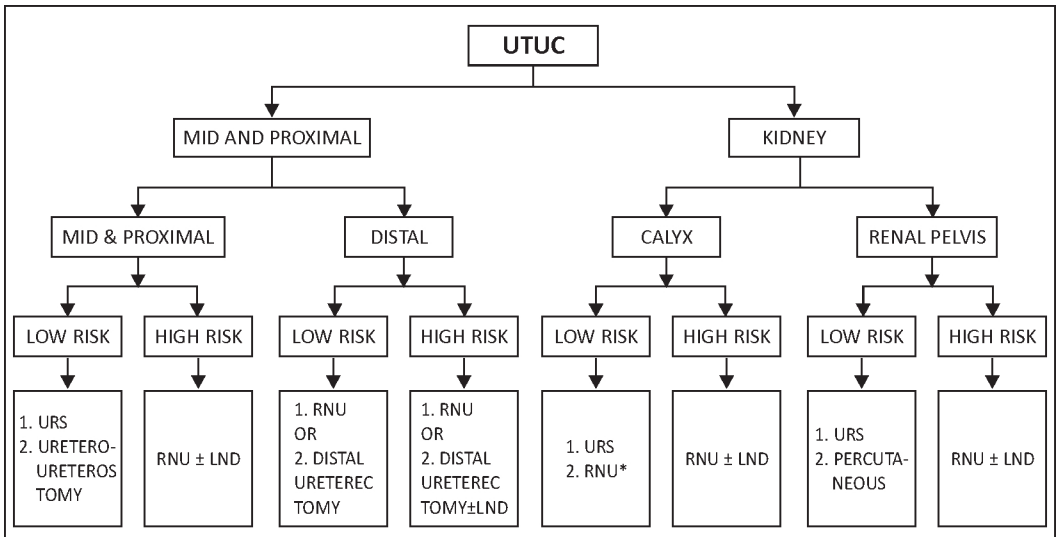
8. RADIATION MANAGEMENT

The rationale for focal radiation therapy (RT) is to decrease the risk of local relapse after radical surgery for locally advanced non–organ-confined disease (stage T3 to T4, N+). The role of radiation in adjuvant management of UTUC is poorly defined, with few retrospective non-randomized trials addressing this topic. A study evaluated clinical outcomes in patients with stage III/IV UTUC. 3-year locoregional recurrence-free survival rates were 89% vs. 61% respectively in the RT vs. non-RT groups (P = 0.01). The improved overall survival for patients receiving adjuvant chemoradiation following RNU vs. chemotherapy and salvage radiation therapy was demonstrated by another study by Fan et al. Adjuvant radiation without chemotherapy for high-stage disease does not protect against a high rate of distant failure. There may be a role for combined radiation-chemotherapy regimens in patients with advanced disease with adverse features; however, the current evidence supporting this is small and retrospective in nature.

9. STAGE WISE MANAGEMENT ALGORITHMS



Algorithm for the Management of Upper Urinary Tract Urothelial Cell Carcinom



Surgical Treatment According to Location and Risk Status

*In case not amendable to endoscopic management.
1 = first treatment option; 2 = secondary treatment option.

10. STAGE WISE PROGNOSIS WITH CURRENT TREATMENT

STAGE	5 YEAR SURVIVAL
I	> 90 %
II	73 %
III	41 %
IV	< 20%

11. MANAGEMENT OF RECURRENT DISEASE INCLUDING SPECIFIC PALLIATIVE MEASURES

The RNU alone in patients with metastatic UTUC except for palliative considerations have no oncological benefit. There is an overall survival benefit to combine chemotherapy and RNU vs. chemotherapy alone in a select cohort of patients fit enough to receive systemic chemotherapy for metastatic UTUC. Second-line treatment in metastatic UTUC remains a challenge but in recent trials new immunotherapeutic drugs (PD1 inhibitors) have demonstrated a response in a proportion of patients with UTUCs.

WHAT HAS CHANGED IN UPPER TRACT UROTHELIAL CARCINOMA IN THE LAST DECADE

- Recent improvement in endoscopic technology have helped in better diagnosis, conservative management and surveillance
- Risk stratification for selecting patients for conservative management

- Role of perioperative chemotherapy has stronger evidence and it appears to have benefit in overall survival and disease-free survival
- Robotic surgery can be considered while performing nephroureterectomy
- Peri-operative single dose of intravesical therapy shortly after nephroureterectomy has shown reductionin bladder tumor recurrence

SUGGESTED READING:

1. Abbott JE, Cicic A, DiMatteo AD, et al. Contemporary management and trends in the treatment of upper tract urothelial carcinoma. World J Nephrol Urol 2015; 4: 189–200.
2. Miyazaki J, Nishiyama H. Epidemiology of urothelial carcinoma. Int J Urol. 2017 Oct;24(10):730-734.
3. Azemar MD, Comperat E, Richard F, Cussenot O, Rouprêt M. Bladder recurrence after surgery for upper urinary tract urothelial cell carcinoma: frequency, risk factors, and surveillance. Urol Oncol 2011;29: 130-136.
4. Colin P, Koenig P, Ouzzane A et al. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. BJU Int. 2009; 104: 1436–40.
5. Gokmen MR, Cosyns JP, Arlt VM et al. The epidemiology, diagnosis, and management of aristolochic acid nephropathy: a narrative review. Ann. Intern. Med. 2013; 158: 469–77.
6. Tan LB, Chen KT, Guo HR. Clinical and epidemiological features of patients with genitourinary tract tumour in a blackfoot disease endemic area of Taiwan. BJU Int. 2008; 102: 48–54.

7. Koornstra JJ, Mourits MJ, Sijmons RH, Leliveld AM, Hollema H, Kleibeuker JH. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol. 2009; 10: 400–8.

8. Reekhaye, A., Sriprasad, S., & Madaan, S. A review of the contemporary management of upper urinary tract urothelial carcinoma. Journal of Clinical Urology. 2018; 11(1):51–57.

9. Roupret M, Babjuk M, Bohle A, et al. Guidelines on urothelial carcinomas of the upper urinary tract. European Association of Urology, 2015.

10. Jovanovic M, Soldatovic I, Janjic A, Vuksanovic A, Dzamic Z, Acimovic M, Hadzi-Djokic J. Diagnostic value of the nuclear matrix protein 22 test and urine cytology in upper tract urothelial tumors. Urol Int. 2011;87(2):134-7.

11. Garcia-Gonzalez R, Cuesta-Roca C, Garcia-Navas R, Gonzalez-Peramato P. Upper urinary tract tumors pathology (ureter, pelvis and renal calyces). Arch Esp Urol. 2004;57(3):241-250.

12. Rink, M., et al. Impact of histological variants on clinical outcomes of patients with upper urinary tract urothelial carcinoma. J Urol, 2012. 188: 398.

13. Amin MB, Edge SB, Greene FL, et al. Renal Pelvis and Ureter. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017, 749–55.

14. Leow, J.J., *et al.* A Systematic Review and Meta-analysis of Adjuvant and Neoadjuvant Chemotherapy for Upper Tract Urothelial Carcinoma. Eur Urol, 2014. 66: 529.

15. Jwa, E., *et al.* Adjuvant radiotherapy for stage III/IV urothelial carcinoma of the upper tract. Anticancer Res, 2014. 34: 333.

16. Lughezzani G, Sun M, Perrotte P, Shariat SF, Jeldres C, Budaus L, et al. Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study. Eur Urol. 2010;57(6):956-962.

17. M. Rouprêt, M. Babjuk, M. Burger, E. Compérat, N.C. Cowan, P. Gontero et al. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94 92671-01-1.

18. Arancibia MF, Bolenz C, Michel MS, Keeley FX, Jr., Alken P. The modern management of upper tract urothelial cancer: surgical treatment. BJU Int. 2007;99(5):978- 981.

19. Aboumohamed, A.A., et al. Oncologic Outcomes Following Robot-Assisted Laparoscopic Nephroureterectomy with Bladder Cuff Excision for Upper Tract Urothelial Carcinoma. J Urol, 2015. 194: 1561.

20. Moschini, M., et al. Trends of lymphadenectomy in upper tract urothelial carcinoma (UTUC) patients treated with radical nephroureterectomy. World J Urol, 2017.

21. Lughezzani, G., et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology, 2010. 75: 118.

22. O'Brien, T., et al. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol, 2011. 60: 703.

23. Cutress ML, Stewart GD, Zakikhani P, et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): Systematic review. BJU Int 2012; 110: 614–628.

24. Kobayashi K, Saito T, Kitamura Y, et al. Effect of preoperative chemotherapy on survival of patients with upper urinary tract urothelial carcinoma clinically involving regional lymph nodes. Int J Urol 2016;23:153–8.

25. Leow JJ, Martin-Doyle W, Fay AP, et al. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol 2014;66:529–41.

26. Shirotake S, Kikuchi E, Tanaka N, et al. Impact of an adjuvant chemotherapeutic regimen on the clinical outcome in high risk patients with upper tract urothelial carcinoma: a japanese multiinstitution experience. J Urol 2015;193:1122–8.

27. A. Birtle, M. Johnson, R. Kockelbergh, F. Keeley, J. Catto, R. Bryan, et al. Results of POUT - a phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC). European Urology Supplements; Volume 17, Issue 2, March 2018, Pages e1431-e1432.

28. Kim TS, Oh JH, Rhew HY. The efficacy of adjuvant chemotherapy for locally advanced upper tract urothelial cell carcinoma. J Cancer. 2013;4(8):686-690.

29. Chen B, Zeng ZC, Wang GM, Zhang L, Lin ZM, Sun LA, et al. Radiotherapy may improve overall survival of patients with T3/T4 transitional cell carcinoma of the renal pelvis or ureter and delay bladder tumour relapse.BMC Cancer. 2011;11:297.

30. Seisen, T., et al. Efficacy of Systemic Chemotherapy Plus Radical Nephroureterectomy for Metastatic Upper Tract Urothelial Carcinoma. Eur Urol. 71: 714.

31. Sharma, P., et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol, 2017. 18: 312.

32. Veccia, A., Antonelli, A., Francavilla, S. *et al.* Robotic v Veccia, A., Antonelli, A., Francavilla, S. et al. Robotic versus other nephroureterectomy techniques: a systematic review and meta-analysis of over 87,000 cases. World J Urol (2019)

CHAPTER 7

Adrenal Cortical Cancer

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1. INCIDENCE & EPIDEMIOLOGY

Adrenal cortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with a reported annual incidence of approximately 1–2 cases per million . It can occur at any age although there are two peak incidences: in early childhood and the 4 –5 decades of life. Women are more frequently affected with a female to male ratio of 1.5–2.5:1.

2. GENETIC PREDISPOSITION

The current understanding of the pathogenesis of ACC is incomplete and limited. Although most cases of adult ACC are sporadic, paediatric ACC can be associated with several genetic disorders, such as Li–Fraumeni syndrome (LFS), Beckwith–Wiedemann syndrome, Multiple Endocrine Neoplasia Type 1, Carney complex, Congenital Adrenal Hyperplasia, McCune–Albright syndrome, and Familial Adenomatous Polyposis. Thus, TP53 mutations, seen in LFS and the alterations of the insulin-like growth factor 2

(IGF-2) of Beckwith–Wiedemann syndrome, are considered to be involved in the pathogenesis of ACC.

3. CLINICAL PRESENTATION

Clinical presentation of ACC is heterogeneous and the natural history is highly variable. Many ACCs are asymptomatic and non-functional as adrenal incidentalomas identified on abdominal imaging; however, approximately 60–70% of ACCs in adults present with clinical syndrome of autonomous adrenocortical steroid excess. While clinical Cushing's syndrome and virilisation in females are the most common manifestations of hormonally active ACCs, they can also present with features of hyperaldosteronism, such as hypertension and hypokalaemia, or pheochromocytoma. Oestrogen hypersecretion is rare with gynaecomastia and testicular atrophy present in only 5–10% of male patients.

Hormonally inactive ACCs present with symptoms related to local mass effects of the tumour, such as abdominal discomfort, back pain, nausea, or vomiting. Due to their location in the retroperitoneum, the majority of ACCs are large and locally advanced at the time of diagnosis. Frequently, ACCs invade adjacent large vessels, such as the renal vein or inferior vena cava.

4. EVALUATION & WORK UP

A. Hormonal Assessment

As ACCs secrete excessive adrenal hormones, the European Network for the Study of Adrenal Tumors (ENSAT) recommends a detailed pre-operative endocrine

assessment for suspected ACC including dexamethasone suppression test or urinary free cortisol or late night salivary cortisol, DHEA-S, 17-hydroxyprogesterone, testosterone, androstenedione, and oestradiol(Figure 1). Measurements of plasma free metanephrines or urinary fractionated metanephrines and the aldosterone/renin ratio is also recommended to exclude pheochromocytoma and primary hyperaldosteronism, respectively.

Table 1: Diagnostic Work For An Adrenal Mass

GLUCOCORTCOID WORK UP

- Dexamethasone suppression test (1 mg, 23:00 h) Excretion of free urinary cortisol (24 h urine) Basal cortisol (serum) Basal ACTH (plasma)

SEXUAL STEROIDS AND STEROID PRECURSORS

- DHEA-S
- 17-OH-progesterone
- Androstenedione
- Testosterone
- 17-beta-estradiol (serum, only in men and postmenopausal women)
- 24-h urine steroid metabolite examination

MINERALOCORTICOID EXCESS

- Serum Potassium
- Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalemia)

CATECHOLAMINE EXCESS

- Normetanephrine, metanephrine, and methoxytyramine (plasma) Alternatively: fractionated metanephrine excretion (24 h urine)

IMAGING

- CT or MRI of abdomen and CT thorax

FDG -PET

- HC-metomidate PET and I-iodometomidate single photon emission computed tomography (SPECT)
- MffiG scintigraphy, DOTA-TATE-PET orFDG-PET if pheochromocytoma is proved

B. Radiology

Various imaging techniques, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), have greatly increased the detection rates of adrenal masses. However, no single imaging method can identify an adrenal mass as ACC. Some radiological features that suggest the likelihood of ACC include large tumour size, irregular margin, lobulated shape, heterogeneous appearance (due to haemorrhages and/or necrotic areas), calcifications, low fat content, and high attenuation on an unenhanced CT with irregular enhancement after contrast. ACC is more likely if the mass is >4 cm (sensitivity 97%; specificity 52%) and >6 cm (sensitivity 91%; specificity 80%).

CT SCAN

Low fat concentration of malignant lesions produces high attenuation on unenhanced CT; hence, it is recommended to perform a preliminary unenhanced CT attenuation measurement followed by an intravenous contrast scan for optimal imaging of the adrenal glands . A cut-off value of <10 HU in unenhanced CT has been used for the diagnosis of benign lesions. However, a recent analysis from the German ACC registry suggests 13 HU is the most sensitive threshold to distinguish adenoma from carcinoma . If unenhanced CT is indeterminate, a contrast enhanced CT should be performed to detect the washout, which is either absolute (the pre-contrast density is known) or relative (only a portal venous phase baseline is available), where an absolute washout of >50% suggests a benign lesion .

MRI

Overall, MRI is as accurate as CT in differentiating adrenal adenomas and carcinomas, with a reported sensitivity of 84–100% and a specificity of 92–100%, similar to unenhanced CT . The presence of isointense to hypointense signals on T1-weighted images, a hyperintense signal on T2-weighted images and a heterogeneous signal drop on chemical shift are the MRI features helpful in the diagnosis of ACC, where CT fails to characterise the adrenal lesion perfectly .

In addition, imaging plays an important role in staging as well as assessing the involvement of surrounding organs and vessels to evaluate the feasibility of radical surgery, and to monitor treatment response during follow-up.

PET CT SCANS-

18F-fluorodeoxyglucose positron emission tomography (PET) is a second-line investigation for indeterminate cases or in staging of known ACC. In patients with impaired renal function, PET/CT may be an alternative to CT. PET was reported to be more sensitive than CT in the detection of local recurrence, while CT was more sensitive in detecting small peritoneal or lung metastases. PET/CT also demonstrates response to chemotherapy earlier than CT, as well as predicting the chemotherapeutic response of ACC before anatomic changes are detected with CT. Moreover, PET/CT may be useful for selecting the optimal treatment in patients with advanced disease.

Advanced imaging modalities, such as 11C-metomidate PET and I-iodometomidate single photon emission

computed tomography (SPECT), use metomidate which binds to CYP11B enzymes expressed in the adrenal cortex and are taken up by adrenocortical tissue. Such techniques were recently demonstrated to be useful in differentiating ACC from metastatic carcinoma .

C. Role of biopsy

There is a long-standing debate over the use of transcutaneous adrenal biopsy in adrenal masses. Currently, the only widely-accepted indication for an adrenal biopsy is a suspected metastasis from a known primary tumor in a patient for whom the result would change the therapeutic approach, e.g. surgery for limited disease vs. chemotherapy for metastatic disease. Biopsy should only be conducted after biochemical exclusion of a pheochromocytoma because of potentially fatal catecholamine surge during biopsy. Biopsy does not significantly affect patient outcome and should not majorly affect adjuvant therapeutic decisions.

D. Pathology

Macroscopically, most ACCs are large, heterogeneous tumours with necrosis and invasion of the tumour capsule, surrounding soft tissues, blood vessels, or lymphatics. The colour of the mass varies from brown, orange, or yellow depending on the lipid content of the cells . Since ACC is a rare condition with special variants (paediatric, oncocytic, myxoid, and sarcomatoid) histopathological challenges encountered include differentiation of adrenocortical from adrenomedullary tumours, as well as adrenocortical adenomas from carcinomas. There are no clear-cut

pathognomonic histological features for a carcinoma; thus, a combination of multiple features are used to diagnose ACC. The Weiss scoring system is widely used, which is based on 9 morphological parameters on light microscopy: 3 each for tumour structure (diffuse architecture, confluent necrosis, clear cells), cytological features (nuclear atypia, mitotic index, atypical mitoses), and invasion (sinusoidal, venous, capsular) (Table 1). It is established that a Weiss score of e”3 indicates an ACC, whereas scores between 0 and 2 define an adenoma.

Table 2: Weiss Scoring System

HISTOLOGICAL CRITERIA	SCORE 0	SCORE 1
Nuclear Grade	1 and 2	3 and 4
Mitoses	≤5 for 50 fields x 400	≤6 for 50 fields x 400
Atypical mitoses	No	Yes
Clear cells	>25 %	d” 25 %
Diffuse Architecture	d” 33 % Surface	>33 %
Confluent Necrosis	No	Yes
Venous Invasion	No	Yes
Sinusoidal Invasion	No	Yes
Capsular Infiltration	No	Yes

Grade 1: (round nuclei, homogenous, small size, no nucleoli)

Grade 2: (nuclei slightly irregular, more voluminous, conspicuous nucleoli at ×400)

Grade 3: (irregular nuclei, voluminous nucleoli at ×100)

Grade 4: (the same as Grade 3 with monstrous cells and very irregular nuclei).

The Ki-67 labelling index (Ki-67 LI), a marker of proliferation, plays a pivotal role in differential diagnosis of adrenocortical carcinomas from adenomas, with a cut-off value of 2.5–5.0%, although a cut-off of 5% was reported to yield high sensitivity (87.5%) and specificity (97.5%). It is also one of the important prognostic indicators of survival in ACC patients, with a value of >10% leading to shorter overall survival (OS) and more recurrences.

5. STAGING OF ACC

The tumour, lymph node, and metastasis (TNM) classification system, proposed by ENSAT, is used to assess the local extension of primary tumours, lymph node involvement, and the presence of distant metastasis (Table 2). Both the Weiss system and TNM staging are useful in predicting the prognosis of ACCs and correlate with each other, with patients at TNM Stages III and IV having a high Weiss score.

Table 3: TNM classification system, proposed by ENSAT.T1, <5 cm; T2, >5 cm; T3, infiltration of surrounding adipose tissue; T4, invasion into adjacent organs

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

The ENSAT (European Network for the Study of Adrenal Tumors) staging system maintains the tumor-node-metastasis (TNM) classifications used in the AJCC staging system; however, stage III disease includes patients with positive lymph nodes (N1), infiltration of surrounding tissues (T3 and T4), and venous tumor thrombus, whereas stage IV disease is reserved for any tumor associated with distant metastatic disease.

6. PRINCIPLES OF MANAGEMENT –

Management involves the correct diagnosis and staging. Appropriate and adequate investigations are needed. Ideally, it would be a multidisciplinary team (MDT) effort. If amenable by staging, surgery to excise disease completely would be the first choice. Adjuvant therapies, salvage therapies, and treatment of metastatic disease are quite tricky, often not so easy to administer and may not give the desired result. They are judiciously used as recommended by MDT.

7. SURGICAL MANAGEMENT

Surgery is the key therapeutic option that offers a possibility of cure for resectable ACCs: either open adrenalectomy (OA), or minimally invasive surgery (FIGURE 2). Therefore, staging prior to surgery is essential to rule out invasion of adjacent organs and distant metastases as one-third of patients present with distant metastases, especially lung and liver. A meta-analysis of data from nine retrospective case-control studies reported no difference in the overall recurrence rate, time to recurrence, cancer specific mortality between open and laparoscopic

adrenalectomy. Laparoscopic adrenalectomy can offer a shorter hospital stay and a faster recovery; however, it is associated with higher development of peritoneal carcinomatosis (that may possibly be attributed to violation of the tumour capsule during manipulation).

Complete surgical resection is critical in the management of ACCs and approximately two-thirds to three-quarters had lymph node involvement in autopsy studies . Moreover, regional lymph node metastasis is an established predictor of poor long-term outcome; however, routine lymphadenectomy during surgical resection of ACC is not commonly performed and its therapeutic role remains controversial. However, lymphadenectomy should be considered in patients with locally advanced tumours (T3 and T4) which have a higher rate of lymph node metastasis.

Debulking surgery is utilised for the removal of large tumours with mechanical signs and to reduce hormone excess; however, the median survival is <12 months. Between 30% and 40% of ACC are metastatic at the onset, and surgical treatment of liver or lung metastasis is associated with long-term survival. Recurrence of ACC is relatively common even after curative resection and can be detected in 40–65% within 2 years with a median time to recurrence of 19 months. Repeat curative-intent resection for recurrent ACC in carefully selected patients with two or more factors (solitary tumour, disease-free interval >12 months, and locoregional or pulmonary recurrence) could result in a favourable long-term survival.

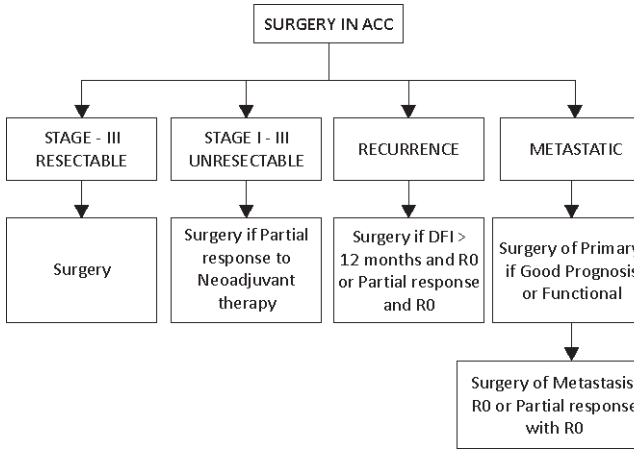

Figure 1: Recommendations for surgery in patients with ACC. DCR, disease control rate; DFI, disease-free interval; R0, margin free resection expected.

8. MEDICAL MANAGEMENT

a. Mitotane

Mitotane is an adrenocorticotropic drug used for adjuvant therapy after surgical resection, for primary therapy of unresectable cases, and for advanced ACC as a single treatment or in combination with chemotherapy. The European Society for Medical Oncology (ESMO) guidelines recommend adjuvant mitotane therapy in high-risk surgically treated patients, defined as Stage III, Ki-67 LI >10%, R1 or Rx resection. However, it is not mandatory for low-risk patients with Stage I or II, R0 resection and Ki-67 LI £10% . Adjuvant mitotane is routinely started within

3 months of surgery with appropriate monitoring of blood levels and titrating the dose to a concentration of 14–20 mg/L. Side effects include gastrointestinal upset, elevation of liver function tests, leukopenia, and confusion .

b. Chemotherapy

According to the first international randomised trial in locally advanced and metastatic adrenocortical carcinoma treatment (FIRM-ACT trial), patients who received mitotane plus a combination of etoposide, doxorubicin, and cisplatin (M-EDP) had a higher response rate than those in the streptozocin mitotane group (23.2% versus 9.2%), although there was no significant difference in the OS. For failed cases with M-EDP, second-line chemotherapy using a combination of gemcitabine and capecitabine is proposed which leads to disease stabilisation for at least 6 months in 29% of patients.

c. Targeted therapy

Trials on monoclonal antibodies against various angiogenic receptor tyrosine kinases, such as bevacizumab, sorafenib, sunitinib, and axitinib, yielded disappointing results. Similarly, inhibitors of epithelial growth factor receptor (erlotinib and gefitinib) and IGF-1 (linsitinib, cixutumumab) are not promising in ACC. Recently, novel agents to target steroidogenic factor-1, mTOR, and Wnt signalling pathways have been developed. Inhibitors of acetyl-coA cholesterol acetyl transferase 1, an enzyme for intracellular cholesterol handling, have gained some interest as a potential therapy.

With trials underway, these novel targeted agents might be useful for clinical applications in the future.

9. RADIATION MANAGEMENT

The role of adjuvant radiotherapy[AR] in ACC is unclear and the benefits or recommendations cannot be well established due to the lack of prospective large studies. In a retrospective study, AR prolongs 5-year recurrence-free survival, with no effect on OS and disease-free survival . AR was associated with a 4.7-fold reduction in the risk of local failure compared to treatment regimens without radiotherapy. Thus, AR should be considered in patients with incomplete, R1, or Rx resection, who are at high risk for local recurrence. Stereotactic radiosurgery which deliver high-dose radiation beams to tumours with extreme accuracy, can be safe and effective for advanced adrenocortical carcinoma, though there are only a few case reports currently available for this option.

10. STAGE WISE MANAGEMENT ALGORITHMS (FIGURE 2):

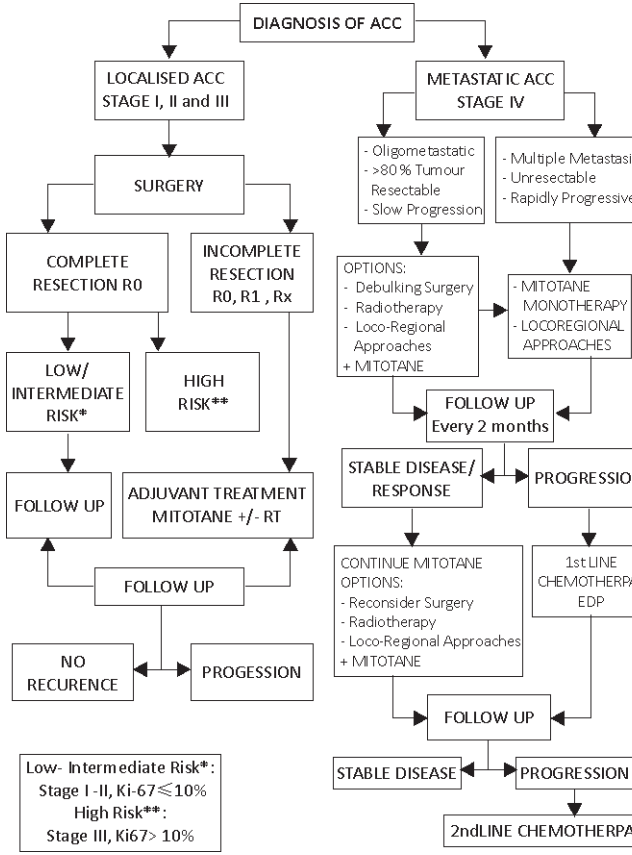

Figure 2: Flowchart for ACC management.

R0 – Complete resection; R1 -Microscopic incompleteresection;R2 – Macroscopic incomplete resection; Rx -Unknown; EDP - Etoposide, Doxorubicin, Cisplatin

11. PROGNOSTIC FACTORS & STAGEWISE PROGNOSIS WITH CURRENT TREATMENT : (TABLE 4)

Prognostic factors :

a) Male Gender
b) Age (years) (50+)
c) Stage of disease (III–IV)
d) Tumour weight (300+ g)
e) Lymphatic metastasis
f) Distant metastases
g) Local infiltration
h) Hormonal activity non-functional
i) Symptomatic presentation
j) The completeness of surgery
k) Margin positivity
l) ki-67

are risk factors significantly associated with ACC recurrence.

Table 4 : Stagewise Prognosis

STAGE	5 YEAR SURVIVAL
I	33- 66 %
II	20 - 58 %
III	18 -24 %
IV	<5%

12. PALLIATIVE MEASURES:

The therapeutic strategy of metastatic disease aims to control excessive catecholamine secretion and tumor burden, but no curative treatment is achievable. Treatment choices include a wait and see policy, locoregional therapies, systemic chemotherapy, and radiopharmaceutical agents , and should be discussed per case in a multidisciplinary team. Metastatic disease palliation may also benefit from local therapy with embolization and or radiofrequency ablation. Radionuclide therapy with ^{131}I MIBG is an effective treatment in activities ranging from 5.5 to 38 GBq (150–1000 mCi). Several studies have been published on the efficacy of 131I-MIBG treatment. Responses were observed in 22–47% of cases with long-term survival of 4.7 years or 72 months. Objective responses were mainly observed in patients with soft tissue metastases .

WHAT HAS CHANGED IN ADRENOCORTICAL CARCINOMA IN THE LAST DECADE

- Advanced imaging modalities have demonstrated to be useful in differentiating ACC from metastatic carcinoma.
- The Weiss scoring system is developed to differentiate carcinoma from adenoma.
- Ki-67 labelling index, a proliferative marker , is one of the important prognostic indicators of survival in ACC.
- Options for systemic therapy still remain limited. Trials involving novel target agents are ongoing.

SUGGESTED READING

1. Baudin E; Endocrine Tumor Board of Gustave Roussy. Adrenocortical carcinoma. Endocrinol Metab Clin North Am. 2015;44(2):411-34.
2. Else T et al. Adrenocortical carcinoma. Endocr Rev. 2014;35(2):282-326.
3. Golden SH et al. Clinical review: Prevalence and incidence of endocrine and metabolic disorders in the United States: A comprehensive review. J Clin Endocrinol Metab. 2009;94(6):1853-78.
4. Libé R. Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment. Front Cell Dev Biol. 2015;3:45.
5. Fassnacht M et al. Adrenocortical carcinoma: a clinician's update. Nat Rev Endocrinol. 2011;7(6):323-35.
6. Zini L et al. Contemporary management of adrenocortical carcinoma. Eur Urol. 2011; 60(5):1055-65.
7. Stigliano A et al. Management of adrenocortical carcinoma: a consensus statement of the Italian Society of Endocrinology (SIE). J Endocrinol Invest. 2016;39(1):103-21.
8. Fassnacht M et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016; 175(2): G1-34.
9. Petersenn S et al.; German ACC Study Group. Computed tomography criteria for discrimination of adrenal adenomas and adrenocortical carcinomas: analysis of the German ACC registry. Eur J Endocrinol. 2015;172(4):415-22.

10. Bharwani N et al. Adrenocortical carcinoma: the range of appearances on CT and MRI. AJR Am J Roentgenol. 2011;196(6): W706-14.

11. Takeuchi S et al. Impact of 18F-FDG PET/CT on the management of adrenocortical carcinoma: analysis of 106 patients. Eur J Nucl Med Mol Imaging. 2014;41(11):2066-73.

12. Hahner S, Sundin A. Metomidate based imaging of adrenal masses. Horm Cancer. 2011;2(6):348-53.

13. Fassnacht M, Allolio B. Clinical management of adrenocortical carcinoma. Best Pract Res Clin Endocrinol Metab. 2009; 23:273–289.

14. Vanderveen KA, Thompson SM, Callstrom MR, Young WF Jr, Grant CS, Farley DR et al. Biopsy of pheochromocytomas and paragangliomas: potential for disaster. Surgery.2009; 146:1158–1166.

15. Williams AR, Hammer GD, Else T. Transcutaneous biopsy of adrenocortical carcinoma is rarely helpful in diagnosis, potentially harmful, but does not affect patient outcome. Eur J Endocrinol 2014; 170: 829–35.

16. Duregon E et al. Pitfalls in the diagnosis of adrenocortical tumors: a lesson from 300 consultation cases. Hum Pathol. 2015;46(12):1799-807.

17. Papotti M et al. The Weiss score and beyond—histopathology for adrenocortical carcinoma. Horm Canc. 2011;2(6):333-40.

18. Choi YM et al. Clinicopathological Features Associated with the Prognosis of Patients with Adrenal Cortical Carcinoma: Usefulness of the Ki-67 Index. Medicine (Baltimore). 2016;95(21): e3736.

19. Mondal SK et al. Histopathological study of adrenocortical carcinoma with special reference to the Weiss system and TNM staging and the role of immunohistochemistry to differentiate it from renal cell carcinoma. J Cancer Res Ther. 2013;9(3):436-41.

20. Autorino R et al. Open Versus Laparoscopic Adrenalectomy for Adrenocortical Carcinoma: A Metanalysis of Surgical and Oncological Outcomes. Ann Surg Oncol. 2016;23(4):1195-202.

21. Didolkar MS et al. Natural history of adrenal cortical carcinoma: a clinicopathologic study of 42 patients. Cancer. 1981;47(9):2153-61.

22. Nilubol N et al. Does Lymphadenectomy Improve Survival in Patients with Adrenocortical Carcinoma? A Population-Based Study. World J Surg. 2016;40(3):697-705.

23. Kemp CD et al. Pulmonary resection for metastatic adrenocortical carcinoma. Ann Thorac Surg. 2011;92(4):1195-200.

24. Ripley RT et al. Liver resection and ablation for metastatic adrenocortical carcinoma. Ann Surg Oncol. 2011;18(7):1972-9.

25. Tran TB et al. Clinical Score Predicting Long-Term Survival after Repeat Resection for Recurrent Adrenocortical Carcinoma. J Am Coll Surg. 2016;223(6):794-803.

26. Berruti A et al.; ESMO Guidelines Working Group. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23(Suppl 7): vii131-8.

27. Terzolo M et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med. 2007;356(23): 2372-80.

28. Fassnacht M et al.; FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012;366(23):2189-97.

29. Sperone P et al. Gemcitabine plus metronomic 5-fluorouracil or capecitabine as a second-/third-line chemotherapy in advanced adrenocortical carcinoma: a multicentre phase II study. Endocr Relat Cancer. 2010;17(2):445-53.

30. Konda B, Kirschner LS. Novel targeted therapies in adrenocortical carcinoma. Curr Opin Endocrinol Diabetes Obes. 2016; 23(3):233-41.

31. Sabolch A et al. Adjuvant and definitive radiotherapy for adrenocortical carcinoma. Int J Radiat Oncol Biol Phys. 2011;80(5):1477-84.

32. Harada Y, Miyazaki S. Adrenocortical Carcinoma Treated by CyberKnife. Intern Med. 2016;55(15):2031-4.

33. Gonias S, Goldsby R, Matthay KK, et al. Phase II study of high-dose [131I] metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma, J Clin Oncol, 2009, vol. 27 (pg. 4162-4168)