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INDIAN COUNCIL OF MEDICAL RESEARCH

Consensus Document for Management of Urinary Bladder Cancer

Prepared as an outcome of ICMR's Subcommittee on Urinary Bladder Cancer

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New Delhi - 110029
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Division of Non Communicable Diseases

Indian Council of Medical Research,
New Delhi – 110029
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Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This document has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline verbatim. One can use an alternative mode of therapy on the basis of discussions with the patient and institution and national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but serves as a guide for clinicians in complex decision-making processes.

Dr. Rajiv Bahl
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

With great pleasure and a sense of accomplishment I introduce this Consensus Document for Management of Urinary Bladder Cancer, the result of collective efforts and shared dedication. With a focus on improvement of patient care in the Indian context, ICMR had set-up subcommittees to prepare consensus documents for cancers of various sites. This document is the result of such an initiative with inputs from experts across the country working in oncology.

Bladder cancer though not the commonest cancer in Indian population, is showing an increasing trend in certain parts of the country. National Cancer Registry Program (NCRP) 2020 Report shows that incidence rates are comparatively higher among males. Geographical variation has been noted among different regions with maximum number of cases reported from Delhi.

This document summarizes evidence pertaining to available diagnostic methods, multimodal treatment approaches, site specific cancer therapies tailored as per clinical profile of Indian patients. Information on utility of newer molecular markers have also been summarised for the readers. The contributors have identified research questions for future research in aspects of prevention, diagnosis, and treatment of bladder cancer.

This document represents the current thinking of subject experts on based on available evidence. Mention of specific drugs and clinical tests for therapy do not imply endorsement or recommendation for their use by ICMR; these are given as examples to help clinicians in complex decision-making process. We are confident that this edition of Consensus Document for Management of Urinary Bladder Cancer would serve its purpose to improve quality of care across the country..

Rajiv Bahl

(Dr. Rajiv Bahl)
Secretary, Department of Health Research
and Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer. The Task Force on management of cancers has been constituted to plan various research projects. In phase-I; 20 documents were published in selected cancer sites viz: lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non-Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome, Pediatric Lymphoma, Pancreatic Cancer, Hepatocellular Carcinoma and Neuroendocrine Tumours. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. In phase-II; it is planned to formulate guidelines for 18 cancer sites. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its coordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three-year report of PBCR's (2016-2018) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the consensus document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three-part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson,
ICMR Task Force Project

Preface

Bladder cancer is a rare malignancy in the Indian population. As per the GLOBOCAN 2020 database, bladder cancer is the 17th most common malignancy in India. The 5-year prevalence appears to be 3.57 per 100000 population leading to about 11000 deaths each year. The incidence of bladder cancer is higher in males compared to females (Relative incidence being 4:1 in most urban population-based cancer registries in India). Bladder cancer incidence does vary across the country. Among males, Delhi has the highest incidence rates (7.4), followed by Thiruvananthapuram (4.9) and Kolkata (4.0), and lowest rate is in Dibrugarh (1.1); however, among females, the rate is highest in Delhi (1.7) followed by Mumbai (1.1) and Mizoram (1.1), respectively, and lowest in Barshi (0.2). Over time, bladder cancer incidence has increased in Delhi, Bangalore and Mumbai, while it has decreased in Chennai. Tobacco consumption is the most important risk factor in bladder cancer. The treatment of localized bladder cancer is either radical surgery with neo-adjuvant chemotherapy or bladder preservation with tri-modality therapy. There has been several advances and refinement in the treatment modalities for treatment of bladder cancer in past few years. The management of bladder cancer should be well defined and accomplished. It has been noticed that there are variations in the treatment pattern across the country.

It is an admirable initiative of the ICMR for setting-up task force to bring out the consensus document for the management of cancer of the urinary bladder. These guidelines will be useful to the practicing clinicians and students to optimize the treatment of their patients. This will also bring the uniformity in the management across the country and establish collaborative studies. This will also help in bringing out Indian data related to outcome and toxicity of the treatment and further refinement of management and research in this area.

I am grateful to all members of the task group, who have been expert in their field, for devoting their valuable time from their busy schedule and remained committed to their assigned task. I would like to thank Dr GK Rath for his untiring support, inspiration and guidance and Dr Tanvir Kaur for her continuous efforts and support in all meetings and invaluable suggestions. The ICMR deserves special thanks for these consensus documents. The consensus on the management of cancers is a dynamic process in view of emerging evidence, and these will also be updated regularly as the evidence evolves with newer knowledge. We would be happy to receive constructive feedback to further improve this document for the benefit of our patients.

(Dr Prashanth Giridhar)
Chairperson
Subcommittee on Urinary Bladder Cancer

Preface

Cancer is a leading cause of death worldwide. Globally cancer of various types affects millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India. Among males, cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females, cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country

(Dr. R.S. Dhaliwal)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Urinary Bladder Cancer is a concerted outcome of efforts made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee, Dr. Prashanth Giridhar is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking special interest and understanding the need of formulating the guidelines which are expected to benefit the cancer patients. I would like to thank Dr. RS Dhaliwal for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

Tanvir Kaur

(Dr.Tanvir Kaur)
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Contents

1 Epidemiology and Risk Factors

Bladder cancer is a rare malignancy in the Indian population. As per the GLOBOCAN 2020 database, bladder cancer is the 17th most common malignancy in India [1]. The 5-year prevalence appears to be 3.57 per 100000 population leading to about 11000 deaths each year [1]. The incidence of bladder cancer is higher in males compared to females (Relative incidence being 4:1 in most urban population-based cancer registries in India) [2]. Bladder cancer incidence does vary across the country. Among males, Delhi has the highest incidence rates (7.4), followed by Thiruvananthapuram (4.9) and Kolkata (4.0), and lowest rate is in Dibrugarh (1.1); however, among females, the rate is highest in Delhi (1.7) followed by Mumbai (1.1) and Mizoram (1.1), respectively, and lowest in Barshi (0.2) [3]. Over time, bladder cancer incidence has increased in Delhi, Bangalore and Mumbai, while it has decreased in Chennai [4,5]. Tobacco consumption is the most important risk factor in bladder cancer. Risk for smokers is 3–4-fold higher compared to non-smokers and is estimated to cause 31% of bladder cancer deaths among men and 16% among women [6,7]. Industrial exposure to aromatic amines and carbon black dust in rubber, leather and dye industries has also been associated with an increased risk [8,9]. The above two factors mark the modifiable risk factors to prevent bladder cancer. No genetic variation/ mutation has been overtly associated with bladder cancer though familial clustering of cases is found, probably due to similar modifiable risk factors [10 – 12].

2 Diagnosis and Staging of Bladder Cancer

Painless visible haematuria is the most common presenting complaint. Other rarer symptoms may include frequency and urgency in urination and pelvic pain. Patients presenting with these symptoms should undergo a bimanual examination of rectum and vagina. The examination helps identify a pelvic mass as well as fixity to pelvic sidewalls. Patients must then be evaluated by urine cytology. Examination of voided urine for exfoliated cancer cells has high sensitivity in high-grade tumours and is a useful indicator in cases of high-grade malignancy or carcinoma in situ (CIS) [13]. However, positive urinary cytology may originate from a urothelial tumour (UC) located anywhere in the urinary tract. At present, there is no role of urine molecular testing in diagnosis.

Identifying upper urinary tract urothelial carcinoma:

The diagnosis of upper tract UC depends on CT urography and ureteroscopy (Level 2b) Approximately 2–4% of patients with bladder cancer have concurrent upper tract urothelial carcinoma [14, 15]. Evaluation of the upper urinary tract can be done with both CT and MR urography with CT urography showing a sensitivity of 96.6% and specificity of 87–91.5% while MR urography showing a sensitivity of 82.8–86.2% and a specificity of 83.1–83.3% [16, 17]. Hence, CT urography is considered the imaging of choice with MRU urography reserved for patients in whom the CT urography is contraindicated.

Imaging for staging

Local staging: Local staging imaging of bladder cancer is recommended before patient is taken up for TURBT.

Recommendations:

Ideal: MRI pelvis

Essential: CECT pelvis

Summary of evidence:

Local staging:

MRI is superior to CT in terms of differentiating T1 from T2 disease (Level 2b). Both CT and MRI may be used for assessment of local invasion, with MRI having superior soft tissue contrast resolution compared with CT. A meta-analysis showed 91% sensitivity and 96% specificity for 3.0-T device MRI combined with diffusion-weighted imaging to differentiate ≤T1 tumours from ≥T2 tumours before surgery [18]. VI-RADS is an mpMRI scoring system for defining muscle invasion, with a sensitivity and specificity of 0.83

[95% confidence interval (CI) 0.70-0.90] and 0.90 (95% CI 0.83-0.95), respectively [19].

Although CT has restrictions in identifying the different layers of the bladder wall, it may provide useful staging information regarding the perivesical invasion of high-grade T3b and T4 tumours [20]. Mirmomen et al. conducted a review of CT staging studies and demonstrated 49–93% accuracy in detecting perivesicular invasion with tumors staged ≥T3 [21].

Confirmation of bladder cancer

The diagnosis of bladder cancer (BC) is confirmed with a flexible **cystoscopy and biopsy** from lesion. If a bladder tumour has been visualized unequivocally by imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to trans-urethral resection of bladder tumour (TURB) for histological diagnosis and resection

Transurethral resection of bladder tumours (TURBT)

The goals of TURBT are to make correct diagnosis and pathologically grade and stage the tumour. It is a crucial procedure in the management of BC. It should be performed systematically in following individual steps [22,23].

Surgical steps

- Give antibiotic prophylaxis.
- Dorsal lithotomy position after giving anaesthesia.
- Do bimanual palpation. It may be omitted in case of non-invasive or early treatment for invasive bladder cancer is planned.
- Cystoscopy with rigid cystoscope for complete inspection of urethra and urothelial lining of bladder.
- Assess the number of tumours, their site, size, shape, characteristics, multifocality and extent.
- Resection of tumour along with deep muscle biopsy with resectoscope. Take prostatic urethral biopsy if indicated.
- Avoid excess use of electrocautery to prevent tissue distortion and cautery artefacts.
- Secure haemostasis.
- Empty the bladder and do bimanual palpation again.
- Send the biopsy and resection specimens to pathologist in separately labelled containers.

Surgical and technical aspects of tumour resection

1. Surgical strategy of resection (piecemeal/separate resection, en-bloc resection)

A complete resection of bladder tumour performed by either fractioned or en-bloctechnique, is essential to achieve a good prognosis [24,25]. Piecemeal resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good estimation of vertical and horizontal extent of the tumour [26]. While En-blocresection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is feasible in selected exophytic tumours. It

provides high-quality resected specimens with the presence of detrusor muscle in 96-100% of cases [27-30]. The technique used for TURBT is dependent on the size, location of the tumour as well as familiarity and experience of the surgeon.

2. Evaluation of resection quality

The lack of detrusor muscle in the surgical specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour under-staging [31]. The presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required if possible (except in TaG1/LG tumours). It has been shown that surgical experience can improve TURBT results, which supports the role of teaching and training programs [32]. Virtual training on simulators is an emerging non-invasive approach for practice of surgical steps [33].

3. Monopolar/Bipolar resection

TURBT can be performed with either monopolar or bipolar electrocautery as per the availability of cautery device. The monopolar require 1.5% glycine as an irrigation fluid while bipolar needs 0.9% normal saline. Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation, bleeding etc) and to produce better specimens. Currently, which is better, the results remain controversial [34-37].

4. Office-based fulguration and laser vaporization

Patients with history of small size Ta-LG/G1 tumours can be managed by fulguration or laser vaporization of small papillary recurrences on day care basis to reduce the therapeutic burden [38,39]. However, there are no prospective comparative studies assessing the oncological outcomes.

5. Resection of bladder tumours at the time of transurethral resection of the prostate

TURBT can be done followed by TURP if bladder tumours are small, papillary with low tumour burden. [40,41]. Although high-quality evidence is limited, it does not seem to increase risk of tumour recurrence or progression [42].

6. Bladder biopsies

Random bladder biopsies can be performed if there is suspicion of carcinoma in situ (red velvety flat area, indistinguishable from inflammation, non-papillary tumours, patients with positive urine cytology ('suspicious for high-grade lesion') but no mass seen on radiological imaging's or with a history of high-grade non-muscle invasive bladder tumours. These representative biopsies (mapping or photodynamic/PDD guided) from normal appearing bladder mucosa should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall area [43,44]. One should rule out upper tract urothelial cancer and take prostatic urethral biopsies in case of positive urinary cytology and negative cystoscopy.

7. Prostatic urethral biopsies

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.* showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% [45]. The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS, multiple tumours, abnormal looking prostatic urethra and positive

urine cytology without obvious bladder mass [46]. Based on this observation, a biopsy from the prostatic urethra is necessary in selected cases [45, 47, 48].

8. Photodynamic diagnosis (fluorescence cystoscopy)

This procedure is performed using violet light after intra-vesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It is shown to have higher sensitivity (93%vs. 65%) for diagnosis of bladder cancer especially CIS and decreased recurrence as compared to procedure done under white light endoscopy. The limitations are decreased specificity (63% vs. 81%), cost and availability [49,50]. It can have false positivity due to inflammation, post TURBT or post intravesical BCG instillation. So TURBT can be performed under white light in routine.

9. Narrow-band imaging (NBI)

Similar to fluorescence cystoscopy, NBI has been shown to have higher diagnostic rate for bladder cancer. In this procedure hyper-vascular tissue shows more enhancement as compared to normal one. In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced [51-54]. The limitations are cost and availability of the technique.

10. Confocal laser micro-endoscopy

It is a newer technique with limited available literature. It uses a high-resolution probe for providing endoscopic histological grading in real time but requires further validation [55].

Ideal: TURBT/TUR biopsy of bladder mass should be performed for histopathological diagnosis and staging. The type, technique and energy used during resection may depend on facilities and expertise available.

Essential: TURBT/TUR biopsy of bladder mass can be performed with cheaper and easily available mono-polar energy with equally comparable outcomes in developing countries like India.

Second resection or restage TURBT

There is high risk of upstaging and residual tumour (51%) on second resection for NMIBC [4,34]. In approximately 8-11% of patients with T1 can show under staging [56,57]. A second TURB can lead to increase in recurrence-free survival (RFS), progression free survival [58,59] improve outcomes after BCG treatment [60] and provide prognostic information [61-65]. Second stage procedure should be performed within 2-6weeks of initial TURBT. It is indicated in T1 tumours, absence of detrusor muscle in pathological specimen with the exception of Ta-LG/G1 tumours, in primary CIS and following incomplete first TURBT. In second TURBT scar, area at primary malignancy area should be resected.

Imaging of lymph node and distant metastases: Metastatic work up is recommended in case of muscle invasive bladder cancer (Diagnosed radiologically or TURBT)

Recommendations:

Ideal: CECT- Thorax, Abdomen and Pelvis with CT urography for upper tract evaluation

[MR urography can be done if CT is contraindicated for reasons related to contrast administration or radiation dose]

Essential: CECT- Thorax, Abdomen and Pelvis

Optional: 18F FDG PET/CECT.

Summary of evidence

Lymph nodes and distant metastases:

Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment. (Level 2b)

The risk of lymph node metastasis increases proportionally with the advancing local tumour stage [66, 67] and both CECT and MRI are useful in identifying pathologically enlarged nodes. Size is a well-established and important index for detecting malignancy in the pelvic lymph nodes. The accuracy of CT scan in identification of nodal metastases ranges from 54 to 86% [68] and using lower or higher size threshold, there is increased rates of false positives or false negatives, respectively. By general consensus, pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short-axis diameter should be considered as suspicious for LN metastasis [69].

The most common sites of distant metastases are lung and liver, with computed tomography and MRI being the diagnostic techniques of choice to detect lung [70] and liver metastases [71].

18F FDG PET/CT scan is the most common molecular imaging technique for preoperative staging of various malignancies. However, there are some limitations in the evaluation of bladder cancer since 18F FDG is excreted in the urine and accumulates in the bladder and makes detection of bladder lesions become challenging.

For nodal staging, whether 18F PET-CT is better than CECT is still unclear. Few studies have claimed higher sensitivity for 18F PET-CT [72 – 74], ranging from 36 to 78% for PET-CT versus 9.1–44% for CECT and while some others have not [75 – 77].

After work up as above, further management depends on stage, grade and risk stratification of bladder cancer

2017 TNM staging of bladder cancer		
T stage	Description	Comments
Tx	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	Papillary tumor involving mucosa
Tis	Carcinoma *in situ*: 'flat tumour'	Flat tumor (Usually high grade) non-invasive
T1	Tumour invades subepithelial connective tissue	Papillary tumor involving Lamina propria **Ta, Tis, T1 are NMIBC**
T2	Tumour invades muscle	
T2a	Tumour invades superficial muscle (inner half)	
T2b	Tumour invades deep muscle (outer half)	
T3	Tumour invades perivesical tissue	
T3a	Microscopically	
T3b	Macroscopically (extravesical mass)	
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	

2017 TNM staging of bladder cancer		
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina	
T4b	Tumour invades pelvic wall or abdominal wall	
N stage		
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or Presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M stage		
M0	No distant metastasis	
M1a	Non-regional lymph nodes	
M1b	Other distant metastases	

Grading of bladder cancer (Urothelial carcinoma)

Papillary tumors (WHO classification 2004/2016)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma
Flat tumors (WHO classification 2004)
Non-malignant lesions • Urothelial proliferation of uncertain malignant potential (flat lesion without atypia or papillary aspects). • Reactive atypia (flat lesion with atypia). • Atypia of unknown significance
Potential) Pre-malignant lesion • Urothelial dysplasia
Malignant lesion • Urothelial CIS is always high grade

3 Management of NMIBC

Risk stratification of non-muscle invasive bladder tumors (NMIBC):

Risk category	Criterion
Low risk	A primary, single, Ta/T1 LG < 3 cm in diameter without CIS in a patient < 70 years A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (Age > 70 years, multiple papillary tumours, tumour diameter > 3 cm
Intermediate risk	Patients without CIS who are not included in either the low, high or very high-risk groups
High risk	All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group All CIS patients, EXCEPT those included in the very high-risk group
Very high risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1 G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

Adjuvant intravesical therapy

As bladder cancer have high early recurrence rates, adjuvant intravesical therapies are indicated to decrease recurrence and progression [78].

Duration of intravesical therapy according to EAU-NMIBC scoring model

1. **Low risk group -** This group have minimal risk of progression. So, single instillation of chemotherapy is sufficient.
2. **Intermediate risk group -** Patients in this group have low risk of disease progression (7.4 and 8.5% after 10 years according to the 2021 EAU NMIBC scoring model). So intravesical BCG (induction plus 3-weekly instillations at 3, 6 and 12 months), or chemotherapy for 1year is recommended.
3. **High risk group -** There is high risk of disease progression (14.1 - 14.2%). So full dose BCG for 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months) is recommended.
4. **Very high-risk group -** They have an extremely high risk of tumor progression (53.1 and 58.6% after 10 years). They should be advised immediate RC or intravesical BCG for 1-3years in patient not signing consent or fit for RC.

Ideal: Adjuvant intravesical therapy in form of BCG or chemotherapy should be given as per guidelines to decrease recurrence and progression. BCG is usually preferred over chemotherapy especially in intermediate and high-risk patients.

Essential: The available adjuvant intravesical therapy should be given if indicated or patient should be referred at higher tertiary care centre.

Summary of evidence for intravesical treatment in NMIBC

Intravesical chemotherapy

Immediate single instillation (SI) has been shown to act by destroying circulating tumor cells after TURBT, ablative effect on residual tumor cells at the resection site and on small overlooked tumours [79-82]. Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURBT, SI significantly reduces the recurrence rate up to 14% compared to TURBT alone. Only patients with primary tumours or intermediate-risk recurrent tumours with a prior recurrence rate of less than or equal to one recurrence per year and those with a 2006 EORTC recurrence score < 5 benefited from SI. In patients with a 2006 EORTC recurrence score ≥ 5 and/or patients with a prior recurrence rate of > 1 recurrence per year, SI was not effective as a single adjuvant treatment. No randomized comparisons of individual drugs have been conducted [83-86].

The SI with mitomycin C (MMC), epirubicin or pirarubicin, gemcitabine, apaziquone and normal postoperative saline irrigation for 24hours have all shown a beneficial effect [87 - 90]. In all SI studies, the instillation was administered within 24 hours. Instillation to be given as soon as possible after TURBT, preferably within the first two hours in the recovery room or even in the operating theatre. One-hour instillation of MMC is effective compared to 30 mins [91]. As severe complications have been reported in patients with drug extravasation, safety measures should be maintained [92, 93].

In low-risk patients, a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [94, 95]. For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression. In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients. There is evidence from several studies in intermediate and high-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given [96 - 99]. The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [99].

Newer techniques of MMC administration

1. Microwave-induced hyperthermia effect

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [100]. In one RCT comparing one year of BCG with one year of microwave-induced hyperthermic MMC in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [101]

2. Electromotive drug administration

The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [102]. The definitive conclusion, however, needs further confirmation.

Complications of intravesical chemotherapy

Patients usually complaint of temporary local irritative urinary tract symptoms following instillation which subside spontaneously or on oral medications. Sometimes serious sequelae and rare deaths have also been noticed, especially in patients with perforation during resection. So instillation are not advised in patient having or suspicious of bladder perforation in case of extensive resection with haematuria. The other reported complications are chemical cystitis, cutaneous desquamation, decreased bladder capacity as a result of contractures, calcified eschars, and complications or added difficulty of subsequent cystectomy [103].

Intravesical bacillus Calmette-Guérin (BCG) immunotherapy

Five meta-analyses have confirmed that BCG after TURBT is superior to TURBT alone or TURB + chemotherapy for preventing the recurrence of NMIBC. It leads to approximate 32% reduction in the risk of recurrence for BCG as compared to adjuvant MMC [104]. So BCG is more effective as compared to MMC in reducing recurrence rate in both type of groups previously treated and not previously treated with chemotherapy [105]. There is reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [106 - 110].

Mechanism of Action of intravesical BCG

Intravesical BCG results in a robust local immune response characterized by induced expression of cytokines in the urine and bladder wall and by an influx of granulocytes and mononuclear and dendritic cells [111].

BCG strain

There may be some differences among different strains in smaller studies [112 - 114], but meta-analysis involving various BCG strains could not confirm superiority of one over another [115 - 117].

Intravesical BCG versus chemotherapy

In literature intravesical BCG therapy appears to be significantly better in preventing recurrences than chemotherapy however, BCG instillation may lead to higher rate of side effects than chemotherapy [118, 119]

BCG toxicity

Though BCG therapy 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 [120]. The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [121]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [122]. Side effects leading to treatment discontinuation were seen more often in the first year of therapy [123]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [124]. On comparison of different BCG strains, no significant difference in toxicity was seen [113]. Bacillus Calmette-Guerin should be used with caution in immunocompromised patients; e.g., immunosuppression, human immunodeficiency virus (HIV) infection pose relative contraindications [125], The management of side effects after BCG should reflect their type

and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [126, 127].

Optimal BCG schedule

After BCG instillation, the patient should retain the solution for at least 1 to 2 hours. Induction therapy involve 6 weekly instillations as introduced by Morales et al. [128]. For optimal efficacy, after induction BCG maintenance therapy must be given [102,103,107]. Many different maintenance schedules have been used, ranging from a total of ten instillations given in eighteen weeks to 27 over three years [129]. Safety analysis after 345 randomised patients demonstrated that a reduced number of instillations (3 instillations in induction and 2 instillations at 3, 6 and 12 months) proved inferior to the standard schedule (6 instillation in induction and 3 instillations at 3, 6 and 12 months) regarding the time to first recurrence [130]. In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, three years' maintenance (3-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS [131].

Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [132, 133]. The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [134]. The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [119, 127]. It is also technically difficult to constitute one-third dose BCG routinely.

Combination treatment using interferon

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2 did not show a clear difference in recurrence and progression over BCG alone [131]. Additionally, an RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and IFN for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [132].

Role of intravesical therapy in Carcinoma in situ (CIS)

It is difficult to completely cure CIS endoscopically. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or immediate RC. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [133] BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or immunotherapy [102].

Refractory High-Grade Disease

If disease is still persistent after BCG therapy (2 cycles of induction therapy or within 6 months of induction plus maintenance therapy or intolerance of BCG, it is classified under BCG refractory disease

[135]. These patients are high risk group and should be offered immediate cystectomy if found fit surgically. If patient is not fit for surgery or not giving consent, can be offered additional intravesical therapies [136].

Management of Refractory High-Grade Disease

If patient has received intravesical chemotherapy, BCG instillation has demonstrated superior outcomes over 2nd course of intravesical chemotherapy [137]. For patients who have failed initial intravesical BCG therapy, a second course still gives a 30% to 50% response [138]. Patients with intermediate- or high-risk disease if persistent or recurrent Ta disease or CIS is noted after a single course of intravesical BCG, second course of BCG is still indicated [135]. Patients not tolerating or opting second course of BCG therapy can be offered salvage chemotherapy, but the risk of failure and progression is high. Further BCG or chemotherapy beyond 2 courses are not advocated because they will fail 80% of the time, although recent studies suggest some potential for newer agents, investigational protocols, and IFN alone or in combination with reduced doses of BCG [139].

Other alternative options for refractory disease are photodynamic therapy (PDT), radiation therapy or newer check point inhibitors [140, 141]. In PDT a photosensitizing agent such as porfimer sodium (Photofrin) systemically or hexaminolevulinate (HAL) intravesical is administered followed by intravesical therapy with light irradiation. After excitation by light, the photosensitizer molecules react with oxygen to form free radicals and reactive singlet oxygen species to have cytotoxic effect on cancer cells. In CIS, its response rate is approximate 66%, with a duration of 37 to 84 months. A complete response to radiation therapy and TUR is seen in 50% to 75% of patients, but the additional benefit of radiation to TUR remains unclear.

Checkpoint inhibitors are a newer class of therapy under investigation for use in NIMBC. Current phase II clinical trials with atezolizumab, durvalumab, and pembrolizumab or their combination with intravesical BCG are ongoing in patients with BCG-refractory disease. Their efficacy still remains under investigation [142].

Follow up of NMIBC:

- Patients with low-risk tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.
- Patients with high-risk and very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly
- Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy
- Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk and very high-risk tumours
- Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.

Management of intravesical BCG failure:

Type of failure	Management options
BCG-unresponsive	Radical cystectomy Bladder preservation strategies if unfit for RC
Late BCG relapsing: T1Ta/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	Radical cystectomy. Repeat BCG may be tried Bladder preservation strategies if unfit for RC
LG recurrence after BCG for primary intermediate-risk tumour	Repeat BCG or intravesical chemotherapy Radical cystectomy

4 Management of Muscle Invasive Bladder Cancer (MIBC)

Radical cystectomy as primary modality

Role of neo-adjuvant chemotherapy before radical cystectomy:

Recommendations:

NACT is strongly recommended for cT2-T4aN0M0 disease with cisplatin-based combination chemotherapy regimens.

Summary of evidence

Neoadjuvant Chemotherapy in Urothelial Cancer of Bladder

The choice of regimen differs across institutions and depends primarily on the patient's performance status and Glomerular Filtration Rate (GFR). For cisplatin-ineligible candidates, there is no data to support a recommendation for perioperative chemotherapy. Carboplatin should not be substituted for cisplatin in the perioperative setting [143]. NACT is preferred over adjuvant chemotherapy (ACT) on a higher level of evidence data. The SWOG-8710 study showed that NACT was associated with OS and DSS benefit, and it reduced the risk of death by 33%. However, it should be noted that the MVAC regimen was associated with 33% grade 4 neutropenia. The JCOG-0209 study [144] concluded that NACT is associated with OS and PFS benefit, significant pCR rates. However, the trial was terminated early due to slow accrual. The International Collaboration of Trialists Study [145] showed that NACT was associated with statistically non-significant improvement in 3-year OS and DFS, 15% and 13% decrease in risk of death and locoregional disease respectively, statistical significant improvement in 3-year MFS (21% decrease in risk of metastases). NACT-arm had higher pCR rates with no increase postoperative complications. The updated results showed that NACT was associated with 3-year and 10-year OS benefit (50% vs 56% and 30% vs 36% respectively) with 16% reduction in risk of death (HR: 0.84; 95% CI: 0.72 to 0.99; p = 0.037), 18% reduction in risk of disease (p = 0.008), 23% reduction in risk of metastases (p = 0.001), 13% reduction in local disease (p = 0.067) and four percent reduction in risk of locoregional relapse (p = 0.632), and median survival improvement of seven months (37 to 44 months) [146]. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration group [147] analysed 3005 individual patients' data (IPD) from 11 RCTs that compared NACT and local treatment vs local treatment alone. They found a statistically significant 5-year OS and DFS benefit with platinum-based combination NACT; five percent and nine percent absolute improvement in OS (from 45% to 50%) and DFS, and 14% reduction in the risk of death with NACT.

SWOG-8710 Study

- This was a multicenter phase III randomised study (1987-1998) with 126 institutions involved.
- It included patients with cT2-T4aN0M0 as per AJCC 4th Edition.
- The patients were randomised to undergo upfront Radical Cystectomy (RC) along with bilateral pelvic lymph node dissection (BPLND) versus 3 cycles of NACT with MVAC regimen followed by RC+BPLND
- The primary end-point of the study was overall survival (OS)

	RC-arm	NACT-arm	P value
Total sample size =307	154	153	
Median follow-up (years)	8.4	8.7	
Five-years OS	43%	57%	0.06 (HR: 1.33; 95% CI 1.00 to 1.76)
Median OS (months)	46	77	
Disease specific survival	77 deaths	54 deaths	0.002 (HR: 1.66; 95% CI: 1.22 to 2.45)
pCR	15%	38%	< 0.001, (85% pT0 patients were alive at 5-years)
Post-operative complications	Statistically significant difference was not detected		

Neoadjuvant Immunotherapy in Urothelial Bladder Cancer

Two phase II studies PURE-01 [148] and ABACUS [149] evaluated the role immunotherapy in neoadjuvant setting. ABACUS study is yet to complete with final results, however, the clinical efficacy and biomarker analysis has been published [150].

	ABACUS Study	PURE-01 Study
Study design	Single-arm Phase II RCT to establish efficacy, safety and biomarker signals	Single-arm Phase II
Method	2 cycles atezolizumab (1200 mg) x 3 weekly followed by RC	3 cycles pembrolizumab (200 mg) every three weeks followed by RC
Sample size	95	50
Eligibility Criteria	i. cT2-T4aN0M0 ii ECOG 0-1 iii. Adequate hematologic and end-organ function iv. Ineligible or refusal of cisplatin-based NACT	i. cT2-T3bN0M0 ii. ECOG 0-2 iii. GFR 20 ml/min iv. Regardless of their cisplatin eligibility
Duration	May 2016 to June 2018	February 2017 to March 2018
Median follow-up	13.1 months	6.2 months

Radical cystectomy (RC)

Radical cystectomy is the gold standard procedure for localized bladder cancer. It is usually preferred for patient with good performance status and higher life expectancy considering its high morbidity and complications rate.

Indications

1. T2–T4a, N0–Nx, M0 disease
2. High risk NMIBC
3. Endoscopically unresectable disease
4. BCG-refractory, BCG-relapsing and BCG unresponsive bladder cancers

5. Non-urothelial bladder cancer
6. Salvage radical cystectomy for recurrence/non-responsive after bladder preservation strategies.

Ideal: Radical cystectomy (RC) should be performed to maximize survival. Open technique has shown to have equal survival outcomes as compared to laparoscopic and robotic techniques.

Essential: Open RC can be performed with equally comparable survival outcomes in developing countries like India.

Summary of evidence for RC:

Extent

In men standard radical cystectomy specimen include bladder, prostate, seminal vesicles, distal ureters, and regional pelvic LNs while in women it includes removal of the bladder, the entire urethra and adjacent vagina, uterus, distal ureters, and regional pelvic LNs.

The optimal extent of pelvic LND has not been established till date. It can be standard, extended and super-extended. The literature suggest, extended LND might have therapeutic benefit as compared to standard or limited LND [151,152]. Similarly, removal of at least 10 LNs have shown to be sufficient for staging and OS benefits [153].

Standard pelvic LNDs - It extending cranially up to the common iliac bifurcation, with the ureter being the medial border, the genitofemoral nerves laterally, caudally till the circumflex iliac vein, the lacunar ligament and the LN of Cloquet. It involves removal of common iliac LNs below ureteric crossing, internal iliac, external iliac, obturator and presacral group of LNs [154].

Extended pelvic LNDs - Apart from standard pelvic LNDs, its cranial extent is up to aortic bifurcation [155-159].

Super extended pelvic LNDs - Its upper limit is up to origin of inferior mesenteric artery [160 - 161].

Sexual function preserving RC

In men sexual function preserving techniques of RC can also be performed by sparing of prostate/ prostatic capsule/ neurovascular bundle or seminal vesicles sparing. Sexual potency can be improved ranging from 80–90%, 50–100% and 29–78% for prostate-, capsule- or nerve-sparing techniques, respectively without difference in urinary continence rate. The studies did not show any difference in oncological outcomes between standard and sexual function preserving RC. For techniques preserving prostatic tissue (prostate- or capsule-sparing), rates of incidental prostate cancer in the intervention group ranged from 0–15% [162-175]. So, patients for sexual function preserving RC should be carefully selected and counselled. Patients are selected based on localized disease, absence of involvement of prostate, prostatic urethra and bladder neck.

In females' sexual function or pelvic organ sparing RC should not be offered as standard of care as date supporting pelvic sparing is still not robust. It can be performed in selected cases with benefits of hormones preservation, preserved sexual function, decreased risk of cognitive impairment, osteoporosis, cardiovascular diseases, preserved pelvic support so reducing post-operative prolapse and risk of urinary retention in orthotopic neobladder and reduced operating time, blood loss and early convalescence in elderly fragile patients [176-182].

Minimally invasive laparoscopic radical cystectomy (LRC) /robotic-assisted laparoscopic radical cystectomy (RARC)

When compared with open RC, RARC have shown to be beneficial regards to shorter hospital stay (1–1.5 days), decreased blood loss but longer intraoperative time (1–1.5 hours), higher cost and similar complication rates. All RCTs including largest RAZOR RCT (RARC versus open RC) have shown similar margin positivity rate, recurrence-free survival, CSS and OS in both the groups [183-185]. LRC have shown to similar results like RARC when compared with open RC [186]. In developing countries like India open RC is still most commonly performed cost-effective approach. Patient should be counselled regarding advantages and disadvantages of each approach. The surgeon's experience, familiarity and institutional case burden volume are key parameters as compared to techniques of RC.

Urinary diversion after radical cystectomy

Urinary diversion can be created with ileum (most commonly), colon, stomach or appendix. Broadly, it can be classified under 3 categories [187].

1. Abdominal - Uretero-cutaneostomy, ileal or colonic conduit or continent pouch (infrequently used).

2. Continent orthotopic urinary diversion - Neobladder.

3. Rectosigmoid diversions - Uretero-(ileo-)rectostomy or uretero-sigmoidostomy (infrequently used).

Currently it is difficult to recommend one type of urinary diversion as there are no difference in oncological outcomes. The selection for type of urinary decision should be patient's informed decision. It also depends on surgeon's clinical experience and various patient and disease related factors. Ileal conduit is still considered as gold standard. But both ileal conduit and neobladder are commonly used diversion depending on institute's preference. Orthotopic neobladder can be used with similar oncological outcome unless there are contraindications like invasive urethral tumour, urothelial carcinoma with positive surgical margins, N2 or N3 stage, debilitating neurological and psychiatric illnesses precluding postoperative clean intermittent catheterization, short life expectancy and impaired hepatic or renal function [188]. The relative contraindications include high-dose pre-operative RT, age > 80 years, history of complex urethral stricture and severe urethral sphincter-related incontinence [189]. In case of prostatic urethral involvement in cysto-prostatectomy specimen, or CIS in males and bladder neck involvement in females, urethral frozen section should be taken before doing neobladder in selected cases. The presence of NMIBC in biopsy from prostatic urethra or bladder neck do not absolutely preclude neobladder creation if patient is closely followed later with cystoscopy and urine cytology [190]. The uretero-cutaneostomy is simplest of all diversions and preferred in case of single kidney and elderly frail patients.

Morbidity and mortality following urinary diversion

The perioperative mortality following radical cystectomy is up to 3.2% within 1 month and up to 8% at 3 months follow up [191, 192]. The 5-year RFS and CSS was 58% and 66% following radical cystectomy [193]. In another study RFS and OS at 5 years was 68% and 66% respectively [194]. There can be complications related to stoma, bowel, urinary tract, metabolic, infectious, bleeding and blood transfusion, nutritional, formation of stones and cancer. Complication rates (except stomal stenosis) and hospital stay are lower in uretero-cutaneostomy group as compared to in ileal conduit [195]. In a retrospective study by Nieuwenhuijzen JA et al, following ileal conduit, up to 48% of the patients developed early complications

including UTIs, pyelonephritis, ureteroileal leakage and stenosis etc. The early and late complication rate were 48% and 51% in ileal conduit group while 42% and 59% in orthotopic neobladder group respectively. The ileal conduit group had relatively fewer late complications as compared to neobladder group because of reduced uncomplicated urinary tract infections. Metabolic complication was present in 24% and 28% patients in ileal conduit and orthotopic neobladder group respectively [196]. The other long-term complications were stomal (24%) and and functional and/or morphological changes in upper urinary tract in 30% of patients [196 - 198]. The complicate rate increases as the duration of follow up increases, 45% at 5years to 94% (upper urinary tract changes in 50%, urolithiasis in 38%) in patients surviving > 15 years. The morbidity, complications and mortality have shown to be lower in centers with experienced surgeons having high operative burden [199 - 203].

ERAS (Early Recovery After Surgery) protocol

ERAS protocols are also known as "enhanced recovery programs" or "fast-track protocols" used in bowel surgeries. These are mainly extrapolated from colorectal surgeries. The cornerstones of ERAS protocol are preoperative education and medical optimization, preoperative carbohydrate loading in non-diabetic patients, use of early feeding, early mobilization of patient and removal of tubes and catheters, perioperative fluid management, use of metoclopramide, chewing gum and alvimopan to stimulate gastro-intestinal motility, reduce use of opioids, use of venous thromboembolism prophylaxis, antibiotics prophylaxis and use of multimodal antiemetics postoperatively. Preoperative antibiotics should be given 1-2 hour before the start of surgery to reduce infectious complication. Venous thromboembolism prophylaxis like low molecular weight heparin should be started on postoperative day 1, for a period of 28 days. Patients using ERAS protocol score better in terms of emotional and physical functioning scores, decreased ileus and less wound healing disorders, fever and thrombosis except they may perform poor in terms of postoperative pain [204 - 206].

Adjuvant therapy after RC:

Recommendations:

Adjuvant chemotherapy is advisable to pT3/T4 and/or pN+ disease if NACT has not been given. No role of adjuvant radiotherapy after RC with available evidence.

Summary of evidence for adjuvant therapy:

Adjuvant Chemotherapy (ACT) in Urothelial Bladder Cancer

Only 50% of patients who are proposed to receive ACT, receive it due to low glomerular filtration rate (GFR), older age, poor ECOG status, comorbidities and refusals.

Advanced Bladder Cancer meta-analysis [207] analysed IPD from six trials (491 patients) which represented 90% of all patients randomized in CCC trials. All the patients were administered CCC and the choice of local treatment was cystectomy. The meta-analysis concluded that ACT was associated with 25% decrease in the risk of death (29% for CCC) ($p = 0.019$), nine percent absolute improvement in 3-year OS (11% for CCC), 32% decrease in risk of recurrence (38% for CCC) ($p = 0.004$), and 12% absolute improvement in 3-year DFS. This meta-analysis had analyzed IPD and was hence able to answer some criticism of the individual trials, as all the individual trials were underpowered with major criticism against their design, analysis and reporting. The 2013 Updated Systemic Review and Meta-analysis of Randomized Trials

[208] was built on the 2005 Cochrane meta-analysis [209] and incorporated additional RCTs published after 2005 (ACT-arm: 475 patients, Control-arm: 470 patients). The inclusion criteria were ≥pT2, N0/N+M0 except the RCT by Stadler et al [210] and Studer et al. [211] which included pT1 patients also. The primary and secondary outcomes were OS and DFS respectively. The meta-analysis concluded that ACT was associated with 23% decrease in risk of death ($p = 0.049$), 34% decrease in risk of recurrence ($p = 0.014$), and greater absolute DFS benefit in pN+ (HR = 0.39). The 2019 Systematic Review and Meta-Analysis of Randomized Trials evaluated the role of ACT in locally-advanced MIBC (pT3/pT4 and/or pN+) from four RCTs [212 – 215]. The meta-analysis concluded that ACT was associated with significant PFS and OS benefit. There was 17% and 10% absolute increase in PFS (NNT = 5.9; $p < 0.00001$) and OS (NNT = 10; $p = 0.0009$) respectively. 52% and 48% relative risk reduction in progression and death respectively. However, when pT2 was included, ACT had marginal OS benefit (four percent increase; NNT = 25).

Adjuvant radiotherapy in Bladder Cancer

Data on adjuvant RT after RC are limited. Data are available from phase II trials or retrospective data analysis. In a phase II trial including 120 patients with locally advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive), comparing sequential chemotherapy and radiotherapy with adjuvant chemotherapy alone showed an improved loco-regional control with addition of adjuvant RT by 27% at 2 years with only 7% Rt associated late GI toxicity [216]. In an European multicentric phase II trial including 72 high risk MIBC patients even in patient with neo-bladder the adjuvant radiotherapy could be administered without excessive severe toxicity.GI and GU toxicity was acceptable with 2 yr > grade 2 GI toxicity (acute +late) at 17% and GU toxicity at 18% (acute +late) [217]. Iwata et al. in a systematic review found no clear benefit of ART after radical surgery in Bladder Cancer and upper tract urothelial carcinoma [218]. In the retrospective NCDB analysis of more than 1600 patients' data from 2004-2013 by Lewis et al. only patients with positive surgical margin derived benefit from adjuvant radiotherapy [219]. Many phase III trials are ongoing to address this question of use of radiotherapy along with adjuvant chemotherapy after radical surgery around the world [220].

5 Bladder Preservation Treatment in MIBC (Tri-modality Therapy)

Bladder preservation strategies can be chosen in 2 settings.

1. When the patient is unfit for major surgeries like radical cystectomy (e.g.- old age, co morbidities)
2. When patient chooses for bladder preservation instead of radical surgery despite being fit for surgery.

Ideal candidate for Bladder preservation in fit patients

1. <T3 lesion
2. No diffuse CIS
3. No hydro-nephrosis

Select patients who do not meet all these criteria can still be successfully treated with this approach

Tri-modality therapy (TMT)

There are 3 components of bladder preservation strategy

1. Visibly complete Transurethral resection of bladder tumor. (TURBT)
2. Radical Radiotherapy
3. Concurrent Chemotherapy

These 3 are together called as Tri-modality therapy (TMT)

Maximal TURBT – TURBT is done during the tissue diagnosis of the bladder cancer but its completeness is of importance in bladder preservation strategies. A second look TUR has revealed residual tumour in >50% patients even after initially presumed complete TURBT [221].

Summary of evidence for complete TURBT

In the pooled analysis of prospective RTOG trials Mak et al. reported complete response rates of 73% Vs 56%, 5 years' overall survival rates of 43% Vs 29% and salvage cystectomy rates of 11% Vs 22% in patients with complete TURBT and with incomplete TURBT [222]. Better OS and DSS was seen with complete TURBT as compared to incomplete TURBT in a retrospective analysis of the Massachusetts general hospital data [223].

Radical Radiotherapy

Two radiotherapy schedules are used

Split Course radiotherapy with interval cystoscopy (RTOG)

Around 40 Gy/ 20 fractions over 4 weeks in Phase 1 to the whole pelvis followed by interval cystoscopy to look for response. In complete responders (If initially maximal TURBT was incomplete), consolidation with further 24-26 Gy of radiation is done. Incomplete responders undergo radical cystectomy [224].

Continuous Course Radiotherapy

The bladder and pelvis are treated till 45-50 Gy followed by whole bladder only or tumor bed only till 64-66 Gy at conventional fractionations [225]. The pelvic lymph node radiation may be optional in N0 staging. And if only bladder irradiation is being considered moderate hypo fractionation of 55 Gy in 20 fractions to bladder only can be considered as this schedule has been proven to be non-inferior to the conventional 64Gy in 32 fractions in terms of terms of invasive loco-regional control, OS and late toxicity [226].

Concurrent chemotherapy

Among many chemotherapeutic agents, most data exist for cisplatin and 5FU+ mitomycin- c.

Summary of evidence for concurrent chemotherapy

In the BC 2001 trial, concurrent chemotherapy with 5FU and MMC showed benefit in terms of 2 year loco-regional control by 14% (67% Vs 53%) with 5-year OS reaching up to 48% in concurrent chemo-radiotherapy arm. Hypoxic sensitizers like nicotinamide and carbogen and concurrent gemcitabine chemotherapy are options for cisplatin ineligible patients as they have shown benefit in terms of OS and local relapse without any difference in morbidity as compared to only Radiotherapy. [227, 228].

6 Follow up After Radical Treatment in MIBC

Follow up after RC:

- After radical cystectomy with curative intent, regular follow-up is needed.
- After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g., multifocality, carcinoma *in situ* and tumour in the prostatic urethra). The frequency should be based on institutional protocols
- CT scan of thorax, abdomen and pelvis (every 6 months) until the third year, followed by annual imaging thereafter is recommended.
- In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid base balance includes regular measurements of pH and sodium bicarbonate substitution according to the measured value
- Vitamin B12 should be measured annually following RC and bowel diversion and supplemented as needed

Follow up after TMT:

- After tri-modality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–6 months initially; then after 3 years, every 6 months in the majority of patients
- It is recommended that patients undergo cystoscopy and urine cytology every 3 – 6 months along with CT scan of thorax, abdomen and pelvis every 6 months for initial 3 years. The frequency may be reduced there-after.

7 Management of Metastatic Bladder Cancer

50% of urinary bladder cancers recur after surgery while 10 – 15% patients are metastatic at presentation itself. Data from Tata Memorial Hospital, Mumbai showed 17 percent (72 out of 419) patients having metastatic disease at baseline [229]. Platinum based chemotherapy has shown the best response in metastatic disease. Although the initial responses to platinum based chemotherapy is high, it is seldom sustained with median overall survival of approximately 15 months and 5-years survival of about 15%. [230] Some of the factors associated with poor prognosis include the presence of bone or liver metastases and a poor performance status [231].

Molecular Markers

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor, [232] circulating tumour cells as well as defects in DNA damage repair (DDR) genes including ERCC2, ATM, RB1 and FANCC that may predict response to cisplatin-based chemotherapy [233, 234].

Immunotherapy is now an established treatment option, however, the search for biomarker for response to immunotherapy continues. Programmed death-ligand 1 (PD-L1) expression by immunohistochemistry has been evaluated in several studies with mixed results. At present, the only indication for PD-L1 testing relates to the use of immune checkpoint inhibitors (ICI) as monotherapy in patients with locally advanced or metastatic UC unfit for cisplatin-containing chemotherapy who have not received prior therapy.

Next generation sequencing (NGS) is now increasingly being used in patients with advanced cancers. The only approved target identified by NGS that has clear therapeutic implications is FGFR2/3 alterations, for which targeted therapy with Erdafitinib is now available on compassionate basis in India [235, 236].

Choosing patients fit for cisplatin based chemotherapy

Cisplatin based chemotherapy should be considered in the first line treatment of metastatic bladder cancer. Unfortunately, less than 50% patients are fit for cisplatin based chemotherapy. The following criteria must be fulfilled to consider patients fit for cisplatin-based chemotherapy [237]:

1. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status 2 or greater, or a Karnofsky Performance Status of 60 to 70 or less.
2. Glomerular filtration rate (GFR) less than 60 mL/min. Please note that lower GFR due to tumor obstruction is not a contraindication for cisplatin, if it can be reversed with drainage procedures.

3. Hearing loss (measured by pure tone audiometry) of 25 dB at two contiguous frequencies (CTCAE version 5.0 grade 2 hearing loss)
4. Grade 2 or greater peripheral neuropathy (ie, sensory alteration or paresthesia, including tingling, but not interfering with activities of daily living)
5. New York Heart Association class III or greater heart failure (marked limitation of physical activity; less than ordinary activity causing symptoms of shortness of breath, fatigue, and/or pain).

Patients fit for Cisplatin-based chemotherapy

In patients who are fit to receive cisplatin based chemotherapy, the options include:

1. GC –Gemcitabine (1200 mg/m^2 on days 1 and 8) and cisplatin (75 mg/m^2 on day 2), repeated every 21 days for upto six cycles.
2. MVAC – Methotrexate (30 mg/m^2 on days 1, 15, and 22), vinblastine (3 mg/m^2 on days 2, 15, and 22), doxorubicin (30 mg/m^2 on day 2), and cisplatin (70 mg/m^2 on day 2), repeated every 28 days for upto six cycles.
3. Dose-dense MVAC – Methotrexate (30 mg/m^2 on day 1), vinblastine (3 mg/m^2 on day 2), doxorubicin (30 mg/m^2 on day 2), and cisplatin (70 mg/m^2 on day 2) with granulocyte-colony stimulating factor (G-CSF) support, repeated every 14 days for upto six cycles.

MVAC regimen was the first regimen found to superiority over single agent cisplatin with a significant improvement in the overall response rate (ORR; 39 versus 12 percent), median progression-free survival (PFS; 10 versus 4 months), and median overall survival (OS; 13 versus 8 months) [238]. Toxicity remains a major problem with this regimen with significant proportion of patients experiencing myelosupression and mucositis. A series from Princess Margaret Hospital showed as many as 54% admission due to toxic complications, making this regimen difficult to use in limited resource settings [239]. Increasing the dose intensity by administration every two weeks with utilization of GCSF has also been tried. This has shown equivalent responses with reduced toxicities [240].

GC regimen was used in a superiority design, phase III trial against MVAC regimen in which 405 patients were randomized [230]. Compared with MVAC, GC resulted in a similar ORR (49 versus 46 percent), similar time to progression (7 months in each arm), similar OS (14 versus 15 months) [230]. Patients in GC arm experienced less weight loss, a better performance status, and less fatigue, and less grade toxicities, including neutropenic sepsis (2 versus 14 percent), and mucositis (1 versus 22 percent) [230]. Thus, GC regimen is widely used with most of the oncologists preferring it to the other regimens. Also, split dose of cisplatin is preferred by most of the Medical Oncologists based on a phase II data in neoadjuvant setting in which cisplatin was split to 35mg/m^2 on day 1, 8, 15 every 4 weeks [241]. The split dose regimen allows the use of cisplatin based regimen in patients with GFR between 40-60 ml/min, though the authors prefer to use the split dose regimen in all patients with GFR more than 50ml/min.

Patients not fit for Cisplatin-based chemotherapy

In patients not fit to receive cisplatin, the options include carboplatin, or non-platin based therapies.

Carboplatin:

Patients with GFR more than 30ml/min but less than 50 ml/min are typically administered carboplatin based regimen, if there are no other contraindications for carboplatin. The benefit of carboplatin-based

therapy was demonstrated in the EORTC trial 30986 of 238 chemotherapy-naïve patients with impaired renal function (glomerular filtration rate <60 but >30 mL/min) and/or a poor performance status (ECOG 2) were randomly assigned to treatment with carboplatin and gemcitabine, or methotrexate, carboplatin, and vinblastine (MCAVI) [242]. The benefit of gemcitabine carboplatin regimen was higher ORR (41 versus 30 percent, not reached statistical significance, and less grade toxicities overall (9 versus 21 percent). However, there was no difference in median OS (nine versus eight months, HR for death 0.94, 95% CI 0.72-1.22), no difference in median PFS (six versus four months, HR for progression 1.04, 95% CI 0.80-1.35).

Non-platinum based regimens:

Regimens that combine gemcitabine with a taxane (paclitaxel or docetaxel) rather than a platinum are options for initial therapy in patients with advanced urothelial cancer. The combination of gemcitabine with paclitaxel is reported have objective response rates of 54-70 percent and median survival of 13-16 months [243]. Grade 3/4 toxicity was primarily hematologic, including leukopenia (46%), thrombocytopenia (13%), and anemia (28%). A phase II study employing gemcitabine and docetaxel reported overall response rate of 52% with median OS of 15 months [244].

Immunotherapy for patients unfit for any platinum based chemotherapy

Pembrolizumab:

In the phase II KEYNOTE-052 study, 370 patients with advanced urothelial carcinoma who were not eligible for a cisplatin-based regimen received initial systemic therapy with pembrolizumab at 200 mg every three weeks for up to two years [245]. The objective response rate, the primary endpoint of the study, was 29 percent for the entire cohort. The median duration of response was 33 months. The objective response rate was higher in patients with combined positive score (CPS) >10 compared with those with CPS 10 (47 versus 21 percent). Overall, the median OS was 11.3 months and three-year OS was 22 percent. Based on this data, pembrolizumab is approved for patients who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (CPS 10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Atezolizumab:

In a single-arm phase II study, Atezolizumab (total dose 1200 mg every three weeks) was used as first-line therapy in 119 patients in cisplatin-ineligible patients [246]. The objective response rate was 23 percent), including 9 percent with a complete response. The median OS for the entire cohort was 16 months. Based on this data, Atezolizumab is approved for patients not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering 5% of the tumor area, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Though immunotherapy with Atezolizumab or Pembrolizumab is an option in patients who are not eligible for cisplatin, however, carboplatin based chemotherapy should be preferred in these patients. If carboplatin based therapy is also not possible, then immunotherapy can be considered in such patients.

Maintenance therapy after first line chemotherapy

Avelumab (PD – L1 inhibitor) maintenance after 4 – 6 cycles of GC or gemcitabine carboplatin has shown a median OS of 24 months versus 15 months (HR HR 0.76, 95% CI 0.63-0.92) in patients with supportive care alone (p = 0.001) in the phase III JAVELIN bladder 100 study [247]. For eligibility for Avelumab maintenance, patient should have at least stable disease after chemotherapy. The benefit was observed irrespective of PDL1 positivity, cisplatin or carboplatin, 4 versus 6 cycles of chemotherapy used. The benefit was more pronounced in those with PD-L1 positive tumors (three-year OS 45 versus 35 percent, median 31 versus 19 months, HR 0.69, 95% CI 0.52-0.90) [248]. The grade ≥3 immune-related adverse event rate in those treated with avelumab was 7 percent.

Management of patients on progression after first line treatment

Evidence to provide guideline on further chemotherapy is weak and only available in the form of phase 2 trials. For patients who have progressed more than 6 months after initial platinum based chemotherapy, re-challenge with platinum based chemotherapy may be considered. Pembrolizumab has been tested in patients progressing during or after platinum-based first line chemotherapy in a phase III RCT and may be considered in patients who progress less than 6 months of platinum based therapy. In the trial, patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS in the pembrolizumab arm was 10.3 months (95% CI: 8.0–11.8) vs. 7.4 months (95% CI: 6.1–8.3) for the chemotherapy arm (HR for death, 0.73, 95% CI: 0.59–0.91, p = 0.002) independent of PD-L1 expression levels [236]. OS benefit from maintenance avelumab was still maintained despite a high proportion of patients treated with BSC receiving subsequent therapy (72 percent), most commonly PD-1 or PD-L1 inhibitors (53 percent).

Second line therapy post progression on platinum

Pembrolizumab

In the phase III KEYNOTE-045 trial, 542 patients who recurred or progressed on a platinum-containing regimen were randomly assigned to pembrolizumab (200 mg every three weeks for 24 months) or investigator's choice chemotherapy (paclitaxel, docetaxel, or vinflunine). Patients were enrolled regardless of the level of PD-L1 expression [249]. At median follow-up of 28 months, there was improved OS (median 10.1 versus 7.3 months, hazard ratio [HR] 0.70, 95% CI 0.57-0.85; one-year OS 44 versus 30 percent; two-year OS 27 versus 14 percent). Based on this data, pembrolizumab is approved for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Nivolumab

In a phase II study, 270 patients were treated with nivolumab (3 mg per kilogram every two weeks) [250]. The overall objective response rate was 19.6 percent. At seven months of follow-up, OS for the entire cohort was 8.7 months; for those with PD-L1 expression <1 and 1 percent, median OS durations were 6.0 and 11.3 months, respectively.

Avelumab

In combined analysis of two expansion of phase I studies (n=161), the objective response rate for the entire cohort was 17 percent [251].

Durvalumab and Atezolizumab are no longer used in this setting as they have failed to provide OS benefit [252].

Further lines of treatment

Patients who have progressed on platinum-based chemotherapy and immunotherapy, and have preserved performance status are candidates of further therapy, based on availability of further options and clinical trials. Patients with FGFR2/3 alterations are candidates of Erdafitinib, which is available presently on compassionate access program. Phase II trial of this drug found objective response rate of 40% with median PFS and OS of 6 and 11 months, respectively [253]. Hyperphosphatemia is a class effect of FGFR inhibitor and it occurs in upto 78% patients, other adverse effects include stomatitis (35%), diarrhoea (54%) and dry mouth (46%) [254]. Enfortumab vedotin was evaluated in an open-label phase II trial (EV-201) of 91 patients with locally advanced or metastatic disease who were ineligible for cisplatin, had not received prior platinum-based chemotherapy in the locally advanced or metastatic setting, and were previously treated with either a PD-1 or PD-L1 inhibitor [255]. The study found objective response rate of 52% with complete response of 20%. Presently this drug is not available in India. There is randomized phase II trial of 199 in which nabpaclitaxel and paclitaxel demonstrated similar overall survival (7.5 versus 8.8 months), progression-free survival (3.4 versus 3.0 months), and objective response rates (22 versus 25 percent) [256]. Based on this data, in patients who have progressed on platinum based therapy and immunotherapy (or, not eligible for immunotherapy), taxanes are commonly used in real-world scenario.

8 Areas of Research

There is an initial data of activity of Androgen receptor (AR) inhibitors in advanced urothelial cancers. AR is expressed in 11-55% patients of urothelial cancer [257]. In a I/Ib trial, 10 patients were enrolled to evaluate the effects of enzalutamide and gemcitabine and cisplatin in metastatic urothelial cancer. This combination enzalutamide and gemcitabine and cisplatin was well tolerated with expected toxicities, and having median OS of 10.6 months and median PFS of 7.7 months, while in a female patient showed complete response (CR) and continued to remain in CR for 24 months [258]. In resource constrained settings, where Avelumab maintenance is not feasible, this approach can be considered in a trial setting.

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10 Executive Summary

- Painless visible haematuria is the most common presenting complaint in bladder cancer.
- Examination of voided urine for exfoliated cancer cells has high sensitivity in high-grade tumours and is a useful indicator in cases of high-grade malignancy or carcinoma in situ (CIS).
- Local staging imaging of bladder cancer with MRI/ CECT is recommended before patient is taken up for trans-urethral resection of bladder tumour (TURBT).
- If a bladder tumour has been visualized unequivocally by imaging studies trans-urethral resection of bladder tumour (TURB) to be done.
- Metastatic work up is recommended in case of muscle invasive bladder cancer (Diagnosed radiologically or TURBT). CECT thorax/ abdomen and pelvis with CT urography is recommended.
- Adjuvant intra-vesical therapies (BCG) are indicated to decrease recurrence and progression in non-muscle invasive bladder cancer. The duration of adjuvant therapy depends on risk stratification.
- Neoadjuvant chemotherapy is strongly recommended for muscle invasive bladder cancer before radical cystectomy. No role of adjuvant radiotherapy.
- In patients not suitable for surgery, bladder preservation with chemo-radiation is alternative.
- Metastatic bladder cancer patients treated by platinum based chemotherapy in first line therapy. Avelumab maintenance to be considered after chemotherapy. Role of immune checkpoint inhibitors is evolving.