BLADDER CANCER

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- Chair of the Committee of Egyptian health council Guidelines: Prof Hussein Khaled.
- The Oncology Committee Members: Ebtesam Saad Eldin, Ehab Khalil, Emad Hamada, Fouad Abuotaleb, Hesham Elghazaly, Hesham Tawfik, Khaled Abdelkarim, Lobna ezz Elarab, Mary Gamal, Mohamed Abdel Mooti, Mohamed Gamil, Nervana Hussein, Ola Khorshid, Omar Sherif Omar, Rasha Fahmi, Rasha Shaltout, Samir Shehata, Yousri Wasef and Yousri Rostom.
- The Genito-urinary Cancer Scientific Committee Members: Ehab Khalil , Emad Hamada, Hatem Abul Kasem, Hesham Tawfik, Nervana Hussein.
- The Urology Committee Members: Hassan Abol-Enein, Amr Elsawy, Ahmed Moein, Adel Atta

➢ Abbreviations

BCG, bacillus Calmette-Guerin.
ChT, chemotherapy.
CIS, carcinoma in situ.
EORTC, European Organization for Research and Treatment of Cancer.
G, grade.
HG, high grade.
LG, low grade.
NMIBC, non-muscle-invasive bladder cancer.
PD-L1, Programmed death ligand 1
PLND, pelvic lymph node dissection
PUNLMP, papillary urothelial neoplasm of low malignant potential.
TCGA, The Cancer Genome Atlas
TURBT, transurethral resection of the bladder tumor.
UTUC, Upper Tract Urothelial Carcinoma

➢ Executive Summary

Recommendations	***Strength of the recommendation***
DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY	
Painless hematuria is the most common presenting symptom in bladder cancer and should in all cases be investigated	*Strong*
The diagnosis of bladder cancer is based on cystoscopic examination of the bladder and histological evaluation of tissue obtained either with cold-cup biopsy or TURBT, where complete resection of all tumor tissue should be achieved whenever possible and muscle tissue should be included in the biopsies, except when a Ta/LG is expected	*Strong*
Cross-sectional upper tract imaging (CT/MRI urography) is recommended to screen for synchronous UTUC, in cases of HG bladder cancer	*Conditional*
Pathological diagnosis should be made according to latest WHO classification	*Strong*
In addition to stage and grade, presence and percentage of variant histology, lymphovascular invasion and presence of muscularis propria should be reported	*Strong*
Urine cytology can facilitate the diagnosis of HG UC but cannot be used as the primary method of histological diagnosis	*Conditional*
Molecular diagnostics such as The Cancer Genome Atlas (TCGA) classification and PD-L1 status can be considered in selected cases.	*Conditional*
STAGING AND RISK ASSESSMENT	
Staging of NMIBC	
Patients with NMIBC should be classified into four risk categories based on tumor characteristics (low , intermediate , high and very-high-risk) as shown in table 1.	*Strong*

Regional and distant staging of MIBC	
In patients with invasive disease (≥T1), regional and distant staging should be carried out with further imaging studies such as contrast-enhanced CT of chest-abdomen-pelvis or MRI of abdomen/pelvis combined with chest CT	*Strong*
FDG-PET-CT may aid in the detection of LN and distant metastases	*Conditional*
MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE	
Treatment of NMIBC	
In patients with low-risk NMIBC and those with small papillary recurrences, detected >1 year after the previous tumor, single, immediate, intravesical chemotherapy instillation, such as mitomycin C, or gemcitabine is recommended, in combination with continued cystoscopic surveillance	*Strong*
In patients with intermediate-risk NMIBC, additional courses of intravesical therapy are recommended, and is consisting of either instillations of Chemotherapy for a maximum of 1 year, or 12 months of BCG instillation therapy with six BCG instillations at weekly intervals, followed by three BCG instillations each at 3, 6 and 12 months	*Strong*
In patients with high-risk NMIBC, full dose intravesical BCG for 1-3 years (at least 1 year) is recommended with induction as previously mentioned for 6 weeks followed by instillations at 3, 6, 12, 18, 24, 30 and 36 months	*Strong*
Planned cystoscopic surveillance per high risk NMIBC schedule should be performed.	*Strong*
In case of very high risk or BCG unresponsive, radical cystectomy could be offered	*Conditional*
Treatment of MIBC	
RC with standard PLND is the standard treatment of MIBC T2-T4a, N0 M0	*Strong*
Patients with radiological suspicious node-positive disease (cN1) should be considered for preoperative platinum-based Chemotherapy, however surgery can be considered in selected cases	*Strong*
Organ-preservation therapy with radiotherapy, as part of multimodal schema for MIBC, is a reasonable option for patients with solitary tumors <7cm with no or unilateral hydronephrosis, and no extensive carcinoma in situ, also for patients seeking an	*Conditional*

alternative to RC and those who are medically unfit for surgery	
Contemporary organ-preservation protocols should utilize tri-modality combination of TURBT, radiotherapy and chemotherapy	*Strong*
Following completion of bladder preserving therapy, clinicians should perform regular surveillance with computed tomography (CT) scans, cystoscopy, and urine cytology.	*Strong*
Three to four cycles of cisplatin-based neoadjuvant chemotherapy should be given for MIBC	*Strong*
The use of adjuvant cisplatin-based Chemotherapy in patients with pathologic T3, T4, N+ after cystectomy who did not receive neoadjuvant therapy should be considered	*Strong*
DDMVAC with growth factor support is the preferred regimen in the neoadjuvant setting , however Gemcitabine and cisplatin is a reasonable alternative	*Strong*
Carboplatin should not be substituted for cisplatin in the perioperative setting	*Strong*
For patients who are not candidates for cisplatin , there are no data to support a recommendation for perioperative chemotherapy	*Strong*
Standard radical cystectomy with curative intent need to obtain negative margins and should include removal of the bladder, prostate, and seminal vesicles in males; bladder in females and should consider removal of adjacent reproductive organs based on individual disease characteristics. Bilateral pelvic lymphadenectomy should include removal of a minimum, the external and internal iliac and obturator lymph nodes.	*Strong*
Indications of Adjuvant radiotherapy after cystectomy 1- P T3 / T4 MIBC 2- Pathologically node positive 3- Positive margins	*Strong*
<u>Postoperative adjuvant RT</u> Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, lymph nodes. Areas at risk for harboring residual microscopic disease should receive 45–50.4 Gy EBRT.	*Strong*

Involved resection margins and areas of extranodal extension should be boosted to 54–60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66–70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer can be considered for added tumor cytotoxicity	
Treatment of advanced/metastatic disease	
First line systemic therapy	
For Cisplatin eligible patients, gemcitabine and cisplatin or dd-MVAC (with growth factor support) regimens should be used	*Strong*
For Cisplatin ineligible patients, gemcitabine and carboplatin regimens should be used	*Strong*
Second and subsequent lines of therapy	
Patients with good PS *Second line of therapy should include either single agents as gemcitabine, paclitaxel or docetaxel, vinflunine, or combination regimens as Gemcitabine and paclitaxel, or Ifosfamide, doxorubicin, and gemcitabine or other combinations*	*Strong*
In patients with progression free survival > 12 months after platinum (cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible	*Conditional*
Palliative RT can be offered for palliation (bleeding, pain) *For palliative RT, consider a dose of 30 Gy in 10 fractions or 21 Gy in 3 fractions.*	*Strong*

➢ Introduction

Bladder cancer is the second most common cancer in males and the third most common in the Egyptian population with more than 13 thousand newly diagnosed cases. [(1)] Moreover, it is also the third cause of cancer death in Egypt after hepatocellular carcinoma and breast cancer with estimated number of more than 7 thousand deaths in 2022.

Purpose and scope

These guidelines will help to improve the quality of care for both NMIBL and MIBC patients via providing a uniform standard of care across the country to help in early diagnosis and treatment for bladder cancer, with less aggressive treatment options and improved clinical outcomes. These guidelines cover primary diagnosis, staging, treatment and follow-up of bladder cancer patients.

➢ Target audience

Clinicians who are involved in the care and treatment of patients with bladder cancer, including medical oncologists, radiation oncologists, clinical oncologists, onco- and uro-surgeons, interventional radiologists, radiologists and pathologists.

➢ Methodology

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation. inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guidelines must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence). - Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cutoff point or rank the guidelines (any guideline scoring above 50% on the rigor dimension was retained)

The NCCN, ESMO, NICE guidelines are the main sources used while formulating the national guidelines for breast cancer.

➢ Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine how to upgrade or downgrade the quality of evidence.

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

➢ The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations: With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations: These are made when there is greater uncertainty about the four factors above (Table 2) or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations; when there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

➢ Recommendations

1. DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

- **Painless hematuria is the most common presenting symptom in bladder cancer and should in all cases be investigated**

Strong recommendation, retrospective cohort studies or case control studies, strong evidence for efficacy with a substantial clinical benefit (1).

- **The diagnosis of bladder cancer is based on cystoscopic examination of the bladder and histological evaluation of tissue obtained either with cold-cup biopsy or TURBT. Complete resection of all tumour tissue should be achieved when possible. Muscle tissue should be included in the biopsies, except when a Ta/LG is expected**

Strong recommendation, retrospective cohort studies or case control studies, strong evidence for efficacy with a substantial clinical benefit (2).

- **Cross-sectional upper tract imaging (CT/MRI urography) is recommended to screen for synchronous UTUC, in cases of HG bladder cancer**

Conditional recommendation, retrospective cohort studies or case control studies, strong or moderate evidence for efficacy but with a limited clinical benefit (2).

- **Pathological diagnosis should be made according to latest WHO classification**

Strong recommendation, retrospective cohort studies or case control studies, strong evidence for efficacy with a substantial clinical benefit (3).

- **In addition to stage and grade, presence and percentage of variant histology, lymphovascular invasion and presence of muscularis propria should be reported**

Strong recommendation, retrospective cohort studies or case control studies, strong evidence for efficacy with a substantial clinical benefit (3).

- **Urine cytology can facilitate the diagnosis of HG UC but cannot be used as the primary method of histological diagnosis**

Conditional recommendation, retrospective cohort studies or case control studies, strong or moderate evidence for efficacy but with a limited clinical benefit (4).

- **Molecular diagnostics such as The Cancer Genome Atlas (TCGA) classification and PD-L1 status can be considered for selected cases**

Conditional recommendation, retrospective cohort studies or case control studies, insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (5).

2. STAGING AND RISK ASSESSMENT

Staging of NMIBC

- **Patients with NMIBC are classified into four risk categories based on tumor characteristics (low , intermediate , high and very-high-risk) as shown in table 1.**

Strong recommendation, retrospective cohort studies or case control studies, strong or moderate evidence for efficacy but with a limited clinical benefit (6,7).

Regional and distant staging of MIBC

- **In patients with invasive disease (>T1), regional and distant staging should be carried out with further imaging studies such as contrast-enhanced CT of chest-abdomen-pelvis or MRI of abdomen/pelvis combined with chest CT**.

Strong recommendation, retrospective cohort studies or case control studies, strong or moderate evidence for efficacy but with a limited clinical benefit (8).

- **FDG-PET-CT may aid in the detection of LN and distant metastases**

Conditional recommendation, retrospective cohort studies or case control studies, Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), (9).

3. MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Treatment of NMIBC

- **In patients with low-risk NMIBC and those with small papillary recurrences, detected >1 year after the previous tumor, single, immediate, intravesical chemotherapy instillation, such as mitomycin C or gemcitabine, is recommended, in combination with continued cystoscopic surveillance.**

Strong recommendation, evidence from large randomized, controlled trial of good methodological quality, meta-analyses of well-conducted randomized trials without heterogeneity, strong evidence for efficacy with a substantial clinical benefit (10,11)

- **In patients with intermediate-risk NMIBC, additional courses of intravesical therapy are recommended, and is consisting of either instillations of Chemotherapy for a maximum of 1 year, or 12 months of BCG instillation therapy with six BCG instillations at weekly intervals, followed by three BCG instillations each at 3, 6 and 12 months.**

Strong recommendation, meta-analyses of well-conducted randomized trials without heterogeneity, strong evidence for efficacy with a substantial clinical benefit (12).

- **In patients with high-risk NMIBC, full dose intravesical BCG for 1-3 years (at least 1 year) is recommended with induction as previously mentioned for 6 weeks followed by instillations at 3, 6, 12, 18, 24, 30 and 36 months.**

Strong recommendation, evidence from large randomized, controlled trial of good methodological quality, strong evidence for efficacy with a substantial clinical benefit (13).

- **Planned cystoscopic surveillance per high risk NMIBC schedule should be performed.**

Strong recommendation, evidence from large randomized, controlled trial of good methodological quality, strong evidence for efficacy with a substantial clinical benefit (13)

- **In case of very high risk or BCG unresponsive, radical cystectomy could be offered.**

Conditional recommendation, prospective cohort studies, strong or moderate evidence for efficacy but with a limited clinical benefit (14).

Treatment of MIBC

- **RC with standard PLND is the standard treatment of MIBC T2-T4a, N0 M0**

Strong recommendation, meta-analyses of well-conducted randomized trials, strong evidence for efficacy with a substantial clinical benefit (15).

- **Patients with radiological suspicious node-positive disease (cN1) should be considered for preoperative platinum-based Chemotherapy , however surgery can be offered in selected cases**

Strong recommendation, retrospective cohort studies or case control studies, Strong or moderate evidence for efficacy but with a limited clinical benefit (16-18).

- **Organ-preservation therapy with radiotherapy, as part of multimodal schema for MIBC, is a reasonable option for patients with solitary tumors <7cm with no or unilateral hydronephrosis, and no extensive carcinoma in situ, also for patients seeking an alternative to RC and those who are medically unfit for surgery**

Conditional recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta analyses of such trials or of trials with demonstrated heterogeneity, strong or moderate evidence for efficacy but with a limited clinical benefit (19).

- **Contemporary organ-preservation protocols should utilize tri-modality combination of TURBT, radiotherapy and chemotherapy**.

Strong recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta analyses of such trials or of trials with demonstrated heterogeneity, strong or moderate evidence for efficacy but with a limited clinical benefit (20).

- **Following completion of bladder preserving therapy, clinicians should perform regular surveillance with computed tomography (CT) scans, cystoscopy, and urine cytology.**

Strong recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta analyses of such trials or of trials with demonstrated heterogeneity, strong or moderate evidence for efficacy but with a limited clinical benefit (20).

- **Three to four cycles of cisplatin-based neoadjuvant chemotherapy should be given to MIBC.**

Strong recommendation, meta-analyses of well-conducted randomized trials, strong evidence for efficacy with a substantial clinical benefit (21-25).

- **The use of adjuvant cisplatin-based Chemotherapy in patients with pathological T3/T4/N+ who did not receive neoadjuvant therapy should be considered.**

Strong recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or metanalyses of such trials or of trials with demonstrated heterogeneity, Strong or moderate evidence for efficacy but with a limited clinical benefit (24).

- **DDMVAC with growth factor support is the preferred regimen in the neoadjuvant setting , however Gemcitabine and cisplatin is a reasonable alternative**

Strong recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or metanalyses of such trials or of trials with demonstrated heterogeneity, Strong or moderate evidence for efficacy but with a limited clinical benefit (24).

- **Carboplatin should not be substituted for cisplatin in the perioperative setting**

Strong recommendation, retrospective analysis , Strong or moderate evidence for efficacy but with a limited clinical benefit (26)

- **For patients who are not candidates for cisplatin , there are no data to support a recommendation for perioperative chemotherapy**

Strong recommendation, retrospective analysis , Strong or moderate evidence for efficacy but with a limited clinical benefit (26)

- **Standard radical cystectomy with curative intent need to obtain negative margins and should include removal of the bladder, prostate, and seminal vesicles in males; bladder in females and should consider removal of adjacent reproductive organs based on individual disease characteristics. Bilateral pelvic lymphadenectomy should include removal of a minimum, the external and internal iliac and obturator lymph nodes.**

Strong recommendation, multi-institutional analysis , Strong or moderate evidence for efficacy but with a limited clinical benefit (27)

- **Indications of Adjuvant radiotherapy after cystectomy 1-P T3 / T4 MIBC 2-Pathologically node positive 3-Positive margins**

Strong recommendation, prospective studies , Strong or moderate evidence for efficacy but with a limited clinical benefit (28)

- **Postoperative adjuvant RT : Treatment field should encompass areas at risk for harboring residual microscopic disease based on pathologic findings at resection and may include resection bed, lymph nodes.Areas at risk for harboring residual microscopic disease should receive 45–50.4 Gy EBRT. Involved resection margins and areas of extranodal extension should be boosted to 54–60 Gy if feasible based on normal tissue constraints. Areas of gross residual disease should be boosted to 66–70 Gy, if feasible based on normal tissue constraints. Concurrent chemotherapy with regimens used for bladder cancer can be considered for added tumor cytotoxicity**

Strong recommendation, consensus guidelines , Strong or moderate evidence for efficacy but with a limited clinical benefit (29)

4- Treatment of advanced/metastatic disease

First line systemic therapy

- **For Cisplatin eligible patients, gemcitabine and cisplatin or dd-MVAC (with growth factor support) regimens should be used.**

Strong recommendation, evidence from at least one large randomized, controlled trial of good methodological quality, strong evidence for efficacy with a substantial clinical Benefit (30-35).

- **For Cisplatin ineligible patients, gemcitabine and carboplatin regimens should be used.**

Strong recommendation, evidence from at least one large randomized, controlled trial of good methodological quality, strong evidence for efficacy with a substantial clinical Benefit (36).

Second and subsequent lines of therapy

- **Patients with good PS**
  Second and subsequent lines of therapy should include either single agents as gemcitabine, paclitaxel or docetaxel, vinflunine, or combination regimens as Gemcitabine and paclitaxel, or Ifosfamide, doxorubicin, and gemcitabine or other combinations
  Strong recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality), Strong or moderate evidence for efficacy but with a limited clinical benefit, (37, 38).

- **In patients with progression free survival > 12 months after platinum (cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible**

Conditional recommendation, small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality), Strong or moderate evidence for efficacy but with a limited clinical benefit, (37, 38).

• Palliative RT can be offered for palliation (bleeding, pain) , For palliative RT, consider a dose of 30 Gy in 10 fractions or 21 Gy in 3 fractions.
Strong recommendation, Retrospective multicenter study , Strong or moderate evidence for efficacy but with a limited clinical benefit (39**)**

5- Urinary diversion after radical cystectomy

Different types of segments of the intestinal tract can be used to reconstruct the urinary tract, including the ileum, colon and appendix, with ileum used in most cases. Several studies have compared advantages and disadvantages in terms of quality of life (QoL), sexual function, urinary continence and body image between different urinary diversions (40)

Different types of urinary diversion

For the choice of urinary diversion, comorbidity, cardiac, pulmonary and cognitive function are important factors that should be considered, along with the patient's social support and preference). Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication (41).

- **Uretero-cutaneostomy**

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, blood loss, transfusion rate, stay at intensive care and length of hospital stay are lower in patients treated with ureterocutaneostomy as compared to ileal conduit. In frail patients and/or in those with a solitary kidney who need a supravesical diversion, uretero-cutaneostomy is the preferred procedure (42).

Due to the smaller diameter of the ureters, stoma stenosis and ascending UTIs have been observed more frequently for this technique as compared to using small or large bowel to create an intestinal stoma.

- **Ileal conduit**

The ileal conduit is an established option with well-known/predictable results. Early post-operative complications include UTIs, pyelonephritis, ureteroileal leakage and stenosis which occur in 48% of patients (43)

- **Orthotopic neobladder**

According to the published literature, an orthotopic bladder substitution to the urethra is used in approximately 10–20% of both male and female patients. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, and sphincter relaxation. The terminal ileum is most often used for orthotopic bladder substitution. Early and late morbidity in up to 22% of patients is reported (44)

Various forms of upper urinary tract reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described (45). According to the long-term results, the upper urinary tract is protected sufficiently by either method (46).

- **Continent cutaneous urinary diversion**

Continent cutaneous urinary diversion (a low-pressure detubularised ileal reservoir for self-catheterisation) and uretero-rectosigmoidostomy are rarely used techniques nowadays, due to their high complication rates, including stomal stenosis, incontinence in the continent cutaneous diversion, UUT infections and stone formation in case of uretero-rectosigmoidostomy (47).

- **Patient selection**

Ensuring that patients make a well-informed decision about the type of urinary diversion is associated with less decision regret post-operatively, independent of the method selected (48). Therefore, all applicable forms of urinary diversion should be discussed, taking into account patient preference, comorbidities, age and tumor characteristics.

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy which is a contraindication for a neobladder reconstruction. Non-muscle-invasive BC in prostatic urethra or bladder neck biopsies does not necessarily preclude orthotopic neobladder substitution, provided that patients undergo regular follow-up cystoscopy and urinary cytology (49). Localization of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Bladder neck biopsies prior to RC are important in women scheduled for an orthotopic bladder substitute (50).

In the presence of positive LNs, orthotopic neobladder can be considered in case of N1 disease, but not in N2 or N3 tumors (51).

Oncological results after orthotopic neobladder or ileal conduit are similar in terms of local or distant metastasis recurrence, but secondary urethral tumors seem less common in patients with a neobladder compared to those with conduits or continent cutaneous diversions (52).

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and to be manually skillful to be able to deal with their diversion. Contraindications to continent urinary diversions include: debilitating neurological and psychiatric illnesses; limited life expectancy; severe impaired liver or renal function.

Relative contraindications for an orthotopic neobladder are high-dose pre-operative RT, complex urethral strictures and severe urethral sphincter-related incontinence (53).

Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions prefer ileal orthotopic neobladders and ileal conduits based on clinical experience.

➢ Research Gaps

- This guideline will be updated whenever there is new evidence.
- Evaluation of real world data on the use on new targeted and immune-therapeutic agents in bladder cancer in Egypt.
- Cost effective analysis of new therapeutic agents in Egypt.
- Define the molecular biologic profiles of our patients with mixed and variant tumors.

➢ Annexes

Annex 1. Risk group stratification of patients with NMIBC and treatment recommendations	
Risk group stratification	**Characteristics**
Low-risk tumors	Primary, solitary, Ta G1 (PUNLMP, LG), <3 cm, no CIS
Intermediate-risk tumors	All tumors not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumors	Any of the following: _ T1 tumour _ HG tumour _ CIS _ Multiple, recurrent and large (>3 cm) Ta G1-G2/LG tumours (all features must be present
Subgroup of highest-risk tumors	_ T1 G3/HG associated with concurrent bladder CIS _ Multiple and/or large T1 G3/HG and/or recurrent T1 G3/HG, T1 G3/HG with CIS in the prostatic urethra _ Some forms of variant histology of urothelial carcinoma, lymphovascular invasion

Annex 2. American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer 8th ed., 2017)

T Primary Tumor

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Ta** Noninvasive papillary carcinoma
- **Tis** Urothelial carcinoma in situ: "flat tumor"
- **T1** Tumor invades lamina propria (subepithelial connective tissue)
- **T2** Tumor invades muscularis propria
  - **pT2a** Tumor invades superficial muscularis propria (inner half)
  - **pT2b** Tumor invades deep muscularis propria (outer half)
- **T3** Tumor invades perivesical tissue
  - **pT3a** Microscopically
  - **pT3b** Macroscopically (extravesical mass)
- **T4** Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  - **T4a** Extravesical tumor invades prostatic stroma, seminal vesicles, uterus, vagina
  - **T4b** Extravesical tumor invades pelvic wall, abdominal wall

N Regional Lymph Nodes

- **NX** Lymph nodes cannot be assessed
- **N0** No lymph node metastasis
- **N1** Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
- **N2** Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
- **N3** Lymph node metastasis to the common iliac lymph nodes

M Distant Metastasis

- **M0** No distant metastasis
- **M1** Distant metastasis
  - M1a Distant metastasis limited to lymph nodes beyond the common iliacs
  - M1b Non-lymph-node distant metastases

Annex 3. AJCC Prognostic Groups (T N M)

Stage 0a	Ta N0 M0
Stage 0is	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2a N0 M0
	T2b N0 M0
Stage IIIA	T3a N0 M0
	T3b N0 M0
	T4a N0 M0
	T1-T4a N1 M0
Stage IIIB	T1-T4a N2,N3 M0
Stage IVA	T4b Any N M0
	Any T Any N M1a
Stage IVB	Any T Any N M1b

➢ References

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