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First Brazilian consensus on the management of localized and locally advanced urothelial bladder cancer: a SBU-SBOC-SBRT-LACOG-GU panel review

Primeiro consenso brasileiro sobre o manejo do câncer de bexiga urotelial localizado e localmente avançado: uma revisão do painel SBU-SBOC-SBRT-LACOG-GU

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ABSTRACT

Introduction: Urothelial carcinoma, especially localized bladder cancer, has a substantial prevalence in Brazil with 9,480 new cases each year and 3,903 deaths, therefore progress is required in its management in order to decrease its recurrence and progression, and improve survival. **Material and Methods:** Medical oncologists, radiation oncologists, and urologists from Brazil conducted a meeting to vote the best approaches available in this country in the diagnosis, staging, and treatment of localized and locally advanced urothelial bladder carcinoma. The panel drew up 73 questions and answers were chosen considering the feasibility according to the access to drugs and the procedures used in this country. Each answer reaching 75% of voters was considered a consensus. The results of this consensus were compared with evidence published in the medical literature and rated with a level of evidence and grade of recommendation using the Oxford classification. **Results:** Transurethral resection of bladder tumors confirms the diagnosis of and provides initial treatment for non-muscle-invasive bladder cancers. Repeated resection is necessary in selected cases and should not delay

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further treatment. The use of intravesical Bacillus Calmette-Guérin is performed according to risk stratification, showing a significant reduction in tumor recurrence and progression, and improved disease-specific survival in intermediate- and high-risk patients. Radical cystectomy should be considered for high-progression risk cases after Bacillus Calmette-Guérin treatment failure and for localized muscle-invasive bladder cancer. **Conclusion:** Management of urothelial carcinoma often requires a multidisciplinary team with surgical and clinical approaches, based on the expertise of professionals and evidence from the literature.

Keywords: Urinary bladder neoplasms; Cystectomy; Consensus; Carcinoma, Transitional cell; Administration, Intravesical.

RESUMO

Introdução: O carcinoma urotelial, principalmente o câncer localizado de bexiga, tem prevalência substancial no Brasil com 9.480 novos casos a cada ano e 3.903 óbitos, portanto, é necessário avançar no seu manejo para diminuir sua recorrência e progressão, e melhorar a sobrevida. **Material e Métodos:** Médicos oncologistas, oncologistas de radiação e urologistas do Brasil realizaram uma reunião para votar as melhores abordagens disponíveis no país no diagnóstico, estadiamento e tratamento do carcinoma de bexiga urotelial localizado e localmente avançado. O painel elaborou 73 perguntas e as respostas foram escolhidas considerando a viabilidade de acordo com o acesso aos medicamentos e os procedimentos utilizados no país. Cada resposta que atingiu 75% dos eleitores foi considerada um consenso. Os resultados desse consenso foram comparados com as evidências publicadas na literatura médica e avaliados com um nível de evidência e grau de recomendação usando a classificação de Oxford. **Resultados:** A ressecção transuretral de tumores de bexiga confirma o diagnóstico e fornece tratamento inicial para cânceres de bexiga não músculo-invasivo. A ressecção repetida é necessária em casos selecionados e não deve atrasar o posterior tratamento. O uso do Bacillus Calmette-Guérin intravesical é realizado de acordo com a estratificação de risco, mostrando redução significativa na recorrência e progressão tumoral e melhora na sobrevida específica da doença em pacientes de risco intermediário e alto. A cistectomia radical deve ser considerada para casos de alto risco de progressão após falha no tratamento com Bacillus Calmette-Guérin e para câncer de bexiga músculo-invasivo localizado. **Conclusão:** O manejo do carcinoma urotelial muitas vezes requer uma equipe multidisciplinar com abordagens cirúrgicas e clínicas, com base na experiência dos profissionais e evidências da literatura.

Descritores: Neoplasias da bexiga urinária; Cistectomia; Consenso; Carcinoma de célula transicional; Administração intravesical.

INTRODUCTION

Urothelial carcinoma (UC), formerly known as transitional cell carcinoma, comprises carcinomas of the urethra, bladder, ureters, and renal pelvis, and it is the most frequent bladder cancer worldwide. Urothelial bladder carcinoma (UBC) is a common malignancy and was the sixth most prevalent cancer worldwide in 2018, with 539,393 new cases and 199,992 deaths.[1] In Brazil, 3,903 deaths occurred due to UBC in 2015 and 9,480 new cases are expected per year for the 2018-2019 biennium.[2] It is more frequent in Caucasians and in men (3:1), but women present with a worse prognosis, and incidence increases with age.[3-5] Tobacco use is the main risk factor, increasing recurrence risk[6] and decreasing disease-specific and overall survival (OS).[7] Other important risk factors are contact with other carcinogens, especially through occupational exposure, such as working with dye, rubber, paints, and solvents, a family history of bladder cancer, use of cyclophosphamide and pioglitazone, pelvic radiation, long-term bladder catheterization, HPV infection and *Schistosoma haematobium* infection.[3,8,9] UBC can be categorized into non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), or metastatic disease. The non-muscle-invasive category encompasses Ta, T1 reaching the lamina propria but sparing the detrusor muscle and carcinoma *in situ*

(CIS). It is usually multifocal and corresponds to approximately 75% of the diagnoses of UBC.[3,10] Despite available treatments, the recurrence rate of NMIBC is high – approximately 50% risk in 5 years,[10-12] with a notable risk of progression – up to 20% of cases progress to the muscle-invasive stage,[12] demanding life-long disease monitoring. MIBC at first diagnosis comprises the minority of cases, and despite a more aggressive approach such as radical cystectomy, perioperative chemotherapy or tri-modal treatment (TMT), it presents a high mortality rate for patients with distant metastatic disease, with a 5-year OS of less than 10%.[13]

This paper aimed to provide a consensus on the management of urothelial carcinoma in Brazil, to facilitate decision-making and provide a straightforward reference for physicians for the best practice available in this country considering the feasibility according to the limited access to drugs and procedures, such as unavailability of mitomycin, Bacillus Calmette-Guérin (BCG), and blue light cystoscopy.

MATERIAL AND METHODS

Experts representing The Brazilian Society of Clinical Oncology (SBOC), the Latin American Cooperative Oncology Group-Genitourinary (LACOG-GU), the Brazilian Society of Urology (SBU) and the Brazilian Society of Radiotherapy (SBRT) prepared 73 questions related to localized and locally advanced urothelial carcinoma and held a meeting in Sao Paulo, Brazil, to establish recommendations in the management of the disease with a focused on bladder cancer. They were 19 medical oncologists, 4 radiation oncologists, and 18 urologists with expertise in the management of bladder cancer, who were chosen by the above-mentioned institutions. The questions were presented to all participants for voting using electronic input device, and a consensus was achieved if one answer was chosen by at least 75% of the voters. Questions not reaching the consensus were voted once more after a brief discussion, and in case of failure to achieve at least 75% of total voters again, the most voted answer was considered the recommendation. Each participant could had abstain from voting if judged to be not prepared/not experienced enough to choose an answer or if they had any conflict of interest with the specific question.

Each chosen answer was rated with a level of evidence (LE) and grade of recommendation (GR), according to the medical literature using the 2009 Oxford Center for Evidence-Based Medicine Levels of Medicine classification[14] (Table 1).

RESULTS

Diagnosis and staging in NMIBC

The goal of cancer screening is to provide an early diagnosis with the aim of achieving higher odds for cure. Screening tests should be cost-effective and accurate with high sensitivity and specificity, causing minimum harm and providing the best benefit. There is no standard screening test for urothelial

Table 1. Levels of evidence - Oxford Centre for Evidence-based Medicine, 2009.

Level	Type of evidence
Ia	Systematic review with homogeneity of randomized control trials
1b	Individual randomized control trial with a narrow confidence interval
1c	All or none related outcome
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low-quality randomized control trials, e.g., <80% follow-up)
2c	"Outcomes" research; Ecological studies
3a	Systematic review with homogeneity of case – control studies
3b	Individual case – control study
4	Case-series (and poor-quality cohort and case – control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

bladder carcinoma, and therefore, routine screening should not be performed (consensus, LE: 5 GR: D). Most bladder cancer (BCa) cases are symptomatic; asymptomatic random findings being very rare, with only 2% of the general incidence.[15,16] Screening could be evaluated in selected high-risk patients;[17] however, there is still not enough evidence for this to be recommended as daily practice.

In patients with a suspicion of BCa, evaluation with white light cystoscopy (WLC) is indicated, since it is considered the gold standard approach for BCa diagnosis and monitoring, especially for papillary lesions.[18] However, cystoscopy is an invasive, costly, and time- consuming procedure that causes discomfort and pain for the patient,[19] since flexible cystoscopies are not widely available in Brazil due to prohibitive costs. Therefore, in cases of suspected bladder lesions already seen on previous imaging examination, cystoscopy might be omitted, being used as necessary in the minority of cases prior to transurethral resection (TUR) where lesions had already been seen on previous imaging examination (consensus, LE: 5 GR: D). WLC is the most commonly used technique, despite limitations such as being unable to identify flat lesions, CIS or small papilloma.

Technologies such as narrow-band imaging or fluorescent cystoscopy should be used, if available, during the endoscopic evaluation of lesions in most cases (recommendation, LE: 1a GR: A), as they can improve tumor detection,[20-22] with a 90% detection rate for CIS[23] and a higher sensitivity compared to WLC.[20,24] A better visualization results in a more complete resection, reducing the residual tumor rate[25]and recurrence[20], and potentially improving recurrence-free survival (RFS).[26] Positive cytology and negative standard cystoscopy are a good indication for these new, yet more expensive and expendable, technologies. The upper urinary tract (UUT) should also always be evaluated in cases of positive cytology and negative standard cystoscopy (consensus, LE: 5 GR: D). UUT carcinoma is less frequent than UBC and usually presents as asymptomatic hematuria.[27] The investigation should be performed by computed tomography (CT) or magnetic resonance imaging (MRI) and ureteroscopy (consensus, LE: 4 GR: C) because normal ultrasonography cannot rule out a diagnosis.[28,29] CT urography has higher sensitivity, specificity, and detection rate accuracy of UUT carcinomas than intravenous urography.[30] MRI also has substantial sensitivity, specificity, and detection rate accuracy,[31] but is mostly preferred in patients for whom CT is contraindicated, including an allergy to iodinated contrast agents or renal insufficiency.[32] In patients with bladder tumors demonstrated by cystoscopy, imaging (CT or MRI) before TUR should be indicated only in those patients with high-grade tumors or suspicion of muscle layer invasion (consensus, LE: 5 GR: D).[9]

CIS is a non-muscle-invasive, high-grade tumor with a high-risk of recurrence and progression, corresponding to 10% of NMIBC cases.[33] In cases of suspected CIS, random cold-cup biopsies should be performed, sampling the trigone, bladder dome, right, left, anterior and posterior bladder wall (consensus, LE: 1b GR: A) because CIS is usually a flat, multifocal tumor that can be macroscopically indistinguishable from normal mucosa.[34,35] Random biopsies in suspected patients have shown a diagnosis of CIS in up to 25% of the population.[36,37]

Non-urothelial bladder carcinoma corresponds to less than 5% of bladder cancer cases[38] and should be considered high-risk tumors (consensus, LE: 2b GR: B). In general, non-urothelial BCa is associated with lower survival rates when compared to UC, with median survival ranging from 17 months to 179 months, depending on the histology, and 5-year survival rates from 31 to 58%.[39]

Transurethral resection of the bladder

Transurethral resection of bladder tumor (TURBT) is the standard procedure for treating and diagnosing NMIBC. It consists of removing all visible tumors, including the apparently normal mucosa of the border, and resection of the muscle layer at the base of the tumor.[40] The quality of the TURBT results in a decrease in the tumor recurrence rate.[41,42] The presence of the muscular layer in a TURBT specimen is of utmost importance for the diagnosis, staging, and management of the disease. The presence of muscle in the initial specimen is associated with lower recurrence rates compared to TURBT without muscle,[43] and it should always be present in the TURBT specimen; otherwise, a second TURBT will be necessary[44] (consensus, LE: 1b GR: A). Sampling of the prostatic urethra leads to the detection of the involvement of the prostate as a result of the bladder cancer ascending through the prostatic urethra and the prostatic ducts/acini, which is related to higher urethral recurrence[45] and lower survival rate.[46] This sampling should be performed in the presence of CIS, in cases of tumors affecting the bladder neck and trigone, in the presence of multiple tumors or following positive cytology[47,48] (consensus, LE: 1b GR: A).

Advanced age is one of the most important risk factors for bladder cancer; thus, it is not unusual to have patients with concomitant prostate hyperplasia. TUR of the prostate can be performed simultaneously with bladder tumor resection in most cases (recommendation, LE: 2a GR: B), as it does not interfere in overall tumor recurrence or recurrence in the bladder neck/prostatic fossa.[49,50]

TURBT must be repeated in cases where complete resection of the lesion was not feasible in the initial procedure (consensus, LE: 2b GR: A) and when the detrusor muscle was not present in the initial TURBT specimen in order to perform correct staging and decrease the recurrence risk[43,44] (consensus, LE: 1b GR: A), except in cases of TaLG/G1 tumors and primary CIS. Incomplete resection is one of the mechanisms of early tumor recurrence,[10] usually detected in the first three months after the initial TURBT.[12] Repeat-

ing TURBT (re- TURBT) removes the persistent tumor, confirms staging, and improves prognosis.[10]

A second endoscopic resection (re-TURBT) is indicated in high-grade cases, (consensus, LE: 4 GR: C), as the rate of recurrence of the remaining tumor from the first TURBT is reported to be up to 75%,[51] in cases of invasion of the lamina propria (consensus, LE: 1b GR: A), reducing the recurrence rate and progression,[52] and in cases with lymphovascular invasion in the specimen from the first surgery (consensus, LE: 2b GR: B), because these findings are related to a worse prognosis, with a high recurrence rate and low RFS.[53,54] Moreover, re-TURBT must not be delayed; it should be performed 1 to 6 weeks after the initial TURBT.[11]

TURBT can be replaced by fulguration (without sample removal) in most cases of small low-grade lesions (consensus, LE: 2b GR: B), and this practice is accepted without restraint, as it has been shown to be feasible, safe, and cost-effective.[55-57]

Intravesical therapy

During the consensus, the panel used a practical definition for risk stratification proposed by the International Bladder Cancer Group, which divides cases into low-, intermediate-, and high-risk diseases based on the risk of recurrence and disease progression.[58] Low-risk cases are comprised of a single lesion, pTa and low-grade tumors. Intermediate risk cases are recurrent or multiple low-grade pTa tumors. High-risk patients are those presenting with pT1 or high-grade tumors with or without CIS.

The indicated treatment in patients with low-risk, non-muscle-invasive disease after initial TURBT is single, immediate instillation of intravesical chemotherapy (IVC) (consensus, LE: 1a GR: A), except for those patients with bladder perforation after TURBT. Three meta-analyses with more than 2,000 patients each showed that a single dose of IVC is superior to resection only in NMIBC, as it prevents recurrence in up to 38% of cases and might decrease the 5-year recurrence rate in approximately 10%.[59-61] In patients with an indication for a single instillation of IVC, the best drug to be administered is mitomycin C or gemcitabine (consensus, LE: 1b GR: A). Randomized studies have shown benefits for both medications,[62,63] but there is no robust evidence supporting the superiority of either one. Unfortunately, mitomycin C is not widely available in Brazil; therefore, gemcitabine is the most recommended. Studies with gemcitabine have shown a substantial 12% reduction in recurrence rate, but no difference in progression compared to placebo,[61] and a safer profile compared to mitomycin C.[64]

The treatment indicated in patients with intermediate-risk and high-risk non-muscle- invasive disease after initial TURBT is Bacillus Calmette-Guérin (BCG) (consensus, LE: 1a GR: A). Intravesical BCG is considered first-line therapy, especially in high-risk patients, showing a significant reduction of tumor recurrence and progression, and improved disease-specific survival, superior to those of TURBT alone and IVC.[65-70] Induction with BCG consists in 6 weekly treatments, and maintenance once a week for three weeks, at months 3, 6, 12, 18, 24, 30, and 36.[71]

Patients with non-muscle-invasive intermediate- and high-risk disease with an indication of intravesical therapy (IVT) with BCG should receive maintenance treatment with BCG (consensus, LE: 1a GR: A). Maintenance with BCG downshifts and potentially reduces progression risk, showing significantly lower recurrence than mitomycin C alone, intravesical epirubicin alone or a combination of epirubicin and interferon in intermediate- and high-risk patients.[65-68,72-75]

Maintenance should be used for one year in intermediate-risk patients (consensus, LE: 1a GR: A) because BCG maintenance is superior to mitomycin C in progression prevention only if it is used in this manner.[76] High-risk patients require three years of maintenance (consensus, LE: 1b GR: A) to significantly decrease tumor recurrence rate and progression and mortality.[71,77-79]

The appropriate dose of BCG (strain Moreau, Rio de Janeiro) to be administered is 80mg or its equivalent (consensus, LE: 5 GR: D), which is the full dose. A retrospective analysis comparing the TICE and Moreau strains did not show any difference in recurrence or progression to MIBC between the treatments.[80] Dose reduction is appropriate in most selected cases for patients treated with BCG in order to reduce side effects (recommendation, LE: 1b GR: A), as a one-third dose is as effective as the full dose in intermediate- and high- risk patients – but inferior in patients with multifocal tumors – with a lower toxicity.[81,82]

In the absence of BCG, in patients with intermediate-risk and high-risk disease, the best treatment option is IVC (consensus, LE: 1a GR: A) with maintenance therapy (consensus, LE: 1b GR: A). Mitomycin C was shown to be efficient in decreasing recurrence and progression; however, it is inferior to BCG.[66] Chemohyperthermia with mitomycin C offers additional benefits with a higher rate of reduction in recurrence compared to mitomycin alone.[83] Intravesical gemcitabine shows comparable results with BCG in intermediate-risk patients but a higher recurrence rate in high-risk patients.[84,85] Evidence of maintenance therapy with IVC is still not clear. Individual randomized trials have shown a decrease in recurrence rates.[86-88] However, the results from other studies and meta-analyses did not demonstrate improvement in recurrence, progression, or survival.[89-91] Maintenance with IVC should be used for up to one year for intermediate-risk patients (consensus, LE: 1b GR: A), with the aim of increasing disease-free survival (DFS),[92] and for three years for high-risk patients (recommendation, LE: 5 GR: D).

Follow-up NMIBC

Regardless of the risk group, a follow-up cystoscopy is indicated 3-4 months after the initial TUR (with or

without adjuvant BCG) in NMIBC patients (consensus, LE: 2b GR: B). The importance of follow-up is to detect recurrence and/or progression as early as possible. Recurrence at 3 months is considered the main prognostic factor.[93] Low-grade tumors present a 50% recurrence rate[94] and high-grade tumors a 15-40% progression rate.[95]

The evaluation of the UUT should be performed only in high-risk patients (recommendation, LE: 4 GR: C) and annually for up to 5 years (recommendation, LE: 4 GR: C), as the chance of developing upper tract urothelial carcinoma (UTUC) after bladder cancer is approximately 5%.[96]

Urinary cytology has a role in NMIBC follow-up in cases of high-risk tumors (recommendation, LE: 3a GR: B), as cytology has lower sensitivity in low-grade tumors.[97]

In cases of urothelial CIS, we indicated performing random vesical biopsies during follow-up cystoscopy (recommendation, LE: 4 GR: C) because CIS can be difficult to visualize. Moreover, CIS is a high-risk tumor, and random biopsies increase the chance of diagnosis.[34-37]

The panel does not routinely recommend, in clinical practice (outside of research protocols), any type of urinary molecular biomarkers (e.g., FISH, NMP22) in NMIBC follow- up (recommendation, LE: 3a GR: B). Although it seems very promising data, the cost- effectiveness of these markers is still limited.[97]

Failure after BCG

BCG response is an important prognostic factor. Approximately 40% of patients will not respond to BCG,[(98)] of which 60% will progress to invasive disease.[90,100] Non-responder patients are classified as follows: refractory/unresponsive, with persistent high-grade disease despite 6 months of adequate therapy (induction and maintenance cycle), or any stage or grade progression within 3 months after the first cycle of BCG or recurring for up to 6 months; recurrent, with recurrent high-grade disease after 6 months of response with adequate therapy; and intolerant, with persistent disease due to the impossibility of adequate therapy because of high toxicity.[101,102]

In high-risk patients with refractoriness/unresponsiveness to IVT with BCG, the best- recommended treatment is radical cystectomy (RC) (consensus, LE: 2b GR: B). Patients who failed first-line BCG therapy should not be re-exposed to BCG unless unfit or unwilling to undergo cystectomy. In these cases, the standard of care is radical cystectomy.[103,104] There is some evidence for successful IVC treatment in patients with refractory/non-responsive disease, but no study has yet compared IVC to cystectomy. Valrubicin for BCG-refractory CIS shows 21% complete response and an 87.7% recurrence rate.[105] Treatment with intravesical gemcitabine in these cases provides only 20% RFS in one year.[106] Intravenous immunotherapy with pembrolizumab showed 28% complete response at the time of last follow-up (14 months) in patients with BCG-unresponsive disease associated with CIS and its indication was recently approved in this scenario. This data was not available at the time of the consensus meeting.

In patients with recurrent disease after complete response following IVT with BCG, the best recommended treatment is BCG re-exposure (consensus, LE: 2b GR: B), with full dose induction and maintenance (consensus, LE: 2b GR: B) if the recurrence occurred at least 1 year following the last BCG cycle, as the previous treatment does not preclude the new course of BCG showing similar cancer-free rates between retreatment and first treatment.[107] Re- exposure to BCG shows significant recurrence-free and progression-free survival[108] and a high rate of complete response.[109] Patients who recurred after BCG treatment have a 20% chance of responding to BCG again.[110] If the recurrence occurred up to 1 year following the initial treatment, the ideal treatment is cystectomy. In patients not eligible for or not willing to undergo RC, the option is IVC. High-risk patients should be treated with RC;[111] if the patient is not eligible or the treatment is rejected by the patient, inclusion in clinical studies or other IVC could be considered.

In patients with BCG therapy failure due to intolerance or lack of suitability for RC, the best recommended treatment is IVC (consensus, LE: 5 GR: D) because it has a better safety profile despite its inferior results.[73]

Failure after IVC

In patients with low-grade (recurrent or otherwise) disease, and patients who progressed to high-grade disease after IVC (single dose post-TUR), the best-recommended treatment is new resection and intravesical BCG induction and maintenance (consensus, LE: 1a GR: A). Low-grade patients with recurrence are considered intermediate-risk, and those with progression, high-risk. For both situations, patients should undergo TUR and be treated with intravesical BCG, as it has been shown to be superior to chemotherapy when administered with maintenance, presenting a 32% decrease in recurrence and a 34% decrease in progression rate in patients.[66,73]

In patients with pre-existing high-grade disease, those currently with recurrent (low grade) or for those who recurred but maintained high-grade disease after IVC (induction and maintenance), the best-recommended treatment is new resection and intravesical BCG - induction and maintenance (consensus, LE: 1a GR: A). For intermediate- and high-risk patients, the recommended first-line treatment is BCG with induction and maintenance after TUR. If for any reason they were treated with IVC, which shows inferior results,[66,73] at recurrence they should receive BCG because it is the most optimal treatment.

RC in NMIBC

RC is the standard treatment for MIBC.[112] In NMIBC, RC should be indicated as a therapeutic option in patients with high-risk Ta, T1, and CIS based on the substantial risks of recurrence and progression to muscle-invasive disease. It can be performed after

NMIBC diagnosis or after BCG failure, depending on the aggressiveness of the disease.[113] CIS is a high-grade disease with a risk of progression occurring in up to 53% of patients.[114] Isolated CIS can positively respond to BCG therapy[115] and RC. [116] RC is indicated for high-risk non-responsive/refractory patients or those intolerant to intravesical therapy, with isolated CIS or without associated CIS (consensus, LE: 2b GR: B), particularly for those who recurred early. Surgery must be performed within 2 years because DSS is directly related to the delay of RC.[104,117] Cystectomy should be considered in cases with associated CIS after staging-TUR or after refractory or intolerance of BCG (recommendation, LE: 2b GR: B), as it shows high cancer-specific survival, up to 92% in 10 years follow-up.[118] High-risk patients without CIS but presenting lymphovascular invasion with T1 disease, a histological variant, T1 disease on repeat TUR, or high-volume multifocal high-grade disease are also candidates for RC after TUR.[119]

RC in MIBC

RC with lymphadenectomy is the standard treatment for MIBC without distant metastasis, with up to 60% rate of cure for pT3 disease and 30% in pT4 or low-volume lymph node-positive pN1,[112] providing the highest rates of cure and lowest risk of recurrence.[120-122] RC is a complex surgery; the expertise of the medical team should always be considered in the RC indication and urinary diversion (UD) technique decision. For this reason, preference should be given to centers with large surgical volumes and an uro-oncological team, as the literature shows the benefit of centralized care for UBC, demonstrating better OS at high- volume centers, with lower positive surgical margins[123-125] (consensus, LE: 2a GR: B). Furthermore, RC is associated with important hospitalization costs and significant in-hospital mortality,[126] imposing risks that could discourage professionals from performing the procedure, especially on older patients with comorbidities, despite its potential benefits[127] and evidence that age should not be a factor for contraindication, as literature shows acceptable complications and mortality rates of RC with UD in octogenarians.[128] The enhanced recovery after surgery (ERAS) protocol is indicated in cases of RC because it reduces the incidence of complications with lower bleeding and fewer readmissions, reduces the hospital internment period by 10 days,[129] and does not increase costs[130] (consensus, LE: 2b GR: B).

Regarding the technique and extent of cystectomy in men, the removal of the bladder, prostate, seminal vesicles, portions of the distal ureters, and regional lymph nodes is indicated. Preservation of the prostate can be performed only in extremely selected cases with the aim of achieving better functional results because sparing it is associated with a 10 to 15% higher oncological failure rate.[131] RC in women should include the removal of the bladder, uterus, adjacent vagina, urethra, a portion of the distal ureters, and regional lymph nodes (consensus, LE: 5 GR: D).

Pelvic lymphadenectomy associated with RC has a potentially curative role[111] and reflects the quality of the surgery. Lymph node involvement is related to a higher recurrence of BCa and a shorter OS;[112] therefore, it is used for staging, prognosis, and influencing subsequent therapy, e.g., the use of adjuvant therapy[132] (consensus, LE: 2b GR: B). The standard lymphadenectomy technique is preferentially recommended, including removal of lymph nodes to the intersection of the ureters (recommendation, LE: 5 GR: D), but there is no consensus for this practice. Extended lymphadenectomy is widely used, as it removes a greater number of lymph nodes with the advantage of identifying positive nodal involvement outside the standard technique area,[133,134] but a comparative trial did not show significant difference in terms of mortality and time to recurrence.[135]

Regarding the decision of UD type after an RC, each type of diversion has its advantage and disadvantages. The decision should take into account the aspects of the disease, the patient's clinical conditions such as renal failure, liver function impairments, and bowel disorders, the surgeon's experience and the patient's preference (consensus, LE: 5 GR: D). Two main forms of diversions are used after cystectomy: nonorthotopic diversions (such as ureterocutaneostomy, ileal or colonic conduits, and continent conduits) and orthotopic diversions (such as orthotopic neobladder) (consensus, LE: 5 GR: D). There is no evidence to support the superiority of orthotopic or continent diversion over conduit diversion.[136] Orthotopic neobladder is the closest choice to the natural bladder's function, and it seems to provide a better quality of life;[137] however, it should be contraindicated in patients presenting with tumors with urethral invasion or positive urethral margins leading to urethrectomy (consensus, LE: 4 GR: C). In those cases, heterotopic continent bladder replacement (pouch) could be an option.[138] Patients undergoing orthotopic neobladder with urethral involvement have a 0.5 to 17% recurrence rate.[139-142] Therefore, after treatment with the curative intent for MIBC where the urethra has not been resected, we recommend regular follow-up of this region with examination defined on a per-case basis (recommendation, LE: 4 GR: C).

Short-term mortality rates show no difference among the types of urinary reconstruction performed.[143,144] Oncological outcomes, such as all-cause and cancer-specific mortality,[145] are also not impacted according to the type of UD chosen (consensus, LE: 2b GR: B).

Most post cystectomy complications are related to UD, especially in patients with American Society of Anesthesiologists (ASA) scores higher than 3.[146] Cutaneous ureterostomy (CU) should be offered to patients as a form of UD in selected cases during intraoperative complications or clinical conditions (consensus, LE: 2b GR: B). CU requires shorter operative and hospitalization times and less blood transfusion compared to ileal conduit,[147,148] enabling cystectomy in high-risk patients. However, long-term use of ureteral catheters is advised to avoid stenosis.

In patients submitted to pelvic irradiation before cystectomy, as in bladder-sparing treatment modality protocols, the decision of the type of UD has no interference (consensus, LE: 5 GR: D). The basic principle of surgery is not to use irradiated tissue; however, with new protocols, tissues are usually spared, allowing the performance of any type of diversion. Radiotherapy cannot be considered a contraindication for UD, but there has been no formal comparison made between UD types and radiotherapy protocols.[149] Prior pelvic radiotherapy does not increase complication rates of RC.[150] The part of the intestine to be used in the diversion will depend on the state of the organs observed during surgery.[151]

Partial cystectomy can be attractive as a lower complexity procedure, with lower morbidity compared to RC;[152,153] however, it should be avoided in both non-muscle- invasive and muscle-invasive tumors (consensus). Partial cystectomy should be an exception because it is associated with a high recurrence rate.[154-156] Only in patients with T2 disease, with a solitary lesion in an area amenable to wide resection, with clear margins. This refers to open or minimally invasive procedures and not endoscopic resection. Some selected cases can be evaluated for partial cystectomy, such as solitary tumors without associated CIS located in a position that is amenable to wide excision.[152,157]

After curative treatment of MIBC with bladder preservation (e.g., TMT, radiotherapy, partial cystectomy or TURBT), the panel recommends regular cystoscopy in the follow-up (consensus). These patients still present a higher recurrence rate compared to RC and should receive life-long follow-up[158] (LE: 4 GR: C).

Preservation treatment in localized BCa

TMT is a strategy of preservation therapy for the bladder in MIBC, and it could be considered an option in high-risk T1 for patients who failed BCG treatment, after second line chemotherapy and for those patients not candidates for cystectomy. This procedure consists of maximum TURBT followed by chemotherapy-associated radiotherapy (consensus, LE: 1c GR: A). Complete response rate may be achieved by 50 to 70% of patients treated with TMT,[159-162] the 5-year OS by 57% of patients and the 10-year OS by 36% of patients.[162]

Re-TURBT is not mandatory, but it is the recommendation of this panel to confirm maximum resection (recommendation, LE: 4 GR: C), which is one of the most important prognostic factors affecting OS in TMT.[163]

TMT is considered in selected cases of localized BCa and should be recommended according to the patient's preference but is unfit for patients due to age[164] or comorbidities (consensus, LE: 2b GR: B), as RC involves risks and might impact quality of life. The ideal patient for multimodal therapy is as follows: T2, single tumor, with a favorable location that can undergo maximum resection in TUR, without CIS, without hydronephrosis, with urothelial histology, with tumors smaller than 5cm and good bladder function (consensus, LE: 2b GR: B), in which the treatment will provide significant benefit[(165)] with comparable 5- and 10-year OS rates to RC with lymphadenectomy.[163,165-169] TMT in primary or recurrent high-risk T1 bladder-cancer patients provides better 5-year disease-specific survival (DSS) compared to only radiotherapy.[170] In a small case series of 18 NMIBC patients ith recurrent and progressive disease, TMT provided a 7-year DSS for 70% and OS for 58% of patients.[171] This consensus did not include voting on follow-up recommendations for patients treated with TMT.

CIS, multifocality, hydronephrosis, and/or T3/T4 are contraindications for multimodal treatment with intention of bladder preservation (recommendation, LE: 4 GR: C). However, patients with T3/T4 are not absolute contraindications; they present inferior results compared to patients with T2 or lower, [168] but we should consider that RC in those patients does not offer important oncological outcomes either. The results for T3b-T4 or N+ and M0 patients treated with TMT show 30% OS,[172] making it an alternative for those not eligible for surgery. Patients with hydronephrosis present a worse complete response rate but no difference in OS compared to patients without hydronephrosis.[168]

We recommend a complete tumoricidal dose of radiotherapy (55-66Gy) in the preservation therapy (consensus, LE: 2a GR: B), including the irradiation of pelvic lymphatic drainage (consensus, LE: 2a GR: B), targeting occult pelvic lymph node involvement.[(173)] Patients with clinical contraindication to or not willing to undergo RC should receive a full- dose, straight course of radiotherapy.[174,175] Split-course radiotherapy (induction with a dose of 40-46Gy, revaluation with cystoscopy and an additional 20-26Gy in the absence of neoplasia) was not the preferred treatment scheme in this consensus,[176] as 40Gy is a subclinical dose, maximum tumor response may take up to three months, and the absence of response before this period does not conclude ineffectiveness. Considering the complete dose and evaluation *versus* split dose and evaluation, there is some evidence that the first offers better outcomes, with less salvage cystectomy rates, better complete response rates, and better overall survival.[168] Nonetheless, in the discussion held by the consensus, it was considered that split course treatment could be offered as an alternative at the physician's discretion.

Treatment of locally advanced BCa encompasses neoadjuvant chemotherapy followed by RC. In general, there is no indication for adjuvant radiotherapy in bladder cancer (recommendation, LE: 4 GR: C), except for patients presenting with pT3-pT4N+ with positive margins, where adjuvant radiotherapy could provide improvement in OS,[177-179] and for non-urothelial bladder tumors, with 78% of local-regional control.[180] The recommendations for systemic chemotherapy were discussed in a separate manuscript.

When there is an indication of radical radiotherapy (with or without chemotherapy) or adjuvant, the ideal technique for radiation dose administration is intensity-modulated radiation (IMRT) and image-guided radiotherapy (IGRT) (consensus, LE: 5 GR: D) because these two techniques complement each other, as IGRT helps with accurately targeting, and together the two therapies limit the high dose regions to the targets, sparing normal tissue.[181] The minimally acceptable technique is conformal radiotherapy (RT3D), which can be used with IGRT (recommendation, LE: 5 GR: D).

CONCLUSION

Effective treatment and optimal follow-up are the primary means for minimizing recurrence and progression in urothelial carcinoma, significantly changing the patient's prognosis. The expertise of a multidisciplinary team with the best evidence in the medical literature available should be sought to improve the treatment of oncologic patients and offer better care.

ABBREVIATIONS:

American Society of Anesthesiologists (ASA); Bacillus Calmette-Guérin (BCG);

Bladder cancer (BCa);

Brazilian Society of Clinical Oncology (SBOC); Brazilian Society of Radiotherapy (SBRT); Brazilian Society of Urology (SBU);

Carcinoma in situ (CIS); Computed tomography (CT); Cutaneous ureterostomy (CU); Disease-free survival (DFS); Disease-specific survival (DSS);

Enhanced recovery after surgery (ERAS); Grade of recommendation (GR);

Intravesical chemotherapy (IVC); Intravesical therapy (IVT);

Latin American Cooperative Oncology Group (LACOG); Level of evidence (LE);

Magnetic resonance imaging (MRI); Muscle-invasive bladder cancer (MIBC);

Non-muscle-invasive bladder cancer (NMIBC); Overall survival (OS);

Radical Cystectomy (RC); Recurrence-free survival (RFS); Repeating TURBT (re-TURBT); Transurethral resection (TUR);

Transurethral resection of bladder tumor (TURBT); Tri-modality therapy (TMT);

Upper urinary tract (UUT); Urothelial carcinoma (UC); Urothelial bladder carcinoma (UBC); Urinary diversion (UD);

With white light cystoscopy (WLC).

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AUTHORS' CONTRIBUTIONS

All authors participated in the conceptualization, review, and revision of this manuscript. In addition, all authors have read and approved the final version of this manuscript.

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