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Brazilian consensus in muscle-invasive and metastatic urothelial carcinoma

Consenso brasileiro em carcinoma urotelial músculo invasivo e metastático

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ABSTRACT

Urothelial carcinoma is a frequent worldwide malignancy. Poor survival rates in muscle-invasive and metastatic urothelial carcinoma impose major challenges for management. We conducted a consensus meeting to discuss the optimal treatment for urothelial carcinoma in Brazil, which was developed by a panel of multidisciplinary experts consisting of oncologists, urologists and radiation therapists. This paper provides recommendations for perioperative treatment, metastatic disease management, bone directed therapy and genetic counselling in urothelial carcinoma based on the specialists opinions and was classified according to the level of evidence found in the medical literature according to the Oxford classification. The recommendations were based on the available treatments in Brazil to guide health professionals in the management of urothelial carcinoma in low- and middle- income countries with limited access to therapy.

Keywords: Urothelial carcinoma; Bladder cancer; Cystectomy; Chemotherapy, muscle-invasive; Metastatic urothelial carcinoma; Upper urinary tract carcinoma.

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RESUMO

O carcinoma urotelial é uma malignidade mundial frequente. As baixas taxas de sobrevivência no carcinoma urotelial músculo invasivo e metastático impõem grandes desafios em relação ao manejo. Realizamos uma reunião de consenso para discutir o tratamento ideal para o carcinoma urotelial no Brasil, desenvolvido por um painel de especialistas multidisciplinares composto por oncologistas, urologistas e radioterapeutas. Este artigo fornece recomendações para tratamento perioperatório, tratamento da doença metastática, terapia dirigida aos ossos e aconselhamento genético no carcinoma urotelial, com base nas opiniões dos especialistas e foi classificado de acordo com o nível de evidência encontrado na literatura médica, de acordo com a classificação de Oxford. As recomendações foram baseadas nos tratamentos disponíveis no Brasil para orientar os profissionais de saúde no tratamento do carcinoma urotelial em países de baixa e média renda com acesso limitado à terapia.

Descritores: Carcinoma urotelial; Câncer de bexiga; Cistectomia; Quimioterapia músculo invasiva; Carcinoma urotelial metastático; Carcinoma do trato urinário superior.

INTRODUCTION

Urothelial carcinoma (UC) represents 90% of all urinary tract malignancies, with bladder cancer (BCa) being the most frequent among them.[1,2] BCa is the 8th most common cancer worldwide in men.[3] In Brazil, BCa is the 7th most common cancer in men and 14th in women, with an estimated 5-year prevalence of 118,293 cases, including both sexes regardless of age, and 6,690 new cases in men and 2,790 in women are expected annually between 2018 and 2019.[4,5] Upper tract urothelial carcinoma (UTUC) corresponds to 5% to 10% of UC cases,[1,2] whereas 17% of patients present with concomitant BCa, and 15-75% of patients with UTUC demonstrate a risk for developing BCa within 5 years.[6]

BCa has an approximately 3-fold higher incidence in men than in women;[7] however, disease-specific mortality is higher among women.[7,8] Tobacco smoking is a well-established risk factor for BCa that is directly related to addiction length and daily consumption.[9,10] Other risk factors include chemical exposure, bladder schistosomiasis, human papilloma virus (HPV) infection, chronic urinary tract infection, prior pelvic radiotherapy, use of cyclophosphamide and genetic factors.[11-13] Dietary habits remain controversial.[12]

Most cases of BCa are categorized as non-muscle invasive disease. Muscle-invasive bladder cancer (MIBC) and metastatic disease correspond to approximately 25% of patients with BCa.[12] It is estimated that 50% of MIBC patients undergoing radical cystectomy (RC) have local or distant disease recurrence, and 10-15% already have metastasis at the time of diagnosis.[14] Local recurrence corresponds to 10-30% of cases, and distant metastases are more common.[14] Additionally, relative survival has decreased over time.[15] The 5- year survival rate of patients with distant metastasis is no greater than 5% to 10%.[2]

Considering the challenging management of UC, discussion among a multidisciplinary team of experts regarding available therapies is paramount to optimize disease management and patient care. Hence, the aim of this paper was to establish a Brazilian consensus for the management of locally advanced and metastatic urothelial carcinoma, focusing on BCa, to help not only Brazilian health professionals but also others from low- and middle-income countries who have equally limited access to treatment.

METHODS

A consensus meeting was organized by The Brazilian Society of Clinical Oncology (SBOC), the Latin American Cooperative Oncology Group-Genitourinary section (LACOG- GU), the Brazilian Society of Urology (SBU) and the Brazilian Society of Radiotherapy (SBRT), and the meeting was held on April 26, 2019, in São Paulo, Brazil.

A multidisciplinary panel of experts composed of clinical oncologists, urologists, and radiation oncologists developed a questionnaire with multiple-choice answers, voted and debated the optimal management recommendations for UC, considering the best practice available in this country.

Questions were presented and voted. Answers reaching a total vote rate of at least 75% were considered consensus. Those that were not considered consensus were redisplayed, discussed and voted again. The most highly voted answer for this second round was considered consensus if it reached at least 75% of the votes or was considered a recommendation if less than this cutoff. Participants had the option to abstain voting, and they were not considered in the final results. The questionnaire with the results can be found in the additional file of this paper.

All the chosen answers were confronted with medical literature and categorized according to the level of evidence (LE) and grade of recommendation (GR), adapted from the 2009 Oxford Center for Evidence-Based Medicine Levels of Medicine classification, as shown in Table 1.[16]

RESULTS

Genetic counselling in urothelial carcinoma

Tobacco, advanced age, chemical exposure, HPV infection, bladder schistosomiasis, chronic urinary tract infection, and pelvic radiotherapy are well-known risk factors for UC.[11-13,17] Genetic counseling is recommended in selected non-MIBC and MIBC patients but especially for those with UTUC presenting risk factors with less than 50-years-old, for women and/or patients without history of tobacco exposure (consensus, LE:5 GR:D).

Genetic counselling may identify patients with Lynch syndrome, an autosomal dominant genetic disorder associated with the development of malignancy of the gastrointestinal tract, endometrium, ovary, central nervous system, skin and UTUC.[18] For patients with a personal or family history of endometrial and/or gastrointestinal tract polyps, genetic counselling is recommended for most of them (recommendation, LE:5 GR:D), but it is not mandatory. On the other hand, patients with UC and a diagnosis of Lynch syndrome and patients with a personal or family history of endometrial cancer (especially the endometrioid subtype) and/or colorectal cancer (especially the mucinous subtype) as well as their families should undergo genetic evaluation (consensus, LE:5 GR:D). The location of UTUC in patients with Lynch syndrome is usually the ureter and renal pelvis. The risk estimates of developing urinary cancers may vary depending on sex and the gene involved, with up to 22% of cancers in female patients presenting with MSH6 mutations.[19]

Treatment selection

Cisplatin

Cisplatin was the first metal-based chemotherapy agent and has been widely used ever since.[20] The use of cisplatin in chemotherapy doubles the overall survival (OS) rates of patients with advanced UC[21] (21) and is the first-line treatment for metastatic patients.[11] Cisplatin use may be limited by its toxicity, particularly its nephrotoxicity. Renal function should be evaluated before drug administration. The glomerular filtration rate limit to consider the patient eligible to receive cisplatin-based chemotherapy in full dose is 50mL/min, calculated with Cockroft-Gault equation (recommendation, LE: 1b GR:B). Although cisplatin eligibility criteria of 50mL/min - 60mL/min have been documented in the literature, part of the panel considered that this criterion could be re-evaluated depending on the clinical situation. Cisplatin should not be used in patients with performance 2 or higher, hearing loss (grade II or higher), clinically significant peripheral neuropathy (grade II or higher), or congestive heart failure class III or worse (consensus, LE:5 GR:D). According to these criteria, in general, less than 50% of patients are eligible for cisplatin-based chemotherapy.[22,23] Although the creatinine clearance (CrCl) limit typically defined for cisplatin use is ≥60mL/min in clinical trials,[24-26] a CrCl cutoff of 50mL/min appears to be safe, as reported in the POUT trial,[27] and should be considered in clinical practice, especially in patients with potentially curative disease or with the goal of improved survival.

Neoadjuvant and adjuvant treatment in MIBC

Neoadjuvant chemotherapy (NAC) is indicated in all non-metastatic patients in the treatment of MIBC who are candidates for cisplatin (recommendation, LE:1a GR:A), followed by RC. Lymphadenectomy should be performed with the RC in all patients with localized bladder UC T2-T4a, regardless of previous lymph node status (consensus, LE:2b GR: B). The preferred regimen of NAC is dose dense methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) (recommendation, LE:2b GR: B).

Cisplatin-based NAC in MIBC patients prior to cystectomy significantly improves oncological outcomes, with an absolute OS benefit of approximately 6.5%.[28,29] Moreover, NAC is associated with an improvement in survival of 5% compared to definitive local therapy alone, with a median survival ranging from 46 months with surgery alone to 77 months with combined therapy,[30,31] a 9% disease-free survival (DFS) rate at 5-years,[30] and an increase in 10-years survival from 30% to 36%.[32] Cisplatin should not be used as a single agent in chemotherapy because it does not show significant improvement in survival.[30,33] NAC based on methotrexate, vinblastine, and cisplatin (MVC) and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) increases survival;[31,32,34] however, MVAC presents high toxicity and a long treatment period. Dose dense MVAC offers a safer profile, shorter treatment duration (12 weeks with classic MVAC versus 6 to 8 weeks for dose dense), efficacy in disease downstaging[35,36,37] and significant higher complete response rate compared to gemcitabine/cisplatin and gemcitabine-carboplatin.[37]

Dose-dense gemcitabine/cisplatin also demonstrates benefits as a neoadjuvant therapy, with a downstaging pathologic response rate in 57% of patients, improving recurrence-free survival (RFS) and OS.[38] Unfortunately, the available data demonstrate that NAC has been underutilized in eligible patients despite being considered the standard of care for MIBC and is able to promote disease downstaging, eradicate micrometastasis, and improve survival.[39] A high-volume tertiary centre reported that only 17% of eligible patients received NAC, which can be explained by the patient's preference, the lack of

signs of progression and, potentially, the surgeon's preference not to delay cystectomy.[40]

The standard of care in MIBC is NAC followed by RC. Lymphadenectomy provides accurate staging and provides prognosis because lymph node-positive disease is related to higher recurrence, especially in distant sites, and worse overall survival compared to no lymph node involvement.[41-46] Additionally, lymphadenectomy may provide a benefit in terms of survival for all patients with lymph node-positive and node-negative disease.[47] The risk of lymph node metastasis is significant in MIBC patients, estimated in up to 25% of patients at the time of cystectomy.[48]

NAC is not recommended for patients undergoing bladder preservation therapy or those who are not candidates for cisplatin (consensus, LE:5 GR:D). There is not enough evidence to support carboplatin as a neoadjuvant therapy for patients unfit for cisplatin. Until clear evidence of benefits becomes available, carboplatin-based regimens should not be used for NAC outside clinical trials.[49] In patients with localized/locally advanced urothelial carcinoma of the bladder who receive NAC with a cisplatin-based regimen followed by cystectomy and who present with an unsatisfactory pathologic response, we recommend follow-up (consensus, LE:2b GR:B). The evidence for the use of adjuvant chemotherapy in this population is still limited. The results from an observational study showed a 5-month OS benefit in a cohort of pT3/T4 and/or pN+ patients with adverse pathologic features after NAC and RC; however, the chemotherapy regimen administered was not reported.[50]

Patients not willing to undergo RC and patients ineligible for surgery could benefit from bladder preservation therapy depending on the tumour location and size, tumour extension, presence of tumour associated hydronephrosis, and status of in situ carcinoma.[51] They should be informed of the high risk of local recurrence. Chemoradiation preceded by maximal transurethral resection of bladder tumour (TURBT) is the mainstay treatment for these selected patients.[52] Cisplatin-eligible patients should receive cisplatin with radiation therapy (consensus, LE:1c GR:A) without previous NAC, as this treatment without NAC is associated with a 5-year and 10-year OS of 57% and 36%, respectively.[53] Low-dose gemcitabine could be used in patients unfit for cisplatin in preservation therapy (consensus, LE:1c GR:A). In a phase II trial, 82% of patients receiving low-dose gemcitabine associated with radiotherapy achieved 3-year cancer-specific survival, and the OS was 75%.[54] In a retrospective analysis, treatment with low-dose gemcitabine and radiotherapy demonstrated local progression-free survival (PFS), DSS and OS rates comparable to cisplatin-based regimens in MIBC patients who were inoperable due to comorbidities with a feasible toxicity profile.[55] We do not routinely recommend 5-fluorouracil with mitomycin-C[56] in patients who are ineligible for cisplatin in Brazil since mitomycin is not available in the country.

Adjuvant treatment should be used in all patients with stage > pT2N0 that are eligible for cisplatin (consensus, LE:2a GR: B) and that not received NAC. In patients pT3-4, pN+, eligible for cisplatin who did not receive NAC, we recommend adjuvant chemotherapy (AC) with gemcitabine and cisplatin (recommendation, LE: 1c GR: A). AC could benefit patients who did not receive NAC, but these patients are usually cisplatin-based chemotherapy unfit because of renal function decline.[22,57] Patients with advanced pathologic stage (≥ T3) and nodal involvement or with positive surgical margins are the most likely to benefit, showing longer OS or significant DFS with adjuvant therapy.[58-60] There is no consensus in the best regimen for AC in MIBC. Limited evidence showed that adjuvant therapy with gemcitabine, cisplatin and paclitaxel significant prolong OS, improving DFS and disease specific survival (DSS) compared to no treatment.[61] Cisplatin-based regimens in AC show a trend to improve OS with 20 to 25% decrease in mortality risk compared with control, but more robust studies are necessary to confirm these findings.[30,43,62] There is no recommendation for the routine use of AC for patients with pathologic staging T2N0 after cystectomy, since these patients were not included in most of the adjuvant trials and have an overall high OS.

Patients ineligible for cisplatin with an indication of adjuvant therapy correspond to more than 40% of patients aged 70 years or older.[22] Although the recommendation of adjuvant carboplatin and gemcitabine reached consensus in the multidisciplinary voting (consensus, LE:2b GR: B), it should be highlighted that there is no strong evidence based on phase III trials to support this regimen in the adjuvant setting, and this regimen in patients with MIBC may be considered in highly selected cases when chemotherapy is considered the most appropriate treatment and when the patient is "unfit" for cisplatin. Evidence for carboplatin and gemcitabine as adjuvant treatments is limited and based on exploratory data in UTUC. From the subgroup analysis of a cohort in which 20% of patients received carboplatin and gemcitabine as AC, the median survival rate was similar to the rate in those receiving cisplatin-based therapy.[63]

Neoadjuvant and adjuvant treatment in UTUC

Limited evidence related to the treatment of UTUC is available. Radical nephroureterectomy is the standard treatment, followed by AC and surveillance. The POUT trial showed that AC significantly improved DFS and metastasis-free survival in patients with UTUC compared with only surveillance, with a trend towards an improvement in OS.[27] Thus, AC is indicated in locally advanced UTUC patients (recommendation, LE:1b GR:A), and gemcitabine-cisplatin is the recommended regimen for patients fit for cisplatin (consensus, LE:1b GR:A). Patients who are cisplatin-

ineligible may benefit from adjuvant carboplatin and gemcitabine (consensus, LE:1b GR:A). Evidence of carboplatin and gemcitabine from the POUT trial showed a trend towards a clinical benefit, although it did not reach statistical significance.[27]

Considering NAC in UTUC, the data are very limited. Retrospective analyses have shown a low mortality risk in the treated group; with a significant improvement in OS and DFS,[64] and 14% of patients demonstrate complete remission.[65] There is not enough evidence to demonstrate a preference for one cisplatin-based chemotherapy over another. For patients eligible for cisplatin, we recommend gemcitabine and cisplatin (recommendation, LE:5 GR:D). MVAC dose dense could also be used, as reported in a study including 44 bladder/urethral carcinoma patients and 16 UTUC patients, showing a 2-year OS in 82% of patients and 78% DFS.[66] NAC is not recommended for patients with UTUC ineligibles to cisplatin (consensus, LE: 5 GR: D), because carboplatin or any other agent has not shown benefit in this indication.

Treatment of metastatic disease

First-line treatment

Cisplatin in combination with gemcitabine is the most recommended option for cisplatin-eligible patients with metastatic urothelial carcinoma (mUC) as a first-line treatment, regardless of PD-L1 expression (consensus, LE:1b GR:B). In patients unfit for cisplatin who are PD-L1 negative or have unknown status, the most recommended treatment option for patients with mUC in terms of first-line treatment is carboplatin with gemcitabine (consensus, LE:1b GR:A). In patients unfit for cisplatin who are PD-L1 positive, the option is immunotherapy (consensus, LE:1c GR: A) with pembrolizumab or atezolizumab because they are the only drugs that have been involved in clinical studies and have been approved as first-line treatments,[67,68] with no preference between them (recommendation, LE:5 GR:D).

Cisplatin-based chemotherapy has been the standard of care for mUC for more than 30 years. Cisplatin and gemcitabine are superior to MVAC in terms of the pathological complete response in metastatic patients,[65] with a better safety profile but with no difference in OS, DSS, or DFS.[66,69] As mentioned previously, cisplatin should not be used as a single agent since it is inferior to MVAC in terms of response rate, PFS and OS.[70]

Carboplatin with gemcitabine shows no difference compared to methotrexate with carboplatin and vinblastine (M-CAVI) in terms of OS (9.3 months versus 8.1 months, respectively), but it has an improved safety profile.[71] Results from non-comparative studies with advanced patients who are unfit for cisplatin and who were treated with carboplatin-based therapy showed an OS between 7 and 16 months.[72-76]

There is no evidence that immunotherapy is superior to chemotherapy in terms of first-line therapy for patients unfit for cisplatin. When indicated, there is no preference between atezolizumab and pembrolizumab; both showed clinical benefits for this indication.[76,77] In the IMvigor210 study,[67] atezolizumab showed minimal differences in the objective response rate (ORR) between PD-L1-positive and PD-L1-negative patients (28% versus 20%, respectively). However, in the KEYNOTE-052 study, treatment with pembrolizumab had superior results in PD-L1-positive patients (ORR: 51% versus 23% in PD-L1-negative patients).[68] Phase III studies comparing chemotherapy, immunotherapy and associated immunotherapy with chemotherapy are ongoing, and results are expected soon and may therefore change the scenario of first-line UC treatment.[78-81]

Biomarkers in mUC

To date, the role of tissue or circulating biomarkers in UC is unclear. The material for analysis of PD-L1 and FGFR should be preferably the most recent possible; however, there is no formal recommendation for a new biopsy (consensus, LE:5 GR:D). For the treatment of naïve cisplatin-ineligible patients with mUC, the analysis of PD-L1 expression is indicated to guide first-line therapy (consensus, LE:1c GR: A). The evaluation of FGFR mutations is indicated for all patients after progression with first-line treatment (consensus, LE:1c GR:A). PD-L1 is considered positive when expression in tumor cells are >5% using Ventana-sp142 kit, or ≥10 in the Combined Positive Score (CPS, tumor + infiltrate cells) using Dako-22C3 kit (consensus, LE:5 GR: D).

FGFR 3 is a tyrosine kinase receptor that regulates many cellular processes, such as growth, differentiation, and angiogenesis. It was identified as an oncogene, and its dysregulation is related to urothelial BCa.[77] Treatment targeting FGRF can be considered for patients with first-line treatment failure. The literature demonstrates preliminary and conflicting results regarding the immunotherapy response in patients with FGFR mutations, as there were shown to be fewer responders to anti-PD-L1 immunotherapy in one post hoc analysis;[82] there was no difference in response rate, PFS or OS according to FGFR 3 mutation or gene expression with nivolumab treatment,[83] and there was up to a 40.4% response rate with erdafitinib treatment.[84] Erdafitinib has recently been approved by Brazilian authorities (ANVISA).[85]

Second-line treatment

The preferential second-line treatment after chemotherapy failure with platinum- based therapy as a first-line treatment, regardless of FGFR status, is immunotherapy (consensus, LE:1b GR:A). Pembrolizumab is the preferred immunotherapy (consensus, LE:1b GR:A) because it is the only one with a phase III study showing significant benefit, with a longer OS (10.3 months versus 7.4 months with chemotherapy)[86] and quality of life improvements.[87]

Immunotherapy offers an additional option for patients progressing after first-line treatment. Unlike first-line therapy, the response to immunotherapy as a second-line therapy does not depend on the expression of PD-L1. In the IMvigor211 study, the OS of atezolizumab was not different from that of chemotherapy (vinflunine, paclitaxel and docetaxel) but had a better safety profile.[88] Durvalumab has an ORR of 17%, PFS of 1.5 months and OS of 18.2 months, with a 1-year OS rate of 55%.[89] Nivolumab demonstrated an OS of 7 months,[90] and all of these results occurred regardless of PD-L1 expression.

Patients with disease progression following platinum-based chemotherapy and immunotherapy, without FGFR mutation, should be treated with vinflunine (recommendation, LE: 1b GR:A), as it was shown to be superior to best supportive care alone; there was a significantly longer OS, and the mortality risk decreased by 23%.[91]

The treatment of choice indicated for patients with disease progression following platinum-based chemotherapy and immunotherapy, with FGFR mutation, is erdafitinib if available (consensus, LE:4 GR:C). If not available, third-line treatment with chemotherapy (vinflunine or paclitaxel) may be considered. This recommendation is based on the following results of a phase II trial: of 99 patients receiving erdafitinib, 3% showed a complete response, and 37% showed a partial response; the PFS was 5.5 months, and the OS was 13.8 months.[92] A phase III trial is ongoing to evaluate erdafitinib versus chemotherapy (docetaxel or vinflunine) or pembrolizumab in patients with FGFR mutations who progressed on or after first-line systemic therapy.[93]

Follow-up

During and after systemic therapy (chemotherapy, target therapy/immunotherapy) for mUC, the follow-up for evaluation of disease response and progression should be individualized, depending on each case (patient conditions, treatment, therapeutic response and evolution, the protocol that was chosen for treatment, etc.) (consensus, LE:5 GR:D) and the chosen therapy, always taking into account what is recommended in studies of indicated therapy.

Bone therapy

Bone is a common local for metastasis in mUC patients.[94] The occurrence of bone metastasis is associated with metastasis to the brain, liver or lungs; a high primary tumour stage; a high regional lymph node stage; and poorly differentiated tumours.[95] Bone metastasis compromises a patient's quality of life by causing pain and pathologic fractures. It decreases treatment response and OS.[96]

Bone-modifying agents (zoledronic acid, denosumab) should be prescribed for all patients with UC and bone metastases (recommendation, LE:5 GR:D). Calcium and vitamin D supplementation should also be recommended (consensus, LE:5 GR:D) because bone- modifying agents, especially denosumab, increase the risk of hypocalcaemia.[97] Denosumab should be the treatment of choice, including for patients with impaired renal function (consensus, LE:5 GR:D). We recommend denosumab at a dose of 120mg, subcutaneously, every 4 weeks (consensus, LE:5 GR:D), and for patients taking zoledronic acid, the dose and frequency recommended are 4mg, intravenously, every 4 weeks (consensus, LE:5 GR:D). The duration of therapy with bone-modifying agents should be up to 24 months (recommendation, LE:5 GR:D). There is no evidence of benefit with prolonged use in mUC, as reported in breast and prostate cancer patients.

Extrapolating data from breast cancer, prostate cancer and other solid tumours, denosumab is superior to zoledronic acid in preventing skeletal-related events, and it has the advantage of not needing to adjust the dose according to renal function.[98] Subgroup analysis evaluating only genitourinary cancers (1901 prostate, 155 renal, 63 bladder, and 9 transitional cell patients) confirmed the result, with a significant delay in the occurrence of skeletal-related events in 4 months compared to zoledronic acid.[99]

For patients with bone metastases and who are undergoing therapy with bone- modifying agents that have a bony event, we recommend treating the event and proceeding with bone-modifying agents (consensus, LE:5 GR:D), as they delay or prevent skeletal related events such as pathologic fracture, spinal cord compression, bone surgery or radiation.[100]

Patients should have access to dental care before treatment with bone-modifying agents and should have a follow-up in order to avoid invasive procedures during treatment.[101] For patients who have a history of dental disturbances (tooth extraction, periodontal disease or extraction and dental implants), we recommend the use of bone-modifying agents only after dental evaluation/treatment (consensus, LE:5 GR:D), because dental extraction increases the risk of osteonecrosis of the jaw by up to 14.8%.[102] In patients having or who had osteonecrosis of the jaw, we do not recommend the use of bone-modifying agents (consensus, LE:5 GR:D).

CONCLUSION

This multidisciplinary meeting consensus discussed and voted on important and clinically relevant questions to guide the management of patients with muscle-invasive and metastatic urothelial carcinoma. All answers took into account the availability of treatment in Brazil and were supported by the highest level of evidence found in the medical literature. These recommendations are useful not only in Brazil but also for professionals in other low- and middle-income countries, where there is limited access to treatment.

Table 1. Level of evidence and grade of recommendation for therapy and prevention, adapted for the Oxford classification.[16]

Level of evidence	
1a	Systematic reviews (with homogeneity) of randomized controlled trials.
1b	Individual randomized controlled trials (with narrow confidence intervals).
1c	All or none randomized controlled trials.
2a	Systematic reviews (with homogeneity) of cohort studies.
2b	Individual cohort study or low-quality randomized controlled 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".
Grade 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.

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