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SPECIAL ARTICLE

Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

T. Powles[1], J. Bellmunt[2], E. Comperat[3], M. De Santis[4], R. Huddart[5], Y. Loriot[6], A. Necchi[7], B. P. Valderrama[8], A. Ravaud[9,10], S. F. Shariat[11], B. Szabados[1,12], M. S. van der Heijden[13] & S. Gillessen[14], on behalf of the ESMO Guidelines Committee*

[1]Barts Cancer Centre, Barts Health NHS Trust, Queen Mary University of London, London, UK; [2]Beth Israel Deaconess Medical Centre-IMIM Lab, Harvard Medical School, Boston, USA; [3]L'Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Paris, France; [4]Department of Urology, Charité Universitätsmedizin, Berlin, Germany; [5]Royal Marsden Hospital, Institute of Cancer Research, London, UK; [6]Département de Médecine Oncologique, Université Paris-Saclay and Gustave Roussy, Villejuif, France; [7]Vita-Salute San Raffaele University, Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy; [8]University Hospital Virgen del Rocio, Seville, Spain; [9]Hôpital Saint-André CHU, Bordeaux; [10]Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France; [11]Department of Urology, Medical University of Vienna, Vienna General Hospital, Vienna, Austria; [12]Department of Urology, University College London Hospital, London, UK; [13]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [14]Oncology Institute of Southern Switzerland (IOSI), EOC, Lugano, Switzerland

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INCIDENCE AND EPIDEMIOLOGY

Urothelial carcinoma (UC), also described as bladder cancer, is the 10th most common cancer type worldwide, with an estimated 549 000 new cases and 200 000 deaths in 2018. The highest incidence rates in Europe are observed in Southern Europe, e.g. Greece (5800 new cases and 1537 deaths in 2018), Spain and Italy, and Western Europe, e.g. Belgium and the Netherlands.[1] The most important risk factor for developing bladder cancer is tobacco smoking, which accounts for ∼50% of cases,[2] followed by occupational exposure to aromatic amines and ionising radiation.[3]

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis

Painless haematuria is the most common presenting symptom in bladder cancer and should be investigated in all cases. Other common symptoms include dysuria, increased frequency and/or urgency (Figure 1). Bladder ultrasonography or cross-sectional imaging can identify an intraluminal mass in the bladder, but the final diagnosis is based on cystoscopic examination of the bladder and histological evaluation of the tissue obtained either with cold-cup biopsy or transurethral resection of the bladder tumour (TURBT). Complete resection of all tumour tissue should be achieved when possible. The presence of lamina propria and detrusor muscle in the resected specimen is essential for accurate staging in most cases. Concurrent carcinoma *in situ* (CIS) is an adverse prognostic factor;[4] hence, bladder biopsies from suspicious urothelium or mapping biopsies from normal-looking mucosa in patients with positive urine cytology, or a history of high-grade (HG) non-muscle-invasive bladder cancer (NMIBC) should be taken.[5] In patients with high-risk NMIBC (described in Table 1), and in particular those with CIS, upper tract imaging should be carried out to screen for synchronous upper urinary tract urothelial carcinoma (UTUC). Computed tomography (CT) urography or magnetic resonance imaging (MRI) urography is used to detect papillary tumours in the urinary tract.[6] The management of bladder cancer is based on the pathological findings of the biopsy, with attention to histology, grade and depth of invasion (Table 1). Muscle-invasive bladder cancer (MIBC) should be staged according to the Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) eighth edition and the American Joint Committee on Cancer (AJCC) TNM staging systems and should be grouped into categories (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2021.11.012).

Pathology/molecular biology

Pathological diagnosis should be made according to the World Health Organization (WHO) 2016 classification

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).

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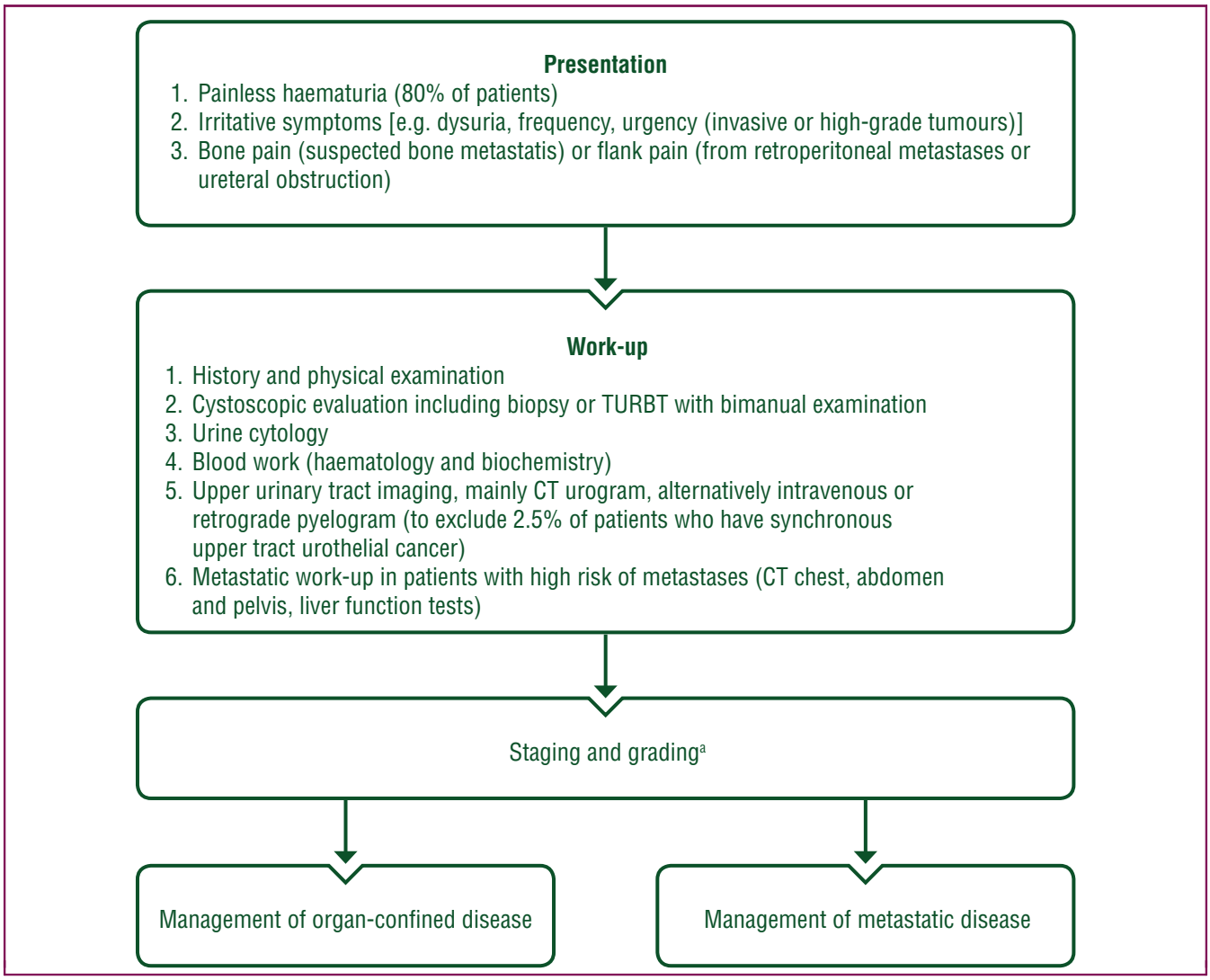

Figure 1. Diagnostic work-up of patient with suspected bladder cancer.
CT, computed tomography; TURBT, transurethral resection of the bladder tumour.
[a] See Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2021.11.012.

(Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.11.012).[7]

Approximately 75% of patients with bladder cancer present with NMIBC pTa-pT1, pTis).[3] The majority of patients with MIBC (pT2a-pT4b) are diagnosed with primary invasive bladder cancer and up to 15% of patients have a previous history of NMIBC, almost exclusively high-risk NMIBC.[3] All MIBCs are considered as HG.

TURBT or bladder biopsy only allow for staging up to T2. Clinical T3 or T4 disease is identified by bimanual exam under anaesthesia and/or cross-sectional imaging. NMIBC is graded as low grade (LG) or HG according to the latest WHO 2016 criteria.

Ninety percent of carcinomas of the upper and lower urothelial tract are UCs, with or without other variants (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.11.012). The percentage of the variant morphology should be given in the pathological report. If the squamous or adenocarcinoma part is >95%, the UC should be considered as a pure squamous/adenocarcinoma. The variant histology group comprises nested carcinoma, large nested, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid/signet ring cell/diffuse, sarcomatoid, giant cell, poorly differentiated, lipid rich and clear-cell UC, all of which are of urothelial origin.[7] Small-cell/neuroendocrine subtypes should be specified when they are present and the percentage should be noted.

Urine cytology can facilitate the diagnosis of HG UC but should not be used as the primary method of histological diagnosis. It has a high sensitivity in HG tumours including CIS (84%), but low sensitivity in G1/LG tumours (16%).[8]

Further molecular diagnosis is being investigated in the advanced disease setting, but its role has yet to be clearly defined. Oncogenic alterations [e.g. fibroblast growth factor receptor (*FGFR*) DNA alterations] and other forms of immuno-oncology therapy biomarker testing, such as programmed death-ligand 1 (PD-L1) expression, are being used for patient selection. Multiple methodologies exist for biomarker measurement and clinicians should follow European Medicines Agency (EMA) guidance for PD-L1,

Table 1. Risk group stratification of patients with NMIBC and treatment recommendations

Risk group stratification	Characteristics	Treatment recommendations
Low-risk tumours	Primary, solitary, Ta G1 (PUNLMP, LG), <3 cm, no CIS	One immediate instillation of intravesical ChT after TURBT [I, A] followed by cystoscopic surveillance
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score <5, one immediate instillation of intravesical ChT after TURBT [IV, C] In all patients, either: • instillations of ChT for a maximum of 1 year [I, A] Or • one-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months) [I, A]
High-risk tumours	Any of the following: • T1 tumour • G3, HG tumour • CIS • Multiple, recurrent and large (>3 cm) Ta G1-G2/LG tumours (all features must be present)	Full-dose BCG instillations for 1-3 years or radical cystectomy [I, A]
Subgroup of highest-risk tumours	• 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	Radical cystectomy or BCG induction and 3 years of maintenance if achievable [I, A]

BCG, bacillus Calmette-Guerin; ChT, chemotherapy; CIS, carcinoma *in situ*; EORTC, European Organisation for Research and Treatment of Cancer; G, grade; HG, high grade; LG, low grade; NMIBC, non-muscle-invasive bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential; TURBT, transurethral resection of the bladder tumour.

linking specific biomarkers methods with specific agents. Molecular diagnostics such as molecular subtype classification, FGFR and PD-L1 status are not routinely required [IV, C]. Molecular subtype analysis does not currently have a role in treatment selection. Genomic testing (PCR- or next-generation sequencing-based) should be used for detection of *FGFR2/3* mutations and fusions.[9,10] A personalised medicine synopsis is shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.11.012.

Recommendations

- Painless haematuria is the most common presenting symptom in bladder cancer and should in all cases be investigated [IV, A].
- 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 [IV, A].
- Cross-sectional upper tract imaging (CT/MRI urography) is recommended to screen for synchronous UTUC, in cases of HG bladder cancer [IV, B].
- Pathological diagnosis should be made according to latest WHO classification [IV, A].
- In addition to stage and grade, presence and percentage of variant histology, lymphovascular invasion and presence of detrusor muscle should be reported [IV, A].
- Urine cytology can facilitate the diagnosis of HG UC but cannot be used as the primary method of histological diagnosis [IV, B]. The Paris system should be used for reporting.
- Molecular diagnostics such as The Cancer Genome Atlas (TCGA) classification and PD-L1 status are not required for all tumours [IV, C].

STAGING AND RISK ASSESSMENT

Staging of NMIBC

A scoring system and risk assessment table has been developed to predict 1- and 5-year disease recurrence and progression in patients with Ta-T1 disease, using the WHO 1973 grading system.[11] An updated model has been developed for patients with Ta-T1 bladder cancer, treated with 1-3 years of bacillus Calmette-Guerin (BCG) maintenance. Patients with CIS alone were not included. The scoring system takes into account the number and size of tumours resected, depth of invasion, prior recurrences, presence of CIS and grade of the tumours after TURBT. Based on the above, the European Association of Urology classified the patients into four risk categories: low-risk, intermediate-risk, high-risk and very-high-risk tumours (Table 1), which constitutes the basis for treatment and follow-up recommendations in NMIBC [IV, B]. Patients with NMIBC have a heterogeneous prognosis. While patients with high-risk NMIBC suffer from a high recurrence rate (up to 50% at 5 years), they also have a low progression rate (<5% at 5 years). Those with T1/HG (grade 3) do poorly, with 1- and 5-year disease progression rates with 11% and 20%, respectively. Cancer-specific 5-year survival for these patients is >90%.[12,13]

Regional and distant staging of invasive bladder cancer

If muscle invasion has been confirmed, regional and distant staging should be carried out with further imaging

studies such as contrast-enhanced CT of the chest, abdomen and pelvis or MRI of the abdomen and pelvis (with CT of the chest). The risk of lymph node (LN) metastasis increases proportionally with advancing local tumour stage.[14,15] Both tests can be used to assess extravesical invasion but are often unable to reliably differentiate between T stages. Imaging is recommended before TURBT. Both tests are useful to detect enlarged LNs, but have low sensitivity (48%-87%) and specificity for the detection of LN metastasis.[16,17] Overall, pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short-axis diameter, detected by CT or MRI, should be considered as suspicious for LN metastasis.[18,19] MRI generally is more accurate for determining depth of invasion and is recommended when imaging definition of stage of invasion is important. A scoring system for defining muscle invasion has been proposed (VI-Rads) with some accuracy, with a sensitivity and specificity of 0.83 [95% confidence interval (CI) 0.70-0.90] and 0.90 (95% CI 0.83-0.95), respectively.[20,21] A chest-abdomen-pelvis CT should also be carried out for staging of potential distant metastatic disease [III, A]. The authors did not reach a consensus on the role of [^{18}F]2-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET)-CT in MIBC. Despite inconsistencies in sensitivity (23%-89%), FDG-PET-CT seems to have a high specificity (81%-100%) for LN staging.[22]

Recommendations

- Patients with NMIBC are classified into four risk categories based on tumour characteristics (low risk, intermediate risk, high risk and very-high-risk; Table 1), which constitutes the basis for treatment and follow-up recommendations [IV, B].
- 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 [IV, B]. FDG-PET-CT may aid in the detection of LN and distant metastases [IV, C], but no clear consensus was reached.

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Treatment of NMIBC

Optimal treatment of NMIBC is the complete removal of all visible lesions in the bladder, followed by intravesical instillations or early radical cystectomy (RC), according to risk stratification described in the preceding text [I, A] (Figure 2, Table 1, Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.11.012). If available, improved tumour visualisation techniques (fluorescence cystoscopy, narrow-band imaging) during TURBT are recommended.

In patients with low-risk NMIBC and those with small papillary recurrences, detected >1 year after the previous tumour, single, immediate, intravesical chemotherapy (ChT) instillation, such as mitomycin C (MMC), is recommended [I, A], in combination with continued cystoscopic surveillance. Immediate, intravesical ChT instillation significantly reduces the 5-year recurrence rate compared with TURBT alone (59% versus 45%).[23] The rate of progression is negligible (<2% at 5 years).[13]

In patients with intermediate-risk NMIBC, additional courses of intravesical therapy are recommended to reduce risk of recurrence [I, A]. This can consist of either:

1. Instillations of ChT for a maximum of 1 year.

Or

2. 12 months of BCG instillation therapy (induction therapy with six BCG instillations at weekly intervals, followed by maintenance therapy with three BCG instillations each at 3, 6 and 12 months after the start of the induction cycle) is recommended [I, A]. In trials with BCG therapy (induction and maintenance therapy) in intermediate- and high-risk NMIBC, there was a 32% reduction in the risk of recurrence ($P < 0.0001$) for BCG compared with MMC. However, no statistically significant difference was observed in progression rate between the two groups.[24]

In patients with high-risk NMIBC, full-dose intravesical BCG for 1-3 years (at least 1 year) is recommended [I, A]. Three-year maintenance is more effective than 1 year to prevent recurrences.[25] Induction consists of weekly instillations for 6 weeks while maintenance consists of weekly instillations for 3 weeks. Instillations at 3, 6, 12, 18, 24, 30 and 36 months are recommended [I, A]. The 3-year maintenance BCG schedule significantly reduces the risk or recurrence compared with 1-year maintenance [hazard ratio (HR) for 1 versus 3 years: 1.61, 95% CI 1.13-2.30, $P = 0.01$] in patients with high-risk tumours. This benefit of 3-year therapy does not occur for patients with intermediate-risk tumours.[25]

In patients with high-risk NMIBC, there is a significant risk of residual disease after initial TURBT.[26] Therefore, a second resection should be carried out 4-6 weeks after the first resection when:

- The initial TURBT was incomplete.
- If there is no detrusor muscle in the specimen on the initial resection, except for Ta LG and CIS.
- In all pT1 tumours and all HG tumours, except for patients with primary CIS [I, A].

The second TURBT should include a resection of the previous tumour site.

Treatment after failure of BCG therapy. The definition of failure after BCG therapy is important to identify patients who are unlikely to respond to further BCG therapy. In patients with very-high-risk NMIBC, these recommendations apply, except in those in whom early RC is planned. Early RC should be considered and discussed with all very-high-risk NMIBC cases. The final choice is made based on a shared decision-making process between patient and physician.

BCG failure is divided into the following four types:[27]

1. BCG-refractory:
   - persistent HG disease at 6 months despite adequate BCG treatment; OR

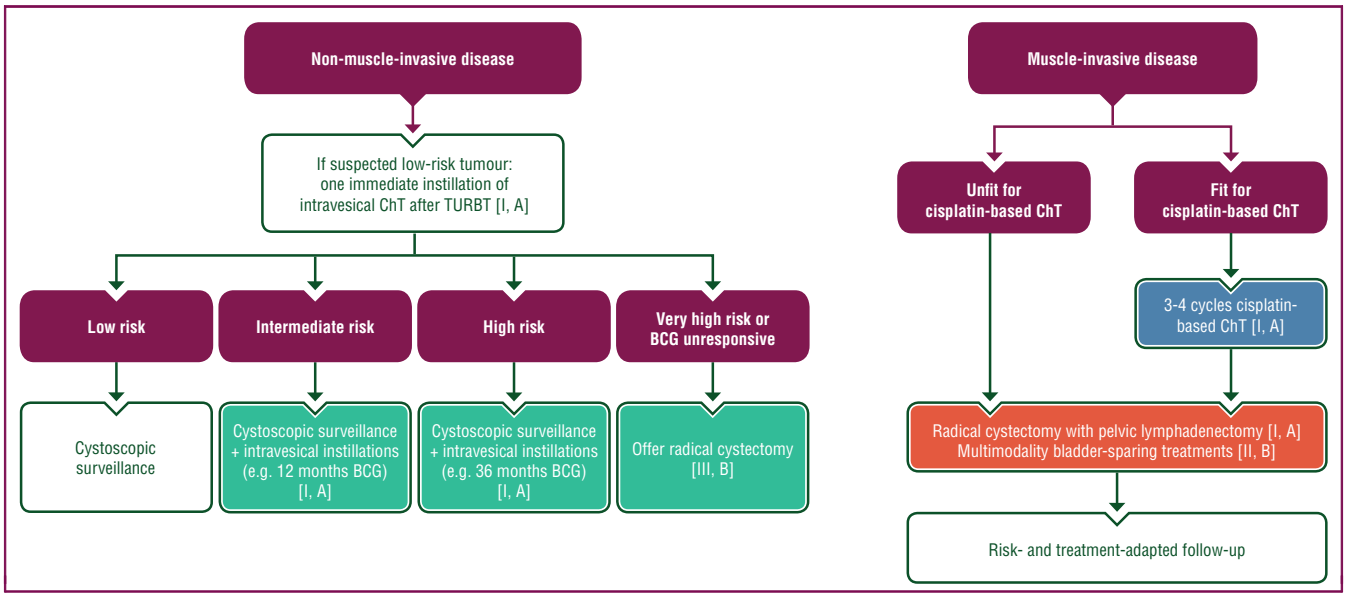

Figure 2. Management of patients with histopathologically confirmed bladder cancer.
Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
BCG, bacillus Calmette-Guerin; ChT, chemotherapy; TURBT, transurethral resection of the bladder tumour.

- stage progression at 3 months after adequate BCG induction (i.e. HG T1 at 3 months after initial CIS or HG Ta).

2. BCG-relapsing: recurrence of HG disease after achieving a disease-free state at 6 months after adequate BCG.
3. BCG-intolerant: disease persistence as a result of inability to receive adequate BCG because of toxicity.
4. BCG-unresponsive: combination of BCG-refractory and BCG-relapsing within 6 months of last BCG.

RC should be carried out in HG tumours (T1/HG, Ta/HG, CIS) that are unresponsive to BCG due to the high risk of progression [III, B]. Thermo-ChT can be offered as an alternative, only in patients unwilling or unable to have RC and can obtain 2-year disease-free survival (DFS) in 47% of patients.[28] BCG re-induction achieved similar disease control to thermo-ChT in a randomised trial [II, B][29] and can be considered as an alternative.

The immune checkpoint inhibitor (ICI) pembrolizumab given intravenously was evaluated in a single-arm phase II trial (KEYNOTE-057), in patients with BCG-unresponsive NMIBC with CIS who were ineligible for or elected not to undergo RC ($n = 102$).[30] At 3 months, the study showed a complete response (CR) rate of 41% (95% CI 31%-51%) in 96 patients with high-risk NMIBC with CIS with or without papillary tumours, and a median duration of response of 16.2 months (range: 0.0-30.4). Intravenous pembrolizumab can be considered in patients with BCG-unresponsive disease who are not fit for or refuse RC [III, C]. More robust data are required before stronger recommendations can be made.

Intravesical nadofaragene firadenovec therapy [not Food and Drug Administration (FDA) or EMA approved as of November 2021] has also been studied in BCG-refractory NMIBC with CIS ($n = 103$; 53% CR at 3 months; 24% CR at 12 months) [III, C].[31] These data have the same recommendations as pembrolizumab in this population.

Treatment of MIBC

Multidisciplinary care via tumour board discussions and/or directed consultations with a medical oncologist, radiation oncologist and urologist is recommended for the optimal management of bladder cancer [IV, B].

Radical cystectomy. RC with pelvic lymph node dissection (PLND) is the standard treatment of MIBC cT2-T4a, N0 M0 [I, A].[32] RC with PLND is strongly recommended in very-high-risk and BCG-unresponsive NMIBC (Figure 2). A continent orthotopic (neobladder), continent cutaneous (catheterisable pouch) or incontinent cutaneous (conduit) reconstructions are chosen based on patient's general health and wishes.[33] A neobladder can be offered to patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection [IV, C]. Standard PLND is defined as the removal of all lymphatic tissues around the common iliac, external iliac, internal iliac and obturator regions up to the crossing of the ureters over the common iliac vessels at a minimum.[34,35] Extended lymphadenectomy includes lymphatic tissues in the region of the aortic bifurcation and presacral and common iliac vessels above the crossing ureters, in addition to the standard PLND region. The optimal extent of PLND is not established to date. In a recent prospective phase III, randomised trial, extended PLND failed to show a significant advantage in absolute improvement of 5-year recurrence-free survival compared with standard PLND, though the study suffered from many limitations.[36]

Patients with radiological suspicious node-positive disease (cN1) can be considered for surgery[37] (with or without neoadjuvant ChT) [IV, B]. Patients with clinical node positivity benefit from preoperative platinum-based ChT followed by RC plus PLND.[38-40] Overall, the number of positive LNs is significantly associated with increased risk of

cancer-specific death (HR 1.9, 95% CI 1.04-3.46 for N1 disease; HR 4.3, 95% CI 2.25-8.34 for ≥2 LNs).[41]

Organ-preservation therapy. Organ-preservation therapy for MIBC is a reasonable option for patients seeking an alternative to RC and for those who are medically unfit for surgery (Figure 2) [II, B]. Contemporary protocols utilise aggressive TURBT alone, TURBT plus radiotherapy (RT), TURBT plus ChT or a tri-modality combination of TURBT plus RT and ChT, the latter being preferred [II, B]. There are multiple patient- and tumour-related factors which contribute to the selection of trimodal therapy versus RC. The ideal patient for trimodal therapy has a tumour that can undergo a visible complete resection, has no associated hydronephrosis, does not invade the prostatic urethra and is not associated with diffuse CIS throughout the bladder. Select patients who do not meet all these criteria can still be successfully treated with this approach. The initial prospective, randomised comparison of RT alone versus concomitant chemoradiotherapy (CRT) demonstrated improved local control rate when cisplatin was given with RT (HR 0.50, 90% CI 0.29-0.86) [II, B].[42] A second trial showed that hypoxic sensitisation with carbogen and nicotinamide (bladder carbogen nicotinamide) reduced the risk of relapse (54% versus 43% with RT alone) and death [II, B].[43] A third randomised trial (BC2001) demonstrated improved results for CRT using the combination of 5-fluorouracil and MMC in terms of locoregional survival (67%) and DFS (54%) [I, A].[44] A multidisciplinary approach including urologists, medical oncologists and radiation oncologists is necessary. A cystoscopy with bladder biopsy is mandatory for response evaluation either midway through treatment or 2-3 months thereafter. If persistent or recurrent muscle-invasive disease is observed at response evaluation or during follow-up (cystoscopy and urinary cytology every 3 months during the first 2 years, and every 6 months thereafter), prompt RC is recommended when possible [II, A]. NMIBC recurrences can occur in up to one-fourth of patients after completion of trimodal therapy, with many being treated by routine and standard therapy for NMIBC. In this population after trimodal therapy, however, early salvage RC should be considered in those with adverse features, including T1 disease, tumour >3 cm, CIS or lymphovascular invasion. The 5-year cancer-specific survival and overall survival (OS) rates range from 50% to 82% and from 36% to 74%, respectively, with salvage RC rates of ∼20% for studies with a follow-up >5 years.[45,46] The pooled rate of non-response to trimodal therapy and local recurrence after trimodal therapy, the two primary reasons for salvage RC, is approximately 16% and 29%, respectively.[46] Salvage RC can be carried out for local recurrences with acceptable oncological control and no clear evidence of any greater risk of early complications; however, there may be a slightly increased risk for late complications, namely small bowel obstruction, ureteral stricture and parastomal hernia. The pooled rates of 5- and 10-year DFS after salvage RC have been estimated at 54% and 46%, respectively.[46,47] Trimodal therapy with other sensitising agents has been investigated in series from single-centre cooperative groups and meta-analysis [III, B]. There are clinical activity and acceptable outcome data. Patient selection may play a role in these outcomes. Cross-trial comparisons with RC should be avoided due to biases arising from patient selection and follow-up.[45,48-51]

Neoadjuvant and adjuvant therapy. The use of cisplatin-based neoadjuvant ChT for bladder cancer is supported by a meta-analysis of 11 randomised trials of 3005 patients [I, A] (HR 0.86, 95% CI 0.77-0.95), which translated to a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year DFS compared with cystectomy alone.[52] There is a lack of clarity about the optimal regimen.

Cisplatin—gemcitabine or accelerated methotrexate, vinblastine, adriamycin and cisplatin (MVAC) are the most widely given neoadjuvant ChT regimens and can be recommended [III, B].[53-55] There is also a lack of clarity on the number of cycles to be given. Three cycles were given in the original positive randomised phase III study, although most regimens/physicians currently administer four cycles.[56] Pure squamous cell or adenocarcinoma MIBC should be treated with primary RC [IV, B].[57] MIBC with small-cell neuroendocrine variant should be treated with neoadjuvant ChT followed by consolidating local therapy [IV, B].[57] A recent consensus meeting recommended cystectomy without neoadjuvant ChT for micropapillary disease, while data show no difference in response rates (RRs) compared with pure UC [IV, B].[57,58] Phase II data exist for neoadjuvant ICI therapy and they are not currently recommended in cisplatin-eligible or -ineligible patients [III, B].[59,60] There is no role for adjuvant treatment (ChT or RT) for those who have received neoadjuvant ChT. These patients have been included in the adjuvant immunotherapy trials.

Adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy remains an area of debate. There are no published positive randomised, phase III studies for survival. An updated meta-analysis of nine randomised trials including 945 patients found an OS benefit (HR 0.77, 95% CI 0.59-0.99) and DFS benefit (HR 0.66, 95% CI 0.45-0.91) among those who received cisplatin-based adjuvant ChT versus observation [II, B].[61] Subsequently, a randomised trial [European Organisation for Research and Treatment of Cancer (EORTC) 30994] reported a significant benefit of cisplatin-based ChT for DFS (HR 0.54, 95% CI 0.4-0.73) compared with observation.[62] A statistically significant OS benefit was not shown (adjusted HR 0.78, 95% CI 0.56-1.08) possibly due to insufficient recruitment. Adjuvant ChT in cisplatin-unfit patients is not recommended [I, D].

Adjuvant atezolizumab for 1 year versus observation did not improve DFS or OS in a large ($n = 809$) randomised study for high-risk UC [HR for DFS 0.89 (95% CI 0.74-1.08)[63] and HR for OS 0.85 (95% CI 0.66-1.09)]. There was no enrichment for outcome with the PD-L1 biomarker. Adjuvant atezolizumab is not recommended.

Adjuvant nivolumab for 1 year versus placebo showed improved DFS of 0.70 (95% CI 0.54-0.89; median follow-up

of 20.9 months). There were also positive results in the 26% of patients who were PD-L1-positive [DFS 0.53 (95% CI 0.34-0.84)]. OS (a secondary endpoint) has not yet been presented.[64] 17.9% grade 3 or more treatment-related adverse events occurred in the nivolumab arm. These results are promising, especially in the biomarker-positive population. Due to the inconsistency across trials and uncertainty of the relationship between DFS and OS with immunotherapy, OS results are awaited before this treatment can be recommended [I, D].

Recommendations

Treatment of NMIBC

- Treatment of NMIBC should follow a risk-stratified approach with TURBT and intravesical ChT or BCG in intermediate- and high-risk patients [I, A].
- Subsets of patients with very-high-risk disease should be offered RC. RC should be carried out in CIS or HG T1 that are unresponsive to BCG due to the high risk of progression [III, B].
- In patients who are BCG-unresponsive and -ineligible for or refuse cystectomy, pembrolizumab or nadofaragene firadenovec can be considered; however, more robust data are required before stronger recommendations can be made for these and other bladder-sparing approaches in BCG-unresponsive disease [III, C]. A multidisciplinary approach is required for these patients [IV, C].

Treatment of MIBC

- Multidisciplinary care via tumour board discussions and/or directed consultations with a medical oncologist, radiation oncologist and urologist is recommended for the optimal management of bladder cancer [IV, B].
- RC with standard PLND is the standard treatment of MIBC T2-T4a, N0 M0 [I, A].
- Patients with radiological suspicious node-positive disease (cN1) can be considered for surgery but should be considered for preoperative platinum-based ChT [IV, B].
- Organ-preservation therapy with RT, as part of multimodal schema for MIBC, is a reasonable option for patients seeking an alternative to RC and an option for those who are medically unfit for surgery [II, B].
- Contemporary organ-preservation protocols should utilise tri-modality combination of TURBT, RT and ChT [II, B].
- Palliative RT can be offered for palliation (bleeding, pain) [III, C].
- Adjuvant RT (with or without radiosensitising ChT) is not standard treatment of patients with MIBC [III, C].
- Three to four cycles of cisplatin-based neoadjuvant ChT should be given for MIBC [I, A]. Cross-sectional imaging should occur after ChT before RC [IV, B].
- There is weak evidence to support the use of adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy [II, B]. Neoadjuvant ChT is preferred.
- Inconsistent results exist for adjuvant ICIs in UC [I, A]. An OS advantage is needed before it can be recommended as standard therapy [I, D].

MANAGEMENT OF ADVANCED/METASTATIC DISEASE

Advanced or metastatic UC in patients fit enough to tolerate cisplatin-based combination ChT

Cisplatin-containing combination ChT is standard in advanced or metastatic patients fit enough to tolerate cisplatin (Figure 3). A number of cisplatin-containing ChT regimens are acceptable although gemcitabine—cisplatin [I, A] is the most widely used.[65] Dose-dense MVAC [I, B], MVAC with granulocyte colony-stimulating factor [I, B] and gemcitabine, cisplatin and paclitaxel [I, C] have been tested against gemcitabine and cisplatin.[66-68] Although these alternative regimens may lack proven advantages over gemcitabine and cisplatin, similar results are reported and either can be considered as an option in selected patients. New treatments which build on the gemcitabine—platinum backbone will require clinically meaningful progression-free survival (PFS) advantages, significant OS or non-inferiority with better tolerability to be recommended. For these reasons, gemcitabine, cisplatin and bevacizumab regimen is not recommended.[69,70] The combination of platinum-based ChT with ICIs has not resulted in positive significant survival advantages and is not currently recommended.[71] Potential benefits in other endpoints such as PFS are modest. Final results for atezolizumab with ChT are awaited.[72] There is currently no role for ICI therapy alone in this population.[73]

Advanced or metastatic UC in patients not eligible for cisplatin-based combination ChT

Carboplatin-based ChT is recommended in patients unfit for cisplatin [I, A]. Criteria for these have been defined.[74] Carboplatin with gemcitabine is the preferred regimen [II, B].[75] Gemcitabine and cisplatin can be considered for patients otherwise fit without comorbidities, a good performance status (0-1) and a creatine clearance between 50 and 60 ml/min [III, B].[76,77] This alternative has been established over time as a standard treatment and can, therefore, be supported despite a lack of robust data. A recent randomised trial evaluated the safety of split-dose cisplatin due to renal toxicity;[78] the authors did not reach consensus on its role. Six cycles of ChT are considered the standard of care, although fewer cycles are acceptable, with cumulative toxicity.[79]

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1-positive and not eligible for cisplatin-based ChT, although randomised trials, which have reported, failed to show significant superiority compared with ChT [III, B] (final results are awaited for atezolizumab) (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2021.11.012).[73,80] In exploratory analyses, the OS HR for pembrolizumab and atezolizumab versus gemcitabine and carboplatin in this subset of biomarker positives was 0.82 (95% CI 0.57-1.17) and 0.53 (95% CI 0.30-0.94), respectively. Final OS results for the atezolizumab study are awaited. Biomarkers (SP142 for atezolizumab; 22C3 for pembrolizumab) should be used to match the drug, as recommended by the EMA.[72,81]

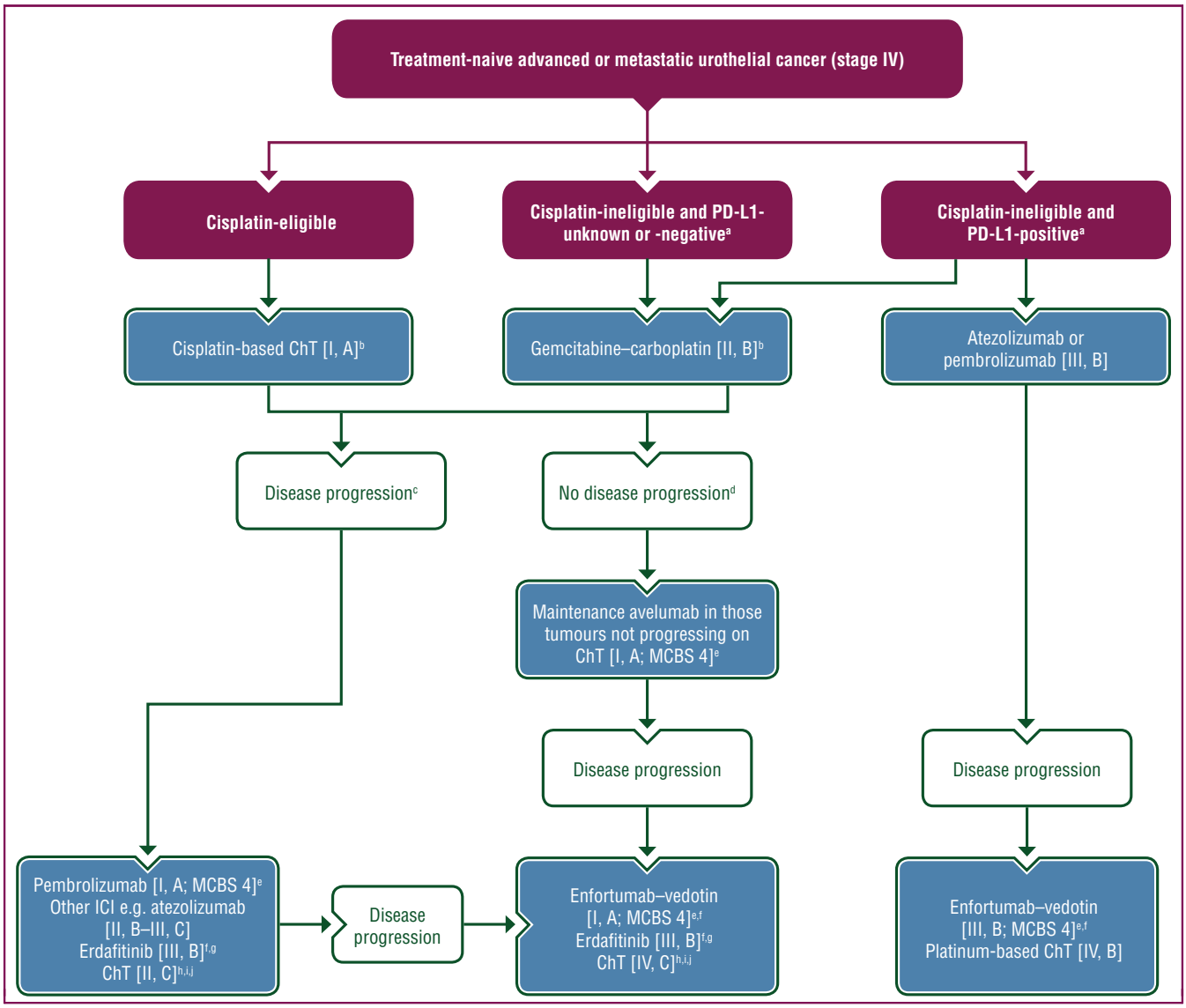

Figure 3. Management of patients with metastatic bladder cancer.
Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; MCBS, ESMO-Magnitude of Clinical Benefit Scale.
[a] Creatinine clearance <60 ml/min or World Health Organization (WHO) performance status 2 or comorbidity [neuropathy/hearing loss >grade 2 and New York Heart Association (NYHA) class III heart failure].
[b] Re-challenge with platinum-based ChT may be considered if progression occurred ≥12 months after the end of previous platinum-based ChT or ≥12 months after the end of previous platinum-based ChT and maintenance avelumab.
[c] For progressive disease on ChT or after the completion of ChT where maintenance avelumab was not given.
[d] This should be assessed within 10 weeks of completion of ChT.
[e] ESMO-MCBS v1.1[120] was used to calculate scores for new therapies/indications approved by the EMA or the FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[f] FDA approved; not currently EMA approved.
[g] With selected *FGFR* DNA fusions and mutations.
[h] Platinum doublets should be recommended if the treatment-free interval from the last platinum ChT is >1 year.
[i] To be considered when other therapies are not available.
[j] Paclitaxel, docetaxel or vinflunine should be used.

Well-tolerated durable responses were observed with both immunotherapy drugs; however, in randomised trials, ChT had higher RRs and longer PFS while immunotherapy had longer duration of response.[82,83] Median OS (mOS) was not better with the use of ICIs. The PD-L1 biomarker for pembrolizumab (22C3) was not associated with improved outcomes compared with the biomarker negatives; the authors question this approach. Final data from randomised trials with durvalumab are similar with no OS benefit.[73]

Treatment should continue for 2 years for pembrolizumab and until progression for atezolizumab. Treatment post-progression is not recommended.

Platinum-based ChT followed by maintenance avelumab is preferential compared with upfront ICIs in PD-L1

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biomarker-positive patients. No consensus could be reached for ICIs in PD-L1 biomarker-negative patients not eligible for any ChT.

Data for enfortumab—vedotin (EV) with pembrolizumab in first-line cisplatin-ineligible population are encouraging but no recommendations can be proposed due to the small size of the study ($n = 43$).[84]

Maintenance avelumab, started within 10 weeks of completion of first-line platinum-based ChT, is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after four to six cycles of gemcitabine plus cisplatin or carboplatin, and is recommended (HR 0.69, 95% CI 0.56-0.86) [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4] (Figure 3).[85,86] An increase in mOS from 14 to 21 months was observed with avelumab. Treatment was given until progression.

Treatment of relapsed advanced/metastatic UC

Pembrolizumab has a significant survival advantage compared with ChT in patients with tumours which have relapsed after platinum-based therapy and did not receive previous immunotherapy [mOS: 10.3 for pembrolizumab and 7.4 months for ChT (HR 0.73, 95% CI 0.59-0.91)] [I, A; ESMO-MCBS v1.1 score: 4] (Figure 3). Responses were more frequent and durable for pembrolizumab compared with ChT (21% versus 11%, respectively).[87] An update with a minimum follow-up of 5 years showed 3-year response duration of 44% for pembrolizumab compared with 28.3% for ChT [I, A].[87,88] The IMVigor211 trial explored atezolizumab in PD-L1 biomarker-positive tumours in this population and failed to show a significant OS advantage. Results in the intention-to-treat population favoured atezolizumab, but statistical significance could not be drawn due to the study design (HR 0.85, 95% CI 0.73-0.99). The drug was associated with an RR of 13%.[89] In a recent updated analysis, atezolizumab showed a 30-month OS of 18% compared with 10% for ChT.[90] Phase I-IV trials for atezolizumab exist in this population and the results are consistent.[91-93] For these reasons, the authors support the use of atezolizumab in this setting [II, B] with a weaker recommendation than for pembrolizumab.

Three other drugs (nivolumab [III, B], durvalumab [III, C] and avelumab [III, C]) have data from single-arm trials.[94-96] Durable responses occurred in ~15%-20% of patients. It is premature to assume that all these drugs have the same activity in this setting.

Treatment with further ChT for platinum-refractory disease is an alternative for patients in whom anti-programmed cell death protein 1/PD-L1 therapy is not possible. This approach is, however, not clearly associated with a survival benefit. Vinflunine [II, C], docetaxel [III, C] and paclitaxel [III, C] can be considered,[97,98] although vinflunine is the only EMA-approved agent. Combinations with taxanes may be considered as an option in selected patients.[99] Retreatment with platinum-based ChT for those tumours that relapse >1 year after previous ChT is a reasonable option, particularly where ICI therapy is not available [IV, B].

Erdafitinib is a pan-FGFR tyrosine kinase inhibitor of FGFR1-4 that has been tested in a phase II trial in 99 patients with locally advanced or metastatic previously treated UC and *FGFR* DNA genomic alterations (*FGFR2* or *3* fusions, or *FGFR3* mutations). In this trial, 45% of patients had previously received only first-line platinum-based ChT.[9] In a recent update with a median follow-up of 24 months, confirmed RR in all populations was 39% in ChT-relapsed/-refractory patients. Median PFS (mPFS) and mOS were 5.5 months (95% CI 4.0-5.7) and 10.6 months (95% CI 9.0-14.7), respectively, in ChT-relapsed/-refractory patients.[9,100] mPFS and mOS were 5.5 months (95% CI 4.0-5.7) and 10.6 months (95% CI 9.0-14.7), respectively, in ChT-relapsed/-refractory patients.[9,100] Erdafitinib is recommended in platinum-refractory tumours with *FGFR* alterations [III, B]. No consensus could be reached on whether second-line ICI therapy or erdafitinib should be used in preference in these patients.

Treatment of tumours that have relapsed after first-line immunotherapy

There are no prospective randomised data regarding treatment of patients with progression of disease after ICIs in advanced UC. Retrospective data support the use of standard first-line platinum-based therapy [IV, B].[101] RRs and PFS are in line with those seen for first-line platinum-based ChT. Recommendations are similar to those for front-line ChT. Gemcitabine with cisplatin or carboplatin are the preferred regimens.

EV is an antibody drug conjugate targeting nectin-4. Monomethyl auristatin E is the payload drug within this molecule (microtubule-disrupting agent). A single-arm phase II trial for EV in this population shows RRs of 52%, PFS of 5.8 months (95% CI 5.0-8.3) and OS of 14.7 months (95% CI 10.5-18.2).[102] This agent can, therefore, be recommended as an alternative to ChT in this population irrespective of nectin-4 expression [III, B].

Treatment of ChT and immunotherapy-relapsed disease

This population included third-line therapy after the sequence of platinum-based ChT and ICIs. It also included second-line therapy after first-line ChT and maintenance avelumab. EV has been tested in phase II and phase III trials in advanced disease UC after progression with ChT and ICIs. Confirmed RRs were 44% (95% CI 35% to 53%) in the phase II study.[103] The phase III trial showed superior RRs (41% versus 17%), PFS (HR 0.62, 95% CI 0.51-0.75) and OS (HR 0.70, 95% CI 0.56-0.89; 12.8 versus 9.0 months) for EV versus ChT (vinflunine or taxanes).[104] Grade 3 or more adverse events of special interest associated with the new class of drug were rash (15%), peripheral neuropathy (5%) and hyperglycaemia (4%). EV should be considered the standard of care in this population, which includes patients with progression of disease after first-line ChT and maintenance avelumab [I, A].

The erdafitinib phase II trial described previously included 22 patients whose tumours had progressed after immunotherapy and ChT. The RR to erdafitinib was 59% in this population. mPFS and mOS were 5.7 months (95% CI 4.9-8.3) and 10.9 months (95% CI 8.0-21.1), respectively.[100] Therefore, erdafitinib is also recommended, with less robust evidence, in this FGFR-selected population [III, B].

ChT (taxanes or vinflunine) is a less attractive alternative to EV or erdafitinib in patients who have had progressive disease on platinum-based ChT and ICIs (RR of 21%) [IV, C].[105]

UTUC

UTUCs account for only 5%-10% of UCs.[106,107] Multifocal tumours are found in 10%-20% of UTUC cases.[108] The presence of concomitant CIS of the upper tract is between 11% and 36%.[107]

At first diagnosis, 60% of UTUCs are invasive compared with 15%-25% of bladder tumours.[109] The most common histological type is UC; variants are present in up to 25% of the cases.[110] The most common symptom is haematuria (70%-80%) or flank pain (10%-20%).[111,112]

The key investigations for UTUC are CT urography and diagnostic ureteroscopy. During the ureteroscopy, an *in situ* cytology sample of the upper tract should be collected, despite the fact that cytology is less sensitive for UTUC than UC of the bladder.[113]

UTUCs invading the muscle wall usually have a poor prognosis. The 5-year cancer-specific survival is $<$50% for patients with pT2-pT3 tumours and $<$10% for those with pT4.[114-116]

UTUCs are stratified into two risk categories, low- and high-risk tumours. Low-risk tumours include unifocal tumours of $<$1 cm, LG disease at cytology/biopsy and no invasive features on CT urography. High-risk tumours are $>$2 cm, with possible hydronephrosis, HG disease at cytology/biopsy, multifocal disease, variant histology or previous RC for bladder cancer.[116]

Kidney-sparing management, such as endoscopic laser ablation, should be offered as primary treatment option to patients with low-risk UTUC. High-risk UTUC patients should undergo open or laparoscopic radical nephroureterectomy with bladder cuff excision regardless of tumour location [II, B].[109]

There are limited studies in UTUC evaluating systemic therapy in patients with locally advanced or metastatic disease. Most of the clinical decision making is extrapolated from evidence of the bladder literature and small, single-centre UTUC studies ($<$50 patients). Systemic therapy for advanced disease should follow the recommendations for urothelial bladder cancer [IV, B]. This included adjuvant cisplatin-based ChT. A randomised, phase III adjuvant ChT study [the Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer trial (POUT): gemcitabine—cisplatin/carboplatin versus observation] showed improved DFS (HR 0.45, 95% CI 0.30-0.68) in patients with locally advanced UTUC (pT2-T4 pN0-N3 M0 or pT any N1-3 M0).[117] The study was not powered for OS (HR 0.7, 95% CI 0.46-1.06). There is evidence to support the use of adjuvant cisplatin-based ChT, based on the POUT data and the OS meta-analysis for cisplatin-based treatment of urothelial bladder cancer [II, C]. The role of adjuvant carboplatin-based treatment is not fully elucidated due to power limitations on the analyses for the subgroup of patients included in the POUT trial. Therefore, adjuvant carboplatin-based ChT should not be recommended at the present time in this setting [II, D]. The role for adjuvant ICIs in this population is controversial. Patients with UTUC who were included in CheckMate 274 study seemed to benefit less from adjuvant nivolumab compared with the bladder tumour counterpart and OS data are unavailable. Therefore, at the present time, ICIs cannot be recommended in this setting.[64]

Recommendations

Treatment of advanced or metastatic UC in patients fit enough to tolerate cisplatin-based combination ChT

- Cisplatin-based ChT [I, A] followed by maintenance avelumab in those tumours not progressing on ChT is the standard of care [I, A; ESMO-MCBS v1.1 score: 4].

Treatment of advanced or metastatic UC in patients not eligible for cisplatin-based combination ChT

- Gemcitabine/carboplatin [II, B] followed by maintenance avelumab (in those tumours not progressing on ChT) for those not eligible for cisplatin-based therapy is the standard of care [I, A].
- Atezolizumab or pembrolizumab are alternatives for patients with PD-L1 biomarker-positive tumours who are not eligible for cisplatin-based combination ChT. The level of evidence, however, is weaker than for ChT followed by maintenance avelumab and this approach requires careful consideration [III, B].

Treatment of relapsed advanced/metastatic UC

- Pembrolizumab has the most robust data for treatment in the setting of progression of disease after platinum-based ChT [I, A; ESMO-MCBS v1.1 score: 4]. Other ICIs such as atezolizumab can be given with less robust evidence [II, B-III, C].
- Erdafitinib is an alternative to ICIs in tumours with FGFR alterations. This has weaker levels of evidence than pembrolizumab [III, B].
- ChT can be considered instead of best supportive care when other options are not available (vinflunine [II, C]; taxanes [III, C]).

Treatment of tumours that relapse after first-line single-agent immunotherapy

- Randomised data are lacking in immunotherapy-refractory disease. EV [III, B; ESMO-MCBS v1.1 score: 4] or platinum-based ChT [IV, B] should be given.

Treatment of ChT and immunotherapy-relapsed disease

- EV is recommended as standard treatment in this population [I, A; ESMO-MCBS v1.1 score: 4].
- Erdafitinib is an alternative in patients with FGFR alterations with a weaker level of evidence [III, B].

- ChT can be considered instead of best supportive care [IV, B], if clinically appropriate.
- Retreatment with ChT for those patients that relapse after all other treatment options can be considered. Single-agent taxane therapy or vinflunine can be considered [IV, C].

Treatment of UTUC

- Kidney-sparing management should be offered to low-risk UTUC and radical nephroureterectomy with bladder cuff excision for high-risk UTUC [II, B].
- Systemic therapy recommendations for advanced UTUC should follow those for advanced bladder cancer [IV, B].
- There is evidence to support the use of adjuvant cisplatin-based ChT based on the POUT data and the OS meta-analysis for cisplatin-based treatment of UC [II, C].

FOLLOW-UP AND LONG-TERM IMPLICATIONS

NMIBC

There is no generally accepted follow-up protocol as recommendations are mainly based on retrospective data. Therefore, the frequency and duration of cystoscopy and subsequent imaging should reflect the individual patient's degree of risk of recurrence and progression [IV, B].[11,118] In all patients with a new diagnosis of Ta-T1 tumours and/or CIS, the first cystoscopy should be carried out at 3-month intervals [IV, B].[119] Regular cystoscopy and cytology is subsequently recommended every 3-6 months during the first 2 years of follow-up, and every 6-12 months thereafter. Regular upper tract imaging (CT intravenous urography) is recommended for high-risk tumours.

MIBC

There is no generally accepted follow-up protocol for muscle-invasive UC [IV, B]. Current surveillance protocols are based on patterns of recurrence drawn from retrospective series. Imaging of the chest, upper tract, abdomen and pelvis should be carried out to detect relapse after potentially curative therapy every 3-4 months for 2 years, and then every 6-12 months up to 5 years [IV, B].[57] The benefits of follow-up beyond 5 years are unclear and it is reasonable to discharge patients. UTUC occurs in 4%-10% of cases after RC;[32] hence, regular upper tract imaging is recommended [IV, B].

After bladder-sparing procedures with curative intent, such as trimodal therapy, follow-up must investigate for local as well as systemic relapses. Cystoscopic examination should be carried out every 3-6 months for the first 5 years. CT of the thorax and abdomen is recommended as the imaging method for follow-up every 3-4 months for the first 2 years, and then every 6 months up to 5 years [IV, B].[57] The role of surveillance beyond 5 years is uncertain.

Advanced/metastatic disease

Response evaluation every 2-3 months should occur for those patients on systemic therapy for advanced disease. Regular (3-4 months) cross-sectional imaging should occur for 2 years upon completion of systemic therapy. Bone scans/MRI may be required if CT cannot address these adequately [IV, B].

Recommendations

- Follow-up for NMIBC requires regular cystoscopic examination according to the patient's risk category [IV, A].
- Follow-up after curative therapy for MIBC requires cross-sectional imaging for 5 years. This should include 3-4 monthly imaging for the first 2 years. Bladder-sparing approaches also require regular cystoscopy [IV, B].
- Follow-up during and after systemic therapy for advanced UC should focus on regular cross-sectional imaging of the chest, abdomen and pelvis and other target lesions [IV, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the European Society for Medical Oncology (ESMO) standard operating procedures for Clinical Practice Guideline development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. An ESMO-MCBS table with MCBS scores is included in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2021.11.012. ESMO-MCBS v1.1[120] was used to calculate scores for new therapies/indications approved by the EMA and/or the FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA approval status of new therapies/indications is correct at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2021.11.012.[121] Statements without grading were considered justified standard clinical practice by the authors.

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