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EAU-ESMO Consensus statements on the management of advanced bladder cancer - a global collaborative multi-stakeholder effort

[NOTE: Author order is: Consensus Chairs first/last, steering committee members (alphabetically) then all other authors (alphabetically)]

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ABSTRACT

In 2018, the European Association of Urology and the European Society for Medical Oncology formed a collaboration to assess recommendations for bladder cancer management with a view to providing further expert guidance using a Delphi survey and consensus conference approach. A steering committee of 13 experts compiled 115 statements relating to bladder cancer management, focussing on areas where evidence is lacking/conflicting. These statements were assessed by a multidisciplinary panel of 113 experts in a Delphi survey. All participants ranked statements according to their level of agreement: 1-3 (disagree), 4-6 (equivocal), 7-9 (agree) and 'unable to score'. A priori (Level 1) consensus was defined as agreement by ≥70% and disagreement by ≤15%, or vice versa. A second analysis was restricted to specific stakeholder group(s) considered to have adequate expertise relating to the specific statement (to achieve Level 2 consensus). Level 1 consensus was achieved for 33 (28%) statements, with Level 1 or 2 consensus achieved for 49 (42%) statements. The remaining 67 (58%) statements were prioritised for further review at a consensus conference held on 8 November 2018 in Amsterdam, The Netherlands. This included a multidisciplinary panel of 45 experts, with all panel members allocated to one of 6 working groups: (1) strategies for variant histologies, (2) the role of prognostic markers, (3) bladder preservation strategies, (4) treatment of curative intent for oligometastatic disease, (5) immune checkpoint inhibitors, and (6) follow-up strategies and survivorship. Statements were discussed by each working group during parallel breakout sessions, and revised as necessary. Final statements were presented to the entire panel for further deliberation, amendment and voting. This resulted in the presentation of 27 statements, 22 (81%) of which achieved consensus. This manuscript presents the results of the Delphi survey as well as a summary of expert panel discussions and recommendations from the consensus conference.

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KEY WORDS:

Bladder cancer, consensus, diagnosis, treatment, follow-up

KEY MESSAGE

- This EAU-ESMO manuscript on bladder cancer was compiled by a multidisciplinary panel of experts based on results of a Delphi survey and consensus conference
- It provides guidance on controversial issues surrounding the diagnosis, treatment and follow-up of bladder cancer
- Statements achieving consensus at the conference are accompanied by relevant supporting evidence

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INTRODUCTION

Bladder cancer is the 10th most common form of cancer globally, with 549,393 new cases and 199,922 bladder cancer-related deaths estimated in 2018 [1]. It is around 4 times more common in men, where it is the 6th most common cancer and the 9th leading cause of cancer death. The incidence of bladder cancer varies globally, with the highest rates in men and women reported in Southern and Western Europe and North America, which appears to reflect the prevalence of tobacco smoking, the main risk factor for bladder cancer [1, 2].

Various oncology and urology societies, including the European Society for Medical Oncology (ESMO) [3], the European Association of Urology (EAU) [4, 5] and the National Comprehensive Cancer Network (NCCN) [6], all produce Clinical Practice Guidelines (CPGs) that provide guidance to healthcare professionals (HCPs) regarding the optimal strategies for diagnosis, treatment and follow-up of patients with bladder cancer based on the latest evidence and expert opinion. However, evidence is limited and/or conflicting in some areas of bladder cancer management, and the optimal approach remains controversial, warranting further discussion and clarification. For example, the pathological features and prognosis of bladder cancer with variant histologies differ from pure urothelial bladder cancer, and evidence regarding response to systemic therapy in these variant histologies is scarce and divergent [7]. In addition, although efforts have been made to identify molecular subtypes of bladder cancer and to link these with clinical-pathological features and treatment response [8-11], there is no consensus regarding the number of subtypes that can be defined and available evidence to link subtypes with response to specific therapies is conflicting [12].

In terms of disease management, although transurethral resection of the bladder tumour (TURBT) is the initial treatment of choice for non-muscle invasive bladder cancer (NMIBC), with subsequent treatment tailored according to risk stratification [3, 4], TURBT followed by concurrent chemoradiotherapy (i.e. trimodality treatment) is also an option for muscle

invasive bladder cancer (MIBC) in patients considered medically unfit for surgery and in those wishing to avoid radical surgery [3, 4]. However, patient selection for bladder-sparing strategies varies globally and there are no uniform criteria on which to base these decisions. The optimal chemotherapy regimen to use as part of trimodality treatment has also not been defined [13].

Radical cystectomy with extended lymphadenectomy is considered the standard treatment of MIBC, and although neoadjuvant therapy has been used in this setting for several decades, the role of adjuvant therapy remains controversial [3, 5, 13]. The benefit of adding (neo)adjuvant therapy to local therapy in oligometastatic disease is also unknown. In the metastatic setting, cisplatin-based chemotherapy remains the first-line treatment of choice for patients considered fit enough to receive this regimen, but the preferred approach for cisplatin-ineligible patients is less clear [5, 13]. Options include various carboplatin-based regimens or the immune checkpoint inhibitors (ICIs), pembrolizumab or atezolizumab, although approvals of these ICIs are based on data from single-arm, Phase II trials [14, 15] and their use is currently restricted to programmed death ligand 1 (PD-L1)-positive patients. In terms of second-line treatment, various chemotherapy options have been evaluated but results are highly variable [5]. Three ICIs (pembrolizumab, atezolizumab and nivolumab) are also approved in this setting in Europe (durvalumab and avelumab are also approved in the United States but not in Europe), although only pembrolizumab has demonstrated an overall survival benefit versus chemotherapy in a Phase III randomised controlled trial [16]. There are no data to provide guidance regarding the optimal treatment sequencing approach for ICIs and chemotherapy.

Finally, although there is no evidence to suggest that regular follow-up after definitive treatment is associated with any survival benefit in patients with bladder cancer, most

guidelines recommend regular follow-up, but no high-level, evidence-based follow-up protocol exists.

Collectively, these and other topics represent points in the bladder cancer care pathway where evidence is limited/conflicting and thus where a consistent approach may be lacking. Given this, the aim of this project was to gain insights from a multidisciplinary group of experts in order to produce further guidance to HCPs on selected clinically relevant topics. It was anticipated that this guidance could complement existing society guidelines and facilitate an optimal approach to the diagnosis, treatment and follow-up of patients with bladder cancer.

METHODS

In 2018, the EAU and ESMO formed a collaboration to assess current recommendations for the management of bladder cancer. The objectives were to:

1. Identify areas where good quality evidence is currently lacking or where available evidence is conflicting
2. Gain insights from a multidisciplinary group of experts in the management of bladder cancer using a Delphi survey and consensus conference approach
3. Provide further guidance in these areas to HCPs.

A project steering committee was established, which comprised a multidisciplinary panel of 13 experts from EAU and ESMO, including two chairpersons (**A. Horwich** and **J.A. Witjes**). This steering committee worked together to develop a series of statements, based on their knowledge of the field, relating to potential management strategies for patients with bladder cancer. They were asked to focus on specific situations where good quality evidence is lacking or where available evidence is conflicting. A systematic literature review was not conducted. Statements were divided into 6 discrete topic areas with members of the steering committee appointed to chair each of these working groups as follows:

1. Strategies for variant histologies (Chairs: **S.F. Shariat** and **M. De Santis**)
2. The role of prognostic molecular markers in MIBC (Chairs: **M. Ribal** and **J. Bellmunt**)
3. Bladder preservation strategies (Chairs: **N. James** and **J.A. Witjes**)
4. Treatment of curative intent for patients with oligometastatic disease (OMD) (Chairs: **A. Horwich** and **M. Babjuk**)
5. ICIs in urothelial bladder cancer (Chairs: **T. Powles** and **M. Bruins**)
6. Follow-up strategies and survivorship (Chairs: **S. Gillessen** and **J. Palou**).

All final statements were entered into DelphiManager (a bespoke online Delphi tool, written in C# using WebForms and a MySQL backend) [17]. The resulting Delphi survey was distributed to key stakeholder groups including 1. Urologists, 2. Oncologists (including Medical and Radiation Oncologists) and 3. 'Others' (consisting of Radiologists, Pathologists, Specialist Nurses, Clinical Oncologists and Specialists in Nuclear Medicine). These were chosen as key stakeholders because they represent the HCPs who take the most responsibility for patients with bladder cancer. Combining the specialities in the 'others' group was a pragmatic decision based on the anticipated likelihood of recruiting low numbers of these professionals to the study. Participants were purposefully sampled by contacting professional societies. These included the EAU, ESMO, the American Society of Clinical Oncology, American Urological Association, European Society for Radiotherapy and Oncology, European Forum for Primary Care, European Association of Urology Nurses, Canadian Urological Association, International Society of Urological Pathology, Urological Society of Australia and New Zealand, European Society of Urogenital Radiology, Urological Association of Asia, American Society for Radiation Oncology, EAU bladder cancer panels (both muscle-invasive bladder cancer & non-muscle-invasive bladder cancer panel) and the EAU Section of Oncological Urology. These societies then either nominated the appropriate experts or cascaded the invitation to their members. Consent to participate was implied by

registering and completing the questionnaire. All HCPs were asked to rate their strength of agreement with each statement on a scale of 1 (strongly disagree) to 9 (strongly agree). An additional option of 'unable to score' was included to allow participants to refrain from rating any statements where they felt that they had insufficient expertise to do so. Two iterative rounds of the Delphi survey were conducted. In the first round, participants were also encouraged to propose additional statements; these were reviewed by the chairmen in order to decide whether they were novel and should be included in the subsequent round or if they were already adequately covered by existing statements. In the second round, participants were reminded of their own scores from round 1 and were also provided with a summary score from each of the 3 stakeholder groups. From this, participants had the opportunity to revise or retain their original scores. None of the statements were amended between rounds.

Descriptive statistics were used to summarise the results of each survey round, which included calculating the percentage of participants who scored each statement as 1-3 (disagree), 4-6 (equivocal), 7-9 (agree) and 'unable to score'. Results were summarised according to the 3 stakeholder groups described above. After the final survey round, the level of agreement for each statement was assessed for all 3 stakeholder groups separately, with consensus defined a priori as:

- Item scored as agree (7-9) by ≥70% of participants AND disagree (1-3) by ≤15%, OR
- Item scored as disagree (1-3) by ≥70% of participants AND agree (7-9) by ≤15%

Results of this analysis showed that consensus was reached for relatively small (28%) number of statements. On further review, the steering committee felt that these results might have been affected by some participants who provided a score of 4-6 (i.e. equivocal) instead of selecting 'unable to score' in cases where they had insufficient expertise to adequately assess the statement. To address this, a second analysis was conducted using the same consensus rules as described above but where the analysis was restricted to specific

stakeholder group(s) considered to have adequate relevant expertise relating to the specific statement. Stakeholder group(s) considered as having adequate relevant expertise for each statement were defined by the chairmen prior to this second analysis.

Final results were tabulated according to the 3 stakeholder groups with a consensus level defined for each statement which considered both of the analyses conducted as follows:

- **Level 1**: A priori consensus threshold met across all 3 stakeholder groups (i.e. original consensus analysis)
- **Level 2**: A priori consensus threshold not met across all 3 stakeholder groups but is met when analysis restricted to relevant stakeholder group(s)
- **Level 3**: A priori consensus threshold not met.

A subsequent review of the results was performed by the steering committee in order to identify statements where a consensus was almost reached. These statements were prioritised for further review and discussion as part of a consensus conference meeting held on 8 November 2018 in Amsterdam, The Netherlands.

All HCPs who completed the survey were invited to attend the consensus conference. However, based on limited availability, additional HCPs also considered as important stakeholders in the management of bladder cancer were invited, irrespective of whether they had participated in the original survey. Overall, the consensus conference included a multidisciplinary panel of 45 experts in the management of bladder cancer, with all panel members allocated to one of the 6 working groups defined earlier. During the conference, statements prioritised for further review were discussed by each of the working groups during parallel breakout sessions. This included a review of related supporting and/or conflicting evidence informing each statement, and revision of these statements, where necessary. The final statements from each working group were then presented to the entire expert panel for

further deliberation and amendment, as needed. Finally, the expert panel were asked to rate their strength of agreement with each of the revised statements using the same scale applied during the Delphi survey using online voting software (https://www.polleverywhere.com/). All voting was conducted using individual smartphone devices and was anonymous. Panel members could abstain from voting in cases where they had insufficient expertise to adequately assess the statement (which negated the requirement for an 'unable to score' option).

Results from the Delphi survey and consensus conference are described in this article. For statements revised and re-assessed during the consensus conference, the updated results as well as a summary of evidence and/or the rationale for statement revisions are also included. This article was reviewed and approved by all Delphi survey participants and consensus conference attendees.

RESULTS

The steering committee generated 115 statements relating to the management of bladder cancer for assessment as part of the Delphi survey; after round 1, an additional statement was added for assessment during round 2.

Overall, 221 HCPs were invited to participate in the Delphi survey, and of these, 113 registered and completed at least some of the survey (scores for completed questions were retained); 106 completed round 1 and 97 completed round 2 of the survey. A summary of participants who completed the Delphi survey according to specialty is shown in **Table 1**.

The initial (a priori) analysis resulted in a Level 1 consensus for 18 (16%) statements in round 1 and 33 (28%) statements in round 2, with inclusion of statements reaching Level 2 consensus increasing this to 49 (42%) statements after round 2. At the consensus conference meeting, 27 statements were amended/presented for voting and 22 (81%) achieved consensus

among the group, giving a total of 71 statements that achieved consensus throughout the whole process.

The following section provides detailed results according to each of the 6 topic areas ([1] strategies for variant histologies, [2] the role of prognostic markers, [3] bladder preservation strategies, [4] treatment of curative intent for oligometastatic disease, [5] ICIs, and [6] follow-up strategies and survivorship), which includes:

1. All Delphi survey statements developed by the steering committee for each topic area
2. Delphi survey results for each of these statements highlighted according to the consensus level reached for each statement, as shown in **Table 2**
3. All statements generated by the consensus conference working groups for each topic area (based on statements that almost reached consensus in the original Delphi survey)
4. Consensus conference voting results for each of these statements
5. A summary of expert panel discussions from the consensus conference to support these statements

Strategies for variant histologies

The Delphi survey included 14 proposed statements regarding the management of bladder cancer with variant histologies (**Table 3**).

According to the Delphi survey results, 5 of the 14 statements reached consensus among all stakeholder groups (**Table 3**). For the remaining statements where no consensus was achieved, 7 were prioritised for further discussion at the consensus meeting. During the breakout session, these statements were revised in order to provide 4 new/modified statements which were presented to the consensus meeting panel and discussed prior to

voting. Results from the consensus panel voting are shown in **Table 4** and supporting text is provided below.

1. Treatment of high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with micropapillary variant

Variant histology of bladder cancer includes urothelial carcinoma with divergent differentiation, such as urothelial carcinoma with micropapillary features (World Health Organization 2016 classification) [18]. The proportion of carcinoma with micropapillary features can vary significantly, with a larger component being associated with a worse prognosis [19]. Micropapillary variant is strongly associated with lymphovascular invasion and metastasis to the lymph nodes, and pT1 bladder cancer with micropapillary variant is often upstaged to more advanced stages [19]. Its pathological diagnosis on a transurethral resection (TUR) specimen is subject to both underreporting by pathologists and understaging due to intrinsic biological properties of the variant histology in addition to the normal risk of understaging with TURBT. In one study, after adjustment for the effects of pathological stage, only the presence of micropapillary variant, but not that of squamous or sarcomatoid differentiation, was associated with a worse survival [20].

Given the poor response rate to intravesical Bacillus Calmette-Guerin (BCG) administration, the current standard of care treatment for most cT1 urothelial carcinomas of the bladder, a recent study evaluated the potential benefits of early (immediate) radical cystectomy for cT1 micropapillary variant urothelial carcinoma [21]. In this retrospective, comparative design study, which included 72 patients with cT1 micropapillary bladder cancer, 40 patients received primary intravesical BCG and 26 underwent upfront radical cystectomy. Of those who received intravesical BCG, 75%, 45% and 35% experienced disease recurrence,

progression and lymph node metastasis, respectively, during a median follow-up of 67.5 months. However, patients treated with upfront radical cystectomy had improved survival compared with those treated with BCG (5-year disease-specific survival of 100% vs 60% p=0.006) and those who underwent delayed radical cystectomy after disease recurrence (5-year disease-specific survival of 62%, p=0.015). Patients in the delayed radical cystectomy group also had higher rates of pT3 disease (25% vs 0%, p=0.04) and overall pathological disease progression (pT2 or greater, or nodal disease: 40% vs 27% in the upfront radical cystectomy group) [21].

Given the above, the panel decided to add the recommendation for concomitant lymph node dissection (LND) to the original statement regarding the treatment of T1 high-grade bladder urothelial carcinoma with micropapillary variant to read as follows:

Statement 1: *T1 high-grade bladder urothelial carcinoma with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.*

Level of consensus: 86% Agree, 14% disagree (29 voters)

2. Treatment of high-grade bladder urothelial carcinoma with plasmacytoid, sarcomatoid, squamous, glandular or nested variant histologies

Under-staging at the time of transurethral resection is more frequent in urothelial carcinomas with variant histology compared with pure urothelial carcinomas and has been shown to be closely associated with a lower median overall survival (1.4 versus 10.6 years, p<0.001) [22]. Therefore, immediate radical cystectomy for better staging and definitive treatment purposes seems to be an appropriate option. However, the resulting statement shown below failed to

reach consensus among the panel, and this is likely due to the low level of evidence currently available to support this approach in urothelial carcinomas with variant histology.

Statement 2: *T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with plasmacytoid, sarcomatoid, squamous, glandular or nested variant should be treated with immediate radical cystectomy and concomitant LND.*

Level of consensus: 48% Agree, 39% disagree, 13% equivocal (31 voters)

3. Treatment of MIBC with micropapillary or plasmacytoid variant, or with squamous or glandular differentiation

Given the lack of consensus reached for the three initially proposed statements for the management of muscle-invasive bladder urothelial carcinoma with select variant histologies (statements 4, 5 and 6 in **Table 3**), the panel decided to group these into one overarching statement and to incorporate the use of neoadjuvant chemotherapy.

Only limited evidence is available regarding the added benefit of neoadjuvant chemotherapy for bladder cancers with variant histology due to lack of prospective studies [23]. In one retrospective population-based study, Vetterlein et al. evaluated the added benefit of neoadjuvant chemotherapy administration in patients with muscle-invasive urothelial carcinoma harbouring variant histologies (369 patients underwent neoadjuvant chemotherapy followed by radical cystectomy whereas 1,649 patients underwent upfront radical cystectomy) [7]. Patients with neuroendocrine tumours benefited most from neoadjuvant chemotherapy administration, as evidenced by better overall survival (hazard ratio [HR] 0.49; 95% confidence interval [CI] 0.33-0.74; p=0.01) and lower rates of non-organ-confined disease at the time of radical cystectomy (41.6% vs 76.4%). For tumours with micropapillary

differentiation, sarcomatoid differentiation or adenocarcinoma, neoadjuvant chemotherapy decreased the rates of non-organ-confined disease but did not impact overall survival [7].

The revised statement proposed was as follows:

Statement 3: *Muscle-invasive bladder urothelial carcinoma with micropapillary or plasmacytoid variant, or with squamous or glandular differentiation, should be treated with neoadjuvant chemotherapy followed by radical cystectomy and concomitant lymphadenectomy.*

Level of consensus: 63% Agree, 12% disagree, 24% equivocal (33 voters)

4. The role of adjuvant radiotherapy for the treatment of MIBC with variant histologies

Patients with urothelial carcinoma with squamous and/or glandular differentiation are more likely to have pT3-T4 tumours (70% vs 38%, $p<0.0001$) and pN+ disease (20% vs 15%, $p=0.05$) than those with pure urothelial carcinoma, confirming the observation that they are more likely to die of local than distant metastatic disease [24]. This would provide a strong argument to consider improving local control by adjuvant radiotherapy especially in cases of positive margins at areas amenable for radiotherapy [25, 26].

Statement 4: *Adjuvant radiotherapy (with or without radiosensitizing chemotherapy) is a standard treatment for patients with muscle-invasive urothelial carcinoma with variant histologies.*

Level of consensus: 41% Agree, 37% disagree, 21% equivocal (29 voters)

The role of prognostic molecular markers in MIBC

The Delphi survey included 21 statements relating to the role of prognostic molecular markers in MIBC, which included 11 statements on the value of genetic profiling and specific mutation patterns or ribonucleic acid (RNA) subtypes when making therapeutic decisions, and 10 statements covering the value of tumour mutation burden (TMB), microsatellite instability (MSI), neutrophil to lymphocyte ratio (NLR), albumin and lactate dehydrogenase (LDH) when making treatment decisions regarding cystectomy, chemotherapy or immunotherapy (**Table 5**).

According to the Delphi survey results, 10 out of these 21 statements achieved consensus, 4 among all stakeholder groups and 6 among relevant stakeholder groups only (**Table 5**). For the remaining statements, 3 controversial topics were identified and prioritised, and related statements were discussed and reassessed at the consensus conference. Results from the consensus panel scoring of the relevant statements are shown in **Table 6** and supporting text is provided below.

1. Before prescribing checkpoint inhibitor therapy, do we need to identify molecular subtypes based on RNA analysis?

The molecular classification of bladder cancer has gained momentum in recent years and is still under development. Several attempts have been made and there is still no agreement regarding how many subgroups can be established and defined. All of these molecular classifications have been updated in the last 4 years, with The Cancer Genome Atlas (TCGA) and the Lund classifications the most recently updated [8, 27]. Clearly, different subtypes persist, and among them, two main subtypes can be distinguished: luminal and basal. According to their molecular appearance, the urothelial carcinomas react differently to different therapies. However, it is important to consider that TCGA data provide no

information regarding response to subsequent treatment after cystectomy for MIBC. There is only one report based on retrospective data from patients receiving different types of neoadjuvant chemotherapy where RNA subtypes have been linked to outcome [28]. For immunotherapy, conflicting findings have been reported regarding response enrichment in luminal II and basal subtypes [29]. Lack of consensus on the description of the different RNA subtypes is also a problem. Data linking responses of atezolizumab with the 'genomically unstable' subgroup of the Lund classification is discordant with previously reported findings for the luminal II subtype [30].

Given the currently available evidence, the panel agreed that RNA subtypes are not needed when ICIs are prescribed since it is too early and requires further validation. The original statement from the Delphi survey was therefore retained and a consensus regarding this statement was reached by the expert panel, as shown below.

Statement 1: *Before prescribing checkpoint inhibitor therapy, RNA subtypes always need to be identified.*

Level of consensus: 3% Agree, 91% disagree, 6% equivocal (31 voters)

2. Before radical cystectomy or chemotherapy, do we need to assess the NLR?

Several studies have already demonstrated that systemic inflammation correlates with worse prognosis in several malignancies. In this setting, biomarkers such as C-reactive protein (CRP), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) have been investigated. Recently, NLR has emerged as a prognostic factor in upper urinary tract tumours [31] and other non-urological malignancies. The use of the NLR as a predictive tool is derived from studies using chemotherapy in oesophageal, gastric and colorectal cancers. Data has also emerged for NLR as a potentially predictive biomarker in patients receiving

immunotherapy for melanoma, lung cancer and renal cell carcinoma (RCC). In a recent pooled analysis of 21 studies analysing the prognostic role of NLR in bladder cancer, the authors correlated elevated pre-treatment NLR with overall survival (OS), recurrence-free survival (RFS) and disease-specific survival (DSS) in patients with localised disease and in those with metastatic disease [32]. In contrast, in a recent secondary analysis from the Southwest Oncology Group (SWOG) 8710 trial which assessed the role of neoadjuvant chemotherapy in MIBC, the authors could not demonstrate any correlation between NLR and OS (prognostic) or the OS benefit from neoadjuvant chemotherapy (predictive) [33].

After considering the available data, the panel agreed that before radical cystectomy or chemotherapy, the NLR does not need to be assessed. Although it is easy to do, we require prospective data before this can be used to drive or change treatment decisions.

Statement 2: *Before radical cystectomy or chemotherapy the NLR does NOT need to be assessed.*

Level of consensus: 97% Agree, 3% disagree (31 voters)

3. In patients with metastatic disease, do we need to assess LDH and/or serum albumin?

No strong data exist regarding the value of albumin or LDH as prognostic factors in metastatic bladder cancer. In Bajorin's risk factor analysis in patients with previously untreated metastatic bladder cancer, neither LDH nor albumin were identified as significant risk factors in multivariate analysis despite being significant in the univariate analysis [34]. However, as albumin and LDH are easy to measure in peripheral blood and are already validated in other cancers, these parameters are being used in daily clinical practice. For patients treated with 2nd line chemotherapy, haemoglobin, performance status (PS) and liver metastasis are recognised prognostic factors [35]. However, in a pooled analysis of data from

10 Phase 2 trials evaluating various different therapies, the addition of albumin to these already-established prognostic factors emerged as significant [36]. A recent metanalysis has also confirmed the prognostic role of LDH in urological cancer [37].

After considering the available data, Working Group 2 proposed that LDH and/or serum albumin should always be measured in patients with metastatic disease as a general prognostic marker of outcome, not relating to bladder cancer specifically but rather as a prognostic cancer marker. Although there was some agreement by the expert panel for this statement, it failed to reach the consensus threshold.

Statement 3: *In patients with metastatic disease, always measure the LDH and/or serum albumin as general prognostic markers of patient outcome.*

Level of consensus: 65% Agree, 16% disagree, 19% equivocal (31 voters)

Bladder preservation strategies

The Delphi survey included 19 statements relating to bladder preservation strategies, including patient selection, chemoradiation and radiosensitisers, adjuvant therapy and pelvic lymph node dissection (**Table 7**). An additional statement was added to this category following results of round 1 of the survey.

According to the Delphi survey results, 9 of the 20 statements reached consensus, 6 among all stakeholder groups and 3 among relevant stakeholder groups only (**Table 7**). For the remaining statements, 9 were prioritised for further discussion and revision. Results from the consensus panel scoring of the new/revised statements are shown in **Table 8** and supporting text is provided below.

1. Patient selection for bladder preservation strategies

Patient selection depends on the organisation of the healthcare system per country in general and per department in particular. Specialist bias and available therapeutic options can and will influence treatment of cancer patients. For example, despite the known benefits of neoadjuvant chemotherapy, its use is strongly associated with communication with and referral to a medical oncologist. In colorectal cancer, collaboration between surgeons and oncologists has been shown to improve both all-cause and cancer-specific survival [38]. The role of the specialist nurse, which also differs according to the country and department, has also been shown to improve patient quality of life, is cost-effective and lowers the workload of the physician [39].

Statement 1: *Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral healthcare professional such as a specialist nurse.*

Level of consensus: 83% Agree, 6% disagree, 12% equivocal (34 voters)

2. Chemoradiation for inoperable, locally advanced MIBC

For MIBC, multiple studies have shown that the addition of chemotherapy to radiotherapy improves local control and survival rates compared with radiotherapy alone, and also results in good long-term bladder function and low rates of salvage cystectomy [40-43]. The addition of gemcitabine, cisplatin (NCIC), carbogen/nicotinamide (BCON) or 5-fluorouracil (5FU)/mitomycin C (MMC) (BC2001) to radiotherapy have all either been compared with radiotherapy alone or have single arm data and extensive use in clinical practice [40-43].

Statement 2: *Chemoradiation should be given to improve local control in cases of inoperable locally advanced tumours.*

Level of consensus: 85% Agree, 3% disagree, 12% equivocal (32 voters)

3. Radiosensitisers

As there are no comparative data available for the use of radiosensitisers in MIBC, there was consensus among the expert panel not to recommend any specific radiosensitizer in case of chemoradiation therapy. Obviously, the patient needs to be fit enough to undergo chemotherapy. If not, radiotherapy alone is an option to be discussed with the patient as a palliative treatment strategy.

Statement 3: *In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/MMC, carbogen/nicotinamide or gemcitabine.*

Level of consensus: 100% Agree, 0% disagree (29 voters)

4. Pelvic lymph node dissection (PLND)

According to several large cystectomy series, micrometastases in the pelvic lymph nodes are found in 25%-44% of patients with MIBC. For patients receiving chemoradiation, a group who often have a worse prognosis, this might be even higher. For patients with cN0 disease, it is currently not standard radiotherapy practice to include the pelvic lymph nodes in order to minimize bowel toxicity. However, with modern intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) techniques, this is now much more feasible. Surprisingly, findings from the large BC2001 and BCON trials, which included radiotherapy confined to the bladder only, did not report high rates of lymph node relapse (typically <10%) as might have been expected from surgical pathological staging on cystectomy, suggesting that chemoradiotherapy partially eradicates pelvic lymph node micrometastases

[44]. However, this was not confirmed in a chemoradiotherapy trial comparing radiotherapy to the whole pelvis versus the bladder (tumour site) alone. Among complete responders, the incidence of pelvic lymph node recurrence was 15.8% and 17.6%, respectively [45]. Consequently, given the current literature, no consensus could be reached regarding whether or not to perform a PLND in bladder preservation strategies.

Statement 4: *In patients with cN0 disease, PLND in case of bladder preservation is not recommended.*

Level of consensus: 64% Agree, 14% disagree, 22% equivocal (31 voters)

5. Radiotherapy techniques

IMRT is a modern type of external beam radiotherapy (EBRT) that delivers precise dose distribution to the target area whilst minimising dose to the surrounding at-risk organs. Limitations of IMRT are organ motion and inaccuracy in delineation of tumour and other adjacent organs. However, these limitations can be overcome by IGRT. Therefore, the combination of IMRT with image guidance is essential. Lower toxicities can also be achieved with the combination of IGRT and IMRT in bladder cancer [46].

Statement 5: *Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.*

Level of consensus: 84% Agree, 16% equivocal (25 voters)

6. Radiotherapy dosing

Brachytherapy for MIBC is not widely performed and data are therefore limited to highly selected patients in 'enthusiast' centres. So far, only retrospective studies have been

performed, which have included a wide variation in patient and tumour characteristics. In the majority of patients who received brachytherapy, this was preceded by EBRT [47]. Moreover, it is an invasive procedure that requires surgical catheter placement. Since prospective or randomised controlled trials on brachytherapy are lacking, there was consensus among the expert panel not to recommend brachytherapy for MIBC. There was also a consensus not to recommend dose escalation by IMRT based on limited early results [48]. A UK-based randomised trial (RAIDER) addressing the potential value of dose escalation has just completed accrual and will provide further insights on this topic.

Statement 6: *Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended.*

Level of consensus: 86% Agree, 8% disagree, 8% equivocal (28 voters)

The role of treatment of curative intent in OMD

OMD is generally defined as occurrence of ≤5 metastases, and may be found synchronous with the primary tumour or as a metachronous recurrence. There has been much biological research regarding how OMD may arise as an early phase in the metastatic cascade, and on how this might be distinguished from polymetastatic disease [49]. Although the finding of OMD may offer hope of cure, for the responsible clinician, an important consideration is the avoidance of toxicities associated with radical therapies in a palliative setting.

There are few published series about the radical treatment of OMD in urothelial cancers, hence no guidelines have addressed its management [50]. Thus, questions need to be addressed, at least in part, by reference to other cancers or other disease stages. For example, a multicentre review of radical surgery for 5206 cases of lung metastases reported a 5-year survival rate of 36%, encouraging the belief that an early stage of metastasis exists which

may be very limited in extent and thus curable by radical treatment [51]. Important prognostic factors in this series included whether the OMD was solitary and whether the recurrent OMD occurred a long time (>36 months) after treatment of the primary tumour. Similarly, in non-small cell lung cancer (NSCLC), findings from a systematic review and pooled analysis showed that among 110 patients who had an adrenalectomy for an isolated adrenal metastasis, overall survival was shorter for those with synchronous versus metachronous metastasis (12 versus 31 months, respectively; p=0.02) [52]. Similarly encouraging series based on the radical treatment of metastases with stereotactic radiotherapy have also been reported.

This Delphi survey included 21 statements relating to the role of treatment of curative intent in OMD, including the number of metastatic sites consistent with possible cure, the curability of different OMD organ locations, synchronous versus metachronous OMD, the question of delayed restaging and staging technology, use of adjuvant chemotherapy, choice of radical OMD therapy, extent of primary surgery and the sequence of treating synchronous presentations (**Table 9**).

According to the Delphi survey results, 4 of the 21 statements reached consensus across all stakeholder groups (**Table 9**). For the remaining statements, 3 controversial topics were identified and prioritised, and related statements were discussed and reassessed at the consensus conference. Results from the consensus panel scoring of the relevant statements are shown in **Table 10** and supporting text is provided below.

1. Number of metastatic sites consistent with possible cure

Results from the Delphi survey showed that there was a consensus among participants that the presence of >2 metastatic sites should discourage attempted cure, that liver or bone are

adverse prognostic sites and that longer time to metachronous OMD recurrence is associated with a more favourable outcome. However, there was no consensus regarding whether cure should be attempted for patients with 1 or 2 metastatic sites.

Based on results from prospective Phase III trials, approximately 10% of patients with urothelial cancer and visceral metastases survive 5 years after chemotherapy [53]. Prognostic factors include performance status, laboratory parameters (albumin, haemoglobin, leukocyte count or CRP), visceral metastasis and number of metastatic sites. Number of metastatic sites was identified as an independent predictive factor for survival with the best prognosis seen in those with a single metastatic site only [54].

Although there is only low-level evidence, encouragingly long survival times have been reported for patients with favourable prognostic factors after the combination of systemic chemotherapy and local treatment (radical cystectomy, metastasectomy). A retrospective study of 44 patients treated across 15 German centres reported a 5-year survival of 28% [55], and in a series of 42 patients from Japan treated by metastasectomy, in patients with solitary nodal or lung metastasis (15 patients), the median survival reached 81 months [56]. A small series from Korea [50] also supported these conclusions. As summarized in a recent collaborative systematic review in metastatic bladder cancer [57], the beneficial role of metastasis surgery remains unproven by a prospective trial but may be considered in those with low volume disease (especially pelvic node disease) and ideally in those with chemo-sensitive disease.

Statement 1: *In a minority of patients with one metastatic lesion, cure is possible after radical treatment.*

Level of consensus: 91% Agree, 6% disagree, 3% equivocal (31 voters)

2. The role of positron emission tomography-computed tomography (PET-CT) in staging of OMD

To minimise the risk of overtreatment, patients with OMD should be restaged using the most sensitive imaging technique available. 18F-fluoredeoxyglucose (FDG)-PET-CT scanning is generally more sensitive than CT in urothelial cancer, although its use around the bladder is compromised by the urinary excretion of the isotope and its use in staging of the primary tumour currently lacks sufficient evidence to support its recommendation. However, in a staging study of 42 patients prior to cystectomy, FDG-PET-CT detected metastases in 7 patients who showed no evidence of disease on CT and bone scans [58]. A published review of 6 series also found a high diagnostic accuracy for metastatic lesions using FDG-PET-CT [59], and a recent review from The National Institutes of Health, Bethesda, concluded that FDG-PET-CT was the optimal technology in this setting [60].

Statement 2: *PET-CT scanning should be included in oligometastatic disease staging when considering radical treatment.*

Level of consensus: 88% Agree, 3% disagree, 9% equivocal (32 voters)

3. The role of (neo)adjuvant therapy in OMD

There are no direct comparative studies regarding whether or not to combine systemic therapy with local therapy for urothelial OMD. However, outcomes research on OMD in other tumours emphasises the high risk of recurrence after local treatment alone. There is evidence to support the use of systemic chemotherapy as a component of treatment for high-risk (muscle-invasive) primary bladder cancer. Neoadjuvant chemotherapy with cisplatin/methotrexate/vinblastine (CMV) was associated with a 16% reduction in mortality

risk. An overview of adjuvant chemotherapy trials has also suggested a reduction in mortality risk by over 20%, with a particular benefit seen in higher-risk (i.e. node-positive) cases [61].

Statement 3: *Radical treatment of oligometastatic disease should be accompanied by adjuvant or neoadjuvant systemic therapy.*

Level of consensus: 72% Agree, 6% disagree, 22% equivocal (32 voters)

ICIs in urothelial bladder cancer

The Delphi survey included 20 statements relating to ICIs in urothelial bladder cancer, including patient selection, timing and duration of ICI therapy (**Table 11**).

According to the Delphi survey results, 9 of the 20 statements reached consensus, 5 among all stakeholder groups and 4 among relevant stakeholder groups only (**Table 11**). For the remaining statements, 4 key topics were prioritised and related statements were discussed and reassessed at the consensus conference. Results from the consensus panel scoring of the corresponding new/revised statements are shown in **Table 12** and supporting text is provided below.

1. Pseudo-progression with ICIs

Pseudo-progression, defined as tumour growth followed by tumour response after initiation of ICI therapy has been described in melanoma [62]. It is thought that the initial immune infiltration may make the tumour appear radiologically larger without defining treatment failure. It tends to occur at the start of therapy and can confuse clinical assessment.

Progression of disease is the commonest radiological outcome with single-agent ICI therapy in urothelial cancer [14, 16, 63]. However, there is a lack of data to support the hypothesis

that a proportion of these tumours can recede after initial progression, and the consensus panel agreed that pseudo-progression has not been demonstrated in urothelial cancer. The biology of urothelial cancer and melanoma are distinct, as are responses to ICI therapy. Treatment with ICIs beyond progression in the hope of pseudo-progression may therefore be counterproductive in urothelial cancer.

Statement 1: *Pseudo-progression has not been demonstrated in urothelial cancer.*

Level of consensus: 89% Agree, 11% equivocal (28 voters)

2. The role of PD-L1 biomarkers to guide the use of ICI therapy

There are 5 different ICI cancer drugs currently available, all of which have different companion diagnostic to measure PD-L1 (142-atezolizumab, 288-nivolumab, 263-durvalumab, 7310-avelumab, 223-pembrolizumab) [64]. Each has a different antibody and method of measurement (immune cell versus tumour cell expression, different percentage cut-points, Daco versus Ventana technology). For these reasons, positivity varies between 20% and 60% in the platinum-refectory setting for the 5 different methods. The biomarkers are also inconsistent in the platinum-refractory metastatic setting and appear more prognostic than predictive [16, 63]. None can be reliably used to select treatment due to their lack of sensitivity and specificity [64].

In the front-line, cisplatin-ineligible setting, only data from single-arm trials of atezolizumab and pembrolizumab are in the public domain [14, 15], and again, the data appear inconsistent. However, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have changed their scope of use to restrict them to only PD-L1-positive patients in this setting. This must be related to publicly unavailable data suggesting that the biomarker is predictive. It suggests that the biomarker is effective for selecting patients in the front-line,

cisplatin-ineligible setting, unlike the platinum-refractory setting. The reasons for this are unclear.

Statement 2: *In contrast to the first-line setting, the PD-L1 biomarker is not useful for selecting patients for immunotherapy in platinum-refractory metastatic urothelial cancer.*

Level of consensus: 81% Agree, 4% disagree, 15% equivocal (28 voters)

3. The role of chemotherapy in cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma

While ICIs are associated with long-term, durable remissions as a first-line treatment of cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma, response rates (RRs), progression-free survival (PFS) and OS have not been proven to be superior to carboplatin-based chemotherapy [14, 15]. Chemotherapy is associated with significant RRs in this setting. Data from randomised Phase III trials of ICIs in this setting will be available soon and, as results are unpredictable, it seems prudent to wait until these data are available before definitive decisions are made.

Statement 3: *Carboplatin-based chemotherapy remains a viable first-line treatment option in cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma until data from randomised Phase III trials of ICIs are available.*

Level of consensus: 87% Agree, 3% disagree, 10% equivocal (29 voters)

4. The role of chemotherapy in cisplatin-ineligible, immunotherapy-refractory patients with metastatic urothelial carcinoma

To our knowledge, there is no evidence that sequencing ICIs in the face of disease progression is of clinical benefit in urothelial carcinoma. The drugs have, at least in part, an overlapping mechanism of action and therefore sequencing of these drugs is counterintuitive [64]. Retrospective data suggest that patients who progress on first-line immunotherapy appear to maintain a reasonable objective RR to a subsequent line of chemotherapy [65]. Thus, sequencing chemotherapy after first-line immune therapy is attractive whilst we await data from prospective clinical trials.

Statement 4: *Cisplatin-ineligible, immunotherapy-refractory patients with metastatic urothelial carcinoma should be considered for chemotherapy instead of sequencing of immunotherapy.*

Level of consensus: 81% Agree, 7% disagree, 12% equivocal (27 voters)

Follow-up strategies and survivorship

The Delphi survey included 20 statements relating to follow-up strategies and survivorship after radical cystectomy, trimodality therapy or chemotherapy for urothelial carcinoma (**Table 13**).

According to the Delphi survey results, 12 of the 20 statements reached consensus, 9 among all stakeholder groups and 3 among relevant stakeholder groups only (**Table 13**). Of the 8 remaining statements, 7 were prioritised for further discussion and revision at the consensus conference. Results from the consensus panel scoring of the new/revised statements are shown in **Table 14** and supporting text is provided below.

1. Follow-up after radical cystectomy

After cystectomy, depending on the stage (pT and pN), up to 70% of patients will have tumour recurrence which may be local or systemic. There is also a risk of second cancers in the remaining urothelial tract (upper urinary tract tumours and in the urethra). There are no prospective data evaluating the benefit of regular follow-up in patients with urothelial cancer of the bladder after treatment with curative intent versus staging when symptoms occur.

In general, chemotherapy is better tolerated and is associated with more favourable outcomes in patients with a good PS, suggesting that earlier detection of metastases may be beneficial for patients compared with waiting for symptomatic progression. Regular follow-up is recommended in most guidelines despite the lack of high-level evidence. As such, follow-up protocols after cystectomy are mainly based on the natural history of the disease.

Incidence rates and timing of recurrence after cystectomy vary according to the type of recurrence observed. Systemic recurrence occurs in 22%–30% of patients, mostly in the first 3 years, whereas local recurrence occurs in 5%–15% of patients, mostly in the first 2 years and typically between 6 and 18 months [66-68]. The lifetime incidence of a second cancer in the urethra is 4%–6%, with most diagnosed during the first 3 years, although such cancers have been reported beyond 5–10 years. The lifetime incidence of upper urinary tract tumours is 2%–6%. Here, the median time to diagnosis exceeds 3 years in 70% of cases, indicating that they are typically a late event [66-68].

The probability of a systemic or a local recurrence is largely related to the final pathological stage of the cystectomy specimen. The highest likelihood of onset of extravesical recurrence is related to the presence of multifocal disease (a common risk factor), tumour in the distal ureter in the case of upper urinary tract tumours, and tumour in the prostatic urethra in men in the case of urethral tumours [68]. In women, where urethrectomy is becoming less common

during radical cystectomy, the main risk factors for urethral recurrence are bladder neck and anterior vaginal wall involvement [69].

According to these recurrence rates, it seems reasonable to apply a more intense follow-up protocol during the first 2–3 years in order to detect systemic relapse after cystectomy with the recommendation to stop follow-up after 5 years for the majority of patients. Those with risk factors of urethral and/or upper urinary tract tumours should, however, be followed-up for a longer duration by specific examinations based on their higher risk of a late recurrence. **Supplementary Table 1** shows the follow-up strategies after cystectomy and trimodality treatment according to guidelines issued by ESMO, EAU and the NCCN [3, 5, 6].

Statement 1: *To detect relapse after radical cystectomy with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 years in the majority of patients.*

Level of consensus: 88% Agree, 3% disagree, 9% equivocal (32 voters)

Statement 2: *To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.*

Level of consensus: 94% Agree, 0% disagree, 6% equivocal (34 voters)

Statement 3: *After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g. multifocality, carcinoma in situ [CIS] and tumour in the prostatic urethra).*

Level of consensus: 88% Agree, 6% disagree, 6% equivocal (33 voters)

2. Follow-up after trimodality treatment

Between 26% and 43% of patients treated with trimodality treatment will present with recurrences, which mostly occur within the first 2 years [70]. Follow-up after trimodality treatment must not only detect systemic recurrences but also local and non-muscle-invasive bladder recurrences. Indeed, studies with a longer follow-up protocol mainly use cystoscopy in order to follow patients after the trimodality treatment [71]. The NCCN guidelines suggest cystoscopy every 3 months for the first 2 years, every 6 months for years 3 and 4 and then annually until 10 years. CT every 3–6 months for the first 2 years, annually until 5 years and as clinically indicated thereafter is also recommended [6].

There are no data to show whether regular follow-up after systemic therapy for patients with a partial or complete response is associated with any benefit.

Statement 4: *To detect relapse (outside the bladder) after trimodality treatment with curative intent, CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.*

Level of consensus: 100% Agree (34 voters)

Statement 5: *To detect relapse (outside the bladder) after trimodality treatment with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 years in the majority of patients.*

Level of consensus: 84% Agree, 3% disagree, 13% equivocal (30 voters)

3. Follow-up monitoring of carcinoembryonic antigen (CEA), LDH and vitamin B12

There is no evidence that any tumour markers are helpful in monitoring recurrence in patients with bladder cancer. LDH is non-specific and can be elevated in a multitude of clinical

scenarios independent of a recurrence. CEA is also not specific for bladder cancer and can be positive in follow-up since it can be elevated in smokers. Low vitamin B12 levels have been reported in 17% of patients with bowel diversion [72]. Thus, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured.

Statement 6: *Levels of LDH and CEA are NOT essential in the follow-up of patient with urothelial cancer to detect recurrence.*

Level of consensus: 100% Agree (34 voters)

Statement 7: *Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent.*

Level of consensus: 75% Agree, 17% disagree, 7% equivocal (29 voters)

DISCUSSION

The aim of this project was to bring together a large multidisciplinary group of leading experts in the management of bladder cancer with a view to identifying specific situations where guidance is lacking and defining the optimal approach as far as possible based on the available evidence and their collective experience and expert opinions. To achieve this, a multidisciplinary panel of 13 experts compiled a series of statements relating to potential management strategies for patients with bladder cancer focussing on specific situations where good quality evidence is lacking or where available evidence is conflicting. These statements were then sent to a large (221) group of HCPs in this field as a Delphi survey in order to assess the level of agreement with each statement. Using this approach, 49 (42%) statements achieved consensus and serve to provide further guidance to HCPs without the need for further discussion. Among the remaining 58%, topics were identified where consensus was almost reached since it was felt that further review and discussion, with possible amends to

these statements, could make a consensus achievable. For the remaining topics, where opinion remained divergent, it was felt that further discussion was unlikely to result in a consensus. These topics therefore remain a high unmet need and, given the lack of consensus, should be prioritised in future research.

At the consensus conference meeting, the topics that almost reached consensus were reviewed, with related statements amended and voted on by a multidisciplinary panel of 45 experts. This resulted in the presentation of 27 statements for voting, 22 (81%) of which achieved consensus among the group.

Collectively, this project resulted in the development of 71 recommendations that will help to address controversial topics in the management of bladder cancer. Although too many to discuss here in detail, some key conclusions are worthy of highlighting. For example, since variant histologies are increasingly recognised and diagnosed, our recommendations in this area are important and provide additional guidance for the management of this group of patients, although not for all variant histologies. In spite of advice from the FDA and EMA, markers are not yet adequate for clinical decision making, including PD-(L)1 status, (epi)genetic markers and several simple serum measurements. Bladder preservation with chemoradiation is gaining consensus. It is a multidisciplinary decision where several sensitizers can be used. Modern radiotherapy techniques are preferred whereas dose escalation and brachytherapy are not. The role of LND in case of chemoradiation remains unresolved. OMD can still be cured in selected cases, depending on the site and number of metastases and the interval between diagnosis of the primary tumour and metastases. Treatment is a multimodal approach. ICIs are an option in the treatment of metastatic urothelial cancer in unfit, PD-L1-positive patients or after platinum-based chemotherapy. When ICIs are used, pseudo-progression has not been demonstrated in urothelial cancer. When progression occurs on ICI therapy, chemotherapy should be considered rather than

sequencing another ICI. Oncological follow-up after cystectomy or bladder preservation should last 5 years, with the highest intensity in the first 2 years since most recurrences occur within 18-24 months. Follow-up should consist of CT of the thorax and abdomen and cystoscopy/cytology in case of bladder preservation, with vitamin B12 levels checked after cystectomy.

Taken together, the findings reported here serve to complement existing guidelines and promote a consistent approach to the management of patients with bladder cancer. As these recommendations represent the collective expert opinion of over 100 leading experts in the field, it is anticipated that they will have a positive impact on the everyday management of patients with bladder cancer, especially those treated at smaller hospitals where a high level of expert guidance may be lacking.

Whilst we believe that the methodology applied here is novel and represents an effective approach to obtain expert guidance for the management of bladder cancer, it is not without its limitations. For example, no systematic literature review was conducted ahead of the Delphi survey and proposed statements were compiled based on the collective expert opinion of the steering committee members. However, as this compiled a group of 13 leading experts, it is unlikely to have resulted in any significant omissions or bias. Another potential limitation was the difference in participants of the Delphi survey versus those who attended the consensus conference. Ideally, this would have comprised the same group of experts; however, based on limited availability of survey participants, it was felt that additional HCPs should also be invited in order to ensure sufficient collective expertise at the consensus conference. This resulted in the inclusion of 21 HCPs at the meeting who had not completed the Delphi survey. However, all meeting participants were provided with an adequate briefing and summary of the survey results to allow their active participation and contribution to the meeting.

Regarding the Delphi survey methodology, a potential limitation was the inclusion of an 'equivocal' score in addition to 'unable to score'. On reflection, it is likely that some participants could have scored statements as 'equivocal' when they did not have sufficient expertise to assess the statement rather than selecting 'unable to score', which could have increased the proportion of statements that failed to reach consensus as part of the Delphi survey. We attempted to address this limitation by conducting a second, ad hoc analysis, restricting results to specific stakeholder groups considered to have adequate relevant expertise relating to the specific statement. Indeed, this increased the number of statements achieving consensus from 33 (28%) to 49 (42%). This point was also raised during the consensus conference with participants advised to refrain from voting in cases of uncertainty or insufficient expertise, and this likely influenced the high level (81%) of consensus achieved for statements discussed and voted for at the meeting.

As with all guidelines, the development of specific statements and recommendations poses a challenge since treatment decisions are typically based on a multitude of parameters unique to the individual patient being treated, with specific parameters rarely considered in isolation. Voting on the level of agreement for each statement is therefore also challenging without a broader clinical context. However, providing such additional information would make statements unwieldy and may also restrict their applicability and use. It is also assumed that the treating physician is able to consider the recommendations provided and adapt his/her approach in light of the individual clinical context faced.

Taken together, and notwithstanding the limitations described above, we believe our results represent a significant achievement by providing collective expert opinion and guidance on the optimal management strategies to employ in controversial situations until a time where further evidence is available to guide our approach. Together with existing Clinical Practice

Guidelines, it is anticipated that the recommendations provided here will help to optimise and standardise the diagnosis, treatment and follow-up of patients with bladder cancer.

ABBREVIATIONS

5-FU, 5-fluorouracil; BCG, Bacillus Calmette-Guerin; CEA, carcinoembryonic antigen; CI, confidence interval; CMV, cisplatin/methotrexate/vinblastine; CPG, Clinical Practice Guideline; CRP, C-reactive protein; CT, computed tomography; DSS, disease-specific survival; EAU, European Association of Urology; EBRT, external beam radiotherapy; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; FDG, 18F-fluoredeoxyglucose; HCP, healthcare professional; HR, hazard ratio; ICI, immune checkpoint inhibitor; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; LDH, lactate dehydrogenase; LMR, lymphocyte-monocyte ratio; LND, lymph node dissection; MIBC, muscle invasive bladder cancer; MMC, mitomycin C; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NLR, neutrophil to lymphocyte ratio; NMIBC, non-muscle invasive bladder cancer; NSCLC, non-small cell lung cancer; OMD, oligometastatic disease; OS, overall survival; PD-L1, programmed death ligand 1; PET, positron emission tomography; PFS, progression-free survival; PLND, pelvic lymph node dissection; PLR, platelet-lymphocyte ratio; PS, performance status; RCC, renal cell carcinoma; RFS, recurrence-free survival; RNA, ribonucleic acid; RR, response rate; TCGA, The Cancer Genome Atlas; TMB, tumour mutation burden; TUR, transurethral resection; TURBT, transurethral resection of the bladder tumour.

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[Authors – please confirm the information below is complete and accurate, and/or provide additional details as needed. Please also see specific queries to some authors below]

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TABLES

Table 1. Delphi survey participants according to specialty

Specialty	Round 1, N	Round 2, N
Urology	52	45
Oncology		
Medical Oncology	18	18
Radiation Oncology	18	14
Other		
Nuclear Medicine	3	3
Pathology	8	5
Radiology	9	7
Specialist nurse	3	3
Clinical Oncology	2	2
Total	113	97

Table 2. Consensus levels applied for original Delphi survey

Consensus level	Definition
1	A priori consensus* threshold met across all 3 stakeholder groups
2	A priori consensus* threshold not met across all 3 stakeholder groups but is met when analysis restricted to relevant† stakeholder group(s)
3	Consensus threshold not met

*A priori consensus: Item scored as agree (7-9) by ≥70% of participants AND disagree (1-3) by ≤15%, OR item scored as disagree (1-3) by ≥70% of participants AND by agree (7-9) ≤15%

†Relevant stakeholder groups: Urologists; others (includes specialties in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); Oncologists

Table 3. Delphi results regarding proposed statement for the management of bladder cancer with variant histologies

Statements highlighted in green achieved Level 1 consensus, those in blue achieved Level 2 consensus and those in yellow failed to reach consensus (Level 3) as part of the Delphi survey (see **Table 2** for details of consensus level criteria). Statements indicated in bold were subsequently reviewed at the consensus conference with revised statements and voting shown in **Table 4**.

Proposed statements	Level of agreement												Relevant stakeholder groups	Consensus level (see table 2)
	Urologists (n=45)				Oncologists (n=32)				Others (n=20)					
	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)		
1. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with micropapillary variant should be treated with immediate radical cystectomy	7	11	82	0	44	22	33	5	36	27	36	9	Ur+O	3
2. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with plasmacytoid or sarcomatoid or nested variant should be treated with immediate radical cystectomy	2	7	91	0	22	7	70	5	27	18	55	9	Ur+O	3
3. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with squamous or glandular variant or nested variant should be treated with immediate radical cystectomy	16	20	64	0	41	7	52	5	64	18	18	9	Ur+O	3
4. Muscle-invasive bladder urothelial carcinoma with micropapillary variant should be treated with primary radical cystectomy and lymphadenectomy	11	11	78	0	30	17	53	2	8	8	83	8	Ur+On+O	3

5.	**Muscle-invasive bladder urothelial carcinoma with plasmacytoid variant should be treated with primary radical cystectomy and lymphadenectomy**	9	9	82	0	29	19	52	1	17	17	67	8	Ur+On+O	3
6.	**Muscle-invasive bladder urothelial carcinoma with squamous or glandular variant should be treated with primary radical cystectomy and lymphadenectomy**	16	4	80	0	20	23	57	2	17	25	58	8	Ur+On+O	3
7.	Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy	2	2	96	0	0	0	100	1	0	0	100	8	Ur+On+O	1
8.	Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy	2	0	98	0	0	16	84	0	8	17	75	8	Ur+On+O	1
9.	Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy	4	2	93	0	3	9	88	0	8	8	83	8	Ur+On+O	1
10.	**Radiotherapy (with or without radio-sensitizing chemotherapy) is an effective therapy for patients with muscle-invasive urothelial carcinoma with variant histologies**	58	40	2	0	13	28	59	0	40	30	30	10	Ur+On	3
11.	Muscle-invasive small cell neuroendocrine variant of bladder urothelial carcinoma should receive preventive brain irradiation to avoid brain recurrence	76	20	4	0	74	19	6	1	86	14	0	13	On	1
12.	Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions	7	14	80	1	6	19	74	1	0	8	92	8	Ur+On+O	1
13.	Patients with pT3/4 pure adenocarcinoma or squamous carcinoma of the bladder should receive perioperative radiotherapy	75	23	2	1	58	13	29	1	14	29	57	13	Ur+On	3

14. Checkpoint inhibitor therapy is effective in metastatic urothelial carcinoma with variant histology	5	56	40	2	7	37	56	5	0	75	25	12	On	3

A, agree; D, disagree; E, equivocal; O, others (includes specialties in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); On, Oncologists; TURBT, transurethral resection of bladder tumour; U, unable to respond; Ur, Urologists

Table 4. Consensus meeting statements regarding the management of bladder cancer with variant histologies

Proposed statements	Level of agreement			N	Consensus achieved
	Disagree (%)	Equivocal (%)	Agree (%)		
1. T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lyphadenectomy	14	0	86	29	Yes
2. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with plasmacytoid, sarcomatoid, squamous, glandular or nested variant should be treated with immediate radical cystectomy and concomitant LND	39	13	48	31	No
3. Muscle-invasive bladder urothelial carcinoma with micropapillary or plasmacytoid variant, or with squamous or glandular differentiation, should be treated with neoadjuvant chemotherapy followed by radical cystectomy and concomitant lymphadenectomy	12	24	63	33	No
4. Adjuvant radiotherapy (with or without radiosensitizing chemotherapy) is a standard treatment for patients with muscle-invasive urothelial carcinoma with variant histologies	37	21	41	29	No

LND, lymph node dissection; N, number of consensus meeting voters; TURBT, transurethral resection of bladder tumour

Table 5. Delphi results regarding proposed statements for the role of prognostic molecular markers in MIBC

Statements highlighted in green achieved Level 1 consensus, those in blue achieved Level 2 consensus and those in yellow failed to reach consensus (Level 3) as part of the Delphi survey (see **Table 2** for details of consensus level criteria). Statements indicated in bold were subsequently reviewed at the consensus conference with revised statements and voting shown in **Table 6**.

Proposed statements	Level of agreement												Relevant stakeholder groups	Consensus level (see Table 2)
	Urologists (n=45)				Oncologists (n=32)				Others (n=20)					
	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)		
1. In patients with metastatic disease, genetic profiling should never be done	87	13	0	0	87	10	3	2	83	8	8	8	On	1
2. In patients with metastatic disease, genetic profiling should be done before any type of therapy	34	55	11	1	43	43	13	2	9	64	27	9	On	3
3. In patients with metastatic disease, genetic profiling should only be done after failing standard therapy	5	34	61	1	50	27	23	2	45	18	36	9	On	3
4. Before prescribing neoadjuvant chemotherapy, RNA subtypes always need to be identified	63	37	0	4	87	13	0	2	78	11	11	11	On	2
5. Before prescribing neoadjuvant chemotherapy, RNA subtypes only need to be identified in patients with anticipated limited benefit from neoadjuvant chemotherapy	40	38	23	5	76	21	3	3	29	43	29	13	On	2
6. Before prescribing checkpoint inhibitor therapy, RNA subtypes always need to be identified	44	46	10	4	69	7	24	3	50	25	25	12	On	3
7. Before prescribing checkpoint inhibitor therapy, RNA subtypes only need to be identified in selected patients	21	40	38	3	69	17	14	3	14	29	57	13	On	3

8.	Before prescribing neoadjuvant chemotherapy, DDR or ERCC mutations always need to be identified	53	40	8	5	79	21	0	3	38	13	50	12	On	2
9.	Before prescribing neoadjuvant chemotherapy, DDR or ERCC mutations only need to be identified in selected patients with anticipated limited benefit from neoadjuvant chemotherapy	28	40	33	5	59	24	17	3	13	63	25	12	On	3
10.	Before offering subsequent treatment to patients failing first-line (platinum based) treatment and immunotherapy, selected targeted mutations (TSC1, HER2, FGFR3 mutations/translocations) always need to be identified	43	33	25	5	39	32	29	4	44	22	33	11	On	3
11.	Before offering subsequent treatment to patients failing first-line (platinum based) treatment and immunotherapy, selected targeted mutations (TSC1, HER2, FGFR3mut/translocations) only need to be identified in selected patients	18	25	58	5	41	24	34	3	22	22	56	11	On	3
12.	Before prescribing a checkpoint inhibitor, TMB always needs to be assessed	70	20	10	5	85	11	4	5	78	0	22	11	On	1
13.	Before prescribing a checkpoint inhibitor, TMB only needs to be assessed in selected patients	17	51	32	4	44	26	30	5	40	30	30	10	On	3
14.	Before selecting patients for checkpoint inhibitor therapy, MSI and DDR mutations always need to be assessed	67	30	2	2	74	26	0	5	71	0	29	13	On	2
15.	**Before radical cystectomy or chemotherapy, the NLR always needs to be assessed**	78	20	2	0	86	14	0	4	67	11	22	11	Ur+On	2
16.	**Before radical cystectomy or chemotherapy, the NLR does NOT need to be assessed**	13	36	51	0	7	14	79	4	25	13	63	12	Ur+On	3

17. Before radical cystectomy or chemotherapy, the NLR ratio only needs to be assessed in selected patients	40	42	18	0	57	36	7	4	86	14	0	13	Ur+On	3
18. In patients with metastatic disease, always measure the LDH and/or serum albumin	16	24	60	0	24	10	66	3	0	0	100	14	On	3
19. In patients with metastatic disease, LDH and/or serum albumin only need to be assessed in selected patients	50	23	27	1	82	14	4	4	100	0	0	14	On	2
20. In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy must be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy)	0	11	89	1	4	11	85	5	0	0	100	13	U+On	1
21. In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy need NOT be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy)	84	11	5	1	81	11	7	5	86	14	0	13	U+On	1

A, agree; D, disagree; DDR, DNA damage response; DNA, deoxyribonucleic acid; E, equivocal; ERCC, DNA excision repair protein; FGFR3, fibroblast growth factor receptor 3; HER2, human epidermal growth factor receptor 2; LDH, lactate dehydrogenase; MIBC, muscle invasive bladder cancer; MSI, microsatellite instability; NLR, neutrophil to lymphocyte ratio; O, others (includes specialties in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); On, Oncologists; RNA, ribonucleic acid; TMB, tumour mutational burden; TSC1, tuberous sclerosis complex 1; U, unable to respond; Ur, Urologists

Table 6. Consensus meeting statements regarding the role of prognostic molecular markers in MIBC

Proposed statements	Level of agreement			N	Consensus achieved
	Disagree (%)	Equivocal (%)	Agree (%)		
1. Before prescribing checkpoint inhibitor therapy, RNA subtypes always need to be identified	91	6	3	31	Yes
2. Before radical cystectomy or chemotherapy, the NLR does NOT need to be assessed	3	0	97	31	Yes
3. In patients with metastatic disease, always measure the LDH and/or serum albumin as general prognostic markers of patient outcome	16	19	65	31	No

LDH, lactate dehydrogenase; MIBC, muscle invasive bladder cancer; N, number of voters; NLR, neutrophil to lymphocyte ration; RNA, ribonucleic acid

Table 7. Delphi results regarding proposed statements for bladder preservation strategies

Statements highlighted in green achieved Level 1 consensus, those in blue achieved Level 2 consensus and those in yellow failed to reach consensus (Level 3) as part of the Delphi survey (see **Table 2** for details of consensus level criteria). Statements indicated in bold were subsequently reviewed at the consensus conference with revised statements and voting shown in **Table 8**.

Proposed statements	Level of agreement												Relevant stakeholder groups	Consensus level (see Table 2)
	Urologists (n=45)				Oncologists (n=32)				Others (n=20)					
	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)		
1. Patients should be counselled on all treatment options by a neutral healthcare professional (e.g. a nurse specialist)	**42**	**24**	**33**	**0**	**19**	**19**	**63**	**0**	**6**	**13**	**81**	**4**	**All**	**3**
2. All patients diagnosed with muscle-invasive bladder cancer should be seen by an Oncologist as well as a Urologist	23	18	59	1	0	3	97	0	0	0	100	1	All	3
3. All patients over 75 years of age should be evaluated preoperatively by a geriatrician	13	24	62	0	16	16	69	0	11	11	78	2	All	3
4. An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma in situ	4	7	89	0	3	13	84	1	7	7	86	6	Ur+On	1
5. An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis	0	7	93	0	10	6	84	1	7	7	87	5	Ur+On	1
6. When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking)	0	7	93	0	9	6	84	0	6	6	88	4	Ur+On	1

7.	In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiotherapy can be offered accepting that this may be palliative rather than curative in outcome	9	20	71	0	3	3	94	0	0	6	94	4	Ur+On	1
8.	The preferred radiotherapeutic schedule is radiotherapy alone (single block)	100	0	0	3	93	0	7	2	90	0	10	10	On	1
9.	The preferred radiotherapeutic schedule is radiotherapy given concurrently with BCON	87	11	3	7	60	23	17	2	71	29	0	13	On	3
10.	The preferred radiotherapeutic schedule is radiotherapy alone, split course with interval cystoscopy and immediate cystectomy for non-responders	58	19	23	2	74	13	13	1	50	38	13	12	On	2
11.	**The preferred radiosensitiser is 5-fluorouracil + mitomycin C**	26	39	34	7	19	13	69	0	17	17	67	14	On	3
12.	**The preferred radiosensitiser is cisplatin**	5	13	82	6	10	13	77	1	33	17	50	14	On	2
13.	**The preferred radiosensitiser is gemcitabine**	42	37	21	7	42	26	32	1	0	50	50	14	On	3
14.	**The preferred radiosensitiser is i.v. carbogen nicotinamide**	67	31	3	9	58	26	16	1	50	50	0	14	On	3
15.	**Brachytherapy has a role in the treatment of muscle-invasive bladder cancer**	87	4	9	0	59	24	17	3	44	22	33	11	Ur+On	3
16.	**PLND should be an integral part of bladder preservation strategies in patients with muscle-invasive bladder cancer**	38	16	47	0	69	6	25	0	0	17	83	8	Ur+On	3
17.	When adjuvant chemotherapy is offered, patients should be selected based on the result of PLND (if done)	11	4	84	0	13	16	71	1	0	17	83	8	Ur+On	1
18.	When adjuvant chemotherapy is offered, patients should be selected based on response to trimodality therapy	35	26	40	2	33	37	30	2	33	44	22	11	Ur+On	3
19.	When adjuvant chemotherapy is offered, patients should be selected based on pT3 or	7	4	89	0	3	10	87	1	17	17	67	8	Ur+On	2

pT4 at cystectomy														
20. Irradiation of the lymph nodes should be standard during trimodality treatment	7	24	68	4	33	10	57	2	25	13	63	12	All	3

A, agree; BCON, carbogen/nicotinamide; D, disagree; E, equivocal; i.v., intravenous; N, node; On, Oncologists; PLND, Pelvic lymph node dissection; pT, pathological tumour stage; T, tumour; U, unable to respond; Ur, Urologists

Table 8. Consensus meeting statements regarding bladder preservation strategies

Proposed statements	Level of agreement			N	Consensus achieved
	Disagree (%)	Equivocal (%)	Agree (%)		
1. Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral healthcare professional such as a specialist nurse	6	12	83	34	Yes
2. Chemoradiation should be given to improve local control in case of inoperable locally advanced tumours	3	12	85	32	Yes
3. In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/MMC, carbogen/nicotinamide or gemcitabine	0	0	100	29	Yes
4. In patients with cN0 disease, PLND in case of bladder preservation is not recommended	14	22	64	31	No
5. Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects	0	16	84	25	Yes
6. Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended	8	8	86	28	Yes

5FU, 5-fluorouracil; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; MMC, mitomycin c; N, number of voters;

PLND, pelvic lymph node dissection

Table 9. Delphi results regarding proposed statements for the role of treatment of curative intent in OMD

Statements highlighted in green achieved Level 1 consensus, those in blue achieved Level 2 consensus and those in yellow failed to reach consensus (Level 3) as part of the Delphi survey (see **Table 2** for details of consensus level criteria). Statements indicated in bold were subsequently reviewed at the consensus conference with revised statements and voting shown in **Table 10**.

Proposed statements	Level of agreement												Relevant stakeholder groups	Consensus level (see Table 2)
	Urologists (n=45)				Oncologists (n=32)				Others (n=20)					
	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)		
1. In patients with one metastatic site, cure is still possible	18	13	69	0	13	19	69	0	21	0	79	6	Ur+On	3
2. In patients with two metastatic sites, cure is still possible	40	18	42	0	47	22	31	0	46	8	46	7	Ur+On	3
3. In patients with more than two metastatic sites, cure is still possible	91	4	4	0	88	6	6	0	86	7	7	6	Ur+On	1
4. Liver is a favourable OMD site for curative therapy	95	2	2	1	81	16	3	1	93	7	0	6	Ur+On	1
5. Bone is a favourable OMD site for curative therapy	93	2	5	1	77	16	6	1	87	0	13	5	Ur+On	1
6. Lung is a favourable OMD site for curative therapy	36	9	56	0	55	6	39	1	43	21	36	6	Ur+On	3
7. Extrapelvic lymph node is a favourable OMD site for curative therapy	22	13	64	0	19	13	68	1	29	14	57	6	Ur+On	3
8. OMD is more favourable prognostically as a relapse syndrome (metachronous disease) than as a presentation syndrome (synchronous disease)	16	36	48	1	6	31	63	0	18	45	36	9	Ur+On	3

9.	After staging reveals OMD, curative therapy should be deferred pending confirmation restaging 6 weeks later using the same staging method as the initial staging	36	44	20	0	44	31	25	0	40	60	0	10	Ur+On	3
10.	**It is important to include PET-CT scanning in OMD staging**	16	13	71	0	22	16	63	0	6	6	88	3	Ur+On+O	3
11.	Radiotherapy to the whole bone should follow resection of a bone metastasis	33	40	26	3	16	23	61	1	60	40	0	10	On	3
12.	Radiotherapy to the whole brain should follow resection of a brain metastasis	44	34	22	4	53	13	34	0	56	11	33	11	On	3
13.	**Radical treatment of oligometastases should be accompanied by neoadjuvant chemotherapy only**	33	28	40	2	26	42	32	1	43	14	43	13	Ur+On	3
14.	**Radical treatment of oligometastases should be accompanied by adjuvant chemotherapy only**	57	38	5	3	58	35	6	1	43	29	29	13	Ur+On	3
15.	**Radical treatment of oligometastases should be accompanied by no chemotherapy at all**	100	0	0	2	65	26	10	1	63	13	25	12	Ur+On	3
16.	Curative treatment of OMD is especially indicated for pure squamous cell cancers	30	58	13	5	37	47	17	2	0	50	50	12	Ur+On	3
17.	In case of OMD at first presentation, the primary site must be treated first before treating distant metastatic sites	35	28	37	2	27	50	23	2	17	42	42	8	Ur+On	3
18.	In metachronous OMD, time to relapse is an important prognostic indicator	2	4	93	0	0	3	97	0	0	8	92	7	Ur+On	1
19.	Initial local treatment for OMD should be radical surgery rather than radiotherapy, when possible	24	38	38	0	42	42	16	1	30	40	30	10	Ur+On	3
20.	In case patients with visceral OMD are offered a radical cystectomy, a standard LND should be offered (pelvic lymph nodes up to crossing of ureter with common iliac vessels)	7	20	73	0	39	32	29	4	10	30	60	10	Ur+On	3

21. In case patients with visceral oligometastatic disease are offered a radical cystectomy, an extended LND should be offered (up to inferior mesenteric artery)	38	27	36	0	57	36	7	4	30	40	30	10	Ur	3

A, agree; CT, computed tomography; D, disagree; E, equivocal; LND, lymph node dissection; O, others (includes specialties in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); On, Oncologists; OMD, oligometastatic disease; PET, positron emission tomography; U, unable to respond; Ur, Urologists

Table 10. Consensus meeting statements regarding the role of treatment of curative intent in OMD

Proposed statements	Level of agreement			N	Consensus achieved
	Disagree (%)	Equivocal (%)	Agree (%)		
1. In a minority of patients with one metastatic lesion, cure is possible after radical treatment	6	3	91	31	Yes
2. PET-CT scanning should be included in OMD staging when considering radical treatment	3	9	88	32	Yes
3. Radical treatment of OMD should be accompanied by adjuvant or neoadjuvant systemic therapy	6	22	72	32	Yes

N, number of voters; OMD, oligometastatic disease; PET-CT, positron emission tomography-computed tomography

Table 11. Delphi results regarding proposed statements for ICIs in urothelial bladder cancer

Statements highlighted in green achieved Level 1 consensus, those in blue achieved Level 2 consensus and those in yellow failed to reach consensus (Level 3) as part of the Delphi survey (see **Table 2** for details of consensus level criteria). Statements indicated in bold were subsequently reviewed at the consensus conference with revised statements and voting shown in **Table 12**.

Proposed statements	Level of agreement												Relevant stakeholder groups	Consensus level (see Table 2)
	Urologists (n=45)				Oncologists (n=32)				Others (n=20)					
	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)		
1. **In patients with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy but with high PD-L1 expression (as per approved drug specific methodology), both treatment with an ICI and chemotherapy can be offered**	7	4	89	0	4	0	96	4	0	20	80	10	On	1
2. Since no data exists for cisplatin ineligible PD-L1 positive patients in order to differentiate between different ICIs (atezolizumab and pembrolizumab), either agent can be administered	2	7	91	0	0	0	100	5	0	0	100	11	On	1
3. **Sequencing of ICIs and chemotherapy maximises outcomes for patients with cisplatin ineligible advanced/metastatic urothelial cancer**	2	50	48	3	7	36	57	4	0	45	55	9	Ur+On	3
4. **Sequencing of different ICIs is indicated in cisplatin ineligible advanced/metastatic urothelial cancer**	34	51	15	4	81	19	0	5	0	71	29	13	On	2
5. Treatment with ICIs past radiological progression in patients with cisplatin ineligible advanced/metastatic urothelial cancer is	58	26	16	7	59	19	22	5	40	20	40	15	On	3

	associated with potentially disease-related harmful risk. This approach should usually be avoided														
6.	Enrolment in a clinical trial remains the preferred option for patients with cisplatin ineligible advanced/metastatic urothelial cancer until ongoing randomised trials report in this population	0	2	98	0	0	0	100	1	0	0	100	8	Ur+On	1
7.	Hyper-progression occurs frequently and is a clinical problem in patients with cisplatin ineligible advanced/metastatic urothelial cancer	33	40	28	5	50	32	18	4	40	20	40	15	On	3
8.	Treatment with an ICI should be offered to patients with advanced/metastatic urothelial cancer with progression after platinum-based chemotherapy. This includes tumours which have progressed within a year or following perioperative (cystectomy) chemotherapy	0	2	98	0	3	0	97	3	0	0	100	10	Ur+On	1
9.	In patients with advanced/metastatic urothelial cancer with progression after platinum-based chemotherapy, there are no data to differentiate between the five different ICIs. All are well tolerated with long term durable remissions and can be used interchangeably	27	7	67	0	36	0	64	4	0	17	83	14	On	3
10.	**PD-L1 biomarkers should be used to select patients eligible for ICIs in patients with advanced/metastatic urothelial cancer with progression after platinum-based chemotherapy**	30	23	48	1	52	10	38	3	0	11	89	11	Ur+On	3
11.	Sequencing of different ICIs is indicated when one fails in patients with advanced/metastatic urothelial cancer with progression after platinum-based chemotherapy	24	29	48	3	68	7	25	4	13	13	75	12	On	3
12.	Pembrolizumab is the preferred agent in patients with advanced/metastatic urothelial	0	29	71	0	3	21	76	3	17	33	50	14	On	2

	cancer with progression after platinum-based chemotherapy, and should be offered where possible														
13.	ICIs should not be recommended as neoadjuvant or adjuvant treatment in patients with non-metastatic muscle-invasive bladder cancer	16	16	69	0	3	7	90	2	14	0	86	13	Ur+On	3
14.	ICIs can be considered in patients with locally advanced (T4b), but potentially operable, bladder cancer who are ineligible for cisplatin based neoadjuvant therapy	14	23	64	1	33	30	37	2	29	0	71	13	Ur+On	3
15.	ICI therapy should not be recommended in patients with non-muscle-invasive bladder cancer	16	18	67	0	10	10	80	2	20	0	80	15	Ur+On	3
16.	**Each ICI has a different PD-L1 biomarker to define positivity. The biomarkers define distinct populations and therefore are not interchangeable in clinical practice**	28	23	49	2	18	32	50	4	57	29	14	13	On	3
17.	In patients with advanced/metastatic urothelial cancer, it is not recommended to use combinations of ICIs, or a combination of ICIs with other anti-cancer treatments prior to the reporting of randomised trials	2	7	91	1	3	7	90	2	17	17	67	14	On	2
18.	Once initiated, ICI therapy should be continued until progression of disease in patients with advanced/metastatic urothelial cancer	2	4	93	0	7	3	90	3	0	25	75	12	On	1
19.	**Pseudo-progression with ICIs is rare in patients with advanced/metastatic urothelial cancer. Treatment past radiological progression is of unproven benefit in advanced/metastatic urothelial cancer but should be considered especially in platinum-refractory disease where other treatment options are lacking**	5	21	74	2	0	21	79	3	0	33	67	14	On	2

20. ICIs are cost effective in licenced indications in advanced/metastatic urothelial cancer	28	44	28	6	8	32	60	7	40	40	20	15	On	3

A, agree; D, disagree; E, equivocal; ICI, immune checkpoint inhibitor; On, Oncologists; PD-L1, programmed death ligand 1; U, unable to respond; Ur, Urologists

Table 12. Consensus meeting statements regarding ICIs in urothelial bladder cancer

Proposed statements	Level of agreement			N	Consensus achieved
	Disagree (%)	Equivocal (%)	Agree (%)		
1. Pseudo-progression has not been demonstrated in urothelial cancer	0	11	89	28	Yes
2. In contrast to the first-line setting, the PD-L1 biomarker is not useful for selecting patients for immunotherapy in platinum-refractory metastatic urothelial cancer	4	15	81	28	Yes
3. Carboplatin-based chemotherapy remains a viable first-line treatment option in cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma until data from randomised Phase III trials of ICIs are available	3	10	87	29	Yes
4. Cisplatin-ineligible, immunotherapy-refractory patients with metastatic urothelial carcinoma should be considered for chemotherapy instead of sequencing of immunotherapy	7	12	81	27	Yes

ICI, immune checkpoint inhibitor; N, number of voters; PD-L1, programmed death ligand 1

Table 13. Delphi results regarding proposed statements for follow-up strategies and survivorship

Statements highlighted in green achieved Level 1 consensus, those in blue achieved Level 2 consensus and those in yellow failed to reach consensus (Level 3) as part of the Delphi survey (see **Table 2** for details of consensus level criteria). Statements indicated in bold were subsequently reviewed at the consensus conference with revised statements and voting shown in **Table 14**.

Proposed statements	Level of agreement												Relevant stakeholder groups	Consensus level (see Table 2)
	Urologists (n=45)				Oncologists (n=32)				Others (n=20)					
	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)	D (%)	E (%)	A (%)	U (n)		
1. After radical cystectomy with curative intent, no regular follow-up is needed	100	0	0	0	100	0	0	0	100	0	0	4	Ur	1
2. To detect relapse after radical cystectomy with curative intent, patients should be followed up every 3-4 months for 2 years, every 6 months up to 5 years and then annually	16	4	80	0	3	9	88	0	0	0	100	5	Ur	3
3. To detect relapse after radical cystectomy with curative intent, patients should be followed up every 6 months for 5 years and then annually	33	24	42	0	53	31	16	0	53	33	13	5	Ur	3
4. After radical cystectomy with curative intent, regular follow-up in the majority of patients should stop after 5 years	80	16	4	0	42	16	42	1	60	7	33	5	Ur	2
5. After radical cystectomy, patients should be followed up with a CT scan of the thorax/abdomen alone	67	7	27	0	55	0	45	1	75	0	25	4	Ur+O	3
6. After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended	0	4	96	0	0	13	87	1	0	7	93	5	Ur	1
7. After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended	29	11	60	0	0	11	89	4	7	27	67	5	Ur	3

	in all patients														
8.	After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3-4 months initially; then after 3 years, every 6 months in the majority of patients	0	4	96	0	0	0	100	0	0	0	100	4	Ur+On	1
9.	After trimodality treatment with curative intent, NO regular follow-up for the detection of relapse is needed in the majority of patients	100	0	0	0	100	0	0	0	100	0	0	4	Ur+On	1
10.	**After trimodality treatment with curative intent, follow-up should stop after 5 years in the majority of patients**	91	7	2	0	56	9	34	0	57	7	36	6	Ur+On	3
11.	**After trimodality treatment with curative intent, follow-up imaging to assess distant recurrence or recurrence outside the bladder should be done by CT scan of the thorax/abdomen alone**	40	4	56	0	31	0	69	0	33	0	67	2	Ur+On+O	3
12.	After trimodality treatment with curative intent, NO follow-up imaging to assess distant recurrence or recurrence outside the bladder is needed	100	0	0	0	100	0	0	0	94	0	6	3	Ur+On+O	1
13.	After trimodality treatment with curative intent, assessment of the urothelium to detect recurrence is recommended every 6 months in the majority of patients	2	5	93	1	9	6	84	0	0	6	94	2	Ur	1
14.	After trimodality treatment with curative intent, in addition to a CT scan, NO other investigations of the bladder are recommended	100	0	0	0	100	0	0	0	100	0	0	2	Ur	1
15.	In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, NO regular follow-up is needed. Imaging studies may be done according to signs/symptoms	91	7	2	0	97	0	3	2	88	13	0	4	Ur+On	1

16.	In the majority of patients with a long-lasting complete response after chemotherapy for metastatic urothelial cancer, regular follow-up should be stopped after 3 years	91	7	2	0	100	0	0	2	81	0	19	4	Ur+On	2
17.	No routine assessment of the urothelium is required in patients with a partial or complete response after chemotherapy for metastatic urothelial cancer	80	9	11	0	77	10	13	2	81	0	19	4	Ur+On	2
18.	**When following up patients with urothelial cancer, LDH and CEA do NOT need to be assessed**	11	31	58	0	19	13	68	1	33	33	33	11	Ur+On	3
19.	In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value	4	4	91	0	4	13	83	9	0	25	75	12	Ur	1
20.	**In patients treated with radical cystectomy with curative intent and who have a neobladder, management of vitamin B12 levels does not require any measurements**	77	2	20	1	59	27	14	10	63	38	0	12	Ur	3

A, agree; CEA, carcinoembryonic antigen; CT, computed tomography; D, disagree; E, equivocal; O, others (includes specialties in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); On, Oncologists; LDH, lactate dehydrogenase; U, unable to respond; Ur, Urologists

Table 14. Consensus meeting statements regarding follow-up strategies and survivorship

Proposed statements	Level of agreement			N	Consensus achieved
	Disagree (%)	Equivocal (%)	Agree (%)		
1. To detect relapse after radical cystectomy with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 years in the majority of patients	3	9	88	32	Yes
2. To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients	0	6	94	34	Yes
3. After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g. multifocality, CIS and tumour in the prostatic urethra)	6	6	88	33	Yes
4. To detect relapse (outside the bladder) after trimodality treatment with curative intent, CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients	0	0	100	34	Yes
5. To detect relapse (outside the bladder) after trimodality treatment with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 years in the majority of patients	3	13	84	30	Yes
6. Levels of LDH and CEA are NOT essential in the follow-up of patient with urothelial cancer to detect recurrence	0	0	100	34	Yes
7. Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent	17	7	75	29	Yes

CEA, carcinoembryonic antigen; CIS, carcinoma in situ; CT, computed tomography; LDH, lactate dehydrogenase; N, number of voters

SUPPLEMENTARY TABLES

Supplementary Table 1. Follow-up strategies after cystectomy and trimodality treatment according to guidelines issues by ESMO, EAU and NCCN [3, 5, 6]

	ESMO [3]	EAU [5]	NCCN [6]

Follow-up after cystectomy		• Ab/UT/Ch every 3-6 months for 2 years and thereafter based on risk of recurrence • Urethral wash every 3-6 months if urethrectomy was not carried out or there is history of CIS	• CT every 6 months until third year and annually thereafter • In patients with multifocal disease, NMIBC, positive ureteral margin (risk of UTUC) monitoring the UUT is mandatory (>3 years)	• NMIBC: Ab/UT at 3 and 12 months, then annually up to 10 years • MIBC: Ab/UT every 3-6 months for 2 years, then annually up to 10 years
Follow-up after trimodality treatment	**Cystoscopy**	• Every 3-6 months for 2 years	NA	• Every 3 months for 2 years, every 6 months for years 3 and 4, then annually up to 10 years
	Imaging	• Same follow-up regimen as for cystectomy	NA	• Ab/UT every 3-6 months for 2 years, then annually up to 5 years • Ch every 3-6 months for 2 years, then annually up to 5 years • More follow-up when clinically indicated

Ab, abdomen imaging; Ch, chest imaging; CIS, carcinoma in situ; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; m, month; MIBC, muscle-invasive bladder cancer; NA, not available; NCCN, National Comprehensive Cancer Network; NMIBC, non-muscle-invasive bladder cancer; UT, upper tract imaging; UTUC, upper urinary tract urothelial carcinomas; UUT, upper urinary tract

[NOTE: All references will be checked for format/style prior to submission]

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