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SPECIAL ARTICLE

EAU–ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multi-stakeholder effort: under the auspices of the EAU and ESMO Guidelines Committees†

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[†]These consensus statements were developed by the European Association of Urology (EAU) and the European Society for Medical Oncology (ESMO) and are published simultaneously in European Urology and Annals of Oncology.

Background: Although guidelines exist for advanced and variant bladder cancer management, evidence is limited/conflicting in some areas and the optimal approach remains controversial.

Objective: To bring together a large multidisciplinary group of experts to develop consensus statements on controversial topics in bladder cancer management.

Design: A steering committee compiled proposed statements regarding advanced and variant bladder cancer management which were assessed by 113 experts in a Delphi survey. Statements not reaching consensus were reviewed; those prioritised were revised by a panel of 45 experts before voting during a consensus conference.

Setting: Online Delphi survey and consensus conference.

Participants: The European Association of Urology (EAU), the European Society for Medical Oncology (ESMO), experts in bladder cancer management.

Outcome measurements and statistical analysis: Statements were ranked by experts according to their level of agreement: 1–3 (disagree), 4–6 (equivocal), 7–9 (agree). A priori (level 1) consensus was defined as ≥70% agreement and ≤15% disagreement, or vice versa. In the Delphi survey, a second analysis was restricted to stakeholder group(s) considered to have adequate expertise relating to each statement (to achieve level 2 consensus).

Results and limitations: Overall, 116 statements were included in the Delphi survey. Of these, 33 (28%) statements achieved level 1 consensus and 49 (42%) statements achieved level 1 or 2 consensus. At the consensus conference, 22 of 27 (81%) statements achieved consensus. These consensus statements provide further guidance across a broad range of topics, including the management of variant histologies, the role/limitations of prognostic biomarkers in clinical decision making, bladder preservation strategies, modern radiotherapy techniques, the management of oligometastatic disease and the evolving role of checkpoint inhibitor therapy in metastatic disease.

Conclusions: These consensus statements provide further guidance on controversial topics in advanced and variant bladder cancer management until a time where further evidence is available to guide our approach.

Key words: bladder cancer, consensus, Delphi, diagnosis, treatment, follow-up

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 four times more common in men, where it is the sixth most common cancer and the ninth 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] and the European Association of Urology (EAU) [4, 5], all produce Clinical Practice Guidelines (CPGs) that provide guidance to health care 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 advanced and variant 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 [6]. 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 [7–10], 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 [11].

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 chemoradiation (i.e. trimodality bladder preservation 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 bladder preservation treatment has also not been defined [12].

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, 12]. The benefit of adding (neo)adjuvant chemotherapy to radical cystectomy and node dissection in oligometastatic disease (OMD) 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, 12]. 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 [13, 14], and their use in Europe is currently restricted to programmed death-ligand 1 (PD-L1)-positive patients with different companion diagnostics and cut-offs used for each ICI. 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 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 (OS) benefit versus chemotherapy in a phase III randomised controlled trial [15]. 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 variation in practice may exist. Given this, the aim of this consensus-finding project was to gain insights from a multidisciplinary group of experts in order to produce consensus statements that would further guide HCPs on selected clinically relevant topics. It was anticipated that these consensus statements would underpin clinical practice guideline recommendations produced by existing society guidelines and

facilitate an optimal approach to the diagnosis, treatment and follow-up of patients with advanced and variant bladder cancer.

Methods

In 2018, the EAU and ESMO formed a collaboration to produce consensus statements for the management of bladder cancer. A project steering committee was established, which comprised a multidisciplinary panel of 13 experts from EAU and ESMO, including two chairpersons (J.A. Witjes and A. Horwich). 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 advanced and variant 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 six 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.J. Ribal and J. Bellmunt)
3. Bladder preservation strategies (Chairs: N. James and J.A. Witjes)
4. Treatment of curative intent for patients with OMD (Chairs: A. Horwich and M. Babjuk)
5. ICIs in urothelial bladder cancer (Chairs: T. Powles and H.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) [16]. The resulting Delphi survey was distributed to key stakeholder groups including (i) Urologists, (ii) Oncologists (including Medical and Radiation Oncologists) and (iii) 'Others' (consisting of Radiologists, Pathologists, Specialist Nurses, Clinical Oncologists and Specialists in Nuclear Medicine). Participants were purposefully sampled by contacting professional societies, including the EAU, ESMO, the American Society of Clinical Oncology (ASCO), American Urological Association (AUA), European Society for Radiotherapy and Oncology (ESTRO), European Forum for Primary Care (EFPC), European Association of Urology Nurses (EAUN), Canadian Urological Association (CUA), International Society of Urological Pathology (ISUP), Urological Society of Australia and New Zealand (USANZ), European Society of Urogenital Radiology (ESUR), Urological Association of Asia (UAA), American Society for Radiation Oncology (ASTRO), EAU bladder cancer guideline panels (both MIBC and NMIBC panels) and the EAU Section of Oncological Urology (ESOU). 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, which were reviewed for relevance by the chairpersons. 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 three 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 three stakeholder groups described above. After the final survey round, the level of agreement for each statement was assessed for all three stakeholder groups separately, with consensus defined *a priori* as:

- Item scored as agree (7–9) by $\geq$70% of participants AND disagree (1–3) by $\leq$15%, OR
- Item scored as disagree (1–3) by $\geq$70% of participants AND agree (7–9) by $\leq$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 before this second analysis.

Final results were tabulated according to the three 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 three stakeholder groups (i.e. original consensus analysis).
- Level 2: *A priori* consensus threshold not met across all three stakeholder groups but met when analysis restricted to most relevant stakeholder group(s).
- Level 3: *A priori* consensus threshold not met.

A subsequent review of the results was carried out 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 for a face-to-face meeting, additional HCPs also considered as important stakeholders in the management of bladder cancer were invited, with all attending experts allocated to one of the six 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

Table 1. Delphi survey participants according to speciality

Speciality	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[a] threshold met across all three stakeholder groups
2	*A priori* consensus[a] threshold not met across all three stakeholder groups but is met when analysis restricted to relevant[b] stakeholder group(s)
3	Consensus threshold not met

[a]*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%.
[b]Relevant stakeholder groups: Urologists; others (includes specialities in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); Oncologists.

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. Finally, the expert panel was asked to rate its 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/, 15 October 2019, date last accessed). 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. The authors of this article include all Delphi survey participants, consensus conference attendees and other individuals who provided significant contributions to this project, all of whom have reviewed and approved the final manuscript.

Results

The steering committee generated 115 statements relating to the management of advanced and variant 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 speciality is shown in Table 1. A total of 45 experts attended the consensus conference, 24 of whom also participated in the Delphi survey. As such, this project included the participation of 134 experts with representation from 23 different countries (The Netherlands: 19, UK: 18, France: 12, Germany: 12, Spain: 11, USA: 10, Italy: 8, Austria: 7, Switzerland: 6, Belgium: 6, Australia: 5, Denmark: 3, Czech Republic: 2, Romania: 2, Norway: 2, Finland: 2, Sweden: 2, Russia: 1, Greece: 1, Canada: 1, Portugal: 1, Colombia: 1, New Zealand: 1).

In the Delphi survey, 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 six topic areas, including:

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.
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, including the role of different treatment approaches such as radical cystectomy, lymphadenectomy, radiotherapy, chemotherapy and checkpoint inhibitor therapy, in this setting (Table 3).

According to the Delphi survey results, five of the 14 statements reached consensus among all stakeholder groups (Table 3). For the remaining statements, seven were prioritised and four new/modified statements were presented at the consensus conference for further discussion and voting. Results from the

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

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

Continued

Table 3. *Continued*

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*)		
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-sensitising 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

Statements highlighted in green achieved level 1 consensus and those in yellow failed to reach consensus (level 3) as part of the Delphi survey; numbers highlighted in red indicate where the level of agreement among individual stakeholder groups reached ≥70% (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.

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

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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 lymphadenectomy	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 radiosensitising chemotherapy) is a standard treatment of patients with muscle-invasive urothelial carcinoma with variant histologies	37	21	41	29	No

Statements highlighted in green achieved consensus.
LND, lymph node dissection; *N*, number of voters; TURBT, transurethral resection of bladder tumour.

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) [17]. The proportion of carcinoma with micropapillary features can vary significantly, with a larger component being associated with a worse prognosis [18]. 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 [18]. 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 [19].

Given the poor response rate (RR) to intravesical bacillus Calmette–Guérin (BCG) administration, the current standard of care treatment of 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 [20]. 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 [DSS] of 100% versus 60%, $P = 0.006$) and those who underwent delayed radical cystectomy after disease recurrence (5-year DSS of 62%, $P = 0.015$). Patients in the delayed radical cystectomy group also had higher rates of pT3 disease (25% versus 0%, $P = 0.04$) and overall pathological disease progression (pT2 or greater, or nodal disease: 40% versus 27% in the upfront radical cystectomy group) [20].

Given the above, the panel decided to add the recommendation for concomitant pelvic lymph node dissection (PLND) 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. Understaging at the time of TUR 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 OS (1.4 versus 10.6 years, $P < 0.001$) [21]. 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 lymph node dissection.
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. Only limited evidence is available regarding the added benefit of neoadjuvant chemotherapy for bladder cancers with variant histology due to a lack of prospective studies [22]. In one retrospective population-based study, Vetterlein et al. [6] 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 1649 patients underwent upfront radical cystectomy). Patients with neuroendocrine tumours benefited most from neoadjuvant chemotherapy administration, as evidenced by better OS (hazard ratio 0.49; 95% confidence interval 0.33–0.74; $P = 0.01$) and lower rates of non-organ-confined disease at the time of radical cystectomy (41.6% versus 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 OS [6].

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% versus 38%, $P < 0.0001$) and pN+ disease (20% versus 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 [23]. 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 [24, 25].

Statement 4: Adjuvant radiotherapy (with or without radiosensitising chemotherapy) is a standard treatment of 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 RNA subtypes when making therapeutic decisions, and 10 statements covering the value of tumour mutation burden, microsatellite instability, 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, four among all stakeholder groups and six among relevant stakeholder groups only (Table 5). For the remaining statements, three 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 [7, 26]. Clearly, different subtypes exist, 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 [27]. For immunotherapy, conflicting findings have been reported regarding response enrichment in luminal II and basal subtypes [28]. 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 [29].

Given the currently available evidence, the panel agreed that RNA subtypes are not needed when ICIs are prescribed because 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).

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

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, FGFR3 mut/translocations) only need to be identified in selected patients	18	25	58	5	41	24	34	3	22	22	56	11	On	3

Continued

Table 5. *Continued*

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*)		
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 therapy 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 therapy and Bellmunt for second-line therapy)	84	11	5	1	81	11	7	5	86	14	0	13	U+On	1

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; numbers highlighted in red indicate where the level of agreement among individual stakeholder groups reached ≥70% (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.

A, agree; D, disagree; DDR, DNA damage response; 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; On, Oncologists; RNA, ribonucelic acid; TMB, tumour mutation 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

Statements highlighted in green achieved consensus.
LDH, lactate dehydrogenase; MIBC, muscle-invasive bladder cancer; *N*, number of voters; NLR, neutrophil-to-lymphocyte ratio; RNA, ribonucleic acid.

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 and platelet–lymphocyte ratio have been investigated. Recently, NLR has emerged as a prognostic factor in upper urinary tract tumours [30] 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 have also emerged for NLR as a potentially predictive biomarker in patients receiving immunotherapy for melanoma, lung cancer and renal cell carcinoma. 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 OS, recurrence-free survival and DSS in patients with localised disease and in those with metastatic disease [31]. 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) [32].

After considering the available data, the panel agreed that before radical cystectomy or chemotherapy, 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 was identified as significant risk factors in multivariate analysis despite being significant in the univariate analysis [33]. 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 second-line chemotherapy, haemoglobin, performance status (PS) and liver metastasis are recognised prognostic factors [34]. However, in a pooled analysis of data from 10 phase II trials evaluating various different therapies, the addition of albumin to these already-established prognostic factors emerged as significant [35]. A recent meta-analysis has also confirmed the prognostic role of LDH in urological cancer [36].

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 PLND (Table 7). An additional statement was added to this category following results of round 1 of the survey.

According to the Delphi survey results, nine of the 20 statements reached consensus, six among all stakeholder groups and three among relevant stakeholder groups only (Table 7). For the remaining statements, nine 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 health care 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 [37]. The role of the specialist nurse,

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

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 health care professional (e.g. a nurse specialist)	**42**	**24**	**33**	**0**	**19**	**19**	**63**	**0**	**6**	**13**	**81**	**4**	**Ur+On+O**	**3**
2. All patients diagnosed with MIBC should be seen by an Oncologist as well as a Urologist	23	18	59	1	0	3	97	0	0	0	100	1	Ur+On+O	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	Ur+On+O	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 chemoradiation 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

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Table 7. *Continued*

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)		
14. The preferred radiosensitiser is BCON	67	31	3	9	58	26	16	1	50	50	0	14	On	3
15. Brachytherapy has a role in the treatment of MIBC	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 MIBC	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 pT4 at cystectomy	7	4	89	0	3	10	87	1	17	17	67	8	Ur+On	2
20. Irradiation of the lymph nodes should be standard during trimodality treatment	7	24	68	4	33	10	57	2	25	13	63	12	Ur+On+O	3

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; numbers highlighted in red indicate where the level of agreement among individual stakeholder groups reached ≥70% (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.

A, agree; BCON, carbogen/nicotinamide; D, disagree; E, equivocal; i.v., intravenous; MIBC, muscle-invasive bladder cancer; N, node; O, others (includes specialities in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); 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 health care 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 carried out 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	7	7	86	28	Yes

Statements highlighted in green achieved consensus.
5FU, 5-fluorouracil; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; MMC, mitomycin C; *N*, number of voters; PLND, pelvic lymph node dissection.

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 [38].

> **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 health care 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 [39–42]. 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 [39–42].

> **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 radiosensitiser 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 nodes. 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. In order to minimise bowel toxicity for patients with cN0 disease, many centres do not target pelvic lymph nodes. 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 chemoradiation partially eradicates pelvic lymph node micrometastases [43]. However, this was not confirmed in a chemoradiation 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 [44]. Consequently, given the current literature, no consensus could be reached regarding whether or not to carry out 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. Possible challenges for 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 [45].

Statement 5: Radiotherapy for bladder preservation should be carried out 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 carried out and data are therefore limited to highly selected patients in centres with a particular interest in this field. So far, only retrospective studies have been carried out, which have included a wide variation in patient and tumour characteristics. In the majority of patients who received brachytherapy, this was preceded by EBRT [46]. Moreover, it is an invasive procedure that requires surgical catheter placement. As 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 [47]. 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, 7% disagree, 7% equivocal (28 voters).

The role of treatment of curative intent in OMD

OMD is generally defined as occurrence of $\leq$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 [48]. 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 [49]. 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 [50]. 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, findings from a systematic review and pooled analysis showed that among 110 patients who had an adrenalectomy for an isolated adrenal metastasis, OS was shorter for those with synchronous versus metachronous metastasis (12 versus 31 months, respectively; $P = 0.02$) [51]. 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, four of the 21 statements reached consensus across all stakeholder groups (Table 9). For the remaining statements, three 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 more than two metastatic sites should discourage attempted cure, that liver and 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 one or two metastatic sites.

Based on results from prospective phase III trials, ~10% of patients with urothelial cancer and visceral metastases survive 5 years after chemotherapy [52]. Prognostic factors include PS, 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 [53].

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 rate of 28% [54], and in a series of 42 patients from Japan treated by metastasectomy, in patients with solitary nodal or lung metastasis (15 patients), the median OS reached 81 months [55]. A small series from Korea [49] also supported these conclusions. As summarised in a recent collaborative systematic review in metastatic bladder cancer [56], the beneficial role of metastasis surgery remains unproven by a prospective trial but may be considered in those with low volume

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

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 of 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

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Table 9. *Continued*

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)		
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 OMD 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

Statements highlighted in green achieved level 1 consensus and those in yellow failed to reach consensus (level 3) as part of the Delphi survey; numbers highlighted in red indicate where the level of agreement among individual stakeholder groups reached ≥70% (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.

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

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 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)-positron emission tomography (PET)–computed tomography (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 before cystectomy, FDG-PET-CT detected metastases in seven patients who showed no evidence of disease on CT and bone scans [57]. A published review of six series also found a high diagnostic accuracy for metastatic lesions using FDG-PET-CT [58], and a recent review from The National Institutes of Health, Bethesda, USA, concluded that FDG-PET-CT was the optimal technology in this setting [59].

Statement 2: PET-CT scanning should be included in OMD staging when considering radical treatment.
Level of consensus: 88% Agree, 3% disagree, 9% equivocal (32 voters).

3. The role of downstaging chemotherapy 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 of high-risk (muscle-invasive) primary bladder cancer. Neoadjuvant chemotherapy with cisplatin/methotrexate/vinblastine 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 [60].

Statement 3: Radical treatment of OMD 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, nine of the 20 statements reached consensus, five among all stakeholder groups and four among relevant stakeholder groups only (Table 11).

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

Statements highlighted in green achieved consensus.
CT, computed tomography; *N*, number of voters; OMD, oligometastatic disease; PET, positron emission tomography.

For the remaining statements, four 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 [61]. 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 [13, 15, 62]. 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 five different ICI cancer drugs currently available, all of which have a different companion diagnostic to measure PD-L1 (142-atezolizumab, 288-nivolumab, 263-durvalumab, 7310-avelumab, 223-pembrolizumab) [63]. 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-refractory setting for the five different methods. The biomarkers are also inconsistent in the platinum-refractory metastatic setting and appear more prognostic than predictive [15, 62]. None can be reliably used to select treatment due to their lack of sensitivity and specificity [63].

In the front-line, cisplatin-ineligible setting, only data from single-arm trials of atezolizumab and pembrolizumab are in the public domain [13, 14], and again, the data appear inconsistent. However, the European Medicines Agency (EMA) has 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. Although ICIs are associated with long-term, durable remissions as a first-line treatment of cisplatin-ineligible, PD-L1-positive patients with metastatic urothelial carcinoma, RRs, progression-free survival and OS have not been proven to be superior to carboplatin-based chemotherapy [13, 14]. 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).

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

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 exist 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 associated with potentially disease-related harmful risk. This approach should usually be avoided	58	26	16	7	59	19	22	5	40	20	40	15	On	3
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

Continued

Table 11. *Continued*

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)		
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 cancer with progression after platinum-based chemotherapy, and should be offered where possible	0	29	71	0	3	21	76	3	17	33	50	14	On	2
13. ICIs should not be recommended as neoadjuvant or adjuvant treatment in patients with non-metastatic MIBC	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 NMIBC	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 anticancer treatments before 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

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; numbers highlighted in red indicate where the level of agreement among individual stakeholder groups reached ≥70% (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.

A, agree; D, disagree; E, equivocal; ICI, immune checkpoint inhibitor; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; On, Oncologists; PD-L1, programmed death-ligand 1; U, unable to respond; Ur, Urologists.

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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

Statements highlighted in green achieved consensus.
ICI, immune checkpoint inhibitor; *N*, number of voters; PD-L1, programmed death-ligand 1.

4. The role of chemotherapy in cisplatin-ineligible, immunotherapy-refractory patients with metastatic urothelial carcinoma. To the best of 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 [63]. Retrospective data suggest that patients who progress on first-line immunotherapy appear to maintain a reasonable objective RR to a subsequent line of chemotherapy [64]. Thus, sequencing chemotherapy after first-line immunotherapy 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 bladder preservation treatment or chemotherapy for urothelial carcinoma (Table 13).

According to the Delphi survey results, 12 of the 20 statements reached consensus, nine among all stakeholder groups and three among relevant stakeholder groups only (Table 13). Of the eight remaining statements, seven 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 [65–67]. 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 [65–67].

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 [67]. 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 [68].

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

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

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 in all patients	29	11	60	0	0	11	89	4	7	27	67	5	Ur	3
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

Continued

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Table 13. *Continued*

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)		
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

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; numbers highlighted in red indicate where the level of agreement among individual stakeholder groups reached ≥70% (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.

A, agree; CEA, carcinoembryonic antigen; CT, computed tomography; D, disagree; E, equivocal; LDH, lactate dehydrogenase; O, others (includes specialities in Nuclear Medicine, Pathology, Radiology, Specialist Nurse, Clinical Oncology); On, Oncologists; 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	No

Statements highlighted in green achieved consensus.
CEA, carcinoembryonic antigen; CIS, carcinoma *in situ*; CT, computed tomography; LDH, lactate dehydrogenase; *N*, number of voters.

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 S1, available at *Annals of Oncology* online, shows the follow-up strategies after cystectomy and trimodality bladder preservation treatment according to guidelines issued by ESMO and EAU [3, 5].

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 bladder preservation treatment. Between 26% and 43% of patients treated with trimodality bladder preservation treatment will present with recurrences, which mostly occur within the first 2 years [69]. Follow-up after trimodality bladder preservation treatment must detect not only 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 bladder preservation treatment [70].

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, 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. Carcinoembryonic antigen (CEA) is also not specific for bladder cancer and can be positive in follow-up as it can be elevated in smokers. Low vitamin B12 levels have been reported in 17% of patients with bowel diversion [71]. 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

This international, multi-stakeholder consensus-finding collaborative project was the first of its kind to bring together a large multidisciplinary group of professional medical societies and world-leading experts in the management of advanced and variant 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 collective experience and expert opinions.

This project resulted in the development of 71 consensus statements that will help to address controversial topics in the management of advanced and variant bladder cancer and can be used to underpin future guideline recommendations. Although too many to discuss here in detail, some key conclusions are worthy of highlighting. For example, as variant histologies are increasingly recognised and diagnosed, our consensus statements 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 Food and Drug Administration and EMA, markers are not yet adequate for clinical decision making, including PD-L1 status, (epi)genetic markers and several simple serum measurements. Trimodality bladder preservation treatment with chemoradiation is gaining consensus. It is a multidisciplinary decision where several sensitisers can be used. Modern radiotherapy techniques are preferred, whereas dose escalation and brachytherapy are not. The role of PLND 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 as 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.

Taken together, these findings serve to complement existing guidelines and promote a consistent approach to the management of patients with advanced and variant bladder cancer, especially across smaller hospitals where a high level of expert guidance may be lacking.

Although we believe that the methodology applied here is novel and represents an effective approach to obtain a consensus of expert opinion, 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 comprised 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 for a face-to-face meeting, it was felt that additional HCPs should also be invited in order to ensure sufficient collective expertise at the consensus conference.

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 rectified 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.

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 consensus statements provided and adapt his/her approach in light of the individual clinical context faced.

Conclusions

The results reported here represent a significant achievement by providing collective international 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 CPGs, it is anticipated that the consensus statements provided here will help to optimise and standardise the diagnosis, treatment and follow-up of patients with advanced and variant bladder cancer.

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