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

J Alfred Witjes.6 Marek Babjuk,2,3 Joaquim Bellmunt,4,5 Harman M Bruins,6 Theo M De Reijke,7 Maria De Santis,8 Silke Gillessen,9-12 Nick James,13,14 Steven Maclennan,15 Juan Palou,16 Tom Powles,17,18 Maria J Ribal,19 Shahrokh F Shariat,3,20,21 Theo Van Der Kwast,22 Evanguelos Xylinas,23,24 Neeraj Agarwal,25 Aristotle Bamias,26 Alison Birtle,9,27 Peter Black,28 Bernard H Bochner,20,29 Michel Bolla,30 Joost Boormans,31 Alberto Bossi,32 Alberto Briganti,33 Max Burger,34 Daniel Castellano,35 Richard Cathomas,36 Arturo Chiti,37,38 Ananya Choudhury,9,10 Eva Compérat,39,40 Simon Crabb,41 Stephane Culine,42 Berardino De Bari,43 Willem De Blok,44 Pieter De Visschere,45 Karel Decaestecker,46 Konstantinos Dimitropoulos,47 Jose L Dominguez Escrig,48 Stefano Fanti,49 Valerie Fonteyne,50 Mark Frydenberg,51 Jurgen J Futterer,52 Georgios Gakis,53 Bogdan Geavlete,54 Paolo Gontero,55 Bernhard Grubmüller,3 Shaista Hafeez,56,57 Donna Hansel,58 Arndt Hartmann,59 Dickon Hayne,60 Ann M. Henry,61 Ken Herrmann,62 Virginia Hernandez,63 Harry Herr,29 Peter Hoskin,64 Barbara Alicja Jereczek-Fossa,65,66 Rob Jones,67 Ashish M Kamat,68 Vincent Khoo,69 Anne Kiltie,70 Susanne Krege,71 Sylvain Ladoire,72 Pedro C Lara,73 Annemarie Leliveld,74 Estefania Linares-Espinós,75 Vibeke Løgager,76 Anja Lorch,77 Yohann Loriot,78 Richard Meijer,79 Carme Mir,48 Marco Moschini,80 Hugh Mostafid,81 Arndt-Christiaan Müller,82 Christopf Muller,83 James N'Dow,15,47 Andrea Necchi,84 Yann Neuzillet,85 Jorg R Oddens,86 Jan Oldenburg,87,88 Susanne Osanto,89 Wim Oyen,37,90 Luis Pacheco-Figueiredo,91 Helle Pappot,92 Manish Patel,93 Bradley R Pieters,94 Mesut Remzi,95 Margitta Retz,96 Jonathan Richenberg,97,98 Michael Rink,99 Florian Roghmann,100 Jonathan Rosenberg,101,102 Morgan Roupret,103 Olivier Rouviere,104,105 Carl Salembier,106 Antti Salminen,107 Paul Sargos,108 Shomik Sengupta,109,110 Amir Sherif,111 Robert J Smeenk,112 Anita Smits,6 Arnulf Stenzl,53 George N Thalmann,113 Bertrand Tombal,114 Baris Turkbey,115 Susanne Vahr,116 Riccardo Valdagni,117 Antoine Van Der Heijden,6 Hein Van Poppel,118 Mihai D Vartolomei,3,119 Erik Veskimäe,120 Antoni Vilaseca,121 Franklin A Vives Rivera,122 Thomas Wiegel,123 Peter Wiklund,124,125 Andrew Williams,126 Richard Zigeuner,127 Alan Horwich,1

*1Emeritus Professor, The Institute of Cancer Research, London, UK; 2Depatment of Urology, 2nd Faculty of Medicine, Hospital Motol, Charles University, Prague, Czech Republic; 3Department of Urology, Medical University of Vienna, Vienna, Austria; 4IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain; 5Harvard Medical School, Boston, Massachusetts, USA; 6Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands; 7Department of Urology, Amsterdam University Medical Center, University of Amsterdam, The Netherlands; 8Department of Urology, Charité University Hospital, Berlin, Germany; 9Division of Cancer Sciences, University of Manchester, Manchester, UK; 10The Christie NHS Foundation Trust, Manchester, UK; 11Division of Oncology and Division of Haematology, Kantonsspital St Gallen, St Gallen, Switzerland; 12University of Bern, Bern, Switzerland; 13University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; 14Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK; 15Academic Urology Unit, University of Aberdeen, Aberdeen, Scotland, UK; 16Urological Oncology Unit, Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain; 17The Royal Free NHS Trust, London, UK; 18Barts Cancer Institute, Queen Mary University of London, London, UK; 19Uro-Oncology Unit, Hospital Clinic, University of Barcelona, Spain; 20Department of Urology, Weill Cornell Medical College, New York, New York, USA; 21Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; 22Department of Pathology, Erasmus Medical Center, Rotterdam, The Netherlands; 23Department of Urology, Bichat-Claude Bernard Hospital, Assistance Publique Hôpitaux de Paris, Paris, France; 24Paris Descartes University, Paris, France; 25Department of Medical Oncology, Huntsman Cancer Institute, University of Utah (NCI-CCC), Salt Lake City, Utah, USA; 26Department of Clinical Therapeutics, Oncology Unit, Alexandra Hospital, Athens, Greece; 27Rosemere Cancer Centre, Lancashire Teaching Hospitals, Preston, UK; 28Department of Urologic Sciences, Vancouver Prostate Centre, University of British Columbia, Vancouver, British Colombia, Canada; 29Urology Service, Department of Urology, Memorial Sloan Kettering Cancer Center, New York, New York, USA; 30Department of Radiation Oncology, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; 31Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands; 32Department of Radiation Oncology, Gustave Roussy Institute, Villejuif, France; 33Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy; 34Department of Urology and Paediatric Urology, Julius-Maximilians-University Würzburg, Würzburg, Germany; 35Medical Oncology Department, 12 de Octubre University Hospital (CIBERONC), Madrid, Spain; 36Departement Innere Medizin, Abteilung Onkologie und Hämatologie, Kantonsspital Graubünden, Chur, Switzerland; 37Department of Biomedical Sciences, Humanitas University, Milan, Italy; 38Humanitas Research Hospital, Milan, Italy; 39Department of Pathology, Tenon hospital, HUEP, Paris, France; 40Sorbonne University, Paris, France; 41Cancer Sciences Unit, University of Southampton, Southampton, UK; 42Department of Cancer Medicine, Hôpital Saint Louis, Paris, France; 43Radiotherapy Department, CHU Jean-Minjoz, Besançon, France; 44Department of Urology, University Medical Center Utrecht, Utrecht, The Netherlands; 45Department of Radiology and Nuclear Medicine, Division of Genitourinary Radiology and Mammography, Ghent University Hospital, Gent, Belgium; 46Ghent University Hospital, Gent, Belgium; 47Department of Urology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK; 48Servicio de Urología, Fundación Instituto Valenciano de Oncología, Valencia, Spain; 49Department of Nuclear Medicine, Policlinico S Orsola, University of Bologna, Italy; 50Department of Radiotherapy Oncology, Ghent University Hospital, Ghent, Belgium; 51Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia; 52Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; 53Department of Urology, Eberhard Karls University Tübingen, Tübingen, Germany; 54Department of Urology, Saint John Emergency Clinical Hospital, Bucharest, Romania; 55Division of Urology, Molinette Hospital, University of Studies of Torino, Torino, Italy; 56The Institute of Cancer Research, London, UK; 57The Royal Marsden NHS Foundation Trust, London, UK; 58Department of Urology, University of California, San Diego Pathology, La Jolla, California, USA; 59Institute of Pathology, Friedrich-Alexander University (FAU) Erlangen-Nürnberg, Erlangen, Germany; 60Department of Urology, UWA Medical School, University of Western Australia, Perth, Australia; 61Leeds Cancer Centre and St. James's University Hospital, Leeds, UK; 62Department of Nuclear Medicine, Universitaetsklinikum Essen, Essen, Germany; 63Department of Urology, Hospital Universitario Fundación de Alcorcón, Madrid, Spain; 64Mount Vernon Centre for Cancer Treatment, London, UK; 65Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy; 66Division of Radiotherapy, IEO European Institute of Oncology, IRCCS, Milan, Italy; 67Institute of Cancer Sciences, College of Medicine, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; 68Department of Urology - Division of Surgery, The University of Texas, MD Anderson Cancer Center, Houston, Texas, USA; 69Department of Clinical Oncology, Royal Marsden NHS Foundation Trust, London, UK; 70CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford, UK; 71Department of Urology, Pediatric Urology and Urologic Oncology, Kliniken Essen-Mitte, Essen, Germany; 72Department of Medical Oncology, Centre Georges François Leclerc, Dijon, France; 73Department of Oncology, Hospital Universitario San Roque/Universidad Fernando Pessoa, Canarias; 74Department of Urology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 75Department of Urology, University Hospital La Paz, Madrid, Spain; 76Department of Radiology, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark; 77Genitourinary Medical Oncology, Department of Urology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany; 78Département de Médecine Oncologique, Gustave Roussy, INSERM U981, Université Paris-Sud, Université Paris-Saclay, Villejuif, France; 79UMC Utrecht Cancer Center, MS Oncologic Urology, Urecht, The Netherlands; 80Department of Urology, Luzerner Kantonsspital, Luzern, Switzerland; 81Department of Urology, Royal Surrey County Hospital, Guildford, Surrey, UK; 82Department of Radiation Oncology, Eberhard Karls University, Tübingen, Germany; 83Cancer Treatment Centre, Sorlandet Hospital, Kristiansand, Norway; 84Department of Medical Oncology, Istituto Nazionale Tumori of Milan, Milan, Italy; 85Department of Urology, Hospital Foch, University of Versailles-Saint-Quentin-en-Yvelines, Suresnes, France; 86Amsterdam Academic Medical Center, Amsterdam, The Netherlands; 87Department of Oncology, Akershus University Hospital, Lørenskog, Norway; 88Faculty of Medicine, University of Oslo, Oslo, Norway; 89Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; 90Department of Radiology and Nuclear Medicine, Rijnstate Hospital, Arnhem, The Netherlands; 91Department of Urology, Centro Hospitalar São João, Porto, Portugal; 92Department of Oncology, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; 93Department of Urology, Westmead Hospital, University of Sydney, Sydney, Australia; 94Department Radiation Oncology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands; 95Facharzt für Urologie und Andrologie, Universitätsklinik für Urologie, Wien, Austria; 96Department of Urology, Rechts der Isar Medical Center, Technical University of Munich, Munich, Germany; 97Department of Imaging and Nuclear Medicine, Royal Sussex County Hospital, Brighton, Sussex, UK; 98Brighton and Sussex Medical School, Brighton, Sussex, UK; 99Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 100Department of Urology, Ruhr-University Bochum, Marien Hospital, Herne, Germany; 101Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; 102Weill Cornell Medical College, New York, New York, USA; 103Department of Urology, Sorbonne Université, GRC n°5, ONCOTYPE-URO, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; 104Hospices Civils de Lyon, Service d’Imagerie Urinaire et Vasculaire, Hôpital Edouard Herriot, Lyon, France; 105Université de Lyon, Université Lyon 1, faculté de médecine Lyon Est, Lyon, France; 106Department of Radiation Oncology, Europe Hospitals Brussels, Belgium; 107Department of Urology, University Hospital of Turku, Finland; 108Department of Radiotherapy, Institut Bergonié, Bordeaux, France; 109Department of Surgery, Austin Health, University of Melbourne, Melbourne, Victoria, Australia; 110Eastern Health Clinical School, Monash University, Melbourne, Victoria, Australia; 111Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå university, Umeå, Sweden; 112Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; 113Department of Urology, Inselspital, Bern University Hospital, Berne, Switzerland; 114Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCL, Brussels, Belgium; 115Molecular Imaging Program, National Cancer Institute, Bethesda, Maryland, USA; 116Department of Urology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 117Department of Oncology and Hemato-oncology, Università degli Studi di Milano, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 118Department of Urology, University Hospitals Leuven, Louvain, Belgium; 119Department of Cell and Molecular Biology, University of Medicine and Pharmacy, Tirgu Mures, Romania; 120Department of Urology, Tampere University Hospital, Tampere, Finland; 121Department of Urology, Uro-Oncology Unit, Hospital Clinic, Univeristat de Barcelona, Barcelona, Spain; 122Clinica HematoOncologica Bonadona Prevenir, Universidad Metropolitana, Clinica Club de Leones, Barranquilla, Colombia; 123Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany; 124Icahn School of Medicine, Mount Sinai Health System New York City, New York, USA; 125Department of Urology, Karolinska Institutet, Stockholm, Sweden; 126Department of Urology, Auckland City Hospital, Auckland, New Zealand; 127Department of Urology, Medizinische Universität Graz, Graz, Austria.*

*[Authors: Please check that your affiliation details are complete and accurate – this should include your affiliated department where possible]*

\*Correspondence to:

Ann Oncol:

Professor Alan Horwich, ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Viganello-Lugano, Switzerland.

E-mail: clinicalguidelines@esmo.org

Eur Urol:

Professor Johannes Alfred Witjes, Department of Urology, internal mail 659, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel. +31 024 36 13 735.

E-mail: Fred.Witjes@radboudumc.nl

**Running header:** ESMO-EAU Consensus on Bladder Cancer

**Word count:** 9177 (excluding abstract, tables & references); Tables: 14; Supplementary Tables: 1; Figures: 0; References: 70

**ABSTRACT**

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

**Word count: 300 (limit: 300 words for both *Ann Oncol* and *Eur Urol*)**

**KEY WORDS:**

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

**KEY MESSAGE**

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

**Character count: 372 (limit: 400, including spaces - required for *Ann Oncol* only)**

**INTRODUCTION**

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

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

In terms of disease management, although transurethral resection of the bladder tumour (TURBT) is the initial treatment of choice for non-muscle invasive bladder cancer (NMIBC), with subsequent treatment tailored according to risk stratification [3, 4], TURBT followed by concurrent chemoradiotherapy (i.e. trimodality treatment) is also an option for muscle invasive bladder cancer (MIBC) in patients considered medically unfit for surgery and in those wishing to avoid radical surgery [3, 4]. However, patient selection for bladder-sparing strategies varies globally and there are no uniform criteria on which to base these decisions. The optimal chemotherapy regimen to use as part of trimodality treatment has also not been defined [13].

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

Finally, although there is no evidence to suggest that regular follow-up after definitive treatment is associated with any survival benefit in patients with bladder cancer, most guidelines recommend regular follow-up, but no high-level, evidence-based follow-up protocol exists.

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

**METHODS**

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

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

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

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

All final statements were entered into DelphiManager (a bespoke online Delphi tool, written in C# using WebForms and a MySQL backend) [17]. The resulting Delphi survey was distributed to key stakeholder groups including 1. Urologists, 2. Oncologists (including Medical and Radiation Oncologists) and 3. ‘Others’ (consisting of Radiologists, Pathologists, Specialist Nurses, Clinical Oncologists and Specialists in Nuclear Medicine). These were chosen as key stakeholders because they represent the HCPs who take the most responsibility for patients with bladder cancer. Combining the specialities in the ‘others’ group was a pragmatic decision based on the anticipated likelihood of recruiting low numbers of these professionals to the study. Participants were purposefully sampled by contacting professional societies. These included the EAU, ESMO, the American Society of Clinical Oncology, American Urological Association, European Society for Radiotherapy and Oncology, European Forum for Primary Care, European Association of Urology Nurses, Canadian Urological Association, International Society of Urological Pathology, Urological Society of Australia and New Zealand, European Society of Urogenital Radiology, Urological Association of Asia, American Society for Radiation Oncology, EAU bladder cancer panels (both muscle-invasive bladder cancer & non-muscle-invasive bladder cancer panel) and the EAU Section of Oncological Urology. These societies then either nominated the appropriate experts or cascaded the invitation to their members. Consent to participate was implied by registering and completing the questionnaire. All HCPs were asked to rate their strength of agreement with each statement on a scale of 1 (strongly disagree) to 9 (strongly agree). An additional option of ‘unable to score’ was included to allow participants to refrain from rating any statements where they felt that they had insufficient expertise to do so. Two iterative rounds of the Delphi survey were conducted. In the first round, participants were also encouraged to propose additional statements; these were reviewed by the chairmen in order to decide whether they were novel and should be included in the subsequent round or if they were already adequately covered by existing statements. In the second round, participants were reminded of their own scores from round 1 and were also provided with a summary score from each of the 3 stakeholder groups. From this, participants had the opportunity to revise or retain their original scores. None of the statements were amended between rounds.

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

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

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

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

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

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

All HCPs who completed the survey were invited to attend the consensus conference. However, based on limited availability, additional HCPs also considered as important stakeholders in the management of bladder cancer were invited, irrespective of whether they had participated in the original survey. Overall, the consensus conference included a multidisciplinary panel of 45 experts in the management of bladder cancer, with all panel members allocated to one of the 6 working groups defined earlier. During the conference, statements prioritised for further review were discussed by each of the working groups during parallel breakout sessions. This included a review of related supporting and/or conflicting evidence informing each statement, and revision of these statements, where necessary. The final statements from each working group were then presented to the entire expert panel for further deliberation and amendment, as needed. Finally, the expert panel were asked to rate their strength of agreement with each of the revised statements using the same scale applied during the Delphi survey using online voting software (<https://www.polleverywhere.com/>). All voting was conducted using individual smartphone devices and was anonymous. Panel members could abstain from voting in cases where they had insufficient expertise to adequately assess the statement (which negated the requirement for an ‘unable to score’ option).

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

**RESULTS**

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

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

The initial (a priori) analysis resulted in a Level 1 consensus for 18 (16%) statements in round 1 and 33 (28%) statements in round 2, with inclusion of statements reaching Level 2 consensus increasing this to 49 (42%) statements after round 2. At the consensus conference meeting, 27 statements were amended/presented for voting and 22 (81%) achieved consensus among the group, giving a total of 71 statements that achieved consensus throughout the whole process.

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

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

**Strategies for variant histologies**

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

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

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

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

Given the poor response rate to intravesical Bacillus Calmette-Guerin (BCG) administration, the current standard of care treatment for most cT1 urothelial carcinomas of the bladder, a recent study evaluated the potential benefits of early (immediate) radical cystectomy for cT1 micropapillary variant urothelial carcinoma [21]. In this retrospective, comparative design study, which included 72 patients with cT1 micropapillary bladder cancer, 40 patients received primary intravesical BCG and 26 underwent upfront radical cystectomy. Of those who received intravesical BCG, 75%, 45% and 35% experienced disease recurrence, progression and lymph node metastasis, respectively, during a median follow-up of 67.5 months. However, patients treated with upfront radical cystectomy had improved survival compared with those treated with BCG (5-year disease-specific survival of 100% vs 60% p=0.006) and those who underwent delayed radical cystectomy after disease recurrence (5-year disease-specific survival of 62%, p=0.015). Patients in the delayed radical cystectomy group also had higher rates of pT3 disease (25% vs 0%, p=0.04) and overall pathological disease progression (pT2 or greater, or nodal disease: 40% vs 27% in the upfront radical cystectomy group) [21].

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

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

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

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

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

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

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

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

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

Only limited evidence is available regarding the added benefit of neoadjuvant chemotherapy for bladder cancers with variant histology due to lack of prospective studies [23]. In one retrospective population-based study, Vetterlein et al. evaluated the added benefit of neoadjuvant chemotherapy administration in patients with muscle-invasive urothelial carcinoma harbouring variant histologies (369 patients underwent neoadjuvant chemotherapy followed by radical cystectomy whereas 1,649 patients underwent upfront radical cystectomy) [7]. Patients with neuroendocrine tumours benefited most from neoadjuvant chemotherapy administration, as evidenced by better overall survival (hazard ratio [HR] 0.49; 95% confidence interval [CI] 0.33-0.74; p=0.01) and lower rates of non-organ-confined disease at the time of radical cystectomy (41.6% vs 76.4%). For tumours with micropapillary differentiation, sarcomatoid differentiation or adenocarcinoma, neoadjuvant chemotherapy decreased the rates of non-organ-confined disease but did not impact overall survival [7].

The revised statement proposed was as follows:

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

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

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

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

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

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

**The role of prognostic molecular markers in MIBC**

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

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

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

The molecular classification of bladder cancer has gained momentum in recent years and is still under development. Several attempts have been made and there is still no agreement regarding how many subgroups can be established and defined. All of these molecular classifications have been updated in the last 4 years, with The Cancer Genome Atlas (TCGA) and the Lund classifications the most recently updated [8, 27]. Clearly, different subtypes persist, and among them, two main subtypes can be distinguished: luminal and basal. According to their molecular appearance, the urothelial carcinomas react differently to different therapies. However, it is important to consider that TCGA data provide no information regarding response to subsequent treatment after cystectomy for MIBC. There is only one report based on retrospective data from patients receiving different types of neoadjuvant chemotherapy where RNA subtypes have been linked to outcome [28]. For immunotherapy, conflicting findings have been reported regarding response enrichment in luminal II and basal subtypes [29]. Lack of consensus on the description of the different RNA subtypes is also a problem. Data linking responses of atezolizumab with the ‘genomically unstable’ subgroup of the Lund classification is discordant with previously reported findings for the luminal II subtype [30].

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

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

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

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

Several studies have already demonstrated that systemic inflammation correlates with worse prognosis in several malignancies. In this setting, biomarkers such as C-reactive protein (CRP), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) have been investigated. Recently, NLR has emerged as a prognostic factor in upper urinary tract tumours [31] and other non-urological malignancies. The use of the NLR as a predictive tool is derived from studies using chemotherapy in oesophageal, gastric and colorectal cancers. Data has also emerged for NLR as a potentially predictive biomarker in patients receiving immunotherapy for melanoma, lung cancer and renal cell carcinoma (RCC). In a recent pooled analysis of 21 studies analysing the prognostic role of NLR in bladder cancer, the authors correlated elevated pre-treatment NLR with overall survival (OS), recurrence-free survival (RFS) and disease-specific survival (DSS) in patients with localised disease and in those with metastatic disease [32]. In contrast, in a recent secondary analysis from the Southwest Oncology Group (SWOG) 8710 trial which assessed the role of neoadjuvant chemotherapy in MIBC, the authors could not demonstrate any correlation between NLR and OS (prognostic) or the OS benefit from neoadjuvant chemotherapy (predictive) [33].

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

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

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

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

No strong data exist regarding the value of albumin or LDH as prognostic factors in metastatic bladder cancer. In Bajorin’s risk factor analysis in patients with previously untreated metastatic bladder cancer, neither LDH nor albumin were identified as significant risk factors in multivariate analysis despite being significant in the univariate analysis [34]. However, as albumin and LDH are easy to measure in peripheral blood and are already validated in other cancers, these parameters are being used in daily clinical practice. For patients treated with 2nd line chemotherapy, haemoglobin, performance status (PS) and liver metastasis are recognised prognostic factors [35]. However, in a pooled analysis of data from 10 Phase 2 trials evaluating various different therapies, the addition of albumin to these already-established prognostic factors emerged as significant [36]. A recent metanalysis has also confirmed the prognostic role of LDH in urological cancer [37].

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

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

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

**Bladder preservation strategies**

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

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

**1. Patient selection for bladder preservation strategies**

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

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

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

**2. Chemoradiation for inoperable, locally advanced MIBC**

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

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

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

**3. Radiosensitisers**

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

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

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

**4. Pelvic lymph node dissection (PLND)**

According to several large cystectomy series, micrometastases in the pelvic lymph nodes are found in 25%-44% of patients with MIBC. For patients receiving chemoradiation, a group who often have a worse prognosis, this might be even higher. For patients with cN0 disease, it is currently not standard radiotherapy practice to include the pelvic lymph nodes in order to minimize bowel toxicity. However, with modern intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) techniques, this is now much more feasible. Surprisingly, findings from the large BC2001 and BCON trials, which included radiotherapy confined to the bladder only, did not report high rates of lymph node relapse (typically <10%) as might have been expected from surgical pathological staging on cystectomy, suggesting that chemoradiotherapy partially eradicates pelvic lymph node micrometastases [44]. However, this was not confirmed in a chemoradiotherapy trial comparing radiotherapy to the whole pelvis versus the bladder (tumour site) alone. Among complete responders, the incidence of pelvic lymph node recurrence was 15.8% and 17.6%, respectively [45]. Consequently, given the current literature, no consensus could be reached regarding whether or not to perform a PLND in bladder preservation strategies.

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

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

**5. Radiotherapy techniques**

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

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

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

**6. Radiotherapy dosing**

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

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

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

**The role of treatment of curative intent in OMD**

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

There are few published series about the radical treatment of OMD in urothelial cancers, hence no guidelines have addressed its management [50]. Thus, questions need to be addressed, at least in part, by reference to other cancers or other disease stages. For example, a multicentre review of radical surgery for 5206 cases of lung metastases reported a 5-year survival rate of 36%, encouraging the belief that an early stage of metastasis exists which may be very limited in extent and thus curable by radical treatment [51]. Important prognostic factors in this series included whether the OMD was solitary and whether the recurrent OMD occurred a long time (>36 months) after treatment of the primary tumour. Similarly, in non-small cell lung cancer (NSCLC), findings from a systematic review and pooled analysis showed that among 110 patients who had an adrenalectomy for an isolated adrenal metastasis, overall survival was shorter for those with synchronous versus metachronous metastasis (12 versus 31 months, respectively; p=0.02) [52]. Similarly encouraging series based on the radical treatment of metastases with stereotactic radiotherapy have also been reported.

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

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

**1. Number of metastatic sites consistent with possible cure**

Results from the Delphi survey showed that there was a consensus among participants that the presence of >2 metastatic sites should discourage attempted cure, that liver or bone are adverse prognostic sites and that longer time to metachronous OMD recurrence is associated with a more favourable outcome. However, there was no consensus regarding whether cure should be attempted for patients with 1 or 2 metastatic sites.

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

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

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

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

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

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

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

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

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

There are no direct comparative studies regarding whether or not to combine systemic therapy with local therapy for urothelial OMD. However, outcomes research on OMD in other tumours emphasises the high risk of recurrence after local treatment alone. There is evidence to support the use of systemic chemotherapy as a component of treatment for high-risk (muscle-invasive) primary bladder cancer. Neoadjuvant chemotherapy with cisplatin/methotrexate/vinblastine (CMV) was associated with a 16% reduction in mortality risk. An overview of adjuvant chemotherapy trials has also suggested a reduction in mortality risk by over 20%, with a particular benefit seen in higher-risk (i.e. node-positive) cases [61].

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

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

**ICIs in urothelial bladder cancer**

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

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

**1. Pseudo-progression with ICIs**

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

Progression of disease is the commonest radiological outcome with single-agent ICI therapy in urothelial cancer [14, 16, 63]. However, there is a lack of data to support the hypothesis that a proportion of these tumours can recede after initial progression, and the consensus panel agreed that pseudo-progression has not been demonstrated in urothelial cancer. The biology of urothelial cancer and melanoma are distinct, as are responses to ICI therapy. Treatment with ICIs beyond progression in the hope of pseudo-progression may therefore be counterproductive in urothelial cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Follow-up strategies and survivorship**

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

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

**1. Follow-up after radical cystectomy**

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

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

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

The probability of a systemic or a local recurrence is largely related to the final pathological stage of the cystectomy specimen. The highest likelihood of onset of extravesical recurrence is related to the presence of multifocal disease (a common risk factor), tumour in the distal ureter in the case of upper urinary tract tumours, and tumour in the prostatic urethra in men in the case of urethral tumours [68]. In women, where urethrectomy is becoming less common during radical cystectomy, the main risk factors for urethral recurrence are bladder neck and anterior vaginal wall involvement [69].

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

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

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

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

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

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

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

**2. Follow-up after trimodality treatment**

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

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

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

**Level of consensus:** 100% Agree (34 voters)

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

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

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

There is no evidence that any tumour markers are helpful in monitoring recurrence in patients with bladder cancer. LDH is non-specific and can be elevated in a multitude of clinical scenarios independent of a recurrence. CEA is also not specific for bladder cancer and can be positive in follow-up since it can be elevated in smokers. Low vitamin B12 levels have been reported in 17% of patients with bowel diversion [72]. Thus, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured.

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

**Level of consensus:** 100% Agree (34 voters)

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

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

**DISCUSSION**

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

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

Collectively, this project resulted in the development of 71 recommendations that will help to address controversial topics in the management of bladder cancer. Although too many to discuss here in detail, some key conclusions are worthy of highlighting. For example, since variant histologies are increasingly recognised and diagnosed, our recommendations in this area are important and provide additional guidance for the management of this group of patients, although not for all variant histologies. In spite of advice from the FDA and EMA, markers are not yet adequate for clinical decision making, including PD-(L)1 status, (epi)genetic markers and several simple serum measurements. Bladder preservation with chemoradiation is gaining consensus. It is a multidisciplinary decision where several sensitizers can be used. Modern radiotherapy techniques are preferred whereas dose escalation and brachytherapy are not. The role of LND in case of chemoradiation remains unresolved. OMD can still be cured in selected cases, depending on the site and number of metastases and the interval between diagnosis of the primary tumour and metastases. Treatment is a multimodal approach. ICIs are an option in the treatment of metastatic urothelial cancer in unfit, PD-L1-positive patients or after platinum-based chemotherapy. When ICIs are used, pseudo-progression has not been demonstrated in urothelial cancer. When progression occurs on ICI therapy, chemotherapy should be considered rather than sequencing another ICI. Oncological follow-up after cystectomy or bladder preservation should last 5 years, with the highest intensity in the first 2 years since most recurrences occur within 18-24 months. Follow-up should consist of CT of the thorax and abdomen and cystoscopy/cytology in case of bladder preservation, with vitamin B12 levels checked after cystectomy.

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

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

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

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

Taken together, and notwithstanding the limitations described above, we believe our results represent a significant achievement by providing collective expert opinion and guidance on the optimal management strategies to employ in controversial situations until a time where further evidence is available to guide our approach. Together with existing Clinical Practice Guidelines, it is anticipated that the recommendations provided here will help to optimise and standardise the diagnosis, treatment and follow-up of patients with bladder cancer.

**ABBREVIATIONS**

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

**ACKNOWLEDGEMENTS**

The authors would like to thank Tom Arends and Iris Brummelhuis from Radboud University Medical Center, Nijmegen, The Netherlands, and Jorge Huguet from Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain, for their support throughout the whole consensus process. The authors also thank Peter E Clark from Atrium Health, Levine Cancer Institute, Charlotte, NC, USA, for his contribution to the Delphi survey. Angela Corstorphine of Kstorfin Medical Communications Ltd provided medical writing support with the preparation of this manuscript. This support was funded jointly by EAU and ESMO.

**AUTHOR CONTRIBUTIONS**

**Study concept and design:** Marek Babjuk, Joaquim Bellmunt, Harman M Bruins, Theo M De Reijke, Maria De Santis, Silke Gillessen, Alan Horwich, Nick James, Steven Maclennan, Juan Palou, Tom Powles, Maria J Ribal, Shahrokh F Shariat, J Alfred Witjes.

**Acquisition of data:** Marek Babjuk, Joaquim Bellmunt, Harman M Bruins, Theo M De Reijke, Maria De Santis, Silke Gillessen, Alan Horwich, Nick James, Steven Maclennan, Juan Palou, Tom Powles, Maria J Ribal, Shahrokh F Shariat, J Alfred Witjes.

**Analysis and interpretation of data:** Marek Babjuk, Joaquim Bellmunt, Harman M Bruins, Theo M De Reijke, Maria De Santis, Silke Gillessen, Alan Horwich, Nick James, Steven Maclennan, Juan Palou, Tom Powles, Maria J Ribal, Shahrokh F Shariat, J Alfred Witjes.

**Drafting of the manuscript:** Marek Babjuk, Joaquim Bellmunt, Harman M Bruins, Theo M De Reijke, Maria De Santis, Silke Gillessen, Alan Horwich, Nick James, Steven Maclennan, Juan Palou, Tom Powles, Maria J Ribal, Shahrokh F Shariat, Theo Van Der Kwast, J Alfred Witjes, Evanguelos Xylinas.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Steven Maclennan.

**Obtaining funding:** Not applicable (funding provided by EAU and ESMO with no author involvement).

**Administrative, technical or material support:** Steven Maclennan.

**Supervision:** Alan Horwich, Nick James, Steven Maclennan, J Alfred Witjes.

# FUNDING

All costs relating to the consensus conference were covered jointly by the European Association of Urology and the European Society for Medical Oncology. There was no external funding of the event or manuscript production.

**DISCLOSURE**

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

**Neeraj Agarwal** (consulting and honoraria from Pfizer, Novartis, Merck, Genentech, Eisai, Exelixis, Clovis, EMD Serono, BMS, Astra Zeneca, Astellas, Ely Lilly, Bayer, Pharmacyclics; research funding [to institution] from Active Biotech, Astra Zeneca, Bavarian Nordic, BMS, Calithera, Celldex, Eisai, Exelixis, Genentech, GSK, Immunomedics, Janssen, Medivation, Merck, New link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Sanofi, Takeda, Tracon), **Marek Babjuk** (consultant activities for Roche, MSD, Olympus, Ipsen, Ferring), **Aristotelis Bamias** (steering committee member and advisor for Roche; research support, honoraria and advisor for BMS; research support from AstraZeneca), **Joaquim Bellmunt** (lecture fees, advisory boards, institutional research funding/support from Pfizer; lecture fees and advisory boards for Merck, AstraZeneca, BMS, Pierre Fabre; institutional research funding/support from Merck GmbH, Takeda), **Alison Birtle** (advisory boards for Roche, MSD), **Peter Black** (research support from GenomeDx Biosciences; clinical trial support, advisory board and speaker for Roche/Genentech; advisory boards for Merck, BMS, Astra Zeneca, Urogen, Abbvie, Bayer, Lilly, Spectrum, Allergan, Biocancell; advisory boards and speaker for Janssen, Sanofi, Ferring; speaker for BioSyent; grants from iProgen, New B Innovation), **Michel Bolla** (lecture fees and travel support from Astra-Zeneca, Ipsen, Janssen), **Joost Boormans** (personal fees for consultancy work from BMS, Merck, Roche; advisory board fees from Janssen), **Alberto Briganti** (personal fees from Astellas, Janssen, Opko Health, MDx Health, Bayer, Ferring; grant/research support from Sandoz), **Max Burger** (consultant for Medac GmbH; speaker honorarium from Medac GmbH), **Daniel Castellano** (personal fees, speaker and advisory boards for Roche, Pfizer, Janssen, Astellas, MSD, Bayer, Astra Zeneca, Lilly, Novartis, BMS, Ipsen), **Richard Cathomas** (personal fees from Roche, Pfizer, MSD, BMS, Astra Zeneca, Janssen, Astellas, Bayer, Sanofi Aventis, Debiopharm, Novartis, Ipsen), **Arturo Chiti** (personal fees from General Electric, Blue Earth Diagnostics, Sirtex Medical System, Advanced Accewlerator Applications; grant from Sanofi Genzyme), **Ananya Choudhury** (non-financial support from EAU; grant from Cancer Research UK, Prostate Cancer Research UK, Medical Research Council), **Simon Crabb** (grant/research funding and personal fees for advisory work from Clovis Oncology; grant/research funding from Astex Pharmaceuticals; personal fees for advisory work from MSD, Janssen, Roche), **Stephane Culine** (grant and personal fees from Roche; personal fees from Merck, Janssen; grant from Astellas), **Willem de Blok** (grant for development of patient information from Roche, Astellas, Combat Hivec, Hollister, Hoogland Medical, Pfizer), **Maria de Santis** (consultant for Amgen, Astellas, AstraZeneca, Bayer, BMS, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Incyte, Ipsen, Janssen, Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncology, Roche, Sanofi Aventis, Seagen, Shionogi, Synthon, Takeda, Teva, OncoGenex, Sandoz; speaker honoraria from Amgen, Astellas, Astra Zeneca, Bayer, BMS, Ferring, GSK, Ipsen, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncology, Roche, Sanofi Aventis, Synthon, Takeda; trial participation for Amgen, Astellas, Astra Zeneca, Bayer, BMS, Celgene, Dendreon, Eisai Inc., Ferring, GSK, Ipsen, Incyte, Janssen, Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncology, Roche, Sanofi Aventis, SOTIO, EORTC GU Group member, IIT [Technische Universität München], Exelixis/Ipsen, Incyte, Astra Zeneca; grant, fellowship and travel grants from Amgen, Astellas, Astra Zeneca, Bayer, BMS, Celgene, Dendreon, Ferring, GSK, Ipsen, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Roche, Pierre Fabre Oncology, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, Teva/OncoGenex; grants/research support from Pierre Fabre Oncology; reviewing protocols for EORTC GUCA group; reviewing grants and protocols for Cancer Research UK; reviewer for Annals of Oncology, Journal of Clinical Oncology, European Urology, European Urology Focus, Prostate, European Journal of Cancer, Cancer and New England Journal of Medicine), **José Dominguez-Escrig** (trial participation for COMBAT BRS, BTS, Presurgy, Ipsen, STORZ, Arguer, Angiodynamics), **Stefano Fanti** (advisory boards for Bayer, Astellas), **Silke Gillessen** (pending patent application for a method for biomarker WO 2009138392 A1; advisory boards fees from Astellas Pharma, CureVac, Janssen Cilag, Pfizer, Sanofi Aventis Group, Bayer, Dendreon Corporation, Millenium Pharmaceuticals, Orion, Sanofi, Roche; advisory boards fees paid to institution from Bayer, Novartis, Astellas Pharma, Janssen Cilag, Roche, AAA International, BMS, CureVac, Ferring, Sanofi, Orion, Innocrin Pharmaceuticals, Clovis, CellSearch, Menarini; uncompensated advisory boards for Menarini, Astellas Pharma, Bayer, ESSA Pharmaceuticals Corporation, Nectar, ProteoMediX, Sanofi; speaker bureau fees paid to institution from Janssen, Novartis; uncompensated speaker bureau for Amgen, Astellas Pharma, Bayer, Janssen, Sanofi Aventis Group; independent data monitoring committee [IDMC] fees from MaxiVAX SA; independent data monitoring committee fees paid to institution from Active Biotech AB, Janssen Cilag), **Paolo Gontero** (grant from Ipsen; advisory board fees from Arkuer, Cepheid, Ferring), **Shaista Hafeez** (grant from the National Institute for Health Research [NIHR] Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research; non-financial support from Elekta [Elekta AB, Stockholm, Sweden], MSD), **Donna Hansel** (advisory boards for Astra Zeneca, Genentech; consultant for Taris), **Arndt Hartmann** (grants and personal fees from Roche, Janssen, Cepheid; grants from Qiagen, Biontech; personal fees from Astra Zeneca, Diaceutics, BMS, MSD, Abbvie, Boehringer Ingelheim), **Ken Herrmann** (personal fees for speaker bureau and consultancy from Bayer; personal fees for speaker bureau from Sirtex; board member of Sofie Biosciences; other no money for ABX; advisory board fees from Adacap, Curium, Endocyte, Ipsen; grant and personal fees from BTG; advisory board fees and collaboration with Siemens Healthineers; non-financial support and collaboration with GE Healthcare), **Nick James** (trial funding as investigator and chief investigator for studies; trial funding for BC2001 trial from Cancer Research UK and the UK National Cancer Research Network), **Rob Jones** (research grant, honoraria for advisory board, speaker honoraria and trial funding for institution from Roche; travel support, honoraria for advisory board, speaker honoraria and trial funding for institution from MSD; speaker honoraria and trial funding for institution from Merck Serono; honoraria for speaker and advisory board and trial funding for institution from BMS), **Ashish Kamat** (personal fees for advisory board and consulting and research funding from Merck; personal fees for advisory boards and consulting from BMS, Photocure, Elsai, Arquer, MDx Health, Astra Zeneca, Abbott Molecular, US Biotest, Ferring, BioClin; research funding from FKD Industries), **Vincent Khoo** (personal fees for lecture from Astellas; personal fees and non-financial support for lecture, meeting and educational attendance from Bayer; non-financial support for meeting and educational attendance from Janssen), **Anja Lorch** (principal investigator for phase II and III trials with several sponsors; advisory boards for several sponsors; honoraria for lectures and travel fees from Roche, Astra Zeneca, Novartis, Ipsen), **Yohann Loriot** (grant, personal fees and non-financial support from Janssen, MSD; personal fees and non-financial support from Astellas, Roche, Astra Zeneca, BMS, Seattle Genetics; grant and personal fees from Sanofi; personal fees from Clovis, Incyte, Pfizer), **Andrea Necchi** (grant and personal fees from Merck, BMS, Astra Zeneca, Incyte; personal fees from Roche, Bayer, Janssen, BioClin Therapeutics, Clovis Oncology), **Yann Neuzillet** (consultant for Astellas, AstraZeneca, Bouchara-Recordati, BMS, Ipsen, Janssen, Medac, MSD, Roche, Sanofi Pasteur, Sanofi Aventis), **Jorg Oddens** (speaker fees from Janssen, Astellas; advisory board fees from Amgen), **Luis Pacheco-Figueiredo** (personal fees from Lilly Farma, Ldª; non-financial support from Laboratórios Pfizer Portugal, Ldª, Jaba Recordati, S.A., Menarini Portugal), **Joan Palou** (honoraria or consultation fees from Combat BRS, Olympus, Sanofi Pasteur, Cepheid; trial participation for Ipsen, COMBAT BRS, Presurgy, STORZ, Archer), **Helle Pappot** (research grants from MSD, Roche; lecture fees from BMS), **Thomas Powles** (consultant, speaker honoraria, research support/grants from Novartis, Pfizer, Pierre Fabre Oncology, Roche, Sanofi Aventis, Seagen; consultant, speaker honoraria, trial participation and research support/grants from Pfizer, GlaxoSmithKline; speaker honoraria and trial participation for Genentech; grant and personal fees for trial participation from BMS, MSD, Merck, Ipsen, Exelexis, Seattle Genetics, Astra Zeneca), **Mesut Remzi** (advisory board and/or speaker for Astellas, Bayer, Ipsen, Janssen, Pfizer, Baxter, Novartis), **Margitta Retz (**presentations and advisory boards for Astellas, Astra Zeneca, BMS, Ipsen, Janssen-Cilag, MSD, Pfizer, Roche; scientific support from BMS), **Maria J Ribal** (speaker honoraria from Astellas, Janssen, Ipsen, Olympus), **Florian Roghmann** (personal fees from Ipsen, Roche, Novartis), **Jonathan Rosenberg** (clinical trial funding from Astellas; clinical trial funding, personal fees and non-financial support from Roche; clinical trial funding and personal fees from Seattle Genetics, Astra Zeneca, Mirati; personal fees and non-financial support from BMS; personal Fees from Merck, Bayer, Lilly, EMD Serono, Adicet Bio, Inovio, QED Therapeutics, Sensei Biotherapeutics, Chugai Pharma), **Morgan Rouprêt** (grants/research support from GSK, Pfizer, Roche; honoraria or consultation fees from Lilly, GSK, Ipsen, Astellas, Takeda, Sanofi Pasteur, Medac), **Olivier Rouvière** (travel expenses from Philips), **Antti Salminnen** (lecture fee from Roche), **Shomik Sengupta** (speaker honorarium [donated to institutional research fund] from Mundipharma Australia, Ipsen Australia, MSD Australia, Eastern Melbourne Primary health network; consulting honorarium for advisory board [donated to institutional research fund] from Janssen Australia), **Shahrokh Shariat** (honoraria, consulting or advisory role and speaker bureau for Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf Roche, Sanochemia, Sanofi, Urogen; patents: method to determine prognosis after therapy for prostate cancer granted 2002-09-06, methods to determine prognosis after therapy for bladder cancer granted 2003-06-19, prognostic methods for patients with prostatic disease granted 2004-08-05, soluble Fas urinary marker for the detection of bladder transitional cell carcinoma granted 2010-07-20), **Arnulf Stenzl** (advisory boards for BMS, Stebabiotech, Synergo; advisory board/consultant for Ipsen Pharma, Roche, Janssen, Alere; speaker for Janssen, Ipsen Pharma, Sanofi Aventis, CureVac, Astellas; clinical studies for Johnson & Johnson, Roche, Cepheid, Roche, Bayer AG, CureVac, Immatics biotechnologies GmbH, GemeDx Biosciences; research grants from Amgen Inc, Immatics biotechnologies GmbH, Novartis AG, Karl Storz AG), **Bertrand Tombal** (personal fees from Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi), **Thomas Wiegel** (advisory board for Ipsen; speaker honorarium from Ipsen, Hexal; trial participation for Atlas trial; member of steering committee for Janssen), **J Alfred Witjes** (personal fees as advisor for Roche, Merck, BMS), **Richard Zigeuner** (fellowships, travel grants, company grants, research support and speaker honoraria from Bayer Healthcare; fellowships, travel grants, consultant and speaker honoraria from Pfizer; speaker honoraria, fellowships and travel grants from Novartis, Astellas, Takeda; fellowships, travel grants and speaker honoraria from Amgen, GSK; speaker honoraria from Roche, BMS, Esai). All remaining authors declared no conflict of interest.

**TABLES**

**Table 1. Delphi survey participants according to specialty**

|  |  |  |
| --- | --- | --- |
| Specialty | Round 1, N | Round 2, N |
| Urology | 52 | 45 |
| Oncology Medical Oncology Radiation Oncology | 1818 | 1814 |
| Other Nuclear Medicine Pathology Radiology Specialist nurse Clinical Oncology | 38932 | 35732 |
| Total | 113 | 97 |

**Table 2. Consensus levels applied for original Delphi survey**

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

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

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Proposed statements** | **Level of agreement** | **Relevant stakeholder groups** | **Consensus level****(see table 2)** |
| **Urologists (n=45)** | **Oncologists (n=32)** | **Others (n=20)** |
| **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** |
| **1. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with micropapillary variant should be treated with immediate radical cystectomy** | 7 | 11 | 82 | 0 | 44 | 22 | 33 | 5 | 36 | 27 | 36 | 9 | Ur+O | 3 |
| **2. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with plasmacytoid or sarcomatoid or nested variant should be treated with immediate radical cystectomy** | 2 | 7 | 91 | 0 | 22 | 7 | 70 | 5 | 27 | 18 | 55 | 9 | Ur+O | 3 |
| **3. T1 high-grade bladder urothelial carcinoma (established after complete TURBT and/or re-TURBT) with squamous or glandular variant or nested variant should be treated with immediate radical cystectomy** | 16 | 20 | 64 | 0 | 41 | 7 | 52 | 5 | 64 | 18 | 18 | 9 | Ur+O | 3 |
| **4. Muscle-invasive bladder urothelial carcinoma with micropapillary variant should be treated with primary radical cystectomy and lymphadenectomy** | 11 | 11 | 78 | 0 | 30 | 17 | 53 | 2 | 8 | 8 | 83 | 8 | Ur+On+O | 3 |
| **5. Muscle-invasive bladder urothelial carcinoma with plasmacytoid variant should be treated with primary radical cystectomy and lymphadenectomy** | 9 | 9 | 82 | 0 | 29 | 19 | 52 | 1 | 17 | 17 | 67 | 8 | Ur+On+O | 3 |
| **6. Muscle-invasive bladder urothelial carcinoma with squamous or glandular variant should be treated with primary radical cystectomy and lymphadenectomy** | 16 | 4 | 80 | 0 | 20 | 23 | 57 | 2 | 17 | 25 | 58 | 8 | Ur+On+O | 3 |
| 7. Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy  | 2 | 2 | 96 | 0 | 0 | 0 | 100 | 1 | 0 | 0 | 100 | 8 | Ur+On+O | 1 |
| 8. Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy  | 2 | 0 | 98 | 0 | 0 | 16 | 84 | 0 | 8 | 17 | 75 | 8 | Ur+On+O | 1 |
| 9. Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy | 4 | 2 | 93 | 0 | 3 | 9 | 88 | 0 | 8 | 8 | 83 | 8 | Ur+On+O | 1 |
| **10. Radiotherapy (with or without radio-sensitizing chemotherapy) is an effective therapy for patients with muscle-invasive urothelial carcinoma with variant histologies**  | 58 | 40 | 2 | 0 | 13 | 28 | 59 | 0 | 40 | 30 | 30 | 10 | Ur+On | 3 |
| 11. Muscle-invasive small cell neuroendocrine variant of bladder urothelial carcinoma should receive preventive brain irradiation to avoid brain recurrence  | 76 | 20 | 4 | 0 | 74 | 19 | 6 | 1 | 86 | 14 | 0 | 13 | On | 1 |
| 12. Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions | 7 | 14 | 80 | 1 | 6 | 19 | 74 | 1 | 0 | 8 | 92 | 8 | Ur+On+O | 1 |
| 13. Patients with pT3/4 pure adenocarcinoma or squamous carcinoma of the bladder should receive perioperative radiotherapy | 75 | 23 | 2 | 1 | 58 | 13 | 29 | 1 | 14 | 29 | 57 | 13 | Ur+On | 3 |
| 14. Checkpoint inhibitor therapy is effective in metastatic urothelial carcinoma with variant histology  | 5 | 56 | 40 | 2 | 7 | 37 | 56 | 5 | 0 | 75 | 25 | 12 | On | 3 |

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

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

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

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Proposed statements** | **Level of agreement**  | **Relevant stakeholder groups** | **Consensus level****(see Table 2)** |
| **Urologists (n=45)** | **Oncologists (n=32)** | **Others (n=20)** |
| **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** |
| 1. In patients with metastatic disease, genetic profiling should never be done | 87 | 13 | 0 | 0 | 87 | 10 | 3 | 2 | 83 | 8 | 8 | 8 | On | 1 |
| 2. In patients with metastatic disease, genetic profiling should be done before any type of therapy | 34 | 55 | 11 | 1 | 43 | 43 | 13 | 2 | 9 | 64 | 27 | 9 | On | 3 |
| 3. In patients with metastatic disease, genetic profiling should only be done after failing standard therapy | 5 | 34 | 61 | 1 | 50 | 27 | 23 | 2 | 45 | 18 | 36 | 9 | On | 3 |
| 4. Before prescribing neoadjuvant chemotherapy, RNA subtypes always need to be identified | 63 | 37 | 0 | 4 | 87 | 13 | 0 | 2 | 78 | 11 | 11 | 11 | On | 2 |
| 5. Before prescribing neoadjuvant chemotherapy, RNA subtypes only need to be identified in patients with anticipated limited benefit from neoadjuvant chemotherapy | 40 | 38 | 23 | 5 | 76 | 21 | 3 | 3 | 29 | 43 | 29 | 13 | On | 2 |
| **6. Before prescribing checkpoint inhibitor therapy, RNA subtypes always need to be identified** | 44 | 46 | 10 | 4 | 69 | 7 | 24 | 3 | 50 | 25 | 25 | 12 | On | 3 |
| **7. Before prescribing checkpoint inhibitor therapy, RNA subtypes only need to be identified in selected patients** | 21 | 40 | 38 | 3 | 69 | 17 | 14 | 3 | 14 | 29 | 57 | 13 | On | 3 |
| 8. Before prescribing neoadjuvant chemotherapy, DDR or ERCC mutations always need to be identified | 53 | 40 | 8 | 5 | 79 | 21 | 0 | 3 | 38 | 13 | 50 | 12 | On | 2 |
| 9. Before prescribing neoadjuvant chemotherapy, DDR or ERCC mutations only need to be identified in selected patients with anticipated limited benefit from neoadjuvant chemotherapy | 28 | 40 | 33 | 5 | 59 | 24 | 17 | 3 | 13 | 63 | 25 | 12 | On | 3 |
| 10. Before offering subsequent treatment to patients failing first-line (platinum based) treatment and immunotherapy, selected targeted mutations (TSC1, HER2, FGFR3 mutations/translocations) always need to be identified | 43 | 33 | 25 | 5 | 39 | 32 | 29 | 4 | 44 | 22 | 33 | 11 | On | 3 |
| 11. Before offering subsequent treatment to patients failing first-line (platinum based) treatment and immunotherapy, selected targeted mutations (TSC1, HER2, FGFR3mut/translocations) only need to be identified in selected patients | 18 | 25 | 58 | 5 | 41 | 24 | 34 | 3 | 22 | 22 | 56 | 11 | On | 3 |
| 12. Before prescribing a checkpoint inhibitor, TMB always needs to be assessed | 70 | 20 | 10 | 5 | 85 | 11 | 4 | 5 | 78 | 0 | 22 | 11 | On | 1 |
| 13. Before prescribing a checkpoint inhibitor, TMB only needs to be assessed in selected patients  | 17 | 51 | 32 | 4 | 44 | 26 | 30 | 5 | 40 | 30 | 30 | 10 | On | 3 |
| 14. Before selecting patients for checkpoint inhibitor therapy, MSI and DDR mutations always need to be assessed | 67 | 30 | 2 | 2 | 74 | 26 | 0 | 5 | 71 | 0 | 29 | 13 | On | 2 |
| **15. Before radical cystectomy or chemotherapy, the NLR always needs to be assessed** | 78 | 20 | 2 | 0 | 86 | 14 | 0 | 4 | 67 | 11 | 22 | 11 | Ur+On | 2 |
| **16. Before radical cystectomy or chemotherapy, the NLR does NOT need to be assessed** | 13 | 36 | 51 | 0 | 7 | 14 | 79 | 4 | 25 | 13 | 63 | 12 | Ur+On | 3 |
| **17. Before radical cystectomy or chemotherapy, the NLR ratio only needs to be assessed in selected patients**  | 40 | 42 | 18 | 0 | 57 | 36 | 7 | 4 | 86 | 14 | 0 | 13 | Ur+On | 3 |
| **18. In patients with metastatic disease, always measure the LDH and/or serum albumin** | 16 | 24 | 60 | 0 | 24 | 10 | 66 | 3 | 0 | 0 | 100 | 14 | On | 3 |
| **19. In patients with metastatic disease, LDH and/or serum albumin only need to be assessed in selected patients** | 50 | 23 | 27 | 1 | 82 | 14 | 4 | 4 | 100 | 0 | 0 | 14 | On | 2 |
| 20. In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy must be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy) | 0 | 11 | 89 | 1 | 4 | 11 | 85 | 5 | 0 | 0 | 100 | 13 | U+On | 1 |
| 21. In all fit metastatic patients receiving chemotherapy, established prognostic factors for first-line and second-line therapy need NOT be considered when making treatment decisions (Bajorin for first-line and Bellmunt for second-line therapy) | 84 | 11 | 5 | 1 | 81 | 11 | 7 | 5 | 86 | 14 | 0 | 13 | U+On | 1 |

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

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

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

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Proposed statements** | **Level of agreement**  | **Relevant stakeholder groups** | **Consensus level****(see Table 2)** |
| **Urologists (n=45)** | **Oncologists (n=32)** | **Others (n=20)** |
| **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** |
| **1. Patients should be counselled on all treatment options by a neutral healthcare professional (e.g. a nurse specialist)**  | **42** | **24** | **33** | **0** | **19** | **19** | **63** | **0** | **6** | **13** | **81** | **4** | **All** | **3** |
| 2. All patients diagnosed with muscle-invasive bladder cancer should be seen by an Oncologist as well as a Urologist | 23 | 18 | 59 | 1 | 0 | 3 | 97 | 0 | 0 | 0 | 100 | 1 | All | 3 |
| 3. All patients over 75 years of age should be evaluated preoperatively by a geriatrician | 13 | 24 | 62 | 0 | 16 | 16 | 69 | 0 | 11 | 11 | 78 | 2 | All | 3 |
| 4. An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma in situ | 4 | 7 | 89 | 0 | 3 | 13 | 84 | 1 | 7 | 7 | 86 | 6 | Ur+On | 1 |
| 5. An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis | 0 | 7 | 93 | 0 | 10 | 6 | 84 | 1 | 7 | 7 | 87 | 5 | Ur+On | 1 |
| 6. When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking) | 0 | 7 | 93 | 0 | 9 | 6 | 84 | 0 | 6 | 6 | 88 | 4 | Ur+On | 1 |
| 7. In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiotherapy can be offered accepting that this may be palliative rather than curative in outcome  | 9 | 20 | 71 | 0 | 3 | 3 | 94 | 0 | 0 | 6 | 94 | 4 | Ur+On | 1 |
| 8. The preferred radiotherapeutic schedule is radiotherapy alone (single block) | 100 | 0 | 0 | 3 | 93 | 0 | 7 | 2 | 90 | 0 | 10 | 10 | On | 1 |
| 9. The preferred radiotherapeutic schedule is radiotherapy given concurrently with BCON  | 87 | 11 | 3 | 7 | 60 | 23 | 17 | 2 | 71 | 29 | 0 | 13 | On | 3 |
| 10. The preferred radiotherapeutic schedule is radiotherapy alone, split course with interval cystoscopy and immediate cystectomy for non-responders | 58 | 19 | 23 | 2 | 74 | 13 | 13 | 1 | 50 | 38 | 13 | 12 | On | 2 |
| **11. The preferred radiosensitiser is 5-fluorouracil + mitomycin C** | 26 | 39 | 34 | 7 | 19 | 13 | 69 | 0 | 17 | 17 | 67 | 14 | On | 3 |
| **12. The preferred radiosensitiser is cisplatin** | 5 | 13 | 82 | 6 | 10 | 13 | 77 | 1 | 33 | 17 | 50 | 14 | On | 2 |
| **13. The preferred radiosensitiser is gemcitabine** | 42 | 37 | 21 | 7 | 42 | 26 | 32 | 1 | 0 | 50 | 50 | 14 | On | 3 |
| **14. The preferred radiosensitiser is i.v. carbogen nicotinamide** | 67 | 31 | 3 | 9 | 58 | 26 | 16 | 1 | 50 | 50 | 0 | 14 | On | 3 |
| **15. Brachytherapy has a role in the treatment of muscle-invasive bladder cancer** | 87 | 4 | 9 | 0 | 59 | 24 | 17 | 3 | 44 | 22 | 33 | 11 | Ur+On | 3 |
| **16. PLND should be an integral part of bladder preservation strategies in patients with muscle-invasive bladder cancer**  | 38 | 16 | 47 | 0 | 69 | 6 | 25 | 0 | 0 | 17 | 83 | 8 | Ur+On | 3 |
| 17. When adjuvant chemotherapy is offered, patients should be selected based on the result of PLND (if done) | 11 | 4 | 84 | 0 | 13 | 16 | 71 | 1 | 0 | 17 | 83 | 8 | Ur+On | 1 |
| 18. When adjuvant chemotherapy is offered, patients should be selected based on response to trimodality therapy | 35 | 26 | 40 | 2 | 33 | 37 | 30 | 2 | 33 | 44 | 22 | 11 | Ur+On | 3 |
| 19. When adjuvant chemotherapy is offered, patients should be selected based on pT3 or 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 | All | 3 |

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

**Table 8. Consensus meeting statements regarding bladder preservation strategies**

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

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Proposed statements** | **Level of agreement**  | **Relevant stakeholder groups** | **Consensus level****(see Table 2)** |
| **Urologists (n=45)** | **Oncologists (n=32)** | **Others (n=20)** |
| **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** |
| **1. In patients with one metastatic site, cure is still possible** | 18 | 13 | 69 | 0 | 13 | 19 | 69 | 0 | 21 | 0 | 79 | 6 | Ur+On | 3 |
| 2. In patients with two metastatic sites, cure is still possible | 40 | 18 | 42 | 0 | 47 | 22 | 31 | 0 | 46 | 8 | 46 | 7 | Ur+On | 3 |
| 3. In patients with more than two metastatic sites, cure is still possible | 91 | 4 | 4 | 0 | 88 | 6 | 6 | 0 | 86 | 7 | 7 | 6 | Ur+On | 1 |
| 4. Liver is a favourable OMD site for curative therapy  | 95 | 2 | 2 | 1 | 81 | 16 | 3 | 1 | 93 | 7 | 0 | 6 | Ur+On | 1 |
| 5. Bone is a favourable OMD site for curative therapy | 93 | 2 | 5 | 1 | 77 | 16 | 6 | 1 | 87 | 0 | 13 | 5 | Ur+On | 1 |
| 6. Lung is a favourable OMD site for curative therapy | 36 | 9 | 56 | 0 | 55 | 6 | 39 | 1 | 43 | 21 | 36 | 6 | Ur+On | 3 |
| 7. Extrapelvic lymph node is a favourable OMD site for curative therapy  | 22 | 13 | 64 | 0 | 19 | 13 | 68 | 1 | 29 | 14 | 57 | 6 | Ur+On | 3 |
| 8. OMD is more favourable prognostically as a relapse syndrome (metachronous disease) than as a presentation syndrome (synchronous disease)  | 16 | 36 | 48 | 1 | 6 | 31 | 63 | 0 | 18 | 45 | 36 | 9 | Ur+On | 3 |
| 9. After staging reveals OMD, curative therapy should be deferred pending confirmation restaging 6 weeks later using the same staging method as the initial staging  | 36 | 44 | 20 | 0 | 44 | 31 | 25 | 0 | 40 | 60 | 0 | 10 | Ur+On | 3 |
| **10. It is important to include PET-CT scanning in OMD staging**  | 16 | 13 | 71 | 0 | 22 | 16 | 63 | 0 | 6 | 6 | 88 | 3 | Ur+On+O | 3 |
| 11. Radiotherapy to the whole bone should follow resection of a bone metastasis | 33 | 40 | 26 | 3 | 16 | 23 | 61 | 1 | 60 | 40 | 0 | 10 | On | 3 |
| 12. Radiotherapy to the whole brain should follow resection of a brain metastasis | 44 | 34 | 22 | 4 | 53 | 13 | 34 | 0 | 56 | 11 | 33 | 11 | On | 3 |
| **13. Radical treatment of oligometastases should be accompanied by neoadjuvant chemotherapy only** | 33 | 28 | 40 | 2 | 26 | 42 | 32 | 1 | 43 | 14 | 43 | 13 | Ur+On | 3 |
| **14. Radical treatment of oligometastases should be accompanied by adjuvant chemotherapy only** | 57 | 38 | 5 | 3 | 58 | 35 | 6 | 1 | 43 | 29 | 29 | 13 | Ur+On | 3 |
| **15. Radical treatment of oligometastases should be accompanied by no chemotherapy at all** | 100 | 0 | 0 | 2 | 65 | 26 | 10 | 1 | 63 | 13 | 25 | 12 | Ur+On | 3 |
| 16. Curative treatment of OMD is especially indicated for pure squamous cell cancers  | 30 | 58 | 13 | 5 | 37 | 47 | 17 | 2 | 0 | 50 | 50 | 12 | Ur+On | 3 |
| 17. In case of OMD at first presentation, the primary site must be treated first before treating distant metastatic sites | 35 | 28 | 37 | 2 | 27 | 50 | 23 | 2 | 17 | 42 | 42 | 8 | Ur+On | 3 |
| 18. In metachronous OMD, time to relapse is an important prognostic indicator  | 2 | 4 | 93 | 0 | 0 | 3 | 97 | 0 | 0 | 8 | 92 | 7 | Ur+On | 1 |
| 19. Initial local treatment for OMD should be radical surgery rather than radiotherapy, when possible  | 24 | 38 | 38 | 0 | 42 | 42 | 16 | 1 | 30 | 40 | 30 | 10 | Ur+On | 3 |
| 20. In case patients with visceral OMD are offered a radical cystectomy, a standard LND should be offered (pelvic lymph nodes up to crossing of ureter with common iliac vessels) | 7 | 20 | 73 | 0 | 39 | 32 | 29 | 4 | 10 | 30 | 60 | 10 | Ur+On | 3 |
| 21. In case patients with visceral oligometastatic disease are offered a radical cystectomy, an extended LND should be offered (up to inferior mesenteric artery) | 38 | 27 | 36 | 0 | 57 | 36 | 7 | 4 | 30 | 40 | 30 | 10 | Ur | 3 |

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

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

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

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Proposed statements** | **Level of agreement**  | **Relevant stakeholder groups** | **Consensus level****(see Table 2)** |
| **Urologists (n=45)** | **Oncologists (n=32)** | **Others (n=20)** |
| **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** |
| 1. **In patients with advanced/metastatic urothelial cancer who are ineligible for cisplatin-based therapy but with high PD-L1 expression (as per approved drug specific methodology), both treatment with an ICI and chemotherapy can be offered**  | 7 | 4 | 89 | 0 | 4 | 0 | 96 | 4 | 0 | 20 | 80 | 10 | On | 1 |
| 2. Since no data exists for cisplatin ineligible PD-L1 positive patients in order to differentiate between different ICIs (atezolizumab and pembrolizumab), either agent can be administered  | 2 | 7 | 91 | 0 | 0 | 0 | 100 | 5 | 0 | 0 | 100 | 11 | On | 1 |
| 3. **Sequencing of ICIs and chemotherapy maximises outcomes for patients with cisplatin ineligible advanced/metastatic urothelial cancer**  | 2 | 50 | 48 | 3 | 7 | 36 | 57 | 4 | 0 | 45 | 55 | 9 | Ur+On | 3 |
| 4. **Sequencing of different ICIs is indicated in cisplatin ineligible advanced/metastatic urothelial cancer** | 34 | 51 | 15 | 4 | 81 | 19 | 0 | 5 | 0 | 71 | 29 | 13 | On | 2 |
| 5. Treatment with ICIs past radiological progression in patients with cisplatin ineligible advanced/metastatic urothelial cancer is 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 |
| 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 muscle-invasive bladder cancer  | 16 | 16 | 69 | 0 | 3 | 7 | 90 | 2 | 14 | 0 | 86 | 13 | Ur+On | 3 |
| 14. ICIs can be considered in patients with locally advanced (T4b), but potentially operable, bladder cancer who are ineligible for cisplatin based neoadjuvant therapy  | 14 | 23 | 64 | 1 | 33 | 30 | 37 | 2 | 29 | 0 | 71 | 13 | Ur+On | 3 |
| 15. ICI therapy should not be recommended in patients with non-muscle-invasive bladder cancer | 16 | 18 | 67 | 0 | 10 | 10 | 80 | 2 | 20 | 0 | 80 | 15 | Ur+On | 3 |
| 16. **Each ICI has a different PD-L1 biomarker to define positivity. The biomarkers define distinct populations and therefore are not interchangeable in clinical practice**  | 28 | 23 | 49 | 2 | 18 | 32 | 50 | 4 | 57 | 29 | 14 | 13 | On | 3 |
| 17. In patients with advanced/metastatic urothelial cancer, it is not recommended to use combinations of ICIs, or a combination of ICIs with other anti-cancer treatments prior to the reporting of randomised trials  | 2 | 7 | 91 | 1 | 3 | 7 | 90 | 2 | 17 | 17 | 67 | 14 | On | 2 |
| 18. Once initiated, ICI therapy should be continued until progression of disease in patients with advanced/metastatic urothelial cancer | 2 | 4 | 93 | 0 | 7 | 3 | 90 | 3 | 0 | 25 | 75 | 12 | On | 1 |
| **19. Pseudo-progression with ICIs is rare in patients with advanced/metastatic urothelial cancer. Treatment past radiological progression is of unproven benefit in advanced/metastatic urothelial cancer but should be considered especially in platinum-refractory disease where other treatment options are lacking**  | 5 | 21 | 74 | 2 | 0 | 21 | 79 | 3 | 0 | 33 | 67 | 14 | On | 2 |
| 20. ICIs are cost effective in licenced indications in advanced/metastatic urothelial cancer  | 28 | 44 | 28 | 6 | 8 | 32 | 60 | 7 | 40 | 40 | 20 | 15 | On | 3 |

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

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

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

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Proposed statements** | **Level of agreement**  | **Relevant stakeholder groups** | **Consensus level****(see Table 2)** |
| **Urologists (n=45)** | **Oncologists (n=32)** | **Others (n=20)** |
| **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** | **D (%)** | **E (%)** | **A (%)** | **U (n)** |
| 1. After radical cystectomy with curative intent, no regular follow-up is needed  | 100 | 0 | 0 | 0 | 100 | 0 | 0 | 0 | 100 | 0 | 0 | 4 | Ur | 1 |
| 2. To detect relapse after radical cystectomy with curative intent, patients should be followed up every 3-4 months for 2 years, every 6 months up to 5 years and then annually  | 16 | 4 | 80 | 0 | 3 | 9 | 88 | 0 | 0 | 0 | 100 | 5 | Ur | 3 |
| 3. To detect relapse after radical cystectomy with curative intent, patients should be followed up every 6 months for 5 years and then annually | 33 | 24 | 42 | 0 | 53 | 31 | 16 | 0 | 53 | 33 | 13 | 5 | Ur | 3 |
| **4. After radical cystectomy with curative intent, regular follow-up in the majority of patients should stop after 5 years** | 80 | 16 | 4 | 0 | 42 | 16 | 42 | 1 | 60 | 7 | 33 | 5 | Ur | 2 |
| **5. After radical cystectomy, patients should be followed up with a CT scan of the thorax/abdomen alone** | 67 | 7 | 27 | 0 | 55 | 0 | 45 | 1 | 75 | 0 | 25 | 4 | Ur+O | 3 |
| 6. After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended | 0 | 4 | 96 | 0 | 0 | 13 | 87 | 1 | 0 | 7 | 93 | 5 | Ur | 1 |
| **7. After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended 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 |
| 12. After trimodality treatment with curative intent, NO follow-up imaging to assess distant recurrence or recurrence outside the bladder is needed | 100 | 0 | 0 | 0 | 100 | 0 | 0 | 0 | 94 | 0 | 6 | 3 | Ur+On+O | 1 |
| 13. After trimodality treatment with curative intent, assessment of the urothelium to detect recurrence is recommended every 6 months in the majority of patients | 2 | 5 | 93 | 1 | 9 | 6 | 84 | 0 | 0 | 6 | 94 | 2 | Ur | 1 |
| 14. After trimodality treatment with curative intent, in addition to a CT scan, NO other investigations of the bladder are recommended | 100 | 0 | 0 | 0 | 100 | 0 | 0 | 0 | 100 | 0 | 0 | 2 | Ur | 1 |
| 15. In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, NO regular follow-up is needed. Imaging studies may be done according to signs/symptoms | 91 | 7 | 2 | 0 | 97 | 0 | 3 | 2 | 88 | 13 | 0 | 4 | Ur+On | 1 |
| 16. In the majority of patients with a long-lasting complete response after chemotherapy for metastatic urothelial cancer, regular follow-up should be stopped after 3 years | 91 | 7 | 2 | 0 | 100 | 0 | 0 | 2 | 81 | 0 | 19 | 4 | Ur+On | 2 |
| 17. No routine assessment of the urothelium is required in patients with a partial or complete response after chemotherapy for metastatic urothelial cancer  | 80 | 9 | 11 | 0 | 77 | 10 | 13 | 2 | 81 | 0 | 19 | 4 | Ur+On | 2 |
| **18. When following up patients with urothelial cancer, LDH and CEA do NOT need to be assessed** | 11 | 31 | 58 | 0 | 19 | 13 | 68 | 1 | 33 | 33 | 33 | 11 | Ur+On | 3 |
| 19. In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value | 4 | 4 | 91 | 0 | 4 | 13 | 83 | 9 | 0 | 25 | 75 | 12 | Ur | 1 |
| **20. In patients treated with radical cystectomy with curative intent and who have a neobladder, management of vitamin B12 levels does not require any measurements** | 77 | 2 | 20 | 1 | 59 | 27 | 14 | 10 | 63 | 38 | 0 | 12 | Ur | 3 |

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

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

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

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

**SUPPLEMENTARY TABLES**

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

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

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

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

**REFERENCES**

1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

2. Antoni S, Ferlay J, Soerjomataram I et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol 2017; 71: 96-108.

3. Bellmunt J, Orsola A, Leow JJ et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3: iii40-48.

4. Babjuk M, Burger M, Compérat E et al. EAU Guidelines on Non-muscle-invasive Bladder Cancer. 2018; <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/> (8 February 2018, date last accessed).

5. Witjes JA, Bruins M, Compérat E et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. 2018; <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/> (7 February 2019, date last accessed).

6. Network NCC. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. 2018; <https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf> (8 November 2018, date last accessed).

7. Vetterlein MW, Wankowicz SAM, Seisen T et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer 2017; 123: 4346-4355.

8. Robertson AG, Kim J, Al-Ahmadie H et al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell 2017; 171: 540-556.e525.

9. Choi W, Porten S, Kim S et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 2014; 25: 152-165.

10. Lindgren D, Frigyesi A, Gudjonsson S et al. Combined gene expression and genomic profiling define two intrinsic molecular subtypes of urothelial carcinoma and gene signatures for molecular grading and outcome. Cancer Res 2010; 70: 3463-3472.

11. Damrauer JS, Hoadley KA, Chism DD et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. Proc Natl Acad Sci U S A 2014; 111: 3110-3115.

12. Ingersoll MA, Li X, Inman BA et al. Immunology, Immunotherapy, and Translating Basic Science into the Clinic for Bladder Cancer. Bladder Cancer 2018; 4: 429-440.

13. González Del Alba A, De Velasco G, Lainez N et al. SEOM clinical guideline for treatment of muscle-invasive and metastatic urothelial bladder cancer (2018). Clin Transl Oncol 2019; 21: 64-74.

14. Balar AV, Castellano D, O'Donnell PH et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017; 18: 1483-1492.

15. Balar AV, Galsky MD, Rosenberg JE et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017; 389: 67-76.

16. Bellmunt J, de Wit R, Vaughn DJ et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017; 376: 1015-1026.

17. Comet Initiative DelphiManager. 2011-2015; <http://www.comet-initiative.org/delphimanager/> (1 February 2019, date last accessed).

18. Humphrey PA, Moch H, Cubilla AL et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol 2016; 70: 106-119.

19. Compérat E, Roupret M, Yaxley J et al. Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. Pathology 2010; 42: 650-654.

20. Monn MF, Kaimakliotis HZ, Pedrosa JA et al. Contemporary bladder cancer: variant histology may be a significant driver of disease. Urol Oncol 2015; 33: 18.e15-18.e20.

21. Willis DL, Fernandez MI, Dickstein RJ et al. Clinical outcomes of cT1 micropapillary bladder cancer. J Urol 2015; 193: 1129-1134.

22. Weizer AZ, Wasco MJ, Wang R et al. Multiple adverse histological features increase the odds of under staging T1 bladder cancer. J Urol 2009; 182: 59-65; discussion 65.

23. Black PC, Brown GA, Dinney CP. The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol 2009; 27: 3-7.

24. Honma I, Masumori N, Sato E et al. Local recurrence after radical cystectomy for invasive bladder cancer: an analysis of predictive factors. Urology 2004; 64: 744-748.

25. Zaghloul MS, Awwad HK, Akoush HH et al. Postoperative radiotherapy of carcinoma in bilharzial bladder: improved disease free survival through improving local control. Int J Radiat Oncol Biol Phys 1992; 23: 511-517.

26. Lewis GD, Haque W, Verma V et al. The Role of Adjuvant Radiation Therapy in Locally Advanced Bladder Cancer. Bladder Cancer 2018; 4: 205-213.

27. Marzouka NA, Eriksson P, Rovira C et al. A validation and extended description of the Lund taxonomy for urothelial carcinoma using the TCGA cohort. Sci Rep 2018; 8: 3737.

28. Seiler R, Ashab HAD, Erho N et al. Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy. Eur Urol 2017; 72: 544-554.

29. Rosenberg JE, Hoffman-Censits J, Powles T et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016; 387: 1909-1920.

30. Mariathasan S, Turley SJ, Nickles D et al. TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature 2018; 554: 544-548.

31. Rouprêt M, Babjuk M, Burger M et al. In EAU Annual Congress Copenhagen EAU Guidelines Office, Arnhem, The Netherlands. <http://uroweb.org/guidelines/compilations-of-all-guidelines/> 2018. ISBN 978-94-92671-01-1.

32. Wu S, Zhao X, Wang Y et al. Pretreatment Neutrophil-Lymphocyte Ratio as a Predictor in Bladder Cancer and Metastatic or Unresectable Urothelial Carcinoma Patients: a Pooled Analysis of Comparative Studies. Cell Physiol Biochem 2018; 46: 1352-1364.

33. Ojerholm E, Smith A, Hwang WT et al. Neutrophil-to-lymphocyte ratio as a bladder cancer biomarker: Assessing prognostic and predictive value in SWOG 8710. Cancer 2017; 123: 794-801.

34. Bajorin DF, Dodd PM, Mazumdar M et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999; 17: 3173-3181.

35. Bellmunt J, Choueiri TK, Fougeray R et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010; 28: 1850-1855.

36. Sonpavde G, Pond GR, Rosenberg JE et al. Improved 5-Factor Prognostic Classification of Patients Receiving Salvage Systemic Therapy for Advanced Urothelial Carcinoma. J Urol 2016; 195: 277-282.

37. Zhang Y, Xu T, Wang Y et al. Prognostic Role of Lactate Dehydrogenase Expression in Urologic Cancers: A Systematic Review and Meta-Analysis. Oncol Res Treat 2016; 39: 592-604.

38. Hussain T, Chang HY, Veenstra CM, Pollack CE. Collaboration Between Surgeons and Medical Oncologists and Outcomes for Patients With Stage III Colon Cancer. J Oncol Pract 2015; 11: e388-397.

39. Cook O, McIntyre M, Recoche K. Exploration of the role of specialist nurses in the care of women with gynaecological cancer: a systematic review. J Clin Nurs 2015; 24: 683-695.

40. Choudhury A, Swindell R, Logue JP et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol 2011; 29: 733-738.

41. Coppin CM, Gospodarowicz MK, James K et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1996; 14: 2901-2907.

42. Hoskin PJ, Rojas AM, Bentzen SM, Saunders MI. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. J Clin Oncol 2010; 28: 4912-4918.

43. James ND, Hussain SA, Hall E et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012; 366: 1477-1488.

44. Koga F, Kihara K, Fujii Y et al. Favourable outcomes of patients with clinical stage T3N0M0 bladder cancer treated with induction low-dose chemo-radiotherapy plus partial or radical cystectomy vs immediate radical cystectomy: a single-institutional retrospective comparative study. BJU Int 2009; 104: 189-194.

45. Tunio MA, Hashmi A, Qayyum A et al. Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: single-institution experience. Int J Radiat Oncol Biol Phys 2012; 82: e457-462.

46. Collins SD, Leech MM. A review of plan library approaches in adaptive radiotherapy of bladder cancer. Acta Oncol 2018; 57: 566-573.

47. Bos MK, Marmolejo RO, Rasch CR, Pieters BR. Bladder preservation with brachytherapy compared to cystectomy for T1-T3 muscle-invasive bladder cancer: a systematic review. J Contemp Brachytherapy 2014; 6: 191-199.

48. Whalley D, Caine H, McCloud P et al. Promising results with image guided intensity modulated radiotherapy for muscle invasive bladder cancer. Radiat Oncol 2015; 10: 205.

49. Weichselbaum RR. The 46th David A. Karnofsky Memorial Award Lecture: Oligometastasis-From Conception to Treatment. J Clin Oncol 2018; doi: 10.1200/jco.18.00847: Jco1800847.

50. Kim T, Ahn JH, You D et al. Pulmonary Metastasectomy Could Prolong Overall Survival in Select Cases of Metastatic Urinary Tract Cancer. Clin Genitourin Cancer 2015; 13: e297-e304.

51. Pastorino U, Buyse M, Friedel G et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997; 113: 37-49.

52. Tanvetyanon T, Robinson LA, Schell MJ et al. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. J Clin Oncol 2008; 26: 1142-1147.

53. von der Maase H, Sengelov L, Roberts JT et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005; 23: 4602-4608.

54. Galsky MD, Moshier E, Krege S et al. Nomogram for predicting survival in patients with unresectable and/or metastatic urothelial cancer who are treated with cisplatin-based chemotherapy. Cancer 2013; 119: 3012-3019.

55. Lehmann J, Suttmann H, Albers P et al. Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). Eur Urol 2009; 55: 1293-1299.

56. Abe T, Shinohara N, Harabayashi T et al. Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. Eur Urol 2007; 52: 1106-1113.

57. Abufaraj M, Dalbagni G, Daneshmand S et al. The Role of Surgery in Metastatic Bladder Cancer: A Systematic Review. Eur Urol 2018; 73: 543-557.

58. Kibel AS, Dehdashti F, Katz MD et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol 2009; 27: 4314-4320.

59. Lu YY, Chen JH, Liang JA et al. Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. Eur J Radiol 2012; 81: 2411-2416.

60. Bagheri MH, Ahlman MA, Lindenberg L et al. Advances in medical imaging for the diagnosis and management of common genitourinary cancers. Urol Oncol 2017; 35: 473-491.

61. Leow JJ, Martin-Doyle W, Rajagopal PS et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014; 66: 42-54.

62. Nishino M, Giobbie-Hurder A, Manos MP et al. Immune-Related Tumor Response Dynamics in Melanoma Patients Treated with Pembrolizumab: Identifying Markers for Clinical Outcome and Treatment Decisions. Clin Cancer Res 2017; 23: 4671-4679.

63. Powles T, Durán I, van der Heijden MS et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018; 391: 748-757.

64. Powles T, Smith K, Stenzl A, Bedke J. Immune Checkpoint Inhibition in Metastatic Urothelial Cancer. Eur Urol 2017; 72: 477-481.

65. Szabados B, van Dijk N, Tang YZ et al. Response Rate to Chemotherapy After Immune Checkpoint Inhibition in Metastatic Urothelial Cancer. Eur Urol 2018; 73: 149-152.

66. Giannarini G, Kessler TM, Thoeny HC et al. Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? Eur Urol 2010; 58: 486-494.

67. Volkmer BG, Kuefer R, Bartsch GC, Jr. et al. Oncological followup after radical cystectomy for bladder cancer-is there any benefit? J Urol 2009; 181: 1587-1593; discussion 1593.

68. Huguet J. Follow-up after radical cystectomy based on patterns of tumour recurrence and its risk factors. Actas Urol Esp 2013; 37: 376-382.

69. Chan Y, Fisher P, Tilki D, Evans CP. Urethral recurrence after cystectomy: current preventative measures, diagnosis and management. BJU Int 2016; 117: 563-569.

70. Pieras E, Palou J, Salvador J et al. Management and prognosis of transitional cell carcinoma superficial recurrence in muscle-invasive bladder cancer after bladder preservation. Eur Urol 2003; 44: 222-225; discussoion 225.

71. Giacalone NJ, Shipley WU, Clayman RH et al. Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience. Eur Urol 2017; 71: 952-960.

72. Nieuwenhuijzen JA, de Vries RR, Bex A et al. Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. Eur Urol 2008; 53: 834-842; discussion 842-834.