Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Oncology 32 (2020) 347–353

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Guidelines

Clinical Guidance for the Management of Patients with Urothelial Cancers During the COVID-19 Pandemic – Rapid Review

K. Patel [*†], A. Choudhury [‡†], P. Hoskin [§‡], M. Varughese [¶], N. James [||**], R. Huddart [||**], A. Birtle [*††]

[*] The Rosemere Cancer Centre, Preston, Lancashire Teaching Hospitals, NHS Foundation, UK
[†] The Christie NHS Foundation Trust, Manchester, UK
[‡] Division of Cancer Sciences, University of Manchester, UK
[§] Mount Vernon Cancer Centre, Northwood, UK
[¶] The Beacon Centre, Musgrove Park Hospital, Taunton and Somerset NHS Foundation Trust, Taunton, UK
[||] Institute of Cancer Research, London, UK
[**] Royal Marsden Hospital, London, UK
[††] Division of Cancer Science, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK

Received 9 April 2020; accepted 16 April 2020

Abstract

The current COVID-19 pandemic presents a substantial obstacle to cancer patient care. Data from China as well as risk models suppose that cancer patients, particularly those on active, immunosuppressive therapies are at higher risks of severe infection from the illness. In addition, staff illness and restructuring of services to deal with the crisis will inevitably place treatment capacities under significant strain. These guidelines aim to expand on those provided by NHS England regarding cancer care during the coronavirus pandemic by examining the known literature and provide guidance in managing patients with urothelial and rarer urinary tract cancers. In particular, they address the estimated risk and benefits of standard treatments and consider the alternatives in the current situation. As a result, it is recommended that this guidance will help form a framework for shared decision making with patients. Moreover, they do not advise a one-size-fits-all approach but recommend continual assessment of the situation with discussion within and between centres.

Keywords: Chemotherapy; COVID-19; Guidelines; Radiotherapy; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Urothelial cancer

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly virulent, establishing the COVID-19 pandemic within three months of the first case [1]. With the caveat of a small and heterogenous study population [2,3], data from China infers that patients with cancer have higher incidence and severity of the illness [4,5]. Those undergoing chemotherapy or surgery may have a further risk of severe events such as invasive ventilation and death [4]. Notably, risk models propose that most oncology patients possess an at least five percent mortality risk if infected with COVID-19 – equal to or greater than the benefits of many adjuvant regimens [6]. Service disruption including reduced access to theatres as well as high dependency care [7] is also expected to heavily impact cancer care.

NHS England guidelines written in response to the extreme threat posed by COVID-19 advise the categorisation of cancer treatments according to the ***intent and risk-benefit ratio*** (Tables 1–3). They also advocate considering less resource-intensive regimens, accounting for other patient risk factors such as age, cardiac and chest disease, offering treatment-breaks where appropriate, using growth factors to reduce neutropaenia and prescribing hypofractionated radiotherapy regimens where possible [8].

Author for correspondence: Alison Birtle, The Rosemere Cancer Centre, Preston, Lancashire Teaching Hospitals, NHS Foundation, UK.
E-mail address: alison.birtle@lthtr.nhs.uk (A. Birtle).

https://doi.org/10.1016/j.clon.2020.04.005
0936-6555/

Table 1
Table of priority groups 1–6 for systemic anti-cancer therapy if services are disrupted during COVID-19 pandemic; adapted from NHS England Clinical guide for the management of non-coronavirus patients requiring acute treatment: Cancer

Systemic anti-cancer treatments - Categorisation of patients
Priority level 1
• Curative therapy with a high (>50%) chance of success
• Adjuvant (or neo) therapy which adds at least 50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
Priority level 2
• Curative therapy with an intermediate (20–50%) chance of success
• Adjuvant (or neo) therapy which adds 20–50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
Priority level 3
• Curative therapy of a low chance (10–20%) of success
• Adjuvant (or neo) therapy which adds 10–20% chance of cure to surgery or radiotherapy alone or treatment given at relapse
• Non-curative therapy with a high (>50%) chance of >1 year life extension
Priority level 4
• Curative therapy with a very low (0–10%) chance of success
• Adjuvant (or neo) therapy which adds a less than 10 chance of cure to surgery or radiotherapy alone or treatment given at relapse
• Non-curative therapy with an intermediate (15–50%) chance of >1 year life extension
Priority level 5
• Non-curative therapy with a high (>50%) chance of palliation/temporary tumour control but <1 year life extension
Priority level 6
• Non-curative therapy with an intermediate (15–50%) chance of palliation or temporary tumour control and <1 year life extension

Table 2
Table of priority groups 1–5 for radiotherapy if services are disrupted during COVID-19 pandemic; adapted from NHS England Clinical guide for the management of non-coronavirus patients requiring acute treatment: Cancer

Radiation therapy - Categorisation of patients
Priority level 1
• Patients with category 1 (rapidly proliferating) tumours currently being treated with radical (chemo)radiotherapy with curative intent where there is little or no scope for compensation of gaps
• Patients with category 1 tumours in whom combined External Beam Radiotherapy (EBRT) and subsequent brachytherapy is the management plan and the EBRT is already underway
• Patients with category 1 tumours who have not yet started and in whom clinical need determines that treatment should start in line with current cancer waiting times
Priority level 2
• Urgent palliative radiotherapy in patients with malignant spinal cord compression who have useful salvageable neurological function
Priority level 3
• Radical radiotherapy for Category 2 (less aggressive) tumours where radiotherapy is the first definitive treatment.
• Post-operative radiotherapy where there is known residual disease following surgery in tumours with aggressive biology
Priority level 4
• Palliative radiotherapy where alleviation of symptoms would reduce the burden on other healthcare services, such as haemoptysis
Priority level 5
• Adjuvant radiotherapy where there has been compete resection of disease and there is a <20% risk of recurrence at 10 years, for example most ER positive breast cancer in patients receiving endocrine therapy
• Radical radiotherapy for prostate cancer in patients receiving neo-adjuvant hormone therapy

The aim of this review is to place these guidelines into clinical context for patients with urothelial cancers during this unprecedented time. As per Gillessen and Powles, who have submitted guidance in European Urology for systemic treatment [9], these recommendations reflect the published literature but do not endorse a one-size-fits-all approach. Over the coming weeks, each department will have unique stresses and resource issues where decision-making will require a level of pragmatism and fluidity out with these guidelines.

Table 3
Table of priority groups 1–3 for radiotherapy if services are disrupted during COVID-19 pandemic; adapted from NHS England Clinical guide for the management of non-coronavirus patients requiring acute treatment: Cancer

Surgical patients - Categorisation of patients
Priority level 1a • Emergency: operation needed within 24 hours to save life
Priority level 1b • Urgent: operation needed within 72 hours
Examples Urgent/emergency surgery for life threatening conditions such as obstruction, bleeding and regional and/or localised infection/permanent injury/clinical harm from progression of conditions such as spinal cord compression
Priority level 2 • Elective surgery with the expectation of cure, prioritised according to: o Surgery within 4 weeks to save life or before progression of disease beyond operability depending on: • urgency of symptoms • complications such as local compressive symptoms • biological priority (expected growth rate) of individual cancers
Local complications may be temporarily controlled, for example with stents if surgery is deferred and/or interventional radiology
Priority level 3 • Elective surgery can be delayed for 10–12 weeks with no predicted negative outcome

Management of Urothelial Cancer

Muscle-invasive bladder cancer, T2 – T4a, is treated via radical cystectomy or radiotherapy in conjunction with radiosensitisation [10,11]. For locally advanced and metastatic disease, first line immunotherapy can be offered to those PDL-1 positive where cisplatin is unsuitable [12]. Second line options include taxane-based regimens [13] or atezolizumab [14]. Management of rarer urinary tract pathologies is also discussed below.

T2 - T4a N0 M0 Urothelial Bladder Cancer Patients Suitable for Radical Treatment

Neoadjuvant Chemotherapy before Radical Cystectomy or Radical Radiotherapy

Neoadjuvant chemotherapy offers a 5% improvement in overall survival at five years [15]. Although deferral of patients' definitive treatment using neoadjuvant chemotherapy may seem strategically advantageous, the potential period of immunosuppression is six to nine weeks depending on regimen used. Additionally, dates of radical treatment may be threatened because of illness from treatment. Consequently, omission of neoadjuvant chemotherapy should be considered - **priority level 4.**

Radical Cystectomy

Radical cystectomy is a valid treatment option for younger fitter patients needing curative therapy - **priority level 2**.

However in the present situation, the risks are substantial for older, less fit patients who often have significant comorbidities and a high risk of death from hospital acquired COVID-19. Acquisition of randomised, phase III data comparing radical cystectomy and chemo-radiotherapy has proven challenging [16]. In its absence, retrospective non-randomised trials have shown radical radiotherapy to offer very similar cancer-specific outcomes to cystectomy despite older radiation techniques and minimal use of concurrent chemotherapy [17–19]. Chemo-radiotherapy has also demonstrated comparable outcomes [20] and even improved overall survival [21] to surgery more recently, and is accepted as valid alternative by the joint EAU-ESMO consensus panel [22] and NICE [10]. In the current pandemic, bladder preservation therapy offers a sound choice for patients.

Adjuvant Chemotherapy Post-radical Cystectomy

NICE recommend adjuvant combination cisplatin chemotherapy after surgery for muscle-invasive or lymph-node-positive urothelial bladder cancer where neo-adjuvant chemotherapy was deemed unsuitable [10]. A meta-analysis observing the effect of adjuvant chemotherapy demonstrated an absolute increase in overall survival by 9% at three years [23]. However, patients aged 40 and over possess a greater risk of death if infected with COVID-19 than the benefit offered by adjuvant treatment [6]. Therefore chemotherapy post-cystectomy is not advised for most - **priority level 4**.

Radical Radiotherapy with Radiosensitisation

Radiosensitisation with carbogen and nicotinamide or Mitomycin C and 5-fluorouracil (MMC-5FU) via the BCON and BC2001 trials has been shown to improve loco-regional recurrence-free and overall survivals [24,25]. Although difference in overall survival with addition of MMC-5FU to radiotherapy was non-significant ($p = 0.16$), muscle-invasive recurrence essentially halved [25]. In addition, improvement in bladder cancer specific survival became significant and the salvage cystectomy rate reduced to 11% with longer follow-up [26]. Carbogen and nicotinamide would be ideal radiosensitisers at present, especially in patients with significant necrotic areas in tumour [27], because of their lack of immunosuppression. However, most radiotherapy departments do not have BCON up and running. Given the worldwide shortage of Mitomycin C, weekly gemcitabine [28] is an acceptable alternative and has been used as a standard option with 20 fraction

radiotherapy in the RAIDER trial, a Randomised phase II trial of Adaptive Image guided standard or Dose Escalated tumour boost Radiotherapy in the treatment of transitional cell carcinoma of the bladder. Radiosensitisation cures muscle invasive bladder cancer and reduces numbers of salvage cystectomies, and is recommended at the highest priority - **priority level 1**.

Radiotherapy Dose and Fractionation

No statistically significant differences in locoregional disease–free survival or toxicity were seen between the conventionally (64 Gy in 32 fractions) and hypofractionated (55 Gy in 20 fractions) treated groups within the BC2001 and BCON trials [24,25]. A meta-analysis by Porta *et al.* confirmed that hypofractionated radiotherapy was non-inferior, and possibly superior, to conventionally fractionated radiotherapy for overall survival and late toxicity. Moreover, the hypofractionated population possessed better rates of invasive locoregional control [29]. Hence, hypofractionated radiotherapy is recommended ideally with a radiosensitiser where radical treatment is appropriate - **priority level 1** (soft tissue image guidance (e.g. with cone beam CT) significantly improves accuracy and should be maintained whenever possible).

Weekly radiotherapy in the form of 36Gy in six fractions or 21Gy in three fractions on alternate days has been shown as effective regimens in patients unsuitable for daily radical radiotherapy – albeit with limited long-term data [30,31]. The Hypofractionated bladder Radiotherapy with or without image guided adaptive planning (HYBRID) study reported over 70% of patients achieving local control at 3 months in an unfit patient group [32]. In the event of significantly reduced staffing and capacity, 21 Gy in three fractions or 36Gy in six fractions may be considered in patients unsuitable for or when daily radiotherapy is unavailable.

Locally Advanced or Metastatic Urothelial Bladder Cancer Patients

First Line Systemic Treatment

Cisplatin-containing chemotherapy, either as gemcitabine-cisplatin or methotrexate, vinblastine, adriamycin and cisplatin is the recognised standard in this setting [10,11]. A study comparing the two demonstrated similar response rates of over 50% but a better side-effect profile with gemcitabine-cisplatin [33]. Keynote-052 observed an objective response rate of 24% with pembrolizumab in 370 patients with metastatic bladder cancer unfit for cisplatin [34]. Given the change in risk/benefit of palliative chemotherapy during the COVID-19 pandemic, patients with slowly growing metastatic disease should be observed; with chemotherapy reserved for rapidly progressive disease, and patients counselled specifically for the increased risk of COVID complications leading to death. Overall, immunotherapy should be the primary choice in PDL1 positive disease but the possibility of severe COVID-19 infection mimicking immunotherapy-induced pneumonitis should be recognised. In the absence of PDL1 positivity, chemotherapy remains an option for symptomatic control depending on capacity levels - **priority level 4**.

Second Line Systemic Treatment

Studies examining the efficacy of second line treatment are highly dependent on the characteristics of participants. NICE has removed approval for Pembroluzimab from 15th April 2020 but atezoluzimab remains available via the Cancer Drugs Fund for patients who have had platinum-containing chemotherapy. This is predicated on the IMvigor studies [10]. In IMvigor 211, atezolizumab exhibited more durable response but not an improved overall survival compared to chemotherapy [35]. Four weekly atezolizumab may be considered in view of reduced hospital visits and lack of immunosuppression - **priority level 4**.

Overall, the risk-benefit ratio of second line single agent chemotherapy is questionable in most cases - **priority level 6**.

Palliative Radiotherapy for Bleeding or Local Symptom Control

Ali *et al.* detailed the importance of appropriate patient selection for palliative radiotherapy for bladder cancer. Their study demonstrated that palliative radiotherapy including 8 Gy in a single fraction improved haematuria, dysuria and pain [36] - **priority level 4**.

Upper Tract Urothelial Cancer

Upper tract urothelial carcinomas are rare [37] with treatment data previously lacking. The POUT trial recently addressed this paucity and observed a benefit of 17% on three-year disease-free survival following adjuvant gemcitabine-platinum for completely resected pT2–T4 pN0–N3 M0 or pTany N1–3 M0 disease [38]. Accordingly, post-nephroureterectomy chemotherapy should be discussed with this patient cohort - **priority level 3**.

Non-urothelial Cancer of Urinary Tract

The prognosis of small cell carcinoma remains poor. Previous literature has shown an important role for the use of neoadjuvant chemotherapy prior to surgery or radiotherapy to downstage and increase overall survival [39–41]. More recent studies have not demonstrated differenced in survival rates between surgery and radiotherapy [42,43]. Thus a conservative approach is warranted currently - **priority level 2**. In metastatic disease, a median overall survival of 15 months was seen with both cisplatin- and carboplatin-based regimens [43] - **priority level 4**.

Pure squamous cell carcinomas of the urinary tract are relatively chemo-resistant and the peri-operative systemic therapy is not well-established [44] - **priority level 6**.

Table 4
Table summarising priority level recommendations for management of urothelial cancers during COVID-19 pandemic

	Surgery	Radiation therapy	Systemic treatment
Priority level 1		• Radical radiotherapy with Radiosensitisation	
Priority level 2	• Radical Cystectomy		• Neoadjuvant chemotherapy for small cell cancer of bladder
Priority level 3			• Adjuvant chemotherapy post-nephro-ureterectomy (pT2–T4 pN0–N3 M0/pTany N1–3 M0)
Priority level 4		• Palliative radiotherapy for bleeding or local control	• Neoadjuvant chemotherapy for urothelial MIBC • Adjuvant chemotherapy post-radical cystectomy for urothelial MIBC • First line systemic treatment for metastatic urothelial cancer of bladder • First line systemic treatment for metastatic small cell cancer of bladder • Adjuvant chemotherapy post-radical cystectomy • Neoadjuvant chemotherapy for adenocarcinoma cancer of bladder • Second line immune therapy treatment for metastatic urothelial cancer of bladder
Priority level 5			
Priority level 6			• Neoadjuvant/adjuvant chemotherapy for squamous cell cancer of bladder • First line systemic treatment for metastatic adenocarcinoma cancer of bladder • Second/third line chemotherapy treatment for metastatic urothelial cancer of bladder

Abbreviation: MIBC – muscle invasive bladder cancer.

Data describing perioperative chemotherapy in primary bladder adenocarcinoma is scarce. Vetterlain *et al.* found that neoadjuvant chemotherapy reduced the incidence of regional or distal disease at time of surgery but had no statistically significant effect on overall survival [45]. A retrospective study in Korea suggested a modest benefit with chemotherapy in the metastatic setting [46] - **priority level 6**.

Discussion

The COVID-19 pandemic presents a significant challenge for cancer care and patient safety. Timely and thorough planning would seem paramount in order to maintain essential services and vital treatments. Examining the efficacy and toxicity of treatments at the earliest opportunity will allow departments to determine which therapies to prioritise, what services to restructure in order to help key areas and most importantly which patients will derive the most benefit and least harm. Fortunately, the evidence base for anti-cancer therapies is relatively robust, which facilitates decision-making.

This review highlights the literature underpinning the treatments used for urothelial cancers and provides a framework to aid patient discussions and treatment decisions (Table 4). Overall, prioritisation of curative treatments is advised.

Any set of recommendations cannot encapsulate all possible scenarios and liaison within and between centres is strongly advocated. Lastly, submission of information to local and national data sets is also encouraged in order to later evaluate the impact of COVID19-related treatment decisions on outcomes.

Declarations

The authors received no financial support for the research, authorship, and/or publication of this article.

Karan Patel has no declarations or conflict of interests. Peter Hoskin and Ananya Choudhury are supported by the NIHR Manchester Biomedical Research Centre. Mohini Varughese has no conflicts of interests relevant to this submission. Nick James performs consultancy work with Merck and AstraZeneca plus trial funding to institution not personal from AstraZeneca (AZ), Merck and Roche. Robert Huddart has received honoraria/travel expenses from Roche, Merck Sharp & Dohme (MSD), Bristol advisory Squibb, Janssen, Bayer and Nektar. He is partner in Cancer centre London. Alison Birtle is on advisory board for Janssen, Astellas, Sanofi Genzyme, Bayer and Roche, and has received speaker fees from Janssen, Astellas and Sanofi Genzyme.

Acknowledgements

Peter Hoskin and Ananya Choudhury are supported by the NIHR Manchester Biomedical Research Centre. Robert Huddart is supported by ICR/Royal Marsden Hospital NIHR

Biomedical centre. Nicholas James is supported by ICR/ Royal Marsden Hospital NIHR Biomedical centre.

References

[1] Geneva WHO-Switzerland. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020, https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. [Accessed 27 March 2020].

[2] Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for cancer patients. *Lancet Oncol* 2020;20:S1470–S2045. https://doi.org/10.1016/s1470-2045(20)30150-9.

[3] Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020;20:S1470–S2045. https://doi.org/10.1016/s1470-2045(20)30149-2.

[4] Liang W, Guan W, Chen R, *et al*. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21:335–337. https://doi.org/10.1016/s1470-2045(20)30096-6.

[5] Wang D, Hu B, Hu C, *et al*. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020;323:1061–1069. https://doi.org/10.1001/jama.2020.1585.

[6] Williams M, Calvez KL, Chen J, Dadhania S. Estimating risks from COVID-19 in adult cancer patients, https://www.medrxiv.org/content/10.1101/2020.03.18.20038067v1. [Accessed 27 March 2020].

[7] Jombart T, Nightingale ES, Jit M, *et al*. *Forecasting critical care bed requirements for COVID-19 patients in England*. Centre for Mathematical Modelling of Infectious Disease -nCoV Working Group; 2020, https://cmmid.github.io/topics/covid19/current-patterns-transmission/ICU-projections.html. [Accessed 27 March 2020].

[8] NHS England. Clinical guide for the management of non-coronavirus patients requiring acute treatment: Cancer. 23 March 2020 Version 2, https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/specialty-guide-acute-treatment-cancer-23-march-2020.pdf. [Accessed 30 March 2020].

[9] Gillessen S, Powles T. Advice for medical oncology care of urological cancer patients during the COVID-19 pandemic. Editorial seen ahead of publication date in European Urology (Eur Urol) - personal communication of accepted manuscript by author.

[10] National Collaborating Centre for Cancer (UK), National Institute for Health and Clinical Excellence. Bladder Cancer: Diagnosis and management. NICE Guideline 2 – Full guideline, Updated information July 2019, https://www.nice.org.uk/guidance/ng2/evidence/full-guideline-pdf-3744109. [Accessed 27 March 2020].

[11] Bellmunt J, Orsola A, Leow JJ, *et al*. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(S3). iii40–iii48.

[12] National Institute for Health and Clinical Excellence. Bladder cancer – everything NICE says in an interactive flowchart: First-line chemotherapy, https://pathways.nice.org.uk/pathways/bladder-cancer#path=view%3A/pathways/bladder-cancer/managing-locally-advanced-or-metastatic-bladder-cancer.xml&content=view-node%3Anodes-first-line-chemotherapy. [Accessed 30 March 2020].

[13] National Institute for Health and Clinical Excellence. Bladder cancer – everything NICE says in an interactive flowchart: Second-line chemotherapy, https://pathways.nice.org.uk/pathways/bladder-cancer#path=view%3A/pathways/bladder-cancer/managing-locally-advanced-or-metastatic-bladder-cancer.xml&content=view-node%3Anodes-second-line-treatment. [Accessed 30 March 2020].

[14] National Institute for Health and Clinical Excellence. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. Technology appraisal guidance [TA525], https://www.nice.org.uk/guidance/ta525/resources/atezolizumab-for-treating-locally-advanced-or-metastatic-urothelial-carcinoma-after-platinumcontaining-chemotherapy-pdf-82606842153925. [Accessed 30 March 2020].

[15] Collaboration ABC (ABC) M. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005;48: 202–205. https://doi.org/10.1016/j.eururo.2005.04.006. discussion 205-6.

[16] Huddart RA, Birtle A, Maynard L, *et al*. Clinical and patient-reported outcomes of SPARE - a randomised feasibility study of selective bladder preservation versus radical cystectomy. *Bju Int* 2017;120:639–650. https://doi.org/10.1111/bju.13900.

[17] Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P, Kiltie AE. Similar Treatment Outcomes for Radical Cystectomy and Radical Radiotherapy in Invasive Bladder Cancer Treated at a United Kingdom Specialist treatment center. *Int J Radiat Oncol Biol Phys* 2008;70:456–463. https://doi.org/10.1016/j.ijrobp.2007.06.030.

[18] Munro NP, Sundaram SK, Weston PMT, *et al*. A 10-Year Retrospective Review of a Nonrandomized Cohort of 458 Patients Undergoing Radical Radiotherapy or Cystectomy in Yorkshire, UK. *Int J Radiat Oncol Biol Phys* 2010;77:119–124. https://doi.org/10.1016/j.ijrobp.2009.04.050.

[19] Booth CM, Siemens DR, Li G, *et al*. Curative Therapy for Bladder Cancer in Routine Clinical Practice: A Population-based outcomes study. *Clin Oncol* 2014;26:506–514. https://doi.org/10.1016/j.clon.2014.05.007.

[20] Kulkarni GS, Hermanns T, Wei Y, *et al*. Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder cancer clinic. *J Clin Oncol* 2017;35:2299–2305. https://doi.org/10.1200/jco.2016.69.2327.

[21] Arcangeli G, Strigari L, Arcangeli S. Radical cystectomy versus organ-sparing trimodality treatment in muscle-invasive bladder cancer: A systematic review of clinical trials. *Crit Rev Oncol Hemat* 2015;95:387–396. https://doi.org/10.1016/j.critrevonc.2015.04.006.

[22] Witjes JA, Babjuk M, Bellmunt J, *et al*. EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer-An International Collaborative Multistakeholder Effort†: Under the Auspices of the EAU-ESMO guidelines committees. *Eur Urol* 2019;77:223–250. https://doi.org/10.1016/j.eururo.2019.09.035.

[23] Collaboration ABC (ABC) M. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). *The Cochrane Database Syst Rev* 2006;11:CD006018. https://doi.org/10.1002/14651858.cd006018.

[24] Hoskin PJ, Rojas AM, Bentzen SM, Saunders MI. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. *J Clin Oncol* 2010;28:4912–4918. https://doi.org/10.1200/jco.2010.28.4950.

[25] 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. https://doi.org/10.1056/nejmoa1106106.

[26] Hall E, Hussain SA, Porta N, *et al*. BC2001 long-term outcomes: A phase III randomized trial of chemoradiotherapy versus radiotherapy (RT) alone and standard RT versus reduced high-dose volume RT in muscle-invasive bladder cancer. *J Clin Oncol* 2017;35. https://doi.org/10.1200/jco.2017.35.6_suppl.280. 280–280.

[27] Eustace A, Irlam JJ, Taylor J, *et al*. Necrosis predicts benefit from hypoxia-modifying therapy in patients with high risk bladder cancer enrolled in a phase III randomised trial. *Radiother Oncol* 2013;108:40–47. https://doi.org/10.1016/j.radonc.2013.05.017.

[28] 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. https://doi.org/10.1200/jco.2010.31.5721.

[29] Porta N, Song YP, Hall E, *et al*. Hypo-Fractionation in Muscle-Invasive Bladder Cancer: An Individual Patient Data (IPD) Meta-Analysis of the BC2001 and BCON Trials. *Int J Radiat Oncol Biol Phys* 2019;105:S138. https://doi.org/10.1016/j.ijrobp.2019.06.130.

[30] Duchesne GM, Bolger JJ, Griffiths GO, *et al*. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. *Int J Radiat Oncol Biol Phys* 2000;47:379–388. https://doi.org/10.1016/s0360-3016(00)00430-2.

[31] Hafeez S, McDonald F, Lalondrelle S, *et al*. Clinical Outcomes of Image Guided Adaptive Hypofractionated Weekly Radiation Therapy for Bladder Cancer in Patients Unsuitable for radical treatment. *Int J Radiat Oncol Biol Phys* 2017;98:115–122. https://doi.org/10.1016/j.ijrobp.2017.01.239.

[32] Huddart R, Henry A, Staffurth J, *et al*. OC-0058: Clinical outcomes of the first rct of adaptive radiotherapy in bladder cancer (HYBRID CRUK/12/055). *Radiother Oncol* 2018;127:S25–S26. https://doi.org/10.1016/s0167-8140(18)30368-2.

[33] von der Maase H, Hansen SW, Roberts JT, *et al*. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068–3077. https://doi.org/10.1200/jco.2000.18.17.3068.

[34] 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. https://doi.org/10.1016/s1470-2045(17)30616-2.

[35] Powles T, Durán I, von 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* 2017;391:748–757. https://doi.org/10.1016/s0140-6736(17)33297-x.

[36] Ali A, Song YP, Mehta S, *et al*. Palliative Radiation Therapy in Bladder Cancer—Importance of Patient Selection: A Retrospective Multicenter study. *Int J Radiat Oncol Biol Phys* 2019;105:389–393. https://doi.org/10.1016/j.ijrobp.2019.06.2541.

[37] Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol* 2000;164:1523–1525. https://doi.org/10.1016/s0022-5347(05)67019-x.

[38] Birtle A, Johnson M, Chester J, *et al*. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet* 2020. https://doi.org/10.1016/s0140-6736(20)30415-3. Published online: 5 March 2020.

[39] Siefker-Radtke AO, Kamat AM, Grossman HB, *et al*. Phase II Clinical Trial of Neoadjuvant Alternating Doublet Chemotherapy With Ifosfamide/Doxorubicin and Etoposide/Cisplatin in Small-Cell Urothelial cancer. *J Clin Oncol* 2009;27:2592–2597. https://doi.org/10.1200/jco.2008.19.0256.

[40] Lynch SP, Shen Y, Kamat A, *et al*. Neoadjuvant Chemotherapy in Small Cell Urothelial Cancer Improves Pathologic Downstaging and Long-term Outcomes: Results from a Retrospective Study at the MD Anderson cancer center. *Eur Urol* 2013;64:307–313. https://doi.org/10.1016/j.eururo.2012.04.020.

[41] Patel SG, Stimson CJ, Zaid HB, *et al*. Locoregional Small Cell Carcinoma of the Bladder: Clinical Characteristics and treatment patterns. *J Urol* 2014;191:329–334. https://doi.org/10.1016/j.juro.2013.09.009.

[42] Pasquier D, Barney B, Sundar S, *et al*. Small Cell Carcinoma of the Urinary Bladder: A Retrospective, Multicenter Rare Cancer Network Study of 107 patients. *Int J Radiat Oncol Biol Phys* 2015;92:904–910. https://doi.org/10.1016/j.ijrobp.2015.03.019.

[43] Sroussi M, Elaidi R, Fléchon A, *et al*. Neuroendocrine Carcinoma of the Urinary Bladder: A Large, Retrospective Study From the French Genito-Urinary Tumor group. *Clin Genitourin Canc* 2019. https://doi.org/10.1016/j.clgc.2019.11.014.

[44] Zahoor H, Elson P, Stephenson A, *et al*. Patient Characteristics, Treatment Patterns and Prognostic Factors in Squamous Cell Bladder Cancer. *Clin Genitourin Canc* 2017;16:e437–e442. https://doi.org/10.1016/j.clgc.2017.10.005.

[45] Vetterlein MW, Wankowicz SAM, Seisen T, *et al*. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology: Neoadjuvant CTX and Bladder Cancer variants. *Cancer* 2017;123:4346–4355. https://doi.org/10.1002/cncr.30907.

[46] Kim MJ, Kim YS, Oh SY, *et al*. Retrospective analysis of palliative chemotherapy for the patients with bladder adenocarcinoma: Korean Cancer Study Group Genitourinary and Gynecology cancer committee. *Korean J Intern Med* 2018;33:383–390. https://doi.org/10.3904/kjim.2015.162.