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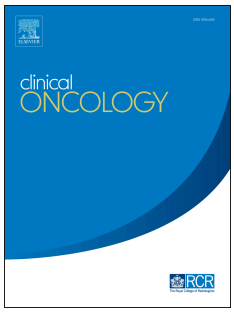

Clinical Guidance for the Management of Patients with Urothelial Cancers During the COVID-19 Pandemic – Rapid Review

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Title page

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

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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.

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Highlights

- Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), COVID-19 presents a significant challenge to cancer care
- Use of cancer therapies often predicated on strong evidence base
- Important to analyse risk/benefit ratio of different cancer treatments for urothelial cancer
- These guidelines present framework to help decision making for urothelial cancers and other rarer urinary tract pathologies during COVID 19 pandemic

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].

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.

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 co-morbidities 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 neoadjuvant 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**.

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.

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

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

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*

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Highlights

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 presents a significant challenge to cancer care
- Use of cancer therapies often predicated on strong evidence base
- Important to analyse risk/benefit ratio of different cancer treatments for urothelial cancer
- These guidelines present framework to help decision making for urothelial cancers and other rarer urinary tract pathologies during COVID 19 pandemic