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Guidance for management of urothelial cancer during COVID-19 pandemic

Authors: AJ Birtle, M Varughese, N James, R Huddart, P Hoskin, A Choudhury

This is in line with the NICE guidance for radiotherapy and chemotherapy.

Radical treatment

<https://www.nice.org.uk/guidance/NG162>

T2-T4a N0 M0 Urothelial cancer patients suitable for radical treatment

Neo-adjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) offers a 5% improvement in overall survival at 5 years. Although there is an advantage in delaying patients' definitive treatment with either radiotherapy or radical cystectomy, the period of potential immunosuppression will be 9 weeks with additional time at risk post chemotherapy of up to 6 months as per SACT estimate. Therefore, it would seem the risk/benefit ratio for NAC is high, and NAC should be considered for omission (**Priority level 4**).

Radical radiotherapy with a radiosensitiser

BC2001 protocol of Mitomycin C and 5FU is currently not available at many sites in view of worldwide shortage of Mitomycin C.

BCON is currently not available in many sites.

Radical radiotherapy is an option for some patients, however adding in a radio-sensitiser reduces risk of muscle invasive recurrence by about 50%. Not giving a radio-sensitiser therefore would potentially increase the risk of salvage cystectomies and/or systemic therapy for metastatic disease.

The Christie have extensive experience of the weekly gemcitabine[1] and this would be an acceptable alternative for patients.

Therefore, for patients fit for radical treatment, the following is advised (**priority level 1**):

- Radical radiotherapy with one of the following:
 - 5FU/mitomycin C if available
 - BCON in centres where this is established
 - weekly gemcitabine

If capacity within the department falls to e.g. < 70% radiographers/planning team, or where individual patient factors preclude giving the radical 55Gy/20# dose, consider a shorter treatment regime:

Adjuvant chemotherapy post cystectomy or radical nephroureterectomy for upper tract urothelial cancer

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Most patients with cancer are at >5% risk of death if infected with COVID-19. This risk is very similar to that seen in most adjuvant treatments and would outweigh benefit for adjuvant chemotherapy post cystectomy or nephroureterectomy (**priority level 4**).

Palliative treatment

Radiotherapy

- 21Gy/3# is a palliative fractionation schedule which improves local symptoms (equivalent to 35Gy/10#) [3]
- 36Gy/6# given weekly has been found to offer good local control with acceptable toxicity in a Phase 2 single-centre study [4].

A palliative dose of 8-10Gy/single # can be given for bleeding or local symptom control (**Priority level 2**).

Systemic treatment

Individual risk/benefit should be discussed with all patients as per [SACT document from NHSE](#).

The table below is taken from a publication in press shared on line by Professors Tom Powles and Silke Gilleson ahead of publication in European Urology Platinum Edition [5]:

	Prostate cancer	Renal cancer	Germ cell tumors	Urothelial cancer
1. Treatment should be commenced where possible	Front line treatment for metastatic disease	Treatment for front line IMDC intermediate and poor risk disease metastatic disease ^b	Treatment with curative intent	Frist line treatment for metastatic disease.
2. Treatment should not be commenced without justification.	Chemotherapy in patients at significant COVID related risk d	Nephrectomy for metastatic disease	Adjuvant therapy post orchidectomy for Stage I disease	CT in platinum refractory disease. Perioperative CT for operable disease ^a
3. Treatment should not be stopped without justification	Androgen-receptor targeted therapy ^c .	Treatment for front line metastatic disease.	Frist and 2 nd line treatment for metastatic disease	Treatment for front line metastatic disease
4. Treatment can potentially be stopped or delayed after careful consideration	Minimising the number of cycles of CT or prolonging cycle length may be justified. Steroids as a cancer therapy.	Immune checkpoint inhibition or oral VEGF targeted therapy after prolonged period (1-2 yrs) ^c		CT for platinum refractory patients who are not responding to therapy Greater than 3 cycles of CT in the perioperative setting.
5. Treatments which can be given preferentially compared to other options	Oral androgen Receptor targeted therapy rather than CT ^f	Oral VEGF therapy rather than IV immune therapy	Conventional dose rather than high dose therapy	ICIs rather than CT in PD-L1 positive front line metastatic disease.

Key: CT= chemotherapy ICI = immune checkpoint inhibitor.

a. Neoadjuvant chemotherapy may be helpful to bridge time to surgery in cases where elective surgery is not possible.

b. Oral vascular endothelial growth factor targeted therapy rather than intravenous immune checkpoint inhibitors may be attractive as it requires less healthcare interaction and resource.

c. Regimens with longer interval (4 weekly nivolumab or 6 weekly pembrolizumab) should be employed where possible..

d. Younger cancer patients, and those without comorbidities may be at less risk which requires consideration.

e. Assuming similar efficacy between the regimens.

f. Palliative chemotherapy was tested with specific number of cycles. The risk associated with stopping prior to this has not been assessed. Nor has the principles of delaying chemotherapy. There are subgroups of prostate and urothelial cancer patients where continuing chemotherapy to the full number of cycles may be associated with more risk than benefit. Patients will need to participate in this discussion.

First line metastatic/advanced urothelial cancer

- Where possible look at use of IO in 1st line metastatic disease (PDL-1 positive patients only) (**Priority level 3**).
- In PDL-1 negative patients, first-line response rate to platinum-based chemotherapy is around 60% . Patients may often be symptomatic from disease and chemotherapy

can offer good palliation in this setting. It would seem appropriate therefore to continue to offer this to patients as long as capacity allows. **(Priority level 4)**.

Second line metastatic urothelial cancer

- Response rate to weekly Taxol is around 18%. The risk/benefit ratio would be high, and should therefore not be considered **(Priority level 6)**.

Response rate to IO is around 22%. Consideration could be given to 4-weekly atezolizumab schedule. Treatment unlikely to affect risk of immunosuppression, however there is a risk that IO mediated toxicity may be untreated/ unrecognised in a COVID affected unit. **(Priority level 5)**.

Non urothelial cancer in urinary tract:

- Small cell carcinoma in fit patient PS 0-1. **(Priority level 2)**
- Adenocarcinoma: **(PRIORITY level 4)**
- Squamous cell carcinoma (usually non-chemo responsive): **(Priority level 6)**

References

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2. Porta, N. 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 Volume 105, Issue 1, S13*. [doi: 10.1016/j.ijrobp.2019.06.130](https://doi.org/10.1016/j.ijrobp.2019.06.130).
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4. Hafeez S, McDonald F, Lalondrelle S, et al (2017). 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 May 1;98(1):115-122. [doi: 10.1016/j.ijrobp.2017.01.239](https://doi.org/10.1016/j.ijrobp.2017.01.239).
5. *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- personal communication of accepted manuscript by author.*