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Guidance for management of urothelial cancer during COVID-19 pandemic

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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

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[a]	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	Andrógen-receptor targeted therapy[c].	Treatment for front line metastatic disease.	Frist and 2nd 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 stetting.
5. Treatments which can be given preferentially compared to other options	Oral androgen Receptor targeted therapy rather than CT[e]	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 were 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

1. 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 Feb 20;29(6):733-8. doi: 10.1200/JCO.2010.31.5721.

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Int J Radiat Oncol Biol Phys Volume 105, Issue 1, S13. doi: 10.1016/j.ijrobp.2019.06.130.

3. 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 May 1;47(2):379-88.
doi: 10.1016/s0360-3016(00)00430-2.

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.

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.*

Appendix 1

Guidance for management of urothelial cancer during COVID-19 pandemic

Radiotherapy

V3 Author AJ Birtle discussed with Uro oncology team Lancs & South Cumbria and The Christie in accordance with RCR guidance

- Updated 13/5/2020 in line with NICE Rapid Review.
- Updated 15/10/2020 after discussion with local colleagues and national colleagues, submitted to RCR for suggestion of management on Fellow website.

T2-T4aNoMo urothelial cancer patients suitable for radical treatment.
Neoadjuvant chemotherapy offers a 5 Percent 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 would be higher than under non covid conditions. Whilst NAC could be omitted careful discussion with the patient as to risk/ benefit is warranted as NAC is the only established systemic manouvre prior to definitive treatment to improve overall survival. Category 4

T2-T4a Radical radiotherapy with a radiosensitiser Category 1

- BCON currently not available on many sites
- BC2001 protocol of Mitomycin C and 5FU significant reduction in local recurrence and shortage of MMC now resolved. Low risk of additional toxicity. Capecitabine may be substituted for 5FU if there are difficulties in PICC availability
- Gemcitabine weekly (GEMX trial) can be used alternatively if Mitomycin C & 5FU not feasible locally. It has been used in 36% of the 20# cohort and 10% of the 32# cohort within RAIDER

Risk/benefit-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 risk of salvage cystectomies and/or systemic therapy for metastatic disease.

Therefore- for patients fit for radical treatment:
Radical radiotherapy with 5FU and MMC Fractions 1-5 and 16-20 , or with weekly gemcitabine as long as there is capacity within chemotherapy unit. Fractionation regime 55Gy in 20F for MMC and 5FU, 52.5 Gy in 20 F for weekly gemex. **Category 1**

For patients unsuitable for chemosensitisation if there are no issues with capacity for 55Gy/20F **Category 1**

If capacity within department falls to eg < 70percent radiographers/planning team for weekly radiotherapy 36Gy/6Fractions or 21Gy/3F
Palliative radiotherapy for bleeding or local control single 8 Gy Fraction

References

Choudhury A, Swindell R, Logue JP, Elliott PA, Livsey JE, Wise M, Symonds P, Wylie JP, Ramani V, Sangar V, Lyons J, Bottomley I, McCaul D, Clarke NW, Kiltie AE, Cowan RA. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol. 2011 Feb 20;29(6):733-8.
Patterns of use of chemotherapy and radiotherapy in patient with muscle invasive bladder cancer; data from the RAIDER randomized trial of adaptive radiotherapy
Huddart, Lewis Hall et al.

Appendix 2

Guidance for management of urothelial cancer during COVID-19 pandemic

Systemic therapy

V3 Author Dr AJ Birtle in discussion with uro-oncology team Lancs and South Cumbria and The Christie

- Updated 9/10/20 after discussion with local and national colleagues

Individual risk benefit should be discussed with all patients as per SACT document from NHSE. First line metastatic treatment offers both survival advantage and improves symptoms and should be initiated after discussion of risk benefit with patient. An alternative to chemotherapy is immunotherapy first line but the patient should be counselled that this has not been shown to have the same efficacy in this setting as chemotherapy but may offer fewer side effects especially in terms of immunosuppression.

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. Amendments to the recommendations given in the table are in the text below, after review of outcomes of cancer patient during the first wave of COIVD-19 in the UK.

	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]
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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 stetting.
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Key: CT= chemotherapy ICI = immune checkpoint inhibitor.

a. Neoadjuvant chemotherapy may be helpful to bridge time to surgery in cases were 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.

T2-T4aNoMo urothelial cancer patients suitable for radical treatment
Discussed above.

Adjuvant chemotherapy post cystectomy – has no definite overall survival benefit although reduces Disease free survival and could be discussed but category 5.
For upper tract urothelial cancer post nephroureterectomy with T2-T4a No-N3 completely resected disease, improvements in DFS are 17% with adjuvant chemotherapy and therefore can be considered on a case by case basis discussing risk and benefit with patient.
CATEGORY 3

First line metastatic/advanced urothelial cancer
Platinum based combination treatment will be more effective in suitable patients but patients should be carefully counselled as to the risk/ benefit of chemotherapy vs first line IO. Where possible look at use of IO in 1st line metastatic disease (PDL-1 positive patients only) (see below for comments re PDL-1 negative patients) Patient should however be counselled that the results from immunotherapy are less good than chemotherapy and therefore each patient should consider both options with regard to toxicity and benefit balance.

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. **Category 4**

The NICE RAPID Review document from 28 April 2020 NG 161 allows use of first line Atezolizumab in metastatic urothelial cancer for patients who are PDL1 positive or negative.

From this NG161- “However, It is important for clinicians to be aware that based on an IMvigor130 trial Data Monitoring Committee recommendation following an early review of

survival data, accrual of patients on the atezolizumab monotherapy arm with tumours staining positive for PD-L1 at the <5% level was stopped in the trial after an observation of decreased overall survival in this subgroup. As a consequence the atezolizumab marketing authorisation was changed such that 1st line use of atezolizumab for patients ineligible for cisplatin was restricted to patients with urothelial tumours having a PD-L1 expression of =5%. Clinicians should consider this information in patients with tumours staining <5% for PD-L1 at the same time as being aware that the trial randomised against cisplatin- or carboplatin-based chemotherapy-containing arms and such chemotherapy may not be in the best interests of patients during the COVID19 pandemic."

Second line metastatic urothelial cancer

Response rate to weekly taxol is around 18% and risk/benefit ratio would be high and should therefore not be considered unless patient highly symptomatic and unsuitable for IO. Response rate to IO is around 22%, consideration could be given to 4 weekly atezolizumab schedule or 6 weekly pembrolizumab. Treatment unlikely to affect risk of immunosuppression however risk that IO mediated toxicity may be untreated/unrecognised in a COVID affected unit. **Category 5**

Non urothelial cancer in urinary tract

Small cell in fit patient PS0-1 **Category 2**
Squamous cell carcinoma usually non chemo responsive **category 6**
Adenocarcinoma Category 4

References

Choudhury A, Swindell R, Logue JP, Elliott PA, Livsey JE, Wise M, Symonds P, Wylie JP, Ramani V, Sangar V, Lyons J, Bottomley I, McCaul D, Clarke NW, Kiltie AE, Cowan RA. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol. 2011 Feb 20;29(6):733-8.

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

NICE Guidance NG161
Interim treatment change options during the COVID-19 pandemic, endorsed by NHS England Published 28 April 2020