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Considerations for treatment of oesophagogastric cancers within the United Kingdom during the COVID-19 pandemic

1. DOCUMENT OUTLINE

1.1. Date and version

25/03/2020 – v3.0

Further revisions of this document and links to forums through which clinicians can provide comment are provided at www.uppergisurgery.com.

1.2. Authors and contributors

Initial draft by Chris Jones (Leeds) and Tom Crosby (Velindre). Revisions and contributions from the Birmingham Upper GI MDT, Lubna Bhatt (Christie), Emma Cattell (MPH), Sebastian Cummins (Surrey), Rebecca Goody (Leeds), Sarah Gwynne (Swansea), Ewen Griffiths (Birmingham), Maria Hawkins (London), Carys Morgan (Velindre), Somnath Mukherjee (Oxford), Russell Petty (Dundee), Ganesh Radhakrishna (Manchester), Hamid Sheikh (Christie), Elizabeth Smyth (Cambridge), Dan Swinson (Leeds), Elizabeth Toy (Devon/Exeter), John Whiting (Birmingham).

2. DOCUMENT AIM

The aim of this document is to bring together expert opinion in order to provide guiding principles for the management of upper gastrointestinal (UGI) cancers in the United Kingdom (UK) during the COVID-19 pandemic. It is anticipated that this document will be updated as evidence emerges relating to the added risks for cancer patients imposed by COVID19. It will also need to be applied in the context of local capacity constraints. There is inevitably uncertainty Nationally regarding the impact on specific cancer services and there will be local variation in capacity constraints across all NHS services, but also variation in capacity of one service (eg SACT, RT, surgery) compared to another.. Despite varying from what we have previously considered standards of care, the emphasis in this document is on forming expert opinion around existing evidence where available, albeit sometimes using a different level of evidence than we may be used to.

3. RATIONALE

As of 18th March 2020, in excess of 200,000 people worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the coronavirus disease 2019 (COVID-19) pandemic.(1) Almost 9000 have died from this disease in the four months following the first reported case in December 2019.(1) In the United Kingdom (UK), the first cases were reported on 31st January 2020 and of 18th March 2020 there are 2626 cases and 103 confirmed deaths, though the undiagnosed burden of disease in the community is considered to be far greater.(2) Common symptoms resulting from infection with SARS-CoV-2 include cough, shortness of breath and fever. However, a majority of patients die from multiple organ dysfunction syndrome rather than respiratory failure.(3)

The COVID-19 pandemic is of particular concern for the management of patients with cancer, who are immunosuppressed both because of the cancer and as a consequence of the anti-cancer treatment they receive, and who frequently have a number of comorbidities. In a prospective Chinese series of 1590 patients, 18 (1%) had cancer (compared with a population cancer prevalence of 0.29%).(4) Cancer was associated with more severe CT findings and a higher risk of severe COVID-19 disease. Whilst drawn from small numbers, it also appears that recent anti-cancer therapy confers a higher risk of more severe COVID-19 disease. Amongst patients with cancer, older age was an additional risk factor for severe events, though the older age of the cancer cohort compared with the

comparator non-cancer cohort may have over exaggerated the risks from cancer.(5) Nevertheless, a further series suggests that patients with cancer are at greater risk of SARS-CoV-2 infection.(6) Given these factors and the increasing prevalence of SARS-CoV-2 in the UK community, there are significant concerns about the impact of COVID-19 on patients with cancer. Of added concern is an expected surge in the number of cases that will threaten intensive treatment unit (ITU) bed availability, and that will reduce numbers of frontline clinical staff. This will be exacerbated by an increasing level of COVID infection or exposure to suspected infection which will require staff isolation. Together with the risk of immunosuppression, and the por outcome for patients with cancer who are infected, these factors mandate re-consideration of treatment pathways for patients with malignancies, including upper GI cancers, in order to account for both service constraints and the increased risks of SARS-CoV-2 infection; i.e. to limit service use whilst directing resources to achieve maximum benefit and to mitigate risks of infection with SARS-CoV-2, such as by avoiding hospital admission or attendance. However, there is very limited data to guide clinicians in adapting their treatment. The following considerations therefore represent the best expert consensus to support the UK upper GI community.

4. CONSIDERATIONS BY TREATMENT CONTEXT IN OESOPHAGEAL CANCERS

4.1. Neo-adjuvant

Elective surgery performed with the expectation of a cure is categorised as surgical priority level 2 by the NHS.

There is concern that due to the expected increase in ITU bed occupancy rates during the COVID-19 pandemic, elective surgery may become a less viable option over the coming weeks to months. For patients in the system who are planned and due to undergo oesophagectomy prior to the expected peak in ITU occupancy, proceeding to oesophagectomy would seem to remain the best option.(7) Further guidance relating to surgical intervention is provided in **5.3.**

If neo-adjuvant chemoradiotherapy is considered – either as planned neo-adjuvant treatment or perhaps as bridge to surgery once ITU bed occupancy rates begin to decrease - a proposed alternative regimen to consider is 40Gy/15# concurrent chemoradiotherapy (CRT) with weekly carboplatin and paclitaxel (carbo-taxol), (modified from the Walsh regimen).(8) This hypofractionated regime would carry the advantage of reducing hospital visits. There is evidence that the benefits delivered by neoadjuvant CRT in terms of pCR and overall survival is seen at doses of 39.6 Gy, but it is less certain that higher doses deliver additional benefit.(9)

It is very important that consideration is given to the prospects of surgical treatment in respect to reduced surgical capacity, especially in higher risk patients. In the case of uncertainty, a definitive chemo-radiotherapy treatment regimen (see below) should be considered with an assessment by endoscopy and CT (+/-CT-PET) at 8 weeks post radiotherapy with a low threshold for surgery in previously fit and operable patients.

Induction chemotherapy prior to the chemoradiotherapy component would add risk of immunosuppression and therefore increase risks relating to COVID-19 infection. If neo-adjuvant chemotherapy felt to be strongly indicated, consider a single cycle of 3 weekly carbo-taxol or 1-2 doses of weekly carbo-taxol during planning of RT. If 3-weekly carbo-taxol is used, consider prophylactic granulocyte-colony stimulating factor (GCSF) as the regimen is myelosuppressive.

If used in the UK, and possibly internationally, we would encourage prospective audit of outcomes from this shortened neo-adjuvant regimen. It is also important to discuss with your local organisation how to document discussions with patients regarding planned treatment in the light of higher risk and reduced capacity for treatment delivery and patient support.

If combination neoadjuvant chemotherapy consisting of 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) is to be used, consider use of prophylactic granulocyte-colony stimulating factor (GCSF). The benefits of this peri-operative approach need to be weighed against local capacity to deliver and the immunosuppressive effects. Consider a lower threshold for using neoadjuvant chemotherapy for gastric or bulky type 3 GOJ disease. For patients with gastric body or antral cancer, consider use of FLOT given the myelosuppression associated with CRT used for this disease site.

Summary points: a. Consider expediting planned surgical resection prior to predicted surge in ITU bed occupancy.
b. Consider hypofractionated neo-adjuvant CRT of 40Gy/15# with weekly carbo-taxol (+/- 1-3 weeks NACT) Consider prospective data collection.
c. Consider avoiding induction chemotherapy in patients planned for neo-adjuvant CRT.
d. Consider use of prophylactic GCSF with neoadjuvant single-modality FLOT.

4.2. Radical

Definitive chemoradiotherapy (dCRT) and neoadjuvant CRT followed by surgery have typically viewed as delivering equivalent outcomes for OSCC. In the light of the COVID-19 pandemic, dCRT may be considered as the most appropriate curative treatment option for OSCC. Whilst as the evidence for delivering equivalent outcomes for OAC is not so robust, good outcomes were seen for this group in SCOPE 1 and dCRT should be considered in order to ensure that patients are able to receive radical treatment.(10)

Consider use of carbo-taxol in place of cisplatin-capecitabine for dCRT due to a more favourable toxicity profile.

Consider likelihood of admission when selecting patients for dCRT; patients at high risk of admission such as those with high-grade dysphagia may not be appropriate for dCRT given the greater risks expected from hospitalisation as a consequence of the COVID-19 pandemic. Consider lowering threshold for prophylactic enteral nutrition (although there may be issues with capacity to place and manage feeding tubes)

In patients not suitable for dCRT, consider hypofractionated definitive radiotherapy alone (dRT). This may include patients who would previously have been considered dCRT but for whom the risks from multiple hospital visits and immunosuppression associated with concurrent chemotherapy in the context of the COVID-19 pandemic would render dCRT unsuitable. In patients with tumours of up to 5cm in length, consider 50Gy/16#. In patients with tumours of up to 10cm in length, consider 50-55Gy/20#.(11)

Summary points: a. Consider dCRT as the most appropriate curative option for OSCC and OAC.
b. Consider use of weekly carbo-taxol in place of cisplatin-capecitabine for dCRT
c. Consider avoiding induction chemotherapy in patients planned for dCRT
e. Consider hypofractionated definitive radiotherapy (dRT) for high-dose control in patients not suitable for dCRT. For tumours of up to 5cm use 50Gy/16# or 45Gy/15#. For tumours up to 10cm use 50-55Gy/20#.

4.3. Adjuvant

Decisions relating to adjuvant therapy in this context likely to be nuanced. Use of CRT in older patients or those with comorbidities is likely to confer considerable risk. Adjuvant FLOT may be considered but the incremental benefit of post-operative FLOT is unclear. Factors against adjuvant treatment after neoadjuvant FLOT in this context include persistent path node positivity as well as R1

status despite neo-adjuvant treatment. Factors that may favour intervention would include a good tumour regression score demonstrating chemosensitive disease and previously tolerated FLOT. If following discussion with patient, adjuvant treatment is favoured, consider delay of 12 weeks prior to commencing therapy. As above, consider use of prophylactic GCSF with FLOT.

Summary points: a. Consider not recommending adjuvant CRT
b. Consider delaying adjuvant treatment by 12 weeks
c. Consider a high threshold for using post-op FLOT and prophylactic GCSF where used.

4.4. Palliative

4.4.1. 1st line systemic therapy

Factors that may change the balance of decision to treat include those relating to poor outcome with COVID-19 (e.g. older age, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, performance status of 2 or above). Consider limiting palliative chemotherapy to 4-6 cycles. Nationally there is a move to doublet over triplet treatment and certainly during the COVID-19 pandemic consider omitting epirubicin (ie oxaliplatin-capecitabine instead of EOX). In line with GO2 data, consider oxaliplatin-capecitabine dose-reduction to 60% following risk-benefit assessment.(12) Consider early imaging to assess response to systemic anti-cancer therapy. In patients for whom response is lacking, consider early cessation of chemotherapy. In patients who achieve response or have non-bulky disease at three months, consider cessation of chemotherapy or switch to maintenance Herceptin after 4 cycles.

Summary points: a. Minimise the duration of systemic cytotoxic treatment
b. Consider dose reduction of ox-cap to 60% as guided by the GO2 trial
c. Consider early imaging to assess response to SACT to enable early treatment discontinuation if not achieving benefit.
d. If response or non-bulky disease at three months, consider cessation of chemotherapy.

4.4.2.. 2nd line systemic therapy

It is unclear that in the context of the COVID-19 pandemic, the benefits of delivering SACT in this setting would outweigh the risks. Consider if prolonged period since 1st line chemotherapy, presence of symptoms and good performance status; factors associated with benefit in COUGAR-02.(13)

Summary points: a. Have a high threshold for giving 2nd line systemic palliative therapy but consider if a prolonged period from 1st line therapy, if the patient is symptomatic and if the patient's performance status is good.

4.4.3. 3rd line systemic therapy

Consider avoiding 3rd line palliative therapy, for which there is no supporting evidence.(reference categories below)

Summary points: a. Consider not delivering 3rd line palliative systemic therapy.

4.4.4. Palliative Radiotherapy

Consider reducing fractionation and use single fraction approaches or 20Gy/5# in place of standard 30Gy/10# or 40Gy/15# approaches. Consider use of alternative approaches, including analgesia, oesophageal stent* and palliative care input.

* As with all guidance in this document, this must be considered by each site's MDT. There may be concerns regarding the safety of endoscopic intervention during the COVID-19 pandemic.

Summary points: a. Consider 8Gy/1# or 20Gy/5# as palliative doses, or seek alternative non-radiotherapy based approaches to disease palliation.

It should be noted that currently there is no data on whether radiotherapy mediated inflammation would worsen COVID pneumonia/ARDS. It is necessary to prospectively audit outcomes from treatment in real time, share experiences and review guidance as appropriate. Patients diagnosed with COVID-19 or experiencing symptoms consistent with COVID-19 should probably avoid thoracic radiotherapy.

5. CONSIDERATIONS BY TREATMENT MODALITY

5.1. Systemic anti-cancer therapy

National Health Service (NHS) England has provided a *Clinical guide for the management of cancer patients during the coronavirus pandemic*.(14) In this, patients are categorised and prioritised for systemic anti-cancer therapy by anticipated outcome, as follows:

Priority level 1: curative therapy with a high (>50%) chance of success
Priority level 2: curative therapy with an intermediate (15-50%) chance of success
Priority level 3: non-curative therapy with a high (>50%) chance of >1 year of life extension
Priority level 4: curative therapy with a low (0-15%) chance of success / 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 / temporary tumour control and <1 year life extension

These factors should be taken into account when weighing up service constraints against the provision of systemic therapies.

When using systemic therapies, consider use of GCSF as primary prophylaxis in order to reduce likelihood of admission.

Summary points: a. Refer to the NHS Clinical guide for the management of cancer patients during the coronavirus pandemic to inform decisions relating to chemotherapy use weighed up against service constraints.
b. Consider use of GCSF as primary prophylaxis in order to reduce admission likelihood.
c. Consider use of GO2 dose-reduced chemotherapy regimens to reduce admission likelihood.
d. Consider use of models, such as those by Williams et al, to inform decisions relating to chemotherapy provision during the COVID-19 outbreak.

5.2. Radiotherapy

Practical advice for radiotherapy departments has been published by Filippi et al.(14)Robust local processes need to be in place to ensure that category 1 patients (which includes patients with oesophageal cancer receiving dCRT) can continue treatment uninterrupted even if they develop COVID-19 e.g. dedicated machine with optimal access, treat end of day with clean post treatment. Clinicians should nevertheless consider the risks of treatment interruption from COVID-19 infection and whether the potential resultant reduction in treatment efficacy changes the risk : benefit profile of delivering that treatment. Guidance has provided by NHS England, as follows: (15)

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.

5.3. Surgery

The Association of Upper Gastrointestinal Surgery of Great Britain & Ireland has published a document pertaining to surgical priority in oesophageal and gastric cancer.(7) This emphasises the need to assess that treatment decisions for interventions that would require level 1 postoperative care should take into account critical care bed status. If this is limited or unavailable, alternative treatment should be considered. Similarly, procedures requiring level 2/3 care should take into account bed pressures, patient symptoms, performance status and tumour biology. In both oesophageal and gastric cancer, T1a and T1b disease may be treated endoscopically, or a delay in treatment of up to 3 months may be considered.

5.3.1. Example prioritisation protocol

The University Hospitals Birmingham Upper GI MDT have developed the following protocol to guide prioritisation of elective surgery into four categories (highest to lowest priority):

1. Curative therapy with a >50% chance of success:
    a. T2N0 or less, low chance of complications
    b. Good response to neo-adjuvant chemotherapy (near or close to a complete response)
    c. T3N0 with low chance of complications
2. Curative therapy with an intermediate (15-50%) chance of success
    a. T3N1 with low chance of complications
    b. T3N2 with low chance of complications
    c. T3N1 disease; mild comorbidities, minimal response to chemotherapy
3. Non-curative therapy with high chance (>50%) of >1 year life extension
    a. T4a or >N2 with low chance of complications
4. Low chance of cure OR high risk of complications

6. Revision history

Date	Version	Section	Revision
20/03/2020	1.0	Version 1.0 released for comment	
22/03/2020	2.0	NA	Document re-ordered to aid readibility

		3.0	Additional notes regarding impacts of staff isolation and patient immunosuppression
		4.1	Evidence for RT dose escalation in neo-adjuvant therapy outlined
		4.1	Suggestion to use GCSF with 3-weekly carbo-taxol added
		4.1	Additional note relating to local pressures on need to assess local ITU capacity prior to considering surgical intervention added
		4.3	Suggestion to consider delaying adjuvant therapy by twelve weeks added
		5	References to Williams et al removed pending peer review
		5.2	Notes relating to radiotherapy prioritisation from NHS England added
		5.3	Notes relating to surgical intervention added, including a proposed model of treatment prioritisation
25/03/2020	3.0	4.1	Additional note added emphasising the need to consider surgical capacity when making treatment decisions relating to neoadjuvant versus definitive non-surgical therapy
		4.1	Additional note concerning risks of myelosuppression with CRT used for gastric body or antral cancer
		4.4.1	Additional note relating to consideration of dose-reduction of ox-cap in line with GO2 data
		4.4.2	Reference added for factors that might contribute to consideration of second line chemotherapy
		4.4.4.	Additional note added related to possible risks of endoscopic intervention for dysphagia

7. GLOSSARY OF TERMS

COVID-19: coronavirus disease 2019
ITU: intensive treatment unit
MDT: multi-disciplinary team
NHS: National Health Service
OAC: oesophageal adenocarcinoma
OC: oesophageal cancer
OSCC: oesophageal squamous cell carcinoma
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
TRG: tumour regression grade
UK: United Kingdom

8. REFERENCES

1.Worldometer: COVID-19 CORONAVIRUS OUTBREAK. Accessed online at worldometers.info/coronavirus/, 18th March 2020.
2. Department of Health and Social Care/Public Health England. Number of coronavirus (COVID-19) cases and risk in the UK. Accessed online at https://www.gov.uk/guidance/coronavirus-covid-19-information-for-the-public, 18th March 2020.
3. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; (published online 24th January 2020).
4. Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; (published online 14th Feb 2020).

5. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *The Lancet Oncology* 2020; (published online 3rd March 2020).
6. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality – preliminary results. Doi: https://doi.org/10.1101/2020.02.24.20027268.
7. Association of Upper Gastrointestinal Surgery of Great Britain & Ireland. Surgical Priority in Oesophageal and Gastric Cancer. March 2020.
8. Walsh TN, Noonan N, Hollywood D et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;335:462-7.
9. Worrell SG, Towe CW, Dorth JA, Machtay M, Perry Y, Linden PA. Higher doses of neoadjuvant radiation for esophageal cancer do not affect the pathologic complete response rate or survival: a propensity-matched analysis. *Ann Surg Oncol* 2020;27:500-508.
10. Crosby T, Hurt CN, Falk S et al. Long-term results and recurrence patterns from SCOPE-1: a phase II/III randomised trial of definitive chemoradiotherapy +/- cetuximab in oesophageal cancer. *BJC* 2017;116(6):709-716.
11. Jones CM, Spencer K, Hitchen C, Pelly T, Wood B, Hatfield P, Crellin A, Sebag-Montefiore D, Goody R, Crosby T, Radhakrishna G. Hypofractionated radiotherapy in oesophageal cancer for patients unfit for systemic therapy: a retrospective single-centre analysis. *Clin Oncol* 2019;31(6):356-64.
12. Hall PS, Swinson D, Waters JS et al. Optimizing chemotherapy for frail and elederly patients (pts) with advanced gastroesophageal cancer (aGOAC): The GO2 phase III trial. *Abstract, available online:* https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.4006. Accessed 18th March 2020.
13. Ford HER, Marshall A, Bridgewater JA et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncology* 2013;15(1):78-86.
14. NHS England. Clinical guide for the management of cancer patients during the coronavirus pandemic. *NHS England* 2020. Version 1 (17 March 2020)
15. Filippi AR, Russi E, Magrini SM, Corvo R. COVID-19 outbreak in Northern Italy: First practical indications for radiotherapy departments. *Int J Radiat Oncol Biol Phys* 2020; epub ahead of print.