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 xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Considerations for the Treatment of Oesophageal Cancer With Radiotherapy During the COVID-19 Pandemic

C.M. Jones [*†‡], M. Hawkins [§], S. Mukherjee [¶], G. Radhakrishna [||], T. Crosby [**]

[*] *School of Molecular & Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds, UK*
[†] *Radiotherapy Research Group, Leeds Institute of Medical Research at St James's, Faculty of Medicine & Health, University of Leeds, Leeds, UK*
[‡] *Leeds Cancer Centre, The Leeds Teaching Hospitals NHS Trust, Leeds, UK*
[§] *Department of Medical Physics & Biomedical Engineering, University College London, London, UK*
[¶] *CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford, UK*
[||] *Christie Hospital, The Christie NHS Foundation Trust, Manchester, UK*
[**] *Velindre Cancer Centre, Cardiff, UK*

Received 27 March 2020; accepted 1 April 2020

The coronavirus disease 2019 (COVID-19) pandemic is a public health emergency caused by widespread infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. For patients with cancer, COVID-19 presents a significant challenge. Many are immunosuppressed, both as a direct result of the malignant disease and as a consequence of anti-cancer treatment. As such, they may be more likely to contract SARS-CoV-2 [2]. Given that hospitals are thought to act as a reservoir from which this virus spreads, the risk of COVID-19 is further exacerbated by the requirement for patients with cancer to frequently attend hospital for follow-up visits, imaging and intensive treatment [2–4]. In a small study in Wuhan, China, the suspected source of the COVID-19 outbreak, patients with cancer seemed to be at a higher risk of SARS-CoV-2 infection than the wider community, and both recurrent hospital visits and hospital admission conferred greater risk still [2]. A cancer diagnosis and recent anti-cancer treatment have additionally been linked to greater COVID-19 severity [3,4].

The impact of healthcare service pressures on the care of patients with cancer is also a concern. In the UK, as in other countries, a surge in critically unwell patients with COVID-19 is expected to significantly diminish bed availability within high-dependency (HDU) and intensive care units (ICUs). Widespread disease transmissibility will also impact on the availability of frontline clinical staff. Together, these service pressures and the shift in the risk:benefit ratio caused by the widespread transmission of SARS-CoV-2 necessitates – at least in the short to medium term – re-consideration of treatment pathways for patients with cancer. This is of particular pertinence to oesophageal cancer, which is typically treated using an intensive multimodality approach that involves thoracic radiotherapy, and for which significant delays in treatment are precluded by disease biology and symptoms such as dysphagia.

In light of this we convened an expert group of UK clinicians with expertise in oesophageal cancer. Consensus was sought for evidence-based approaches to the management of oesophageal cancer that would maintain benefit, minimise risk to the patient, accommodate for service pressures and limit hospital attendance. Guiding principles relevant to radiotherapy provision are described here. As the pandemic progresses, guidance for acting on these will be updated at www.uppergicancer.com.

General Principles

Advice for stratifying and prioritising surgery and systemic treatments has been published elsewhere, as has practical advice for radiotherapy departments and practitioners [5–7]. Wherever possible, hospital attendances should be reduced or avoided. This includes through the provision of telephone-based consultations and either delaying treatment or modifying it to reduce the number of days on which patients must attend for radiotherapy and to limit the chance of acute admission. Departments should also institute measures to limit the spread of infection.

Author for correspondence: T. Crosby, Velindre Cancer Centre, Velindre Road, Whitchurch, Cardiff CF14 2TL, UK. Tel: +44-29-2061-5888.
E-mail address: tom.crosby@wales.nhs.uk (T. Crosby).

https://doi.org/10.1016/j.clon.2020.04.001

There are to our knowledge no data at present to indicate whether thoracic radiotherapy increases the severity of the COVID-19 disease course. A pragmatic approach is for patients diagnosed with COVID-19 or experiencing symptoms consistent with it to avoid or delay thoracic radiotherapy, although this will need to be reviewed as further data emerge.

Radical Approaches

Standard treatment approaches for potentially curable oesophageal cancer typically comprise neoadjuvant chemotherapy or chemoradiotherapy (CRT) followed by either resection or definitive CRT (dCRT), with some patients receiving postoperative chemotherapy or CRT dependent on resection margins and performance status. Guidance for adapting this therapy is provided here based on treatment intention and is summarised in Table 1.

Definitive Treatment

Elective surgery carried out with the expectation of cure is categorised as surgical priority level 2 by the National Health Service. There is concern that the expected increase in HDU/ICU bed occupancy and the risk of postoperative SARS-CoV-2 infection will severely limit or preclude surgical intervention. It is important that consideration is given to the prospects of surgical treatment. For patients who have started or completed neoadjuvant therapy, surgical intervention should be expedited where possible. If there is uncertainty related to surgical capacity, we would suggest that dCRT with no neoadjuvant or induction component is the most appropriate option to provide an upfront definitive treatment approach while limiting infection risk. In the absence of robust head-to-head data, dCRT and neoadjuvant treatment followed by surgery are typically viewed as delivering equivalent outcomes for oesophageal squamous cell carcinoma [8]. The evidence for equivalent outcomes from dCRT is less robust for oesophageal adenocarcinoma but good outcomes were seen for this group in SCOPE1 [9,10].

Despite the theoretical advantages of hypofractionated regimens during the COVID-19 pandemic, there is to our knowledge no robust evidence to advocate for a hypofractionated dCRT approach. Careful patient selection for dCRT using standard 50 Gy/25 fractions fractionation with concurrent chemotherapy is therefore imperative and patients should be counselled regarding the risk:benefit ratio of treatment. Patients at a higher risk include those with comorbidities and who are more likely to require acute admission, such as those with high-grade dysphagia when starting treatment [11]. Risks may also be mitigated through the use of weekly carboplatin–paclitaxel in place of 3-weekly cisplatin–fluoropyrimidine-based chemotherapy, given the more favourable toxicity profile. In a recently presented phase III trial and in a multicentre retrospective analysis from the UK, weekly carboplatin–paclitaxel-based dCRT has shown 2- and 3-year overall survival of 50 and 40%, respectively [12,13]. The regimen was well tolerated and resulted in 10% grade 3 or above haematological toxicity, compared with 28% for cisplatin–-fluoropyrimidine-based treatment in SCOPE1 [9,12,13]. We also suggest considering lowering the threshold for prophylactic enteral nutrition where there is capacity to place enteral feeding tubes, as this would potentially minimise the need for unplanned hospitalisation [14]. Follow-up of patients managed with dCRT should, if service pressures allow, include endoscopy and cross-sectional imaging at 8 weeks post-treatment, with a low threshold for surgery if indicated [15]. It is hoped that HDU and ICU access may be somewhat better in the timeframe for 5–6 months, where such surgery might be considered.

In patients for whom the risks of dCRT are considered too great, or in instances where there is limited chemotherapy provision, consider definitive hypofractionated radiotherapy for locally advanced disease. Tumours of up to 5 cm

Table 1
A summary of recommendations for the radiotherapy-based management of patients with oesophageal cancer during the coronavirus disease 2019 (COVID-19) pandemic. The impact of radiotherapy on disease severity in patients with a diagnosis of COVID-19 is unknown and it may be appropriate to avoid radiotherapy in such patients

Radical approaches
Definitive treatment • Expedite planned surgical resection before the expected surge in higher-level care bed occupancy. • Consider dCRT as the most appropriate curative option for both OSCC and OAC. • Patients who are at high risk for readmission, such as those with high-grade dysphagia, may not be appropriate for dCRT. • Consider use of weekly carboplatin–paclitaxel in place of cisplatin–fluoropyrimidine-based chemotherapy to limit toxicity. • Where dCRT is unavailable or inappropriate, consider hypofractionated dRT of 50 Gy/16 fractions for tumours of up to 5 cm in length or 55 Gy/10 fractions for tumours of up to 10 cm in length. • Consider a low threshold for prophylactic enteral nutrition if there is capacity to place feeding tubes. Neoadjuvant treatment • If neoadjuvant treatment is considered appropriate, consider hypofractionated dCRT 40 Gy/15 fractions with weekly carboplatin–paclitaxel.
Palliative approaches
• Use a single 8 Gy/1 fraction or 20 Gy/5 fractions for relief of dysphagia or disease control in the palliative setting.

CRT, chemoradiotherapy; dCRT, definitive chemoradiotherapy; dRT, definitive radiotherapy; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Please cite this article as: Jones CM et al., Considerations for the Treatment of Oesophageal Cancer With Radiotherapy During the COVID-19 Pandemic, Clinical Oncology, https://doi.org/10.1016/j.clon.2020.04.001

in length may be treated with 50 Gy/16 fractions and tumours of up to 10 cm in length with 50–55 Gy/20 fractions. In a recent single-centre retrospective series, this regimen resulted in reasonable median overall survival of 26 months that compared with 29 months for a dCRT cohort from the same centre that had fewer comorbidities but more advanced disease [16]. Time-to-stent insertion was also similar and grade 3 or above toxicity with definitive radiotherapy was favourable at 16.4%.

Neoadjuvant Treatment

Where neoadjuvant CRT (nCRT) with a view to surgery is still considered to be a viable option, we suggest use of hypofractionated CRT consisting of 40 Gy/15 fractions with weekly carboplatin and paclitaxel; as modified from the Walsh regimen [17]. There is evidence to suggest that the benefits conferred by nCRT for pathological complete response and overall survival are seen at doses of 39.6 Gy, but it is less certain that higher doses deliver additional benefit [18]. Beyond the pandemic peak when surgical capacity begins to be restored but where services remain stretched, nCRT may again represent an appropriate treatment option. Neoadjuvant chemotherapy may also be considered with prophylactic growth factor support, although in both instances (neoadjuvant chemotherapy or nCRT) multidisciplinary teams need to consider whether such patients are likely to proceed to surgical resection within a reasonable timeframe.

Adjuvant

Where performance status allows, patients with oesophageal cancer are typically considered for adjuvant chemotherapy or CRT. Decisions relating to the provision of adjuvant therapy are likely to be nuanced and dependent both on performance status, postoperative resection margins, disease stage and the likely additional benefit of such intervention, especially if neoadjuvant therapy has been given. If treatment is favoured, a delay of 12 weeks should be considered to avoid starting treatment during the peak of COVID-19.

Palliative Approaches

Indications for radiotherapy for oesophageal cancer in the non-curative setting include disease control, haemostasis and the relief of dysphagia. Given the anticipated pressure on palliative care teams and a reduction in endoscopy capacity for procedures such as endoluminal stenting, radiotherapy will probably be an important option for symptom relief [19]. The risks of standard fractionation schedules in this setting of 30 Gy/10 fractions or 40 Gy/15 fractions will probably outweigh any benefits during the COVID-19 pandemic, and add further pressure to radiotherapy departments. As such, we suggest use of single 8 Gy/1 fraction or 20 Gy/5 fractions treatment schedules. There is little evidence that dose escalation above 20 Gy achieves additional symptomatic benefit [20].

Summary

The COVID-19 pandemic represents an unprecedented challenge for healthcare services. The recommendations here should serve to support clinicians in as far as possible mitigating the impact of this crisis on patients with oesophageal cancer and those who care for them.

Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TC is an Advisory Board member for Bristol Myers-Squibb and Astra Zeneca, and has received conference funding from Roche. SM receives research funds from Celgene that do not relate to the published work.

Acknowledgements

Consensus was reached virtually by a number of members of the UK upper gastrointestinal community, with those involved reviewing a number of iterations of the guidance shown here. We are grateful to Lubna Bhatt, Emma Cattell, Sebastian Cummins, Rebecca Goody, Sarah Gwynne, Carys Morgan, Russell Petty, Hamid Sheikh, Elizabeth Smyth and Elizabeth Toy for their valuable input in this. C.M. Jones is supported by a Wellcome Trust Clinical Research Fellowship. M. Hawkins acknowledges funding from the NIHR Biomedical Research Centre at University College London Hospitals NHS Foundation Trust and University College London. S. Mukherjee acknowledges funding from the NIHR Oxford Biomedical Research Centre.

References

[1] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199–1207.
[2] Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol* 2020 Mar 25. https://doi.org/10.1001/jamaoncol.2020.0980.
[3] Liang W, Guan W, Chen R, Wang W, Li J, Ke X, *et al*. Cancer patients in SARS-Co-V-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21(3):335–337.
[4] Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for cancer patients. *Lancet Oncol* 2020. https://doi.org/10.1016/S1470-2045(20)30150-9.
[5] Filippi AR, Russi E, Magrini SM, Corvo R. Letter from Italy: first practical indications for radiation therapy departments during COVID-19 outbreak. *Int J Radiat Oncol Biol Phys* 2020 Mar 19. https://doi.org/10.1016/j.ijrobp.2020.03.007.
[6] NHS England. Clinical guide for the management of cancer patients during the coronavirus pandemic. *NHS Engl* 2020: 2020. Version 1.
[7] Simcock R, Thomas TV, Estes C, Filippi AR, Katz MA, Pereira IJ, *et al*. COVID-19: global radiation oncology's targeted response

for pandemic preparedness. *Clin Trans Radiat Oncol* 2020;22:55–68.

[8] Rackley T, Leong T, Foo M, Crosby T. Definitive chemoradiotherapy for oesophageal cancer – a promising start on an exciting journey. *Clin Oncol* 2014;26:533–540.

[9] Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, *et al*. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicenter, phase 2/3 randomised trial. *Lancet Oncol* 2013;14(7):627–637.

[10] Crosby T, Hurt CN, Falk S, Gollins S, Staffurth J, Ray R, *et al*. Long-term results and recurrence patterns from SCOPE-1: a phase II/III randomized trial of definitive chemoradiotherapy ± cetuximab in oesophageal cancer. *Br J Cancer* 2017;116(6):709–716.

[11] Mohammad NH, Hulshof MCCM, Bergman JJGHM, Geijsen D, Wilmink JW, Henegouwen MIvB, *et al*. Acute toxicity of definitive chemoradiation in patients with inoperable or irresectable esophageal carcinoma. *BMC Cancer* 2014;14:56.

[12] Hulshof MCCM, Geijsen D, Rozema T, Oppedijk V, Buijsen J, Neelis KH, *et al*. A randomized controlled phase III multicenter study on dose escalation in defintiive chemoradiation for patients with locally advanced esophageal cancer: ARTDECO study. *J Clin Oncol* 2020. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.281. [Accessed 26 March 2020].

[13] Owens R, Cox C, Gomberg S, *et al*. Outcome of weekly carboplatin-paclitaxel-based definitive chemoradiation in oesophageal cancer in patients not considered to be suitable for platinum-fluoropyrimidine-based treatment: a multicentre, retrospective review. *Clin Oncol* 2020;32(2):121–130.

[14] Howard A, Banks S, Owens R, Ward L, Warner N, Mukherjee S. The role of active nutritional intervention in patients receiving chemoradiation (CRT) for oesophageal cancer. *Ann Oncol* 2019;30(Suppl 4):iv78.

[15] Markar S, Gronnier C, Duhamel A, Pasquer A, Thereax J, Rieu MC, *et al*. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? *J Clin Oncol* 2015;33(33):3866–3873.

[16] Jones CM, Spencer K, Hitchen C, Pelly T, Wood B, Hatfield P, *et al*. Hypofractionated radiotherapy in oesophageal cancer for patients unfit for systemic therapy: a retrospective single-centre analysis. *Clin Oncol (R Coll Radiol)* 2019;31(6):356–364.

[17] Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP, *et al*. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;335(7):462–467.

[18] 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.

[19] British Society of Gastroenterology (BSG). GI endoscopy activity and COVID-19: next steps. Available at: https://www.bsg.org.uk/covid-19-advice/gi-endoscopy-activity-and-covid-19-next-steps/. [Accessed 26 March 2020].

[20] Walterbos NR, Fiocco M, Neelis KJ. Effectiveness of several external beam radiotherapy schedules for palliation of esophageal cancer. *Clin Trans Radiat Oncol* 2019;17:24–31.

Please cite this article as: Jones CM et al., Considerations for the Treatment of Oesophageal Cancer With Radiotherapy During the COVID-19 Pandemic, Clinical Oncology, https://doi.org/10.1016/j.clon.2020.04.001