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

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Summary:

Oesophageal Cancer Treatment During the COVID-19 Pandemic

Keywords:

Oesophageal cancer; oesophageal squamous cell carcinoma; oesophageal adenocarcinoma; COVID-19; treatment; hypofractionated.

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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, 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 in China, patients with cancer appeared at higher risk of SARS-CoV-2 infection than the wider community, and both recurrent hospital visits and hospital admission conferred greater risk still.(2) In addition, 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 (OC), which is typically treated using an intensive multi-modality 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 OC. Consensus was sought for evidence-based approaches to the management of OC that would maintain benefit, minimize 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 prioritizing 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.

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, though this will need to be reviewed as further data emerges.

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 post-operative chemotherapy or CRT dependent on resection margins and performance status. Guidance for adapting this therapy is provided here based on treatment intention and summarized in **Box 1**.

Definitive treatment

Elective surgery performed with the expectation of cure is categorized as surgical priority level 2 by the National Health Service (NHS). There is concern that the expected increase in HDU/ITU bed occupancy, and the risk of post-operative 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 commenced 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 whilst 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 OSCC.(8) The evidence for equivalent outcomes from dCRT is less robust for OAC 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 50Gy/25# fractionation with concurrent chemotherapy is therefore imperative and patients should be counselled regarding the risk : benefit ratio of treatment. Patients at higher risk include those with comorbidities and who are more likely to require acute admission, such as those with high-grade dysphagia when commencing 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 multi-centre retrospective analysis from the UK, weekly carboplatin-paclitaxel based dCRT has demonstrated 2- year and 3- year OS 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-fluopyrimidine 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 minimize need for unplanned hospitalization.(14) Follow-up of patients managed with dCRT should, if service pressures allow, include endoscopy and cross-sectional imaging at eight weeks post-treatment, with a low threshold for surgery if indicated.(15) It is hoped that HDU and ITU access maybe 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 (dRT) for locally advanced disease. Tumours of up to 5cm in length may be treated with 50Gy/16#, and tumours of up to 10cm in length with 50-55Gy/20#. In a recent single-centre retrospective series, this regimen resulted in reasonable median OS 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 dRT was favourable at 16.4%.

Neo-adjuvant treatment

Where neoadjuvant CRT (nCRT) with a view to surgery is still considered a viable option, we suggest use of hypofractionated CRT consisting of 40Gy/15# with weekly carboplatin and paclitaxel; as modified from the Walsh regimen.(17) There is evidence to suggest that the benefits conferred by neoadjuvant CRT for pathological complete response (pCR) and overall survival (OS) are seen at doses of 39.6Gy, 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 (NaCT) may also be considered with prophylactic growth factor support, though in both instances (NaCT or nCRT) MDTs need to consider whether such patients are likely to proceed to surgical resection within a reasonable timeframe.

Adjuvant

Where performance status allows, patients with OC 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 neo-adjuvant 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 OC 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 is likely to be an important option for symptom relief.(19) The risks of standard fractionation schedules in this setting of 30Gy/10# or 40Gy/15# are likely to outweigh any benefits during the COVID-19 pandemic, and add further pressure to radiotherapy departments. As such, we suggest use of single 8Gy/1# or 20Gy/5# treatment schedules. There is little evidence that dose escalation above 20Gy 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 impacts of this crisis on patients with oesophageal cancer and those who care for them.

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REFERENCES

1. Li Q, Guan X, Wu P et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; published online 29th January. DOI: 10.1056/NEJMoa2001316.

2. Yu J, Ouyang W, Chua MLK et al. SARS-CoV-2 Transmission in Patients with Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol* 2020; published online 25th March. DOI:10.1001/jamaoncol.2020.0980.

3. Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncol.* 2020; published online 14th February. DOI: 10.1016/S1470-2045(20)30096-6.

4. Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for cancer patients. *The Lancet Oncol* 2020; published online 3rd March 2020. DOI: 10.1016/S1470-2045(20)30150-9.

5. 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.

6. NHS England. Clinical guide for the management of cancer patients during the coronavirus pandemic. *NHS England* 2020. Version 1, published 17th March 2020.

7. Simcock R, Thomas TV, Mercy CE et al. COVID-19: Global Radiation Oncology's Targeted Response for Pandemic Preparedness. *Clin Trans Radiat Oncol* 2020; published online 24th March. DOI: 10.1016/j.ctro.2020.03.009.

8. Rackley T, Leong T, Foo M, Crosby T. Definitive chemo-radiotherapy for oesophageal cancer – a promising start on an exciting journey. *Clin Oncol* 2014;26:533-40.

9. Crosby T, Hurt CN, Gollins S 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):627-37.

10. Crosby T, Hurt CN, Falk S 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 M, Bergman J et al. Acute toxicity of definitive chemoradiation in patients with inoperable or irresectable esophageal carcinoma. *BMC Cancer* 2014;14(56):1-6.

12. Hulshof M, Geijsen D, Rozema T et al. A randomized controlled phase III multicenter study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer: ARTDECO study. *J Clin Oncol* 2020. Available from https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.281. Accessed 26th 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 multicenter, retrospective review. *Clin Oncol (R Coll Radiol)* 2020;32(2):121-130.

14. Howard A, Banks S, Owens R et al. The role of active nutritional intervention in patients receiving chemoradiation (CRT) for oesophageal cancer. *Ann Oncol* 2019;30(4):iv78.

15. Markar S, Gronnier C, Duhamel A et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? *J Clin Oncol* 2015;33(33):3866-73.

16. Jones CM, Spencer K, Hitchen C et al. Hypofractionated Radiotherapy in Oesophageal Cancer for Patients Unfit for Systemic Therapy: A Retrospective Single-Centre Analysis. *Clin Oncol (R Coll Radiol)* 2019;31:356-64.

17. 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.

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. Published 26th March 2020. Available at https://www.bsg.org.uk/covid-19-advice/gi-endoscopy-activity-and-covid-19-next-steps/. Accessed 26th 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.

Table

TABLES

RADICAL APPROACHES
Definitive treatment
• Expedite planned surgical resection prior to 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 re-admission, such as those with high-grade dysphagia, may not be appropriate for dCRT. • Consider use of weekly carboplatin-paclitaxel in place of cisplatin-fluopyrimidine based chemotherapy to limit toxicity. • Where dCRT is unavailable or inappropriate, consider hypofractionated dRT of 50Gy/16# for tumours of up to 5cm in length or 55Gy/10# for tumours of up to 10cm in length. • Consider a low threshold for prophylactic enteral nutrition if there is capacity to place feeding tubes.
Neo-adjuvant treatment
• If neo-adjuvant treatment is considered appropriate, consider hypofractionated dCRT 40Gy/15# with weekly carboplatin-paclitaxel.
PALLIATIVE APPROACHES
• Use a single 8Gy/1# or 20Gy/5# for relief of dysphagia or disease control in the palliative setting.

Box 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 (RT) in such patients. CRT: chemoradiotherapy; dCRT: definitive CRT; OAC: oesophageal adenocarcinoma; OSCC: oesophageal squamous cell carcinoma; dRT: definitive RT

AUTHOR CONTRIBUTIONS

1. Guarantor of integrity of the entire study – TC, MH, SM, GR, TC
2. Study concepts and design – CJ, MH, SM, GR, TC
3. Literature research – CJ, MH, SM, GR, TC
4. Clinical studies – N/A
5. Experimental studies/data analysis – N/A
6. Statistical analysis – N/A
7. Manuscript preparation – CJ
8. Manuscript editing – CJ, MH, SM, GR, TC

***Declaration of Interest Statement**

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒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.

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Editorial

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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 (A head)

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.

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Radical Approaches (A head)

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.

Table 1 here

Definitive Treatment (B head)

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].

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Adjuvant (B head)

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 (A head)

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Summary (A head)

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Conflicts of interest

T. Crosby is an Advisory Board member for Bristol Myers-Squibb and Astra Zeneca, and has received conference funding from Roche. S. Mukherjee receives research funds from Celgene that do not relate to the published work.

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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 et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020. doi:10.1056/NEJMoa2001316.
[2] Yu J, Ouyang W, Chua MLK et al. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol 2020. doi:10.1001/jamaoncol.2020.0980.
[3] Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020. doi:10.1016/S1470-2045(20)30096-6.
[4] Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for cancer patients. Lancet Oncol 2020. doi:10.1016/S1470-2045(20)30150-9.
[5] 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.
[6] NHS England. Clinical guide for the management of cancer patients during the coronavirus pandemic. NHS England 2020. Version 1; 2020.

[7] Simcock R, Thomas TV, Mercy CE et al. COVID-19: global radiation oncology's targeted response for pandemic preparedness. Clin Trans Radiat Oncol 2020. doi:10.1016/j.ctro.2020.03.009.
[8] Rackley T, Leong T, Foo M, Crosby T. Definitive chemo-radiotherapy for oesophageal cancer – a promising start on an exciting journey. Clin Oncol 2014;26:533–40.
[9] Crosby T, Hurt CN, Gollins S 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):627–37.
[10] Crosby T, Hurt CN, Falk S 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):709–16.
[11] Mohammad NH, Hulshof M, Bergman J et al. Acute toxicity of definitive chemoradiation in patients with inoperable or irresectable esophageal carcinoma. BMC Cancer 2014;14(56):1–6.
[12] Hulshof M, Geijsen D, Rozema T et al. A randomized controlled phase III multicenter study on dose escalation in definitive 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):121–30.
[14] Howard A, Banks S, Owens R et al. The role of active nutritional intervention in patients receiving chemoradiation (CRT) for oesophageal cancer. Ann Oncol 2019;30(4):iv78.
[15] Markar S, Gronnier C, Duhamel A et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol 2015;33(33):3866–73.
[16] Jones CM, Spencer K, Hitchen C et al. Hypofractionated radiotherapy in oesophageal cancer for patients unfit for systemic therapy: a retrospective single-centre analysis. Clin Oncol 2019;31:356–64.
[17] 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.
[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;27:500–8.
[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.

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.

Author queries

In reference list, please provide 6 authors before et al and update publication details if possible

ITU has been changed to ICU for consistency