Review Article

Indications for definitive chemoradiotherapy for oesophageal cancer

Sweet Ping Ng[1,2,3], Trevor Leong[2,4]

[1]Department of Radiation Oncology, Olivia Newton-John Cancer Centre, Austin Health, Melbourne, Australia; [2]Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [3]School of Molecular Sciences, La Trobe University, Melbourne, Australia; [4]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Australia

Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Sweet Ping Ng, MBBS, FRANZCR. Department of Radiation Oncology, Olivia Newton-John Cancer Centre, Austin Health, 145 Studley Road, Heidelberg, Melbourne Victoria 3084, Australia. Email: sweetping.ng@austin.org.au.

Abstract: Oesophageal cancer is the ninth most common cancer diagnosed, and seventh most common cause of cancer-related deaths worldwide. Despite significant advances in imaging, surgery, radiotherapy and systemic therapy over the past few decades, treatment outcomes in patients with localised oesophageal cancer remain suboptimal with a 5-year overall survival of less than 50%. Current treatment guidelines recommend surgery with/without pre-operative chemotherapy or chemoradiotherapy for patients with localised resectable disease. Hence, definitive radiotherapy (with or without chemotherapy) has predominantly been reserved for those who are deemed unsuitable for surgery. The role of radiotherapy in definitive management of oesophageal cancer has been recognised since the 1960s. The addition of concurrent chemotherapy has shown to improve treatment outcomes and has remained standard of care since the RTOG 85-01 and Intergroup 0123 trials. This review discusses the current literature on definitive radiotherapy with/without chemotherapy for localised oesophageal cancer, and evaluates current radiation modalities and technological developments in radiotherapy planning and delivery. We will provide an overview on the literature for definitive chemoradiotherapy in oesophageal cancer, the epidemiological and treatment response differences between squamous cell carcinoma and adenocarcinoma of the oesophagus, followed by a review of the current literature on different radiation treatment modalities (intensity modulated radiotherapy, brachytherapy and proton therapy) and the use of different imaging modalities for radiation treatment planning.

Keywords: Definitive; imaging; oesophageal cancer; radiotherapy

Received: 20 October 2020; Accepted: 10 December 2020; Published: 25 December 2021.
doi: 10.21037/aoe-2020-09
View this article at: http://dx.doi.org/10.21037/aoe-2020-09

Introduction

Oesophageal cancer is the ninth most common cancer diagnosed, accounting for 3.2% of cancer incidences, and seventh most common cause of cancer-related deaths worldwide (1). Over the past few decades, although there have been significant advances in imaging, surgery, radiotherapy and systemic therapy, treatment outcomes in patients with localised oesophageal cancer remain suboptimal with a 5-year overall survival of less than 50% (1-3). With no standard screening program for oesophageal cancer worldwide, the majority of patients are diagnosed with advanced disease (locally advanced disease with/without distant metastatic disease). In this group of patients, those with distant disease have a 5-year survival rate of 5% whilst those with locally advanced, non-metastatic disease

have a 5-year survival rate of 13% (1-3). Current treatment guidelines recommend surgery with/ without pre-operative chemotherapy or chemoradiotherapy for patients with localised resectable disease. Hence, definitive radiotherapy (with or without chemotherapy) has predominantly been reserved for those who are deemed unsuitable for surgery due to performance status, comorbidities and/or extent of disease. Here we aim to discuss the current literature on definitive radiotherapy (with/without chemotherapy) for localised oesophageal cancer, and evaluate current technological developments in radiotherapy planning and delivery.

Definitive radiotherapy alone

The role of radiotherapy in definitive management of oesophageal cancer has been recognised since the 1960s. As radiotherapy was effective for treatment of squamous cell carcinoma of the skin, Pearson (4) investigated the use of radiotherapy for squamous cell carcinoma of the oesophagus in patients who were deemed unsuitable for surgery. In a cohort of 228 patients, Pearson reported a 5-year overall survival of 17% with radiotherapy treatment alone. However, other investigators found it difficult to replicate these results. The average 5-year survival reported in the literature up to 1979 was 6% for patients who had radiotherapy alone (5).

Definitive chemoradiotherapy

RTOG 85-01, a randomised trial comparing radiotherapy alone (64 Gy in 32 fractions) to radiotherapy (50 Gy in 25 fractions) with concurrent cisplatin and 5-FU, was the landmark trial demonstrating the survival benefit of concurrent chemotherapy with radiation therapy (6). Longer term follow up showed that patients who received concurrent chemoradiotherapy had significantly better 5-year overall survival than those who had radiotherapy alone (27% *vs*. 0%) (7). Although this trial showed promising results and established the role of definitive chemoradiotherapy in oesophageal cancer, it also highlighted the high rates of local recurrence and persistent disease after treatment. Similar patterns of recurrence were reported in other studies (8,9). Therefore, following RTOG 85-01, there was a heightened interest and effort in investigating dose escalation to improve local control.

The Intergroup 0123 trial was designed to compare standard dose radiation therapy of 50.4 Gy to escalated dose of 64.8 Gy (10). Both arms received concurrent chemotherapy with cisplatin and 5-FU. The trial was stopped after an interim analysis demonstrating no significant differences in survival and locoregional control between the two arms, but there were 11 treatment-related deaths in the escalated dose arm compared to 2 in the standard dose arm. The investigators noted that 7 out of the 11 treatment-related deaths in the escalated dose arm occurred in patients who received 50.4 Gy or less. A secondary analysis evaluating the longitudinal quality of life in this trial showed no clear improvement in quality of life in those who received 64.8 Gy compared to patients who had 50.4 Gy (11). Similar findings were demonstrated in the ARTDECO study, which randomised 260 patients with inoperable oesophageal cancer to either standard dose radiation therapy of 50.4 Gy or escalated dose of 61.6 Gy (11.2 Gy delivered as an integrated boost to the primary tumour), and demonstrated no significant difference in local control and overall survival between the two groups (12). The ongoing randomised SCOPE2 trial (ClinicalTrials.gov Identifier: NCT02741856) is investigating the role of dose escalation to 60 Gy, compared to standard dose of 50 Gy, using simultaneous integrated boost, with chemotherapy adaptation based on initial PET response to 1 cycle of chemotherapy (2×2 design). Therefore, without any demonstrable benefit of a higher dose, 50.4 Gy has remained the standard of care for definitive radiation therapy in patients with oesophageal cancer.

In both RTOG 85-01 and Intergroup 0123 studies, cisplatin and 5-FU chemotherapy was used as concurrent agents with radiotherapy (6,10). More recently the CROSS trial (neoadjuvant chemoradiotherapy to 41.4 Gy followed by surgery) used carboplatin and paclitaxel as concurrent chemotherapy agents with good effect (92% R0 resection and overall survival of 49 months) (13). The various chemotherapy regimens and targeted agents that were studied in oesophageal cancer will be covered comprehensively in the other accompanying reviews in this series.

In the last decade, there has been a surge in the development of targeted systemic therapy. One targeted drug that was promising for oesophageal cancer was cetuximab, which is a monoclonal antibody against the epidermal growth factor receptor (EGFR). Wang *et al*. (14) studied 103 tumour specimens and showed that up to 55% of oesophageal cancers overexpress EGFR and this was associated with poor outcomes. The use of cetuximab in cancers with EGFR overexpression has been

associated with improved outcomes in patients with head and neck squamous cell carcinomas (15), and colorectal adenocarcinomas (16). Therefore, the Cancer Research UK designed SCOPE-1, a randomised phase II/III study compared definitive chemoradiotherapy with conventional cisplatin and capecitabine with or without the addition of cetuximab (17). The trial met its criteria for futility and was terminated at phase II. In a cohort of 258 patients with a median follow up of 17 months, no survival benefit with the addition of cetuximab was demonstrated (18). Furthermore, the group that received cetuximab had more grade 3 or 4 non-haematological toxicity (79% *vs*. 63%, P=0.004) and worse median overall survival (22 *vs*. 25 months, HR 1.53, P=0.035) (18). A subsequent report on the long-term outcome in this cohort showed no significant difference in overall and progression-free survival in the two groups (19). Better overall survival was associated with earlier disease stage, the delivery of full radiation dose and higher cisplatin dose intensity (19). Only 78% of the patients in the cetuximab arm received the full radiation dose, whilst 90% of the conventional arm completed full course of radiotherapy (18).

Squamous cell carcinoma (SCC) vs. adenocarcinoma

The above studies included patients with both squamous cell carcinoma (SCC) and adenocarcinoma, the two most common histopathological subtypes of oesophageal cancer. Although these two subtypes arise from the same anatomical area, they have quite distinct differences in terms of epidemiology and tumour biology. In general, patients with oesophageal SCC tend to have more proximal tumours and have lifestyle risk factors such as smoking and alcohol consumption (20). As there may be a field effect due to smoking and alcohol consumption, these patients may have a previous history/be at risk of developing a second primary malignancy, typically SCC of the head and neck mucosa or lung (20). On the contrary, patients with oesophageal adenocarcinomas tend to have more distal tumours, close to the gastro-oesophageal junction and have a history of long-standing gastro-oesophageal reflux disease (20). On the whole, the incidence of SCC is declining in the Western world secondary to increasing community awareness of the risks of smoking and alcohol consumption, while the number of adenocarcinoma cases is on the rise due to increasing incidence of gastro-oesophageal reflux disease associated with obesity (21). In the 8th edition of the American Joint Committee on Cancer (AJCC), the committee recognised the differences in tumour biology and patient outcomes between SCCs and adenocarcinomas with tumour location (upper, middle or lower oesophagus, as defined by the epicentre of the tumour) incorporated into the staging of oesophageal SCCs.

Although the above studies included patients with SCCs and adenocarcinomas, the pathologic complete response after chemoradiotherapy is notably higher in those with SCCs (13,22). However, regardless of this, the survival rates remain suboptimal at approximately 30–40% at 2 years (6,10). The Fédération Francophone de Cancérologie Digestive (FFCD) 9102 trial randomised 444 patients with thoracic oesophageal cancer (89% with SCCs and 11% with adenocarcinomas) who responded to induction chemoradiotherapy, to either continuation of chemoradiotherapy or surgery. This trial showed that the addition of surgery provided no additional overall survival benefit compared to continuation of chemoradiotherapy, although the surgical arm had better locoregional control (23). In a separate study, Stahl *et al*. (24) randomised 172 patients with SCC to induction chemotherapy followed by chemoradiotherapy to 40 Gy and surgery, or to induction chemotherapy followed by chemoradiotherapy to at least 65 Gy. Although the 2-year progression free survival was better in those who had surgery, there was no significant overall survival benefit and treatment-related mortality was higher in those who had surgery (24). The post-operative morbidity was high at 70%. Therefore, it may be argued that patients with oesophageal SCC who achieve a complete response after chemoradiotherapy may be observed with surgery reserved as a salvage option. This question will be evaluated in the upcoming NEEDS trial (NEoadjuvant chemoradiotherapy for Esophageal squamous cell carcinoma versus Definitive chemoradiotherapy with salvage Surgery as needed; EudraCT: 2020-000149-15).

In contrast to SCC, the evidence for definitive chemoradiotherapy in adenocarcinoma of the oesophagus is less robust with a smaller number of this patient subgroup represented in clinical trials (6,7,10,19). For this reason, together with the reduced radiosensitivity compared to SCC, definitive chemoradiotherapy for adenocarcinoma is usually reserved for patients who are not suitable for surgical resection.

Cervical oesophageal tumours

Upper oesophageal cancer, particularly those within the cervical oesophagus, is usually considered a separate entity in

management of oesophageal cancer, with improved prognosis compared to thoracic and abdominal oesophageal cancers (25). Cervical oesophageal tumours tend to be SCCs. The management of cervical oesophageal cancer is similar to that of mucosal head and neck cancers. Whilst surgery is the preferred standard of care for patients with resectable thoracic oesophageal cancer, surgery for cervical oesophageal cancer can be morbid as it involves laryngectomy, tracheostomy and upper oesophagectomy (26). Therefore, radiotherapy with/without chemotherapy is generally recommended for definitive treatment of cervical oesophageal cancer. The outcomes of chemoradiotherapy are comparable to upfront surgery, but with the significant advantage of preservation of laryngeal organ function, such as speech and swallowing (26). Distant metastasis, rather than local recurrence, is the most common pattern of failure in cervical oesophageal cancer (27).

Radiation treatment modalities

Intensity Modulated Radiation Therapy (IMRT)

There have been significant developments and advances in radiation treatment planning and delivery over the past two decades. Traditionally, radiation treatment for oesophageal cancer was planned and delivered using 3-D conformal techniques, utilising 3 to 4 radiation beams. The introduction and utilisation of intensity modulated radiotherapy (IMRT) has revolutionised and refined the way patients receive high-dose radiotherapy. IMRT is a sophisticated technique, which produces a highly conformal radiation dose to the delineated target. This is achieved by utilising multiple beams, typically 9 to 12, at different angles and incorporating the use of multi-leaf collimators to vary the shape and intensity of dose to deliver high dose to the tumour whilst reducing dose to the surrounding normal tissues (28).

Some studies have suggested that the dosimetric advantage of IMRT may translate to potential improvements in patients' outcomes (29-31). The largest study was a retrospective study of 587 patients who received a total of 50.4 Gy using an IMRT technique. Shi *et al*. (31) reported 5-year overall survival and locoregional recurrence-free survival rates of 41% and 66%, respectively. Grade 3 or higher toxicities included oesophagitis in 74 (13%), pneumonitis in 8 (1%) and dysphagia in 46 (12%) of patients. These long-term results are promising and indicative that IMRT may reduce radiation-related toxicities in patients. In patients with cervical oesophageal cancers, IMRT is now routinely used, not only to improve target coverage, but also better sparing of dose to critical normal tissues such as spinal cord, swallowing apparatus, parotids and brainstem (32).

Proton therapy

Proton therapy, a form of particle therapy, has a dose distribution with low entry dose, a sharp dose peak known as the Bragg peak, and a steep dose falloff after Bragg peak resulting in almost no exit dose in the beam path. Hence, it has the potential benefit of minimising dose to surrounding normal tissues, thereby reducing treatment-related toxicity. A dosimetry study by Welsh *et al*. (33) has shown that intensity modulated proton therapy (IMPT) plans have lower dose to the surrounding organs at risk compared to IMRT. More recently, a randomised phase IIb study showed that whilst patients who received proton therapy had similar overall and progression-free survival as those who had IMRT, the proton therapy group had 2.3 times lower total toxicity burden compared to the IMRT group (34). Of a cohort of 145 patients, 51 had subsequent surgery and the proton therapy group had a 7.6 times lower post-operative complication score than the IMRT group (34). This is a promising radiation modality for patients with oesophageal cancer, but further studies are required to confirm these findings and demonstrate the cost-benefit of proton therapy, given the high treatment cost and limited availability/access.

Brachytherapy

Brachytherapy has been explored as a modality to deliver escalated radiation dose to the primary tumour, in the effort to further improve local control. Oesophageal brachytherapy refers to the placement of a radioactive source via an applicator into the lumen of the oesophagus. The feasibility and safety of adding brachytherapy to concurrent chemoradiotherapy (50 Gy in 25 fractions with concurrent cisplatin and 5-FU) was evaluated in the RTOG 92-07 phase I/II trial (35). In a cohort of 49 patients, predominantly with squamous cell carcinoma histology (92%), 69% completed the treatment course. Treatment-related oesophageal fistulas occurred in 6 cases (12%), all within 7 months after first brachytherapy, and contributed directly to deaths of 3 patients. The overall survival for the cohort was 49%, which was comparable to the literature where patients only had chemoradiotherapy alone. Hence, the use of brachytherapy, in addition to chemoradiotherapy, was not recommended due to the additional severe

toxicity without meaningful benefit. On further analysis, the investigators noted that higher brachytherapy boost dose of 15 Gy, the use of concurrent chemotherapy with brachytherapy, and a smaller applicator diameter of 0.6 cm contributed to the development of oesophageal fistulas.

More recently, the use of intraluminal brachytherapy has been revisited in patients who are unfit for surgery, and who have early stage oesophageal cancer, or recurrent or persistent disease after initial radiotherapy. In a cohort of 33 patients (19 had recurrent disease), Taggar *et al.* (36) reported relatively good outcomes with a median survival of 21 months and complete response observed in 59% of the cohort. Only one patient developed a tracheoesophageal fistula, in the setting of multiple previous interventions with two prior radiotherapy courses and stent insertion. These promising results support further evaluation of brachytherapy as a treatment modality in patients with early/recurrent/persistent local disease who are not candidates for surgery or further external beam radiotherapy.

Radiation treatment planning

Positron emission tomography (PET)

PET, a form of functional imaging, is commonly used for initial staging of patients with newly diagnosed oesophageal cancer (37-39). The radionuclide that is routinely used is fluorodeoxyglucose (^{18}F-FDG). As the cranial and caudal extent of the oesophageal tumour can be difficult to accurately define on CT imaging, PET imaging has been evaluated in several radiation planning studies as an additional imaging modality to improve target delineation (40-42). These studies showed that PET resulted in a change, both decrease and increase, in gross tumour volume size in more than 50% of patients particularly in the cranial and caudal extent of disease. More importantly, these studies noted that PET imaging, although obtained for radiation treatment planning purposes, detected metastatic disease in up to 24% of patients which resulted in a major change in patients' management plan (40,42). Although the utilisation of PET imaging in radiation treatment planning could potentially lead to a change in treatment volumes, there is no strong evidence to suggest that this improves treatment outcomes (42). However, by allowing the use of smaller radiation treatment volumes with the confidence of not missing the target, the use of PET imaging may result in lesser treatment-related toxicities in a subgroup of patients.

Magnetic resonance imaging (MRI)

More recently, there has been rapid development, exploration and integration of MRI in radiation treatment planning. The accuracy of MRI in staging the primary tumour (T staging) has improved with the application of new MR sequences and ECG-gated techniques. With these techniques, the accuracy of differentiating T4 versus T1–T3 tumours has improved from 60% (43) to 75–87% (44,45). The addition of T2-weighted test support equipment (TSE) sequence further improves the visualisation of the layers of the oesophageal wall, thereby improving T staging accuracy to 50% for T1, 83% for T2, 82% for T3 and 100% for T4 (46). In addition to anatomical evaluation, concurrent functional MR imaging can be performed. Diffusion weighted imaging (DWI) is one of the most studied functional MR sequences, due to its availability and ease of acquisition. The combined use of anatomical imaging with T2-weighted TSE and DWI in oesophageal cancer staging studies has been shown to have an accuracy of 85% for primary tumour and 83% for nodal metastasis (47).

The utility of MRI in improving target delineation during radiation treatment planning has been explored in contouring studies (48,49). Vollenbrock *et al.* (48) assessed and compared the gross tumour volume delineation of 10 observers in 6 cases on PET, T2-weighted MR, and T2-weighted plus DWI MR images. Overall, they demonstrated that the volumes on MR images were significantly smaller than those on PET, and the addition of DWI images to T2-weighted image reduce the caudal extent variability in contours. However, the interobserver variability between the 3 sets of images were similar, with conformity indices of 0.66 to 0.68. The improved target delineation with the addition of DWI was also demonstrated in an imaging-pathology correlative study by Hou *et al.* (49) which showed that DWI images depicted the true pathological length of oesophageal cancer more accurately than CT or T2-weighted MR alone.

Apart from the superior soft tissue contrast on imaging, one of the main advantages of MRI is that it is a non-ionising imaging and hence can be performed on a frequent basis without additional potential radiation-related harm to the patient. Therefore, MRI is a useful tool for intra-treatment assessment of treatment response during radiation therapy. Defize *et al.* (50) evaluated weekly MR images of 29 patients who had neoadjuvant chemoradiotherapy for oesophageal cancer and characterised the rate and pattern of primary tumour volumetric regression during radiotherapy. There

was an approximate 30% reduction in tumour volume over time, suggesting the potential of adaptive radiotherapy. Apart from tumour volume assessment, studies evaluated the use of apparent diffusion coefficient (ADC) value that is calculated from DWI as a response marker to predict prognosis (51-54). In a cohort of 17 patients, Aoyagi *et al*. (51) assessed the ADC values before and after radiotherapy and reported that ADC value is an independent predictor of survival with those with high ADC values had improved survival compared to those with low ADC values. Similar findings were observed in separate study of 27 patients by Imanishi *et al*. (54) where they observed higher absolute ADC value and rate of ADC increase at 20 Gy in treatment responders than non-responders. An increase of 15% in ADC values at 20 Gy of treatment had a positive predictive value of 100% and accuracy of 85% of identifying patients who will respond to treatment.

In radiation oncology, the integration of MR in radiation treatment planning and delivery is undergoing rapid development. The MR-linear accelerator, which is an integrated MR imaging system within a linear accelerator, allows real-time tumour tracking during radiation treatment delivery. The image quality and possibility of tumour tracking on the MR-linear accelerator has been shown to be adequate for tracked radiation delivery (55). There are clinical studies underway to evaluate the feasibility and best use of this new technology in patients (ClinicalTrials.gov Identifier: NCT04172753, NCT04075305).

Conclusions

In patients with localised oesophageal cancer who are not suitable surgical candidates, definitive chemoradiotherapy remains a standard of care. There are continuing efforts to improve 'personalisation' of radiation treatment delivery for patients with locally advanced oesophageal cancer using new imaging and radiation treatment modalities and techniques. Further clinical studies are required to evaluate the role of these new and emerging radiation treatments, potentially in combination with novel targeted drugs/ immunotherapies to optimise the therapeutic ratio and ultimately improve survival outcomes and reduce treatment-related toxicities.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Sjoerd Lagarde, Bas Wijnhoven, and Florian Lordick) for the series "Novel Developments in the Multimodality Treatment of Esophageal Cancer" published in *Annals of Esophagus.* The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoe-2020-09). The series "Novel Developments in the Multimodality Treatment of Esophageal Cancer" was commissioned by the editorial office without any funding or sponsorship. Both authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut 2020;69:1564-71.
3. GBD 2017 Oesophageal Cancer Collaborators. The global, regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5:582-97.

4. Pearson JG. The radiotherapy of carcinoma of the oesophagus and post cricoid region in south east Scotland. Clin Radiol 1966;17:242-57.
5. Earlam R, Cunha-Melo JR. Oesophogeal squamous cell carcinoms: II. A critical view of radiotherapy. Br J Surg 1980;67:457-61.
6. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-8.
7. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623-7.
8. Denham JW, Steigler A, Kilmurray J, et al. Relapse patterns after chemo-radiation for carcinoma of the oesophagus. Clin Oncol (R Coll Radiol) 2003;15:98-108.
9. Button MR, Morgan CA, Croydon ES, et al. Study to determine adequate margins in radiotherapy planning for esophageal carcinoma by detailing patterns of recurrence after definitive chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009;73:818-23.
10. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-74.
11. Kachnic LA, Winter K, Wasserman T, et al. Longitudinal Quality-of-Life Analysis of RTOG 94-05 (Int 0123):A Phase III Trial of Definitive Chemoradiotherapy for Esophageal Cancer. Gastrointest Cancer Res 2011;4:45-52.
12. Hulshof MCCM, 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;38:281.
13. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
14. Wang KL, Wu TT, Choi IS, et al. Expression of epidermal growth factor receptor in esophageal and esophagogastric junction adenocarcinomas: association with poor outcome. Cancer 2007;109:658-67.
15. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78.
16. Baumann M, Krause M. Targeting the epidermal growth factor receptor in radiotherapy: radiobiological mechanisms, preclinical and clinical results. Radiother Oncol 2004;72:257-66.
17. Hurt CN, Nixon LS, Griffiths GO, et al. SCOPE1: a randomised phase II/III multicentre clinical trial of definitive chemoradiation, with or without cetuximab, in carcinoma of the oesophagus. BMC Cancer 2011;11:466.
18. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013;14:627-37.
19. 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. Br J Cancer 2017;116:709-16.
20. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241-52.
21. Offman J, Pesola F, Sasieni P. Trends and projections in adenocarcinoma and squamous cell carcinoma of the oesophagus in England from 1971 to 2037. Br J Cancer 2018;118:1391-8.
22. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005;6:659-68.
23. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-8.
24. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310-7.
25. Coia LR. Factors influencing outcome following radio-chemotherapy for oesophageal cancer. Radiother Oncol 1997;42:91-2.
26. Cao CN, Luo JW, Gao L, et al. Primary radiotherapy compared with primary surgery in cervical esophageal cancer. JAMA Otolaryngol Head Neck Surg 2014;140:918-26.
27. Zhang P, Xi M, Zhao L, et al. Clinical efficacy and failure pattern in patients with cervical esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol 2015;116:257-61.
28. Wu VW, Sham JS, Kwong DL. Inverse planning in three-dimensional conformal and intensity-modulated radiotherapy of mid-thoracic oesophageal cancer. Br J

Radiol 2004;77:568-72.
29. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2012;84:1078-85.
30. Freilich J, Hoffe SE, Almhanna K, et al. Comparative outcomes for three-dimensional conformal versus intensity-modulated radiation therapy for esophageal cancer. Dis Esophagus 2015;28:352-7.
31. Shi A, Liao Z, Allen PK, et al. Long-term survival and toxicity outcomes of intensity modulated radiation therapy for the treatment of esophageal cancer: A large single-institutional cohort study. Adv Radiat Oncol 2017;2:316-24.
32. Fenkell L, Kaminsky I, Breen S, et al. Dosimetric comparison of IMRT vs. 3D conformal radiotherapy in the treatment of cancer of the cervical esophagus. Radiother Oncol 2008;89:287-91.
33. Welsh J, Gomez D, Palmer MB, et al. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. Int J Radiat Oncol Biol Phys 2011;81:1336-42.
34. Lin SH, Hobbs BP, Verma V, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. J Clin Oncol 2020;38:1569-79.
35. Gaspar LE, Winter K, Kocha WI, et al. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. Cancer 2000;88:988-95.
36. Taggar AS, Pitter KL, Cohen GN, et al. Endoluminal high-dose-rate brachytherapy for locally recurrent or persistent esophageal cancer. Brachytherapy. 2018;17:621-7.
37. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000;18:3202-10.
38. Duong CP, Demitriou H, Weih L, et al. Significant clinical impact and prognostic stratification provided by FDG-PET in the staging of oesophageal cancer. Eur J Nucl Med Mol Imaging 2006;33:759-69.
39. Schmidt T, Lordick F, Herrmann K, et al. Value of functional imaging by PET in esophageal cancer. J Natl Compr Canc Netw 2015;13:239-47.
40. Moureau-Zabotto L, Touboul E, Lerouge D, et al. Impact of CT and 18F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. Int J Radiat Oncol Biol Phys 2005;63:340-5.
41. Leong T, Everitt C, Yuen K, et al. A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol 2006;78:254-61.
42. Ng SP, Tan J, Osbourne G, et al. Follow up results of a prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Clin Transl Radiat Oncol 2017;2:76-82.
43. Yamada I, Hikishima K, Miyasaka N, et al. Esophageal carcinoma: ex vivo evaluation with diffusion-tensor MR imaging and tractography at 7 T. Radiology 2014;272:164-73.
44. Katz S, Ferrara T, Alavi A, et al. PET, CT, and MR Imaging for Assessment of Thoracic Malignancy: Structure Meets Function. PET Clin 2008;3:395-410.
45. Markl M, Fluckiger J, Lee DC, et al. Velocity quantification by electrocardiography-gated phase contrast magnetic resonance imaging in patients with cardiac arrhythmia: a simulation study based on real time transesophageal echocardiography data in atrial fibrillation. J Comput Assist Tomogr 2015;39:422-7.
46. Riddell AM, Allum WH, Thompson JN, et al. The appearances of oesophageal carcinoma demonstrated on high-resolution, T2-weighted MRI, with histopathological correlation. Eur Radiol 2007;17:391-9.
47. Zhu Y, Fu L, Jing W, et al. The value of magnetic resonance imaging in esophageal carcinoma: Tool or toy? Asia Pac J Clin Oncol 2019;15:101-7.
48. Vollenbrock SE, Nowee ME, Voncken FEM, et al. Gross Tumor Delineation in Esophageal Cancer on MRI Compared With (18)F-FDG-PET/CT. Adv Radiat Oncol 2019;4:596-604.
49. Hou DL, Shi GF, Gao XS, et al. Improved longitudinal length accuracy of gross tumor volume delineation with diffusion weighted magnetic resonance imaging for esophageal squamous cell carcinoma. Radiat Oncol 2013;8:169.
50. Defize IL, Boekhoff MR, Borggreve AS, et al. Tumor volume regression during neoadjuvant chemoradiotherapy for esophageal cancer: a prospective study with weekly MRI. Acta Oncol 2020;59:753-9.
51. Aoyagi T, Shuto K, Okazumi S, et al. Apparent diffusion coefficient correlation with oesophageal tumour stroma and angiogenesis. Eur Radiol 2012;22:1172-7.
52. Wang L, Liu L, Han C, et al. The diffusion-weighted

magnetic resonance imaging (DWI) predicts the early response of esophageal squamous cell carcinoma to concurrent chemoradiotherapy. Radiother Oncol 2016;121:246-51.
53. van Rossum PS, van Lier AL, van Vulpen M, et al. Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer. Radiother Oncol 2015;115:163-70.
54. Imanishi S, Shuto K, Aoyagi T, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting the early response to chemoradiotherapy of advanced esophageal squamous cell carcinoma. Dig Surg 2013;30:240-8.
55. Lips I, Lever F, Reerink O, et al. SU-E-J-57: MRI-Linac (MRL) Guided Treatment for Esophageal Cancer. Med Phys 2012;39:3665.

doi: 10.21037/aoe-2020-09
Cite this article as: Ng SP, Leong T. Indications for definitive chemoradiotherapy for oesophageal cancer. Ann Esophagus 2021;4:43.