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Oesophagus

Radical treatment

For patients with localised disease, the standard curative approach to treatment is either surgery + perioperative chemotherapy, surgery ± neoadjuvant chemoradiotherapy or definitive radiotherapy ± concomitant chemotherapy. For those who have not achieved a complete pathological response following neoadjuvant chemoradiotherapy and surgery, adjuvant nivolumab has been shown to improve progression-free survival.[1]

Due to the differing chemosensitivity and radiosensitivity of squamous cell cancer (SCC) and adenocarcinoma (ACA), treatment paradigms for oesophageal SCC and ACA have taken divergent paths.[2]

Definitive radiation with concomitant chemotherapy

Radiation with concomitant chemotherapy is superior to radiotherapy alone.[3] Cisplatin and fluorouracil (5-FU) became the standard of care in definitive chemoradiotherapy following the publication of the landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial. This trial showed a survival advantage for concomitant chemoradiation (50 Gray [Gy] in 25 fractions) with two concurrent and two adjuvant cycles of cisplatin and 5-FU) compared with radiotherapy alone (64 Gy in 32 fractions), with 5-year survival rates of 27% versus 0%.[3]

Outcomes have improved in modern trials using more conformal radiotherapy techniques with improved patient selection and radiotherapy quality assurance; in the UK SCOPE1 study, radiotherapy combined with cisplatin and capecitabine reported 2-year survival rates of 56% with a median overall survival of 34.5 months in long-term follow-up.[4]

Cisplatin is associated with significant toxicity. Weekly carboplatin and paclitaxel combined with radiotherapy is increasingly being used in the definitive setting due to its favourable toxicity profile. Several phase II studies have shown that carboplatin and paclitaxel given concurrently with definitive radiotherapy in oesophageal cancer is both tolerable and active.[5,6] Retrospective UK data also suggest that overall survival is comparable with those undergoing cisplatin and 5-FU chemotherapy.[7]

A systematic review of neoadjuvant concomitant chemoradiation confirmed a radiotherapy dose response relationship with pathological complete response.[8] Although an increasing body of evidence is suggestive of the safety and feasibility of doses ≥60 Gy,[9,10] currently there are no randomised control trials to support the use of radiotherapy doses >50.4 Gy in the definitive treatment of oesophageal cancer. The INT0123 trial failed to show a benefit of dose escalation to 64.8 Gy compared with 50.4 Gy with the same cisplatin/5-FU chemotherapy in both arms.[11] Treatment-related deaths were increased in the dose-escalated arm, although the majority of these occurred prior to the delivery of >50 Gy and cannot be attributed to dose escalation.[9] Subsequent studies of dose escalation have focused on attempting to reduce toxicity by taking advantage of the progress in radiotherapy techniques and escalating dose to smaller volumes but have again failed to show an improvement in local control or survival.[12,13]

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Chemoradiotherapy is recommended for tumours of the upper third oesophagus where extensive surgery would also involve a laryngectomy. Unlike SCC of the head and neck region, there is limited evidence for dose escalation beyond 50 Gy for upper third oesophageal SCC. A single-institution retrospective study of 23 patients with SCC of the upper third oesophagus treated with 60–66 Gy in 30 fractions using IMRT demonstrated dose escalation was well tolerated with good local control rates.[14] In addition a single-institution phase II prospective study in India of post-cricoid and upper oesophageal SCC treated with IMRT to a dose of either 66 Gy in 30 fractions or 63 Gy in 35 fractions showed 2-year locoregional control rates and cause-specific survival of 59.6% and 44.8% respectively.[15] However, prospective evidence to support this approach is lacking and future research is required.

Recommendations

Definitive radiation with concomitant chemotherapy:

- 50 Gy in 25 fractions over 5 weeks (Grade A)
- 50.4 Gy in 28 fractions over 5.5 weeks (Grade A)
- For upper third oesophageal carcinoma, moderate dose escalation with intensity-modulated radiotherapy (IMRT) can be considered, wherever possible within the context of a clinical trial (Grade C) 60–66 Gy in 30 fractions over 6 weeks

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

Definitive radiotherapy alone

Single-modality radiotherapy is an option for patients not suitable for concurrent chemotherapy. Hypofractionation has been shown to be safe and tolerable with outcomes superior to those seen with conventionally fractionated radiotherapy. In a series of 101 patients in whom the majority of tumours were <5 cm in length, radiotherapy alone to a dose of 45–52.5 Gy in 15–16 fractions achieved a 5-year survival of 21%.[17] More recently a retrospective UK single-centre analysis of 61 consecutive patients managed with hypofractionated radiotherapy with radical intent (50 Gy in 16 fractions or 50–52.5 Gy in 20 fractions) revealed 3-year survival of 56.9% and median overall survival of 29 months.[18]

Recommendations

Radiotherapy alone:

- 45–52.5 Gy in 15–16 fractions over 3 weeks (Grade C)
- 50–55 Gy in 20 fractions over 4 weeks (Grade C)
- 60 Gy in 30 fractions over 6 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

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Preoperative (neoadjuvant) radiation with concomitant chemotherapy

Despite adequate preoperative staging, 25–30% of patients treated with primary surgery have microscopically positive resection margins (R1) and the 5-year survival rate rarely exceeds 40%. Multimodal therapy including perioperative chemotherapy and neoadjuvant chemoradiotherapy aim to improve outcomes by downstaging the tumour and eradicating micrometastatic disease.

The landmark trial of neoadjuvant chemoradiotherapy is the Dutch CROSS trial. Radiotherapy with concomitant carboplatin and paclitaxel and 41.4 Gy in 23 fractions versus surgery alone demonstrated an increase in median survival from 24 to 49 months and no increase in perioperative mortality.[19] Complete pathologic response rates of 23% in patients with ACA and 49% in patients with SCC were observed in the chemoradiation arm. NEOSCOPE, a multicentre study of preoperative chemoradiotherapy, showed that neoadjuvant carboplatin and paclitaxel with radiotherapy to a dose of 45 Gy could be safely delivered to patients with locally advanced resectable oesophageal adenocarcinoma with acceptable toxicity and low incidence of postoperative mortality.[20] Walsh *et al* investigated a dose of 40 Gy in 15 fractions following 2 cycles of neoadjuvant chemotherapy, demonstrating improved median survival of 17 months versus 12 months with surgery alone.[21] However, due to limited evidence supporting this dose fractionation, this approach should currently be considered only as part of a clinical trial.

Following the results of the Checkmate 577 trial, adjuvant nivolumab for 12 months is recommended for patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual disease after previous neoadjuvant chemoradiotherapy.[1]

Based on the results of two large randomised controlled studies, perioperative chemotherapy represents another standard of care for resectable adenocarcinoma.[22,23] The use of epirubicin, cisplatin and fluorouracil (ECF) chemotherapy has now largely been superseded by fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) due to the expectation of higher efficacy.

Recommendations

Neoadjuvant radiation with concomitant chemotherapy:

Squamous cell carcinoma:

- 41.4 Gy in 23 fractions over 4.5 weeks (Grade A)

Adenocarcinoma:

- 41.4 Gy in 23 fractions over 4.5 weeks (Grade A)
- 45 Gy in 25 fractions over 5 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

Postoperative radiotherapy

There is limited and heterogeneous evidence exploring postoperative radiotherapy, which has hindered attempts at meta-analyses. It may have a role in patients who have positive margins and prognosis estimated to be mainly influenced by local relapse.[24,25] Based on available data,

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if radiotherapy is given, concomitant chemoradiotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy.[26]

Recommendations

Postoperative radiation with concomitant chemotherapy:

- At the current time no clear recommendations around the indications for radiotherapy can be made because of lack of available evidence
- Consider in patients who have positive margins and prognosis estimated to be mainly influenced by local relapse (Grade D)
- If radiotherapy is given, concomitant chemotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

Palliative treatment

Advanced disease can cause local symptoms such as dysphagia, bleeding and pain, but there is a lack of robust controlled trial evidence for the role of palliative radiotherapy in oesophageal cancer and the optimal schedule for symptom control is unknown.

Brachytherapy

There is evidence that intraluminal brachytherapy with palliative intent is a valid alternative to stenting in patients with dysphagia and longer life expectancy.[27–29] An updated Cochrane review on interventions for dysphagia in oesophageal cancer has concluded that, when compared with self-expanding metal stents, brachytherapy provided an improvement in long-term relief from dysphagia and possibly a better quality of life.[30]

Recommendations

Palliative brachytherapy:

- 12 Gy in 1 fraction (Grade B)
- 12–16 Gy in 2 fractions (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

External beam radiotherapy

Palliative radiotherapy alone should be considered for symptom improvement in oesophageal cancer. Concurrent chemoradiotherapy has not been shown to be advantageous in a phase III trial in which radiotherapy doses were 35 Gy in 15 fractions or 30 Gy in 10 fractions.[31]

The UK ROCS study has shown that palliative radiotherapy in addition to oesophageal stenting does not improve outcomes over stent insertion alone and should not be routinely offered.[32]

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Extrapolating evidence from gastric cancer, short-course radiotherapy is an effective treatment that can palliate bleeding from oesophageal and junctional tumours.[33–35]

Recommendations

Palliative external beam radiotherapy:

- 30 Gy in 10 fractions over 2 weeks (Grade C)
- 35 Gy in 15 fractions over 3 weeks (Grade C)
- 20 Gy in 5 fractions over 1 week (Grade C)
- 40 Gy in 15 fractions over 3 weeks (Grade D)
- 8 Gy in 1 fraction (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

Gastric cancer

Perioperative therapy

Surgery (to achieve R0 resection with appropriate lymphadenectomy) remains the only radical treatment for gastric cancer, with combined modality treatment indicated for all but very early, stage IA disease. Potentially operable >stage IB disease should be managed with perioperative chemotherapy[22,23] (Grade A).

The role of neoadjuvant chemoradiotherapy is being investigated by the TOPGEAR[36] and CRITICS II[37] studies, but there is currently no phase III evidence to support this approach.

Adjuvant radiotherapy with concomitant chemotherapy

In 2001, the US Intergroup 0116 trial[38] reported a survival benefit with postoperative chemoradiotherapy compared with surgery alone. However, as only 10% of the trial population had undergone the recommended D2 lymphadenectomy, and patients did not undergo any perioperative chemotherapy, the true benefit of postoperative chemoradiotherapy in the context of optimal surgical technique and perioperative treatment remain unclear.

Subsequent trials (ARTIST I,[39] CRITICS,[40] ARTIST II[41]) have failed to further define the optimal role of adjuvant radiotherapy. As such, adjuvant chemoradiotherapy is reserved only for selected high-risk patients who have not undergone preoperative chemotherapy or have not achieved an R0 resection, following multidisciplinary team discussion (Grade B).

Recommendation

Adjuvant radiotherapy with concomitant chemotherapy:

- 45 Gy in 25 fractions over 5 weeks with concomitant 5-FU or capecitabine (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

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Palliative radiotherapy

Palliative radiotherapy can be an effective treatment for haemostasis of bleeding gastric tumours.[33] Though there is no clear evidence to suggest any dose/fractionation is superior in terms of symptom palliation, single-fraction treatments may be preferred due to reduced toxicity, shorter treatment time and potential for future retreatment if required.[34,35]

Recommendations

- 6–8 Gy in 1 fraction (Grade D)
- 20 Gy in 5 fractions over 1 week (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[16]

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