17.

Upper gastrointestinal cancer

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.

Radiation with concomitant chemotherapy

Radiation with concomitant chemotherapy is superior to radiotherapy alone.[1] The landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial showed a survival advantage for concomitant chemoradiation (50 Gray [Gy] in 25 fractions) with two concurrent and two adjuvant cycles of cisplatin and fluorouracil (5-FU), compared with radiotherapy alone (64 Gy in 32 fractions), with five-year survival rates of 27% versus 0%.[1] The subsequent 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.[2] 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.[3] A systematic review of neoadjuvant concomitant chemoradiation confirmed a radiotherapy dose–response relationship with a pathological complete response.[4] An increasing body of evidence is suggestive of the safety and feasibility of doses ≥60 Gy.[3] Outcomes have improved in modern trials using more conformal radiotherapy techniques with improved patient selection and radiotherapy quality assurance; in a recent UK study, radiotherapy combined with cisplatin and capecitabine showed two-year survival rates of 56%.[5]

Recommendations

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)

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.[6]

Definitive radiotherapy alone

In a series of 101 patients in whom the majority of tumours were <5 centrimeters (cm) in length, radiotherapy alone to a dose of 45–52.5 Gy in 15–16 fractions achieved a five-year survival of 21%.[7] Radiotherapy is an option for patients in whom the use of concurrent chemotherapy is contraindicated.

Recommendations

Radiotherapy alone:

50 Gy in 15–16 fractions over 3 weeks (Grade C)
50–55 Gy in 20 fractions over 4 weeks (Grade D)
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.[6]

Preoperative radiation with concomitant chemotherapy

Recent meta-analyses have demonstrated a significant improvement in overall survival using multimodality treatment over surgery alone; an advantage for neoadjuvant concomitant chemoradiotherapy over chemotherapy has not been established.[8] A recent trial of neoadjuvant radiotherapy with concomitant carboplatin and paclitaxel and 41.4 Gy in 23 fractions versus surgery alone demonstrated an increase in median survival from 24–49 months and no increase in perioperative mortality.[9] A dose of 45 Gy in 25 fractions has been selected for a randomised multicentre UK trial.[10]

Recommendations

Neoadjuvant radiation with concomitant chemotherapy:

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.[6]

Postoperative radiotherapy

Adjuvant (chemo)radiotherapy can be considered for patients with positive margins and prognosis likely to be influenced by local relapse, although evidence for the benefit of adjuvant (chemo)radiotherapy is uncertain.[11] Based on a meta-analysis, radiotherapy with concomitant chemotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy.[12]

Palliative treatment

There is increasing evidence that intraluminal brachytherapy provides effective relief of dysphagia, with improved quality of life. An updated Cochrane review on interventions for dysphagia in oesophageal cancer has concluded that, when compared to self-expanding metal stents, brachytherapy has fewer requirements for re-intervention, improved survival and better quality of life.[13]

Recommendations

Palliative brachytherapy:

12 Gy in 1 fraction (Grade B)[14]
12–16 Gy in 2 fractions (Grade B)[15,16]

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.[6]

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 ten fractions.[17]

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 D)
40 Gy in 15 fractions over 3 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.[6]

Gastric cancer

Adjuvant radiotherapy with concomitant chemotherapy

Perioperative chemotherapy represents a standard of care in the management of locally advanced gastric cancer.[18] Adjuvant radiotherapy with concomitant chemotherapy represents an alternative approach. The INT0116 trial provided evidence of a survival benefit for postoperative concomitant chemoradiotherapy, however, this trial had poor surgical quality control with 54% of patients undergoing a D0 resection.[19] In patients with a high risk of relapse who did not undergo preoperative chemotherapy, especially in the absence of a D2 resection, adjuvant radiotherapy with concomitant 5-FU or capecitabine can be considered (Level 2b).[6,20]

Recommendation

Adjuvant radiotherapy with concomitant chemotherapy:

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.[6]

Palliative treatment

Palliative radiotherapy is an effective treatment for bleeding due to gastric carcinoma, with no clear benefit for more protracted fractionation schedules.[21]

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.[6]

Pancreas cancer

Radical treatment

Chemoradiotherapy

Based on a very limited evidence base, adjuvant radiotherapy with concomitant chemotherapy is occasionally used in some centres for patients who are resection margin positive; a dose of 45 Gy in 25 fractions is appropriate for adjuvant treatment.[22]

Standard treatment options for patients with locally advanced inoperable pancreas cancer include chemotherapy alone or induction chemotherapy followed by radiotherapy and concomitant chemotherapy in responding or stable disease after induction chemotherapy.[23–25] One randomised study showed a small survival benefit in favour of consolidation radiotherapy with concomitant chemotherapy, although this was not confirmed in a subsequent study (Level 1b).[6,23,24]

Recommendations

Radiotherapy with concomitant chemotherapy following induction chemotherapy:

50.4 Gy in 28 fractions over 5.5 weeks (Grade B)
54 Gy in 30 fractions over 6 weeks (Grade B)
45 Gy in 25 fractions over 5 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.[6]

References

1. 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**(24): 1593–1598.
2. 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**(5): 1167–1174.
3. Rackley T, Leong T, Foo M, Crosby T. Definitive chemoradiotherapy for oesophageal cancer – a promising start on an exciting journey. *Clin Oncol (R Coll Radiol)* 2014; **26**(9): 533–540.
4. Geh JI, Bond SJ, Bentzen SM, Glynne-Jones R. Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: evidence of a radiation and chemotherapy dose response. *Radiother Oncol* 2006; **78**(3): 236–244.
5. 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**(7): 627–637.
6. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
7. Sykes AJ, Burt PA, Slevin NJ, Stout R, Marrs JE. Radical radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. *Radiother Oncol* 1998; **48**(1): 15–21.
8. Gwynne S, Wijnhoven BP, Hulshof M, Bateman A. Role of chemoradiotherapy in oesophageal cancer -- adjuvant and neoadjuvant therapy. *Clin Oncol (R Coll Radiol)* 2014; **26**(9): 522–532.
9. Zheng B, Zheng W, Zhu Y, Lin XY, Xu BH, Chen C. Role of adjuvant chemoradiotherapy in treatment of resectable esophageal carcinoma: a meta-analysis. *Chin Med J (Engl)* 2013; **126**(6): 1178–1182.
10. Sjoquist KM, Burmeister BH, Smithers BM *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; **12**(7): 681–692.
11. van Hagen P, Hulshof MC, van Lanschot JJ *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**(22): 2074–2084.
12. Mukherjee S, Hurt CN, Gwynne S *et al*. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. *BMC Cancer* 2015; **15**: 48.
13. Dai Y, Li C, Xie Y *et al*. Interventions for dysphagia in oesophageal cancer. *Cochrane Database Syst Rev* 2014;**10**: CD005048.
14. Homs MY, Steyerberg EW, Eijkenboom WM *et al*. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet* 2004; **364**(9444): 1497–1504.
15. Sur RK, Levin CV, Donde B, Sharma V, Miszczyk L, Nag S. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma – an International Atomic Energy Agency study. *Int J Radiat Oncol Biol Phys* 2002; **53**(1): 127–133.
16. Sharma V, Mahantshetty U, Dinshaw KA, Deshpande R, Sharma S. Palliation of advanced/recurrent esophageal carcinoma with high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002; **52**(2): 310–315.

17. Penniment M. Full report of the TROG 03.01, NCIC CTG ES2 multinational phase III study in advanced esophageal cancer comparing palliation of dysphagia and quality of life in patients treated with radiotherapy or chemoradiotherapy. *J Clin Oncol* 2015; **33**: **3**: abstract 6.

18. Cunningham D, Allum WH, Stenning SP *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**(1): 11–20.

19. Macdonald JS, Smalley SR, Benedetti J *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**(10): 725–730.

20. Foo M, Crosby T, Rackley T, Leong T. Role of (chemo)-radiotherapy in resectable gastric cancer. *Clin Oncol (R Coll Radiol)* 2014; **26**(9): 541–550.

21. Chaw CL, Niblock PG, Chaw CS, Adamson DJ. The role of palliative radiotherapy for haemostasis in unresectable gastric cancer: a single-institution experience. *Ecancermedicalscience* 2014; **8**: 384.

22. Stocken DD, Büchler MW, Dervenis C *et al*. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005; **92**(8): 1372–1381.

23. Huguet F, André T, Hammel P *et al*. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007; **25**(3): 326–331.

24. Hammel P, Huguet F, van Laethem J *et al*. Randomized multicentre phase III study in patients with locally advanced adenocarcinoma of the pancreas:gemcitabine with or without chemoradiotherapy and with or without Erlotinib-LAP 07 study. *J Clin Oncol* 2011; **29**: abstract e14619.

25. Mukherjee S, Hurt CN, Bridgewater J *et al*. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013; **14**(4): 317–326.