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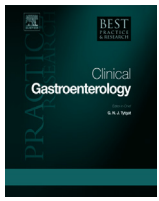

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Chemoradiotherapy in tumours of the oesophagus and gastro-oesophageal junction

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A B S T R A C T

Oesophageal cancer remains a malignancy with a poor prognosis. However, in the recent 10–15 years relevant progress has been made by the introduction of chemoradiotherapy (CRT) for tumours of the oesophagus or gastro-oesophageal junction. The addition of neo-adjuvant CRT to surgery has significantly improved survival and locoregional control, for both adenocarcinoma and squamous cell carcinoma. For irresectable or medically inoperable patients, definitive CRT has changed the treatment intent from palliative to curative. Definitive CRT is a good alternative for radical surgery in responding patients with squamous cell carcinoma and those running a high risk of surgical morbidity and mortality. For patients with an out-of-field solitary locoregional recurrence after primary curative treatment, definitive CRT can lead to long term survival.

Introduction

Until the end of the 20th century, surgery alone was the only treatment with a curative intent for oesophageal cancer. The 5-year survival rate hardly exceeded 20% [1] and locoregional failures occurred in 30–40% of patients. Although the 5-year survival after surgery alone has improved in the

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last 15 years (mainly attributed to improvements in preoperative diagnostics and concentration of surgical care [2]), it barely exceeds 35%, while locoregional control has not improved [3–5]. The lack of effective chemotherapy to control recurrent disease and the poor overall survival (OS) after a locoregional recurrence [6] warranted studies to improve locoregional control. Adjuvant and neoadjuvant radiotherapy (RT), chemotherapy (CT) and chemoradiotherapy (CRT) have been studied in several randomised clinical trials (RCTs).

Adjuvant radiotherapy

Between 1993 and 2003 four non-randomized studies were published on adjuvant RT in squamous cell carcinoma (SCC) of the oesophagus, which were reviewed in a meta-analysis by Malthaner et al. [7]. Postoperative doses on the tumour bed plus 3–5 cm elective node area ranged from 49 to 60 Gy. Although locoregional control was improved in two of the four trials, there was no evidence for an OS benefit. These overall results and the important progress due to combining CT with RT tended to stop further research on the role of postoperative or preoperative RT.

Combining chemotherapy and radiotherapy

Addition of CT to RT (without surgery) in patients with oesophageal cancer was studied in a stratified phase III trial performed by the Radiation Therapy Oncology Group (RTOG 85-01 trial) [8]. Patients with oesophageal cancer ($n = 121$) with potentially curable adenocarcinoma (AC) or SCC were randomised between RT alone (64 Gy in 32 fractions) and CRT consisting of two courses of 5-fluoruracil (5-FU) and cisplatin combined with 50 Gy RT, followed by two courses of 5-FU and cisplatin. Results showed a significant difference in median survival between RT alone (8.9 months) and the combined therapy (12.5 months, $p < 0.001$) as well as an improvement in 5-year survival (0% versus 26%). However, because only 15 (12%) of all analysed patients had AC, it remains unclear to what extent these results are applicable to AC. In a Cochrane meta-analysis eight studies comparing sequential CT and RT to RT alone were analysed [9]. In contrast to concurrent CRT, no clinical improved survival (hazard ratio: HR 0.87) and local control was found by sequential CT; however, toxicity was increased in patients in the sequential CRT arm. Concurrent CRT versus sequential CT and RT was studied in a meta-analysis by Lv et al., demonstrating that concurrent CRT was more effective compared to sequential CRT (OR: 1.45, CI:1.26–1.79. $P = 0.015$ versus OR: 0.85, CI 0.64–1.35, $P = 0.26$) [10].

In summary, concurrent CRT, either alone or followed by surgery, is generally considered the preferred treatment in both AC and SCC of the oesophagus. The superiority of concurrent CRT over RT alone or sequential CT and RT is also generally accepted for nearly all other tumours, with both AC and SCC histologies (lung, head and neck, rectum anus, cervix uteri, bladder).

Postoperative chemoradiotherapy

The role of adjuvant CRT in oesophageal cancer was reviewed in a meta-analysis by Zheng et al. in 2013 [11]; there were only two randomised studies on adjuvant CRT in SCC and none on AC. Tumour stage ranged from II to IV. The authors concluded that adjuvant CRT resulted in a survival benefit, despite a higher rate of toxicity. However, because patient numbers were relatively low ($n = 196$), caution is required when drawing conclusions. With the currently available large number of RCTs on neoadjuvant CRT (nCRT) and the convincing evidence of a significant effect on survival, it is unlikely that further studies on postoperative R(C)T will be conducted. Postoperative treatment may have a role in resected SCC patients without preoperative treatment, in case of positive resection margins and a prognosis estimated to be likely influenced by a locoregional recurrence. For those cases, CRT would be recommended. The demonstrated toxicity of C(R)T in the postoperative setting should be taken into account.