Is surgery necessary following chemoradiation for patients with locally advanced cancer of the oesophagus?

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A landmark study has shown that patients with locally advanced epidermoid cancer of the oesophagus who respond well to induction chemoradiotherapy do not benefit from subsequent surgery and, therefore, seem to be well treated with definitive chemoradiotherapy.

Locally advanced oesophageal cancer carries a poor prognosis, and its treatment presents an interdisciplinary challenge. Therapy generally involves neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy. Chemoradiotherapy has been proven to be superior to radiotherapy alone. The role of surgery has been challenged because of the poor outcome following resection alone and mortality rates of up to 15% after surgery preceded by chemoradiotherapy. It may be questioned whether all patients with locally advanced oesophageal cancer need surgery or whether certain subsets of patients are well treated with chemoradiotherapy alone, which is associated with lower treatment-related mortality than chemoradiotherapy followed by surgery.

Bedenne et al. addressed this question in a phase III trial (see opposite) that included 259 patients (230 with epidermoid cancer; 29 with adenocarcinoma) who responded well to two cycles of induction chemoradiotherapy with cisplatin and fluorouracil. Radiotherapy was performed as conventional (46 Gy over 4.5 weeks) or split-course (15 Gy on days 1–5 and 22–26) treatment. Patients were randomly assigned to receive either further chemoradiotherapy (three cycles of cisplatin and fluorouracil, and 20 Gy conventional or 15 Gy split-course radiotherapy) or surgical resection. The three-month mortality rate was higher with resection than with chemoradiotherapy alone (9.3% vs 0.8%, P=0.002). Surgery resulted in better locoregional control (hazard ratio for further chemoradiation vs surgery 1.63; P=0.03), but was not associated with a significantly better median survival time (17.7 months after surgery vs 19.3 months after definitive chemoradiotherapy) or two-year survival rate (34% vs 40% respectively; P=0.44). These results are consistent with the data from a randomised trial reported by Stahl et al., in which patients with locally advanced squamous cell carcinoma of the oesophagus who had received induction chemotherapy followed by chemoradiotherapy were randomly assigned to receive either surgery or additional chemoradiotherapy. Locoregional control at two years was better after surgery (64% vs 41%; P=0.003), whereas survival was not significantly improved.

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Bedenne and co-workers concluded that patients who respond well to induction chemoradiotherapy do not benefit from resection. The results might have been confounded by methodological issues, however. Patients who had resection received an overall lower dose of chemotherapy, which could have negatively affected outcome. Also, in most other oesophageal cancer studies, staging did not include endoscopic ultrasound. Another problem is the use of split-course radiotherapy, which is associated with significantly worse survival rates than conventional radiotherapy.

Although both treatment groups were balanced regarding the radiotherapy treatment received, the risk of a selection bias still exists because the results were not stratified by radiotherapy regimen. Furthermore, when the study was conducted, it was not recognised that haemoglobin levels before and during chemoradiotherapy are significantly associated with treatment outcome. Maintaining haemoglobin levels at 12.0–14.0 g/dl during chemoradiotherapy could improve outcome by facilitating better tumour oxygenation and enhanced radiosensitivity.

Despite its methodological problems, the study reported by Bedenne et al. is a landmark. It alerts clinicians to be more restrictive in the use of resection for locally advanced oesophageal cancer. This advice is particularly relevant to patients who respond well to induction chemoradiotherapy or have relevant pre-existing comorbidity. In the study reported by Bedenne et al. 89% of patients had epidermoid cancer, so the findings might not be applicable to other histologies.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

L Bedenne, P Michel, O Bouché et al. (2007) **Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102.** *J Clin Oncol 25:1160–1168*

Background. In patients treated with chemoradiation for oesophageal cancer, uncontrolled studies have reported similar survival rates in those treated with or without the addition of surgery.

Objective. To demonstrate in a randomised trial that patients who respond to initial chemoradiation have equivalent overall survival after chemoradiation alone to after chemoradiation followed by surgery.

Design. Between February 1993 and December 2000, this randomised trial recruited patients with resectable T3N0–1M0 epidermoid cancer or adenocarcinoma of the thoracic oesophagus who were candidates for surgery and radiation. Exclusion criteria were as follows: tumour within 18 cm of the dental ridge; tracheobronchial, supraclavicular node or gastric cardia involvement; visceral metastases; weight loss >15%; symptomatic coronary heart disease; Child–Pugh B or C liver cirrhosis; or respiratory insufficiency.

Intervention. All 444 eligible patients received induction chemoradiation consisting of two cycles of cisplatin and fluorouracil and either conventional (46 Gy over 4.5 weeks) or split-course (15 Gy on days 1–5 and 22–26) radiotherapy planned to include the macroscopic tumour and adjacent lymph nodes. Each cycle of chemotherapy comprised fluorouracil (800 mg/m^2 daily for 5 days) as a continuous intravenous infusion and cisplatin (15 mg/m^2 daily for 5 days) as a 1 h intravenous infusion. Response was assessed using endoscopy, biopsies, oesophagogram, chest and abdominal CT, and (if available) endoscopic ultrasonography, and only responders were considered for the randomised section of the trial. Patients in arm A underwent surgery but no further chemoradiation. Patients in arm B received a further three cycles of chemotherapy and either 20 Gy of conventional or 15 Gy of split-course radiotherapy.

Outcome measures. The primary outcome measure was overall survival. Secondary outcome measures were type of recurrence, duration of stay in hospital, quality of life and procedures required for treatment of dysphagia.

Results. Among the patients who responded to induction therapy, 129 were randomly assigned to arm A and 130 to arm B. For arms A and B, median survival times were 17.7 and 19.3 months, respectively, while two-year survival rates were 34% and 40%, respectively. The frequency of metastases was not different between the arms, but there were more locoregional relapses following chemoradiation alone than after chemoradiation plus surgery (hazard ratio for arm B versus arm A 1.63; 95% CI 1.04–2.55; P=0.03). The three-month mortality rate was higher (9.3% vs 0.8%; P=0.002) and the duration of hospital stay was longer (68 days vs 52 days; P=0.02) in arm A than in arm B. A procedure for dysphagia was required in 24% of patients in arm A versus 46% in arm B (P<0.001). Quality-of-life analysis showed no difference between the two arms.

Conclusion. The addition of surgery to chemoradiation does not improve survival or quality of life in patients with locally advanced thoracic oesophageal cancer who respond to initial chemoradiation.

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