OESOPHAGEAL CANCER IN 2014

Advances in curatively intended treatment

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Oesophageal cancer is characterized by poor prognosis, and curatively intended treatment is extensive and demanding. In 2014, well-designed clinical studies have advanced our knowledge of how to improve the treatment of oesophageal cancer at various tumour stages.

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Oesophageal cancer has a poor prognosis: population-based overall and postoperative 5-year survival is <15% and <40%, respectively.[1] Oesophageal adenocarcinoma has the fastest rising incidence in the Western world,[1] and is preceded by Barrett oesophagus, a columnar cell metaplasia that replaces parts of the native squamous cell epithelium (Figure 1). Barrett oesophagus has a prevalence of 1–2% in adults in Western societies and is due to chronic gastro-oesophageal reflux.[1] In patients with Barrett oesophagus and high-grade dysplasia or early oesophageal cancer, endoscopic treatments with mucosal resection and/or radiofrequency ablation are increasingly supported by scientific evidence,[2,3] but the role of such treatment in different stages of the disease pathway needs to be precisely determined. In patients with advanced localized oesophageal cancer, the survival benefit of preoperative oncological therapy has become increasingly evident,[4,5] but the role of such therapy in early tumours and how it influences patterns of recurrence is not well known. This article highlights four studies, published in 2014, addressing the curatively intended treatment of oesophageal cancer of various tumour stages.

A multicentre randomized clinical trial (RCT) at nine specialist centres in Europe assessed the role of endoscopic radiofrequency ablation compared to endoscopic surveillance in patients with Barrett oesophagus and low-grade dysplasia.[6] During 2007–2009, 136 patients (68 in each group) were included and followed up until 2013 (for a median of 36 months) when the RCT was terminated because of better outcomes in the ablation group compared to the endoscopy surveillance group. The trial showed that ablation therapy entailed strongly reduced risks of progression to high-grade dysplasia (2% in the ablation group [$n = 1$] versus 27% in the control group [$n = 18$]; $P < 0.001$) and adenocarcinoma (2% in the ablation group [$n = 1$] versus 9% in the control group [$n = 6$]; $P = 0.03$). The number needed to treat to prevent one case of high-grade dysplasia or adenocarcinoma was as low as 4.0 (95% CI 2.8–7.1), which indicates that this strategy might become useful in clinical practice, particularly given that the adverse effects were few and readily managed (mainly strictures). Tumour progression in patients with Barrett oesophagus and low-grade dysplasia is unpredictable and eradication of the dysplasia might save lives and make surveillance unnecessary. However, these procedures should be carried out by experts, and centralization of these services to dedicated centres is recommended. Such efforts would enhance clinical skills and facilitate precise evaluations and research. This trial should prompt referral of patients with Barrett oesophagus and documented low-grade dysplasia for consideration of radiofrequency ablation.[6]

A large cohort study from the USA compared endoscopic and surgical resection (without preoperative therapy) in the routine clinical practice of 5,390 patients with early invasive oesophageal cancer (T1a [intramucosal] 54% and T1b [submucosal] 46%).[7] Data were collected from 2004–2010 from a hospital-based cancer registry, which covers >70% of all newly diagnosed cancer cases in the country. The endoscopic resection rates of both T1a and T1b tumours increased rapidly during the study period: from 19% in 2004 to 53% in 2010 for T1a tumours and from 7% to 21% for T1b tumours. Among patients who underwent surgical resection, lymph node metastasis was found after pathological evaluation in 5% (91 of 1,810) of patients with a T1a tumour and 17% (358 of 2,153) in patients with a T1b tumour. These rates decreased to 0.5% in T1a tumours and 9% in T1b tumours in patients with low-grade lesions <2 cm in diameter. All-cause 30-day mortality was 0.5% in patients (7 of 1,427) after endoscopic resection and 4% in patients (139 of 3,963) who underwent surgical resection (hazard ratio [HR] 0.33, 95% CI 0.19–0.58). These results highlight the popularity of endoscopic therapy for early oesophageal cancer, but, more importantly, it also shows that a non-negligible frequency of patients with T1 tumours has metastatic disease, particularly those with T1b disease. These patients would typically have improved

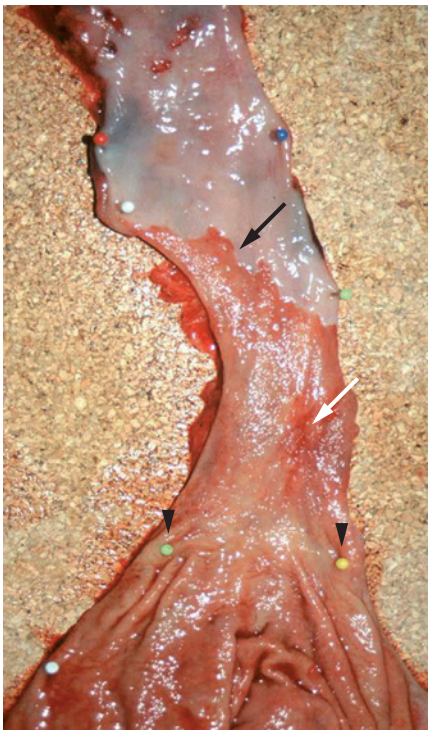

Figure 1 | A surgically resected specimen of the oesophagus with Barrett mucosa and an adenocarcinoma (top) and the proximal stomach (bottom). The black arrow marks the Z-line between the pale squamous cell epithelium and the more red-coloured columnar epithelium of the Barrett oesophagus. The white arrow marks an early oesophageal adenocarcinoma occurring within the Barrett epithelium. The arrowheads mark the gastro-oesophageal junction.

Key advances

- Endoscopic radiofrequency ablation therapy of low-grade dysplasia in Barrett oesophagus can strongly reduce the risks of progression to high-grade dysplasia and adenocarcinoma[6]
- The popularity of endoscopic therapy has increased rapidly in the treatment of early (T1) oesophageal cancer, but the non-negligible rate of patients with lymph node metastasis highlights the need to balance risks and benefits in clinical decision-making[7]
- Survival in patients with early oesophageal cancer (stages I or II) does not seem to be improved by adding chemoradiotherapy to surgery[8]
- Preoperative chemoradiotherapy counteracts tumour recurrence in oesophageal cancer, which should further encourage standard use of preoperative oncological therapy in patients with locally advanced oesophageal cancer[10]

long-term survival if they underwent surgical resection with adequate lymphadenectomy, but at the cost of a worse health-related quality of life.[7] Risks and benefits need to be balanced in clinical decision-making. Older age, more comorbidities and worse fitness might argue for endoscopic therapy, whereas young, otherwise healthy and fit patients might be better off with surgical resection.

Preoperative chemotherapy or chemoradiotherapy improves the postoperative prognosis in a proportion of patients with locally advanced oesophageal cancer (stage III),[4,5] but the role of such treatment in earlier tumour stages is unknown. In a multicentre RCT from France, 195 patients with tumour stage I, IIA or IIB were randomly allocated to either chemoradiotherapy followed by surgery ($n = 98$) or surgery alone ($n = 97$) during 2000–2009.[8] Chemoradiotherapy consisted of two cycles of fluorouracil and cisplatin and 45 Gy in 25 fractions. Complete pathological response was observed in 33% of patients. Surgery was transthoracic oesophagectomy with 2-field lymphadenectomy. The in-hospital postoperative mortality was higher in the chemoradiotherapy group (11% versus 3%; $P = 0.049$). After a median follow-up of 7.8 years, the overall survival (HR = 0.99, 95% CI 0.69–1.40) and disease-free survival (HR = 0.92; 95% CI 0.66–1.30) did not differ when comparing chemoradiotherapy plus surgery with surgery alone.[8] The results from this RCT with long-term follow-up do not support using preoperative chemoradiotherapy for oesophageal cancer of tumour stages I or II.

The CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) RCT from the Netherlands (published in 2012) found a 13% 5-year overall survival benefit by adding preoperative chemoradiotherapy in the treatment of locally advanced oesophageal cancer.[5] Patients in CROSS ($n = 366$) and patients in the phase II trial preceding CROSS ($n = 52$)[9] were included in a trial ($n = 418$) evaluating how chemoradiotherapy might influence patterns of tumour recurrence.[10] Chemoradiotherapy included five cycles of paclitaxel and carboplatin and 41.4 Gy in 23 fractions. The surgical approaches were transthoracic with 2-field lymphadenectomy or transhiatal. Most patients had a T3 tumour (81%) and at least one metastatic lymph node (63%) at diagnosis. A microscopically radical resection (R0) was achieved in 68% in the surgery alone group and in 93% in the chemoradiotherapy plus surgery group; 28% of patients in the latter group had a complete pathological response. Postoperative lymph node metastasis was over-represented in the surgery group (74%) compared with the chemoradiotherapy plus surgery group (31%; $P = 0.001$). Tumour recurrence occurred in 57% in the surgery group and 35% in the chemoradiotherapy plus surgery group. Comparing patients in the surgery and chemoradiotherapy plus surgery groups, recurrences were more frequent in the former group at the anastomosis (9% versus 3%; $P = 0.008$), mediastinum (21% versus 7%; $P < 0.001$), peritoneum (14% versus 4%; $P < 0.001$) and in the blood (35% versus 29%; $P = 0.025$). Tumour recurrence in the irradiated area occurred in only 11 of 213 patients (5%) after chemoradiotherapy, indicating that radiotherapy counteracted recurrence. This large trial shows that preoperative chemoradiotherapy not only improves survival, but also counteracts locoregional and distant tumour recurrences in oesophageal cancer.[10] This knowledge should further encourage standard use of preoperative oncological therapy in patients with locally advanced oesophageal cancer.

These four clinically important studies have advanced our knowledge of how curatively intended treatment of oesophageal cancer can be improved in various aspects. The treatment needs to be tailored depending on the tumour stage and patient characteristics. Hopefully these findings are only the beginning of an era when curatively intended treatment can offer a better chance of cure with improved overall survival, while also taking the morbidity and health-related quality of life aspects of the treatment into account.

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