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Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation

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Abstract

Objective: To compare the incidence and severity of postoperative complications after oesophagectomy for carcinoma of the oesophagus and gastro-oesophageal junction (GOJ) after randomized accrual to neoadjuvant chemotherapy (nCT) or neoadjuvant chemoradiotherapy (nCRT).
Background: Neoadjuvant therapy improves long-term survival after oesophagectomy. To date, evidence is insufficient to determine whether combined nCT, or nCRT alone, is the most beneficial.
Methods: Patients with carcinoma of the oesophagus or GOJ, resectable with a curative intention, were enrolled in this multicenter trial conducted at seven centres in Sweden and Norway. Study participants were randomized to nCT or nCRT followed by surgery with two-field lymphadenectomy. Three cycles of cisplatin/5-fluorouracil was administered in all patients, while 40 Gy of concomitant radiotherapy was administered in the nCRT group.
Results: Of the randomized 181 patients, 91 were assigned to nCT and 90 to nCRT. One-hundred-and-fifty-five patients, 78 nCT and 77 nCRT, underwent resection. There was no statistically significant difference between the groups in the incidence of surgical or nonsurgical complications (P-value = 0.69 and 0.13, respectively). There was no 30-day mortality, while the 90-day mortality was 3% (2/78) in the nCT group and 6% (5/77) in the nCRT group (P = 0.24). The median Clavien-Dindo complication severity grade was significantly higher in the nCRT group (P = 0.001).
Conclusion: There was no significant difference in the incidence of complications between patients randomized to nCT and nCRT. However, complications were significantly more severe after nCRT.
Registration trial database: The trial was registered in the Clinical Trials Database (registration number NCT01362127).

Keywords: Oesophageal cancer; Neoadjuvant treatment; Oesophagectomy complications

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Introduction

Cancers of the oesophagus and the gastro-oesophageal junction (GOJ) have a dismal prognosis with an overall 5-year survival of only about 15%.[1] Only a minority of patients can be offered treatment with curative intention. This is in part because the disease is often disseminated at the time of diagnosis, but also to a large extent because oesophagectomy, with oncologically adequate two-field lymphadenectomy, is a severe physiological trauma[2,3] and is often too demanding for patients with low performance status.

Neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT) have both been found to improve survival when compared to surgery alone,[4–6] but evidence is scarce and inadequate regarding which of these therapy concepts are the most beneficial with regard to important patient outcomes such as postoperative morbidity and mortality, histological tumour response, long-term survival and health related quality of life. To this end, between 2006 and 2013, we have performed a randomized controlled trial, the Neoadjuvant Chemotherapy versus Chemoradiotherapy in Resectable Cancer of the Esophagus and Gastric Cardia Trial (NeoRes). The present study, within the NeoRes Trial, is focused on comparing postoperative morbidity and mortality after nCT and nCRT.

Neither of the two previously published small randomized trials directly comparing nCT and nCRT showed any significant difference regarding postoperative complications,[7,8] although both trials were underpowered with regard to these outcomes. In a recent meta-analysis from our group, where we analysed postoperative complications using both direct and indirect comparisons, we found no overall statistically significant difference between nCT and nCRT regarding the incidence of individual or pooled complications, or postoperative mortality, following oesophagectomy.[9] However, there was a trend towards increased postoperative morbidity and even a statistically significant increased risk of postoperative death in the subgroup analysis of patients with squamous cell carcinoma among patients treated with nCRT.[9]

The objective of this study was to compare the postoperative outcome, i.e. the incidence and severity of complications, in patients undergoing oesophagectomy for cancer of the oesophagus or GOJ, after randomized accrual to nCT or nCRT.

Patients and methods

Setting

The NeoRes trial was performed in seven hospitals in Norway and Sweden between 2006 and 2013. Participating centres in Norway were Oslo University Hospital, St. Olav University Hospital in Trondheim, and Haukeland University Hospital in Bergen. The participating centres in Sweden were Norrland University Hospital in Umeå, Örebro University Hospital, Sahlgrenska University Hospital in Gothenburg, and Karolinska University Hospital in Stockholm.

Eligibility criteria

All patients with histologically confirmed, non-distant-metastatic squamous cell carcinoma or adenocarcinoma of the oesophagus or GOJ, considered to tolerate oesophagectomy, were eligible for inclusion. Tumours located anywhere in the oesophagus or Siewert types I and II junctional tumours, were included, although cervical cancers were required to be resectable without laryngectomy. Study participants were allowed to be no more than 75 years of age, considered fit for oesophagectomy, and have a World Health Organization (WHO) performance status of 0 or 1. All patients were also required to be suitable for chemotherapy and concomitant radiotherapy in terms of adequate renal and haematological functions. Using TNM-6, patients with T1–3, any N (with the exception of T1N0) without evidence of distant metastatic disease, were eligible for inclusion. These inclusion criteria were similar to those used in previous studies.[5,7,8] Manifestations of major heart disease within the last year or a concurrent malignancy within the last five years constituted grounds for exclusion. Patients were stratified by histological tumour type, and all patients were randomized independently through the use of computerized software at the Regional Oncological Centre in Stockholm.

All patients signed a written informed-consent form. The study was approved by the Research Ethics Committees in both Sweden (Regionala etikprövningsnämden in Stockholm, registration numbers 2006/738-32 and 2008-403-32) and Norway (Helseregion Midt-Norge registration number 4.2008.416). The Clinical Trials Database registration number is NCT01362127.

Staging

Clinical tumour stage was assessed through upper gastrointestinal endoscopy and a computed tomography (CT) of the upper abdomen and thorax. The use of FDG-PET-CT and endoscopic ultrasonography (EUS) were optional.

Treatment

Chemotherapy

Treatment was started within two weeks of randomisation. The nCT treatment cycle was 21 days (treatment during weeks 1, 4, and 7). Cisplatin in a dose of 100 mg/m^2 (day 1) was given intravenously, in combination with 5-fluorouracil in the amount of 750 mg/m^2/24 h (days