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Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study

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Abstract ***Aims:*** The aims of this study were to compare short- and long-term outcomes for clinical T2N0 oesophageal cancer with analysis of (i) primary surgery (S) versus neoadjuvant therapy plus surgery (NS), (ii) squamous cell carcinoma and adenocarcinoma subsets; and (iii) neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy.
Methods: Data were collected from 30 European centres from 2000 to 2010. Among 2944 included patients, 355 patients (12.1%) had cT2N0 disease; 285 (S) and 70 (NS), were

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Survival;
Review

compared in terms of short- and long-term outcomes. Propensity score matching analyses were used to compensate for differences in baseline characteristics.
Results: No significant differences between the groups were shown in terms of in hospital morbidity and mortality. Nodal disease was observed in 50% of S-group at the time of surgery, with 20% pN2/N3. Utilisation of neoadjuvant therapy was associated with significant tumour downstaging as reflected by increases in pT0, pN0 and pTNM stage 0 disease, this effect was further enhanced with neoadjuvant chemoradiotherapy. After adjustment on propensity score and confounding factors, for all patients and subset analysis of squamous cell and adenocarcinoma, neoadjuvant therapy had no significant effect upon survival or recurrence (overall, loco-regional, distant or mixed) compared to surgery alone. There were no significant differences between neoadjuvant chemotherapy and chemoradiotherapy in short- or long-term outcomes.
Conclusion: The results of this study suggest that a surgery alone treatment approach should be recommended as the primary treatment approach for cT2N0 oesophageal cancer despite 50% of patients having nodal disease at the time of surgery.

Introduction

In recent years there has been an expansion in the possible treatment options for loco-regional oesophageal cancer [1]. Randomised controlled trials have suggested a prognostic benefit to combined neoadjuvant chemoradiotherapy followed by surgery over surgery alone for locally advanced oesophageal cancer, particularly in nodal positive cancer [2,3]. A recent randomised study has suggested the absence of survival benefit of neoadjuvant chemoradiotherapy over surgery alone in stage I and II oesophageal cancer [4].

Clinical stage T2N0 (cT2N0) oesophageal cancer represents a 'watershed' stage for oesophageal cancer with many possible treatment options available and important considerations that must be accounted for in assigning optimal treatment approach. T2 remains an early stage cancer and the patient is considered to be at risk of nodal disease but this has not been established based upon clinical staging, therefore radical oesophagectomy may be considered sufficient treatment [5,6]. T2 oesophageal cancer has infiltrated the submucosa and therefore there is an increased risk of lymph node metastases [7]. Previously reported rates of pathological node positivity in patients with cT2N0 oesophageal cancer undergoing surgery alone ranges from 25 to 55% [5–10]. Given the risk of nodal disease and concerns regarding accuracy of clinical staging, an endoscopic approach to resection would be uncommon to be utilised [11,12]. Some clinicians advocate systematically a multimodality approach with either neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy followed by surgery [8,9]. However, utilisation of neoadjuvant therapy in particular combined chemoradiotherapy can be associated with grade III–IV toxicity with an adverse impact upon quality of life [13] and an increase in postoperative mortality [4,14].

The previous published literature (Table 1) [5–10,15] concerning cT2N0 oesophageal cancer remains inconclusive regarding the optimal treatment strategy and is limited by small sample sizes and the lack of robust methodology to control for selection biases. The primary aim of this multi-center European study was to compare short- and long-term outcomes from patients receiving primary surgery (S) and those receiving neoadjuvant therapy followed by surgery (NS) for cT2N0 oesophageal cancer. The secondary aims were to compare prognostic outcomes in cT2N0 oesophageal cancer (i) in squamous cell carcinoma and adenocarcinoma subgroups, and (ii) according to the neoadjuvant treatment received, chemoradiotherapy versus chemotherapy.

Methods

Patient eligibility criteria

Data from 2944 consecutive adult patients undergoing surgical resection for oesophageal cancer (including Siewert type I and II junctional tumours) with curative intent in 30 French-speaking European centres between 2000 and 2010 were retrospectively collected through a dedicated website (http://www.chirurgie-viscerale.org), with an independent monitoring team auditing data capture to minimise missing data and to control concordance, as well as inclusion of consecutive patients. Patient malnutrition was defined by weight loss of more than 10% over a 6-month period prior to surgery. High volume centres were defined as performing >8 resections per year during the 10-year study period, with low volume centres as performing ≤ 8 resections per year [16].

As recommended by French national guidelines [17], approach to clinical staging used a combination of endoscopic ultrasound for tranversable tumours,