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Original Research

Prognostic impact of neoadjuvant chemoradiation in cT3 oesophageal cancer – A propensity score matched analysis

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Abstract ***Background:*** The prognostic effect of neoadjuvant treatment in advanced oesophageal cancer is still debated because most studies included undefined T-stages, different radio/chemotherapies or different types of surgery.
Objectives: To analyse the prognostic impact of neoadjuvant chemoradiation in patients with clinical T3 oesophageal cancer and oesophagectomy.
Methods: In a retrospective study 768 patients from two centres with cT3/Nx/M0 oesophageal cancer and transthoracic en-bloc oesophagectomy were selected. Clinical staging was based on endoscopy, endosonography and spiral-CT scan. Propensity score matching using histology, location of tumour, age, gender and ASA-classification identified 648 patients ($n = 302$ adenocarcinoma (AC), $n = 346$ squamous cell carcinoma (SCC)) for the intention-to-treat analysis comparing group-I ($n = 324$) patients with planned oesophagectomy and group-II ($n = 324$) patients with planned neoadjuvant chemoradiation (40 Gy, 5-FU, cisplatin) followed by oesophagectomy. The prognosis was analysed by univariate and multivariate analyses.
Results: In the intention-to-treat analysis group-I had a 17% and group-II a 28% 5-year survival rate (5-YSR) ($p < 0.001$). After excluding patients without oesophagectomy the 5-YSR of group-II increased to 30%. The results were more favourable for patients with AC (5y-SR of 38%) compared to SCC (22%) ($p = 0.060$). In group-II patients with major response ($n = 128$) had a 41% 5-YSR compared to 20% for those with minor response ($n = 155$, $p < 0{,}001$). In multivariate analysis neoadjuvant chemoradiation was a favourable independent prognostic factor.

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Conclusion: Neoadjuvant chemoradiation followed by oesophagectomy results in 11% higher 5-YSR than surgery alone for patients with cT3/Nx/M0 oesophageal cancer. This effect is due to the substantial prognostic benefit of the major responders.

1. Introduction

Recent prospective randomised trials have shown an improved survival after neoadjuvant therapy compared to surgery alone for patients with oesophageal cancer. The most important studies are the CROSS-trial, analysing neoadjuvant chemoradiation for patients with oesophageal adenocarcinoma (AC) or squamous cell carcinoma (SCC) and the MAGIC-trial and the French trial, analysing neoadjuvant chemotherapy for AC including gastric cancer [1–3].

The latest meta-analysis of 2011 presents similar result with a 5.1% improved 2-year survival-rate after induction chemotherapy and 8.7% after chemoradiation followed by surgery [4].

However many studies have shortcomings in inclusion criteria with different T-categories or different therapies concerning type of chemotherapy or chemoradiation or different types of surgery [1,5–7].

If different T-categories are included in a study it remains unclear if all patients have a benefit of induction therapy or only subgroups e.g. those with advanced carcinomas. If different kinds of induction therapy or surgery are included it remains unclear which treatment was really responsible for a benefit.

Therefore the purpose of the present paper was to analyse by intention-to-treat (ITT) and per-protocol (PP) only patients with clinical T3 oesophageal cancer and standardised radical surgery as well as standardised chemoradiation.

2. Patients and methods

From two university departments of surgery, 768 patients treated for clinical T3 Nx M0 oesophageal cancer between 1996 and 2009 were included in the study. The purpose of this analysis was to concentrate on one defined clinical T-category and only on oesophageal cancer (type I) excluding cardia carcinoma (type II and type III) and to perform a subgroup analysis of oesophageal adenocarcinoma and squamous cell carcinoma. Both departments are high-volume centres for this disease and applied the same kind of diagnostics with endoscopy, endoscopic ultrasonography and spiral CT-scan in all patients. The spiral CT scan was performed for thorax and abdomen in all patients. In patients with middle or upper third oesophageal cancer the neck was included in the CT scan.

In the Department of Surgery of the University of Hamburg (HH) induction therapy was not an option and 214 patients were planned for primary transthoracic oesophagectomy without any pretreatment (group I–HH). In the Department of Surgery of the University of Cologne (K) 554 patients with cT3 Nx M0 oesophageal cancer were diagnosed and planned for therapy during the same time period. Of these patients 145 had primary surgery (group I–K), 48 of these patients had a contraindication for neoadjuvant chemoradiation and 97 patients rejected induction therapy after substantial information mostly because of reluctance against radiation or chemotherapy, time loss due to delay of surgery, the small potential prognostic benefit that could be achieved and the impossibility to predict response.

After ruling out distant metastases and proving functional fitness for surgery the patients were treated in curative intention. To improve the comparability of the two treatments we performed a propensity score matching using the variables histology, age, gender, location of tumour and the ASA-classification (measurement of functional fitness according to the American Society of Anaesthesia). There were 340 patients with SCC and 308 patients with AC that could be matched without large imbalance ($|d| > 0.25$) of the used covariates. In total 324 patients had primary surgery and 324 patients had neoadjuvant chemoradiation (Table 1).

This retrospective study was performed according to the criteria of the ethics committees of the two university hospitals.

2.1. Surgical technique

The treatment of choice in both departments was Ivor Lewis oesophagectomy and reconstruction by gastric pull-up. The abdominal approach was first performed open in both departments of surgery via median inverse T-shaped laparotomy. In Cologne a laparoscopic approach was introduced in December 2003 [8,9]. The reconstruction was done by gastric pull-up.

2.2. Neoadjuvant radiochemotherapy

The planned therapy for 324 patients with clinical T3 oesophageal carcinoma was preoperative chemoradiation. On days 1–5, cisplatin (20 mg/m2/d) was administered as a short-term infusion and 5-fluorouracil (1000 mg/m2/d) was administered as a continuous