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Role of neoadjuvant chemoradiotherapy in clinical T2N0M0 esophageal cancer: A population-based cohort study

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ABSTRACT

Background: The aim of this population-based cohort study was to determine whether the addition of neoadjuvant chemoradiotherapy (nCRT) to surgery is associated with improved pathologic outcomes and survival in patients with cT2N0M0 esophageal cancer.

Methods: Patients who underwent nCRT followed by surgery or surgery alone for cT2N0M0 esophageal cancer were identified from The Netherlands Cancer Registry database (2005–2014). Accuracy of clinical staging was assessed using the resection specimen as gold standard. After propensity score matching, influences of both treatment strategies on radical resection (R0) rates and overall survival were compared.

Results: In total 533 patients were included; 353 underwent nCRT followed by surgery and 180 underwent surgery alone. In the nCRT group 32% of patients achieved a pathologic complete response. Clinical understaging was observed in 62% of the patients in the surgery alone group based on pT-stage (n = 30, 27%), pN-stage (n = 26, 23%), or both (n = 55, 50%). Propensity score matching resulted in 78 patients who underwent nCRT plus surgery versus 78 who underwent surgery alone. In the nCRT group radical resections were more frequently observed (99% vs. 89% p = 0.031) and resulted in improved 5-year overall survival (46% vs. 33%, p = 0.017).

Conclusion: In this population-based study, clinical staging of cT2N0M0 esophageal cancer was highly inaccurate. Compared to surgery alone, neoadjuvant chemoradiotherapy was associated with higher radical resection rates and improved overall survival.

Introduction

Esophageal carcinoma is the sixth most common cause of cancer-related death globally, and the incidence of esophageal carcinoma is increasing [1,2]. For patients with locally advanced non-metastatic esophageal cancer, multimodality treatment with neoadjuvant chemoradiotherapy (nCRT) followed by surgery has shown to improve 5-year survival with 14% compared to a surgery alone approach [3,4]. However, controversy still exists regarding the optimal treatment strategy for patients with clinical T2N0M0 (cT2N0M0) esophageal cancer.

Clinical T2 esophageal cancer represents an anticipated early stage disease. In the absence of nodal disease during clinical staging, a surgery alone approach may be regarded as the designated treatment for these tumors [5,6]. Unfortunately, current preoperative staging of patients with cT2N0M0 esophageal cancer is notoriously imprecise, and studies have reported clinical understaging rates between 27% and 56% for cT2N0M0 esophageal cancer [5–11].

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Due to the limitations of the current clinical staging techniques, a multimodality treatment approach for cT2N0M0 esophageal cancer patients is recommended by several studies [7,8,10,12]. However, despite clinical understaging of lymph node metastasis and tumor stage, other studies could not confirm a survival benefit of a multimodality treatment approach compared to a surgery alone approach for cT2N0M0 esophageal cancer [5,6,11,13–15]. Moreover, concerns have been raised with regard to the toxicity of nCRT that could result in an increased risk of postoperative complications [16–19].

The available studies that assess whether nCRT adds any benefit to patients with cT2N0M0 esophageal cancer are equivocal. Therefore, the aim of the present nation-wide multi-center study was to determine whether the addition of nCRT to surgery is associated with improved pathologic outcomes, postoperative mortality, and survival in a large cohort of patients with cT2N0M0 esophageal cancer.

Methods

Data collection and study population

This nation-wide population-based cohort study was conducted with data from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.8 million inhabitants. The NCR is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL) and is mainly based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Information on patient and treatment-related characteristics such as gender, date of birth, tumor histology, tumor stage, and primary treatment are routinely obtained from medical records by trained data managers using the NCR registration and coding manual. Information on vital status was obtained by annual linkage with the Municipal Administrative Databases, in which all deceased and emigrated persons in the Netherlands are registered. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

Patients diagnosed with clinical T2 and N0 histologically proven primary esophageal adenocarcinoma or squamous cell carcinoma, who underwent esophagectomy with curative intent in The Netherlands from 2005 through 2014 were eligible for this study. Inclusion criteria consisted of patients who received nCRT followed by esophagectomy or esophagectomy alone.

Clinical and pathological staging

After initial diagnosis of esophageal cancer, each patient underwent further investigations needed for adequate staging. In the Netherlands, pretreatment clinical staging includes endoscopic ultrasound (EUS), ultrasonography of the neck, and either stand-alone computed tomography (CT) of thorax and abdomen, or integrated ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scanning. Tumors were staged according to the International Union Against Cancer (UICC) TNM classification, that was valid at the time of diagnosis. Patients diagnosed between 2005 and 2009 were staged using the 6th edition, and those diagnosed between 2010 and 2014 according to the 7th edition [20]. Clinical and pathological T and N stage were translated according to the 7th edition for this study for uniformity purposes.

Treatment

In the last decade, nCRT according to the CROSS regimen (carboplatin [AUC 2 mg/mL per min] and paclitaxel [50mg/m2] weekly during 5 weeks and concurrent radiotherapy [41.4 Gy in 23 fractions of 1.8 Gy]) became standard of care for patients with locally advanced esophageal cancer in the Netherlands. In general, eligible patients had a WHO performance status ≤2, and did not lose >10% of their body weight. The surgical procedure consisted of a transthoracic or transhiatal esophagectomy with lymphadenectomy and gastric tube reconstruction with cervical or intrathoracic anastomosis.

Statistical analyses and outcome measures

To estimate the accuracy of clinical staging in the surgery alone group, pathologic staging data were used to calculate the respective rates of clinical T- and N- understaging and overstaging. Due to the use of induction therapy in the nCRT group clinical T- and N-understaging or overstaging could not be truly assessed. The postoperative pathological stages were reported.

Categorical data are presented as numbers and percentages and continuous data are expressed as mean ± standard deviation (SD) or median (range). To determine differences between the two treatment groups regarding baseline characteristics and outcomes (i.e. surgical radicality and 90-day mortality) the Chi square test was used for categorical variables, and Student's *t*-test or Mann-Whitney *U* test for parametric and non-parametric continuous variables, respectively. Kaplan-Meier survival curves were constructed for both treatment groups, and compared using the log-rank test. Second Kaplan-Meier survival curves were constructed for patients in the surgery alone group with a pT2N0-stage versus > pT2N0-stage and for patients in the nCRT group with a pT2N0-stage, <pT2N0-stage or > pT2N0-stage.

In order to avert the effect of confounding influences of covariates on the assessed outcomes between the two study groups (nCRT versus surgery alone), propensity score matching was performed to create comparable groups. First, a propensity score was calculated for each patient using logistic regression, based on available patient and treatment-related characteristics that may influence prognosis (i.e. age, gender, history of previous malignancy, histology, surgical approach, referral for esophagectomy, year of diagnosis, hospital volume; Table 1). Subsequently, nearest-neighbor (1:1; 'greedy') propensity score matching without replacement was performed in which the within-pair difference was minimized by setting a caliper of 0.25 of the standard deviation of the logit of the propensity score. All analyses were performed using IBM SPSS Statistics Version 23.0 for Windows (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' package). To manage missing data, a complete case analysis was carried out. A *p*-value of less than 0.05 was considered statistically significant.

Results

Study population and characteristics

The NCR identified 581 patients diagnosed with cT2N0M0 esophageal adenocarcinoma or squamous cell carcinoma, who underwent esophagectomy with curative intent in The Netherlands from 2005 through 2014. A total of 48 patients were excluded because of neoadjuvant chemotherapy (n = 24) or radiotherapy (n = 2), and due to missing data in any of the studied variables (n = 22). The remaining 533 patients were included in this study; 353 patients received nCRT, and 180 patients underwent surgery alone (Table 1).

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