



The optimal lymph node dissection in patients with adenocarcinoma of the esophagogastric junction

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ABSTRACT

Objective: The aim of this study was to refine the optimal lymph node dissection in Western patients with adenocarcinoma of the esophagogastric junction (AEG).

Background: Lymphadenectomy is essential in addition to surgery for AEG. Asian studies continually present superior survival rates using a more extended lymphadenectomy compared with results reproduced in the West. Thus, the optimal extend of the lymphadenectomy remains unclear in Western patients.

Methods: A retrospective cohort was conducted of patients with AEG from January 1st, 2003 to December 31st, 2011. All patients undergoing curatively intended surgery was included. Two types of resections were constructed; Res1 included patients where only the loco regional lymph nodes were removed (station 1–4, 7 and 9) and Res2 included the additional removal of the more distant stations 8 and/or 11.

Results: We identified 510 patients with AEG. The highest frequency of lymph node metastases was seen in the loco regional stations 1–3, 7 and 9, ranging from 34% to 41.4%. There was no difference in overall survival between the two groups; the median survival rate for Res1 was 30.4 months compared to 24.1 months for Res2 ($p = 0.157$). Furthermore, the extend of lymph node dissection seemed to have no effect on survival (HR = 1.061, 95%CI 0.84–1.33).

Conclusion: No significant difference in survival between the extended and the less extended lymphadenectomy was found. The presence of metastases in distant lymph nodes indicates poor survival and may represent disseminated disease. We do not find evidence that supports an extended lymph node dissection in Western patients.

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1. Introduction

During the past few decades, there has been an increase in the incidence of adenocarcinoma of the esophagogastric junction (AEG) in Western countries [1,2]. Recently, observations in East Asia and Western countries show an increasing tendency in AEG, thus recognizing AEG as a possible health problem [3]. The five-year-survival rate after curative resection is 24–36%, and the presence of lymph node metastases is a well-known negative prognostic

factor [4,5]. Consequently, lymphadenectomy is considered essential in addition to the surgical treatment. Given the borderline location, AEG does not exclusively resemble gastric or esophageal cancer, which reflects the surgical guidelines. In Asia, the standard approach is an extended lymph node dissection compared to a more conservative dissection in European countries [5]. The possibility of improving the prognosis might be greater in an extended dissection, but morbidity and mortality rates might also increase [6,7]. Nonetheless, compared to results presented by the West, Asian studies continually present superior survival rates using the more extended lymphadenectomy. Thus, the optimal extent of lymph node dissection in Western patients remains uncertain [8,9].

The aim of this study was to evaluate the pattern of lymph node metastases of AEG in Danish patients and to estimate the survival rate related to each lymph node station. The intention was to refine

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the optimal lymph node dissection in Western patients.

2. Methods

2.1. Study design

Patients were identified using the Danish Esophageal and Stomach Cancer Group (DECV) database which is a prospectively maintained national database covering all patients with cancer of the esophagus, cardia and stomach. The register was established in 2003 and a cohort study of Danish patients was conducted using this database with permission from the DECV group. The cohort included all consecutive patients diagnosed with AEG and treated with intended curative surgical treatment in the period from January 1st, 2003 to December 31st, 2011. Patients were included from two of the largest esophageal and stomach cancer centers in Denmark, since these two centers were the most consistent regarding the surgical methods. Follow-up was defined at death or at the end of the study period (September 2016). AEG was defined according to guidelines from the UICC TNM Classification of Malignant Tumors 7th edition, where a tumor both with the epicenter within five cm of the esophagogastric junction and extending into the esophagus, is classified and staged according to the esophageal scheme [10].

2.2. Information on patients and procedures

All Danish residents are assigned a Civil Personal Registration (CPR) number at birth or immigration, which is a unique identification number allowing individual-level cross-linkage between several Danish medical registries. The CPR numbers were used to identify the patients' medical records both in paper form and electronically. Information on gender, age, histology, operational approach, lymph node metastasis and complications were retrieved from the records. The tumors were classified according to the UICC TNM Classification of Malignant Tumors 7th edition, where N1 = 1–2 regional lymph node metastases, N2 = 3–6 regional lymph node metastases and N3 = >6 lymph node metastases [10]. The standard preoperative evaluation was abdominal and thoracic Computed Tomography (CT) scans and in most cases supplemental ultrasound of the neck. Before 2009 all patients were treated according to the Macdonald regimen and received chemotherapy post operatively [11]. After 2009 the standard regimen changed and all patients received perioperative chemotherapy according to the Magic regimen [12].

2.3. Data on comorbidity

Carlson's Comorbidity Index (CCI) is a validated, rated scoring system of comorbidities, which was used to assess the burden of comorbidities in the study population. In CCI, each diagnosis associated with a patient is assigned a score related to the risk of 1-year mortality. The CCI score was divided into three different categories: 0 (low comorbidity), 1–2 (moderate comorbidity), and >2 (high comorbidity). Information on diagnoses included in the CCI for each patient was retrieved from the Danish National Patient Registry (DNPR). The DNPR covers every hospital admission in Denmark since 1977 and include information on dates of admission and discharges, surgical procedures, and primary and secondary diagnoses [13]. Diagnoses have been classified according to the 10th edition of the International Classification of Diseases (ICD-10) since 1993. Identification of the patients in the DNPR was possible using the CPR number.

2.4. Study cohort

The hypothesis of this study was that the presence of distant lymph node metastases might reflect advanced disease; hence the removal of these stations may be redundant. During the past decade, different surgical approaches in lymphadenectomy have been used in the two centers due to inconsistency in the guidelines. This especially comprises the question of whether or not to remove the more distant lymph node stations 8 and 11. In order to compare the findings, two types of resection were defined. Resection 1 (Res1) included removal of lymph node stations 1–4, 7 and 9 and Resection 2 (Res2) included the additional removal of stations 8 or/and 11, regardless of metastases.

Medical records containing per- and postoperative information were retrieved and examined systematically. In case of missing data, information was assessed from electronic journals or the Danish Pathology Register. Data was obtained by four of the authors. Survival analyses contained all deaths, including those due to an unrelated cause. The inclusion criteria were adenocarcinoma of the esophagogastric junction. Squamous cell carcinomas, neuroendocrine tumors and cases with unknown histopathology were excluded from further analyses.

The main study outcome was the amount of positive lymph nodes removed according to each lymph node station. In some early-year cases the exact lymph node removal was not specified ($n = 74$). Consequently, those cases could not be included in the analysis of lymph node metastases. In one case, the lymph nodes were not removed during surgery, no reason described. Lymph nodes are presented according to the Japanese Gastric Cancer Association (JGCA) guidelines (Fig. 1) [14].

2.5. Index of estimated benefit of lymph node dissection (IEBLD)

To evaluate the effect of lymph node dissection, the index proposed by Sasako et al. was adopted [15]. This index was calculated for each station by multiplying the amount of metastases by the five-year-survival rate for patients with positive nodes at each station. The frequency of metastases was determined by dividing the number of patients with metastases by the number of patients, where the station was resected. The cumulative five-year-survival rates for patients with metastases at each station were calculated irrespective of the presence or absence of any other nodal metastases. High values represented lymph node stations, where dissection seemed beneficial for survival.

2.6. Statistical analyses

Fisher's exact test or Chi-square was used to compare categorical data. The Mann-Whitney test was used to compare continuous data. Survival data was generated from the life table method. The Kaplan-Meier method was used to generate cumulative survival rates, and the log-rank test was used to compare univariate factors. Multivariate analysis for overall survival was performed using stepwise Cox's proportional hazards model as well as hazard ratios (HR) with 95% confidence intervals of potential prognostic factors. The Cox regression model was tested for assumptions.

All data management and statistical analyses were performed using IBM SPSS Statistics version 23. Data was analyzed by two of the authors and crosschecked by an experienced biostatistician at a separate academic institution. A p -value <0.05 was considered statistically significant.

2.7. Ethical considerations

DECV, the Danish Clinical Registries (RKKP) and the Danish Data

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