



Impact of diagnosis-to-treatment waiting time on survival in esophageal cancer patients – A population-based study in The Netherlands

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Abstract

Background: The aim of this study was to determine whether the waiting time from diagnosis to treatment with curative intent for esophageal cancer impacts oncologic outcomes.

Patients and methods: All patients treated by esophagectomy for esophageal carcinoma in 2005–2013 were identified from the Netherlands Cancer Registry. Patients who underwent multimodality treatment and patients treated with surgery only were analyzed separately. Multivariable logistic regression analyses were performed to evaluate the impact of diagnosis-to-treatment waiting time on pT-status, pN-status, and R0 resection rates. Cox regression was applied to estimate the influence of waiting time on overall survival. Analyses were performed with the original scale and in three categorized groups of waiting time (≤ 5 weeks, 5–8 weeks, and > 8 weeks) based on guidelines and previous studies.

Results: Of 3839 patients, 2589 underwent multimodality treatment and 1250 were treated with surgery only. In both groups, pT-status, pN-status, and R0 resection rates were not significantly influenced by waiting time (p -values > 0.05). Also, waiting time was not significantly associated with overall survival in the multimodality treatment group (5–8 weeks vs. ≤ 5 weeks, hazard ratio [HR] 1.12, $p = 0.171$; and > 8 weeks vs. ≤ 5 weeks, HR 1.21, $p = 0.167$), nor in the surgery only group (5–8 weeks vs. ≤ 5 weeks, HR 0.92, $p = 0.432$; and > 8 weeks vs. ≤ 5 weeks, HR 1.00, $p = 0.973$).

Conclusion: This large population-based cohort study demonstrates that longer waiting time from diagnosis to treatment in patients treated for esophageal cancer with curative intent does not negatively impact pT-status, pN-status, R0 resection rates, and overall survival.

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Keywords: Esophageal cancer; Waiting time; Outcome; Survival; Prognosis

Introduction

Esophageal cancer is the eighth most common type of cancer worldwide.¹ Surgical resection is the treatment

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modality of choice for patients with resectable non-metastatic disease.² Multimodality treatment regimens are increasingly applied as the standard of treatment, with clear overall survival benefits.^{3–6}

Waiting time is considered as an important quality indicator for cancer care. An extended time interval from diagnosis to treatment has been shown to negatively influence patients' quality of life and to result in psychological distress.^{7–9} Furthermore, in various cancers a direct relationship between waiting time and oncological outcome has been demonstrated.^{10–12} In the Netherlands, a maximum of 5 and 6 weeks, respectively, from diagnosis to treatment for any malignancy are recommended by several parties.^{13,14}

Previous studies on the effect of waiting time on survival for esophageal cancer reported that waiting time between operation and surgery did not adversely affect survival.^{15,16} A recent study confirmed these results both for patients who are treated with neoadjuvant therapy followed by surgery and for patients treated with primary surgery.¹⁷ However, these studies were from single institutions with a limited number of patients, and therefore no firm conclusions could be drawn from them. In addition, these studies did not report on the potential negative influence of longer waiting time on important outcomes such as pT-status, pN-status, and microscopically radical (R0) resection rates, through tumor progression. Therefore, the aim of this study was to evaluate the impact of waiting time on pT-status, pN-status, R0 resection rates, and overall survival in a large population based cohort of esophageal cancer patients who underwent multimodality treatment or surgery only.

Patients and methods

Study population

A population-based cohort study with data from the Netherlands Cancer Registry (NCR) was conducted. The NCR is a nationwide population-based registry that gathers data on all newly diagnosed malignancies and is hosted by the Comprehensive Cancer Organisation the Netherlands (IKNL). All data have been obtained from the medical records within all Dutch hospitals by trained datamanagers using the NCR's registration and coding manual. The privacy committees of the NCR approved this study.

The database from the NCR included all patients with histologically proven primary esophageal adenocarcinoma or squamous cell carcinoma in The Netherlands from 2005 through 2013. Patients aged 18 years or older, who underwent transhiatal or transthoracic esophagectomy, without intra-operatively discovered irresectable tumors (T4b) and/or disseminated (M1) disease were included in this study. Exclusion criteria consisted of intra-operatively discovered irresectable tumors (T4b) and/or disseminated (M1) disease, emergency esophagectomy, and missing follow-up.

Patient-specific information that was retrieved from the database included patients' age, gender, history of malignancy, tumor location, histology, staging, multimodality treatment, surgical approach, radicality, referral, year of diagnosis, hospital volume, follow-up status, and follow-up time.

Patients should be diagnosed and treated according to the nationwide guidelines for diagnosis, treatment, after-care and follow-up for patients with esophageal cancer.¹⁸ All patients were staged according to the TNM-system for esophageal cancer in use during the year of diagnosis. Staging was clinically and pathologically translated according to the 7th edition of the TNM classification for this study.¹⁹

Outcome measures

Patients were divided into two groups. The first group consists of patients who received multimodality treatment consisting of neoadjuvant chemoradiation followed by surgery or perioperative chemotherapy, and the second group underwent surgery only. Primary outcome measures were pT-status, pN-status, R0 resection rate, and overall survival. Overall survival was defined as the time from the date of diagnosis until the date of death or last follow-up at December 31st, 2014. The main independent variable was waiting time. In the multimodality treatment group, waiting time was defined as the number of weeks between the date of diagnosis and the start date of multimodality treatment. For the surgery only group, waiting time was defined as the number of weeks between the date of diagnosis and the date of surgery. The date of diagnosis was used as the date of the first gastrointestinal endoscopy, on which the diagnosis of esophageal cancer had been established by histology from biopsies. The waiting time constitutes a combination of time needed to confirm the diagnosis of esophageal cancer, referral time, and pre-therapeutic work-up.

Statistical analysis

Baseline data were described as means with standard deviation (SD) or as frequencies with percentages. Based on the recommendations of the maximum waiting times in the Netherlands and previous literature, waiting time was grouped into three categories of ≤ 5 weeks, 5–8 weeks, and > 8 weeks.^{13,15} Differences between the three groups (≤ 5 , 5–8, and > 8 weeks) were analyzed using the chi-square test or the parametric ANOVA test. Missing baseline data was dealt with using multiple imputation with 20 imputed datasets.²⁰

To assess the difference in waiting time between resectable and non-resectable patients, the median waiting time was compared between the included patients and the excluded patients with intra-operatively discovered irresectable tumors (pT4b) and/or disseminated (pM1) disease,

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