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Original Research

Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study

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Treatment outcome;
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Abstract ***Introduction:*** The optimal time between end of neoadjuvant chemoradiotherapy (nCRT) and oesophagectomy is unknown. The aim of this study was to assess the association between this interval and pathologic complete response rate (pCR), morbidity and 30-day/in-hospital mortality.

Methods: Patients with oesophageal cancer treated with nCRT and surgery between 2011 and 2016 were selected from a national database: the Dutch Upper Gastrointestinal Cancer Audit (DUCA). The interval between end of nCRT and surgery was divided into six periods: 0–5 weeks (n = *157*;A), 6–7 weeks (n = *878*;B), 8–9 weeks (n = *972*;C), 10–12 weeks (n = *720*;D), 13–14 weeks (n = *195*;E) and 15 or more weeks (n = *180*;F). The association between these interval groups and outcomes was investigated using univariable and multivariable analysis with group C (8–9 weeks) as reference.

Results: In total, 3102 patients were included. The pCR rate for the groups A to F was 31%, 28%, 26%, 31%, 40% and 37%, respectively. A longer interval was associated with a higher probability of pCR (≥10 weeks for adenocarcinoma: odds ratio [95% confidence interval]: 1.35 [1.00–1.83], 1.95 [1.24–3.07], 1.64 [0.99–2.71] and ≥13 weeks for squamous cell

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carcinoma: 2.86 [1.23–6.65], 2.67 [1.29–5.55]. Patients operated ≥10 weeks after nCRT had the same probability for intraoperative/postoperative complications. Patients from groups D and F had a higher 30-day/in-hospital mortality (1.80 [1.08–3.00], 3.19 [1.66–6.14]).
Conclusion: An interval of ≥10 weeks for adenocarcinoma and ≥13 weeks for squamous cell carcinoma between nCRT and oesophagectomy was associated with a higher probability of having a pCR. Longer intervals were not associated with intraoperative/postoperative complications. The 30-day/in-hospital mortality was higher in patients with extended intervals (10–12 and ≥15 weeks); however, this might have been due to residual confounding.

1. Introduction

Oesophageal cancer is the eighth most common cancer in the world and the incidence is increasing [1]. Randomised clinical trials have shown that neoadjuvant chemoradiotherapy (nCRT) or chemotherapy improves survival after oesophagectomy. Multimodality treatment for resectable oesophageal cancer has now become standard in the Netherlands [2]. nCRT induces tumour regression, and a pathological complete response (pCR) is observed in 25–30% of patients [3]. A pCR is associated with an improved survival compared with patients who have an incomplete pathological response [3,4].

A longer interval between nCRT and surgery has been suggested to increase the probability of a pCR [5]. In pancreatic and rectal cancer, there is some evidence that a longer interval between end of neoadjuvant treatment and surgery is associated with higher pCR rates and also improved (disease-free) survival [6–8]. However, extended intervals might also lead to residual tumour growth or increased radiation fibrosis resulting in technically more challenging operations with higher postoperative complication rates, resulting in a worse survival. For oesophageal cancer, conflicting data have been published. Most studies modelled the time interval as a dichotomous variable or included only a small number of patients [9–12].

The aim of this population-based study was to assess the association between the time after nCRT and pCR, complications and postoperative mortality in a large national cohort. It was hypothesised that a longer time interval is associated with a higher pCR but also with a higher complication rate.

2. Patient and methods

2.1. Study design

We conducted a retrospective study using data from the Dutch Upper Gastrointestinal Cancer Audit (DUCA), a large prospective national audit facilitated by the Dutch Institute for Clinical Auditing. All patients undergoing surgery for gastric or oesophageal cancer in the Netherlands are registered in this database [13]. Patient, tumour, treatment characteristics, pathological information and postoperative outcome (until 30 days postoperative) were extracted from this database.

2.2. Patient selection

Patients who underwent an elective oesophagectomy with curative intent for oesophageal or junctional cancer after nCRT between 2011 and 2016 were included. Criteria for exclusion were: cervical oesophageal tumours, non-completion of the nCRT regimen, cT1N0 tumours (according to the 7th edition of the Union for International Cancer Control-American Joint Committee on Cancer (UICC-AJCC) tumour, node, metastasis (TNM) staging system [14]), unknown date of birth, unknown curability status of resection (curative/palliative), or unknown 30-day/in-hospital survival status.

Since 2010, nCRT followed by surgery has been the standard treatment according to the Dutch guideline for oesophageal carcinoma (with the exception for T1N0 tumours). Furthermore, in 2014, the guideline specified the nCRT regimen based on the CROSS trial [15]: carboplatin (AUC 2 mg/ml/min) and paclitaxel (50 mg/m^2) is administered on days 1, 8, 15, 22 and 29. Concurrent radiotherapy 41.4 Gray is administered in 23 fractions, 5 days a week starting on the day of first chemotherapy administration [15,16]. Although the exact regimen used was not specified in the database, it was assumed that all patients in this study were treated with this regimen.

2.3. Time interval

In the DUCA, the start of nCRT and the date of surgery are registered. The date of the end of nCRT is not registered. To estimate the interval between the end of nCRT and surgery, 30 days (duration of CROSS schedule) were subtracted from the calculated interval between start of nCRT and operation. In this manuscript 'interval' always refers to the time interval between the end of nCRT and resection.