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## **Goedgekeurde aanvraag gegevens ten behoeve van wetenschappelijk onderzoek** DUCA201812 Borggreve

### **Datum**

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### **Titel onderzoek**

Is there a survival benefit in prolonging the time interval between neoadjuvant chemoradiotherapy and surgery for esophageal cancer?

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### **Beschrijving onderzoek**

Current treatment plans for patients with esophageal cancer suggest that surgical resection may be performed within 6 to 8 weeks of the completion of neoadjuvant therapy.<sup>1-3</sup> However, several studies have shown that longer time intervals between chemoradiotherapy and surgical procedures are associated with increased rates of pathologic complete response, such as reported by the recently published Dutch cohort from 2011-2016.<sup>4</sup> This phenomenon is particularly relevant when this translates into a long-term survival advantage for these patients. A recent meta-analysis including six studies reporting on the five-year overall survival, showed that the prolonged interval between neoadjuvant chemoradiotherapy and esophagectomy was not associated with increased five-year overall survival (pooled estimate OR: 0.87, 95% CI 0.66-1.14, p-value = 0.30).<sup>5</sup> However, these six studies all used different neoadjuvant therapy regimens and have a relatively limited sample size (largest sample size per study: n=276, total number of patients in all six studies together: n=1206). In contrast, a population-based study that included more patients than all six studies together (n=5393) reported a significant worse overall survival in patients in whom the interval between neoadjuvant therapy and surgery exceeded 64 days (HR: 1.16, 95% CI: 1.01–1.33; p = 0.03).<sup>6</sup>

In conclusion, the optimal timing of surgical resection after neoadjuvant therapy in esophageal cancer patients remains unknown. Consequently, the aim of the current study is to identify in a large population-based cohort, with homogenous neoadjuvant therapies used, whether there is an effect of the timing of surgical resection after the completion of neoadjuvant chemoradiotherapy on long-term overall survival in esophageal cancer patients.

### **Onderzoeksvraag:**

**Study aim:** To study whether there is an association between the time interval from neoadjuvant therapy to surgery and overall survival in patients with esophageal cancer.

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**Primary endpoints:**

- Overall survival after neoadjuvant chemoradiotherapy followed by surgical resection in patients with esophageal cancer.

**Onderzoeksopzet:**

Population-based cohort study that studies whether there is an association between the time interval from nCRT to surgery and overall survival in patients with esophageal cancer.

**Onderzoekspopulatie:**

All patients with esophageal cancer in the Netherlands that underwent neoadjuvant chemoradiotherapy followed by surgical resection between 2011-2016, and of whom the number of days between the end of neoadjuvant chemoradiotherapy and surgical resection is known, will be included in this cohort study. Exclusion criteria: histologic subtype other than squamous cell carcinoma or adenocarcinoma and patients who did not undergo a surgical resection with curative intent.

**Statistiek:**

Missing baseline data will be imputed with multiple imputation techniques. In a sensitivity analysis, the time interval will be truncated at 5% and 95% to reduce leverage effects of outliers. The effects of the interval between neoadjuvant therapy and surgery on overall survival will be studied using Cox regression analysis, with and without adjustment for potential delay-related confounders (resulting in unadjusted and adjusted hazard ratio, respectively). Delay-related confounders include, amongst others, comorbidities, performance status (ASA score) and BMI at time of diagnosis. Furthermore, the model will be adjusted for clinical factors such as , pathological TNM status, patient age, and sex and well as surgery-related factors such as type of surgical approach, number of resected lymph nodes, year of surgery and annual hospital volume. Separate analyses will be carried out for adenocarcinomas and squamous cell carcinomas.

Statistical analyses will be performed using SPSS version 23.0 (IBM Corp., Armonk, NY) and R 3.3.1 open-source software (<http://www.R-project.org>). Statistical significance will be set at  $p < .05$ .

**Beoogde publicatie**

Time interval between neoadjuvant chemoradiotherapy and surgery for esophageal cancer and overall survival.

**References:**

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4. van der Werf LR, Dikken JL, van der Willik EM, et al. Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study. *Eur J Cancer*. 2018;91:76–85.
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6. Lee A, Wong AT, Schwartz D, et al. Is There a Benefit to Prolonging the Interval Between Neoadjuvant Chemoradiation and Esophagectomy in Esophageal Cancer? *Ann Thorac Surg*. 2016;102:433–438.