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## **Goedgekeurde aanvraag gegevens ten behoeve van wetenschappelijk onderzoek** DUCA201908

### **Datum**

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### **Titel onderzoek**

Outcome of neoadjuvant chemoradiotherapy for patients with esophageal squamous cell carcinoma treated in Asia versus those treated in the Netherlands outside the CROSS trial.

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### **Beschrijving onderzoek**

Roughly 80% of all esophageal cancer patients worldwide live in Asia with over 90% having squamous cell carcinoma.<sup>1</sup> Patients presenting with locally advanced disease can be curatively treated with neoadjuvant chemoradiotherapy (nCRT) followed by surgery. The CROSS trial showed that after nCRT consisting of carboplatin and paclitaxel with concurrent 41.4 Gy radiotherapy, 23% of patients with adenocarcinoma (AC) and 49% of patients with squamous cell carcinoma (SCC) have a pathologically complete response (pCR) in the resection specimen.<sup>2</sup> For these patients surgical resection might not be necessary. An active surveillance strategy, in which patients who show a clinically complete response (cCR) after nCRT will undergo frequent clinical response evaluations instead of standard esophagectomy, is currently being investigated in the cluster-randomized Dutch SANO-trial.<sup>3</sup> Although this trial is including both patients with adenocarcinoma and patients with squamous cell carcinoma, the majority of patients in the Netherlands and thus included in this trial have adenocarcinoma. The high pCR rate after nCRT according to the CROSS regimen in patients with SCC provides a rationale for a separate clinical trial in Asia comparing active surveillance with standard esophagectomy in patients with SCC showing cCR after nCRT (Surgery If Needed for Oesophageal cancer (SINO)-trial).



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Before starting the planned SINO trial, information on pathological response and survival after nCRT plus surgery according to the CROSS regimen in Asian clinical practice is essential. However, the effectiveness of this regimen in Asian practice has not been reported yet. The CROSS trial itself was performed in Dutch hospitals only and included mostly Dutch patients. Moreover, only 41 of 178 patients (23%) in the nCRT plus surgery arm of the CROSS trial had SCC.<sup>2</sup> Therefore, before the planned SINO trial can be started the effectiveness of nCRT according to the CROSS regimen should be compared between Dutch practice and Asian practice. Data from Asian clinical practice should, however, not be directly compared with the data that were collected in patient with SCC during the CROSS trial under ideal and controlled circumstances. Therefore, the aim of the present study is to compare the outcome of nCRT plus surgery according to the CROSS regimen for esophageal SCC patients treated in Asia with patients treated in the Netherlands outside the CROSS trial.

**Research question:**

We hypothesize that patients with SCC treated with nCRT according to the CROSS regimen in Asia have a comparable pathological response rate and have comparable overall survival in both the primary tumor and locoregional lymph nodes.

**Endpoints:**

Primary endpoint is pCR rate (pT0N0). Secondary endpoints are radical resection rate, overall survival and net survival.

**Study design:** Retrospective cohort study.

**Patients:**

All patients with esophageal squamous cell carcinoma who were treated in the Netherlands outside the CROSS trial (DUCA data), Queen Mary Hospital Hong Kong, Shanghai Chest Hospital, Chang Gung Memorial Hospital Taiwan and Tianjin Medical University Cancer Hospital. Patient have to be treated with neoadjuvant chemoradiotherapy according to the CROSS regimen (intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m<sup>2</sup> of body-surface area] for 23 days, with concurrent radiotherapy 41.4 Gy, given in 23 fractions of 1.8 Gy on 5 days per week) between 2011 and 2016 and should have a minimal follow up of 18 months.

**Statistical analysis:**

Patients who underwent nCRT according to the CROSS regimen will be stratified into two groups based on country of treatment, *i.e.* the Netherlands or Asia. Demographic and clinical characteristics will be compared. Continuous variables will be presented as medians with interquartile ranges and will be compared by using Student's t test or Mann-Whitney U test. Categorical variables will be presented as frequencies and percentages and will be compared by using  $\chi^2$  test or Fisher's exact test.

Multivariate logistic regression will be used to compare the probability of pCR rate between patients treated in the Netherlands and in Asia, adjusting for age, sex, Charlson comorbidity index clinical T-stage, clinical N-stage, surgical technique, number of resected lymph nodes.

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Net survival will be calculated for both groups by using life tables for the general population defined by year, country, sex and age. Overall survival data and net survival data will be presented by using Kaplan-Meier curves and will be compared by using the log-rank test with hazard ratios (HR) and 95% confidence intervals (CI).

Cox proportional hazards model will be used to investigate survival disparity between patients treated in the Netherlands and in Asia, adjusting for age, sex, clinical T-stage, clinical N-stage, surgical technique and comorbidities according to the Charlson Comorbidity index. Two-sided  $p < 0.05$  will be considered statistically significant.

Since DUCA survival data is 5% inaccurate, sensitivity analysis will be performed on with IKNL data to investigate outcome uncertainty.

### **Beoogde publicatie**

Outcome of neoadjuvant chemoradiotherapy plus surgery for patients with esophageal squamous cell carcinoma treated in Asia versus patients treated in the Netherlands.

### **References:**

1. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut*. 2015 Mar;64(3):381-387.
2. van Hagen P, Hulshof MC, van Lanschoot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012 May 31;366(22):2074-2084.
3. Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. *BMC Cancer*. 2018 Feb 6;18(1):142.