Identification of the most important complications after esophageal surgery.

It is well recognized that complications after esophageal surgery are associated with increased length of hospital stay, morbidity and mortality. To be maximally effective, complication related quality initiatives for esophageal surgery should target those complications that impose the greatest overall clinical and economic burden. Indeed numerous studies have already been published describing the incidence of specific complications after esophageal surgery and the associations between these complications and subsequent patient outcomes. However, to our knowledge there has been no published attempt to combine this knowledge of complication frequency and severity into a global measure of overall impact after esophageal surgery.

The population-attributable fraction (PAF) is a population-based global measure to quantify the overall impact of specific postoperative complications on a given adverse outcome. This parameter has traditionally been used in the epidemiologic literature to determine the amount of a given disease (e.g. cancer) state that is due to a specific risk factor (e.g. smoking). This parameter is also an attractive measure to assess overall complication impact because it incorporates information about the frequency of a complication and also the relative risk of an adverse outcome given the presence of that complication. In the context of the currently proposed study the PAF will represent the overall reduction in incidence of a given adverse outcome, such prolonged hospital stay, that would be expected in a theoretical scenario where exposure to a complication within our population was able to be completely prevented. A recent published study used this methodology to analyze the effect of complications after colonic resections, and reported new insight in this field of surgery. To this regard the JAMA surgery encourages researchers to extend this methodology to other surgical populations, as this will facilitate the development of more targeted and effective surgical quality improvement programs (Scarborough, JAMA surg 2017).

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Therefore, the goal of this study will be to use the PAF to identify the highest value complications relative to clinical outcomes after esophageal cancer surgery. These results can aid in the development and prioritization of future quality improvement interventions in esophageal surgery.

Onderzoeksopzet:
Study population: All patients undergoing an elective esophageal resection for esophageal cancer between January 2011 and December 2016, and registered in the DUCA registration. Patients undergoing salvage esophagectomy for recurrent esophageal disease or non-elective surgery will be excluded.

Outcome measures: 30-day mortality, reoperations and prolonged hospitalization. (postoperative length of hospital stay will be defined as hospital stay that exceeds the 75th percentile value for the surgical approach that was used during the initial esophageal resection. In order to account for differences between surgical procedures (e.g., minimally invasive vs. open, transthoracic vs. transhiatal, etc). For the purpose of this study PAF will be used and presented as final outcome to quantify the overall contribution of each complication to each of our 3 outcomes (30-day mortality, reoperations and prolonged hospitalization).

Predictors: The primary predictors for our analysis will include the presence or absence of the following complications: anastomotic leakage, chyle leakage, post-op bleeding, pulmonary complication, cardiac complication, thromboembolic complication, wound infection or urinary tract infection. Additional variables for adjustment analyses will include all perioperative patient and treatment-related characteristics that are recorded in the DUCA and are considered to be associated with our outcome measures after esophageal surgery, as described in previous literature by [Lagarde SM, et al. Ann Thorac Surg. 2008], [Raymond DP, et al. Ann thorac Surg 2016], [Fuchs HF, et al. Dis Esophagus 2016], [Munasinghe A, et al. Ann Surg 2015], [Raj J, et al. Ann Surg Oncol 2008]. In the multivariable analysis the 'maximum of 1 variable per ~10 events' rule will be respected.

Statistiek:
Counts or continuous variables of patient and treatment-related characteristics, complications and the 3 outcome measures will be described as frequencies or mean/median values as appropriate.

First the incidence of each of the 3 outcomes measures will be compared between the patients who suffered from each of the different complications under investigation. Second, a multivariable (poisson) regression model (with log link and robust error variances) will be used to estimate the relative risk for each of the 3 outcomes for each of the complications under investigation. The relative risk is the risk of an outcome (e.g. mortality) in an exposed group (anastomotic leakage) divided by the risk of the event, non-exposed group (no anastomotic leakage). The previously described additional variables (patient and treatment related characteristics) will be included as predictor variables in these regression models to adjust for these characteristics.

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Third, in order to assess the impact of each of the complications under investigation on the 3 outcomes of our study, the population attributable fraction for each complication-outcome pair will be calculated. PAF is calculated as $PAF = (Pc \times (RR - 1))/(Pc \times (RR - 1) + 1)$. In which Pc represents the prevalence of the complication in the study population, and RR represents the relative risk which we can obtain from the previously described regression models. The ‘AF’ package in R will be used to calculate PAF holding all patient- and procedure-related characteristics constant.

In this context, the PAF represents the percentage reduction in the occurrence of an outcome measure (e.g. 30-day mortality) that would be anticipated if exposure of the complication (e.g. anastomotic leakage) were completely prevented. 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; ‘AF’ package). A p-value of <0.05 will be considered statistically significant.

**Beoogde publicatie**

Association of specific postoperative complication with clinical outcomes after elective esophagectomy for cancer. A more targeted approach towards surgical quality improvement.