



TENTACLE STUDY

Treatment of Anastomotic Leakage after esophagectomy

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Short title	TENTACLE study
Study registration number	NCT03829098
Version and period	Version 2.2 – October 2019
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1. SUMMARY

Rationale: Anastomotic leakage occurs in 0% - 30% after esophagectomy for cancer. It is a severe complication with mortality rates approximately ranging from 2% - 12%. In addition, it is associated with a prolonged ICU treatment and hospital stay. Anastomotic leakage severity is currently graded according to how it is treated (grade I: conservative treatment, grade II endoscopic or radiologic intervention and grade III surgical intervention). However, this scoring system cannot be used to guide decision making when anastomotic leakage is diagnosed in a clinical setting.

Factors that may influence the severity of the anastomotic leakage are (amongst others) location of the anastomosis, estimated surface of the defect, estimated circumference of the defect, extent of contamination, degree of sepsis and time from diagnosis until therapy. However, little is known about to what extent these and other factors contribute to anastomotic leakage severity. In addition, there is a paucity of data on what leakage characteristics dictate the success of a specific treatment.

Primary study objectives

1. To investigate which factors contribute to anastomotic leakage severity and to compose an evidence based anastomotic leakage severity score.
2. To investigate which anastomotic leakage characteristics are associated with success of different anastomotic leakage treatments and to compare the effectiveness of different initial anastomotic leakage treatments for anastomotic leakage classified according to severity and leakage characteristics.

Study design: International multicenter retrospective cohort study.

Study population: Adult patients with anastomotic leakage after esophagectomy and gastric conduit reconstruction for esophageal cancer.

Cohort size: At least 1000 patients with anastomotic leakage after esophagectomy for cancer.

Primary outcome parameter: 90 day mortality.

Secondary outcome parameters: in-hospital mortality, 30-day mortality, 180-day mortality, comprehensive complications index, total number of reinterventions, hospital and ICU length of stay, hospital related costs.

Funding: Radboudumc

2. INTRODUCTION AND RATIONALE

The incidence of esophageal cancer is increasing, with an estimated annual incidence of 480.000 cases worldwide [Jemal 2011]. Esophagectomy remains the cornerstone of curative treatment, often in combination with chemotherapy or chemoradiotherapy. However, esophagectomy is associated with considerable morbidity and anastomotic leakage is a severe postoperative complication. Anastomotic leakage is defined as a “full thickness gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification” according to the Esophagectomy Complications Consensus Group (ECCG) definition [Low 2015]. Anastomotic leakage has been described to occur in 0-30%. If anastomotic leakage occurs, it is associated with mortality rates ranging from 2% - 12% [Biere 2011, Saluja 2012]. In addition, it is often associated with a prolonged ICU treatment, hospital length of stay and multiple reinterventions [Lubbers 2019, submitted]. The impact of anastomotic leakage on quality of life is high and it is associated with a substantial burden in terms of hospital resources and costs [Biere 2011, Alanezi 2004, Luketich 2012, Blackmon 2007].

Treatment of anastomotic leakage ranges from conservative management (nil per mouth, antibiotics and nasogastric tube drainage) to radiologic drainage, endoscopic treatment with stents, drains or endoVAC (Vacuum Assisted Closure) systems, and surgical exploration. A recent systematic review performed by our group assessed the current literature for studies that specifically reported on specific therapies and outcome of anastomotic leakage [Verstegen 2018, submitted]. Nineteen studies with 273 patients were included and studies were of low to moderate quality. No meta-analysis was performed because of substantial clinical heterogeneity of the included studies. The main conclusion of the review was that due to small cohorts and clinical heterogeneity no evidence based treatment strategy could be composed from the current literature. A retrospective multicenter study of 79 patients revealed that the used treatment modality of an anastomotic leakage is not only patient dependent, but also hospital dependent [Lubbers 2019, submitted]. Until now the management of an anastomotic leakage is more or less based on expert opinion rather than on an evidence-based anastomotic leakage treatment algorithm. From these studies, it became evident that the absence of an anastomotic leakage severity score complicates performing robust research on this topic.

Anastomotic leakage severity is currently graded according to how it is treated (grade I: conservative treatment, grade II endoscopic or radiologic intervention and grade III surgical intervention) [Low 2015]. Although this scoring system is useful for reporting the consequences of anastomotic leakage, by definition it cannot be used to guide decision making when anastomotic leakage is diagnosed in a

clinical setting. Examples of factors that may influence the severity of the anastomotic leakage are location of the anastomosis (intrathoracic or cervical), circumference of the defect, surface of the defect, extent of contamination (i.e. local, mediastinal, intrathoracic), degree of sepsis and time from diagnosis until therapy. However, little is known about to what extent these and other factors contribute to anastomotic leakage severity. In addition, there is a paucity of data on which leakage characteristics dictate the success of a specific treatment.

3. STUDY OBJECTIVES

3.1 Main study objectives

1. To investigate which factors contribute to anastomotic leakage severity and to compose an evidence based anastomotic leakage severity score.
2. To investigate which anastomotic leakage characteristics are associated with success of different anastomotic leakage treatments and to compare the effectiveness of different initial anastomotic leakage treatments for leakages classified according to severity and leakage characteristics.

3.2 Other study objectives

This is an explorative study and relevant interactions between factors will be investigated. The following other study objectives are predefined. Outcome will be evaluated in terms of mortality, comprehensive complications index (CCI), number of reinterventions, length of stay and costs.

1. To investigate which factors are associated with postoperative mortality in patients with anastomotic leakage after esophagectomy and to compose a model that predicts mortality.
2. To study practice variation in the treatment of anastomotic leakage and to evaluate heterogeneity in outcome.
3. To investigate whether the length of the period between operation and diagnosis of anastomotic leakage is associated with outcome.
4. To investigate whether time from diagnosis to first invasive treatment (in a subgroup of patients that is treated invasively) is associated with outcome.
5. To investigate whether diagnostic tests that are performed within 48 hours of anastomotic leakage diagnosis (e.g. CT scan, endoscopy) are associated with outcome.
6. To investigate whether outcome is different in patients with anastomotic leakage after Ivor Lewis versus McKeown versus Orringer esophagectomy.
7. To investigate whether outcome is different in patients undergoing open versus minimally invasive esophagectomy.
8. To investigate whether outcome is different in patients in whom an omental wrap or pleural flap was used to cover the anastomosis.
9. To compare outcome in patients receiving selective digestive tract decontamination (SDD) versus patients who did not.
10. To compare outcome in patients who have the leakage drained by postoperative drains at the time of diagnosis (e.g. mediastinal drain, cervical drain, chest tube) versus patients who did not have the leakage drained at the time of diagnosis.

11. To investigate whether there is a difference in success rate and outcome for endoVACs that are placed within the esophagus/gastric tube versus endoVACs that are placed through the anastomotic defect.

4. STUDY DESIGN

4.1 Study type

International multicenter retrospective cohort study.

4.2 Duration of the study

Data from a recent cohort of patients that underwent esophagectomy with gastric tube reconstruction from January 1st 2011 until December 31st 2018 will be recorded. The study duration will be from January 2019 until June 2020 (18 months).

4.3 Study timeline

- January 1st – January 15th 2019: Database building and approval of the first version of the protocol.
- January 16th 2019: Invitation of surgeons by sending first version of protocol and CRF.
- January 2019 – March 2019: study document preparation and pilot in Radboudumc, Canisius-Wilhelmina Hospital, Hospital Group Twente (ZGT) in the Netherlands and in the Queen Elizabeth Hospital, Birmingham and in the Nottingham university NHS trust hospital, Nottingham, United Kingdom. Protocol and CRF refinement based on comments of pilot study results.
- March 16st 2019: Final protocol and CRF is sent to participating centers. All participating surgeons receive a Castor database login.
- April 2019 – December 2019: Data collection.
- January 2019 – June 2020: Analysis and manuscript writing.

4.4 Follow-up of patients

Follow-up duration will be 180 days.

4.5 Study setting

This study will be performed in a multicenter and multinational setting. A large group of Dutch hospitals that are currently performing esophagectomies (Dutch Upper-GI Cancer Audit - DUCA group) have consented to participate in this study. The TENTACLE study has also been endorsed by the Oesophago-Gastric Anastomosis Audit (OGAA) study group. In addition, collaboration is sought with the Minimally Invasive Oesophagectomy (MIO) think tank initiative (see *Chapter 5.5 – Feasibility*).

5. STUDY POPULATION

5.1 Population

All adult patients with an anastomotic leakage after esophagectomy and gastric conduit reconstruction for esophageal cancer are suitable for inclusion.

5.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Aged 18 years or older;
- Esophagectomy and gastric conduit reconstruction for resectable esophageal (cT1-4aN0-3M0) cancer;
- Postoperative anastomotic leakage according to the ECCG definition [Low 2015].

5.3 Exclusion criteria

- Esophagectomy for benign disease;
- Emergency resection;
- Patients undergoing extended total gastrectomy.

5.4 Sample size calculation

This is an explorative study and data will be used to investigate to what extent specific characteristics of anastomotic leakages are associated with severity of the leakage and how they relate to the successfulness of different treatments.

In order to create a risk score with 12 candidate predictors, an incidence of 90-day mortality of 10% after anastomotic leakage and a root mean square percentage error (rMSPE) of 5%, 680 patients with anastomotic leakage should be included [van Smeden 2018].

In order to be able to draw robust conclusions from this study, to develop an evidence based anastomotic leakage severity score and to gain a solid basis for future anastomotic leakage related research, we aim to include at least 1000 patients with anastomotic leakage after esophagectomy for cancer.

5.5 Feasibility

In order to include the proposed number of patients and to collect data from international patient cohort, we will acquire data from 3 esophageal surgeon networks. Although there is some overlap

between these groups, we believe that inviting the networks to participate will optimize the chance of obtaining robust results from this study.

1) *The Dutch Upper-GI Cancer Audit (DUCA) group*

A large group of Dutch hospitals performing esophagectomies have agreed to participate in this study. During the study period of 8 years, approximately 750 resections were performed per year and the incidence of anastomotic leakage was around 18%. Therefore, data from 1080 patients with anastomotic leakage ($750 \times 8 \times 0.18$) can be included from the Netherlands.

2) *The Oesophago-Gastric Anastomosis Audit (OGAA) group*

The OGAA was established in 2017 and aimed to identify patient and differences in operative technique that influence outcome. This worldwide network of esophageal surgeons performed a 6 month snapshot study and will include an estimated 1750 cases by December 31st 2018. We will invite the centers in the OGAA to participate in this study and to contribute the cases that have already been registered in the OGAA and to contribute additional data from their 2011-2018 cohorts. We estimate that there will be approximately 263 patients with anastomotic leakage in the OGAA (1750×0.15). Possibly, more cases will be contributed from the participating centers if they contribute additional data from their 2011-2018 cohorts.

3) *The Minimally Invasive Oesophagectomy (MIO) think tank initiative*

The European MIO think tank group includes members from around 15 European high volume centers. We estimate that in the past 8 years, each center performed 40 esophagectomies per year and with a leakage incidence of around 10% this group could contribute around 480 cases ($15 \times 40 \times 8 \times 0.10$).

6. METHODS

6.1 Primary outcome parameter

- 90-day mortality

6.2 Secondary outcome parameters

- In-hospital mortality, 30-day mortality and 180-day mortality.
- Comprehensive complications index (CCI) [Slankamenac 2013].
- Total number of reinterventions (endoscopic, radiologic, surgical).
- Hospital length of stay, ICU length of stay and readmission rates.
- Cost estimation.

6.3 List of study parameters

This is a retrospective study and we expect that not all relevant data can be obtained from the patient files. For example, estimation of leak circumference or leak surface will not be possible without an endoscopy and we expect that not all patients underwent an endoscopy. However, it is expected that the large number of patients will provide enough data to analyze whether factors with a lot of missing data are of influence. Therefore, these factors that are likely to have a lot of missing data are taken up in this list, even though missing data may introduce bias.

- Hospital Characteristics: annual volume, anastomotic leakage percentage, diagnosis & treatment strategy by surgeon-on-call or upper-GI surgeon, types of treatment modalities performed in each hospital.
- Patient and tumor characteristics: year of surgery, sex; age; length, weight, ASA classification; Charlsson comorbidity index; WHO performance score; Karnofsky score; creatinine, bilirubin, platelets (baseline, until three months prior to operation); tumor type; tumor location; preoperative T-stage; preoperative N-stage; preoperative M-stage; neoadjuvant therapy (radiotherapy, chemotherapy, chemoradiotherapy).
- Operation characteristics: resection type (i.e. McKeown, Ivor Lewis, transhiatal); operation type (total MIE, robotic MIE, hybrid MIE, open); anastomotic technique; anastomotic configuration; site of anastomosis; omental wrap; pleural flap; perioperative selective digestive decontamination (SDD) received.

- Anastomotic leakage diagnosis: time from surgery to diagnosis of the leakage (days); assessment that diagnosed anastomotic leakage; anastomosis assessments performed <48 hours of diagnosis of anastomotic leakage; approximate time from diagnosis to invasive (e.g. radiologic drainage, endoscopic, surgical) treatment of the leakage (hours).
- Patient parameters at the time of diagnosis (parameters closest to diagnoses should be used and parameters within 24 hours prior diagnosis can be used): diagnosed at which ward (surgical ward, ICU, medium care/high care, PACU); ventilated if at ICU; q-SOFA score (follows from: altered mental status/GCS<15, respiratory rate, systolic blood pressure); organ failure at time of diagnosis (pulmonary: need for ventilation, cardiovascular: inotropic support, renal: creatinine >170 µg/L, liver: bilirubin >33µmol/L, coagulation: platelets <100*10³/µL); O₂ consumption (if not ventilated) or FiO₂ (if ventilated); NG tube in place; diet; leukocyte count; CRP; creatinine; bilirubin; ABG lactate; ABG pH, paO₂; amylase from surgical drain (highest value in case of multiple drains or measurements).
- Leakage characteristics: location of the leak (e.g. esophagogastric anastomosis, gastric tube, blind loop); estimated circumference of the leakage (0-25%, 25-50%, 50-75% and 75-100%); estimated surface of the leak (in cm²); gastric tube overall condition (e.g. vital, ischemic, necrotic); extent of the contamination (e.g. none, mediastinal fluid collections, pleural fluid or abdominal collections); (postoperative) drains in place at time of diagnosis (e.g. mediastinal drain, cervical drain, chest tubes); clinical drainage of the anastomotic leak by drains (including NG tube) at the time of diagnosis.
- Primary treatment (treatment within 48 hours that was intended to take place when the leak was diagnosed): (re-)admission to ICU or medium care/high care; nil by mouth regime; antibiotic treatment according to local protocols; NG tube placement (with/without suction); NG tube repositioning (with/without suction); tube placement through anastomotic defect; endoVAC/endoSponge placement; stent placement (stent type if applicable); endoscopic clipping; nasoduodenal/nasojejunal feeding tube placement; radiologic drainage (thoracic cavity, mediastinum); bedside surgical chest tube placement; reoperation; reoperation approach; reoperation procedure (drainage only, suturing of the leak; resection of the leak and re-anastomosis; repair of anastomosis with muscle flap; disconnection and cervical esophagostomy; surgical jejunal feeding tube).
- Secondary treatment (treatment at any time that was not intended to take place when the leak was diagnosed): time from surgery to secondary treatment (days); (re-) admission to ICU or medium care/high care; nil by mouth regime; antibiotic treatment according to local

protocols; NG tube placement; NG tube repositioning; tube placement through anastomotic defect; endoVAC/endoSponge placement; stent placement (stent type if applicable); endoscopic clipping; nasoduodenal/nasojejunal feeding tube placement; radiologic drainage (thoracic cavity, mediastinum); bedside surgical chest tube placement; reoperation; reoperation approach; reoperation procedure (drainage only, suturing of the leak; resection of the leak and re-anastomosis; repair of anastomosis with muscle flap; disconnection and cervical esophagostomy; surgical jejunal feeding tube).

- Leak healing: Anastomotic leak healed (assessed by endoscopy, radiologic imaging or clinically. Clinical healing is defined to occur if a patient's is set to solid foods). Time from diagnosis to healing of the anastomotic leak.

Complications with Clavien Dindo grade (ECCG list and definitions unless stated otherwise): for pneumonia the universal pneumonia score (UPS [Weijs 2016]) definition is used; the comprehensive complications index (CCI [Slankamenac 2013]) is calculated from all scored complications.

Reinterventions: total number of endoscopic interventions; total number of stent placements; total number of endoVAC/endoSponge treatments; total number of radiologic interventions; total number of bedside surgical reinterventions (e.g. opening of wounds, chest tube placements); total number of minimally invasive surgical reinterventions; total number of open surgical reinterventions.

Length of stay and mortality: hospital length of stay (total days); ICU length of stay (total days); ICU readmission; in-hospital mortality; 30-day mortality; 90-day mortality; 180-day mortality.

Costs: in-hospital cost estimation based on hospital length of stay, ICU length of stay and reinterventions. Standardized cost lists are used.

7. ANALYSIS

7.1 Analysis strategy – general considerations

The ultimate goal of main study objective 1 is to obtain an evidence based anastomotic leakage severity score that reflects the influence of leakage associated parameters on clinical outcome (e.g. 90-day mortality). This will allow researchers to describe leakage severity in groups of patients and it can be used to correct for differences between groups regarding anastomotic leakage severity. This will therefore aid in performing future comparative effectiveness studies.

Only factors that concern leakage characteristics (listed in *chapter 6.3 – List of study parameters / Leakage characteristics*) and factors that concern the consequences of the leak for a patient (listed in *chapter 6.3 – List of study parameters / Patient parameters at the time of diagnosis*) are used to compose this score.

Other important parameters that are likely to be predictive for 90-day mortality (e.g. age, comorbidity index, preoperative performance status, etc.) are not included in the severity score since these can be reported (and corrected for) separately. Operation characteristics (e.g. resection type, anastomotic site, etc.) may also be predictive for clinical outcome (e.g. 90-day mortality) if anastomotic leakage occurs. Operation characteristics are not included in the severity score since it is likely that these factors are also important for anastomotic leakage strategy, regardless of leakage severity (e.g. cervical anastomotic leakage may require different treatment than intrathoracic anastomotic leakage) and we aim to investigate this in our other study objectives (see *chapter 3.2 – Other study objectives*). In addition, it is one of our other study objectives to compose a model that predicts 90-day mortality in case of anastomotic leakage (see *chapter 3.2 – Other study objectives*) and for this model all predictive factors that are registered in this study will be taken into account.

7.2 Main study objective 1

The first main study objective is to investigate what factors contribute to anastomotic leakage severity and to compose an evidence based anastomotic leakage severity score.

First, univariate analysis is performed on relevant parameters that are described in *chapter 6.3 – List of study parameters / Leakage characteristics* and in *chapter 6.3 – List of study parameters / Patient parameters at the time of diagnosis*. Relevant parameters are entered into separate binary logistic regression models with 90-day mortality as outcome parameter in order to explore associations in the data. Second, factors that are considered to be clinically relevant based on literature and/or expert opinion are selected for multivariate analysis. Backwards stepwise selection is used to exclude values of $p > 0.05$ from the model. Results are presented as odds ratio (OR) with 95% confidence

intervals (CI). A 2-tailed $p < 0.05$ is considered statistically significant. Third, this multivariate model will be internally validated by bootstrapping, using 5000 bootstrap resamples. Finally, a nomogram is constructed based on the final bootstrapped multivariable regression analysis and this nomogram can be used to calculate the anastomotic leakage severity score.

In order to investigate the relative influence of casemix parameters (e.g. age, comorbidity, etcetera) on the leakage severity score, similar analysis will be performed in which casemix parameters (listed in *chapter 6.3 – List of study parameters / Patient and tumor characteristics* and in *chapter 6.3 – List of study parameters / operation characteristics*) are also included. If casemix is found to be very strongly associated with outcome relative to the severity score (to the extent that the severity score is of limited additional value in the regression model), latent class analysis is used [Rabe-Hesketh 2008]. The parameters used for the anastomotic leakage severity score (*chapter 6.3 – List of study parameters / Leakage characteristics* and in *chapter 6.3 – List of study parameters / Patient parameters at the time of diagnosis*) are used to create casemix corrected classes of anastomotic leakage severity.

The results obtained by the described analyses will also be performed in subgroups of patients undergoing McKeown, Ivor Lewis and Orringer esophagectomy. By performing this sensitivity analysis, we will investigate whether the obtained model is useful for all types of esophagectomy or whether different factors are predictive of 90-day mortality for the different types of esophagectomy. If substantial differences are found between the primary analysis and this sensitivity analysis, the possibility of composing different anastomotic leakage severity scoring systems will be considered.

In addition, we will investigate and report whether the anastomotic leakage severity score is also predictive of the other outcome parameters. Together with data from the secondary study objective (see *chapter 3.2 – Other study objectives*) in which associations between 90-day mortality and other outcome parameters are investigated, this will result in defining if other parameters can be used as a proxy for 90-day mortality.

7.3 Main study objective 2

The second main study objective is to investigate what anastomotic leakage characteristics are associated with success of different initial treatments and to compare the effectiveness of different initial anastomotic leakage treatments for leakages classified according to severity and leakage characteristics.

In the first analysis relevant primary treatment parameters (listed in *chapter 6.3 – List of study*

parameters / Primary treatment) are the exposures. The association between anastomotic leakage characteristics and operation characteristics (see *chapter 6.3 – List of study parameters / Leakage characteristics* and *chapter 6.3 – List of study parameters / Operation characteristics*) and outcome parameters (see *chapter 6.1 – Primary outcome parameter* and *chapter 6.2 – Secondary outcome parameters*) will be evaluated for the exposures in regression analysis. Correction for patient characteristics, tumor characteristics and anastomotic leakage severity score is performed, if appropriate.

Based on the results of this first analysis, subgroups of patients are created based on individual operation or leakage characteristics or based on combinations of characteristics. The effectiveness of the primary treatment strategies is assessed in a regression models for the different outcome parameters and correction for patient characteristics, tumor characteristics and anastomotic leakage severity score is performed, if appropriate. Comparison of the primary outcome parameter and secondary outcome parameters will be expressed in terms of a relative risk and corresponding 95% confidence intervals. A two-tailed $P < 0.05$ is considered statistically significant.

7.4 Other study objectives

Analysis of other study objectives will follow the same principles as described in *chapter 7.2 – Main study objective 1* and *chapter 7.3 main study objective 2*. Detailed and predefined analysis plans will be written during the preparation phase of the TENTACLE study (see *Chapter 4.3 – Study timeline*).

8. ETHICS STATEMENT AND REGULATORY APPROVAL

This study will be conducted in compliance with the principles of the declaration of Helsinki. The study protocol and relevant documents have been approved by the medical ethical committee of the Radboud University Medical Center, Nijmegen, the Netherlands. All participating centers are provided with the study protocol and relevant documents in January 2019, so that participating centers can ask their local ethical committees for approval if needed according to local ethical protocols.

9. DATA HANDLING

9.1 Database system

The Castor database system (www.castoredc.com) will be used. This online medical research database system is certified to meet international security standards and is compliant with all relevant regulations, amongst which are ICH-GCP, GDPR, HIPAA, FDA 21 CFR part 11, ISO 27001 and ISO 9001. More information and individual security certificates can be found on <https://www.castoredc.com/security-statement>.

9.2 Case report form (CRF)

A detailed CRF is created from the Castor (www.castoredc.com) database and provided to the invited centers (see also appendix 1). The CRF includes info points with definitions and guidelines that aid in adequate scoring of the listed parameters.

9.3 Data collection and data entering

All patient data will be entered anonymously by or under supervision of the treating physician(s). Up to 4 users per participating center will receive a Castor login username and password and these users can enter data into the database. In addition to entering data per patient individually, local study teams can upload their already existing database into the Castor database system and add only the additional data that is required for this study. The TENTACLE study team will provide a short step-by-step manual and can provide additional help with this, if needed.

9.4 Data privacy statement

All anonymous study data will be available to the TENTACLE study team. The data of a center will be available to that specific center only through the Castor database system website. The data will not contain identifiable patient parameters (e.g. no date of birth, no date of surgery, etc.). In compliance with the General Data Protection Regulation (GDPR - EU 2016/679). Each patient will be coded with a unique patient number so that patients in the study are untraceable from the study database. Surgeons that participate in the TENTACLE study are asked to keep a password coded file that can identify individual patients locked away in their practice. This file can be accessed by the local investigators if needed, for example in case a relevant new research question requires entering of additional data into the database.

10. PUBLICATIONS

10.1 Main publications

We aim to publish two main manuscripts that cover the investigation of our main study objectives:

1. Investigation of what factors are associated with anastomotic leakage severity and composition of the anastomotic leakage severity score.
2. Investigate of what anastomotic leakage characteristics are associated with success of different anastomotic leakage treatments and comparison of the effectiveness of different initial anastomotic leakage treatments for leakages classified according to severity and leakage characteristics.

10.2 Other publications

Other possible publications will cover the secondary study objectives . These manuscripts will be defined at a later stage in the study.

10.3 Publication policy

The TENTACLE study embraces corporate authorship and all collaborators that contribute to this study will form the TENTACLE collaborative group. This group will co-author all publications in which TENTACLE study data is used.

The protocol writing committee is fully involved in conducting this study and will be included as authors in both main publication(s) in which the TENTACLE study data is used. If the manuscript is submitted to a journal that does not allow the full number of authors, some authors will join the collaborative group instead, based on scientific input during the study, manuscript writing and revising.

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12. APPENDIX 1 – PRINTED CASE REPORT FORM (CRF)

Castor database printed CRF. This printed CRF will not be used in the study, all data is entered online into the Castor database system.