TreatmENT of AnastomotiC LeakagE after COLON cancer resection

The TENTACLE – Colon study

Protocol writing committee

Jobbe Lemmens MD[1], Nynke G. Greijdanus MD PhD[1], Kiedo Wienholts MD[2,3,4], Sander Ubels MD[1,5], Marleen M.H.J. van Gelder PhD[6], Albert Wolthuis MD PhD[7], Jérémie H. Lefevre MD PhD[8], Kilian Brown MD[9], Matteo Frasson MD PhD[10], Nicolas Rotholtz MD PhD[11], Quentin Denost MD PhD[12], Rodrigo O. Perez MD PhD[13,14], Tsuyoshi Konishi MD PhD[15], Yves Panis MD PhD[16], Martin Rutegård MD PhD[17,18], Susan L. Gearhart MD PhD[19], Thomas Pinkney[20], Roel Hompes MD PhD[2,3,4], Pieter J. Tanis MD PhD[2,3,4,21], Johannes H.W. de Wilt MD PhD[1]

[1]Department of Surgery, Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands [2]Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam, The Netherlands [3]Cancer Centre Amsterdam, Treatment and Quality of Life, Amsterdam, The Netherlands [4]Cancer Centre Amsterdam, Imaging and Biomarkers, Amsterdam, The Netherlands [5]Department of Surgery, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands [6]IQ Health Science Department, Radboud university medical center, Nijmegen, the Netherlands [7]Department of Surgery, UZ Leuven, Leuven, Belgium [8]Department of Digestive Surgery, Sorbonne Université, AP-HP, Hôpital Saint Antoine, Paris, France [9]Department of Colorectal Surgery, , Royal Prince Alfred Hospital, Sydney, Australia [10]Department of Surgery, Valencia University Hospital La Fe, Valencia, Spain [11]Department of Surgery, Hospital Alemán, Buenos Aires, Argentina [12]Bordeaux Colorectal Institute, Clinique Tivoli, Bordeaux, France [13]Colorectal Surgery, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil [14]Department of Surgery, Hospital Beneficência portuguesa de São Paulo, São Paulo, Brazil [15]Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Anderson, United States of America [16]Colorectal Surgery Center, Groupe Hospitalier Privé Ambroise Paré-Hartmann, Neuilly Seine, France [17]Surgical and Perioperative Sciences, Surgery, Umeå University, Umeå, Sweden [18]Wallenberg Center for Molecular Medicine, Umeå University, Umeå, Sweden [19]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America [20]Academic Department of Surgery, University of Birmingham, United Kingdom [21]Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

Study title	TreatmENT of AnastomotiC LeakagE after COLON cancer resection
Short title	TENTACLE – Colon study
Study registration number	NCT06528054
Version and period	Version 2.3 August 2024
Coordinating investigators	Jobbe Lemmens Department of Surgery Radboudumc; P.O.B. 9101/618 NL 6500 HB Nijmegen, The Netherlands T: 00316 52331762 E: Jobbe.Lemmens@radboudumc.nl
Principal investigators	Pieter Tanis Department of Surgery R-G 219 Dr. Molewaterplein 40 3015 GD Rotterdam T: 00316 2906 8275 E: p.tanis@erasmumsmc.nl Hans de Wilt Department of Surgery Radboudumc; P.O.B. 9101/618 6500 HB Nijmegen, The Netherlands T: 00316 5494 6601 E: hans.dewilt@radboudumc.nl
Sponsor	Radboudumc.
Funding	No funding.

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2 SUMMARY

Rationale: Anastomotic leakage (AL) is a common and severe complication after colon cancer resection. Recent literature reports leak rates up to 8.4% and substantial associations with the need for re-interventions, prolonged hospital stay, a higher likelihood of permanent stomas, and mortality. Despite these alarming numbers, comparative studies on treatment strategies are lacking.

In clinical practice, treatment decisions are frequently influenced by factors such as the clinical presentation, resource availability, and surgeon preferences. Several leakage characteristics (e.g. size of the defect, etc.) also play an important role, but there is limited understanding of all these factors and the relative influence of these factors on treatment decisions and subsequent mortality. Additionally, no previous studies have comprehensively examined the effectiveness of various treatment strategies for AL after colon cancer resection considering all these factors collectively.

Main study objectives:

1. To identify predictive factors associated with 90-day mortality and 90-day Clavien-Dindo grade 4-5 complications amongst patients who developed AL following colon cancer resection and to develop and validate a prediction model for predicting 90-day mortality as well as the co-primary composite endpoint Clavien-Dindo grade 4-5 complications.

2. To explore and compare the effectiveness of various treatment strategies for AL following colon cancer resection, considering patient, tumour, resection and leakage characteristics.

Study design: International multicentre retrospective cohort study.

Study population: Adult patients who developed AL after surgical resection with formation of primary anastomosis for colon cancer (cT1-4bN0-2M0-1).

Primary outcome: 90-day mortality.

Composite primary outcome: 90-day Clavien-Dindo grade 4-5 complications.

Secondary outcomes: time from resection till diagnosis of AL and from diagnosis to initiation of leak treatment, number of reinterventions/readmissions, total length of hospital/intensive care unit stay, mortality (in-hospital, 30-day, and one-year), (type of) stoma present and disease status at last possible date of follow-up.

Sample size calculation: at least 2000 patients with AL after colon cancer resection.

Funding: None.

3 INTRODUCTION AND RATIONALE

Anastomotic leakage (AL) is a common and severe complication after colon cancer resection. Recent literature reports leak rates between 4.5% and 8.4%, despite colon cancer resection is commonly performed and ongoing improvements in perioperative care and surgical techniques have been made. [1-6] Furthermore, AL is substantially associated with the need for re-interventions, prolonged hospital stay, a higher likelihood of permanent stomas, and mortality. [7-13] Numerous population-based studies have shown alarming postoperative mortality rates among patients with AL, varying from approximately 12.0% to 18.6%. [1, 14, 15] Long-term consequences of AL include omission of chemotherapy and a stage-dependent reduction in survival. [16, 17]. Despite these alarming numbers, comparative studies on treatment strategies are lacking.

In current clinical practice, treatment decision-making is frequently based on the clinical presentation, resources availability, surgeon preference and experience, and leakage characteristics. These characteristics that may influence treatment decision-making are defect of the circumference, location of the leak, presence and extent of ischemia, tension on the anastomosis, presence of localized abscess, purulent peritonitis, faecal contamination, and sepsis [18]. However, little is known regarding these leakage characteristics, and to what extent these factors contribute to treatment decision-making as well as postoperative mortality. A prediction model using all relevant factors for predicting 90-day mortality due to AL may aid clinicians in making optimal treatment decisions.

Current treatment options for AL include conservative management with antibiotic regimens, endoscopic clipping, radiological drainage and surgical interventions (e.g. abdominal washout, dismantling of the anastomosis with the creation of an end-ostomy) or a combination of these modalities [19-22]. Although these treatment modalities have been studied, evidence regarding their effectiveness remains scarce, while identifying the optimal treatment modality for a specific patient with specific characteristics could improve patient outcomes.

Therefore, this study has two main aims: (1) to identify predictive factors associated with 90-day mortality and 90-day Clavien-Dindo grade 4-5 complications amongst patients who developed AL following colon cancer resection and to develop and validate a prediction model for predicting 90-day mortality as well as the co-primary composite endpoint Clavien-Dindo grade 4-5 complications and (2) to explore and compare the effectiveness of various treatment strategies for AL following colon cancer resection, considering patient, tumour, resection and leakage characteristics.

4 STUDY OBJECTIVES

4.1 MAIN STUDY OBJECTIVES

1. To identify predictive factors associated with 90-day mortality and 90-day Clavien-Dindo grade 4-5 complications amongst patients who developed AL following colon cancer resection. Moreover, developing and validating a model for predicting 90-day mortality as well as Clavien-Dindo grade 4-5 complications using the identified predictive factors.

2. To explore and compare the effectiveness of various treatment strategies for AL following colon cancer resection, considering patient, tumour, resection and leakage characteristics.

4.2 OTHER STUDY OBJECTIVES

This is an explorative study and relevant interactions between factors will be investigated. The following other study objectives are predefined. Outcomes will be evaluated in terms of mortality, Clavien-Dindo grading of postoperative complications, comprehensive complications index (CCI), preservation of bowel continuity and length of stay.

1. To investigate predictive factors associated with one-year stoma free survival and to compose and validate a model that predicts one-year stoma-free survival.

2. To investigate whether time to and/or delay in diagnosis of AL influences associated outcomes.

3. To investigate whether time between AL diagnosis and initiation of the first treatment strategy is associated with the outcomes.

4. To investigate the influence of time of onset of AL (e.g. early leaks (i.e. <72 hours after resection) vs. on-time leaks (e.g. >72 hours after resection) on associated outcomes.

5. To study practice variation in the treatment of AL and to evaluate heterogeneity in outcome.

6. To investigate whether outcome is different in patient undergoing more extensive surgical or multimodality treatment for their colon cancer resection (i.e. multivisceral resection, additional intervention for metastasis, cytoreductive surgery, resection of metastasis, hyperthermic intraperitoneal chemotherapy) compared to conventional colectomy.

7. To compare outcomes in patients receiving preoperative oral antibiotics and/or mechanical bowel preparation versus patients who did not.

8. To investigate whether the diagnostic modalities that were used to diagnose the AL are associated with the choice of treatment and associated outcomes.

5 STUDY DESIGN

5.1 STUDY TYPE

The TENTACLE - Colon study is an international multicentre retrospective cohort study.

5.2 DURATION OF THE STUDY

Each participating centre will include consecutive patients who underwent surgical resection for colonic cancer from the 1st of January 2018 to the 31st of December 2022. At the time of inclusion, the minimum required duration of follow-up is one year, and maximum follow-up will be registered. The study is scheduled to commence in September 2024 and will continue data collection until March 2025.

5.3 STUDY TIMELINE

- June 2023 – September 2024: creation of the electronic CRF, execution of pilot study among hospitals from writing committee, local ethical approval, publication of protocol.
- September 2024 – February 2025: invitation of (inter)national centres with local ethical approval, the process of data collection, cleaning and validation.
- March 2025 – December 2025: data analysis and writing of the manuscripts.

5.4 FOLLOW-UP OF PATIENTS

The duration of follow-up will be at least one year, with end date December 31, 2023.

5.5 STUDY SETTING

The TENTACLE - Colon study will be open for participation by all centres worldwide that perform colon cancer resections, without any restrictions regarding geographical location. The application process will involve completing an online questionnaire regarding their daily (surgical) practice to gather institutional characteristics (e.g. type of hospital, annual volume of colon cancer resection). The TENTACLE - Colon study will be disseminated across multiple surgical societies (*see Chapter 6.5 Feasibility*).

6 STUDY POPULATION

6.1 POPULATION

All consecutive adult patients who underwent colon cancer resection between the 1st of January 2018 and 31st of December 2022 will be retrospectively screened and evaluated for an anastomotic leakage. All patients with an anastomotic leakage diagnosed within 90 days from colon cancer resection are suitable for inclusion.

6.2 INCLUSION CRITERIA

To be eligible for inclusion in this study, a patient must satisfy all of the following conditions:

- Aged 18 years or older;
- Surgical resection for primary colon cancer (cT1-4b, N0-2, M0-1) with formation of a primary colonic anastomosis above the peritoneal reflection, with or without a diverting stoma;
- Postoperative AL defined as: “any clinical, radiological or intraoperative signs of disrupted integrity of the anastomosis and/or blind loop. This also includes suspected leaks with any degree of extraluminal air or fluid on CT, perianastomotic abscess, purulent peritonitis without clear anastomotic defect, or any other suspicious condition in which there is no ultimate macroscopic proof of disrupted anastomosis.”

Regarding the type of colon cancer resection, the following patients will also fulfil the inclusion criteria: patients who underwent cytoreductive surgery (CRS) simultaneous with resection of the primary colon cancer with or without hyperthermic intraperitoneal chemotherapy (HIPEC), simultaneous ablations/resections of metastasis, multivisceral resection, emergency resection, patients diagnosed with perforated disease/peritumoral abscess or fistula, and acute obstructions.

6.3 EXCLUSION CRITERIA

A participant who meets any of the following conditions will be excluded:

- Surgical resection for benign colon disease;
- Recurrent colon cancer resection;
- Any primary colon malignancy other than adenocarcinoma (e.g. neuroendocrine tumour, gastrointestinal stromal tumour);
- Any clinical condition that does not fulfil the broad definition of AL as used in this study (e.g. only free air on CT that is considered to be compatible with an appropriate postoperative day in the absence of any other clinical signs related to a potential anastomotic leakage)

6.4 SAMPLE SIZE CALCULATION

This study is exploratory in nature, and its primary objective is to utilize data to examine the extent to what extent specific factors of anastomotic leakages are associated with severity of the leakage and the impact of various treatment strategies on primary and secondary outcome parameters.

To establish a risk score comprising at least 12 candidate predictors, with a 10% incidence of 90-day mortality amongst AL patients following colon cancer resection and a root mean square percentage error (rMSPE) of 5%, it is necessary to include 680 patients with anastomotic leakage [23]. However, to ensure robustness, enabling the development and validation of an evidence-based prediction model, and the creation of a solid foundation for future research related to AL, the aim is to include at least 2000 patients with AL following colon cancer resection.

6.5 FEASIBILITY

The TENTACLE study group has already successfully performed a similar project for anastomotic leakage after oesophageal cancer and rectal cancer resection. [18, 24-26] For this project, the existing networks will be used meaning the following (inter)national networks will be invited to participate:

1. Dutch Society of ColoRectal Surgery (DSCRS)

Based on previous experience, a large number of Dutch hospitals performing colorectal cancer surgery will be motivated to participate in collaborative research studies. Moreover, a large number already participated in the TENTACLE - Rectum study and it is expected that these centres will be willing to participate in the TENTACLE - Colon study as well. According to the Dutch National Cancer Registry, the annual incidence of colon cancer is approximately 8,800 patients, of whom a quarter will be diagnosed with stage IV. The latter patients are most likely to undergo systemic therapy or no anti-cancer treatment [27, 28]. Hence, it is expected that roughly 6,600 patients can be screened for eligibility for each year of the inclusion period. According to previous Dutch nationwide studies, the incidence of AL following colon cancer resection is 4.5%. Therefore, the aim is to include 1,485 patients with AL during the 5 year inclusion period (6,600*5*0.045) from the Netherlands.

2. The European Society of Coloproctology (ESCP)

The ESCP conducted extensive international snapshot studies involving over 3,000 European collaborators in the past. The study protocol for the TENTACLE - Colon study and the contact information will be accessible on their website.

3. Latin American Association of Coloproctology (LAAC)

4. American Society of Colon and Rectal Surgeons (ASCRS)

5. Colorectal Surgical Society of Australia and New Zealand (CSSANZ)

6. Japanese Society for Cancer of the Colon and Rectum (JSCCR)

7 METHODS

7.1 PRIMARY OUTCOME

- 90-day mortality

7.2 COMPOSITE PRIMARY OUTCOME

- 90-day Clavien-Dindo grade 4-5 complications [29]

7.3 SECONDARY OUTCOMES

- Time from colon cancer resection to diagnosis of AL and to initial treatment of AL.
- Number of reinterventions and readmissions.
- Hospital length of stay and intensive care unit length of stay.
- Mortality (in-hospital, 30-day, one year).
- Stoma present at last possible date of follow-up; type of stoma present.
- Disease status at last possible date of follow-up.

7.4 LIST OF STUDY PARAMETERS

This is a retrospective study and it is expected that not all relevant data can be obtained from the patient files. For example, estimation of leak circumference will not be possible without surgery or an endoscopy and it is expected that not all patients underwent surgery or an endoscopy. However, it is expected that the targeted number of patients will provide sufficient data to analyse whether factors with many missing values will be of substantial influence. Therefore, these factors that are likely to have a lot of missing data will be collected, even though missing data may introduce bias.

Hospital characteristics

Upon study entry, each participating centre will be required to complete a questionnaire to gather comprehensive information regarding institutional characteristics. This questionnaire covers the following main subjects: hospital type, annual volume of CRC resections, annual volume of colon cancer resections, anastomotic leakage rates, number of hospital beds and availability of hospital resources, protocols and treatment modalities.

Patient and tumour characteristics

The following patient and tumour characteristics will be collected: sex, age, year of surgery, height, weight, body mass index, Charlson comorbidity index (CCI), American Society of Anaesthesiologists (ASA) classification, smoking status, baseline creatinine and hemoglobin level (i.e. within 3 months

before colon cancer resection), and history of immunosuppressant medication. The following tumour characteristics will be collected: tumour histology, tumour location, pathological tumour node metastasis (TNM) stage according to the respective Union for International Cancer Control (UICC) classification, preoperative tumour-related complications (e.g. bleeding, obstruction) and corresponding interventions (e.g. ablation/resection of metastasis, diverting stoma) and neoadjuvant therapeutic regimens.

Surgical and intraoperative characteristics

The following characteristics are about preparation before colon cancer resection: emergency admittance before resection (and if so, at what urgency the resection is performed (e.g. acute, urgent, elective)), selective decontamination of digestive tract received, mechanical bowel preparation received. The following surgical characteristics will be collected: intent of resection (i.e. curative, palliative), abdominal approach, conversion and type of conversion, type of resection (e.g. ileocecal resection, left hemicolectomy), (specification of) multivisceral resection, simultaneous resections/interventions (e.g. metastatectomy, peritonectomies as part of cytoreductive surgery with or without hyperthermal intraperitoneal chemotherapy), number of anastomosis, type of anastomosis (e.g. ileo-colostomy, colo-colostomy), configuration of anastomosis (e.g. end-to-end/side-to-end stapled/hand-sewn), (specification of) problems during anastomosis reconstruction, indocyanine green assessment (and corresponding result), (specification of) intraoperative complications (e.g. bowel perforation), blood loss during resection, amount of blood transfusions and duration of resection.

Diagnostic characteristics

Collected diagnostic characteristics will be: date and time of diagnosis of AL, ward at leak diagnosis, antibiotics around leak diagnosis, nasogastric tube around diagnosis, application of various diagnostic modalities (type, timing and result), clinical parameters (i.e. Glasgow Coma Scale, respiratory rate, systolic blood pressure and modified early warnings sign), biochemical parameters (C-reactive protein, leukocyte count, hemoglobin and creatinine levels) and intensive care unit parameters (i.e. need for inotropic support, mechanical ventilation and/or dialysis) around diagnosis and up to leak treatment.

Anastomotic leakage characteristics at diagnosis

The following leakage characteristics at diagnosis will be collected: radiological characteristics (presence and amount of air/fluid, contrast extravasation, ileus), intraoperative characteristics (presence and extent of purulent peritonitis and faecal contamination, bowel ischemia, abscess), location of the leakage (i.e. anastomosis, blind loop, inconclusive) and estimated circumference of the

leakage, and presence of other complications according to the Clavien-Dindo classification (pulmonary, cardiac, gastrointestinal, urologic, thromboembolic, infection, other infections requiring antibiotics, other complications) with corresponding grading. [29] The comprehensive complications index (CCI) will be calculated from all scored complications. [30]

Treatment of anastomotic leakage

All therapeutic strategies including primary, secondary and tertiary treatment strategies, as well as the modalities employed for managing AL. This comprehensive data collection includes: date and time of start treatment, need for re-admission, applied treatment modalities (i.e. antibiotic regimens, radiologic, endoscopic, (specification of) surgical procedures, and/or abstination/palliative care.

Follow-up of treatment

The following characteristics will be collected to assess outcomes of leakage treatment: leak healing and modality that confirmed leak healing, date of initial discharge, total intensive care unit length of stay, date of death if applicable, presence of disease recurrent (and if so, date and location of recurrence), (type of) stoma present at last moment of follow up, total number of radiologic and surgical interventions one year after colon cancer resection and (start date of) adjuvant chemotherapy.

8 ANALYSIS

8.1 ANALYSIS STRATEGY - GENERAL CONSIDERATIONS

The main goal of this study is to identify predictive factors for 90-day mortality among patients who developed AL following colon cancer resection. Subsequently, a prediction model for predicting 90-day mortality will be developed and internally validated. This model aims to distinguish patients at high risk of mortality from those at low risk and may, therefore, provide valuable guidance in making treatment decisions in clinical practice. The prediction model will be developed with several clinically relevant patient, tumour, resection, diagnostic and leakage characteristics (*see Chapter 7.4 List of study parameters*). In addition, either organ failure or mortality within 90-days following diagnosis of AL (i.e. Clavien-Dindo grade 4-5 complications) will be analysed as a composite primary endpoint in a similar way. These analysis strategies are in line with the previous TENTACLE – Esophagus and TENTACLE – Rectum projects. [18, 24-26]

8.2 MAIN STUDY OBJECTIVE 1

The development and validation of a prediction model for 90-day mortality will be in agreement with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines. [31] First, univariate analysis will be performed on relevant parameters that are described in *Chapter 7.4 – List of study parameters*. Relevant parameters will be 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 will be selected for multivariate analysis. Backwards stepwise selection will be used to exclude values of $P>0.05$ from the model. Results will be presented as odds ratio (OR) with 95% confidence intervals (CI). A 2-tailed $p<0.05$ will be considered statistically significant. Third, this multivariate model will be internally validated by bootstrapping, using 5000 bootstrap resamples. Finally, a nomogram will be created based on the final bootstrapped multivariable regression analysis and this nomogram can be used to calculate the risk of 90-day mortality.

In order to investigate the relative influence of case-mix parameters (i.e. parameters not included in the initial analysis) on 90-day mortality, similar analysis will be performed in which casemix parameters (listed in *Chapter 7.4 – List of study parameters)* will also be included. If casemix is found to be strongly associated with outcome relative to the mortality score (to the extent that the mortality score is of limited value in the regression model), latent class analysis will be used. [32] The

parameters used for the mortality score will be used to create casemix corrected classes of anastomotic leakage severity.

Sensitivity analysis will be performed in subgroups of patients undergoing various type of colectomies. This analysis will investigate whether the obtained model is useful for all types of colon cancer resection. If substantial differences are found between the initial analysis and the sensitivity analysis, the possibility of composing different scoring systems will be considered.

In addition, similar analysis will be performed for the composite primary outcome.

8.3 MAIN STUDY OBJECTIVE 2

The second main objective is to explore and compare the effectiveness of various treatment strategies for AL following colon cancer resection, considering patient, tumour, resection and leakage characteristics.

In the first analysis, relevant treatment parameters will be the exposures. The association between anastomotic leakage and resection characteristics, and outcome parameters will be evaluated for the exposures in regression analysis. Correction for patient, tumour, resection and/or leakage characteristics will be performed, where appropriate.

Based on the results of this first analysis, subgroups of patients will be created based on individual resection or leakage characteristics (or a combination of these). The efficacy of anastomotic leakage treatment strategies will be assessed in regression models for the different outcome parameters and corrected for considering patient, tumour, resection and leakage characteristics, where appropriate. Comparison of the primary outcome parameter and secondary outcome parameters will be expressed in terms of a relative risk with corresponding 95% confidence intervals. A two-tailed $P<0.05$ will be considered statistically significant.

8.4 OTHER STUDY OBJECTIVES

Analysis of other study objectives will follow the same principles as described in *chapter 8.2 Main study objective 1* and *chapter 8.3 Main study objective 2*. Detailed and predefined analysis plans will be written during the preparation phase of the TENTACLE – study.

9 ETHICS STATEMENT AND REGULATORY APPROVAL

This study will be conducted in compliance with the principles of the declaration of Helsinki. The medical ethical committee of the Radboud university medical centre in Nijmegen, The Netherlands, has thoroughly reviewed all pertinent documents, including the study protocol and granted approval. The study protocol and relevant documents will be provided to all participating centres in case the centres need local ethical approval. The TENTACLE – Colon study will be registered on Clinicaltrial.gov. The study protocol will also be made available on the website: https://www.tentaclestudy.com/.

10 DATA HANDLING

10.1 DATABASE

The Castor database system (https://www.castoredc.com/) will be used to collect data through online case report files (CRFs). Castor is an officially certified online medical research database system that fully complies with all pertinent regulations (i.e. GDPR, HIPAA, ICH-GCP, ISO 27001, ISO 9001, FDA 21 CFR part 11) and strictly adheres to international security standards. The entered data will exclusively be visible to collaborators from the designated hospital, and access to the complete study data will be limited to coordinating investigators, lead investigators, and principal investigators.

10.2 CASE REPORT FORM

A comprehensive CRF is created within the Castor database (www.castoredc.com) and distributed to the participating centres (see appendix 1 for details). The CRF contains information points along with definitions and guidelines to facilitate accurate scoring of the specified parameters.

10.3 DATA COLLECTION AND HANDLING

All patient data will be entered anonymously by or under supervision of the treating physician(s). Up to 4 collaborators per participating centre will have access to the Castor database for data entry. In addition to entering patient data individually, local study teams can upload their already existing database into the Castor database system and add the additional required data. The TENTACLE study team will provide a short step-by-step manual for adequate data entry and can provide support if needed.

10.4 DATA PRIVACY STATEMENT

All anonymous data will be available to the TENTACLE study team. The data of a centre will be available to that specific centre only through the Castor database system website. In compliance with the General Data Protection Regulation (GDPR - EU 2016/679), the data will not contain identifiable patients parameters (e.g. no date of birth, no date of surgery, etc.) and each patient will be assigned a unique code upon data entry to ensure that they are only traceable for the participating centre. All participating centres will maintain a password-protected file to identify individual patients that will be included and store this file locally in their practice. If there are additional queries or new pertinent questions, the local principal investigator can upload the necessary information.

10.5 PILOT STUDY

To achieve international consensus and enhance clarity regarding the utilization of pertinent definitions and the online CRF, a pilot study will be conducted following the completion of the study protocol. The pilot study was distributed to the experts who are part of the international writing committee for the TENTACLE - Colon study, and an overview of these experts can be viewed in Table 1. The feedback provided by the experts was used to improve and refine the CRF and study protocol.

Table 1. International writing committee TENTACLE – Colon study.

Writing committee		Hospital	City	Country
1.	Hans de Wilt (PI)	Radboudumc	Nijmegen	The Netherlands
2.	Pieter Tanis (PI)	ErasmusMC	Rotterdam	The Netherlands
3.	Jobbe Lemmens	Radboudumc	Nijmegen	The Netherlands
4.	Nynke Greijdanus	Radboudumc	Nijmegen	The Netherlands
5.	Kiedo Wienholts	AmsterdamUMC	Amsterdam	The Netherlands
6.	Sander Ubels	Radboudumc	Nijmegen	The Netherlands
7.	Marleen van Gelder	Radboudumc	Nijmegen	The Netherlands
8.	Roel Hompes	AmsterdamUMC	Amsterdam	The Netherlands
9.	Albert Wolthuis	UZ Leuven	Leuven	Belgium
10.	Kilian Brown	University of Sydney Central Clinical School	Sydney	Australia
11.	Jérémie Lefevre	Sorbonne Université, AP-HP, Hôpital Saint Antoine	Paris	France
12.	Martin Rutegård	Umeå University	Umeå	Sweden
13.	Quentin Denost	Clinique Tivoli	Bordeaux	France
14.	Yves Panis	Groupe Hospitalier Privé Ambroise Paré-Hartmann	Neuilly Seine	France
15.	Nicolas Rotholtz	Hospital Alemán	Buenos Aires	Argentina
16.	Thomas Pinkney	University of Birmingham	Birmingham	United Kingdom
17.	Rodrigo Perez	Hospital Alemão Oswaldo Cruz	São Paulo	Brazil
18.	Susan Gearhart	Johns Hopkins Medicine	Baltimore	United States of America
19.	Tsuyoshi Konishi	The University of Texas MD Anderson Cancer Center	Anderson	United States of America
20.	Matteo Frasson	Valencia University Hospital La Fe	Valencia	Spain

10.6 DATA CLEANING, VERIFICATION AND VALIDATION

Following the closure of the study to new cases, the coordinating investigator will initiate data cleaning, verification and validation procedures to improve data completeness and assess data quality and case ascertainment. Data cleaning will involve using an algorithm to scrutinize the data for any missing values, data inconsistencies and typographical errors. All identified data will be communicated to the respective local investigators enabling them to verify, adjust or supplement the (missing) data. For data validation, data accuracy and case ascertainment will be assessed. Data accuracy will be assessed by cross-checking data recorded in Castor with medical records by a local independent validator. A subset of predefined key parameters of 10-20% of the inclusions of a centre will be validated. At random, 20% of the participating centres will be selected for data validation. Case

ascertainment will be assessed to identify a systematic difference in the selection of patients per centre, defined as the proportion of cases included compared to the total amount of eligible cases. To assess case ascertainment, collaborators will be asked if they entered data of all consecutive patients with an anastomotic leakage within the study period, or whether a sample was included (and if so; for which period). Furthermore, participating centres will be asked about their annual number of colon cancer resections. The anastomotic leakage rate was conservatively estimated at 3% for all years within the study period. If the number of included cases is lower than the estimated number of cases, the collaborators will be asked to substantiate this discrepancy. For all procedures, a step-by-step manual as well as additional support will be available.

11 PUBLICATIONS

11.1 MAIN PUBLICATIONS

The TENTACLE study team aims to publish two main manuscripts covering the main objectives.

1. To identify predictive factors associated with 90-day mortality and 90-day Clavien-Dindo grade 4-5 complications amongst patients who developed AL following colon cancer resection. Moreover, developing and validating a model for predicting 90-day mortality as well as Clavien-Dindo grade 4-5 complications using the identified predictive factors.

2. To explore and compare the effectiveness of various treatment strategies for AL following colon cancer resection, considering patient, tumour, resection and leakage characteristics.

11.2 OTHER PUBLICATIONS

Other additional publications will be defined at a later stage during the study.

11.3 PUBLICATION POLICY

The TENTACLE – Colon study will be a collaborative effort, and as such, collaborative authorship is appropriate. To be more precise, all members of the international writing committee (see Table 1) will be the main authors, and all (up to 4) collaborators from each participating centre and the local independent validator will be granted corporate authorship under the name 'the TENTACLE – Colon Collaborative Group' in all manuscripts derived from the data gathered in the TENTACLE – Colon study.

11.4 DATA AVAILABILITY FOR OTHER PUBLICATIONS

Data will be available upon reasonable request. Only collaborators with appropriate qualifications and pertinent research inquiries are eligible to request access to the data. The principal investigators of the TENTACLE – Colon study will assess the relevance and appropriateness of the request and their verdict is decisive. If data will be transferred, it will solely be conducted under the appropriate ethical and data transfer agreement.

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