Protocol: Prediction of postoperative outcome in esophageal cancer with body composition estimates based on AI-segmentation of preoperative CT

Principal investigator (PI) and co-workers

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Introduction

Esophageal cancer is the 8th most common cancer worldwide and the 6th according to mortality rates (1, 2). The main histopathological entities include adenocarcinoma and squamous cell carcinoma. Adenocarcinoma represents 70-80% of all cases in western countries. Metastatic or locally advanced malignant disease at time of diagnosis contributes to the poor overall long-term survival of 15-20%. In Norway, some 300 new patients are registered with esophageal cancer annually (3).

Surgery is the mainstay treatment for localized or regional esophageal cancer. Access to the abdomen, thorax and in some cases the neck is required. High rates of morbidity (60%) and mortality (2-5%) are reported. Early cancer (T1a) can be treated endoscopically with less invasive methods. Some 70% of the patients may not be eligible for curative surgery due to advanced malignant disease or comorbidity (4).

Modern diagnostics, including PET-CT, endoscopic ultrasonography and cytology, facilitate patient selection to surgery and have contributed to improved survival following esophagectomy (5). The 5-year relative survival rate after treatment with curative intent is > 40% for localized disease, and 30% for regional disease (6).

Treatment protocols with curative intent are based on neoadjuvant chemoradiotherapy or perioperative chemotherapy in conjunction with surgery (7, 8). Esophageal tumors and metastatic lymph nodes may be eradicated by neoadjuvant therapy in 50% of the patients with squamous cell carcinoma and 20% with adenocarcinoma (8, 9). Definitive oncologic therapy without surgery may thus be a viable option for some patients (10, 11).

Computed tomography (CT) is the workhorse in staging esophageal cancer and is performed before and after neoadjuvant oncologic therapy prior to surgery or prior to surgery in patients undergoing surgery without neoadjuvant therapy. In addition to this imaging based morphological information about tumor extend, the routine CT scans contain valuable and high-precision information about body composition such as skeletal muscle (SM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intermuscular and intramuscular adipose tissue (IMAT).

Recent studies suggest that body composition has predictive value for postoperative complications and survival (15, 16). Therefore, body composition data, which may be collected from routine CT scans, should be used in clinical practice. Although body composition data from clinically acquired CT scans may be used to tailor nutritional interventions (17) and optimize cancer treatment (18, 19), it is currently not part of standard cancer treatment. The lack of utilization of CT-based body composition data may be due to the absence of accurate and automated tools. Even though CT is described as one of the gold standards for the measurement of body composition(20), segmentation has typically been performed manually or semi-manually. Both manual and semi-manual processes are time consuming and requires extensive resources, anatomical knowledge, and software training. This limits the use of CT for body composition purposes in clinical practice and large-scale clinical trials. BodySegAI, a deep learning-based software for automated body composition quantification was recently developed at our institution and has shown state of the art performance in segmentation of VAT, SAT, SM and IMAT (21).

Improved knowledge of body composition and its impact on postoperative complications, hospital stay, and survival may facilitate personalized treatment strategies in esophageal cancer. Body composition may support treatment decisions in favor of definitive chemoradiotherapy when risks associated with resection outweigh potential benefits. Dysphagia is a common adverse effect post-surgery and pre and postop body composition may indicate patients particularly prone to nutritional challenges in need for a tailored follow-up.

Therefore, with this study we aim to improve the knowledge of body composition during the course of treatment with curative intent for esophageal cancer. Furthermore, we want to provide the necessary evidence to introduce body composition into treatment decisions. Study findings may be relevant for future prospective studies to further elaborate on body composition as a contributor to improve patient selection to surgery and for alternative treatment and follow-up strategies after surgery.

Aims

Primary

To evaluate body composition assessment by BodySegAI as prognostic tool for postoperative complications and recovery.

Secondary

To evaluate body composition assessment by BodySegAI as prognostic tool for overall survival and progression free survival in patients with esophageal cancer.

To assess longitudinal variation in parameters of body composition (skeletal muscle [SM], intra- and intermuscular adipose tissue [IMAT], visceral adipose tissue [VAT], and subcutaneous adipose tissue [SAT]) in patients undergoing potentially curative treatment for esophageal cancer.

To compare measurements from BodySegAI to the corresponding semi-manual measurements from Slice-O-Matic®.

Ethics and informed consent:

All patients in the local registry for esophagus cancer-surgery at the Dep. Gastrointestinal surgery have provided informed consent to the use of data for research purposes. Ethical approval is requested from REC south-east and the local data protection officer.

This project will be in accordance with the Helsinki Declaration.

Materials and methods

The study will be registered at ClinicalTrials.gov. Study methods and results will be reported in agreement with STROBE or the “Standards for Reporting of Diagnostic Accuracy Studies” (STARD) statement of 2015, as appropriate (22, 23). It should be noted that the STARD-AI Steering Group is preparing an AI-specific extension (24). If these STARD-AI guidelines are published before end of study, the findings will also be reported in accordance herewith. To compensate for AI specific elements not addressed in STARD, we will, when relevant, rely on the Checklist for Artificial Intelligence in Medical Imaging (CLAIM) (25) which is modelled after the STARD guideline.

Participants and inclusion

Retrospective patient cohort of approximately 150 patients who underwent surgery for esophageal cancer at OUS between 2013 and 2017. It may be required to extend the cohort to 200 patients depending on number of events for some of the subanalyses. Treatment strategy for all patients was determined on a multidisciplinary tumor board in accordance with clinical stage and patient characteristics. In all participants, esophageal reconstruction was achieved through the creation of a tubularized gastric conduit using the Ivor-Lewis surgical approach with intrathoracic anastomosis. Neoadjuvant chemo- or chemoradiotherapy was administered according to national guidelines varying somewhat during the study period.

Clinical data - endpoints/outcome:

Data from the quality assurance registry for esophagus cancer-surgery:

- Demographic data of participants: Age, sex, height, tumor stage at diagnosis, Neoadjuvant/adjuvant chemotherapy and ASA score.
- Weight at the four points in time (T1-T4), Figure 1.
- 5-years overall survival (OS), disease-free survival and cancer-specific survival.
- Postoperative complications (e.g. infection, worsening of comorbidities, anastomotic leakage) according to the Clavien Dindo Classification of Surgical complications.
- Length of stay (LOS)
- Length of stay in postoperative- (POS) or intensive care unit (ICU)

For potential missing data retrieval from the patient journal may be required and will be performed by personal with institutional approved access to the patient journal. This may also apply for retrieval of relevant missing patient data from local hospitals.

Imaging data and body composition assessment:

- Computed tomography (CT) examination at point in time 1 (T1): time of referral/diagnosis (all patients).
- CT examination at T2: response assessment after neoadjuvant treatment (subgroup).
- CT examination at T3 and T4: One or two years postoperative (subgroup)

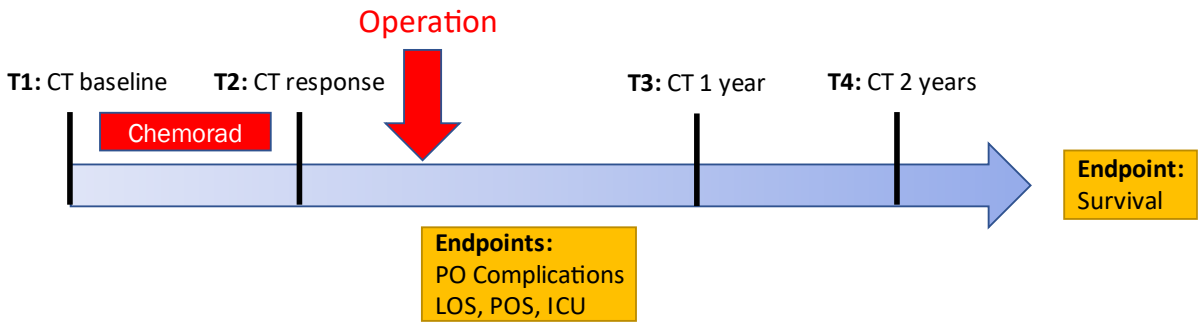

Figure 1 Study concept and timeline. Postoperative (PO); length of stay (LOS); length of stay in postoperative care unit (POS); length of stay in intensive care unit (ICU); point in time 1-4 (T1-T4)

Image extraction and processing

For each patient a single axial image at the midpoint of the 3rd lumbar vertebrae is extracted from the CT examinations at T1 to T4. Segmentation of these images are performed with the artificial intelligence (AI) tool "BodySegAI", and the following tissue compartments are quantified:

- SM
- IMAT
- VAT
- SAT

Whole-body fat mass and fat-free mass is estimated according to the equation by Mourtzakis et al. (26).

Statistical analysis:

Dedicated statistical software like Stata and SPSS are used for analysis of study data. Categorical variables are compared using the chi-squared or Fisher's exact tests. Appropriate parametric or non-parametric tests are used for comparison of continuous data (paired t-test or Mann–Whitney test). Regression and survival analyses are used to assess relations between body composition and outcome parameters. Survival is defined by the time interval from the date of surgery to the date of either death or censoring. Multivariable analysis of predictors of survival is performed to identify independent predictors of outcome parameters. The diagnostic performance for good/poor outcome will be defined by area under the curve, sensitivity, specificity, positive and negative predictive value. Significant differences in sensitivity and specificity will be determined by McNemar's test. Statistical significance is assigned to two-sided P-values < 0.05.

Risks

Risks to study execution

In general, risks to study execution are considered low due to the retrospective nature of the study, the established quality assurance registry for esophagus cancer-surgery (since 2012 consecutive inclusion of patients; based on written consent) and the robustness of the BodySegAI algorithm, Table 1. Patient data will be handled according to institutional guidelines.

Risk	Impact	Likelihood	Mitigating factors and actions
Study approval by regional ethics committee and local data protection officer	High	Low	▪ Study protocol might be slightly modified to obtain necessary approvals for study initiation. ▪ Study approval is main priority of PI and co-workers.
Technical issues with CT exams	Moderate	Low	▪ Retrospective exam inclusion. Exam protocols and quality may vary. ▪ BodySegAI is provides a robust algorithm that compensates for these factors.
Participant recruitment	Moderate	Low	▪ Some exams may not be suitable for all analyses e.g. contrast enhanced when non enhanced is required. ▪ Inclusion period may be extended. The quality assurance registry for esophagus cancer -surgery goes back to the 1980s.

Table 1 Risk assessment of factors that may impair study execution.

Risks to participants

Due to the retrospective nature of the study, there are no study related risks for the participants. The only disadvantage for the participants may arise from further processing of their medical data. We argue that the benefits from this study for the collective of patients with cancer in the esophagus outweigh this considerably small disadvantage.

Time schedule

The necessary approvals will be obtained during Q3 of 2022.

Inclusion and data collection Q3 2022 – Q1 2023.

Data analysis and publication Q4 2022 – Q4 2023.

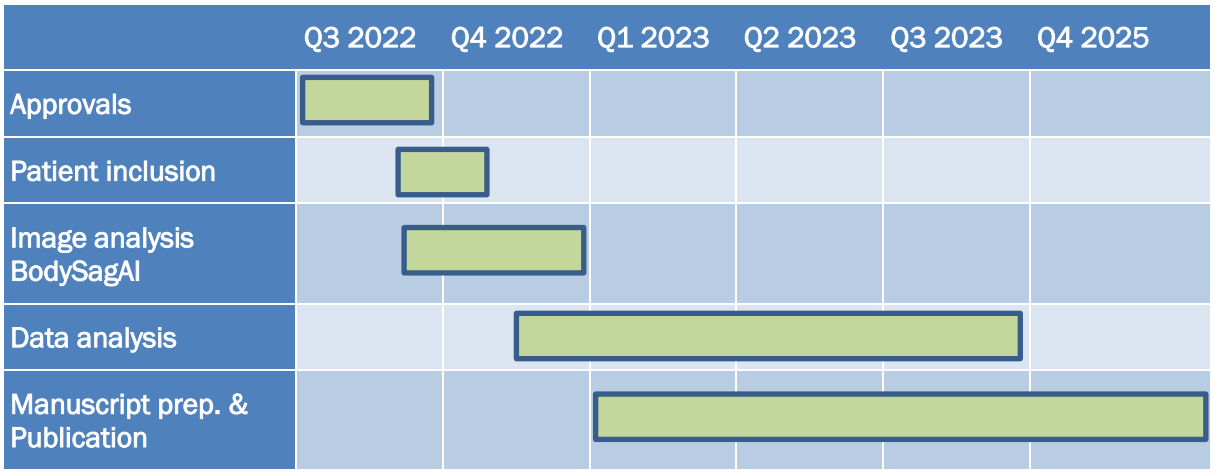

Table 2 Anticipated study time schedule.

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