Trials

STUDY PROTOCOL

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Thromboprophylaxis in oesophageal cancer patients—a study protocol for a randomised, controlled trial (TOP-RCT)

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Abstract

Background The purpose of the study is to examine if prolonged thromboprophylaxis decreases the risk of thrombosis after intended curative surgery for oesophageal cancer.

Study results are expected to inform a guideline for thromboprophylaxis after oesophageal cancer surgery. The perspective is to reduce morbidity and mortality in this critically ill patient group.

Thrombosis is the second-most common cause of cancer death after the cancer itself. The risk of thrombosis depends on the cancer type, and upper gastrointestinal cancers are considered high risk. This risk is further increased when patients undergo surgery. However, only few studies have investigated the peri- and postoperative coagulation profile in oesophageal cancer patients. Due to this lack of knowledge, prophylaxis is currently restricted to 5000 IU (international units) low-molecular weight heparin daily from surgery until discharge from hospital (approximately 10 days), whereas patients with gastric cancer receive 30 days of treatment.

The present study examines whether a 30-day treatment is superior and safe, compared with the current standard treatment.

Methods The study is a randomised controlled trial. Inclusion is ongoing, and we aim to include 100 patients. Blood samples are drawn before and after surgery, and the coagulation is extensively examined. The primary endpoint is the difference in plasma levels of prothrombin fragment 1 + 2 (F1 + 2) 30 days after surgery between the intervention and the standard group. Furthermore, patients are examined with ultrasound to screen for asymptomatic venous thrombotic events (VTE).

Secondary endpoints are incidence of bleeding, symptomatic and asymptomatic VTE and mortality 30 days 1 one year after surgery.

Discussion The study will provide valuable information on the perioperative coagulation profile and VTE risk of oesophageal cancer patients. The study seeks to aid in optimising the postoperative thromboprophylaxis, and the perspective is to reduce morbidity and mortality in this at-risk patient population.

Trials registration The trial was prospectively registered at the EU Clinical Trials Register with ID 2021–001335-24 on 30 June 2021 and at ClinicalTrials.gov with study identifier NCT05067153.

Keywords Oesophageal cancer, Surgery, Venous thromboembolic events, Prothrombin fragment 1 + 2

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Introduction

Oesophageal cancer is an aggressive cancer type. The 5-year survival is as low as 20%, and the majority of patients die within the first 2 years after the diagnosis [1, 2]. The only definitive treatment is extensive surgery with preoperative chemotherapy, sometimes combined with radiotherapy [2]. However, surgery increases the risk of thrombosis, and it is therefore imperative to offer cancer patients undergoing surgery optimal thromboprophylaxis, without compromising safety, to improve survival [3].

Venous thromboembolic events (VTE) are the leading cause of death in cancer patients, after the cancer itself [4]. Recent research indicates that different types of cancer have different impact on coagulation activity and varying VTE risk [5], which makes it necessary to differentiate the thromboprophylactic strategy according to cancer type. Due to the substantial risk of VTE in other gastrointestinal cancers, thromboprophylaxis with low molecular weight heparin (LMWH) is recommended for patients with oesophageal cancer undergoing surgery [6]. However, perioperative bleeding in oesophageal cancer patients is also frequent, and up to 80% of patients require blood transfusion [7–9]. Currently, no national or international standards exist with regards to length of LMWH prophylaxis or dosage due to lack of evidence [10, 11].

Several analyses may contribute to evaluating risk of thrombosis in cancer patients [12, 13]. One of these is prothrombin fragment F1 + 2 (F1 + 2), a split product that is formed when prothrombin is cleaved to the active thrombin [14]. Elevated F1 + 2 levels have been shown to be associated with VTE in several studies, notably also in cancer populations [15–17].

A small number of studies have examined the VTE incidence in oesophageal cancer patients undergoing oesophagectomy. A 2017 meta-analysis estimated the VTE incidence to be 4–19% among a mixed cohort of oesophageal and gastric cancer patients [18]. Gastric cancer was found to be a risk factor for developing VTE in this review and thus may have raised the overall VTE incidence reported in this study. In 2022, the first systematic review on purely oesophageal cancer estimated the VTE risk to be approximately 4% [3]. However, both reviews could only identify 14 relatively heterogenous studies [3, 18]. This relatively small sample size, combined with great variation in received thromboprophylactic regimens, makes it difficult to precisely estimate the incidence of VTE.

Thromboprophylactic strategies vary greatly between countries and even treatment centres [3]. Both aforementioned systematic reviews recommended perioperative prophylaxis with LMWH [3, 18]. Earlier studies have compared LMWH with other drugs [19] and different administration frequencies (once versus twice daily) [20], but to our knowledge, no studies have investigated effect of duration of treatment on coagulation activity and thereby thromboembolic risk.

Short-term LMWH has been demonstrated to lower VTE frequency after oesophageal cancer surgery [20, 21]. However, in a mixed group of cancer patients not receiving surgery, LMWH increased clinically significant bleeding events [22]. This highlights the need for a randomised trial investigating the efficacy and safety of prolonged thromboprophylaxis with LMWH in oesophageal cancer patients undergoing surgery.

Aim and perspective of the study

The aim of the study is to investigate the efficacy and safety of a prolonged (30-day) thromboprophylactic regime compared with the current standard prophylaxis (from surgery until discharge from hospital, approx. 10 days) for patients undergoing intended curative surgery for oesophageal cancer.

The perspective is to reduce morbidity and mortality for this at-risk patient group.

Methods

Design

The study is a single-centre, open-label unblinded randomised controlled trial. The study is performed at Aarhus University Hospital in Denmark, which is a tertiary referral hospital that performs surgery for oesophageal cancer as a highly specialised function. All patients with oesophageal cancer in the form of adeno- or squamous cell carcinoma scheduled for surgery at Aarhus University Hospital are screened for study eligibility (Figs. 1 and 2).

Timeframe

Patient inclusion started September 2021. We aim to include 100 patients, equally distributed between the intervention and the standard group.

Hypotheses

1. The intervention group of oesophageal cancer patients, who receive prolonged thromboprophylaxis with dalteparin has a lower VTE risk, expressed by a lower F1 + 2, 30 days after surgery than the standard group.
2. The intervention group does not demonstrate an increased bleeding tendency compared with the standard group.

	Screening	Allocation					End of FU
TIMEPOINT	*When referred for OP*	*At pre OP interview*	*Pre OP*	*Post OP*	*Post OP day 1*	*Post OP day 30*	*Post OP one year FU*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Standard prophylaxis group		X	←	—	→		
Intervention: prolonged, 30-day prophylaxis group		X	←	—	—	→	
ASSESSMENTS:							
Eligibility criteria (inclusion and exclusion criteria)	X						
F1+2 measurement (primary outcome)			X	X	X	X	
Bleeding, VTE and mortality (secondary outcome)			X	X	X	X	X
Clinical data			X	X	X	X	X
Ultrasound examination			X			X	
Other laboratory analyses (blood sampling)			X	X	X	X	

Fig. 1 Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) figure. Schedule of enrolment, interventions and assessments for trial participants. For details of the inclusion and exclusion criteria, please refer to the applicable sections in the manuscript. For a detailed list of analyses performed on blood samples, please refer to Table 1. Abbreviations: F1 + 2, prothrombin factor 1 + 2; FU, follow-up; OP, operation

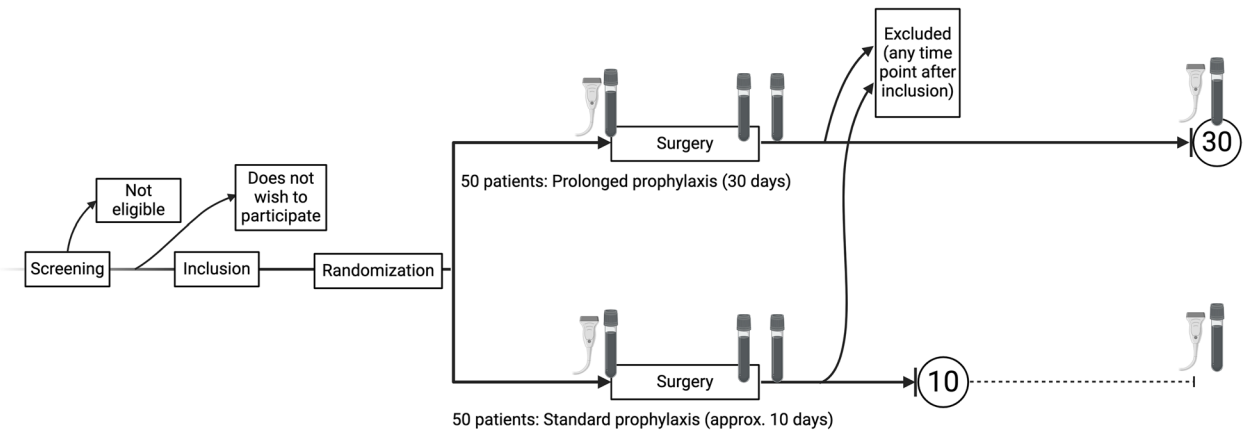

Fig. 2 Patient flow. Sample tubes and ultrasound probes mark the timing of blood sampling and ultrasound scanning, respectively. Patients in the standard and prolonged intervention group receive the same daily dose of 5000 international units (IU) with low molecular weight heparin (LMWH)

The primary endpoint is the difference in F1 + 2 30 days after surgery between the intervention and the standard group.

The secondary endpoints are incidence of bleeding, VTE and mortality 30 days and 1 year after surgery.

Inclusion criteria

The inclusion criteria are as follows:

1. Cancer located in oesophagus and/or cardia
2. Candidate for intended curative surgery
3. Age > 18 years

Exclusion criteria

The study has the following exclusion criteria:

1. Known inherited bleeding disorder
2. Unable to provide informed consent
3. Arterial or venous thromboembolic events within the last 3 months
4. On-going anticoagulant treatment (vitamin K antagonists or direct oral anticoagulants)
5. Pregnant or has given birth within the last 3 months
6. Known allergy to the trial drug dalteparin

Inclusion and randomisation

The patients are screened and included in the study, after giving their informed consent, at their pre-operative interview at Aarhus University Hospital by study investigators or trained study nurses. The interview takes place approximately 1 week before surgery. After inclusion, the patients are randomised to receive either prolonged (30 days) or standard prophylaxis (approx. 10 days, prophylaxis is given until patient is discharged) with 5000 international units (IU) of the LMWH drug dalteparin daily. The randomisation sequence is generated with a 1:1 allocation using varying block sizes of 2, 4, 6 and 8 in the secure eCRF programme REDCap (Research Electronic Data Capture) (REDCap Consortium, Vanderbilt University Medical Center, Tennessee, USA), which is hosted by Aarhus University, Aarhus, Denmark.

Blinding

The patients and the responsible health care staff are not blinded to the intervention, as placebo injections are not utilised in either group. Injection of LMWHs often create a small haematoma that a placebo injection does not, and blinding would therefore be compromised. However, this does not affect the primary endpoint as it is purely biochemical. All laboratory analyses are performed blinded to the intervention and outcome.

Intervention

The formulation used in the study comes in pre-filled syringes containing 5000 IU, which is administered subcutaneously [23].

Patients in the standard group receive dalteparin until they are mobilised and discharged (approx. 10 days) and thus receive identical prophylaxis to patients not included in the study. The intervention group receives dalteparin for 30 days. Patients in the intervention group are taught to administer the drug themselves by nurses at the department prior to discharge or, if unable or unwilling to self-administer, the drug is administered by home nursing. Guidelines recommend 4 weeks of thromboprophylaxis with 5000 IE LMWH daily after laparoscopic and open abdominal gastrointestinal cancer surgery, and the dosage and administration form for the intervention group is therefore based on the current recommendations [6, 24].

The most common serious side effect of dalteparin is bleeding. However, there is a predictable dose–response effect, and for this reason, the drug traditionally does not require monitoring [25]. However, all patients included in the study will be monitored biochemically with platelet counts after surgery, which adds to the safety of the study and is to the benefit of the included patients in both standard treatment and intervention group. For a detailed list of side effects, please refer to the published product resumé [23].

To ensure compliance, patients are asked to keep an injection diary and return the empty syringes at the final outpatient control appointment. Other non-study pharmacological treatment will continue at the discretion of the physician responsible for the treatment of the patient.

Patient flow

Figure 2 shows the inclusion and data collection flow from screening to the 30-day follow up. Furthermore, a follow-up review of patient records is performed 1 year after surgery (Fig. 1).

Data collection

Clinical data

The following information is recorded from electronic patient records and laboratory database.

At study entry:

1. Sex
2. Date of birth
3. Date of diagnosis
4. Medical history including tumour pathology
5. Latest blood electrolyte status, kidney function, and infection parameters
6. Eligibility criteria (i.e. all inclusion and exclusion criteria)

7. Medication
8. Preoperative Caprini score

At 30-day and 1-year follow-up:

1. Medical history including tumour pathology
2. Thromboembolic events including diagnosis by imaging
3. Major bleeding events, defined as leading to transfusion of 2 or more units of blood or packed red cells, decrease in haemoglobin of 2 g/dL, bleeding in critical sites, defined as spinal, epidural, intraocular, intracranial, pericardial, retroperitoneal or leading to death.
4. Medication

Furthermore, information from the registers is used to assign a World Health Organization (WHO) performance status at study entry and at each follow-up for each patient.

Blood sampling and analyses

Samples are drawn from an arterial line if present. Otherwise, they are drawn from a peripheral vein applying minimal stasis. Samples are analysed immediately or frozen at − 80° C for batch analysis as appropriate. Table 1 shows an overview of the analyses performed on the collected samples.

Ultrasound examinations

Ultrasound scans are performed with Hitachi Aloka Arietta 850, GE healthcare LOGIQ E10 and E9 with linear transducer 3–7 MHz and L2–9 MHz. Examinations are performed by a radiologist before surgery and 30 days after surgery. The scan is performed on the patients' lower extremities and include femoral communal and superficial veins, popliteal veins, venae saphena parva and magna as well as superficial and muscular veins and any symptomatic sites. If thrombosis is diagnosed on the preoperative scan, the patient is excluded from the study to receive a therapeutic dalteparin dosage.

Sample size

Due to the rarity of oesophageal cancer, it is necessary to use surrogate biochemical markers for VTE as the primary endpoint. We have chosen F1 + 2 as the basis for the sample size calculation. Our research group has demonstrated this marker to be significantly elevated in patients with localised cancer [16]. Data on patients with oesophageal cancer do not exist yet; thus, the sample size calculation data are obtained from a group of patients with head and neck cancer, as this subset of patients have a VTE frequency close to that of patients with gastrointestinal cancer [3, 26]. F1 + 2 mean was 329 pmol/l with a standard deviation (SD) of 159 pmol/l. We considered a minimal relevant difference (MIREDIF) of F1 + 2 at 105 pmol/l between the two groups 30 days after surgery to be clinically relevant. Using a 5% significance level (2α) and a power of 90% (1-β), a minimum of 49 patients must be included in each group. To take missing data into consideration we plan to include 50 patients in each group.

Statistical analyses

For descriptive statistics, mean and SD will be calculated for data following a Gaussian distribution, and for data

Table 1 Overview of performed analyses

Analyses	Handling	Analysed at
Haemoglobin, haematocrit, platelet count, immature platelet count, immature platelet fraction, mean platelet volume, platelet aggregation, thrombin time, international normalized ratio (INR), activated partial thromboplastin time (aPTT), antithrombin, fibrinogen, fibrin D-dimer and markers of primary haemostasis and global coagulation (ROTEM® EXTEM, INTEM, FIBTEM and HEPTEM) Alanine transaminase (ALT), estimated glomerular filtration rate (eGFR), c-reactive protein (CRP) and markers of organ function	Immediate analysis	Dept. of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark
Ex vivo thrombin generation, Prothrombin factor 1 + 2 (F1 + 2), plasminogen activator inhibiter-1, tissue plasminogen activator, clot lysis assay, markers of secondary haemostasis and fibrinolysis	Frozen and batch analysed	Dept. of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark
Fibrin clot structure	Frozen and batch analysed	Prof. Dietmar Fries Lab, Medizinische Universität, Innsbruck, Austria
M-ficolin, H-ficolin, MBL, CL-L1, MBL-associated serine protease 1, 2 and 3, mannose-binding lectin-associated protein of 44 kDa and 19 kDa (MAp44 and MAp19) and lectin–pathway complement markers	Frozen and batch analysed	Prof. Steffen Thiel Lab, Department of Biomedicine, Aarhus University, Denmark

not following a Gaussian distribution, median and interquartile range (IQR) will be used.

Primary endpoint

The difference in F1 + 2 between the two groups 30 days after surgery will be tested by an unpaired *t*-test if data follows a Gaussian distribution and by a Mann–Whitney *U* test if not.

Secondary endpoints

Incidence of VTE and mortality 30 days as well as one year after surgery will be analysed unadjusted by the Kaplan–Meier method. The difference across sample time points will be investigated using repeated measurements-tests (mixed model analysis). Correlation tests will be performed using a Spearman test. A power calculation of the primary endpoint results will be performed if the expected number of patients are not included to assess the attained power of the study.

Risks and adverse events

Blood sampling

There is a minor risk of infection, superficial thrombophlebitis and localised haematoma associated with blood sampling.

Ultrasound examination

Ultrasound examination is painless, safe and with no radiation.

Dalteparin administration

As described under the " Intervention" section, dalteparin is primarily associated with an increased bleeding risk. All expected and unexpected adverse events and reactions occurring during study treatment will be documented in the applicable case report form (CRF) section in REDCap.

Serious adverse events

A serious adverse event or reaction (SAE) is any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation or results in persistent or significant disability [27]. Thus, any death, whether associated with side effects of the study treatment or due to progressive disease, surgical complications or other causes are considered a SAE. In this study, the following are *not* considered a reportable SAE:

- Hospitalisation due to previously planned procedure or due to convenience.
- Adverse events due to progression of or complications related to the disease.

During the treatment period, all SAEs are documented on the SAE report form, and the sponsor is notified automatically. Based on the SAE report form, the sponsor-investigator and her delegates complete a SAE assessment sheet. These assessments are used for monitoring SAE survival and safety of the experimental treatment. Patients who withdraw from the study due to an adverse event or SAE are followed up to 30 days after the event.

Suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs, which are:

1. Related to the study drug (dalteparin) and
2. Of a nature or severity that is not consistent with information in the reference document (the published product resume [23]). The sponsor will submit all available information about at SUSAR immediately and at the latest within 7 days after the event is known to the sponsor. The sponsor is responsible for informing the ethics committee, the regulatory authorities, the Danish Medicines Agency and all sub-investigators.

Furthermore, a safety report as specified by the Danish Medicines Agency is submitted to the authorities annually.

Termination of trial

If there is an excessive frequency (> 20% in the intervention group) of SAEs, it may be necessary to terminate the study.

If a SUSAR is suspected, the study will terminate for the individual participant.

All participants may at any time leave the study with no warning and no reason given. Furthermore, the participant will leave the study if one of the following occurs:

- Anaphylaxis.
- Thromboembolic event.
- Clinically significant bleeding not related to surgery, defined as leading to transfusion of 2 or more units of blood or packed red cells, decrease in haemoglobin of 2 g/dL, bleeding in critical sites (spinal, epidural, intraocular, intracranial, pericardial or retroperitoneal) or leading to death. If terminated, the participants will receive the standard care for oesophageal cancer patients at Aarhus University Hospital. Participants who leave the study may be replaced.

Discussion

The present study aims to investigate whether a prolonged, 30-day thromboprophylaxis with dalteparin reduces the risk of VTE after surgery for oesophageal cancer. Dalteparin was chosen over other LMWH as this is the nationally recommended drug for thromboprophylaxis after cancer surgery in Denmark, where the study is conducted [6]. The study is performed at one site and is thus a single centre study. However, surgery for oesophageal cancer is a highly specialised function, only undertaken by dedicated teams at the four university hospitals in Denmark. This study therefore still manages to include a significant part of the total amount of patients operated per year in Denmark.

The randomised, controlled study design gives a robustness to the findings, and GCP-monitoring increases the data quality.

The study is designed with a biochemical primary endpoint as a proxy for VTE. This choice was made from two considerations: first is that in a clinical study of the planned size, there would likely be an insufficient amount of VTEs to provide robust statistical analysis; second, a biochemical analysis is easy to obtain, not subject to patient or investigator bias and easy to incorporate in future risk assessment scores in this and other patient groups. The specific choice of F1 + 2 as a predictor of VTE was based on promising prior results in patients with head and neck cancer from our research group [16]. A 2023 review on the use of markers of thrombin generation further supports this choice with the conclusion that F1 + 2 is a robust VTE indicator in cancer patients [17].

The patients included in this study undergo a major surgery with high morbidity and mortality [28, 29]. Several complications, such as postoperative atrial flutter or fibrillation, re-operations and invasive examinations may require an adjustment of thromboprophylaxis for the patient, thus creating a deviation from the study protocol. Although these anticipated deviations create a less uniform study population, the choice of a real-world relatively unselected patient group will make results easier to apply later in a similar clinical setting.

Patients included in the study are examined for VTE both before study entry and 1 month after surgery. This examination is a major advantage, as it enables registration of both symptomatic and asymptomatic VTE. Furthermore, little is known about the VTE rate post oesophagectomy, and the collected data will therefore supplement available knowledge on this topic. With this knowledge, along with the detailed data on peri- and postoperative coagulation activity, this study will provide some of the basis for a more informed choice regarding postoperative thromboprophylaxis in future patients with oesophageal cancer.

In summary, this study evaluates whether prolonged thromboprophylaxis is a safe and superior therapy after surgery for oesophageal cancer compared with the standard short thromboprophylaxis regimen. Furthermore, the study will impart important knowledge on coagulation activity and VTE occurrence after oesophagectomy. The perspective is to contribute to the available knowledge on the topic, forming a first step towards a guideline for thromboprophylaxis in this patient group.

Trial status

Protocol version 1.2, 31 January 2022. Inclusion started on 01 September 2021 and is estimated to close 31 May 2024 (last patient last visit). Final follow-up for final patient expected to be completed 31 May 2025.

Abbreviations

F1 + 2	Prothrombin fragment F1 + 2
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IU	International units
LMWH	Low molecular weight heparin
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse event
VTE	Venous thromboembolic reaction
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08408-y.

Supplementary Material 1.

Authors' contributions

AM is the sponsor-investigator of the study. TG wrote the first draft of the protocol manuscript. All authors (TG, NM, NK, DWK, TDC and AMH) participated in the study design. TG and dedicated research laboratory technicians performed the biochemical analyses, and NM performed the ultrasound analyses. All authors participated in the protocol revision and approved the submission.

Protocol amendment procedure

Any suggested amendments to the protocol will be approved by the trial steering committee, the GCP unit, the regional Scientific Committee and the Danish Medicines Agency in accordance with Danish law. Approved protocol amendments will be added to the Trial Master File and the Investigator Site File. Breaches of the protocol are noted in the applicable deviation form in the project REDCap database.

Insurance

Study participants are insured under the Danish Patient Compensation Association.

Funding

The study is funded by Aarhus University in the form of a PhD scholarship and Oda and Hans Svenningsens' Foundation. The funding parties has no influence on the study design, data collection, analysis, interpretation of data or in manuscript writing.

Availability of data and materials

Data is stored in the eCRF system REDCap hosted by Aarhus University. Data from the study will be published in national and international peer-reviewed journals as well as presented on conferences and other scientific meetings.

The statistical code used to analyse the dataset is available from the corresponding author on reasonable request, as is the full protocol.

Declarations

Ethics approval and consent to participate

All patients give their oral and written informed consent before inclusion. The study has been approved by the Danish Medicines Agency, the regional Scientific Committee and the Danish Data Protection Agency. The project management group holds monthly meetings to review trial conduct; the trial steering group meets every 6 months or more often as required. The study does not have a data monitoring committee, as the intervention was considered low-risk. The associated Good Clinical Practice (GCP) unit perform quarterly on-site monitoring visits and have full access to all original patient documentation. The study adheres to the General Data Protection Regulation (GDPR) and the Data Protection Act.
The study has EudraCT registration number 2021–001315-24 and is registered at ClinicalTrials.gov (study identifier: NCT05067153).
The study is monitored by the Good Clinical Practice (GCP) Unit and conducted in accordance with the Declaration of Helsinki and applicable local regulatory requirements. The protocol manuscript adheres to the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines (Supplementary Material 1).
There was no patient or public involvement in the study conceptualisation.

Consent for publication

The protocol does not contain any pilot data and references only previously published data.

Competing interests

TDC has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb, Chiesi Pharma AB and GlaxoSmithKline and on Advisory Boards for Bayer and Merck Sharp & Dohme (MSD), AstraZeneca and Sanofi.
Other authors: None declared.

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References

1. Engholm G. Statistik om Spiserørskræft: Kræftens Bekæmpelse; 2020. Available from: https://www.cancer.dk/spiseroerskraeft-oesofaguscancer/statistik-om-spiserorskraeft/. Cited 2020 20.07.
2. Shulze S, Sengeløv L, Øgard CG. Spiserørskræft 2020. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/mavetarm/tilstandeogsygdomme/spiseroer/spiseroerskraeft/. Cited 2020 20.07.
3. Theochari NA, Theochari CA, Kokkinidis DG, Kechagias A, Lyros O, Giannopoulos S, et al. Venous thromboembolism after esophagectomy for cancer: a systematic review of the literature to evaluate incidence, risk factors, and prophylaxis. Surg Today. 2022;52(2):171–81.
4. Van Haren RM, Valle EJ, Thorson CM, Guarch GA, Jouria JM, Andrews DM, et al. Long-term coagulation changes after resection of thoracoabdominal malignancies. J Am Coll Surg. 2014;218(4):846–54.
5. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166(4):458–64.
6. Rasmussen MS, Dorff MH, Holt MI, Grove EL, Hvas AM. Cancer og Venøs Tromboembolisme: Dansk Selskab for Hæmostase og Trombose; 2017. Available from: http://www.dsth.dk/pdf/catretningslinje_2017.pdf. Cited 2020 20.07.
7. Boshier PR, Ziff C, Adam ME, Fehervari M, Markar SR, Hanna GB. Effect of perioperative blood transfusion on the long-term survival of patients undergoing esophagectomy for esophageal cancer: a systematic review and meta-analysis. Dis Esophagus. 2018;31(4).
8. Reeh M, Ghadban T, Dedow J, Vettorazzi E, Uzunoglu FG, Nentwich M, et al. Allogenic blood transfusion is associated with poor perioperative and long-term outcome in esophageal cancer. World J Surg. 2017;41(1):208–15.
9. Sakamoto T, Fujiogi M, Matsui H, Fushimi K, Yasunaga H. Comparing perioperative mortality and morbidity of minimally invasive esophagectomy versus open esophagectomy for esophageal cancer: a nationwide retrospective analysis. Ann Surg. 2019.
10. Schmidt LM, Foli-Andersen NJ, Rasmussen HM, Wille-Jorgensen PA. Thrombo-prophylaxis in Danish surgical departments. Status 2005 and 25 years' development. Ugeskr Laeger. 2008;170(11):947–51.
11. Agzarian J, Linkins LA, Schneider L, Hanna WC, Finley CJ, Schieman C, et al. Practice patterns in venous thromboembolism (VTE) prophylaxis in thoracic surgery: a comprehensive Canadian Delphi survey. J Thorac Dis. 2017;9(1):80–7.
12. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2009;27(25):4124–9.
13. Syrigos K, Grapsa D, Sangare R, Evmorfiadis I, Larsen AK, Van Dreden P, et al. Prospective assessment of clinical risk factors and biomarkers of hypercoagulability for the identification of patients with lung adenocarcinoma at risk for cancer-associated thrombosis: the observational ROADMAP-CAT study. Oncologist. 2018;23(11):1372–81.
14. Larsen JB, Hvas AM. Thrombin: a pivotal player in hemostasis and beyond. Semin Thromb Hemost. 2021;47(7):759–74.
15. Ota S, Wada H, Abe Y, Yamada E, Sakaguchi A, Nishioka J, et al. Elevated levels of prothrombin fragment 1 + 2 indicate high risk of thrombosis. Clin Appl Thromb Hemost. 2008;14(3):279–85.
16. Lundbech M, Krag AE, Christensen TD, Hvas AM. Thrombin generation, thrombin-antithrombin complex, and prothrombin fragment F1+2 as biomarkers for hypercoagulability in cancer patients. Thromb Res. 2020;186:80–5.
17. Gyldenholm T, Hvas AM, Christensen TD, Larsen JB. Thrombin generation markers as predictors of cancer-associated venous thromboembolism: a systematic review. Semin Thromb Hemost. 2023.
18. Marshall-Webb M, Bright T, Price T, Thompson SK, Watson DI. Venous thromboembolism in patients with esophageal or gastric cancer undergoing neoadjuvant chemotherapy. Dis Esophagus. 2017;30(2):1–7.
19. Akl EA, Kahale L, Sperati F, Neumann I, Labedi N, Terrenato I, et al. Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer. Cochrane Database Syst Rev. 2014 (6):CD009447.
20. Song JQ, Xuan LZ, Wu W, Huang JF, Zhong M. Low molecular weight heparin once versus twice for thromboprophylaxis following esophagectomy: a randomised, double-blind and placebo-controlled trial. J Thorac Dis. 2015;7(7):1158–64.
21. Tanaka Y, Yamada A, Hirata S, Tanaka H, Sakuratani T, Matsuhashi N, et al. Efficacy and safety of enoxaparin for prophylaxis of postoperative venous thromboembolism after esophagectomy: a single-center prospective randomized controlled phase II study. Anticancer Res. 2019;39(5):2615–25.
22. Khorana AA, Francis CW, Kuderer NM, Carrier M, Ortel TL, Wun T, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. Thromb Res. 2017;151:89–95.
23. DanskLægemiddelInformation. Fragmin 2021. Available from: https://pro.medicin.dk/medicin/praeparater/1245.
24. Shargall Y, Litle VR. European perspectives in Thoracic Surgery, the ESTS venous thromboembolism (VTE) working group. J Thorac Dis. 2018;10(Suppl 8):S963–8.
25. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest. 2001;119(1 Suppl):64S-94S.
26. Lundbech M, Krag AE, Hvas AM. Prevalence of venous thromboembolism following head and neck cancer surgery: a systematic review and meta-analysis. Thromb Res. 2018;169:30–4.

27. World Health Organization. Definitions 2021. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf.
28. Lading T, Kjaer D, Bendixen M, Petersen TI, Christensen TD, Katballe N. Safe and efficient 2-step implementation of totally minimally invasive esophagectomy. J Thorac Dis. 2023;15(10):5362–70.
29. Oesophago-Gastric Anastomosis Study Group on behalf of the West Midlands Research Collaborative. Postoperative outcomes in oesophagectomy with trainee involvement. BJS Open. 2021;5(6).

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