Clinical Trial Protocol

paravertebral Block AnaLgesia vs. epidural: Assessing Novel Care in Esophagectomy- A multi-center randomized phase III trial

BALANCE trial

Trial ID:	BALANCE
Version number:	1.0
Date:	2026-01-27
Sponsor:	Uppsala University Hospital
Sponsor representative and Coordinating Investigator	Jakob Hedberg, Uppsala University Hospital, Sweden
National Investigators:	Michael Partick Achiam (Denmark) Tom Mala (Norway) Jakob Hedberg (Sweden) Joonas Kauppila (Finland) Bjarni Geir Vidarsson (Iceland) Maria Bencivenga and Simone Giacopuzzi (Italy)
International Coordinator:	Magnus Nilsson

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Revision history

Protocol version	Date of Issue	Summary of changes *Describe all changes since the first final protocol.*
Final protocol v1.0	2026-01-27	N/A

1 Signature page

Sponsor representative/Coordinating Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the trial. By signing my name below, I agree to conduct the trial in compliance with this clinical trial protocol, the Declaration of Helsinki, and the current national regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important trial-related information to the staff members and investigators who participate in this trial, so that they can conduct the trial correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this trial informed and trained.

I am aware that quality control of this trial will be performed in the form of monitoring and eventual audits.

Sponsor representative/Coordinating Investigator's signature Date

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Printed name

2 Contact information

Responsibility in the clinical trial	
Sponsor representative and Coordinating Investigator	Jakob Hedberg Uppsala University Hospital 75185 Uppsala +46703785973 Jakob.hedberg@uu.se
Principal National Investigators	Jakob Hedberg (Sweden) Tom Mala (Norway) Michael Achiam (Denmark) Bjarni Geir Vidarsson (Iceland) Peter Grimminger (Germany) Simone Giacopuzzi (Italy)
Organizations involved:	Uppsala University (Scientific lead) Region Uppsala (Clinical lead) Uppsala Clinical Research Center (Project management, monitoring (Sweden)) Statisticon (statistical support) Dynareg (IT systems for randomization, eCRF, and data storage)

3 List of used acronyms and abbreviations

CT	Computed tomography
DMSC	Data Monitoring and Safety Committee
DP	Diastolic blood pressure
EA	Epidural analgesia
eCRF	Electronic Case Report Form
LAST	Local Anesthetic Systemic Toxicity
MIE	minimally invasive esophagectomy
NRS	Numeric Rating Scale
SAE	Serious adverse event
SP	Systolic blood pressure

4 Synopsis

Title:	BALANCE - paravertebral Block AnaLgesia vs. epidural: Assessing Novel Care in Esophagectomy - BALANCE trial
Trial ID:	ISRCTN16853684
Short background/Rationale/Aim:	Cancer in the esophagus and gastroesophageal junction are devastating malignancies with a lethality of over 80 %. Surgical resection is the best chance for cure and this is a demanding thoracoabdominal procedure. Thoracic epidural analgesia (EA) is routine for optimization of pain control and improved mobilization and lung function. Recent studies show suboptimal success rate of pain management with EA. In addition, side effects such as increased use of vasopressor drugs, hypotension, and fluid retention may be detrimental to patients' outcomes, specifically regarding healing of a marginally circulated anastomosis. Increased use of minimally invasive techniques, with or without robot assistance, has also reduced the need for epidural analgesia. Paravertebral block and local/transabdominal plane block have good results in minimally invasive esophagectomy, but there is a paucity of randomized trials.
Primary objective:	To compare safety (superior-less anastomotic leak) of paravertebral block compared to the current routine of epidural analgesia in minimally invasive esophagectomy for malignant disease.
Secondary objectives:	To compare pain relief, complications, postoperative hypotension, surgical time and recovery duration, survival, and more between paravertebral and epidural analgesia in minimally invasive esophageal resection for cancer.
Primary endpoint:	Anastomotic leak assessed up to 30 days after surgery
Secondary endpoint:	Pain relief and patient-reported outcomes, day 1, 2, 3, 7 and 30. All other outcomes (see secondary objectives) defined on postoperative day 30 except survival, which will be followed for 5 years.
Trial design:	A Phase III, multicenter, open-label, randomized, controlled clinical trial comparing the paravertebral analgesia technique to standard epidural analgesia after resection for esophageal cancer.
Trial population:	Adult (≥18 years of age) patients undergoing minimally invasive esophagectomy with gastric conduit reconstruction due to confirmed cancer (cT1 N+ or cT2-4a any N; M0-1).

Number of subjects:	550
Inclusion criteria:	Adult (≥18 years of age) patients undergoing minimally invasive esophagectomy with gastric conduit reconstruction due to confirmed cancer (cT1 N+ or cT2-4a any N; M0-1).
Exclusion criteria:	- Epidural analgesia contraindicated, i.e., known uncontrollable hypersensitivity to the components of the chemotherapeutic agents used in the trial regimens - Use of anticoagulants precluding EDA use - No postoperative nasogastric tube - No ability to understand the study in terms of risk and benefits (including language difficulties) - The subject has any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that would, in the judgment of the investigator, pose excess risk associated with study participation or that, in the judgment of the investigator, would make the patient inappropriate for entry into the trial
Intervention:	Paravertebral analgesia with subpleural intercostal injection during the thoracoscopic phase of esophageal resection and patient-controlled analgesia with intravenous opioids.
Investigational medicinal product(s).	Not applicable
Ethical considerations, benefit/risk:	The risks are considered small because the intervention is a well-established method for postoperative pain treatment in thoracic surgery. If superiority regarding anastomotic leak can be shown, this would lead to great benefits for esophageal cancer patients worldwide. The main risk is inferior pain relief, but recent trials show similarity in this regard. Preoperative written and informed consent will be obtained from all patients.
Planned duration of the trial:	Q3 2026 – Q3 2033

5 Background and rationale

Esophageal cancer is one of the most prevalent cancers globally, with its incidence on the rise in the Western world, predominantly attributed to the increased occurrence of adenocarcinoma. The primary curative approach for esophageal cancer involves esophagectomy, which, when coupled with neoadjuvant therapy, can result in a five-year survival rate exceeding 50%(1). This is one of the most complication laden operations in gastrointestinal surgery and anastomotic leak, when the coupling of the gastric remnant to the esophagus fails to heal completely, entails significant morbidity and suffering for the patient. The consequences of an anastomotic leak still pose a formidable challenge to caregivers and any step to decrease the risk of this occurring, carries high value clinically and scientifically(2).

Esophagectomy has also been linked to significant postoperative thoracic pain, primarily due to intercostal incisions. This pain can lead to reduced mobility, pulmonary complications, and delayed recovery, underscoring the importance of effective postoperative pain management(3). Currently, thoracic epidural analgesia stands as the preferred method for managing pain in these cases and is an integral part of many enhanced recovery protocols, offering better outcomes in pain control and reduction of pulmonary complications compared to systemic opioids(4). However, epidural has also been linked with intra- and postoperative hypotension due to the splanchnic sympathetic blockade, which can reduce preload to the heart and the central blood volume. Treatment of hypotension caused by epidural analgesia may include use of vasopressors or fluid resuscitation(5), which again have been speculated to cause postoperative complications, including anastomotic leak(6).

The advent and introduction of minimally invasive esophagectomy (MIE) techniques, which are associated with less postoperative pain compared to open surgery, alongside the implementation of enhanced recovery protocols aimed at expediting mobilization and recovery post-MIE, challenges the traditional reliance on epidural analgesia. This is due to the abovementioned potential adverse effects along with others such as failed catheter placement, and reduced mobility, which could hinder the goals of enhanced recovery protocols.

Past systematic reviews on postoperative pain management focusing on patients undergoing various thoracotomy or thoracoscopy procedures, predominantly lung surgeries, have indicated that paravertebral analgesia might offer comparable pain relief to epidural analgesia but with fewer side effects such as hypotension, urinary retention, and nausea(7). However, transthoracic esophagectomy involves both an abdominal and thoracic phase, which means these findings might not fully apply to esophagectomy patients. Preliminary systematic reviews exploring paravertebral analgesia in esophagectomy patients suggest it offers similar pain control and potentially fewer hypotensive events than epidural analgesia. Nevertheless, these reviews also point out the current gap in high-quality prospective research specifically focusing on MIE patients, highlighting an area in need of further investigation(8). A recent trial comparing epidural analgesia to paravertebral block shows comparable pain relief but more anastomotic leaks in the epidural group(9). However, the trial was not powered for this outcome and the difference was not significant. We therefore aim to launch a trial with superiority design regarding anastomotic leak.

5.1 Benefit-risk evaluation

Both treatment methods are in clinical use today and have been scientifically and clinically evaluated and deemed safe (8-11). The participation in this trial will therefore not go outside clinical routine in reference to medical treatment.

Even if the investigational procedure in this trial, i.e., no epidural analgesia and paravertebral block, has been demonstrated feasible and safe, there are possible disadvantages and complications, such as suboptimal pain-control and paracostal bleedings, but the standard procedure (epidural analgesia) is not free from side-effects and we consider no additional risk to be added in the interventional arm of this trial. There is ample experience in management of all the potential complications in the interventional arm (paravertebral block) and in the control arm (epidural analgesia). All patients will be followed closely regarding all outcomes, including complications.

There will be some additional questionnaires to assess pain relief and patient-reported postoperative recovery (QoR15, see Appendix 2), but the added discomfort of this is deemed to be minimal.

In addition, an independent data safety and monitoring board will perform evaluations after 100 and 250 patients are included.

The results of the BALANCE trial are expected to provide medical staff with evidence-based guidance to optimize care during esophagectomy. Given that enrolled patients will receive treatments that are currently used in clinical practice and considered safe, the Sponsor concludes that the potential benefits of the trial outweigh any associated risks.

6 Trial objectives

6.1 Primary objectives

To compare safety (superior-less anastomotic leak) of paravertebral block compared to the current routine of epidural analgesia in minimally invasive esophagectomy for malignant disease.

6.2 Secondary objectives

The secondary objectives of the trial are to compare the difference, if any, between paravertebral block analgesia and epidural analgesia in:

1. Postoperative pain
2. Patient-reported quality of postoperative recovery
3. Risk of overall and procedure-specific complications
4. Prevalence of hypotension
5. Time to unassisted ambulatory mobilization
6. Time in operating theatre
7. Duration of surgery
8. Fluid retention
9. Length of hospital stay
10. Time in high-dependency unit
11. Overall survival

6.3 Primary endpoint

Anastomotic leak will be recorded at postoperative day 30 when completing the electronic Case Report Form (eCRF). Any subclinical leaks will also be recorded (mandatory CT peroral contrast day 7).

6.4 Secondary endpoints

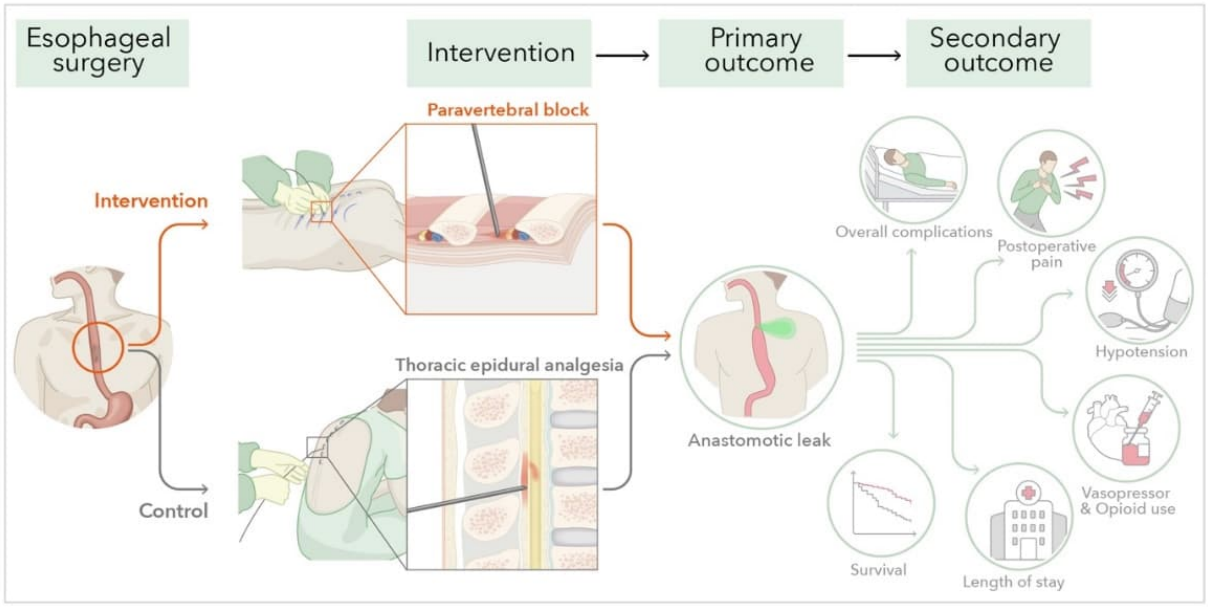
The secondary endpoints of this trial are:

1. Investigation of acute postoperative pain evaluated with NRS at baseline and on day 1, 2, 3, 7 and 30 after surgery (Appendix 1); and total postoperative opioid use (enteral and parenteral), recorded at postoperative day 30.Patient-reported outcomes evaluated with QoR15(12) on day 1, 2, 3, 7 and 30 after surgery (Appendix 2).
2. Risk of overall and procedure-specific complications recorded at postoperative day 30:
    - Overall complications according to Clavien-Dindo (13)
    - Rescue (intervention group)/re-insertion (control group) of EDA (Y/N)
    - Pneumonia
3. Assessment of blood pressure up to postoperative day 5
4. Time to first day of unassisted movement
5. Total operation time
6. Total time used in operation theater
7. Patient weight assessed on baseline, day 1, 2, 3 and 7
8. Postoperative number of days in hospital
9. Postoperative number of days in high-dependency unit
10. Time from surgery to all-cause death

7 Trial design and procedures

7.1 Overall trial design

The BALANCE trial is an open-label, randomized, controlled, phase III, multicenter trial evaluating the paravertebral block technique with local anesthesia combined with patient-controlled analgesia with opioids, compared to the standard technique of thoracic epidural analgesia (local regime if within boundaries of the trial):



7.2 Procedures and flowchart

Procedure	*Screening* *Preoperative inclusion visit*	*Operation* *Baseline information and randomization*	*Postoperative day 1, 2, 3 and 7*	*Postop Day 30 (28-35)* [g]	*3 and 5 years postop*
Incl/exclusion criteria	√				
Informed consent	√				
Medical history/ concomitant medications	√	√			
Randomization [a]	√	√			
Anastomotic leak			Day 7 [b]	√ [c]	
Pain score [d]	√		√	√	
Patient reported outcome [e]			√	√	
Weight	√		√	√	
Registration of all secondary endpoints [f]				√	
Registration of start of epidural and cumulative hours with vasopressor use				√	
Survival data					√

[a] Patients are randomized no later than 12h before surgery
[b] One CT scan to be performed on postoperative day 7
[c] All diagnosed anastomotic leaks will be recorded in the eCRF
[d] Measured using NRS
[e] Reported with QoR15
[f] Recorded secondary endpoints include: postoperative opioid use, overall complications according to Clavien-Dindo, rescue or reinsertion of EDA, pneumonia, hypotension, first day of unassisted movement, total operation time, total time in operating theater, days in hospital, and days in high-dependency unit
[g] Data completion of eCRF is ideally obtained at day 30, but a one-week variance is accepted (day of data completion is noted in the eCRF)

7.3 Start, end, temporary halt, and early termination

7.3.1 Start of the clinical trial

The start of the trial is defined as the first act of recruitment of a potential subject.

7.3.2 Temporary halt or early termination

The trial may be prematurely terminated for safety reasons affecting the risk-benefit balance or if the recruitment of subjects cannot be completed within reasonable time. Decisions on premature termination are taken by the sponsor.

If the trial is prematurely terminated or suspended, the investigator should immediately inform the subjects and ensure appropriate treatment and follow-up.

7.3.3 End of the clinical trial

The trial ends when the last subject has completed the last follow-up, died or withdrawn consent, or is lost to follow-up. The estimated time for last follow-up (survival) is Q3 2033.

8 Subject selection

8.1 Inclusion criteria

To be included in the trial, subjects must meet all of the following criteria:

- ≥ 18 years of age
- Planned thoracoabdominal total minimally invasive resection for histopathologically confirmed esophageal or GEJ cancer in locally advanced stages (cT1a N+ or cT1b-4a any N; M0-1)
- Performance status ECOG 0-1
- Signed informed consent

8.2 Exclusion criteria

Subjects must not be included in this trial if any of the following criteria are met:

- Epidural analgesia contraindicated, i.e., known uncontrollable hypersensitivity to the components of the chemotherapeutic agents used in the trial regimens or anatomical factors precluding epidural catheter placement
- Use of anticoagulants precluding EDA use
- No planned postoperative use of nasogastric tube
- No ability to understand the study in terms of risk and benefits (including language difficulties)
- The subject has any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that would, in the judgment of the investigator, pose excess risk associated with study participation or that, in the judgment of the investigator, would make the patient inappropriate for entry into the trial.

8.3 Screening

Subject eligibility (that subjects fulfil all inclusion criteria and do not meet any exclusion criteria) is established before participation in the study. This screening will take place when surgery is planned and no later than the day before surgery.

Documented informed consent must be provided before performing any protocol-specific procedure.

8.4 Withdrawal criteria

Subjects can discontinue their participation in the trial at any time without any consequence to his/her continued treatment. The investigator/sponsor can at any time terminate the trial for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the clinical trial protocol. If the subject discontinues the trial, follow-up of this subject will be performed according to the clinical routine of the study site in question.

Specific reasons for discontinuing a subject for further assessments include:

- Withdrawal of informed consent.
- Not fulfilling the inclusion/exclusion criteria as stated above (incorrectly included).
- No resection performed (reason specified)
- Operation was converted to open surgery
- If the investigator considers it not to be in the subject´s best interest to continue participation in the study (e.g. due to non-tolerable adverse reactions or serious adverse events (SAEs) during surgery).
- If there is a significant protocol deviation.

A discontinued subject should be asked to come to the clinic for a final assessment, if possible. The reason for subject discontinuation will be documented in the eCRF. The sponsor has the right to keep and use all data that has been collected up until the time that the subject discontinues study participation. A study subject who has been randomized and who is withdrawn from the study will not be replaced.

9 Trial treatments

9.1 Randomization and blinding

Subjects are enrolled and randomized consecutively as they are found to be eligible for inclusion in the trial. Randomization is performed no later than 12h before surgery. If a subject discontinues participation, the subject's trial-specific code will not be reused, and the subject will not be allowed to re-enter the trial.

Randomization will be performed online from within an electronic randomization system, after a multidisciplinary tumor board meeting, once all eligibility criteria have been verified and no exclusion criteria have been fulfilled. Randomization will be stratified by country and level of anastomosis (chest/neck). The electronic randomization module is accessed from each participating site. Treatment

allocation will be open-label, among the two intervention arms at a 1:1 ratio of paravertebral block and opioid PCA (intervention) or standard EDA treatment (control).

All randomized trial subjects will be recorded on the Participant Identification Code List, which includes the participant's name and personal identification number, date of informed consent and randomization date. It is the responsibility of the Investigator to keep the list updated throughout the trial and store it in a secure location to prevent unauthorized access.

No blinding will be used during treatment. Statisticians will be blinded at time of analysis after data-lock.

9.2 Preoperative analgesics (all)

Local routines regarding pain management are followed. We recommend that all patients will receive paracetamol (acetaminophen) 1000 mg. In addition, a non-steroidal anti-inflammatory drug (NSAID) will be given according to in-house protocol unless contraindications exist. We also recommend that Dexamethasone is given intravenously (8 mg) at the time of blockade.

9.3 Intervention

Subjects who are randomized to intervention will receive a paravertebral block at the end of the thoracic phase of surgery. Local anesthetics injected under thoracoscopic vision in 1-4 sites in the intercostal space 3-8 according to local routines. As always, attention to not inject in vessels (aspiration) is crucial. Abdominal port sites are also injected according to local routines. Permitted drugs and combinations are:

- Monotherapy, preferably bupivacain 2,5mg/ml (total volume 40-60ml). Alternatively, ropivacain 3,75mg/ml (total volume 40-60ml) can be used.
- Dexamethasone or betamethasone iv 8 mg
- Klonidin 75-150 µg iv (optional per center but same in both arms)

In addition, patient-controlled analgesia with opioids according to local protocols is used in this arm.

9.3.1 Training and quality control

All participating centers have good knowledge of the control arm EDA. For the intervention, an instructional film is provided, and at least 5 cases of experience with this method is recommended before start of randomization.

Link to instruction film:

https://www.dropbox.com/scl/fi/zlggsfpe7vzftn2p9t6u6/Paravertebral-single-shot-analgesia-BALANCE-trial.mp4?rlkey=3hyhx4euyj7x1vp25xgjkjw9d&e=1&dl=0

9.4 Control

Subjects who are randomized to control will receive routine EDA according to local routines at level Th6-10. After correct placement of the epidural catheter, a local anesthetic (ropivacaine, levobupivacaine, or bupivacaine) is used and according to in-house protocols, an opioid will be added to the epidural solution.

9.5 Escape medication

Patients will be offered patient-controlled analgesia with opioids if EDA pain control is insufficient. Escape (intervention group) or re-insertion (control group) of EDA can also be offered and should be recorded in the eCRF. All opioids given will be recorded.

9.6 Investigational product

Not applicable.

9.7 Non-investigational product

Not applicable.

10 Methods for measurement of endpoints for clinical efficacy and safety

Baseline data will be collected in an electronic randomization module where clinical information and stratification variables will be entered by the site investigator no later than the day before surgery. An eCRF will be filled out for all outcomes at the first postoperative visit, 30 days postop. All study data will be transferred from the eCRF to the study database. Additional outcome data (survival) will be accrued at 3 and 5 years and added to the study database.

10.1 Methods for measurement

10.1.1 Primary endpoint

The primary endpoint of anastomotic leak will be assessed according to local routines. A CT with contrast swallow is performed on postoperative day 7. If this CT is not performed (prior CT performed on clinical suspicion or other reason), this is specified. When the eCRF is filled out, all anastomotic leaks up to 30 days will be recorded, including day of onset. The questions regarding the primary outcome will be:

- Anastomotic leak (yes/no)
- Anastomotic leak type (grade I-III according to Low et al.(14))
- Day of a diagnosed anastomotic leak (1-30/NA)

10.1.2 Secondary endpoints

- Postoperative pain will be evaluated at baseline, and on day 1, 2, 3, 7, and 30 with NRS (0-10) Appendix 1.
- Total postoperative opioid use (enteral and parenteral) in milligrams.
- Patient-reported quality of postoperative recovery will be measured on day 1, 2, 3, 7, and 30 with QoR15(12), Appendix 2.
- Overall complications will be registered in the eCRF at day 30:
  - Complication according to Clavien-Dindo (1-5)
  - Definition of highest graded complication (free text)
- Procedure-specific complications, epidural or paravertebral analgesia including inadequate sensory block, rescue (intervention group)/re-insertion (control group) of EDA (Y/N)
- Pneumonia, according to Seesing et al. (15)
- Blood pressure measured continuously for the first 12 hours and at least three times per day for the following five days.
- Intervention for hypotension (vasoactive drugs/fluids).
- POD of unassisted ambulation > 10 meters
- Total operation time (time from first incision to last suture in minutes)
- Total time used in operating theater (minutes)
- Patient weight is assessed at baseline, and on POD 1, 2, 3 and 7
- Length of hospital stay (days)
- Length of stay in high-dependency unit (days)
- Overall survival will be reported by the investigators during the course of the study

10.1.3 Additional recordings

- Cumulative dose and hours of Norepinephrine or other vasopressor infusion.
- Start of epidural (control group only) early/late

11 Handling of Adverse Events

All complications and other outcomes will be recorded in the eCRF as described above. No new treatments or drugs are investigated in this trial and thus no adverse event recording or evaluation outside the DSMC evaluations are planned.

Local Anesthetic Systemic Toxicity, LAST

LAST is a very rare condition in which systemic effects from local anesthetics (both epidural and other peripheral use) can cause CNS and cardiac toxicity. It is caused by supratherapeutic plasma concentrations, often caused by an inadvertent intravascular injection. This occurs in less than 1/1000 patients and a recent study observed no cases of LAST in over 9000 peripheral nerve blocks. With the doses used in clinical practice and correct injection technique under direct thoracoscopic vision, risks are very low and treatment, including lipid emulsion injection, is known in all participating centers.

12 Independent Data Monitoring and Safety Committee

The Data Monitoring and Safety Committee (DMSC) will be presented with a complete list of complications and other outcomes from each of the two trial arms after 100 and 250 patients have been included in the trial. The DMSC will then at these points in time make an evaluation of patient safety in the trial. The DMSC will, after their assessment, present a brief report to the trial steering committee and, if serious safety issues are detected, actions will be taken to address these. Ultimately, if such serious safety issues cannot be addressed in any other effective way, the trial may be stopped.

13 Statistics

13.1 Sample size calculation

In a recent Dutch trial, anastomotic leak was present in 13.8 % of the patients with epidural analgesia and 6.1% in those without(9). Recent data from the Nordic countries show a leak rate of 15.2%(2). We therefore base the sample size calculation on the aim of finding a reduction from 15% to 7.5% leak in the intervention group.

With a power (1-β) of 80% and a significance (α) of 5%, this would require 275 patients in each group or 550 patients in total.

With some expected drop-outs (e.g., no resection performed due to more advanced disease than anticipated), we expect a total of 600 patients to be randomized.

13.2 Prespecified subgroup analyses

Predefined subgroups to be analyzed include gender (male/female), neck anastomosis (y/n), age >75 (y/n), pyloric drainage procedure (y/n) and ASA (<3/>2).

13.3 Statistical analyses

Baseline characteristics will be described by randomized treatment and in total. Categorical data will be described as total number and percentage, with missing data as a separate category. Numerical data will be described using number of patients with data, and median, quartiles, arithmetic mean and standard deviation for patients with data.

"Statistical testing" comparing the randomized treatment groups will be performed using chi- square tests for categorical variables and Wilcoxon's test for numerical data, using observed cases. The result will be presented as p-values and used only if needed to satisfy a non-CONSORT journal house style that requires Table 1 p-values. Since the groups are randomized, all perceived differences will be due to chance.

Analysis populations:

- Randomized with surgery: Randomized patients who have undergone the complete resection. In this group, analyses will be performed for.

- Intention to treat (ITT) population(16), according to randomization and
- Per protocol/safety population where patients treated with EDA are compared to those not treated with EDA

All outcomes will be analyzed using the intention to treat (ITT) principle where patients randomized to a certain group and undergone surgery will be followed irrespective of the actual treatment, offering unbiased assessments of treatment efficacy. The primary outcome anastomotic leak will also be analyzed with a logistic regression model adjusted for sex, age (as a linear covariate on the log-odds scale) and level of anastomosis (chest or neck).

Secondary dichotomous outcomes will be analyzed using the same method as the primary outcome.

Secondary continuous endpoints will be analyzed using ANCOVA models, adjusted using the same covariates as the primary endpoint.

Subgroup analyses will be performed by introducing (or substitute if term already included) a treatment- subgroup interaction term in the logit model, excluding any patients not possible to classify.

Estimates of treatment differences will be presented with odds ratios, or estimated mean differences, as appropriate, with two-tailed 95% confidence intervals and associated p-values. A two- tailed P-value of <.05 is considered statistically significant. Secondary outcomes will be analyzed without adjustment for multiplicity.

Safety endpoints will be presented using descriptive statistics without any formal comparisons between treatment groups based on the Safety population.

14 Data management

14.1 Recording of data

Baseline and surgical data will be collected in a study database as pseudonymized data. An eCRF will be used for all mandatory primary and secondary outcomes except survival. All study data will be transferred from the eCRF to the study database. An additional survival sweep will be performed at 3 and 5 years from the local study databases and added to the main study database. Written consent will be stored at each study site and the local study staff is responsible for source documents being accessible for monitoring.

14.2 Data storage and management

All data will be recorded, handled, and stored in accordance with Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR), in a way that allows its accurate reporting, interpretation, and verification. All source data, including a copy of the completed study database and the original protocols with amendments will be stored at the Department of Surgical Sciences at Uppsala University Hospital in accordance with Sponsor regulations.

When inclusion is complete, any deviations from the protocol will be recorded. When the study database has been declared complete and accurate, it will be locked and available for analysis.

14.3 Direct access to source data/documents

The Investigators will permit trial-related monitoring and audits, providing access to source data. The Sponsor verifies that each subject has consented in writing to direct access to the original source data by the use of written subject information and signed Informed Consent.

During the monitoring, the data recorded in the eCRFs by the Investigator will be controlled for consistency with the source data/hospital records by the independent trial monitor (source data verification). Any discrepancies in data will be documented and explained in the monitoring reports.

14.4 Quality control and quality assurance

The principal investigator will arrange bi-annual trial meetings in conjunction with the Scandinavian esophagogastric cancer (SEGCG) meetings. This will ensure that the local investigators are adequately informed about the protocol and that data input and storage are according to protocol.

14.5 Source data

The following minimum amount of information should be recorded in the hospital records:

- Trial ID
- Subject identification.
- Date when subject information was given and when signed Informed Consent was obtained.
- Diagnosis.
- Fulfillment of inclusion criteria.
- Specification of visit dates, concomitant medication
- Specification of the subject's cessation in the trial (e.g., completer or premature withdrawal).
- Specification of the subject's outcome in the trial.

15 Monitoring

Monitoring of the trial will be arranged by the Sponsor. During the trial, the Monitor will have regular contacts with the trial sites, including visits to ensure that the trial is conducted and documented properly in compliance with the protocol and applicable regulatory requirements.

The Monitor will review source documents for verification of consistency with the data recorded in the eCRFs. The Monitor will also provide information and support to the Investigators.

The Investigator should provide a curriculum vitae (CV) or equivalent documentation of suitability to be responsible for the trial. All Investigators and other responsible personnel should be listed together with their function in the trial on the signature list.

15.1 Audits

Authorized members of the study group can perform audits at the sites included in the study. The purpose of these audits is to ensure adherence to the study protocol. The local representative is responsible for secure storage of the original consent forms.

16 Ethics

16.1 Ethical conduct of the trial

The trial will be conducted in accordance with the protocol, applicable regulatory requirements, and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions.

16.2 Ethical review of the trial

The final version of the trial protocol and subject information must be approved by the Ethical Review Authority of the countries involved in the trial, before the trial can start. The Ethical authorities will also be informed of any changes in the trial protocol or subject information in accordance with current requirements.

16.3 Subject information and informed consent

It is the responsibility of the Investigator to provide each subject with full and adequate verbal and written information about the objectives, procedures, and possible risks and benefits of the trial. All subjects will be given the opportunity to ask questions about the trial and will be given sufficient time to decide whether or not to participate in the trial. The written subject information must not be changed without prior discussion with the Sponsor.

The subjects will be notified of their voluntary participation and of their freedom to withdraw from the trial at any time and without giving any particular reason. Subjects must also be informed that withdrawing from the trial will not affect their future medical care, treatment or benefits to which the subject is otherwise entitled.

The Investigator is responsible for obtaining written Informed Consent from all subjects prior to enrolment in the trial.

The subjects will consent to:

- Participating in the trial.
- Sponsor representatives gaining full access to hospital records, to verify the accuracy of the data collected in the trial.
- Recording, collecting, and processing of data and storing of data in a database.

It should be clearly stated that the data will not identify any subject taking part in the trial, in accordance with the Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR).

A copy of the subject information and the Informed Consent form will be given to the subject. The Investigator (or the designated representative) who gave the verbal and written information to the subject will sign the Informed Consent form. The Investigator will file the signed Informed Consent forms in the Investigator's File for possible future audits and inspections.

17 Insurance

All subjects are insured according to national regulations, either by national patient and pharmaceutical insurance or local insurance at the participating center. Subjects enrolled in Sweden are insured through the Swedish Patient Insurance (Landstingens Ömsesidiga Försäkringsbolag).

18 Notification of trial completion, reporting, and publication

After completion of the trial, the statistical analyses will be performed by the Sponsor, and the results will be presented to the Investigators. The results will form the basis for a manuscript intended for publication in a scientific peer-reviewed journal.

19 Signed Agreement of the Trial Protocol

Principal Investigator

I, the undersigned, have read and understand the protocol specified above and agree on the contents. The trial protocol and the Clinical Trial Agreement will serve as a basis for co-operation in this trial.

I agree to conduct the trial according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and the applicable national laws and regulations.

Principal Investigator's signature Date

Printed name and title

Study site and address

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Appendix 1

Numeric Rating Scale (NRS)

Associate a number from **0** (no pain) to **10** (maximum imaginable pain): **...../10**

Appendix 2

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time