STUDY PROTOCOL

Clinical Trial Of Safety Of Robot-assisted Thoracic Approach Versus Open Transthoracic Esophagectomy in Esophageal Cancer (CIR·ROB trial)

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Abstract

Background: Radical esophago-lymphadenectomy is crucial to improve overall survival in patients with esophageal cancer. However, esophagectomy is a highly complex surgical technique. Prior to the 1980s, mortality of this intervention was considerably high, reaching 50% in some series. The establishment of multidisciplinary management has been key to achieve a decrease in mortality up to 5% at reference centres and an increase in survival. Still, quality of life and potential complications of this intervention have a major impact with a described morbidity between 30-60% in the literature.

Objective: This study aims to assess the effectiveness of robot-assisted thoracoscopy versus thoracotomy in Ivor Lewis-type esophagectomy for the surgical treatment of resectable esophageal cancer. The main purpose is to demonstrate the superiority of robot-assisted thoracic approach over thoracotomy (conventional surgery) in decreasing respiratory and overall complications in Ivor Lewis-type esophagectomy.

Methods/design: This is an investigator-initiated and investigator-driven monocentre randomized controlled parallel-group, superiority trial. All adult patients (age ≥18 years) with histologically proven, surgically resectable (cT1-4a, N0-3, M0) esophageal or esophageal-gastric junction (EGJ) Siewert I or II cancer, will be assessed for eligibility and included after obtaining informed consent. Patients (n = 108) will be randomized to either Robot-assisted or open thoracic approach esophageal resection. The primary outcome of this study is the percentage of respiratory complications (grade 2 and higher) as stated by the modified Clavien–Dindo classification of surgical complications.

Discussion: Postoperative morbidity, especially respiratory complications, occur in approximately half of patients after open esophagectomy from esophageal cancer. Although previous clinical trials have reported advantages of minimally invasive (laparoscopic and robotic) esophagectomy on open esophagectomy, currently most esophageal surgery is performed through open approach. Therefore, more studies are needed to clarify the role of esophagectomy in minimally invasive surgical treatment in esophageal cancer, especially in the field of robotics.

Conclusion: If our hypothesis is proved correct, robot-assisted thoracic approach will result in a lower percentage of respiratory and overall postoperative complications, lower blood loss, shorter hospital length of stay, but with at least similar oncologic outcomes and better postoperative quality of life compared with the open transthoracic esophagectomy (current standard). We hope that the results of our study will provide clinical evidence to support minimally invasive robotic approach in the treatment of this pathology.

Trial status: Recruitment of patients started in November 2020.

Key words and abbreviations

CGP - Clinical Good Practice

CONSORT - Consolidated Standards of Reporting Trials

CREC - Clinical Research Ethics Committee

GEJ – Gastroesophageal junction tumour

e-CDB - electronic collection database

EORTC - European Organisation for Research and Treatment for Cancer

HRQL - Health Related Quality of Life

IC - Informed consent

ICH - International Conference on Harmonisation

ITT - Intention to treat

MI - minimally invasive approach

MIRO trial - OesophagectoMIe pour cancer paR voie conventionnelle ou coeliO-assistée

RAILE trial - Robot-assisted Ivor-Lewis esophagectomy

ROBOT trial - Thoracolaparoscopic Esophagectomy versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer

ROMIO trial - Randomised Oesphagectomy: Minimally Invasive or Open

TIME trial - Traditional Invasive versus Minimally Invasive Esophagectomy Robot-assisted Minimally Invasive

TNM – Tumour, Node, Metastasis

Background

Esophagectomy and postoperative complications

Esophageal cancer represents the fifth most common tumour of cancers of the digestive system in Spain, between the ten most common cancers and the sixth leading cause of cancer death in the world. Among the standard modalities for treatment with curative intention, surgery is available, in combination with neoadjuvant (pre-surgery) and/or adjuvant (post-surgery) chemotherapy and radiation therapy. Esophageal surgery is crucial to improve overall survival in patients with esophageal cancer.

Esophagectomy is a highly complex surgical technique. Prior to the 1980s, mortality of this intervention was considerably high, reaching 50% in some series [1]. In recent decades, great surgical, cancer and economic efforts have been invested to achieve a remarkable advance in morbidity-mortality results in this pathology. The establishment of multidisciplinary management, a correct selection of patients for surgery, an attentive choice surgical technique, improvement in perioperative care, as well as in the treatment of neo and adjuvant chemoradiotherapy have been key to achieve a decrease in mortality up to 5% at the reference centre [2] and an increase in survival. Still, quality of life and potential complications of this intervention have a major impact physically and in their social function, with a described morbidity between 30-60% in the literature [3, 4, 5].

Surgical treatment is based on esophageal resection and reconstruction of digestive tract using the stomach (gastroplasty) or colon (coloplasty), as well as in the correct lymphadenectomy. Surgical approach is done through 2-3 fields [6, 7]:

- Transhiatal esophagectomy: performed by a left cervical incision and an abdominal approach. Esophageal-gastric anastomosis is performed at the left cervical field. Gastric stump is ascended through anterior mediastinum.
- Ivor Lewis-type esophagectomy: performed by an abdominal and right posterolateral thoracic incision. Esophageal-gastric anastomosis is performed at the right intrathoracic level.
- McKeown-type esophagectomy: firstly, it requires a thoracic approach for esophageal dissection. Secondly, an abdominal approach to perform the gastroplasty. Finally, a cervical incision for the realization of esophageal-gastric anastomosis. The gastric stump is ascended through posterior mediastinum.

The most common complications associated with Ivor Lewis-type esophagectomy are pleuropulmonary (respiratory), related, in part, to transthoracic approach. Atelectasis represents 85% postoperative lung complications [2]. They are usually due to airway obstruction in the face of inability to cough and mobilize bronchial secretions (usually from secondary reduced diaphragmatic mobility) leading to hypoventilation due to inadequate pain management. Other causes include: bronchospasm, oedema, air compression or poorly drained pleural collections, inadequate respiratory physiotherapy, humidification of administered oxygen, or dehydration. They are at high risk infection and can progress to pneumonia [8]. Pleural effusion is the second complication in frequency. The production mechanism takes place as a result of an imbalance between the production and reabsorption of pleural fluid, for instance, during intravenous volume overload [9]. Malnutrition causes the decline of oncotic pressure from hypoproteinaemia (hypoalbuminemia) and promotes pleural effusion, as well as increased permeability in pleural microcirculation and alterations in lymphatic drainage. It is generally sterile and can be uni or bilateral. Although most are resolved without treatment, up to 17% of patients require chest drainage. Its persistence or postoperative reappearance beyond the fourth day should alert us to some other complications, such as anastomosis dehiscence, unadvertised thoracic duct injury, or pleural haemorrhage [8]. Other pleuropulmonary complications (less

common) are: empyema, pneumothorax, chemical pneumonitis, nosocomial pneumonia or adult respiratory distress syndrome (ARDS) [2].

Patients with advanced age, smokers and with altered preoperative respiratory tests are more exposed to such complications. Other well-known risk factors include polytransfusions and alterations in swallowing secondary to the cervicotomy that can trigger bronchoaspiration [2]. With a lower incidence (between 2-20% according to the series [10, 11]), although feared by their morbidity-mortality we find esophageal-gastric anastomosis dehiscence and tracheo-esophageal fistula. Mortality from intrathoracic sepsis was around 64% [1]. Retrospective studies describe 36% mortality in patients with anastomotic dehiscence [2].

As for anastomotic dehiscence treatment, it is complex, requiring a multidisciplinary management. In cases where no signs of sepsis are shown, treatment is conservative with broad-spectrum intravenous antibiotic therapy, parenteral nutrition and proper drainage of dehiscence through thoracic drains, either those placed intraoperatively or percutaneous drains placed after surgery. Generally, overall response is satisfactory. However, in a long-term period, it can condition an anastomosis stenosis that would force endoscopic dilation sessions or even surgical reintervention. In the presence of signs of sepsis management is always surgical with primary repair or, more often, with stump removal and esophageal disconnection [2].

Thus, postoperative complications have a great impact on the patient, even affecting oncologic results. Moreover, postoperative complications may prevent the adjuvant treatment required for the patient. Consequently, they involve a greater hospital stay, either on the hospitalization or in the Intensive Care Unit (ICU). It is, therefore, an increase in health costs.

Minimally invasive surgery (MI)

Minimally invasive surgery has been introduced with the theoretical advantages of causing less damage to tissues dissection and providing faster postoperative recovery. Following the same premise, the use of minimally invasive techniques for esophageal resection offers some potential advantages over conventional open esophagectomy. Some authors have shown a faster recovery, decreased blood loss, decreased postoperative morbidity, a short hospital stay, with comparable oncological outcomes [12].

Luketich et al. published that short-term cancer results obtained with fully minimally invasive surgery were similar in those reported in the open surgery series. *Blencowe et al*. conducted a review studies that described short-term clinical results after esophagectomy laparoscopically assisted, using minimally invasive techniques for abdominal or chest approach [13]. On the other hand, *Smithers et al.* [14], in a cohort study, compared the results of the open esophagectomy (n=114) with combined esophagectomy (minimally invasive and open approach) (n=309) and with a totally minimally invasive approach (n=23). They found no statistically significant differences in terms of survival at 3 and 5 years. So far, few are the studies that have evaluated quality of life following minimally invasive esophagectomy. *Parameswaran* [15] used HRQoL (Health-related Quality of Life) and demonstrated rapid recovery in minimally invasive surgery. However, it is a study with a small sample size and does not have a comparative group.

Retrospective reviews have shown that MI esophagectomy does not compromise oncologic results and is safe compared to traditional open esophagectomy for esophageal cancer [16]. In addition, the Ivor Lewis approach, when done through a minimally invasive approach, has the potential to substantially reduce respiratory complications, a significant morbidity associated with conventional approach. [17,18].

Minimally invasive robotic surgery

Robotic surgery has expanded the capabilities of performing complex operations using a minimally invasive technique. The application of robotic technology to esophagectomy has shown to have some advantages

over minimally invasive conventional techniques, such as an increased precision in dissection due to a better visualization through a three-dimensional camera and a better manoeuvrability through the articulation of the instruments [19]. The use of robotic approach for esophagectomy is demonstrating equivalent cancer results compared to open techniques, but providing a reduction in postoperative morbidity [20]. It has even shown R0 resection rate and number of dried nodes higher than minimally invasive and open boarding [21].

Apart from observational studies and systematic reviews, randomized controlled trials completed in the Netherlands, the United Kingdom and France have reported promising results for the minimally invasive esophagectomy.

Literature review: Clinical Trials That Have Evaluated Minimally Invasive Surgery in Esophagectomy For Esophageal Cancer

MIRO trial (France) [22]

This is a trial involving patients with esophageal cancer, excluding patients with types II and III tumours involving the gastroesophageal junction. It compared OO (abdomen and right chest) with LAO (minimal access for the abdomen and open right chest incision) (http://clinicaltrials.gov/show/NCT00937456). The primary end point was 30 day morbidity and the trial was powered to test the hypothesis that minimal access surgery leads to a reduced rate of complications (45% vs. 25%) at 30 days. Complications were measured as a composite outcome. MIRO completed recruitment of 207 patients in July 2015. There were 104 patients to the OO group and 103 to the LAO group. In an early (not peer-reviewed) report, sixty-seven (64.4%) patients in the OO group had major postoperative morbidity compared with 37 (35.9%) in the minimally invasive group (OR 0·31, 95% CI 0·18-0·55; p=0·0001). Thirty-one (30.1%) patients in the OO group had major pulmonary complications compared with 18 (17.7%) in LAO group p=0·037), whereas 30-day mortality was 5 (4.9%) vs. 5 (4.9%), respectively. The authors concluded that the findings provide evidence for the short-term benefits of minimally invasive surgery for patients with resectable oesophageal cancer. However, there were weaknesses in the study design: randomisation used sealed envelopes, outcome assessors were not blinded to the intervention type and methods to quality assure surgical procedures were not described in the protocol.

TIME trial (The Netherlands) [23]

This trial included patients with oesophageal cancer, excluding patients with type II and III tumours involving the gastro-oesophageal junction [18]. It compared OO with totally minimally invasive esophagectomy (MIO) (both abdomen and chest performed with minimal access approaches in the prone position). The trial was powered to test the hypothesis that totally minimally invasive surgery is associated with fewer pulmonary complications at two weeks after surgery than the standard open procedure. Pulmonary complications are strictly defined and graded. The criteria for surgeon involvement in this trial were evidence of prior completion of 10 minimally invasive procedures and production of one video showing surgical competence. This trial recruited 115 patients from seven surgical centres in four countries (Netherlands, Spain, India and Italy). The published results showed that totally MIO was associated with fewer pulmonary complications at two weeks post-surgery compared to the standard open procedure and provides evidence for efficacy of minimally invasive surgery. In addition, MIO resulted in a better mid-term 1-year quality of life for the physical component summary of the SF-36 questionnaire, EORTC C30 global health domain and OES 18 pain domain compared to OO. There were no differences in survival and late complications at 1 year between the groups. This trial therefore shows that minimal access surgery is safe in the short-term, but a large scale pragmatic trial designed to test patient benefit and cost-effectiveness is required to change UK practice. The trial included a comprehensive assessment of HRQL.

ROBOT trial (The Netherlands) [24]

Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer is a randomized, monocentric controlled clinical trial. This study was designed to compare the results of McKeown-type esophagectomy robot-assisted versus open McKeown-type esophagectomy for resealable esophageal cancer.

Out of a total of 112 patients with resectable intrathoracic esophageal cancer, they were randomly assigned to open esophagectomy or minimally invasive robotic surgery group (thoracolaparoscopic esophagectomy) (RAMIE). The main objective was to assess the occurrence of overall postoperative complications related to surgery, especially respiratory complications (according to Clavien-Dindo's classification of grades II to V). Overall postoperative complications related to surgery occurred less frequently after RAMIE (59%) compared to the open surgery group (80%) (p=0.02). RAMIE presented lower average blood loss (400 versus 568 ml, p<0.001), a lower percentage of respiratory complications (p= 0.005) and heart complications (p=0.006) and less pain (p<0.001) compared to open surgery. Functional recovery in the 14 postoperative daytime was better in the RAMIE group (p=0.038) with the highest quality of life score (difference in average quality of life score 13.4 (p= 0.02) and 6 weeks after (p=0.03)). Short- and long-term cancer results were comparable in a follow-up average of 40 months.

In this way, the study concludes that RAMIE appears to have a lower percentage of cardiopulmonary surgery-related complications, less postoperative pain, better short-term quality of life and better short-term postoperative functional recovery compared to conventional (open) surgery. Oncological outcomes were comparable, in line with current standards.

Ongoing clinical trials:

ROMIO trial (United Kingdom) [25]

The ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) study is a pilot clinical trial, parallel, controlled and randomized three-arm, whose goal is to compare the results of the total minimally invasive esophagectomy (EMI) versus hybrid EMI versus open conventional esophagectomy (open thoracotomy and laparotomy). The procedure used is the Ivor Lewis technique. Patients ≥18 years old are included with histopathological evidence of adenocarcinoma of the gastroesophageal junction, squamous cell carcinoma or high-grade dysplasia, referred to esophagectomy or esophagectomy after neoadjuvant chemo/radiation therapy. Patients are randomly assigned patients to (1) open esophagectomy (open gastric mobilization and right thoracotomy), (2) hybrid group (laparoscopic gastric mobilization and right thoracotomy) or the (3) totally minimally invasive surgery group.

RAILE trial [26]

Robot-assisted Ivor-Lewis esophagectomy (RAILE) is an ongoing, non-randomized clinical trial of one-arm (phase II) to be carried out to assess the short- and long-term results of the minimally invasive laparoscopic chest esophagectomy for esophageal cancer. The planned sample size is 51. The objective of this study is to investigate short- and long-term results to identify any clinical or cancer benefits of RAILE in esophageal cancer. Primary objectives determine short-term postoperative complications (30 days after surgery) and long-term overall survival (5 years after surgery). A secondary objective is to determine perioperative results (within 30 days after surgery).

Research Justification

Postoperative morbidity, especially respiratory complications, occur in approximately half of patients after open esophagectomy from esophageal cancer. If minimally invasive surgery is cost-effective and provides a benefit to the patients in terms of lower incidence of postoperative complications, less hospital stay, faster

incorporation into working life and greater short-term and long-term survival, should be investigated through randomized clinical trials properly designed. Although previously exposed clinical trials have reported advantages of minimally invasive (laparoscopic and robotic) esophagectomy on open esophagectomy, currently most esophageal surgery is performed through open approach. Therefore, more studies are needed to clarify the role of esophagectomy in minimally invasive surgical treatment in esophageal cancer, especially in the field of robotics. This study aims to conduct a monocentre clinical safety trial (phase IV), prospective, randomized, open, controlled parallel-group superiority trial to assess the effectiveness of robot-assisted thoracoscopy versus thoracotomy in Ivor-Lewis-type esophagectomy for the surgical treatment of resectable esophageal cancer. We hope that the results of our study will provide clinical evidence to support minimally invasive robotic approach in the treatment of this pathology.

Hypothesis

If our hypothesis is proved correct, robot-assisted thoracic approach will result in a lower percentage of respiratory and overall postoperative complications, lower blood loss, shorter hospital length of stay, but with at least similar oncologic outcomes and better postoperative quality of life compared with the open transthoracic esophagectomy (current standard).

Methods

Objectives

Main objective:

To estimate the incidence of respiratory complications in patients with esophageal cancer, GEJ cancer Siewert I or II undergoing Ivor Lewis-type esophagectomy through MI thoracic approach by robot or thoracotomy (classic approach).

It will be considered as a respiratory complication: atelectasis, pneumonia, persistent pleural effusion, empyema, haemothorax, pneumothorax, acute respiratory failure, adult respiratory distress syndrome (ARDS).

Secondary objectives:

Objectives of Safety:

• Estimate the incidence of short-term post-surgical complications: up to 28±3 days (1 month) of surgery.
• Estimate the incidence of post-surgical complications in the medium term: up to 84±3 days (3 months) of surgery.
• Estimate the incidence of anastomosis leak between the esophagus and the gastric stump.

Objectives of Efficiency:

• Estimate overall survival at 84±3 days (3 months) after discharge.
• Estimate the hospital length of stay: up to medical discharge.
• Estimate the need for transfusion.
• Evaluate the number of nodes removed in surgery (extension of lymphadenectomy as an oncological result).

Study design

This is a monocentre clinical trial of safety, phase IV, randomized, controlled two parallel-groups superiority trial.

This study aims to demonstrate the superiority of robot-assisted thoracic approach over thoracotomy (conventional surgery) in decreasing respiratory and overall complications in Ivor Lewis-type esophagectomy.

This trial will recruit patients diagnosed of esophageal or GEJ (Siewert I or II) cancer with indication of transthoracic Ivor Lewis-type esophagectomy, whose reference hospital is the Bellvitge University Hospital.

This centre has a team of five Esophago-gastric Surgeons, performing an average between 30 and 40 esophageal cancer resections per year. Esophagectomy techniques performed are 3: transhiatal, Ivor-Lewis (which the study focuses on) and McKeown. Abdominal MI (laparoscopic) approach is a common approach in interventions described above. As for the robotic approach, from 2010 to January 2020, there have been a total of 157 robot-assisted surgeries (Da Vinci Xi Surgical System), of which 32 McKeown technique were performed, and 125 interventions, by benign (non-neoplastic) pathology. Thus, the surgical technique described is used in our usual clinical practice of the General and Gastrointestinal Surgery Department of Bellvitge University Hospital.

Study population

All patients over the age of 18 in the Bellvitge University Hospital's area of influence with esophageal or esophageal-gastric junction (Siewert I or II) cancer diagnosis with the indication of Ivor Lewis-type esophagectomy that meet the inclusion criteria. All patients will be informed about the trial and invited to participate in the study. As for the surgical approach, patients will be randomly selected at each group:

- Group A (active comparator). Open transthoracic esophagectomy, with gastric laparoscopically conduit formation.
- Group B (study group). Robot-assisted thoracic approach esophagectomy, with gastric laparoscopically conduit formation.
  The surgical system used in Bellvitge University Hospital is the DaVinci Xi (serial number: SK0841).

Criteria

Inclusion Criteria:

- Age ≥18 years.
- Histologically proven adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma or carcinoma of the gastroesophageal junction (GEJ) Siewert I or II.
- Surgical resectable (T1-4a, N0-3, M0).
- Childbearing potential women (period between menarche and menopause), pregnancy negative test is mandatory.
- Written informed consent.

Exclusion Criteria:

- Stage IV or GEJ Siewert III esophageal cancer.
- Contraindication of transthoracic esophagectomy in two fields.
- Pre- or concomitant cancer or conditions which interferes with the study (e.g. prior thoracic surgery or trauma. Rationale: these patients may undergo open resection).

Outcome measurements

Primary outcome measure:

1. Respiratory postoperative complications.

The primary outcome of this study is the percentage of respiratory complications as stated by the modified Clavien-Dindo classification of surgical complications (MCDC) by means of Robot-assisted thoracic approach and thoracotomy (classic surgery).

Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 2 weeks up to 84+/-3 days from hospital discharge.

Secondary outcome measures:

1. Postoperative complications.

Estimate the percentage of overall complications as stated by the modified Clavien-Dindo classification of surgical complications (MCDC) by means of Robot-assisted thoracic approach and thoracotomy (classic surgery).

Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 2 weeks up to 84+/-3 days from hospital discharge.

2. Individual components of the primary endpoint (major and minor complications).

Major complications (MCDC Grade 2-4): anastomotic leakage (clinical or radiologic diagnosis), anastomotic stenosis, chylothorax (chylous leakage, presence of chylous in chest tubes or indication start medium chain triglycerides containing tube feeding), gastric tube necrosis (proven by gastroscopy), pulmonary embolus, pneumothorax, deep vein thrombosis, myocardial infarction, vocal cord palsy or paralysis.

Minor complications (MCDC Grade 1): wound infections, pleural effusions, delayed gastric emptying.

Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 2 weeks up to 84+/-3 days from hospital discharge.

3. Postoperative mortality (during hospital stay up to 84+/-3 days after discharge).

(In hospital) mortality and mortality within 84+/-3 days after hospital discharge will be reported. The cause of death will be noted.

Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 2 weeks up to 84+/-3 days from hospital discharge.

4. Operation related events.

Operation time is defined as time from incision until closure (minutes) for both the thoracic and the abdominal phase of the procedure. For the robotic approach, set up time will be recorded separately. Unexpected events and complications occurring during operation will be recorded (e.g. massive haemorrhage, perforation of other organs). Blood loss during operation (ml, per phase). In case of conversion to thoracotomy or laparotomy the reason for conversion has to be explained (absolute numbers/percentage).

Time Frame: Day of surgery, up to 24 hours after surgery.

5. Postoperative recovery.

Pain: type and dose of used analgesics will be noted during the hospital admission period and noted during the follow-up period.

Length of intensive care unit (ICU). Length of hospital stay (days).

Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 2 weeks.

6. R0 resections (%).

The pathological analysis will be finished within 2-3 weeks after surgery.

Time Frame: Participants will be followed for the duration of hospital stay, an expected average of 2 weeks.

7. Oncologic outcomes.

Overall survival within 84+/-3 days after hospital discharge.

NOTE: 2, 3 and 5 years disease free and overall survival will be reported in the study of extension.

Time Frame: From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 84+/-3 days after discharge.

8. Postoperative quality of life.

Questionnaires EORTC QLQ-C30 and EQ-5D will be required from 14+/-2 days after hospital discharge up to 84+/-3 days after hospital discharge.

Time Frame: From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 84+/-3 days after discharge.

Study protocol

Periods and duration of the study:

- Start of study: The study will begin with the protocol design.
- Initiation of the clinical part of the study: The study will begin with the inclusion of the first patient ("First Patient–First Visit").
- Patient recruitment period: The patient inclusion period will end with the inclusion of the last patient included, according to the number of patients indicated in the calculation of the size of the patient Sample. The recruitment period is estimated to be approximately five years.
- Each patient's participation period: Participation in the clinical trial includes 84±3 days from the day of surgery. Patients may terminate their participation in the clinical trial prior to the end-of-study visit or by own decision (own will) or by surgeon's criteria (e.g. adverse event, etc.). At time of completion, all tests specified in the end-of-study visit will be carried out.
- Completion of the study: The study will end when the evaluation of the last patient included ("Last Patient-Last Visit").
- Estimated start date of patient inclusion in the study: The study will start approximately November 2020.

- Estimated study end date: After clinical phase it takes at least 28±3 days (1 month) for the debugging the data and performing the first statistical analyses. The final report will be available within 11 months of the completion of statistical analyses. The expected end date (final report) is December 2026.
- Interim analysis: There will be one interim analysis after two years of recruitment. The final report will be available within 11 months of completion of statistical analyses. The expected end date of interim analysis will be December 2023.

Schedule:

The duration of the clinical trial is expected to be 3 years for field work with recruitment and inclusion of patients. Posteriorly, comes the period of results analysis and elaboration of the resulting work.

1. Application for authorisation to the Clinical Research Ethics Committee (CREC) of the promoter centre (HUB) June 2020.

2. Recruitment of patients: November 2020 – November 2022 (for interim analyses) – November 2025: Obtaining informed consent before of the inclusion of each patient.

3. Presentation of the results: elaboration of the articles with the results of the study, elaboration annual reports and the final report of the project: before December 2023 (interim analyses), before December 2026 (final analyses).

4. The relevant statistical analyses shall be carried out at the end of the field work. The results to the research team for discussion and decision-making if the planned extension study after the clinical trial should continue or end: December 2023 and/or December 2026 (if the study continues after interim analyses).

Patients' withdrawal:

Participation in the study is voluntary and patients can retire at any time without explanation, with no consequences on health care they will receive in the future.

The researcher should remove a patient from the study in the following cases:

- Clinical criteria of the medical-surgical team.
- Patient's request for withdrawal.
- Violation of protocol.
- Follow-up loss.
- Pregnancy during the study.

When a patient withdraws from the study, the researcher will record the reason or reasons for the withdrawal in documents and on the corresponding electronic collection database (e-CDB) page. In any case, every effort will be made to carry out the security and follow-up procedures specified in the protocol.

Patient care after completion of the study:

Once patients complete the study, they will be monitored by their doctor according to the practice regular clinic, with regular checks in accordance with the current protocols of our Health System. However, all patients in this clinical trial will be proposed to participate in the observational extension study.

Number and interval of study visits:

Until the patient (or legal representative, if applicable) has not signed and dated the Written Informed Consent in which voluntarily accept participation, will not be included in the study (Visit 1 or visit screening and patient inclusion) nor will be given any specific tests for the study.

However, data that had previously been collected at visits may be used for the study routine clinics corresponding to the clinical process by which the patient is valued to be included in this study. Patients will be followed up to 84+/-3 days after hospital discharge.

Patient selection: Patients will be selected at the External Consultation Visit of Esophageal-gastric tumours.

Data collection:

Data will be collected by researchers in an electronic collection database (e-CDB) specifically developed for the study. Patient's date of inclusion, data demographics, medical history, relevant comorbidities, clinical data, as well as the analyses results will be properly collected. Monitoring of the study will be carried out by members of the Esophageal-Gastric Surgery Unit of Bellvitge University Hospital.

Confidentiality of clinical trial results:

The results of this clinical trial are confidential and may not be transmitted to third parties of any form or manner without the written permission of the Promoter. Everyone involved in the clinical trial is subject to this confidentiality clause.

Final and interim report:

A final and interim report will be prepared to collect all the data and results obtained in the study. The Promoter will provide (within one year after the end of the clinical trial) the summary of the report of the clinical trial to the Competent Authorities and the CREC. The final report will also be provided to investigators, as agreed.

Surgery

All patients with esophageal or GEJ tumour are introduced and presented at the Esophageal Tumour Committee, which meets once a week at our centre. There are both patients with recent diagnosis of esophageal cancer or GEJ, such as those who have received neoadjuvant treatment (chemo/radiotherapy) for response assessment. An assessment of the general status and an anaesthetic evaluation is also carried out to determine the surgical risk, including performing respiratory functional tests. With the results of the preoperative tests, the patient's operability is defined based on general factors including the absence of severe systemic pathology, an adequate nutritional balance, and related local factors disease from the presence of locally to advanced disease, the presence of remote ganglion metastasis or visceral or peritoneal metastasis and/or positive cytology. Our hospital centre (Bellvitge University Hospital), has a Protocol about Diagnostic and Treatment for Esophageal Cancer (last updated June 2017). Subsequently, the presurgical visit (basal visit) will be made by the team of the Esophageal-gastric Surgery Unit, in which patients will be given information regarding the study. Randomization will be performed prior to surgery. The patient will enter on the same day of the intervention (day 0) for the realization of analysis and Blood Bank. The completion of the data collection will be checked. All patients will receive antibiotic, deep vein

thrombosis prophylaxis in accordance with the hospital policy present. The esophagectomy performed is the Ivor Lewis technique, which consists of an esophagectomy in two phases (abdomen and right thoracic) with lymphadenectomy in two fields (abdomen and thoracic).

Surgical technique description:

Abdominal phase:

In both groups it will be carried out laparoscopically. The steps are as follows:

- Placement of trocars.
- Gastrolysis with preservation of gastroepiploic arcade.
- Dissection, section and ligation of right and left gastric vessels.
- Section splenic short vessels.
- Preparation of gastroplasty by reinforced linear stapler:
    - o In its entirety, in the robotic group.
    - o Without completing it, in the thoracotomy group.
- Celiac trunk lymphadenectomy.
- Preparation of Witzel-type jejunostomy.

Thoracic phase:

The thoracic approach will be carried out by thoracotomy in the control group and robot-assisted in the robotic surgery group.

1. Thoracotomy (control group):

- Selective orotracheal intubation.
- Left lateral decubitus.
- Thoracotomy 5th right intercostal space.
- Section of 5th right rib.
- Dissection, section and ligation of azygos vein.
- Block thoracic esophagus dissection with periesophageal, paratracheal, subcarinal and peribronchial.
- Section of thoracic duct.
- Section of the esophagus.
- Rise of gastric plastia.
- Exeresis of the surgical piece.
- Term-lateral esophageal-gastric anastomosis by posterior transgastric mechanical circular suture.
- Gastrotomy closure with mechanical suture.
- Placement of two thoracic drains.
- Closure of the thoracotomy.

2. Robotic thoracoscopy (Da Vinci Xi Surgical system, serial number SK0841):

- Selective orotracheal intubation.
- Prono decubitus.
- Placement of four trocars.
- Robot docking.
- Dissection, section and ligation of azygos vein.

- Block thoracic esophageal dissection with periesophageal, paratracheal, subcarinal, peribronquial lymphadenectomy.
- Exeresis and ligature of the thoracic duct.
- Section of the esophagus.
- Rise of gastric plastia.
- Exeresis of the surgical piece.
- Manual two planes end-to-side esophageal-gastric anastomosis with barbed suture in major gastric curvature.
- Placement of two thoracic drains.
- Closure of the trocar incisions

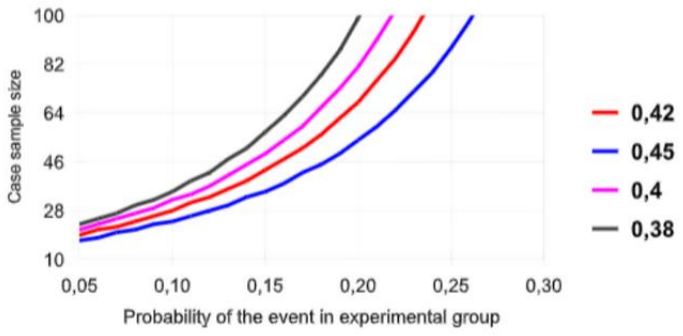
Patients from both groups will subsequently stay in Postsurgical Resuscitation Unit for 3 days, according to the current protocol of the Esophageal-Gastric Surgery.

Sample size calculation

The main objective of the study is to compare the cumulative incidence of complications in patients who underwent Ivor-Lewis esophagectomy. A randomized clinical trial is being proposed with two arms: open surgery versus robotics.

Hypothesis:
- H0: Incidence of open lung complications = robotics.
- H1: Incidence of open lung complications ≠ systems.

Current records of Bellvitge University Hospital estimate the incidence of complications patients with open esophagectomy at 42%. A 25% reduction is expected in the incidence of lung complications with robotic surgery. Consequently, it will take 54 subjects per group to reject the null hypothesis of equality, by means of a Chi-square test with a power of 80%. A 5% type I error is fixed and considered a follow-up loss rate of 5%.
Figure: possible alternative scenarios depending on the incidence of lung complications. X-axis (Robotic surgery) and curves (open surgery):



All variables collected will be summarized in tables using appropriate descriptive statistics (central trend and dispersion measures, and absolute and relative frequencies, as appropriate). Inferences will be made to estimate parameters of population distributions by calculating the 95% bilateral confidence intervals. Baseline data will be described for the entire sample.

Randomization

Participants will be randomly assigned in two treatment groups: control or study, with 1:1 distribution. An electronic programme will be designed for randomization, a block of 10 will be performed, so that every 10 participants groups will be balanced. Stratification will be performed based on prior neoadjuvant treatment (chemo/radiotherapy prior to surgery), so that the groups are as homogeneous as possible. Mechanism for implementing randomization will be through a list of codes, where in each of them will correspond to one of the two treatment groups, which will have been randomly established.

Statistical analysis

Data management:

Data collection will be carried out by the researcher through an electronic collection database (e-CDB), specifically designed for the study.

Participants will be included in numerical order and stored accessible and securely. Participants' files in both paper and computer media will be kept for a period of 3 years after the completion of the study.

Access to study data will be restricted to the study equipment. Appropriate measures will be taken with regard to the confidentiality of the data in accordance with Organic Law 15/1999 on the Protection of Personal Data.

During the study, visits will be made to review data for security reasons, to check adherence to the protocol.

Statistical analysis:

Statistical comparison of qualitative variables and discrete quantitative variables will be used in Chi-square tests. The main variable of the study (incidence of respiratory complications) will also be analysed with the Chi-square test.

The T Student or U Mann Whitney tests will be used for the analysis of continuous variables that do not follow the normal distribution. The analysis shall be stratified on the basis of neoadjuvant treatment. Global survival curves will also be established at age 3 and 5 using Kapplan-Meier curves.

Data analysis will be carried out on intention to treat (as reported in the CONSORT guidelines), keeping all patients selected and randomized in the group in which they were originally included, regardless of adherence to the protocol. The R software version 3.5 will be used for statistical analysis. The alpha error for primary variable has been set to 5%.

Ethical and regulatory procedures

Ethical considerations

This study will be conducted in accordance with ethical principles based on the latest version of the Helsinki Declaration (agreed by the 64th General Assembly of the World Medical Association, in Fortaleza, Brazil, in October 2013), Clinical Good Practice guides (CGP) and applicable regulations.

The CGP is a standard for all aspects concerning clinical trials (design, development, monitoring, auditing, logging, analysis and communication) to ensure that the data and results transmitted are credible and accurate, and that rights, integrity and confidentiality of patients are protected.

The researcher is responsible for ensuring that the clinical trials is conducted in accordance with the protocol, guidelines established by the International Conference on Harmonisation (ICH) on the CGP and local legal requirements.

The study may only begin once the Clinical Research Ethics Committee (CREC) of the Bellvitge University Hospital has given the signed approval of the protocol, as well as the Patient Information document and Informed Written Consent models.

Each person involved in conducting the study must be qualified by their training and experience to perform their specific tasks. Neither the researcher nor the study staff will coerce or pressure patients to participate or continue the study.

Informed Consent

Before performing any procedure related to the study, the researcher will be responsible to provide each patient (or legal representative, if applicable) the Patient Information Document specifically prepared and approved for the study, which should be read by the patient. Language that the patient can understand will be used to inform them about treatment in research, the objectives of the study, and the pros and cons of their participation. Patients will be left long enough to consider their participation and they will be answered about all the questions and doubts.

The researcher will inform patients that their participation in the study is voluntary and that they are free to voluntarily withdraw from the study at any time and for any reason, and none of these decisions are going to affect the treatment they will receive in the future.

The investigator shall be responsible for obtaining the informed written consent of patients before proceeding to any medical procedure specific to the study. The conformity to participate in the clinical trial will be expressed upon signing and date the Informed Consent specifically prepared and approved for study. The researcher who directs the process of obtaining informed consent must also sign and date on the document. Informed Consent will be signed in duplicate, an original copy will be delivered to the patient or their representative and the investigator will keep the other original copy.

If new information were to emerge during the course of the study that could affect the process of informed consent, a review of the Patient Information Sheet will be carried out. Before to be used, the revised version will be sent for approval by CREC.

The patient will be informed as soon as possible if new information is available that could affect the patient's decision to continue in the study. The communication of this information must be recorded. The patient, or their legal representative, will receive a copy of any update Informed Consent or any other relevant written information.

Clinical Research Ethics Committee (CREC)

The protocol of this clinical trial has been reviewed and approved by Bellvitge University Hospital CREC, L'Hospitalet de Llobregat, Barcelona, in June 2020.

Clinical Insurance

The surgical treatments used in this clinical trial correspond to those used in our usual clinical practice. The control group will carry out the classic thoracic approach (thoracotomy or open approach) and the experimental group, minimally invasive robot thoracic approach. Both approaches (thoracotomy and robotic) are surgical techniques used in the usual clinical practice of our hospital. Abdominal approach will be minimally invasive by laparoscopy in both groups.

While this clinical trial is not drug-based, in accordance with the current legality (Royal Decree 1090/2015), this is a low-level clinical trial of intervention:

1) Both surgical techniques are used and validated in the treatment of esophageal cancer.
2) Complementary diagnostic or follow-up procedures involve the same risk or burden additional for the safety of subjects than the risks of clinical practice.

Therefore, and in accordance with Article 9 of Royal Decree 1090/2015: "Damages study subjects that could result as a result of a low-level clinical trial intervention will not need to be covered by an insurance contract or financial guarantee, if they were covered by individual or collective professional liability insurance or equivalent financial guarantee of the health centre where the clinical trial is carried out"; there has not been contracted ad hoc insurance for this clinical trial.

Protocol modifications

Any changes to the protocol during the study will be recorded in the form of a modification. These will be signed by the Promoter and the Principal Investigator, if applicable. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval by the relevant CREC and the Competent Authorities. No deviation or change of protocol that is relevant without prior review and issuance of approval by the relevant CREC and by the Competent Authorities, except if an imminent risk to patients needs to be eliminated, or when the change(s) understand only logistical or administrative aspects of the clinical trial.

Trial status

Recruitment of patients started in November 2020.

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