Universitat de Girona

Use of sentinel node mapping with dual tracer versus D2 lymphadenectomy in patients with early gastric cancer. A multicenter randomized clinical trial.

FINAL DEGREE PROJECT

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0. ABSTRACT

USE OF SENTINEL NODE MAPPING WITH DUAL TRACER VERSUS D2 LYMPHADENECTOMY IN PATIENTS WITH EARLY GASTRIC CANCER

Background:	The most accepted surgical approach for gastric cancer is total or partial gastrectomy plus D2 lymphadenectomy. This implies that patients with early gastric cancer (EGC) undergo extensive lymphadenectomy, which is in most cases unnecessary, resulting in significant morbidity. To reduce these complications, the use of the sentinel lymph node technique has been proposed in these patients. Studies have shown that the best results are obtained with dual tracer techniques, with promising results. However, there is a lack of information from clinical trials comparing both techniques.
Objective:	Study whether the use of sentinel node mapping using dual tracer (patent blue V and ^{99m}Tc-Antimony Sulfur Colloid) in patients with EGC achieves similar survival rate with less morbidity as compared to the conventional approach of D2 lymphadenectomy. Other variables like length of stay and quality of life will be also compared between both techniques.
Design:	Multicenter, randomized, clinical trial conducted in Hospital Universitari Doctor Josep Trueta and six hospitals of Barcelona between 2017 and 2026.
Participants:	Using a non-probabilistic consecutive sampling, 190 patients older than 18 years old presenting an early gastric cancer with tumor size ≤3 cm will be recruited.
Intervention:	Patients will be randomized in a 1:1 ratio to sentinel node mapping (n=95) or D2 lymphadenectomy (n=95).
Main outcomes:	Assess if the sentinel node technique achieves a disease-free survival and an overall survival rate comparable to D2 lymphadenectomy after five years of follow-up. Moreover, we will compare the complications rates between both techniques during the first month after the intervention.
Statistical analysis:	To compare the intervention performed and morbidity, we will use a Chi-square test. To study the overall and the disease-free survival rate, we will use the Kaplan-Meier estimator. For the multivariate analysis, we will use a multiple logistic regression model for the morbidity and Cox models for the overall and disease-free survival rate.
Keywords:	Early gastric cancer, D2 lymphadenectomy, sentinel node mapping, blue dye, lymphogammagraphy.

1. ABBREVIATIONS

ASA: American society of anesthesiology.

BMI: body mass index.

CEIC: comitè ètic d'investigació clínica.

ChT: chemotherapy.

CT: computed tomography.

ECOG: Eastern cooperative oncology group.

EGC: early gastric cancer.

EORTC: European organization for research and treatment of cancer.

FEV1: forced expiratory volume in 1 second.

GC: gastric cancer.

LN: lymph node.

QoL: quality of life.

RT: radiotherapy.

SBD: sentinel basins dissection.

SC: stomach cancer.

VEGF: vascular endothelial growth factor.

2. INTRODUCTION

2.1. STOMACH CANCER

2.1.1. Anatomy

In order to facilitate the correct understanding of this project, it is necessary to explain previously the gastric anatomy and its lymphatic drainage.

The stomach is divided into five parts:

- **Cardia:** the area where the esophagus meets with the stomach (esophagogastric junction).
- **Fundus:** the upper part of the stomach next to the cardia. It lies just under the diaphragm.
- **Body:** the largest part of the stomach, between fundus and pylorus.
- **Antrum:** the lower portion.
- **Pylorus:** the last part of the stomach, which acts as a valve to control emptying of the stomach contents into the small intestine.

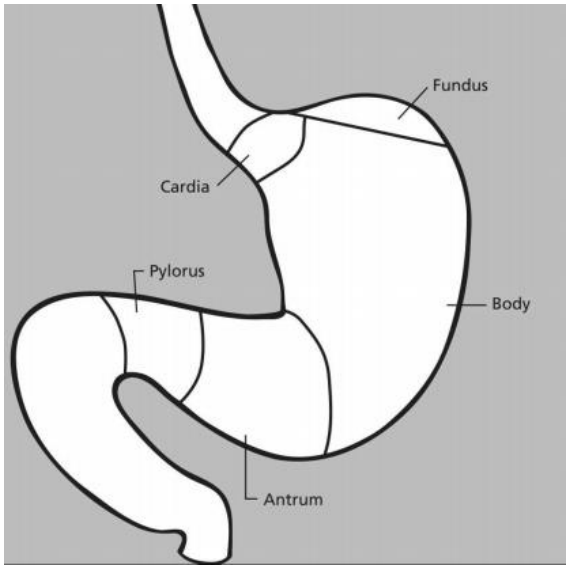


Figure 1: Anatomy of the stomach (1).

Cardia, fundus and body are often called the proximal stomach. In these parts, there are specialized cells that make acid and pepsin (a digestive enzyme) helping to the food digestion. These cells also secrete intrinsic factor, a protein which the body needs to absorb vitamin B12. The lower two parts (antrum and pylorus) are called the distal stomach. The stomach has two curves, called the lesser curvature and greater curvature (1).

The stomach wall has five stratums:

- **Mucosa:** the innermost layer. It has three parts: epithelial cells, which lie over a layer of connective tissue (lamina propria), which is on top of a layer of muscle (muscularis mucosa).
- **Submucosa:** supporting layer.

- **Muscularis propria:** muscle layer. It facilitates the mixture of food with the gastric secretion.
- **Subserosa**
- **Serosa:** the outermost layer.

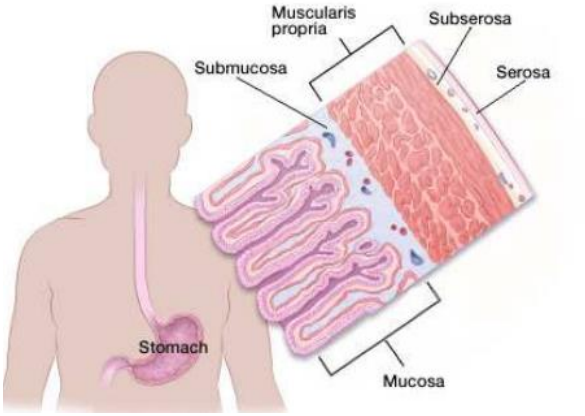


Figure 2: Layers of stomach wall (1).

This is important because this will help us to stage the cancers' extension and this will be of use to know the patients' prognosis (1).

In addition, it is necessary to talk about the lymphatic drainage of the stomach. The lymph nodes (LNs) of the stomach are classified into stations numbered from 1 to 20, plus stations 110, 111 and 112. LN stations 1-12 and 14v are defined as regional stations. The rest of LN stations are considered as distant stations, thence its affectation is considered a metastasis (M1). LN 19, 110 and 111 are considered as regional LN in case of tumor invading the esophagus (2).

Lymph from different parts of the stomach is drained into the paraaortal LN collector through one of four routes (3):

- **Left subdiaphragmatic via**: LNs in the circulation of the left lower diaphragmatic artery.
- **Abdominal via:** LNs along the left gastric, splenic and common hepatic arteries and the celiac trunk.
- **Upper mesenteric via:** it receives lymph from the subpyloric LNs and runs along the upper mesenteric artery.
- **Retropancreatic via:** associated with LNs of the hepatoduodenal ligament, upper mesenteric vessels and common hepatic artery.

The first two routes drain lymph from the upper third of the stomach. LNs of the gastric body drain, mainly, through the abdominal route, while the LNs of the distal stomach drain through abdominal, upper mesenteric and retropancreatic routes.

Table 1: Classification of lymphatic gastric stations. Adapted from (2,3)

NUMBER	DEFINITION
1	Right paracardial LNs.
2	Left paracardial LNs.
3a and 3b	Lesser curvature LNs.
4sa	Left greater curvature LNs along the short gastric vessels.
4sb	Left greater curvature LNs along the left gastroepiploic vessels.
4d	Right greater curvature LNs along the right gastroepiploic vessels.
5	Suprapyloric LNs.
6	Infrapyloric LNs.
7	LNs along the left gastric artery.
8a	LNs along the common hepatic artery (anterosuperior group).
8p	LNs along the common hepatic artery (posterior group).
9	Coeliac trunk nodes.
10	Splenic hilar LNs.
11p	LNs along the proximal splenic artery.
11d	LNs along the distal splenic artery.
12a	LNs in the hepatoduodenal ligament (along the hepatic artery).
12b	LNs in the hepatoduodenal ligament (along the bile duct).
12p	LNs in the hepatoduodenal ligament (behind the portal vein).
13	Retropancreatico-duodenal LNs.
14a	LNs along the superior mesenteric artery.
14v	LNs along the superior mesenteric vein.
15	LNs along the middle colic vessels.
16	Paraaortic LNs.
17	LNs on the anterior surface of the pancreatic head.
18	LNs along the inferior border of the pancreatic body.
19	Infradiaphragmatic LNs.
20	Paraesophageal LNs in the diaphragmatic esophageal hiatus.
110	Paraesophageal LNs in the lower thorax.
111	Supradiaphragmatic LNs separate from the esophagus.
112	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus.

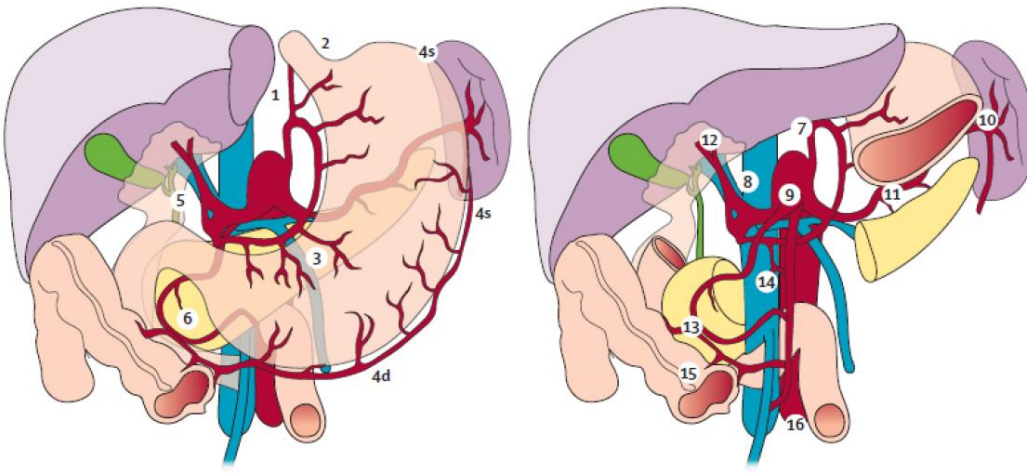


Figure 3: Simplified view of the lymphatic stations of the stomach (4). For more detail, see **Annex 1**.

2.1.2. Epidemiology

Based on the data provided by the National Cancer Institute, recollected between 2009 and 2013, the number of new cases of gastric cancer (GC) was 7.4 per 100.000, and the number of deaths was 3.3 per 100.000 (4). According to World Health Organization, this is the fifth most common malignant neoplasm in the world, after cancers of the lung, breast, colorectal and prostate (5). However, GC is the third leading cause of cancer death worldwide. It presents meaningful global variation in incidence. The highest rates are seen in Eastern Asia, with lower rates in North America and Western Europe (5). Stomach cancer (SC) tends to affect older people. The most affected age range is between 65 and 74 years old (4). In addition, men have higher risk than women, in almost a ratio of 2:1 (5). Nowadays, there have been a gradual descent in its occurrence (6). Some doctors believe that the most important factor is the increased use of refrigeration for food storage. Others think that this decline is due to the use of antibiotics to treat infections. These antibiotics can kill Helicobacter pylori, a bacteria thought to be a major cause of stomach cancer (1).

Survival statistics:

The 5-year survival rate refers to the percentage of patients who live at least 5 years after being diagnosed with SC. According to the data provided by the National Cancer Institute, the 5-year survival rate is 30.4%. However, it depends on the extent of the disease. We will deepen into the stage of GC later, but for now, we will divide this illness in three levels:

- **Localized:** confined in primary site.
- **Regional**: spread to regional lymph nodes.
- **Distant:** presence of metastasis.

At the time of diagnosis, only 27% can be classified as a localized type, with a 5-year relative survival of 66.9%. On the other hand, up to a 35% are classed as a distant variety, with a 5-year relative survival of 5% (4).

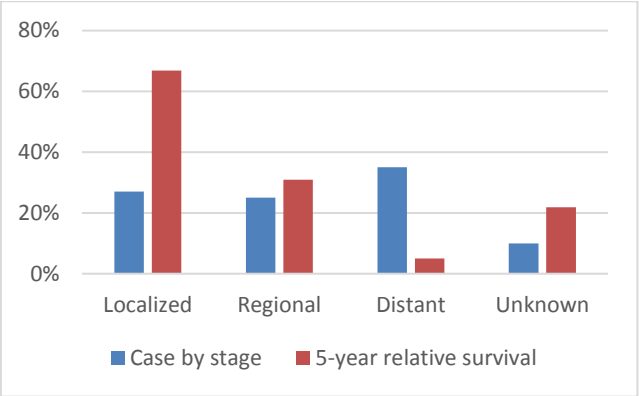


Figure 4: Percentage of diagnoses and 5-year survival per stage. Adapted from (4).

2.1.3. Types of SC

There are different histological types of SC (1). The most common is the adenocarcinoma (almost the 95% of the SC). Throughout this document, when we use the term of GC/SC, we will be referring to adenocarcinoma. There are two types of adenocarcinoma according to Lauren classification: intestinal and diffuse adenocarcinoma. The differences between them are collected in the next table:

Table 2: Differences between intestinal and diffuse adenocarcinoma.

	INTESTINAL ADENOCARCINOMA (well-differentiated)	**DIFFUSE ADENOCARCINOMA (undifferentiated)**
Prevalence	High. Its incidence is decreasing.	Low. Its incidence remains stable.
Age range	65-year-old	Younger people
Gender (M:F)	2:1	1:1
Blood type	No relation	Relation with A type
Heredity	No evidence	Family aggregation
Premalignant injuries	Associated	No relation
Environmental factors	Associated	No relation
Histology	Antrum and lesser curvature. Glands with intestinal-like cells. There is cell cohesion.	Any part of the stomach. Loss of glandular structure. There is not cell cohesion. Associated with linitis plastica[1].
Signet ring cells	-	+

[1] Linitis plastica involves diffuse proliferation of the connective tissue in the submucosa. This leads to subsequent luminal narrowing, rigidity and nondistensibility, resulting in a rigid and constricted stomach (7).

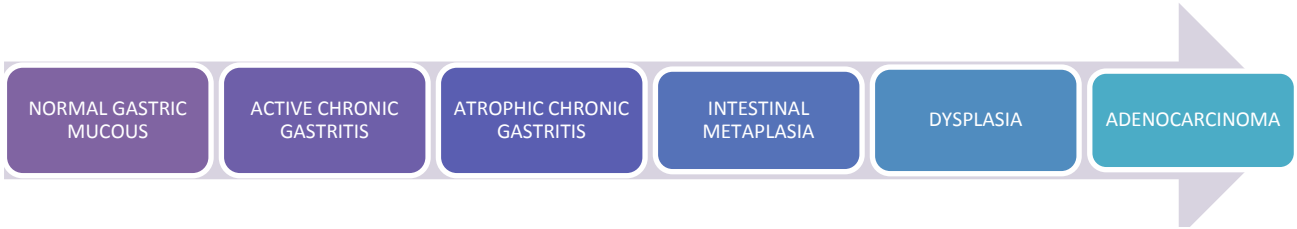


Figure 5: Atrophy–metaplasia–dysplasia–carcinoma sequence in the stomach. Adapted from (8).

2.1.4. Risk factors

Table 3: Summary of risk factors for GC (1,6).

ADAPTABLE
- Helicobacter pylori infection: long-term infection leads to inflammation (chronic atrophic gastritis) and pre-cancerous changes (intestinal metaplasia). - Stomach lymphoma (MALT): it is linked to the Helicobacter pylori's infection. - Diet: salted fish and meat, smoked foods and pickled vegetables. - Tobacco. - Obesity. - Previous stomach surgery: the remaining stomach produces less acid, allowing more nitrite-producing bacteria to be present. - Pernicious anemia. - Premalignant conditions: ▪ Menetrier disease. ▪ Some kind of stomach polyps. ▪ Barrett's esophagus. ▪ Chronic atrophic gastritis, metaplasia and dysplasia. - Epstein-Barr virus: linked to some forms of lymphoma. - Certain occupations: workers in the coal, metal, and rubber industries. - Common variable immune deficiency: it leads to infections, atrophic gastritis and pernicious anemia.

NOT ADAPTABLE
- Gender: men. - Age: between 60s and 80s. - Ethnicity and geography: Eastern Asia, South Eastern Europe and South America. - Type A blood. - Inherited cancer syndromes: Lynch syndrome, familiar adenomatous polyposis, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, hereditary diffuse gastric cancer, mutations BRCA1 and BRCA2. - Family history of SC.

2.1.5. Diagnosis

Screening:

In Asian countries, where the SC rates are higher, screening for SC is a routine, mainly made with an upper endoscopy with biopsy. Therefore, in these countries this cancer is diagnosed at an earlier stage than in other countries. In the Western countries, it has not been proven the routine screening's utility, because of the lower rates of this disease (1,6)

Diagnostic tests (1,6):

- **Medical history and physical exam:** symptoms, risk factors, abdominal exploration.
- **Lab tests:** it is common to find anemia due to cancer's bleeding.
- **Upper endoscopy:** it lets you explore the surface of the gastric mucosa. If abnormal areas are seen, biopsies must be taken in order to make a posterior histology study.
    - **Borrman macroscopic classification:**
        - **Type I:** polypoid tumor.
        - **Type II:** circumscribed ulcerated tumor.
        - **Type III:** infiltrating ulcerated tumor.
        - **Type IV:** infiltrating tumor (linitis plastica).

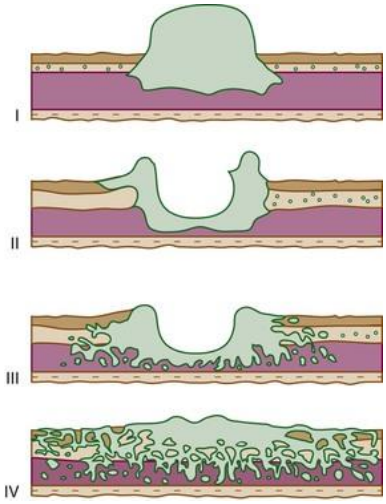


Figure 6: Borrman classification (9).

- **Biopsy:** it is done by removing a piece of an abnormal-looking area seen on endoscopy. If the sample contains adenocarcinoma cells, the fragment is tested in two ways to see if it presents the protein HER2 (a growth-promoting protein):
    - **Immunohistochemistry (IHC):** antibodies that stick to the HER2 protein are applied to the sample, causing cells to change color if copies are present. The results can be: 0, 1+, 2+ or 3+.
        - If the results are 0 or 1+, the cancer is HER2 negative.
        - If the result is 3+, the cancer is HER2 positive. These patients may be treated with drugs like trastuzumab (monoclonal antibodies against this protein).
        - When the result is 2+, the result is not clear, so FISH must be realized.
    - **Fluorescent in situ hybridization (FISH):** it uses fluorescent pieces of DNA that stick to copies of the HER2 gene in cells.
- **X-rays test with barium:** this will outline any abnormalities of the lining of esophagus or stomach.

2.1.6. GC staging

There are two types of stages for SC. The clinical stage (cTNM) is estimated based on the results of physical exams, endoscopy, biopsies, and any imaging tests. If surgery is done, pathologic stage (pTNM) can be assessed, which is more accurate. It can be determined using the same tests used before plus what is found during surgery. The staging described here is the pathologic stage. The system most often used is the American Joint Commission on Cancer (AJCC) TNM system (1,6). This

system is for staging all SC except those starting in either the gastroesophageal junction or in the cardia, which are staged and treated like cancers of the esophagus.

- T describes the extent of the primary tumor.
- N describes the spread to regional lymph nodes.
- M indicates the presence of metastasis.

Table 4: American Joint Commission on Cancer (AJCC) TNM system. Adapted from (1).

PRIMARY TUMOR (T)	REGIONAL LYMPH NODES (N)
- TX: primary tumor cannot be assessed. - T0: no evidence of primary tumor. - Tis: carcinoma in situ: intraepithelial tumor without invasion of the lamina propria. - T1: the tumor has grown from the top layer of cells of the mucosa into the next layers. ▪ T1a: tumor invades the lamina propria or muscularis mucosa. ▪ T1b: tumor invades de submucosa. - T2: tumor invades the muscularis propria. - T3: the tumor is growing into the subserosa layer[2]. - T4: ▪ T4a: tumor invades the serosa. ▪ T4b: tumor invades adjacent structures[3].	- NX: regional lymph nodes cannot be assessed. - N0: no spread to nearby lymph nodes. - N1: the cancer has spread to 1 to 2 nearby lymph nodes. - N2: the cancer has spread to 3 to 6 nearby lymph nodes. - N3: ▪ N3a: the cancer has spread to 7 to 15 nearby lymph nodes. ▪ N3b: the cancer has spread to 16 or more nearby lymph nodes.
DISTANT METASTASIS (M)	
- M0: no distant metastasis. - M1: distant metastasis.	

Early gastric cancer (EGC) is defined as a carcinoma confined to mucosa and/or submucosa (T1), with or without lymph node metastases (10). It should be emphasized that LN status is the strongest prognostic factor for EGC (2). The involvement of regional LNs depends on the depth of primary

[2] T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures.
[3] Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum.

tumor invasion. LN affectation can be found in 15% of patients with a T1a carcinoma, whereas it is detected in 23.4% of patients with T1b cancer, in 48.2% of T2 cancers, and in 69.8% of T3-4 cancers (11).

TNM stage grouping:

Once the TNM has been determined, this information is combined and expressed as a stage.

Table 5: TNM stage grouping. Adapted from (1).

STAGE GROUPING	T	N	M
Stage 0 (carcinoma in situ)	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0-1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2-3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

However, the most important thing is if the tumor is removable (those that surgeons believe can be completely resected) or unremovable (it cannot be removed completely). It is not established which stages are removable and which are not, but the earlier stages are easier to resect.

2.1.7. Management

Surgery:

This procedure is the only potentially curative option. The extension of the surgery will depend on the type, the stage and the localization of the SC. This operation can be done by laparotomy or laparoscopy.

It seems that the laparoscopic approach in gastric cancer has currently limited application in the West (12). It requires an appropriated surgery training, with a considerable learning curve. Only for EGC requiring a distal gastrectomy the majority of surgeons use the laparoscopy. This is supported by the short-term results provided by the KLASS-01 trial, which showed a lower complications rate with this technique (13). These data cannot be transferred to what is expected for advanced gastric cancer or a total gastrectomy (2). These cases are still controversial. Although the short-term results are favorable, the long-term ones are debatable.

The reconstructive surgery made after a partial/total gastrectomy is, mainly, an esophagus/gastro-jejunostomy end-to-side Roux-en-Y.

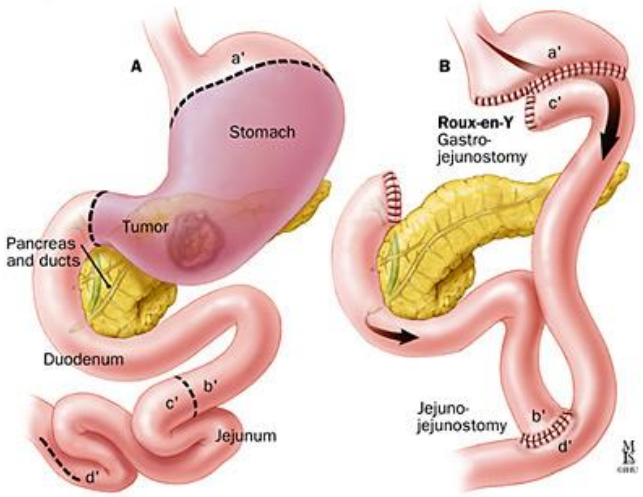


Figure 7: Roux-en-Y. Obtained from (14).

- **Endoscopic resection:** it can be used to treat very early-stage cancers (T1a), confined to the mucosa, ≤2cm, non-ulcerated and well-differentiated (6). This type of surgery is mainly done in countries like Japan, where the SC is found at earlier-stages because of the high prevalence and the screening tests. In addition, this technique requires to be performed in an experienced center (1). There are two types of endoscopic resection (6,15):
    - Endoscopic mucosal resection: the tumor with the surrounding mucosa is lifted by submucosal injection of saline and removed using high-frequency steel snare.

- Endoscopic submucosal dissection: the mucosa surrounding the lesion is circumferentially incised using a high-frequency electric knife, and the submucosal layer is dissected from the proper muscle layer.

- **Partial gastrectomy:** recommended mainly when the cancer affects only the lower part of the stomach. With this technique, the surgeon removes only a part of the stomach with some of the omentum and, sometimes, with the first part of the duodenum too.
- **Total gastrectomy:** used when the cancer has affected all the stomach or it affects the upper part, near the esophagus. The surgeon removes the stomach and omentum.
- **Lymph node removal:** the nearby lymphadenectomy is done in addition to partial or total gastrectomy. There are different types of lymphadenectomies according to their extension. In the Japanese gastric cancer treatment guidelines (2,3,15) there are the definitions of the lymphadenectomies according to the type of gastrectomy indicated.
    - **Total gastrectomy:**
        - D0: lymphadenectomy in a volume less than D1.
        - D1: the LN stations to be dissected are stations from nº 1 to 7.
        - D1+: includes D1 stations + stations nº 8a, 9, and 11p. For tumors invading the esophagus, D1+ includes nº 110.
        - D2: includes D1 stations + stations nº 8a, 9, 10, 11p, 11d and 12a. For tumors invading the esophagus, D2 includes nº 19, 20, 110 and 111.

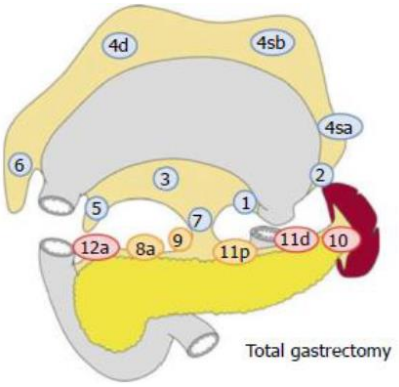


Figure 8: LN included in D2 lymphadenectomy in total gastrectomy (3).

- **Proximal partial gastrectomy:**
    - D0: lymphadenectomy in a volume less than D1.
    - D1: nº 1, 2, 3a, 4sa, 4sb and 7.
    - D1+: includes D1 stations + nº 8a, 9 and 11p.

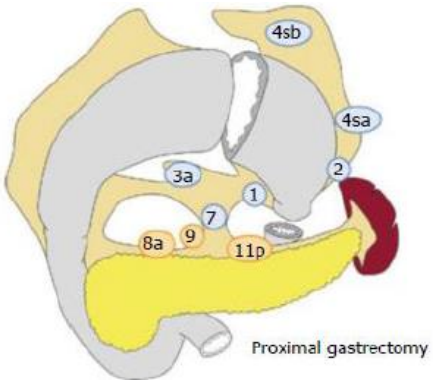


Figure 9: LN included in D2 lymphadenectomy in proximal gastrectomy (3).

- **Distal partial gastrectomy:**
  - D0: lymphadenectomy in a volume less than D1.
  - D1: nº 1, 3, 4sb, 4d, 5, 6 and 7.
  - D1+: includes D1 stations + stations nº 8a and 9.
  - D2: includes D1 stations + stations nº 8a, 9, 11p and 12a.

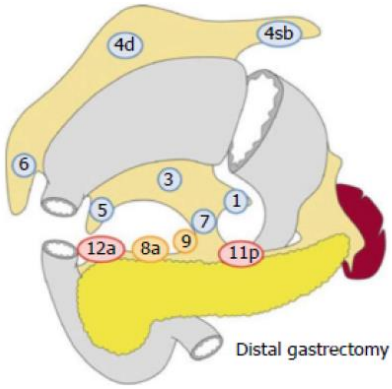


Figure 10: LN included in D2 lymphadenectomy in distal gastrectomy (3).

The American Joint Committee on Cancer recommends to examine at least 16 LN for an accurate pathological examination, even in N0 patients (11). In addition, it is impossible to be categorized as N3b if less than 16 LN are studied (16).

The extension of the nodal resection has been extensively debated. While D2 lymphadenectomy has been performed as the standard procedure in Eastern countries since the 60's, in the West, it was not considered a standard procedure in the clinical practice.

The Medical Research Council (MRC), Dutch and Italian randomized control trials were conducted to show a survival benefit of D2 over D1. However, initially these studies observed a significant increase of postoperative morbidity and mortality mainly due to the spleno/pancreatectomy realized in patients who under-go D2 lymphadenectomy[4] (2). More

[4] Distal pancreatectomy and/ or splenectomy were previously included in the standard D2 lymphadenectomy and considered necessary for an adequate nodal dissection (2).

recently, different studies have proved the splenectomy or the pancreatectomy is unnecessary unless these structures are invaded by the tumor. Consequently, there was an exclusion of the patients who under-go spleno-pancreatectomy in the Dutch trial, and there was a re-evaluation of the data provided. Finally, after a 15-year follow-up to those patients, the Dutch trial reported a significant decrease of cancer recurrence after D2 procedure, associated with a limited risk of complications and postoperative mortality, above all when performed in specialized centers (2,3,17–21).

Nowadays the consensus on D2 lymphadenectomy has increased worldwide, since a trend of improved survival among those patients was recorded, mainly due to spleen and pancreas preservation and to the increase of ability and experience on D2 technique in reference hospitals. Digestive surgeons must be stimulated in performing D2 to avoid wasting the only curative efficient treatment to GC (22,23). In fact, in Hospital Universitari Dr. Josep Trueta it is the procedure realized in all GC's surgeries. However, patients with severe comorbidities may be indicated for limited lymphadenectomy, in order to avoid postoperative complications (24,25).

Complications related with an D2 lymphadenectomy: according to the data provided by our reference center, the complication rate of extensive lymphadenectomy can range from 30 to 40%. The most frequent major complication after a D2 or more extended lymphadenectomy is pancreatic juice leakage and/or left subphrenic abscess. Pancreas juice leakage is often followed by contamination, resulting in a left subphrenic abscess.

D2 dissection includes a wide dissection of the retroperitoneum and causes marked edema in the retroperitoneal space. Together with leakage of lymphatic fluid, this causes considerable retention of fluid in the so-called third space. To keep a good circulation, blood pressure and urine volume, transfusion of large amounts of fluid is required. As the fluid in the third space comes back into the vessels, usually on the third postoperative day, overhydration may easily occur, and acute cardiac failure may follow. Pulmonary complications, mainly pneumonia, often develop as a result. Other possible complications are bleeding, wound infection, lymphorrea and chylous ascites (caused by the obstruction or disruption of the lymphatic vessels).

- **Palliative surgery:** the aim of this surgery is to prevent or relieve symptoms or complications (like bleeding or obstruction) in fit patients with stage IV (15).

According to the protocol of management of patients with SC made in 2008 by the Hospital Universitari Dr. Josep Trueta, the parameters that contraindicate the surgery are:

- Severe and chronic intercurrent disease.

- Presence of metastasis.
- Severe impairment of respiratory function (forced expiratory volume in 1 second (FEV1) <1.500cc; pO_2 <75 mmHg).

The mortality of these techniques is 1-2%. It is higher if the operation is more extensive, and it is lower if it is done in an experienced center with trained surgeons.

Since the objective of our study is to evaluate the surgical technique in early stages, we will not go into detail about other treatment options like chemo, radiotherapy or targeted therapies, because these therapeutic options are for advanced stages and are not surgical. However, it is an important subject, so this information has been included in **Annex 2**.

2.2. SENTINEL LYMPH NODE

We can define a sentinel lymph node as the first LN to which cancer cells are most likely to spread from the primary tumor. Sometimes, as it happens in gastric cancer, there can be more than one sentinel LN.

The sentinel LN biopsy is based on the identification of the sentinel LN, its removal and its examination by the pathologists.

Firstly, the surgeon injects a dye and/or a radioactive substance near the tumor. Then he/she looks for LN that are stained with the dye or uses a device that detects radioactivity to find the sentinel LN. This step is called lymphatic mapping. The mapping procedure takes about one hour, and may be done on the day before of the sentinel node biopsy, or in the same day. When the surgeon localizes it, he/she removes it and send it to the pathologist, who will determine whether cancer cells are present.

This technique is usually done at the same time the primary tumor is extirpated. If the results are positive (there are cancer cells in the LN), it indicates that the cancer has the capacity to spread to other LN, tissues and organs. In this case, the surgeon may remove additional lymph nodes, either during the same biopsy procedure or during the follow-up surgical procedure. On the other hand, if the results are negative, it means that the cancer has not developed the ability to spread to other tissues, and thence, there is no need to extent the LN resection, reducing the potential adverse effects of LN surgery, like lymphedema, increased risk of infection or seroma.

Sentinel LN biopsy is most commonly used to help stage breast cancer and melanoma. However, it is being studied with other cancer types, including the gastric cancer (26). In GC, the perigastric nodes close to the primary lesion are the most common sites of lymphatic metastasis (27).

2.2.1. Sentinel lymph node mapping for gastric cancer

First of all, we have to say that there is not consensus about the best technique to study the sentinel LN in gastric cancer. This is an actual topic, as the oldest studies are only from 2002. The first ones were centered in the use of a colorant dye (mainly the blue dye or the indocyanine green) or the use of a radioactive substance (^{99m}Tc-Antimony Sulfur Colloid). They performed the sentinel lymph node technique and then a D2 lymphadenectomy in all the patients. Next in line, they compared the LN highlighted by the first procedure with the real affected LN after its biopsy.

In these studies, sensitivity was defined as the number of patients with metastatic sentinel LNs divided by the number of patients with LN metastases. Specificity was defined as the number of patients with negative sentinel LNs divided by the number of patients with no LN metastases. Finally, accuracy was defined as the number of patients with true-positive and true-negative sentinel LNs biopsies divided by the number of patients in whom sentinel LNs were identified (28). The dye and the radioisotope method independently, showed a sensitivity of 83.3% and an accuracy of 98.2% (28).

Despite the advantages of all of these techniques, they all showed some weaknesses that hindered their implementation in clinical practice. In order to solve these problems, several recent studies have combined both techniques (colorant dye and radioactive substance) showing promising results, as it allowed to get over the weaknesses of each technique separately, keeping the strengths of each one.

Based on these studies, several clinical trials have recently been initiated in Eastern population. They compare the results of the sentinel node technique vs D2 lymphadenectomy in patients with early gastric cancer. Most of them have not completed the recruitment and follow-up phase, so results are not yet available. In the webs of registry of clinical trials, we can consult in which phase of study is each one of them.

One of the methods that have shown better results and one of the most used in previously named clinical trials is the combination of the blue dye with the ^{99m}Tc-Antimony Sulfur Colloid. The dual procedure gave sensitivity and accuracy of 94-100% (28–31). These results are comparable to previously reported data regarding breast cancer and melanoma (31).

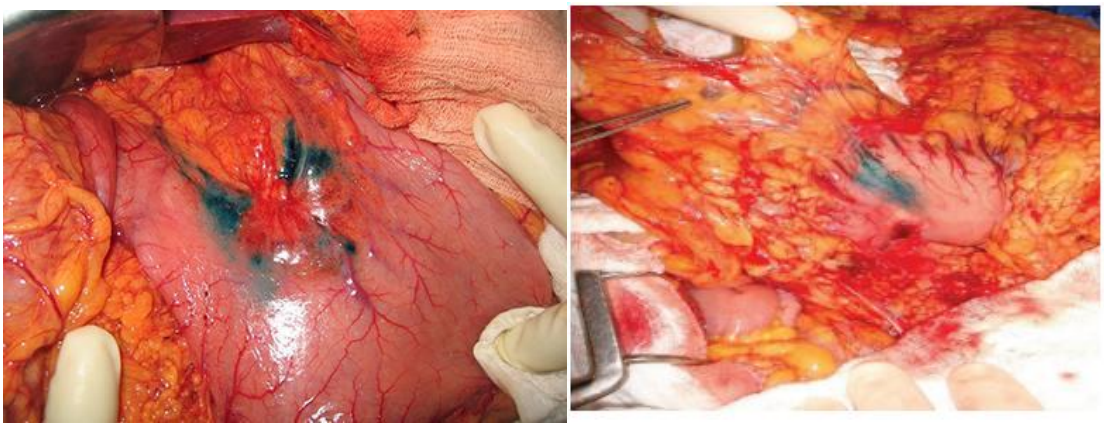


Figure 11: Final aspect after blue dye injection (32).

The radioactive procedure has the advantage of the objective measurement of the intensity of radioactivity in LNs, even in thick adipose tissues. It resides in the LNs for relatively long period of time, allowing its use in laparoscopic surgery. In addition, it enables the surgeons to discover deep-seated sentinel LNs that are difficult to see directly. However, radioactive tracers are expensive and the lymphatic vessels cannot be visualized (33,34).

On the other hand, the dye method has lower costs, enhanced visibility, safety, and it allows you to see not only the LN but also the lymphatic route, giving a visual guide to the surgeon (29,31). Nevertheless, it seems to be associated with a high false-negative rate because of fast transit of dye and blind sites in dense fat (34).

In the radioactive method, ^{99m}Tc-Antimony Sulfur Colloid is applied as a tracer (one-half milliliter at a concentration of 2.5 mCi/mL) (35). It is injected endoscopically in four quadrants of the submucosa layer around the tumor one day before the surgery, and the radioactivity of LNs is measured using a hand-held gamma probe at surgery, in order to detect any isotopically “hot” nodes, defined by a radioactivity level 10 times higher than background (28,31,33,36,37).

Conversely, the colorant dye (in this case 0.25mL of 2% patent blue V in each quadrant) is injected during the surgery into the submucosa in the same manner as the injection of the radioisotope or into the subserosa from luminal outside (27,29,32,33). The tracers can be injected in both ways, as long as they are injected precisely in the area surrounding the tumor (34). Intraoperatively, the gastrocolic ligament is divided to visualize all possible directions of lymphatic flow from the stomach (31). All LNs stained within 15 minutes after dye injection are considered to be ‘‘blue’’ nodes (28,31,36,38).

Depending on the location, the lymph of the upper left part of the stomach is directed to the left gastric and pericardial nodes. Lymph originated from the pylorus is routed to the supra-pyloric and the right supra-pancreatic nodes. Lymph from the fundus flows to the left supra-pancreatic nodes and the left gastroepiploic nodes via the splenic nodes. Lymph from the pyloric and distal portion is

routed to the right gastroepiploic node and then flows to the sub-pyloric nodes. From all regions, the lymph stream continues to the celiac nodes (29). See **Annex 3**.

The gastric lymphatic basins are divided into five compartments based on their location along the major gastric arteries: left and right gastric artery, left and right gastroepiploic artery and posterior gastric artery. Most of the metastatic LN missed by sentinel node biopsy are located in the same lymphatic basin (36,39). Because of this, instead of pick-up biopsy (remove only the hot/blue nodes), it is recommended the sentinel basins dissection (SBD), which is a form of local excision of the lymphatic basins which contain the sentinel lymph nodes. This method has an accuracy rate of LN metastasis of 92.3%, whereas that in the pick-up method is 50% (30).

All hot/blue nodes are dissected and classified into hot node, blue node, both hot and blue nodes and basin nodes (nodes within the sentinel basins, but neither hot nor blue) and labeled with the respective lymph node station numbers (28,31,36,38). The harvested nodes are histologically examined intraoperatively by a pathologist with hematoxylin and eosin staining, using one representative cut plane of a frozen section for LN <4mm. For nodes thicker than 4 mm, a slice is made at a 2-mm interval parallel to the long axis (28,38). If a metastatic node is falsely diagnosed as negative intraoperatively by the hematoxylin and eosin staining, the node would have been already cleared during the SBD. Consequently, it would not have any influence on the disease-free survival of the patient (40). If during the intraoperative pathologic examination macro- or micrometastasis are detected, the surgery is converted to a standard gastrectomy with D2 lymphadenectomy (38).

Complications:

One of the possible complications is an allergic reaction to the radioactive tracer or to dye tracer. However, all studies highlight the safety of these methods. One of these studies (31) showed that no serious allergic reactions were observed after tracer injection, except for instances of transient pigmentation (0.3% of the subjects studied) and decreased pulse oximeter oxygen saturation (0.8%).

Other possible complications observed in a very low percentage of patients (less than 1% each one) were: pneumonia, pancreatic or anastomotic leakage, intra-abdominal abscess, anastomotic stenosis, bleeding, and thrombus/embolism.

3. JUSTIFICATION

Gastric cancer is one of the most common causes of cancer death worldwide. As we have seen before, its incidence and the percentage of deaths related to it are unevenly distributed across territories (5).

Early gastric cancer is defined as a carcinoma confined to mucosa and/or submucosa (T1), independently of the presence of lymph node metastases. In Asian countries, with the highest rate of gastric cancer, 50% of the newly diagnosed cases are early stages thanks to the population screening programs carried out. However, in Western countries, despite growing awareness of the disease, the new cases are usually diagnosed in more advanced stages, mainly because of the lack of screening programs.

The only curative treatment in patients with stomach cancer is surgery. The presence of ganglion affectation in most cancers means that it is a disseminated disease and, consequently, systemic treatment is indicated (like chemo or radiotherapy). Nevertheless, in gastric cancer the presence of regional lymph node metastases is still an indication of surgery. This treatment consists of performing a complete resection of the tumor, doing a complete or a partial gastrectomy depending on the localization of the tumor. Although there has been controversy for many years, nowadays in our reference center (Hospital Universitari Dr. Josep Trueta) and in most of Western hospitals a D2 lymphadenectomy is performed in addition to the gastrectomy, independently of the T and N stage of the tumor (22,23).

Lymph node involvement in gastric cancer is related to the depth of tumor infiltration. In patients with early gastric cancer (T1), lymph nodes metastases are present in 5-20% of the patients, which means that more than 80% undergo an extensive and, sometimes, unnecessary lymphadenectomy, increasing intraoperative and/or postoperative morbidity (28). However, there is no precise preoperative tool to predict the exact status of LNs (28).

Recently, in order to seek a solution to reduce this morbidity in patients with low risk of lymph node metastases, the physicians have begun to consider the use of the sentinel node, already used in breast cancer and melanoma.

In the last 15 years, several studies have been carried out to determine the best technique for detecting sentinel lymph nodes in gastric cancer and to prove their accuracy and safety. Many authors have reported that sentinel node mapping is feasible in gastric cancer even though the lymphatic pathway of the stomach is multidirectional. Furthermore, these studies point out the necessity for clinical trials comparing the use of the sentinel node technique with the use of extensive lymphadenectomy. Due to how recent this issue is, the clinical trials started (mostly in Asian countries) have not published results yet (38). If adequate and statistically significant results

were obtained after these trials, it could offer the possibility of changing the extent of lymphadenectomy which would lead to a decrease in operative morbidity and an improvement in the patients' quality of life.

The sentinel lymph node technique differs between the existing studies. Some of them use a colorant dye, whereas others use a radioactive isotope. Best results have been obtained when both methods have been used together.

The study proposed is a clinical trial comparing the D2 lymphadenectomy with the use of sentinel node mapping with dual tracer (patent blue V and ^{99m}Tc-Antimony Sulfur Colloid) in patients with early gastric cancer. We have chosen this dye because its cost-effectiveness. Indocyanine green have shown great results, too. However, it needs a special camera to detect fluorescence, which is not available in all centers and would greatly raise the price of the trial.

We have selected these patients because they are the ones that would most benefit from this technique, since they are those that present a minor rate of lymphatic affectation. Patients with advanced gastric cancer would not benefit because the lymph node affectation rate is very high, so the extended lymphadenectomy is well-indicated.

Despite this technique has proved its accuracy and sensitivity, it must show a good morbidity, oncological and quality of life results in clinical trials to approve its implementation in the clinical practice.

Our study is about a recent topic and there are no results from the started clinical trials yet. In addition, they are mostly made in Asian population, so there is a need of a study in Caucasians to see if they would benefit also of this technique, despite the fact that the diagnosis in early stage in Western countries is more difficult. Furthermore, this study is clinically relevant because if the results are positive, patients who undergo the sentinel lymph node technique would avoid an extend surgery, reducing the morbidity, the days of hospitalization and increasing the quality of life.

4. HYPOTHESIS

The use of sentinel node mapping using dual tracer (patent blue V and ^{99m}Tc-Antimony Sulfur Colloid) in patients with early gastric cancer achieves similar oncological results and reduces the postoperative morbidity as compared to the conventional D2 lymphadenectomy.

5. OBJECTIVES

5.1. MAIN OBJECTIVE

- **General:** the main aim of this study is to analyze whether the use of sentinel node mapping using dual tracer in patients with early gastric cancer achieve similar oncological results and reduce the postoperative morbidity as compared to the conventional D2 lymphadenectomy.
- **Specific:**
    - Assess if the sentinel node technique achieves a disease-free survival and an overall survival rate comparable with the conventional surgery, after five years of follow-up.
    - Compare the complications rates during the first month between both techniques.

5.2. SECONDARY OBJECTIVES

- Compare length of stay between the two treatment options.
- Compare the quality of life between the two groups in short and long term (in each follow-up visit).

6. METHODS

6.1. STUDY DESIGN

The study will be a multicenter, randomized, controlled clinical trial.

The patients will be randomly divided in two groups in a 1:1 ratio. The first group will consist of those patients receiving the sentinel node mapping (plus gastrectomy) and, the second group will consist of those patients receiving the conventional surgery (gastrectomy + D2 lymphadenectomy).

6.2. SETTINGS

Due to the low incidence of early gastric cancer in our reference center, recruitment should last more than ten years to obtain a representative sample for the study. To solve this problem, we have decided to do a multicenter study. In this, we will include the following hospitals:

- Hospital Universitari Dr. Josep Trueta in Girona (our reference center).
- Hospital Universitari Vall d'Hebron in Barcelona.
- Hospital Clínic i Provincial in Barcelona.
- Hospital del Mar in Barcelona.
- Hospital de la Santa Creu i Sant Pau in Barcelona.
- Hospital Universitari de Bellvitge in l'Hospitalet de Llobregat.
- Hospital Universitari Germans Trias i Pujol in Badalona.

These hospitals have been selected for the number of people they care for, the technologies they have and their high surgical standards. Due to the large population that these hospitals cover (since they are reference centers in Catalonia), we make sure to receive approximately the same number of patients or more than in Hospital Universitari Dr. Josep Trueta. By doing this, it will allow us to shorten the study period, making it more feasible.

With the purpose of form a Steering Trial Committee and favor the communications between the Hospitals, a principal investigator will be assigned in each center.

6.3. STUDY POPULATION

6.3.1. Participants

Patients diagnosed with gastric cancer at early stage by the digestive and general surgery service of the hospitals participating in our study. Inclusion and exclusion criteria are explained in table 6.

Table 6: Inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
- Gastric adenocarcinoma diagnosed by means of a preoperative endoscopic biopsy (single lesion). - T1N0 in the preoperative evaluation (assessed by upper endoscopy and CT). - Tumor size ≤3 cm[5]. - Location: 2cm away from the pylorus or cardia. - Age of patient 18 to 80. - Eastern Cooperative Oncology Group (ECOG) score 0 or 1 or Karnofksy Index ≥70% (Annex 4). - Patients who have read, understood and have signed the informed consent.	- Pregnancy. - Inoperable tumor due to the comorbidities of the patient[6]. - Criteria of endoscopic submucosal dissection. - Multiple lesion or synchronous or metachronous (within 5 years) malignancies. - Prior endoscopic treatment to same lesion or prior gastric surgery. - Non-Caucasian ethnicity.

6.3.2. Sample size

For estimating the sample size, we used the online calculator GRANMO.

The hypothesis of our study is that use of sentinel node mapping instead of D2 lymphadenectomy in patients with early gastric cancer will be traduced in a reduction in postoperative morbidity, maintaining the same overall survival and disease-free survival.

Although we have more than one main objective, to calculate the sample we will look at the complication's rate expected in the two methods. As overall survival and disease-free survival values are expected to be equal in both techniques, we cannot use this variable to calculate the sample with GRANMO, since it is necessary to have different proportions of the variable in the two groups.

Reviewing the bibliography, we have found a complication rate for D2 lymphadenectomy that can range from 30-40%. After commenting it with the surgeons and with the methodological tutor, it has been decided that the highest value (40%) will be taken into account, since we have to put ourselves in the worst-case scenario. Due to the lack of literature about the expected complications of the sentinel node technique in gastric cancer, it has been decided by clinical judgment that the expected complication rate would be 20%.

[5] It has been demonstrated that tumor size is related to the probability of developing lymphatic involvement.

[6] Severe and chronic intercurrent disease, presence of metastasis and severe impairment of respiratory function (FEV1 <1.500cc; pO_2 <75 mmHg).

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 95 subjects are necessary in the first group and 95 in the second to detect statistically significant difference between the two proportions, which is expected to be 0.4 for the first group, and 0.2 for the second. It has been anticipated a drop-out rate of 15%.

Estimated time of recruiting:

According to the data provided by our hospital, the incidence of patients that fulfil our inclusion criteria in Hospital Universitari Dr. Josep Trueta may vary between 10-15 cases/year. We will considerate that 10% of the patients may not want to participate.

As mentioned above, we will do a multicenter clinical trial to get that sample necessary in less years, making the study more feasible. We have included in our study seven reference hospitals of Catalonia. The incidence in these centers is expected to be equal to or greater than expected in Girona, since those centers address more patients.

We need 190 patients to do our clinical trial. Consequently, we have calculated that to manage to reach the required number of patients to carry out our study, we will need two years and a half approximately.

6.3.3. Sample collection

A non-probabilistic consecutive sampling will be performed in this study. All patients with EGC seen by the digestive unit of the hospitals participating in this study that fulfil the inclusion criteria will receive information about the study, and will be requested to participate in. The patient will receive an information sheet which describes the study (**Annex 5**) and the informed consent (**Annex 6**), which will be signed by the subject if he/she agrees to participate in the trial. They will be considered recruited for the study only after reading and signing these documents.

6.3.4. Withdrawal criteria

We define the withdrawal of a clinical trial for individual participant as a condition when the trial therapy, follow-up and documentation are terminated prematurely. Before starting the trial, we have to establish the criteria that will force us to interrupt the study in the subjects. Our withdrawal criteria are:

- Active withdrawal by the study participant. We must take into account that any participant can withdraw him/her informed consent at any time and, consequently, withdraw from the clinical trial.
- Loss of contact: we will consider it when the patient does not attend two follow-up visits. The hospital will try to contact him/her via phone or text message during the following days and make a new appointment.

- Belatedly identified violation of the criteria for inclusion and/or exclusion that imply the premature termination of the therapy:
    - The patient becomes pregnant.
    - The patient on his/her own submits to a treatment not included in the study.
    - The patient is diagnosed with another metachronous cancer.
    - If the tumour does not fulfil the inclusion criteria after the surgery and the histological examination.
- The patient has a relapse or progression of gastric cancer after the surgery.

Subjects withdrawn from the trial will not be replaced. An intention-to-treat analysis will be used for missing data.

6.4. VARIABLES

6.4.1. Independent variable

Our independent variable is the surgical intervention. Therefore, in our study, the independent variable will be the use of the sentinel node mapping or the D2 lymphadenectomy.
As it is a nominal qualitative variable, it will be expressed in proportions or percentages.

6.4.2. Dependent variables

Main dependent variables:

- **Disease-free survival rate:** subjects in the trial who are alive and cancer free after five years. It is considered a nominal qualitative variable, and we will express it in percentages or proportions.
- **Overall survival rate:** it is often stated as a five-year survival rate, which is the subjects in a study or treatment group who are alive five years after their diagnosis or the start of treatment. It is considered a nominal qualitative variable, and we will express it in percentages or proportions.
- **Morbidity:** postoperative morbidity occurring within 30 days after the surgery will be reported and graded according to the modified Clavien-Dindo severity classification (**Annex 7**). This scale was created to facilitate a consensus in reporting postoperative complications, and it divides them in five grades of severity (with some subdivisions). It will be considered an ordinal qualitative variable.

Secondary dependent variables:

- **Length of stay:** defined as the total number of days spent in the hospital (measured from the patient's admission to the discharge of the hospital). It is a quantitative discrete variable.
- **Quality of life (QoL):** QoL will be measured using the European Organization for Research and Treatment of Cancer (EORTC) questionnaires (**Annex 8**). These questionnaires have been developed to assess the quality of life of cancer patients and have been validated in some types of cancer, such as GC. There is a basic questionnaire applicable to all patients with cancer, and another one that is cancer-specific. The patients from both groups of treatment will be requested to fill out the core questionnaire (QLQ-C30) and the gastric cancer-specific one (QLQ-STO22) when the patient is discharged and during the control visits. These visits will be every 6 months during the first 3 years, and then each year, until complete the 5 years of follow-up realized in this study. Both of them have been validated and translated to Spanish. The higher score the patients gets, the more disability he/she presents. The statistical professional will use a linear transformation to standardize the raw score, so that scores range from 0 to 100. Changes in scores of 5–10 represent a small difference (but clinically significant); 10–20 represent a moderate difference while those above 20 represented large differences. We can define it as a quantitative discrete variable.

6.4.3. Co-variables

The co-variables are factors that can influence our result as they are related to our independent and/or dependent variables. We will include them in the multivariate analysis in order to assess its impact on the results of the study.

- **Age:** it will be obtained from the identity card of the patient or other official documentation provided by the patient at the admission department. It is a discrete quantitative variable and it will be expressed in years.
- **Sex:** it will be obtained from any official documentation provided by the patient at the admission department. It is a dichotomous nominal qualitative variable and it will be assessed by male or female.
- **Extension of gastric resection:** it is a dichotomous nominal qualitative variable (gastrectomy or partial gastrectomy). The tumors affecting the lower part of the stomach can be treated with partial gastrectomy. The tumors affecting the upper part or all the stomach are treated with total gastrectomy. However, it will be decided personally according to the characteristics of the patient and the tumor.
- **Type of surgery:** it is a dichotomous nominal qualitative variable (laparoscopy or laparotomy). There is no agreement on what type of surgery must be done. It will be decided

personally according to the characteristics of the patient and the tumor and the experience of the surgeons.

- **Surgical and anesthetic times:** it is a continuous quantitative variable. It will be expressed in minutes. We will record the time when the anesthesia is introduced, when the surgery is started, when the patient is closed and when the anesthetic effect disappears.
- **Removal of nearby organs:** it is a nominal qualitative variable. It will be expressed according the organ removed. Its realization will be decided during the operation if the tumor is more extended than what we thought before starting the surgery.
- **pTNM:** it is a discrete quantitative variable. It will be assessed during the surgery in order to see if the cTNM is equivalent to the pTNM.
- **Mean number of dissected lymph nodes:** it is a discrete quantitative variable. It will be assessed during the surgery.
- **American Society of Anesthesiology (ASA) classification:** it is an ordinal qualitative variable. The patient will be classified in one stage according the anesthesiology assessment (in the preoperative visit).
- **Health center:** we will take into account the possible inter-center variability, because this may alter the results depending on the center's experience. Each one of the participating hospitals will receive a number (1-7), in order to convert this variable in a discrete quantitative one.

All the variables are summarized in the table below.

Table 7: Variables of the study.

Variables	Type of data	Categories or values	Measure instrument
Surgical intervention	Dichotomous nominal qualitative	Sentinel node mapping/ D2 lymphadenectomy.	
Disease-free survival rate at 5 years	Dichotomous nominal qualitative	Yes/no	Disease-free or not after 5 years of follow-up
Overall survival rate at 5 years	Dichotomous nominal qualitative	Death/alive	Alive or death after 5 years of follow-up
Morbidity (Clavien-Dindo scale)	Ordinal qualitative	I-V	Application of the scale

Variables	Type of data	Categories or values	Measure instrument
Length of stay	Discrete quantitative	Number of days	Subtract to the "date of admission" and the "date of discharge" from the hospital
Quality of life (QLQ-C30 and QLQSTO-22)	Discrete quantitative	0-100	Application of the questionnaires
Age	Discrete quantitative	Number of years	Patient's documentation
Sex	Dichotomous nominal qualitative	Male/female	Patient's documentation
Extension of gastric resection	Dichotomous nominal qualitative	Total/partial gastrectomy	Annotated by the surgeon
Type of surgery	Dichotomous nominal qualitative	Laparoscopy/laparotomy	Annotated by the surgeon
Surgical time	Continuous quantitative	Minutes	Annotated by the operating room nurse
Anesthetic time	Continuous quantitative	Minutes	Annotated by the anesthetist
Removable of nearby organs	Nominal qualitative	Organ removed (spleen, pancreas…)	Annotated by the surgeon
pTNM	Discrete quantitative	T1-T4, N0-N3, M0-M1	Annotated by the surgeon after the surgery and pathological examination
Mean number of dissected lymph nodes	Discrete quantitative	Number of lymph nodes	Annotated by the surgeon
ASA	Ordinal qualitative	I-VI	Staged by the anesthesiology
Health center	Discrete quantitative	1-7	Annotated by the surgeon

6.5. RANDOMIZATION

All patients seen or referred to the esophagogastric surgery department of the hospitals involved in this study that fulfil the inclusion criteria, who are been informed by the surgeon, have read the information sheet and have signed the informed consent, will be eligible for our trial.

Our sample system is consecutive. Because of that, the used randomization system does not need to know the entire sample before randomizing it. This process will be done using a covariate adaptive randomization where a new patient is sequentially assigned to an intervention group by taking into account the previous assignments of participants.

This procedure will be done by a statistical specialist using the software SPSS. Consequently, the surgeon will not have access to the randomization sequence, and he or she will know which intervention has to execute by receiving a closed packet two weeks before the intervention.

The main surgeon in each intervention will be also randomized in order to decrease inter-surgeon variation.

6.6. PROCEDURES

6.6.1. Before including the patient in the study

First of all, patients diagnosed with gastric cancer seen or referred to the esophagogastric surgery department of the hospitals involved in this study will undergo some tests to stage cancer. Initial diagnosis will have been made by endoscopy and biopsy of the lesion. The staging of the disease will be made by:

- Abdominal and thoracic computed tomography (CT): it can be practiced with or without contrast (parenteral or enteral way). CT scans help to confirm the location of the cancer and the extent of the affection.
- Ecoendoscopy: it allows you to assess the spread of the cancer into the layers of the stomach wall, the nearby lymph nodes and other structures. Provides further assessment of the T and N stage.
- Laparoscopy in some cases.

Other preoperative tests than can be practiced are:

- Complete blood test.
- Functional respiratory tests.

With this information, the patients will be classified in different stages according to TNM classification. If the patient fulfils the inclusion criteria of our study, without complying any of the

exclusion criteria, he/she will be candidate to participate in our clinical trial. Consequently, the physician responsible of the patient will expose the case to the esophagogastric department, and the surgical team will make an appointment with him/her.

6.6.2. Pre-intervention visits

6.6.2.1. First visit

In this meeting, we will explain to the patient the treatment of his/her illness, its surgical approach and complications. In addition, we will inform about the study, its aim and objectives. We have to ensure that the patient understands all the given information, and answer all the patient's questions. We have to remind the patient that his/her participation in the study has to be completely volunteer, and encourage a good patient-surgeon relationship, based on empathy and understanding. After that, we will give him/her the information sheet about the study (**Annex 5**), advising to read all the papers and discuss it with his/her family. We must remark that all the doubts and concerns that he or she could have the following days will be resolved in the next appointment. We will give him/her also the informed consent (**Annex 6**).

6.6.2.2. Second visit

The patient must have had enough time between the two visits to process all the information. If he/she has some doubts, we will answer them, always based on the best data available. If the patient agrees to participate in the clinical trial, he/she must sign the informed consent of the study (**Annex 6**) and the informed consent of the surgery. Only then we will be able to include him/her to the trial. Once included, we will make an appointment with anesthesiology and we will collect some information about the patient on the data sheet (**Annex 9**):

- Number of clinic history.
- Age.
- Gender.
- TNM stage.
- Expected date of surgery.
- Type of surgical resection planned.

As explained before, the patients will be sorted in two intervention groups: those who will submit to the sentinel node mapping + gastrectomy, and those who will undergo gastrectomy + D2 lymphadenectomy. Once we know which intervention group the patient belongs to, we will write it down on the data sheet (**Annex 9**).

Normally, in surgical clinical trials, the surgeon open the envelope given by the statistical professional and knows the patient's group intervention on the surgery's day. However, due to the necessary steps to perform the sentinel node technique, we will have to know the patient's group

earlier (2 weeks before in our trial), because patients belonging to this group will have to come to the hospital the day before surgery to undergo some tests. Given the cost and possible discomfort and complications of such tests, we have not considered ethical to perform them in subjects who will undergo conventional surgery.

6.6.2.3. Anesthesiology visit

In this visit, the physician will require the consent of the patient to reserve blood from the blood bank for the surgery's day. Moreover, the anesthesiologist will classify the patient into the different stages of ASA classification (**Annex 10**). In addition, the patient will undergo preoperative blood tests. This information will be added to the data collection sheet (**Annex 9**).

6.6.3. Day prior to surgery

Only patients sorted in "sentinel node mapping group" will have to attend to the hospital. The patient will undergo the following tests:

- **Upper endoscopy:** the tumor will be located. Thereafter, the doctor will proceed to a submucosal injection of ^{99m}Tc-Antimony Sulfur Colloid (one-half milliliter at a concentration of 2.5 mCi/mL) in the four quadrants of the lesion.
- **Lymphogammagraphy:** this technique will allow us to obtain the tumor lymphatic drainage pattern. The use of sequential images allows to differentiate between the first of the LN to receive the drainage and the rest of secondary nodes.

Subsequently, the patient will be discharged home to enter the next day.

6.6.4. Intervention day

- The patient will attend to the hospital at the time according to the scheduled surgery.
- Before starting the surgery, one member of the surgery team or a nurse will fil the parameters previous to surgery on the data collection sheet (**Annex 9**).
- General anesthesia and prophylactic antibiotic therapy with 2 grams of amoxicillin-clavulanic intravenous.
- Position: supine position.
- Antisepsis and surgical field sizing.
- Approach ways: the decision will be personally made and based to the best available data.
    - Open surgery: subcostal bilateral incision.
    - Laparoscopy: placement of 5 trocars (Hasson supraumbilical, 5mm right hypochondrium, 5mm right flank, 12mm left flank and 5mm left hypochondrium).

6.6.4.1. Sentinel node mapping group

- Once the tumor is localized, fine-needle injection of patent blue V (0.25mL of 2% patent blue in each quadrant) will be performed into the four quadrants of the lesion. Fifteen minutes later, marked with blue ink we can locate the first LN (one or several; blue nodes) to receive the tumor lymphatic drainage (sentinel node/s).
- Simultaneously, the radioactivity of LNs will be measured using a hand-held gamma probe at surgery, in order to detect any isotopically "hot" nodes. This colloidal substance will have been injected intratumorally the day before the intervention and accumulated in the first tumor drainage nodes.
- All hot/blue nodes will be dissected and classified into hot node, blue node, both hot and blue nodes and basin nodes (nodes within the sentinel basins, but neither hot nor blue) and labeled with the respective lymph node station numbers. In the case of more than one ganglion, they will be numbered in order of more uptake to less, with the number one being the most capturing. This data will be collected in data sheet (**Annex 9**).
- The harvested nodes are histologically examined intraoperatively by a pathologist with hematoxylin and eosin staining, using one representative cut plane of a frozen section for LN <4mm. For nodes thicker than 4 mm, a slice will be made at a 2-mm interval parallel to the long axis.
- Partial/total gastrectomy will be performed as explained in section **6.6.4.2.**
- If during the intraoperative pathologic examination macro- or micrometastasis are detected, the surgery will be converted to a standard gastrectomy with D2 lymphadenectomy, as explained below.

6.6.4.2. Gastrectomy + D2 lymphadenectomy group

The decision to perform a total or partial gastrectomy will be made personally according to the characteristics of the patient and the tumor. The partial one is recommended when the cancer affects only the lower part of the stomach, whereas the total one is indicated when the tumor affects all the stomach or the upper part. The reconstructive surgery will be an esophagus/gastro-jejunostomy end-to-side Roux-en-Y.

- **Total gastrectomy:** ligature and section of the main vessels of the stomach are made in its origin: right and left gastric and gastroepiploic vessels, and this makes lymphadenectomy include all nodes of the first level.
    1. Separation of the omentum of the transverse colon and cranial extension of the dissection with section of the short vessels (station 4sa) until reaching the left diaphragmatic pillar.

2. Caudal extension of the dissection until the right gastroepiploic artery is sectioned, including lymph nodes of station nº 4d and 6.
3. The pyloric artery is identified and sectioned at the upper edge of the first duodenal portion (station 5), which will allow us to perform the duodenal section with mechanical suture (endoghia, white load).
4. After sectioning the duodenum, we access to the celiac trunk (station 9), skeletizing it, following the lymph nodes surrounding the common hepatic artery (station 8a) and the hepatoduodenal ligament (station 12a), and from here the dissection is extended: first upwards, to include the paracardial ganglia (station 1 and 2), and also to the left, to include stations 10 and 11, on the splenic artery and spleen's hilum. We also section the left gastric artery at its origin (station 7). The stomach is completely released and without vascularization, attached to the patient only by the esophagus. The station 3 is extracted with the stomach.
5. We select a segment of jejunum about 25 cm from the angle of Treitz where it is sectioned (endoghia, white load) and extends the section to a part of its meso to facilitate its ascent.
6. The distal portion of the sectioned intestine is passed through the transverse mesocolon to the supramesocolic compartment and the proximal end is latero-lateral anastomosed with mechanical suture (endoghia, white charge) to the jejunum, about 50cm from the raised intestinal margin.
7. The esophagus is sectioned one centimeter above the cardia with a blue charge endotractor. The piece is removed.
8. Though the patient's mouth, a probe is passed with 25mm circular suture head applied at the end. Once the catheter has been removed and the mechanism inserted into the esophageal fundus, a small suture is made in the tobacco pouch around the anvil. The circular suture machine is fitted to the head to perform the esophagojejunal anastomosis.
9. Jackson Pratt drainage will be left at the anastomosis level.

- **Subtotal gastrectomy:**
    1. The surgeons will follow the same steps described for total gastrectomy, stopping the dissection of the major curvature in the transition zone from body to fundus and thus respecting the short vessels.
    2. In the lower curvature, the same steps are also followed, with lymphadenectomy of ganglionic groups 8 and 9 and posterior section of the left gastric artery at its origin

including in the resection of all the lymphograsis tissue of the minor curvature (groups 3 and 7).

3. The transaction of the stomach is made 3-4 cm below the cardia with mechanical suture (endoghia, blue load) and the two anastomoses are performed, the wing foot is a jejunum-jejunostomy lateral-lateral 45 cm below the margin of the raised wing.
4. The upper anastomosis is a lateral-lateral gastrojejunostomy in the anterior gastric face, both performed with mechanical suture. The piece is removed.
5. A Jackson Pratt drain is placed at the anastomosis level.

Once the surgical intervention has been finished, the surgeons will close the muscle-aponeurotic plane with PDS I, an antibacterial suture. After that, they will close the skin with skin staples.

At the end of the surgery, the surgical part will be dissected. Each node group will be shipped separately, in different containers and send to the pathologist for a histologic study.

One member of the surgeon team will fill the following parameters of the data sheet:

- Extension of the resection (total/partial gastrectomy).
- Type of surgery (laparotomy/laparoscopy).
- Need of removable of nearby organs.
- Number of LN dissected.

An operative room nurse will write down on the data sheet the surgical time, and the anesthesiologist will do the same with the anesthetic time.

6.6.5. Anatomopathological results

Once we have the anatomopathological analysis of the surgical specimen and lymphadenectomy, we will collect the following data (**Annex 9**):

- pTNM.
- Histological type.
- Morphology.
- Location.
- Size.
- Proximal margin.
- Distal margin.
- Vascular, lymphatic and perineural infiltration.
- Number of resected nodes.
- Number of total infiltrated nodes.
- Number of lymph nodes infiltrated in each ganglionic group.

6.6.6. Postoperative period

Postoperative morbidity occurring within 30 days after the surgery will be reported and graded according to the modified Clavien-Dindo severity classification. During the stay in the hospital, any complication will be recorded in the data sheet (**Annex 9**) by the responsible doctor.

- **During the hospitalization:**
    - Absolute diet, parenteral nutrition.
    - Nasogastric tube 2-3 days.
    - Control of pain, wounds and drainage.
    - Control of any complication.
    - Thromboembolic prophylaxis.
    - Analytical controls.
    - Respiratory physiotherapy.
    - Esogastroduodenal transit on 5th postoperative day (if total gastrectomy has been done).
    - Begin progressive oral diet, following dietician guidelines.
    - The day the patient is discharged, he/she will be requested to answer the QoL questionnaires. In addition, we will annotate in the case report form the total amount of hospitalization days. The length of the stay will depend on the necessities and requirement of the patient.

6.6.7. Follow-up

- The patient has to be conscious that any complication may be important, so he/she will have to come to the hospital anytime he/she need it, once the discharge has been done. In these cases, the doctor will write the information on the data sheet.
- Every 6 months during the first 3 years:
    - General analytical: hematology, coagulation, biochemistry, nutritional determinations and tumor markers.
    - Thoracic and abdominal CT.
- Once a year, after the first 3 years and until complete the 5-year follow-up: analytical and thoracic and abdominal CT.
- In cases of partial gastrectomy, an upper endoscopy will be performed once a year.

In every control visit the patient will be required to answer the quality of life's questionnaires (QLQ-C30 + QLQSTO-22) and it will be recorded in the data collection sheet.

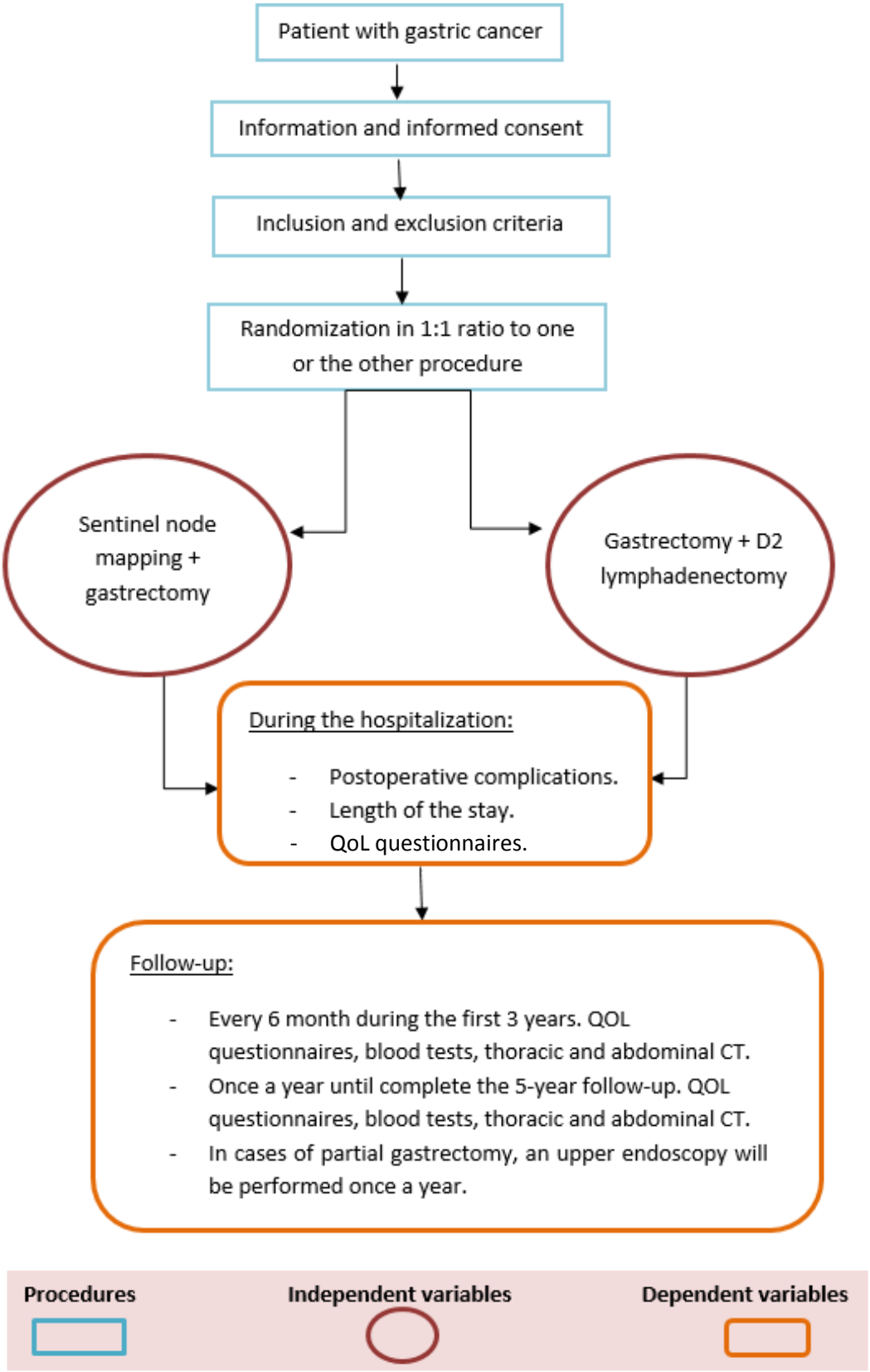
The disease-free survival rate and the overall survival rate will be considered after 5 years of follow-up, and added to the data sheet.

We have to take into account that some of the patients included in the study may die during the follow-up. The data of lost patients will be used until last observation carried forward.

All the detailed information in the data collection sheet (**Annex 9**) will be entered into a database to be analyzed.

A diagram has been created to synthesize the study intervention.

Figure 12: Intervention of the study.



6.7. SAFETY ASSESSMENT

We can define an adverse event as the appearance or worsening of any sign, symptom or undesirable clinical state that occurs after the start of the study intervention. The event may or may not be related to the treatment, and is not the same as a side effect, because it is not always clear whether the intervention has caused the event. Clinical trials record all adverse events occurring during the trial in order to help determine which one might be associated with the intervention, and which might not.

- **Severity of adverse events:** it will be assessed by the investigator as follows:
  - Mild: adverse event that may require only minimal treatment and does not generally interfere with usual activities of daily living.
  - Moderate: adverse event which needs additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but represents no significant or permanent risk of harm to the participant.
  - Severe: adverse event that interrupts usual activities of daily living, and generally requires intensive therapeutic intervention.
- **Causality of adverse events:** the causal relationship between an adverse effect and an intervention must be assessed by the investigator, who will classify it as related or unrelated to studied interventions. The degree of certainty with which an event is attributed to the study intervention will be determined by how well the event can be understood in terms of: plausibility supported by the temporal relationship, similar reaction observed previously with similar procedure or known physiopathology of the adverse effect and plausible context.
- **Reporting procedures for adverse events:** any adverse effect associated with the intervention will be reported and documented in the data collection sheet (**Annex 9**). Each one should be described: its duration (dates of onset and resolution, if resolved), severity, relationship with the intervention and treatment or action taken to solve it.

6.8. DATA COLLECTION

Before starting the trial, each participating hospital will be trained in the procedure method in order to guarantee the homogeneity of the procedures.

In order to preserve the patient confidentiality, an identification number will be given to each patient.

Previously to the surgery, all the patients' data will be collected from the clinical and surgical records, analytic tests, anthropometric measures, and imaging techniques. All these parameters will be collected using the Patient data sheet (**Annex 9**). After the intervention, the extension of the resection, the type of the surgery, the need of removable nearby organs, the mean number of LN dissected and the anatomopathological results of the surgical piece will be added to the data sheet.

Patients will undergo follow-up visits: every 6 month (the first 3 years) and once a year until complete the 5-year follow-up. With the porpoise of guarantee the study adherence, all the patients will receive a phone call one week before the appointment.

All the visits will be performed by the same professional and the patient will be required to answer the QoL questionnaires in each visit. After each visit, the physician will complete the data collection sheet (**Annex 9**) in order to store all the patient's data.

7. STATISTICAL ANALYSIS

All statistical analysis will be performed with Statistical Package for Social Science (SPSS) for Windows®.

Univariate analysis:

In the univariate analysis, the variables will be defined as categorical or continuous.

The independent variable (intervention) is categorical. The dependents variables (overall survival rate, disease-free survival rate and morbidity) are also categorical, apart from the length of stay and quality of life, which are continuous.

The results will be expressed in percentages for the categorical variables. For quantitative continuous variables, if a normal distribution could be assumed, we will use mean and standard deviation; whereas if a normal distribution cannot be assumed, the median and the quartiles will be estimated.

Bivariate analysis:

To detect differences between the two intervention groups, a bivariant analysis will be performed.

In our study, the independent (the intervention performed) and the main dependent variables (overall survival rate, disease-free survival rate and morbidity) are categorical. To make the comparison between the intervention performed and morbidity, we will use a Chi-square test. To compare the intervention done with the overall survival and the disease-free survival rate, we will use the Kaplan-Meier estimator.

For the comparison between the independent variable with the secondary dependent variables (length of stay and quality of life), Student's t-test or Mann-Whitney U test will be needed as the independent variable is a categorical variable and the secondary dependent variables are quantitative.

Multivariate analysis:

A multivariate analysis will be performed to analyze the association between dependent and independent variables after adjusting for the effect of co-variables and to adjust the effect of co-variables, thus we will try to avoid potential confounders that could modify the results.

To facilitate the study of the morbidity variable, we will convert its value (5 ranges; I-V) into a simplified two-rank model. For this, states I and II (no need for intervention) will be assorted in group 0, while stages III-V will be assorted in group 1. After that, we will perform a multiple logistic regression model to assess its relation with the independent variable and the co-variables.

For the analysis of the association between the independent variable and overall survival and disease-free survival rate and its co-variables, we will use the Cox model.

Finally, to adjust the effect of co-variables in the relation between the independent variable and the secondary dependent variable (quantitative variables), we will use a multiple lineal regression model.

These analyses result in p values. A p value <0.05 will be considered significant.

Missing data:

During the post-operative period patients could die. The data of the lost patients will be used until last observation and will be carried forward.

8. ETHICAL AND LEGAL CONSIDERATIONS

Before carrying out the study, the Comitè Ètic d'Investigació Clínica (CEIC) from Hospital Universitari Doctor Josep Trueta must evaluate our research protocol. If the protocol is accepted, it will be sent to the CEIC of all the involved hospitals to be evaluated. Any recommendation from the committee will be taken into account in order to improve the procedure. The authorities of all participating hospitals will be asked to approve the study before starting it.

The study must be approved by the Asociación Española de Medicamentos y Productos Sanitarios (AEMPS).

Following the actual recommendations, our clinical trial will be submitted to ClinicalTrials.gov and will be registered with an International Standard Randomized Controlled Trial Number.

Our trial has been designed following the Ethical Principles for Medical Research Involving Human Subjects stated by the World Health Association in the Declaration of Helsinki (last revision in 2013). It will be performed also in agreement with the Spanish laws related to clinical trials:

- "Ley 29/2006 de 26 Julio, de garantías y uso racional de los medicamentos y productos sanitarios".
- "Ley 14/2007 de 3 de Julio, de investigación biomédica".

Previous to the inclusion, in order to respect the principle of autonomy, patients will be accurately informed about the study, highlighting that their participation is completely voluntary. Then, the information sheet (**Annex 5**) will be provided to all the candidates. On this sheet must be explained the aim and procedures of the study and the risks and benefits of the two interventions. We must ensure that the patient read and understand properly the information. Therefore, the patient (or the patient's legally acceptable representative) will be asked to sign the informed consent (**Annex 6**). Patients at all time have the right to leave the study with no impact on the quality of the health care that they will receive.

All the collected data will be kept strictly confidential, ensuring the compliance of the "Ley orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal". All patient data will be anonymous and codified when collected. An identification number will be used instead of patients' names to maintain confidentially of personal data.

Because of the long period needed to carry out this clinical trial, we will perform an additional data analysis in the middle of the study. With this information, we seek any hint (complications, poor cancer prognosis) that indicates that it is unethical to continue with the study. Once this point is

reached, the study will stop. This additional analysis will be performed by an independent committee.

Information regarding compensation, insurance, and indemnity is addressed in the insurance policy.

The investigators of this project declare that there are no conflicts of interests, and that they do not receive any economic compensation to collaborate in the study.

9. FEASIBILITY

This study will take place between July of 2017 and June of 2026 in 7 hospitals, all of them in Catalonia: Hospital Universitari Dr. Josep Trueta, Hospital Universitari Vall d'Hebron, Hospital Clínic i Provincial, Hospital del Mar, Hospital de la Santa Creu i Sant Pau, Hospital Universitari de Bellvitge and Hospital Universitari Germans Trias i Pujol. These centers are equipped medically and technologically to accomplish the objectives of the trial.

Before the starting of the study, we will organize various meetings with all the professionals involved. In these appointments, we will explain the objectives of the trial, and we will remark the importance of recording all data in the patient data sheet (**Annex 9**).

The study will be carried out by the staff of each hospital (digestologists, esophagogastric surgeons, nurses, anesthesiologists, nuclear physicians and pathologists). Interventions will be performed by the same team in each hospital.

We will hire a statistical specialist to randomize the study population and to do the statistical analysis. We will also employ a data manager, who will take charge of creating a database and introducing there the data collected by the nurses and doctors. The hospitals will provide the needed informatic equipment for data collection.

The hospital will provide all the necessary means regarding personnel salaries, surgeries and their material, and the consecutives visits and tests for the participants.

We have estimated that we will need 2.5 years to assess our sample. However, we cannot predict exactly the number of patients that will come to our participating centers, meeting the inclusion criteria. In addition, we have to take into account that patients may not want to be part of the study. For these reasons, is possible that the recruitment period will have to be prolonged.

10. WORK PLAN

PRINCIPAL INVESTIGATORS: Anna González, Jordi Gironès.

COLLABORATORS: surgeons of the esophagogastric department (EG) of the participating hospitals. From each of the 7 participating hospitals, a principal investigator will be chosen to create a Trial Steering Committee to coordinate the trial. We will also need the collaboration of the digestive department (DD), nuclear medicine service (NM), pathologists (P), anesthesiologists (A), nursing and administrating staff (NAS), a statistician (SS) and a data manager (DM).

The study will be totally achieved in 9 years. The organization of the study will be divided in 5 phases, explained bellow:

PHASE 1: Preparation and coordination phase (6 months): it will involve all the staff. This phase will be divided in the following steps:

- **Step 1**, Bibliographic research and protocol elaboration: prior to the first meeting, a large literature research will be done, in order to define the objectives and the study variables to answer the formulated hypothesis. The protocol of the study will be established in this point. We will present it to the Ethical Committee for its first evaluation.
- **Step 2,** Organizational meeting: several meetings will be performed to coordinate all the staff of the participating hospitals. Its aim is to check that the protocol has been correctly understood and to be sure that it is going to be followed as planned. Moreover, it will take place the training of the collaborators, to minimize the inter-observer variability. Any modification of the protocol will be made in this step.
- **Step 3,** Elaboration of a chronogram: a chronogram will be designed after the agreement between all the involved institutions and staff.
- **Step 4,** Evaluation of the protocol and authorizations: once the protocol is ready, we will present it to the Ethical Committee for its final evaluation and approval.

PHASE 2: Recruitment of patients, intervention and data collection (90 month, 7.5 years): this phase will be divided in the following steps:

- **Step 0,** Database creation: the data manager will perform this activity.
- **Step 1,** Sample collection and group assignment (30 months, DD, EG, SS): the recruitment of the patients will take place in the esophagogastric department of all the participating hospitals. The estimated time of recruitment will be 2.5 years, but it could be prolonged in case of not achieving the predefined sample. Only patients who meet the inclusion criteria and does not meet the exclusion ones will be taken into account. After that, the patients will

be informed about the clinical trial and asked if they want to participate. If they agree, they will be asked to sign the informed consent. Therefore, the patients will be randomized in one of the two groups.

- **Step 2,** Intervention (30 months, EG, A, NM, NAS, P): each group will receive one of the surgical interventions as we have explained in **Procedures section**.
- **Step 3,** Follow-up (90 months, EG): it will start after the intervention of the first subject. Every patient will be followed during 5 years counting from the day of the intervention.
- **Step 4,** Data collection (90 months, EG, NAS, DM, SS): it will start in the recruitment phase and it will last until de follow up of the last patient. In each control visit, all the parameters of our study variables will be collected by our team. All the information recollected, will be updated to our database. This collected data, will be periodically evaluated and analyzed by our statistician to control if the protocol is being followed.

As the study is longitudinal, we will organize meetings with the professionals engaged every six months, in order to verify compliance with the protocol and to assess the progression of the study. The aim of this is to identify deficiencies of the study design and correct the methodological defects.

PHASE 3: Data analysis (3 months, SS):

All data collected in the database will be analyzed using the appropriate statistical test by the statistician.

Because of the long period needed to collect our sample (2.5 years) and the period of follow-up required (5 years), we will perform two data analysis: one in the middle of the study and one at the end. With this information, in the middle of the process we will know if it is ethical to continue with our study. We will cancel the study if the results are negative. The medium-term analysis will be carried out by an independent committee.

PHASE 4: Results interpretation (3 months, investigators):

Once the statistical analysis will be done, the investigators will draw their conclusions about the results.

PHASE 5: Publication of the results (6 months, investigators):

With all the results, the investigators will write the corresponding articles and will be sent to different medical journals for their publication. In addition, the obtained results will be presented in surgery conferences.

11. CHRONOGRAM

ACTIVITIES	PERSONNEL	2017		2018		2019		2020		2021		2022		2023		2024		2025			2026	
		Jul-Sep	Oct-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun
PHASE 1: PREPARATION AND COORDINATION PHASE																						
Bibliographic research and protocol elaboration	Investigators																					
Organizational meeting and elaboration of the chronogram	All personnel																					
Evaluation and authorizations	Investigators																					
PHASE 2: RECRUITMENT OF PATIENTS, INTERVENTION AND DATA COLLECTION																						
Database creation	DM																					
Sample collection and group assignment	DD, EG, SS																					
Intervention	EG, A, NM, NAS, P																					
Follow-up	EG																					
Data collection	EG, NAS, DM, SS																					
Research team meetings	All personnel																					
PHASE 3: DATA ANALYSIS																						
Statistical analysis	SS																					
Medium-term analysis	SS																					
PHASE 4: RESULTS INTERPRETATION																						
Results interpretation	Investigators																					
PHASE 5: PUBLICATION OF THE RESULTS																						
Final report elaboration	Investigators																					
Publication	Investigators																					

12. BUDGET

For our budget, we have done the following estimations:

- Surgeries will not be included in the budget because they are part of the National Health System. Moreover, we will not include the postoperative appointments and diagnostic tests, because they are part of routine cancer control for gastric cancer. In addition, the medical devices necessary to perform this study are available in the study hospitals, so their purchase should not be added to the budget.
- We will hire a statistical specialist who will randomize the subjects in each intervention group and will code the patients of our study, control the data quality, do the statistical analysis and who will help us with the discussion and publication of the results if needed. The salary is 40€ per hour and approximately we believe that we will need his/her services for 80 hours, which means that the estimated cost will be 3.200€.
- We will also hire a data manager associated with the purpose of creating a database and doing the data quality control. The salary estimated will be 30€/hour and approximately 40 hours will be needed. Thus, the estimated cost will be 1.200€.
- Research team meetings will be performed every 6 months to coordinate the study and to check the project evolution. 15 coordination meetings will take place. We have calculated approximately 200 € per meeting. For the 15 meetings required, a total of 3.000 € is budgeted. The investigators and doctors involved in this study will not receive economic compensation for their collaboration.
- We have asked Dr. Rubió, head of nuclear medicine service from Hospital Universitari Dr. Josep Trueta, the costs of the nuclear tests, radiopharmaceuticals, and the displacement of the nuclear doctor to the operating room. He has responded that the Institut Català de Salut considers that the cost of this is 650€ per patient. In addition, we have asked to the esophagogastric department the price of an upper endoscopy (which costs 200€ per patient) and the patent blue V (which costs 10€ per patient).
- Documents necessary to perform this study include 190 copies of the informed consent and the information sheet, at 0.1€/unit, with a total of 38€. In addition, we will have to print the QoL questionnaires for the nine control visits of the 190 patients. The final cost will be 342€.
- We will need an insurance for the patients and for the researchers which is about 6.000€.

- Finally, in case the results are relevant and we decide to publish them, we can approximate that 2.800 euros will be needed, knowing that the costs of publications are around 1.500€ and the national dissemination in the next congress will be around 1.300 euros.

All the planned costs are exposed in the following table:

Table 8: Budget proposal.

	BUDGET PROPOSAL		
	COST	**QUANTITY**	**TOTAL COST**
STAFF			
Statistical specialist	40€/hour	80 hours	3.200€
Data manager	30€/hour	40 hours	1.200€
Coordination meetings	200€	15 (each 6 month during 7.5 years)	3.000€
MATERIAL AND SERVICES			
Preoperative endoscopy	200	95 patients	19.000€
Patent blue V	10€/patient	95 patients	950€
Lymphogammagraphy pre- and intraoperative, preparation of the radiopharmaceutical and displacement of the nuclear doctor to the operating room	650€	95 patients	61.750€
Information sheet and informed consent	0.1€/unit x 2	190 subjects	38€
QoL questionnaires	0.1€/unit x 2	190 patients x 9 times	342€
Insurance policy			6.000€
PUBLICATION AND DISSEMINATION			
Cost of publications	1.500€	1	1.500€
Registration to National meeting of *Spanish association of surgeons*	700€	1	700€
Accommodation	600€	1	600€
TOTAL			
			98.280€

13. LIMITATIONS OF THE STUDY

Reviewing our clinical trial protocol, several limitations have been detected, and they must be taken into account because they can interfere in our study.

First of all, although our study design is a clinical trial (the top study to produce evidence), a blind design is not possible. That means the patient, doctors and the research team will know in which approach is the patient included. As we have explained in **Procedures section**, the patients who will undergo sentinel node mapping have to submit to some tests previous to the surgery. Due to its cost and possible complications/discomfort, we have not considered ethical to perform this tests to patients who will endure a D2 lymphadenectomy. With the intention to overcome this limitation, the statistician will be blind and will not be aware of which participant belongs to which group. Moreover, to reduce this possible information bias, we have tried to select objective variables (disease-free survival, overall survival, postoperative morbidity and length of stay). Nevertheless, the variable "quality of life" is subjective, and the knowledge of the intervention received can influence patients' perception of the effectiveness of the treatment.

Another possible cause of information bias could be the heterogeneity in data collection. Especially in a multicenter study like this, we have to ensure that all the professionals engaged collect the same information in the same way. To make it easier, we have created a data collection sheet with a view to standardize the data and reduce the missing information. Training on how to perform the control visits will also be provided before starting this study, in order to minimize the inter-observer variability.

In the interest of reducing the inter-surgeon variation and its bias, the surgeons participating in each hospital will be randomized. The experience of the center can also condition the results obtained. We will try to minimize this possible bias including the different centers in the multivariate analysis.

We have commented in **Withdrawal criteria section** when we will consider withdrawing a patient from the study. If after the surgery, the extension of the disease exceeds expectations, the patient will be dropped out from the trial, and he/she will receive an appropriate treatment. The same happens if the patient is diagnosed of a relapse of his/her cancer. Moreover, the patient can withdraw the study anytime they wanted, letting us without some important information about the effectiveness of the treatment in some specific group of patients.

In our study, we have more than one main dependent variable (morbidity, disease-free survival and overall survival). To calculate our sample size, we have used the morbidity variable, since it is in this

variable that we expect to obtain differences between the two groups, but any of the other two could have been used.

About the limitations of the sample, its size and time of recruitment has been calculated according the data provided by our reference center. This information may vary between the different engaged hospitals, and may result in a shortening or lengthening of recruitment time.

We will use a consecutive method of recruitment. It is a non-probabilistic method and, therefore, the sample could not be representative of the population, since not all the population has the same probability to be included in the study. However, it is the most suitable method of recruitment for this trial.

Finally, we have mentioned some of possible confusion factors. In order to avoid the confusion bias, we will do a multivariate analysis. Likewise, the randomization performed on our sample contributes to reduce the confusion bias, because doing this the confounders will be equally distributed between both groups.

14. IMPACT OF THE STUDY TO THE NATIONAL HEALTH SYSTEM

The main aim of this project is to compare results obtained with sentinel node mapping versus the D2 lymphadenectomy in patients with early gastric cancer. Nowadays, in most Western countries, it is indicated to perform gastrectomy and D2 lymphadenectomy in all patients with removable cancers, regardless of tumor stage. Because of that, patients with early gastric cancer in which lymphatic involvement occurs in a low percentage of cases, undergo an unnecessary and extended surgery, with the complications that it involves.

In the last years, studies have been conducted to check the feasibility of the sentinel node mapping. However, there are no published results yet that compare this method with the D2 lymphadenectomy, although there are a few studies initiated. For this reason, we have decided to propound this protocol.

If the results obtained validate our hypothesis and are relevant enough, it could suppose a change in the routinely treatment. Firstly, because the rates of overall survival and disease-free survival would be the same and, secondly, because the postoperative complications of the surgery would be reduced, since we would perform a more limited surgery.

Moreover, we will study if all these results will represent a reduction of the hospitalization time (because of the reduction of the complications). Furthermore, we think that the reduction of the postoperative morbidity will entail an improvement in quality of life.

Even though sentinel node mapping is not the cheapest treatment (because of the use of nuclear techniques), the fewer complications expected can lead to a decrease of medical consultation and also hospital stay, which means a reduction of hospital costs (both direct (consumption of in-patient) and indirect (expense incurred from the cessation or reduction of work productivity)).

In conclusion, as a whole, it will be a positive change in the way we treat these patients.

15. BIBLIOGRAPHY

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16.1. INDEX OF FIGURES

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- **Annex 5:** Study information sheet.
- **Annex 6:** Informed consent of the study.
- **Annex 7:** Modified Clavien-Dindo severity classification.
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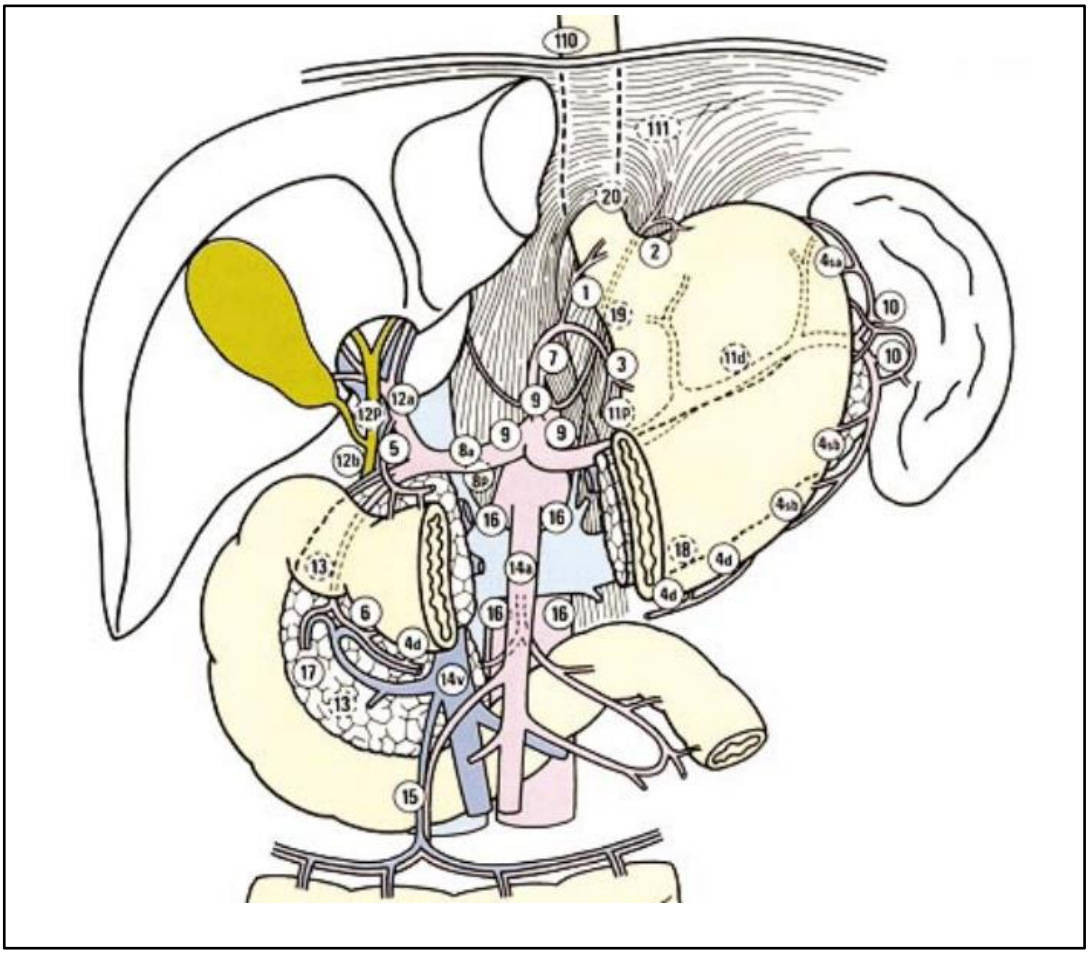
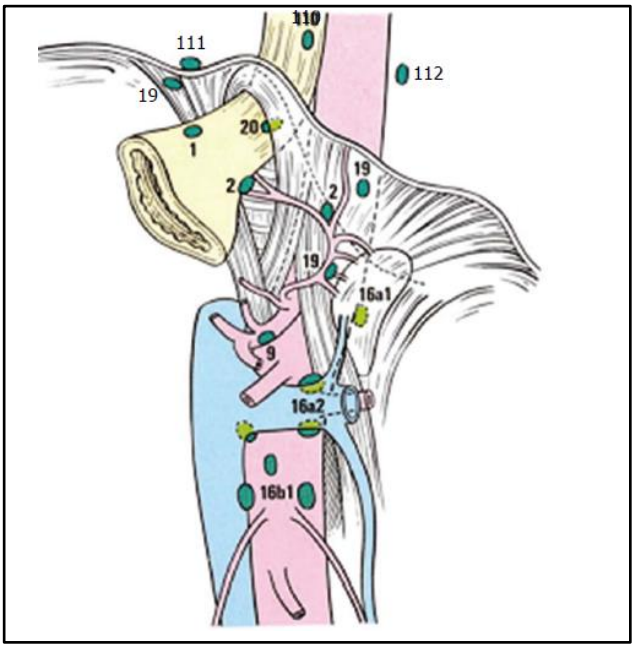
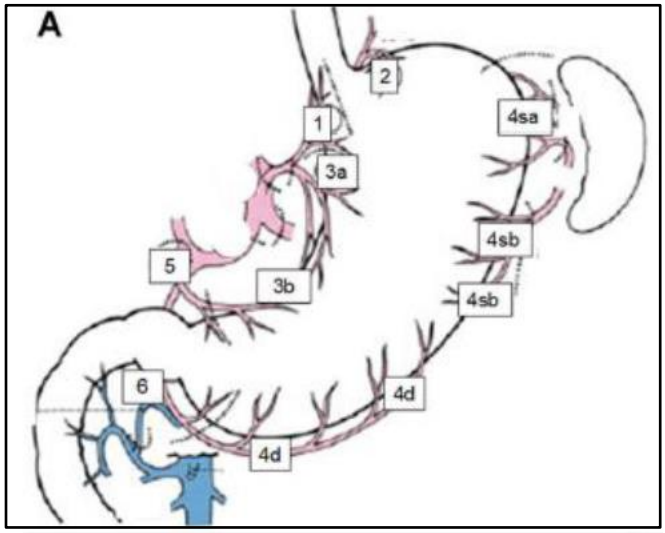
- **Annex 9:** Data collection sheet of the patient.
- **Annex 10:** ASA (American Society of Anesthesiology) classification.

ANNEX 1: LYMPHATIC STATIONS OF THE STOMACH

Figure 13: Images extracted from (2,16).



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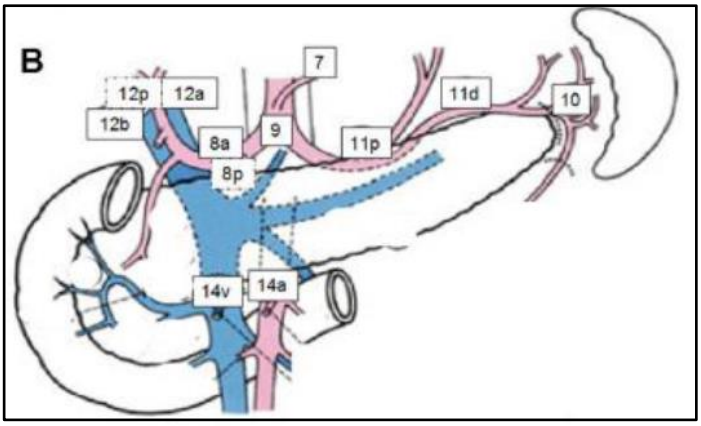
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ANNEX 2: NON-SURGICAL TREATMENT FOR ADVANCED GASTRIC CANCER

Chemotherapy (ChT):

This treatment is based on anti-cancer drugs (epirubicin, 5-fluorouracil, carboplatin, cisplatin, docetaxel, etc[7].) with systemic action, and it is useful for spread cancer. It can be used in different ways (1):

- **Neoadjuvant treatment:** when it is given before the surgery. Its aim is to make the surgery easier by narrowing the tumor.
- **Adjuvant treatment:** it is used after the surgery. Its purpose is to kill possible cancer cells left behind in order to avoid a possible relapse.
- **Main treatment:** it is indicated when the SC has metastasized and its goal is to relieve some symptoms and help the patients live longer. It is necessary to have a general preserved state, with a Karnofsky Index >70% (**Annex 4**).

Radiotherapy (RT):

It can be used for the same purposes and in the same way as chemotherapy. Moreover, doctors can use a combination of both of them, called chemoradiotherapy (1). The clinical target volume encompasses the gastric bed and regional lymph nodes (6).

Targeted therapies:

This kind of drugs act in front of the tumor cells in a more specific way. In addition, they tend to have less side effects than chemo drugs. They are used in front of advanced cancer. Major medications are the following (1):

- **Trastuzumab:** monoclonal antibody which targets the HER2 protein. It only works if it is a HER2 positive tumor. It can be given in addition to the chemo drugs.
- **Ramucirumab:** monoclonal antibody that binds the receptor for vascular endothelial growth factor (VEGF). Its aim is to stop the creation of new blood vessels of the tumor.

In accordance with the protocol of management of patients with SC made in 2008 by the Hospital Universitari Dr. Josep Trueta, the main adjuvant treatment regimens to follow are:

- **MAGIC strategy:** indicated in the patients staged as T3, T4 or N+, who have been treated with three cycles of neoadjuvant ChT (epirubicin, cisplatin and 5-fluoracil) with posterior surgery. Those patients will complete the treatment with three more cycles of the same ChT.

[7] These drugs can be used in monotherapy or in combination, depending on the characteristics of the patient and the cancer.

Each cycle consists in three weeks of the following pattern: epirubicin (50mg/m^2) as bolus at day 1, cisplatin (60mg/m^2) intravenous at day 1, 5-fluoracil (200mg/m^2) in continuous infusion over 21 days. It will be initiated 6-12 weeks after de the surgery (6).

- **McDONALD strategy:** indicated in patients who:
    - Have been staged as T1, T2, N0, but after the surgery we have a pT3, pT4 or N+ stage.
    - Have followed a neoadjuvant treatment following the MAGIC strategy and present:
        - Previous toxicity with MAGIC strategy.
        - Affected margins in the surgical piece.
        - In the restaging phase, show a disease progression.

Those patients will receive five cycles of ChT+RT, initiated between 3-6 weeks after surgery. Each cycle are five days of the following pattern:

- 5-fluoracil 425mg/m^2 intravenous at day 1.
- Leucovorin 20mg/m^2/day in continuous infusion from day 1 to 5.

This pattern will be repeated on week 4 and 8. These two lasts cycles will be concomitant with the RT.

The RT will be initiated on day 28 of treatment, coinciding with the second cycle of ChT. After a month of finishing RT, the patient will receive two more cycles of ChT.

Table 9: McDONALD strategy.

Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
ChT	QT				QT				QT					QT	QT
RT					RT	RT	RT	RT	RT						

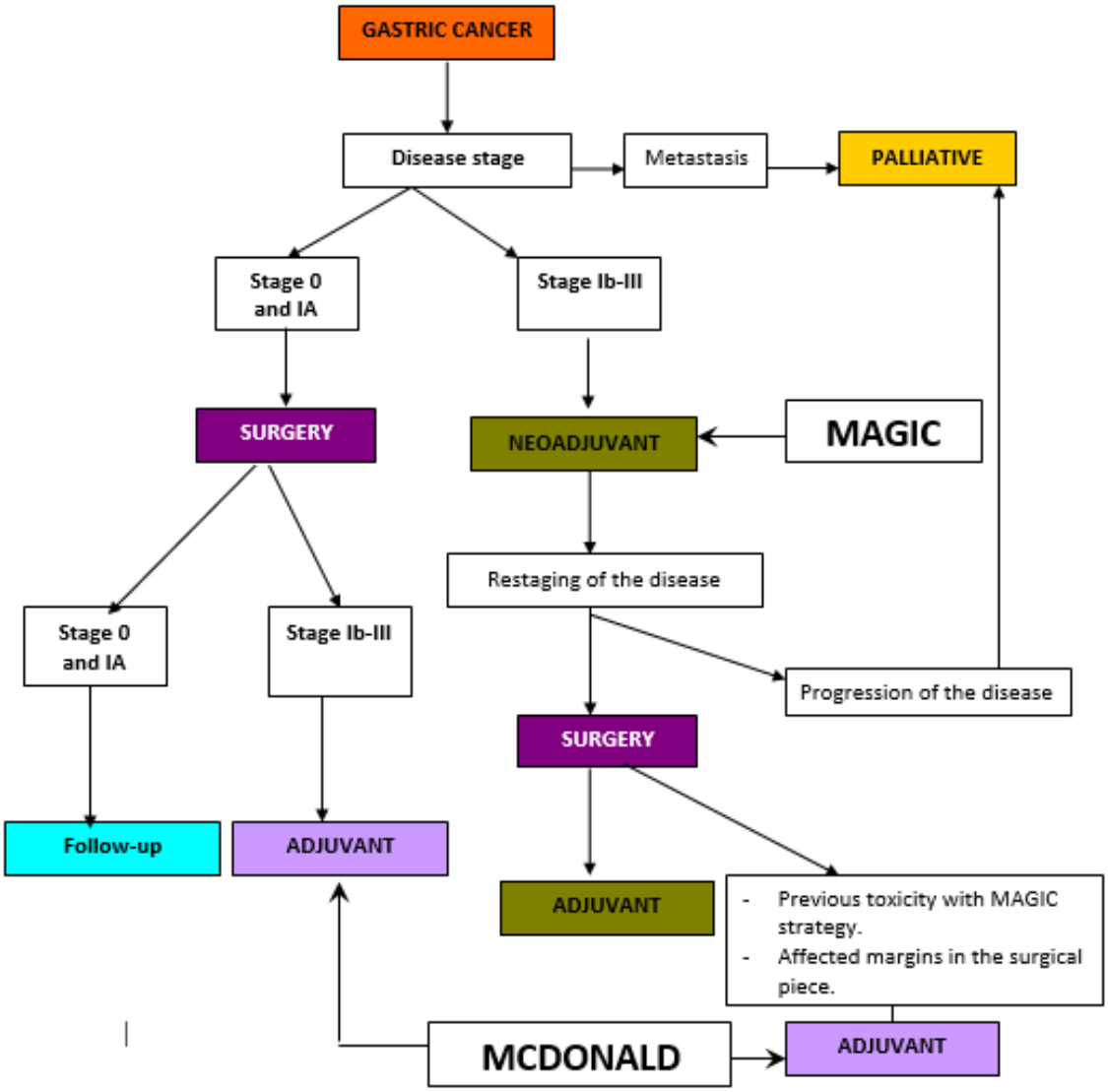

Figure 14: Protocol of management of a patient with SC made in 2008 by the Hospital Universitari Dr. Josep Trueta.

Treatment by stage of SC:

Table 10: Treatment of GC by stage. Adapted from (1).

STAGE 0	- Surgery (subtotal or total gastrectomy) + removal of the nearby LN (it can be done by laparoscopy if the patient is candidate). - No ChT or RT is needed.
STAGE I	**IA:** - Surgery (subtotal or total gastrectomy) + removal of the nearby LN. - No ChT or RT is needed.
	IB: - Neoadjuvant ChT or ChT+QT may be given. - Surgery (subtotal or total gastrectomy) + removal of the nearby LN. - Adjuvant ChT or ChT+RT may be given. - If the patient is not a candidate for surgery, he can be treated with ChT+RT, ChT or RT if he can tolerate it.
STAGE II	- Neoadjuvant ChT or ChT+RT may be given. - Surgery (subtotal or total gastrectomy) + removal of the nearby LN. - Adjuvant ChT or ChT+RT may be given. - If the patient is not a candidate for surgery, he can be treated with ChT+RT, ChT or RT if he can tolerate it.
STAGE III	- Neoadjuvant ChT or ChT+RT may be given. - Surgery (subtotal or total gastrectomy) + removal of the nearby LN. - Adjuvant ChT or ChT+RT may be given. - If the patient is not a candidate for surgery, he can be treated with ChT+RT, ChT or RT if he can tolerate it.
STAGE IV	- Palliative surgery if it is necessary. - ChT and/or RT can help shrink the cancer and relieve ome symptoms. - Targeted therapy can be helpful. It can be given added to ChT.

ANNEX 3: LYMPHATIC STATIONS AFFECTED IN UPPER, MIDDLE AND LOWER THIRD OF THE STOMACH

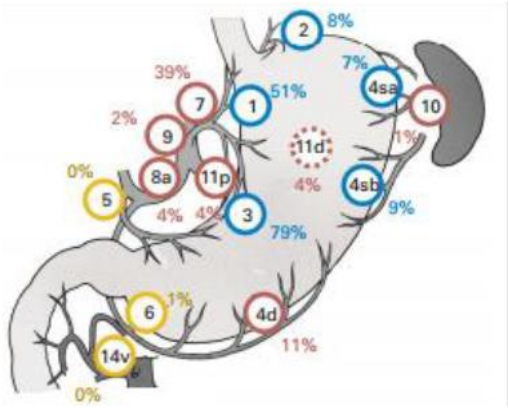

Figure 15: Distribution and incidence of identified sentinel nodes: GC of the upper third of the stomach. Blue circles are LN in the first compartment; red circles are LN in second compartment; gold circles are LN in the third or others (31).

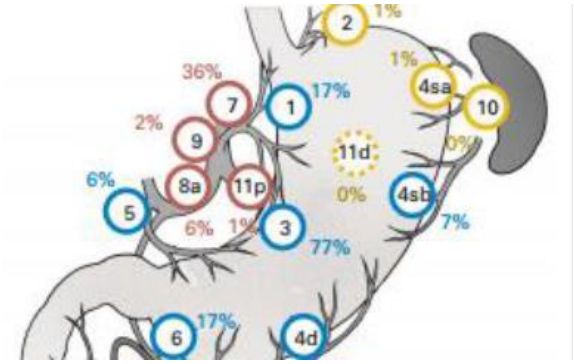

Figure 16: Distribution and incidence of identified sentinel nodes: GC of the middle third of the stomach. Blue circles are LN in the first compartment; red circles are LN in second compartment; gold circles are LN in the third or others (31).

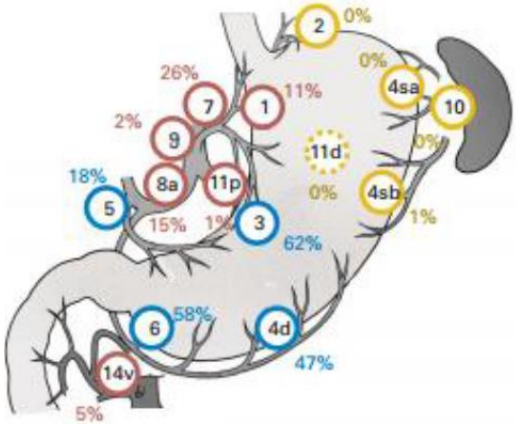

Figure 17: Distribution and incidence of identified sentinel nodes: GC of the lower third of the stomach. Blue circles are LN in the first compartment; red circles are LN in second compartment; gold circles are LN in the third or others (31).

ANNEX 4: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) SCORE AND KARNOFSKY INDEX

The ECOG Performance Status and the Karnofsky Performance Status are two widely used methods to assess the functional status of a patient. These can be used to assess the prognosis in individual patients.

Table 11: ECOG performance status. Adapted from (41,42).

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead.

Table 12: Karnofsky index. Adapted from (41,42).

VALUE (%)	CONDITION
100	Normal, no complains.
90	Able to carry on normal activities. Minor signs or symptoms of disease.
80	Normal activity with effort.
70	Care for self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but able to care for most of his needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled. Requires special care and assistance.
30	Severely disabled. Hospitalization indicated though death nonimminent.
20	Very sick. Hospitalization necessary. Active supportive treatment necessary.
10	Moribund.
0	Dead.

ANNEX 5: STUDY INFORMATION SHEET

FULL D'INFORMACIÓ PEL PARTICIPANT

INVESTIGADORS PRINCIPALS: Anna González Costa, Jordi Gironès Vila.

TÍTOL DE L'ESTUDI: Ús de la tècnica del gangli sentinella amb doble traçador versus la limfadenectomia D2 en pacients amb càncer gàstric precoç.

CODI DEL PROJECTE: _____

L'equip d'investigadors clínics del Servei de Cirurgia Esofagogàstrica de l'Hospital Universitari Doctor Josep Trueta de Girona, juntament amb els equips d'investigadors clínics de la resta d'hospitals participants en l'estudi, proposem la realització de l'estudi citat, basat en observacions pròpies i en treballs científics d'investigació medica. La nostra intenció és que vostè rebi informació de manera correcta i suficient perquè pugui valorar si vol o no participar en aquest estudi. Per això, llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que puguin sorgir.

1) **Generalitats del projecte:** l'estudi que li presentem és un assaig clínic multicèntric, que es durà a terme al Servei de Cirurgia Esofagogàstrica dels següents hospitals: Hospital Universitari Doctor Josep Trueta, Hospital Universitari Vall d'Hebron, Hospital Clínic i Provincial, Hospital del Mar, Hospital de la Santa Creu i Sant Pau, Hospital Universitari de Bellvitge i Hospital Universitari Germans Trias i Pujol. El projecte de recerca ha estat valorat i aprovat pel Comitè Ètic d'Investigació Clínica.

2) **Objectius i finalitats de l'estudi:** l'actual projecte de recerca pretén determinar si la tècnica del gangli sentinella redueix les complicacions postoperatòries, comparat amb la limfadenectomia D2, mantenint la supervivència lliure de malaltia i la supervivència global. Com a objectius secundaris, pretenem demostrar si la tècnica del gangli sentinella disminueix l'estada hospitalària i millora la qualitat de vida en aquests pacients. En el moment actual no hi ha resultats que comparin les dos tècniques, per aquest motiu hem dissenyat l'estudi actual.

3) **Procediments de l'estudi:** un cop vostè hagi estat diagnosticat de càncer gàstric precoç, se'l remetrà al servei de cirurgia esofagogàstrica. Allà se li proposarà l'entrada a l'estudi i, en cas que accepti, se li assignarà de forma aleatòria una tècnica o l'altra i es registrarà la seva evolució. La

primera tècnica és la limfadenectomia D2, realitzada en el mateix curs quirúrgic que la gastrectomia. Aquest procediment és l'estandarditzat en la gran majoria de països, però s'associa a una alta taxa de complicacions postoperatòries. Per altra banda, la tècnica del gangli sentinella es basa en la detecció del/s primer/s gangli/s al que la neoplàsia es dissemina. Aquesta tècnica està aprovada ja pel càncer de mama i el melanoma, i en els últims anys s'ha intentat estendre el seu ús a altres neoplàsies, com el càncer d'estómac. Si al pacient se li assigna aqueta tècnica, haurà d'acudir al centre hospitalari el dia abans de la intervenció. En aquesta visita se li realitzarà una endoscòpia en la qual se li injectarà el radiofàrmac, i se li realitzarà una limfogammagrafia prèvia a la cirurgia. El pacient podrà marxar a casa i tornarà el dia de la intervenció, moment en el que se li tornarà a repetir una gammagrafia intraoperatòria per detectar ganglis. A més, es farà la punció del traçador blau patent i es realitzarà la seva visualització directa.

En cas de ser negatius, indicarà que no hi ha afectació limfàtica, podent evitar una limfadenectomia extensa i disminuint les complicacions que se'n puguin derivar. En cas de ser positius, el procediment es convertirà en una limfadenectomia D2.

Després de la intervenció, es valorarà l'aparició de possibles complicacions durant l'hospitalització i, un cop li donem l'alta, li aconsellem que acudeixi al centre en cas de presentar qualsevol símptoma o molèstia. A més, es farà un seguiment amb visites cada 6 mesos els 3 primers anys i un cop l'any fins completar els 5 anys de control. En aquestes visites es valorarà la qualitat de vida dels pacients i es faran una sèrie de proves (analítica, TC toràcic i abdominal) per valorar la possible progressió/recidiva de la malaltia.

La seva atenció mèdica al llarg de l'estudi serà igual independentment de quin grup formi part. Les visites amb els diferents especialistes, proves diagnòstiques i seguiment post-quirúrgic serà exactament el mateix que si vostè decidís no participar o abandonar l'estudi.

4) **Possibles beneficis:** la participació en aquest estudi implica que rebrà un tractament de forma aleatòria que, tot i haver demostrat bons resultats en diferent estudis, pot ser inferior al tractament convencional, ja que encara no hi ha resultats publicats que comparin les dos tècniques. Nosaltres preveiem que la tècnica del gangli sentinella redueixi les complicacions postoperatòries, mantenint els resultats oncològics de la intervenció convencional. Si es demostra la nostra hipòtesi, el tractament del càncer gàstric precoç podrà passar d'una

limfadenectomia extensa amb les complicacions que això implica, a un tractament més conservador i personalitzat.

5) Riscs i inconvenients:

Les complicacions que es poden derivar de les intervencions són:

- Limfadenectomia D2: la taxa de complicacions pot arribar al 40%. Les més freqüents són: fuga de suc pancreàtic, abscessos intraabdominals, edema retroperitoneal (que pot arribar a provocar una fallada cardíaca), pneumònia, sagnat, infecció de la ferida, limforrea i ascites quilosa.
- Gangli sentinella: l'efecte advers específic d'aquesta tècnica és la reacció al·lèrgica al contrast (pigmentació cutània o lleu dessaturació d'oxigen), tot i que es veu en menys d'un 1% dels pacients. La resta de complicacions que se'n poden derivar són les observades en la limfadenectomia, però s'observen cada una d'elles en menys d'un 1% dels subjectes.

Durant l'estudi es realitzaran controls clínics durant 5 anys. Si en alguna de les visites de seguiment es detecta algun esdeveniment advers greu, es prendran les mesures necessàries.

Tots els pacients de l'assaig tenen una assegurança clínica segons el Real Decreto 223/2004, *del 6 de febrero, para la regulación de los ensayos clínicos con medicamentos*, per fer front a possibles eventualitats derivades de l'assaig. Tots els esdeveniments greus que es manifestin durant l'estudi, es considerin o no relacionats amb el mateix, s'hauran de comunicar a l'investigador principal.

6) Participació: la seva participació en l'estudi és totalment voluntària. Si vostè decideix participar-hi, se li demanarà que firmi un full de consentiment. Vostè és lliure d'abandonar l'estudi si així ho desitja en qualsevol moment, sense necessitat de justificacions i sense que aquest fet afecti la seva assistència sanitària. La participació en l'estudi és totalment gratuïta i no s'obtindrà cap compensació econòmica per la participació.

També ha de saber que vostè pot ser exclòs de l'estudi si el promotor o els investigadors de l'estudi ho consideren oportú, ja sigui per motius de seguretat o perquè considerin que no està complint amb els procediments establerts. En qualsevol dels casos, vostè rebrà una explicació adequada del motiu que ha ocasionat la seva retirada de l'estudi.

7) **Confidencialitat i protecció de dades**: totes les dades de caràcter personal i informació recollida o generada durant l'estudi quedarà protegida segons la Llei Orgànica 15/1999 de "Protecció de Dades de Caràcter Personal". Les dades recollides durant l'estudi estaran identificades mitjançant un codi numèric i només el seu metge de l'estudi i els col·laboradors podran relacionar aquestes dades amb vostè i amb la seva història clínica. Per tant, la seva identitat no serà revelada.

8) **Tasca del participant en l'estudi:** el participant haurà de cedir informació personal i mèdica per tal que el metge que l'ha atès pugui omplir el full de recollida de dades amb la informació facilitada. També es compromet a seguir les visites de control ja esmentades prèviament. Davant de qualsevol dubte/problema, podrà contactar amb nosaltres i li intentarem resoldre.

9) **Resultats i beneficis de la investigació:** el participant està en el seu dret de ser informat dels resultats de la investigació. Els beneficis mèdics derivats de l'estudi seran adequadament utilitzats per millorar l'atenció als pacients amb càncer gàstric i serviran de base per futures investigacions en aquest àmbit.

Si us plau, no dubti en fer més preguntes al seu metge si alguna cosa no li ha quedat clara. Si decideix entrar a l'estudi, signi el consentiment informat.

Gràcies per la seva participació.

ANNEX 6: INFORMED CONSENT OF THE STUDY

CONSENTIMENT INFORMAT

Títol de l'estudi: *Use of sentinel node mapping with dual tracer versus D2 lymphadenectomy in patients with early gastric cancer.*

Declaració del participant:

Jo (noms i cognoms), _____, confirmo que:

- He llegit la fulla informativa sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte l'estudi i els meus dubtes han estat resolts.
- He rebut suficient informació sobre l'estudi.
- He estat informat de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària.
- Entenc que es respectarà la confidencialitat de les meves dades.
- Entenc que puc revocar el meu consentiment de participació a l'estudi, sense haver de donar justificacions i sense afectar la meva assistència sanitària.

➢ Accepto que els investigadors principals de l'estudi puguin contactar amb mi si en un futur es considera oportú?

Sí No

➢ Lliurement, dono la meva conformitat per participar en l'estudi facilitant informació personal i mèdica?

Sí No

Signatura del participant: Signatura de l'investigador:

_____ _____

Data: __ / __ / __

ANNEX 7: MODIFIED CLAVIEN-DINDO SEVERITY CLASSIFICATION

The therapy used to a specific complication is the basis of this classification in order to rank a complication in an objective manner.

Table 13: Classification of surgical complications based on the modified Clavien system. Adapted from (43).

GRADE	DEFINITION	EXAMPLES
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	Atelectasis requiring physiotherapy, neurological transient confusion not requiring therapy, noninfectious diarrhea…
II	Complications requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Pneumonia treated with antibiotics on the ward, transient ischemic attack requiring treatment with anticoagulants, infectious diarrhea requiring antibiotics, urinary tract infection requiring antibiotics…
III	Complications requiring surgical, endoscopic or radiological intervention.	
IIIa	Intervention not under general anesthesia.	Bradyarrhythmia requiring pacemaker implantation in local anesthesia, stenosis of the ureter after kidney transplantation treated by stenting…
IIIb	Intervention under general anesthesia.	Cardiac tamponade after thoracic surgery requiring fenestration, bronchopleural fistulas after thoracic surgery requiring surgical closure, anastomotic leakage…

GRADE	DEFINITION	EXAMPLES
IV	Life-threatening complications (including central nervous system complications) requiring intermediate care/intensive care unit management.	
IVa	Single organ dysfunction (including dialysis).	Heart failure leading to low-output syndrome, lung failure requiring intubation, ischemic stroke/brain hemorrhage, necrotizing pancreatitis, renal insufficiency requiring dialysis…
IVb	Multiorgan dysfunction.	Same as for IVa but in combination with renal failure or hemodynamic instability…
V	Death.	
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix ''d'' (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.	Cardiac insufficiency after myocardial infarction (IVa–d), stroke with sensorimotor hemisyndrome (IVa–d), residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d), hoarseness after thyroid surgery (I–d)…

ANNEX 8: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) QUESTIONNAIRES OF QUALITY OF LIFE

QLQ-C30 QUESTIONNAIRE version 3: provided by (44).

EORTC QLQ-C30 (versión 3)

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

Por favor ponga sus iniciales: ☐☐☐☐

Su fecha de nacimiento (día, mes, año): ☐☐☐☐☐☐☐☐

Fecha de hoy (día, mes, año): ☐☐☐☐☐☐☐☐

		En absoluto	Un poco	Bastante	Mucho
1.	¿Tiene alguna dificultad para hacer actividades que requieran un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4.	¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

Durante la semana pasada:

		En absoluto	Un poco	Bastante	Mucho
6.	¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4
8.	¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9.	¿Ha tenido dolor?	1	2	3	4
10.	¿Necesitó parar para descansar?	1	2	3	4
11.	¿Ha tenido dificultades para dormir?	1	2	3	4
12.	¿Se ha sentido débil?	1	2	3	4
13.	¿Le ha faltado el apetito?	1	2	3	4
14.	¿Ha tenido náuseas?	1	2	3	4
15.	¿Ha vomitado?	1	2	3	4
16.	¿Ha estado estreñido/a?	1	2	3	4
17.	¿Ha tenido diarrea?	1	2	3	4
18.	¿Estuvo cansado/a?	1	2	3	4
19.	¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20.	¿Ha tenido dificultad en concentrarse en coas como leer el periódico o ver la televisión?	1	2	3	4
21.	¿Se sintió nervioso/a?	1	2	3	4
22.	¿Se sintió preocupado/a?	1	2	3	4
23.	¿Se sintió irritable?	1	2	3	4
24.	¿Se sintió deprimido/a?	1	2	3	4
25.	¿Ha tenido dificultades para recordar cosas?	1	2	3	4
26.	¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27.	¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28.	¿Le han causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor en las siguientes preguntas, ponga un círculo en el número del 1 al 7 que mejor se aplique a usted:

29. ¿Cómo valoraría su salud general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

30. ¿Cómo valoraría su calidad de vida en general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

QLQ-STO22 QUESTIONNAIRE: provided by (44).

EORTC QLQ – STO22

Los pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada. Por favor responda rodeando con un círculo el número que mejor se aplique a su caso.

Durante la última semana:

	En absoluto	**Un poco**	**Bastante**	**Mucho**
31. ¿Ha tenido algún problema al comer alimentos sólidos?	1	2	3	4
32. ¿Ha tenido algún problema al comer alimentos licuados o blandos?	1	2	3	4
33. ¿Ha tenido algún problema al beber líquidos?	1	2	3	4
34. ¿Ha sentido molestias mientras comía?	1	2	3	4
35. ¿Ha sentido dolor en la zona del estómago?	1	2	3	4
36. ¿Ha sentido molestias en la zona del estómago?	1	2	3	4
37. ¿Ha tenido sensación de hinchazón en el abdomen?	1	2	3	4
38. ¿Ha tenido problemas de subida de acidez o bilis a su boca?	1	2	3	4
39. ¿Ha tenido indigestión con acidez o ardor de estómago?	1	2	3	4
40. ¿Ha tenido dificultad al eructar?	1	2	3	4
41. ¿Se ha sentido saciado(a) al poco tiempo de comenzar a comer?	1	2	3	4
42. ¿Ha tenido dificultad al disfrutar de sus comidas?	1	2	3	4
43. ¿Tardó mucho tiempo en acabar de comer?	1	2	3	4
44. ¿Ha tenido la boca seca?	1	2	3	4
45. ¿Le saben la comida y la bebida diferente de lo normal?	1	2	3	4
46. ¿Ha tenido dificultad al comer delante de otras personas?	1	2	3	4
47. ¿Ha pensado en su enfermedad?	1	2	3	4

	En absoluto	Un poco	Bastante	Mucho
48. ¿Se ha preocupado por tener un peso demasiado bajo?	1	2	3	4
49. ¿Se ha sentido menos atractivo/a físicamente como consecuencia de su enfermedad o tratamiento?	1	2	3	4
50. ¿Ha estado preocupado por su salud futura?	1	2	3	4
51. ¿Se le cayó algo de pelo?	1	2	3	4
52. Conteste a esta pregunta solo si le cayó algo de pelo: ¿Se sintió preocupado por la caída del pelo?	1	2	3	4

ANNEX 9: DATA COLLECTION SHEET OF THE PATIENT

Project title: USE OF SENTINEL NODE MAPPING WITH DUAL TRACER VS. D2 LYMPHADENECTOMY IN PATIENTS WITH EARLY GASTRIC CANCER

CENTER NUMBER | | | | | | |

PATIENT NUMBER | | | | | | |

Nº clinic history _____

Patients information:

NAME _____ DATE OF BIRTH _____

SURNAME _____ TELEPHONE _____

DIRECTION_____ EMAIL _____

DATE OF INCLUSION ____/____ /____ SEX: MALE ☐ FEMALE ☐

The patient has read the information sheet: YES ☐ NO ☐

The patient has signed the consent form: YES ☐ NO ☐

Investigator's name and ID _____

PHASE 1. TRIAL ENTRY IN THE ESOPHAGOGASTRIC SURGERY DEPARTMENT:

Group of treatment:

SENTINEL NODE MAPPING ☐ **D2 LYMPHADENECTOMY** ☐

Imaging test results:

TNM after imaging tests:

Tumor's location:

Day of intervention: ____/____/____

Type of surgery planned: LAPAROTOMY ☐ LAPAROSCOPY ☐

Extension of the resection: TOTAL GASTRECTOMY ☐ PARTIAL GASTRECTOMY ☐

Preoperative information:

Age (years):		Height (cm):	
Weight (kg):		Body mass index (BMI, kg/m^2):	
Blood pressure:		Heart rate:	
Allergies:			
Regular medication:			
Toxic habits:			
Previous surgical interventions:			

Comorbidities:

Diabetes	☐	Hypertension	☐
Dyslipidaemia	☐	Alcoholism	☐
Tobacco	☐	COPD	☐
Pulmonary failure	☐	Renal failure	☐
Arrhythmia	☐	Cardiac failure	☐
Hepatitis B virus	☐	Hepatitis C virus	☐
Alcoholic liver cirrhosis	☐	HIV virus	☐
Non-alcoholic liver cirrhosis	☐	Biliary illness	☐
Chronic pancreatitis	☐	Coagulopathies	☐
Digestive tract illness	☐	Inflammatory bowel disease	☐
Primary cancer	☐	Metastatic cancer	☐
Active chemotherapy	☐	Immunosuppressive illness	☐
Others:			

ANALITICAL PARAMETERS

Blood count	
Haematites	
Haematocrit	
Haemoglobin	
MCV	
RDW	
Neutrophil	
Lymphocytes	
Platelet	
Biochemical analysis	
Sodium	
Potassium	
Urea	
Creatinine	
Glucose	
Albumin	
Total bilirubin	
Direct bilirubin	
Indirect bilirubin	
GOT	
GPT	
GGT	
Alkaline phosphatase	
Amylase	
Lactic acid	
Coagulation	
PT	
PTT	
INR	
Fibrinogen	
Tumour marker	
Ca 19.9	
CEA	
Others:	

ASA : ☐ I ☐ II ☐ III ☐ IV ☐ V

2- PHASE 2. INTERVENTION:

Surgical time: Anesthetic time:

Type of surgery performed: LAPAROTOMY ☐ LAPAROSCOPY ☐

Final extension of the resection: TOTAL GASTRECTOMY ☐ PARTIAL GASTRECTOMY ☐

Need of removable of nearby organs: YES ☐ NO ☐

- Which? _____

Number of hot lymph nodes _____ Number of blue nodes_____

Number of hot and blue nodes _____ Number of lymph node dissected _____

Necessity of transform the process to a D2 lymphadenectomy because of the presence of metastasis in the lymph nodes?

YES ☐ NO ☐

Observations:

Pathologist inform:

pTNM		Vascular infiltration	
Histological type		Perineural infiltration	
Morphology		Lymphatic infiltration	
Location		Number resected lymph nodes	
Size		Number of metastatic lymph nodes	
Proximal margin		Ganglionar groups affected	
Distal margin		Others	

3- PHASE 3.

Date of discharge ____ /____ / ____

Number of days of hospital stay: _____

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation: ☐

Inhospital stay complications:

4- PHASE 4. FOLLOW-UP:

If the patient comes to the hospital during the first 30 days after the intervention because of any complication, it will be written down. It will be classified according Clavien-Dindo classification. We will annotate if the complication has needed treatment and which one.

Visit 6th months:

Thoracic and abdominal CT results:

General blood tests results:

Presence of progression/relapse of the cancer: YES ☐ NO ☐

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation: ☐

Observations:

Visit 12th months:

Upper endoscopy results if the patient underwent a partial gastrectomy:

Thoracic and abdominal CT results:

General blood tests results:

Presence of progression/relapse of the cancer: YES ☐ NO ☐

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation: ☐

Observations:

Visit 18th months:

Thoracic and abdominal CT results:

General blood tests results:

Presence of progression/relapse of the cancer: YES ☐ NO ☐

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation:

Observations:

Visit 24th months:

Upper endoscopy results if the patient underwent a partial gastrectomy:

Thoracic and abdominal CT results:

General blood tests results:

Presence of progression/relapse of the cancer: YES ☐ NO ☐

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation: | |

Observations:

Visit 30th months:

Thoracic and abdominal CT results:

General blood tests results:

- Answered: YES ☐ NO ☐
- Punctuation: ☐

Observations:

Visit 48th months:

Upper endoscopy results if the patient underwent a partial gastrectomy:

Thoracic and abdominal CT results:

General blood tests results:

Presence of progression/relapse of the cancer: YES ☐ NO ☐

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation: ☐

Observations:

Visit 60th months:

Upper endoscopy results if the patient underwent a partial gastrectomy:

Thoracic and abdominal CT results:

General blood tests results:

Presence of progression/relapse of the cancer: YES ☐ NO ☐

QLQ-C30 + QLQSTO-22

- Answered: YES ☐ NO ☐
- Punctuation:

Observations:

ANNEX 10: ASA (AMERICAN SOCIETY OF ANESTHESIOLOGY) CLASSIFICATION

Table 14: ASA CLASSIFICATION. Obtained from (45).

	DEFINITION	EXAMPLES
ASA I	A normal healthy patient.	
ASA II	A patient with mild systemic disease.	Mild diseases only without substantive functional limitations. Examples: current smoker, social alcohol drinker, pregnancy, obesity (BMI <40).
ASA III	A patient with severe systemic disease.	Substantive functional limitations; One or more moderate to severe diseases. Examples: poorly controlled diabetes mellitus or hypertension, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction.
ASA IV	A patient with severe systemic disease that is a constant threat to life.	Examples: ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction.
ASA V	A moribund patient who is not expected to survive without the operation.	Examples: ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes.	

*The addition of “E” denotes Emergency surgery. An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part.