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Extension of lymphadenectomy for gastric cancer: Audit at European specialist centres.

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Summary

Gastric cancer is still one of the leading causes of cancer-related deaths worldwide, and its treatment management differs between Eastern Asia and Western countries. Screening program, early diagnosis, and surgical treatment was primarily established in Japan and was rapidly disseminated to other countries. In other parts of the world, such as the USA and Western Europe, the incidence of gastric cancer has declined, and efforts for screening and early detection have not been an issue of higher priority over the management of other diseases. Thus, gastric cancer in the West is often more advanced and is either inoperable or needs more radical surgery for resection.

The only treatment method that can potentially cure gastric cancer is the surgical approach. Depending on the extension of the tumor, surgeons may execute an operation that involves removing all or part of the stomach with some nearby lymph nodes (lymphadenectomy).

Lymphadenectomy is a crucial step during surgical operation that involves the removal of one or more lymph nodes located in the drainage area of a tumor, in which there is a high possibility of lymph node metastasis.

The Japanese guidelines define the criteria of lymphadenectomy procedure into D1 D1+ or D2 according to the type of gastrectomy executed.

The extent of lymphadenectomy has long been a subject of debate. Indeed, Japanese surgeons introduced extended lymphadenectomy (D2), which has also been progressively adopted in Europe and included in almost all international guidelines. However, the procedure requires a long learning curve, which involves a high volume of interventions; therefore, US guidelines do not recommend the D2, and many Italian and European centres do not yet perform this procedure. Indeed, the current European Consensus guidelines recommend D2 dissection in regional specialist centres for patients with moderate comorbidity. However, compliance with guidelines is unclear, and in some recent RCTs, the standard approach of surgical treatment is at the "surgeon's discretion."

This study aims to evaluate the current practice of D2 lymphadenectomy in Europe to determine any variation in practice and compare it with the Japanese guidelines.

The study consists of two parts: first, a questionnaire based on hypothetical clinical scenarios was administered to expert surgeons belonging to European Chapter of the International Gastric Cancer Association from high-volume European centers. They were asked to select the appropriate lymphadenectomy extension for each hypothetical case and the associated lymph node stations to remove. In the second part of the study, the same surgeons were asked to collect their data about gastric cancer gastrectomies performed in 2015 for comparative analysis.

The study results show that the expert surgeons of high-volume centres are quite in agreement with the choice of D2 lymphadenectomy in the different clinical scenarios.

The surgical choice seems to have been influenced by the tumor stage, site, and histology of the tumor. More specifically, the D2 procedure is recommended for cases with diffuse histology compared to tumors with intestinal histology. However, the selection of the D2 dissection procedure rarely conformed to Japanese guidelines: the choice of lymph node stations revealed the presence of a wide variation in execution.

In the review of the gastrectomy experience, it was observed that a high surgical standard was achieved: in fact, in 97% of gastric cancer gastrectomies after D2, an adequate number of lymph nodes (≥15 nodes) were removed.

In conclusion, even if an adequate lymphadenectomy was obtained in almost all cases in dedicated centers, there is still significant variability in the number of recovered lymph nodes. The histology of the tumor largely influences the surgeon's choice regarding the extent of the lymphadenectomy; however, the role of histology in the planning of surgical procedures is not considered in the current guidelines and must be verified in prospective studies.

1 BACKGROUND

1.1 Epidemiology of gastric cancer

Gastric cancer (GC) ranks sixth for incidence (5.6%) and fifth for mortality globally in both sexes and all ages (**Figure 1**), with over 1 million new cases and 769,000 deaths in 2020 (7.7% of total cancer deaths) (1,2). It is characterized by high fatality rates, making this pathology a significant public health problem at the international level.

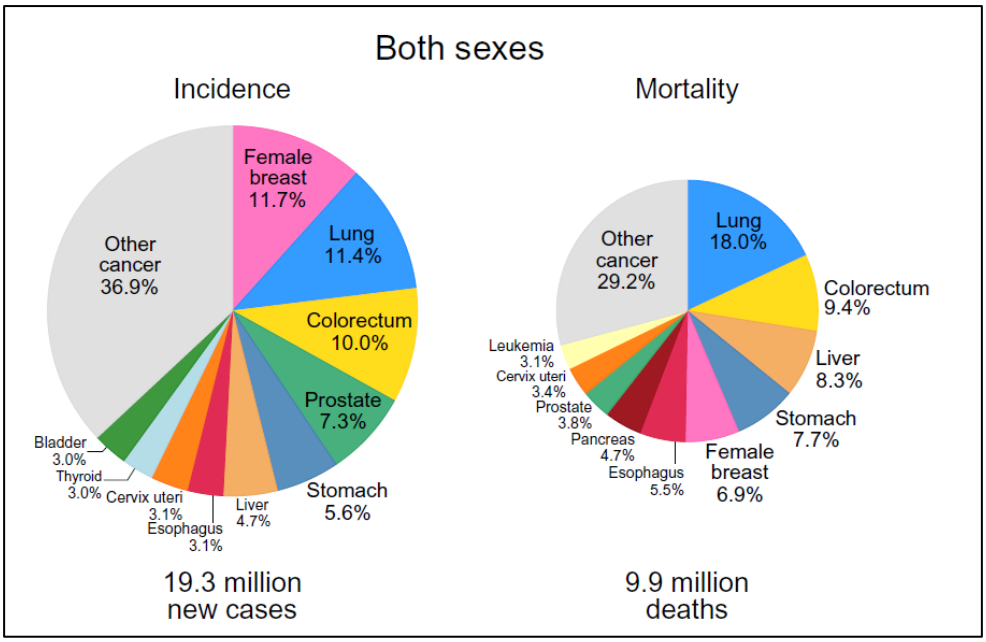

Figure 1. Incidence and mortality in both sexes for primary tumors. Figure modified from Globocan 2020, Global Cancer Observatory (http://gco.iarc.fr/).

The incidence of GC varies considerably with maximum levels in Japan, China and Russia, and minimum levels in Australia and North America. According to the United Nations "GLOBOCAN" monitoring system (2020), 75.3% of new diagnoses of gastric cancer and 74.8% of deaths from the disease worldwide have occurred in Asia; in particular, China contributes to more than half of cases (**Figure 2**).

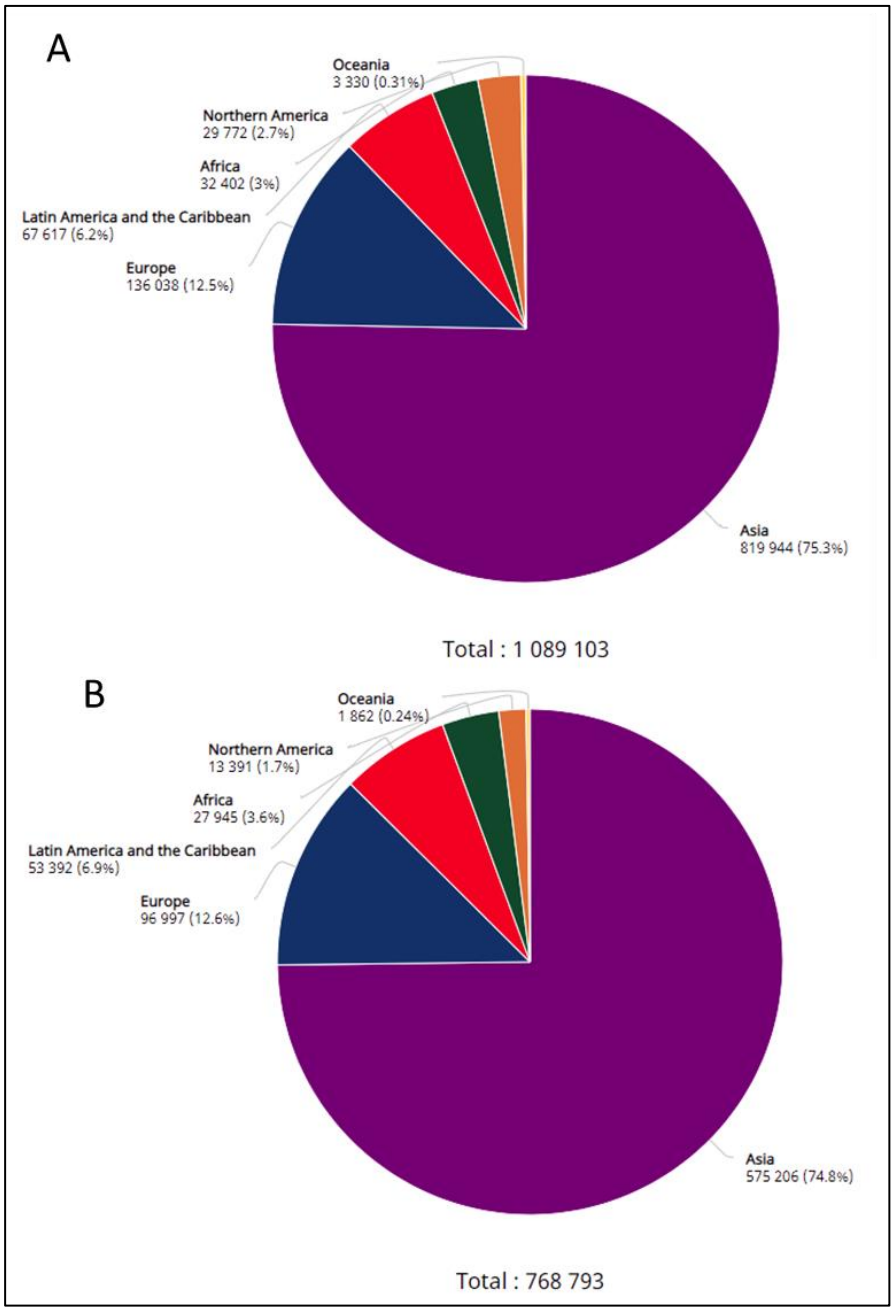

Figure 2. Estimated number of new cases (A) and the number of deaths (B) in 2020, stomach, both sexes, all ages. Figure modified from Globocan 2020, Global Cancer Observatory (http://gco.iarc.fr/).

The different incidence and clinical-pathological presentations between Asian and Western populations suggest different pathogenesis and biological, environmental, and nutritional risk factors (3).

The carcinogenesis of gastric cancer appears to be a multifactorial process determined by environmental and host-related factors such as genetic mutation, familial syndromes, family history of gastric cancer, bacterial infections (*Helicobacter Pylori*), unbalanced food habits, obesity, advanced age, sex, and smoke. The interplay of these factors can result in the progressive transformation of normal epithelium to carcinoma (4).

A direct correlation between *H. Pylori* infection and stomach cancer has been found in countries with a high incidence of this disease. The presence of the bacterium in the stomach would determine the onset of lesions in the gastric mucosa that progresses into chronic gastritis up to cancer (5). Indeed, *H.Pylori* is defined as the most potent environmental risk factor (6) and is classified by the World Health Organization (WHO) as a class I carcinogen (7,8).

In the dietary pattern, the nitrites, particularly rich in salty and smoked foods, sausages, and meat, are transformed in an acidic environment into nitrous acid, which by binding to amines, creates carcinogenic compounds (9).
In contrast, there is compelling evidence that diets high in fruits, vegetables, and whole grains reduce the risk of gastric cancer (10–12). However, the low intake of antioxidant foods, such as whole grains, vitamin C, carotenoids, determines a reduced protective effect, while the impact of nitrosamines in carcinogenesis is enhanced.

A fundamental study provided a molecular classification of four major genomic subtypes of gastric cancer: EBV infected tumors; MSI tumors; genomically stable tumors; and chromosomally unstable tumors. These subtypes present different characteristics that could be considered in clinical trials for distinct populations of gastric cancer patients (13).

1.2 Gastric cancer management

1.2.1 Classification of gastric cancer

Gastric cancer is a disease with aggressive biology, although usually asymptomatic for a long time. The dysplastic evolution of the gastric mucosa appears to be a dynamic process characterized by the progressive appearance of cytological and structural atypia of the epithelium, which, without exceeding the basement membrane, evolve into carcinoma in situ (14). The dysplastic evolution is generally divided into mild, moderate, and severe, where severe dysplasia is highly likely to develop into a carcinoma (15).

Gastric adenocarcinoma originates from the gastric mucosa cells and can be anatomically distinguished as proximal (closer to the esophagus) or distal (closer to the pylorus or duodenum). Tumor of the antrum region is the most common, with about 50% of all stomach cancers (16). Based on the stage of the disease, GC is divided into early or advanced. At the same time, histological characteristics can be classified as intestinal or diffuse (16).

Early gastric cancer is a mucous and submucosal adenocarcinoma, regardless of lymph-node metastases, which does not infiltrate the muscular layer without affecting the vessels. Early GC has a higher chance of recovery, with a five-year survival of 90%. This neoplasm does not exceed two cm in diameter, does not form ulcers, does not involve vessels or lymph nodes, and has a well-differentiated appearance under the microscope (17).

Advanced gastric cancer that invades the own muscle or beyond has a much worse prognosis, with a 5-year survival rate of approximately less than 60% (18). Advanced gastric cancers can have an exophytic, ulcerated, infiltrative, or combined appearance. Histologically, it often exhibits marked architectural and cytological heterogeneity, with different coexisting histological growth patterns (16). Correct evaluation of early or advanced gastric cancer before surgical resection is critical from a clinical point of view as it allows to decide whether preoperative therapy can be recommended. Indeed, it has been shown

that patients treated with neoadjuvant therapy have better overall and disease-free survival (19,20).

Regarding histology, the GC of the intestinal type is the most frequent; it mainly affects men and is associated with the transformation of the gastric epithelium into the intestinal epithelium (intestinal metaplasia) (21).
Diffuse stomach cancer instead has a slightly lower frequency and affects men and women with an average age of 45 years indifferently. It originates from the normal gastric mucosa (without metaplasia) and penetrates deeply into the tissue layers of the stomach walls, expanding laterally and giving rise to ulcers. The main histological characteristic of this tumor is the presence of cells with a particular morphology, similar to a ring with an embedded gem: for this aspect, these cells are called "signet ring cells" (22).

Like many other types of tumors, stomach cancer is also classified according to the TNM system, where the T parameter describes the size of the primary tumor (the one that occurred first, if there is more than one); parameter N takes into consideration any lymph node involvement; finally, the parameter M refers to the presence or absence of metastases (23).
The spread of GC can occur in several ways: directly to the esophagus and peritoneum, by lymphatic route to the lymph nodes, and by blood, giving metastases to the liver, bones, lungs, or ovaries (24).

A large amount of evidence highlights several differences between Eastern and Western countries in histology and in outcomes of gastric cancer. These differences are attributed to biological, surgical, and adjuvant treatment. Furthermore, essential differences concern histology (diffuse vs. intestinal), tumor location (proximal vs. distal), environmental exposures, dietary factors, and Helicobacter pylori eradication.
There is a higher prevalence of diffuse histology in Western countries and a worse outcome, probably due to the poor prognosis of diffuse and signet ring histology (25,26).

In eastern countries, a higher incidence of stomach cancer has supported screening programs that allow an earlier diagnosis. The early detection of gastric cancer by screening programs in the East has led to an increase in the prevalence of early gastric cancer in those regions.

Differences are also present in surgical treatment, where an extensive lymph node dissection is routinely in Eastern countries, while in Western countries fewer cases and a slower learning curve of extended surgical procedures have led to the preference for a less extensive surgical procedure.

1.2.2 Screening and diagnosis for gastric cancer

A screening program, early diagnosis, and surgical treatment were primarily established in Japan and were rapidly disseminated to other countries (27).
Screening aims to reduce cancer mortality by detecting early preclinical disease, which can be effectively treated, unlike advanced cancer (4). In Japan, the screening is based on a double-contrast barium radiograph with photofluorography (28,29), and the guidelines recommend radiographic or endoscopic screening for people aged 50 years and over (28). Instead, the Korean guidelines recommend a screening program endoscopy every two years for people aged >40 years (30).
In other parts of the world, such as the USA and Western Europe, the incidence of gastric cancer has declined, and efforts for screening and early detection have not been an issue of higher priority over the management of other diseases. Thus, gastric cancer in the West is often more advanced and is either inoperable or needs more radical surgery for resection (31).

In Italy, there is no screening program for the general population, i.e., people who have no symptoms and do not fall into high-risk categories (for previous gastric surgery or family history) are not advised to undergo gastroscopy.

In Europe, the diagnostic gold standard is esophagus-gastro-duodenoscopy (EGDS). In EGDS, a 1 cm diameter tube is introduced during mild sedation from the mouth to the stomach and finally to the duodenum. A camera on the top allows viewing the inside of the organs, detecting mucosal changes and tumor and/or benign presence at the esophageal, gastric, and duodenal levels. A biopsy must be performed to obtain an adequate diagnosis of cancer. Once the diagnosis of gastric carcinoma has been received, it will therefore be necessary to perform a further radiological examination (usually a chest-abdomen CT with intravenous contrast medium). This assessment of the staging that is a systemic staging of the disease will allow evaluating the localization of the neoplasm, its extension to the stomach wall, the possible

presence of metastases, and the possible presence of enlarged or pathological lymph nodes since the EGDS allows to see the stomach internally. In contrast, CT allows visualization in its entirety and visualization of the other adjacent organs.

The staging allows the surgeon and oncologist to establish the best therapeutic strategy. Based on this evidence, an advanced disease may require neoadjuvant chemotherapy treatment, which is carried out before surgery, to improve the spread of the disease and allow for radical surgery (32). Conversely, a localized disease without distant metastases or lymph node positivity in preoperative staging will allow for surgery without the need for preoperative chemotherapy (33). Adjuvant chemotherapy, which is carried out after surgery, involves administering drugs that selectively kill cancer cells. Chemotherapy is also called a systemic treatment because the drug is released into the circulation, spreads throughout the body, and can kill cancer cells even outside the stomach (32).

1.2.3 Treatment of gastric cancer: Surgery

The only treatment method that can potentially cure gastric cancer is the surgical approach. However, the evaluation of possible stomach cancer therapy should always be carried out by a multi-disciplinary team of surgeons and oncologists. The chances of recovery (prognosis) and treatment choice depend on the tumor's stage of development (i.e., whether it is localized only to the stomach or whether it has spread to other areas) and the patient's general condition.

Surgery is the best treatment choice to cure cancer for the early stages of the disease if the tumor hasn't spread to other parts of the body (34). Depending on cancer extension, surgeons may execute an operation involving removing all or part of the stomach with nearby lymph nodes (34).

Gastric cancer surgery can be defined as "Curative surgery" and "Non-curative surgery" (35).

In Curative surgery, "Standard gastrectomy" is distinguished and considered the primary surgical procedure with curative intent. The process involves the removal of at least two-thirds of the stomach followed by the removal of specific lymph node stations.

"Non-standard gastrectomy," adopted in the branch of surgery with curative intent, is a procedure where the dissection of the stomach and/or lymph nodes is chosen according to the tumour stage.

Finally, two other approaches are: "Modified surgery" and "Extended surgery." These two approaches reduce the extent of lymph node retrieval compared to standard surgery and gastrectomy with the removal of adjacent organs involved (35).

"Non-curative surgery" is the treatment offered to patients considered incurable. This branch of therapy can be divided into either palliative surgery or reduction surgery. Indeed, if the cancer is too widespread to be eradicated, the surgery approach might still be performed as palliative therapy to prevent

bleeding from the tumor or the stomach from being blocked by the tumor growth.

Moreover, gastric cancer surgery is also defined for the stomach volume to be resected. The primary definition is "total gastrectomy," where all the stomach (including cardia and pylorus, nearby and distant lymph nodes) is removed (**Figure 3**). However, the patient may feed because the operation involves the connection (using a seam called anastomosis) of the esophagus or residual stomach to the small intestine (35).

"Sub-total gastrectomy" (where the only part preserved of the stomach is cardia) removes that part of the stomach that contains the tumor and pieces of other tissues and organs near the tumor site. It is usually indicated in distal neoplasms (for example, the pylorus). Locoregional and distant lymph nodes are also removed, and if necessary, the spleen (**Figure 3**) (35).

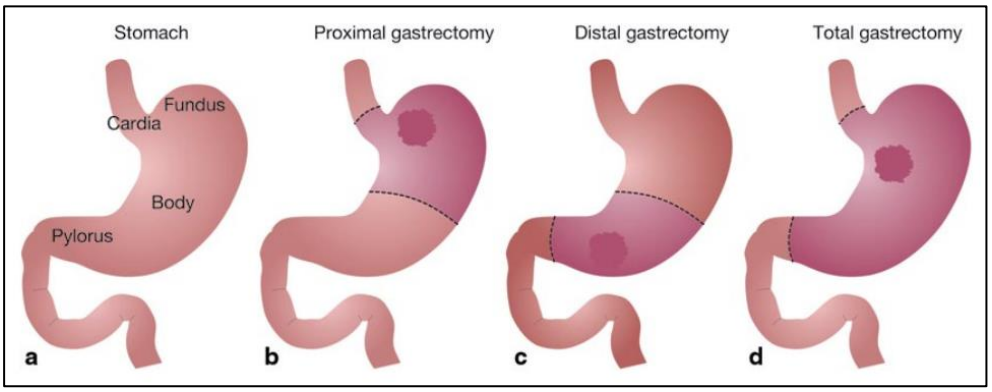

Figure 3. Resection procedures of the stomach. (**a)** The four sections of the human gut. Schematic drawing of proximal gastrectomy (**b**), distal gastrectomy (**c**), and total gastrectomy (**d**). (Figure from Daniel E. Stange et al.2015 (36)).

During operation, surgeons attempt to leave behind as much stomach as possible, allowing patients to return to an almost regular diet afterward (37). If only part of the stomach is removed, the patient should generally feed without substantially altering the quality of life. Indeed, if the stomach is completely

removed, frequent small meals may be necessary, and a diet characterized by foods with low sugar levels and high levels of fats and proteins (37).

However, the primary goal of the surgery is to be sure of the complete removal of the tumor. It is necessary to ensure that after the surgery, the margins of the removed parts of the stomach do not contain tumor residues, even by checking them under a microscope (38). Furthermore, given that in cases of gastric cancer, the metastasis propagation pathway will mainly be via the lymphatic path, a correct surgical intervention must provide for the accurate removal of the gastric lymph nodes (divided into 20 stations), proper staging, and radicality of the intervention.

1.3 What is Lymphadenectomy?

Lymph nodes protect the lymphatic system from infection by catching bacteria and waste products, filtering the lymph node fluid that carries nutrients to the cells, and destroying old and/or abnormal cells such as cancerous ones.
Lymphadenectomy (or lymph node dissection) is a surgical operation that involves the removal of one or more lymph nodes located in the drainage area of a tumor, in which there is a high possibility of lymph node metastasis (39).
It is necessary to remove the lymph nodes in case of tumors with lymph node spread, even if benign. This surgery can also be performed for preventive purposes as lymph node metastases are very high.

The removal of the lymph nodes can be performed with two different procedures: minimally invasive (by inserting a fiber-optic probe through a small incision) or in the open, making a large incision in the affected area to identify the lymph nodes to be removed. After being retrieved, the lymph nodes will be analyzed to determine their nature (benign or malignant).

In some cancers, such as breast cancer, an attempt is made to identify the first lymph node on the path of tumor spread, the so-called sentinel lymph node, using radioactive dyes or tracers, and then perform a targeted lymphadenectomy. This procedure is not possible in gastric cancer because cancer can spread through a lymph node network.

Lymphadenectomy has always been considered a crucial step in gastric cancer surgery, and the removal of a large number of lymph nodes is considered a direct measure of the quality of surgery. (40).
Lymphadenectomy affects a significant and specific number of lymph nodes (**Table 1**), and the lymph nodal stations to be removed also depend on the tumor position, tumor histology, tumor depth, and stomach volume to be resected.

The Japanese guidelines (35) define the D-level criteria, which classify the extent of lymphadenectomy into D1, D1+ or D2 according to the type of gastrectomy executed (Total or Sub-total gastrectomy) (**Figure 4**).

Moreover, in the guidelines are reported indications for lymph node dissection, which suggest performing D2 lymphadenectomy whenever the possibility of nodal involvement cannot be dismissed. Indeed, a D2 lymphadenectomy is indicated for potentially curable cT2–T4 tumors as well as cT1N+ tumors.

Lymph-nodes	Position
1	Right paracardials (including those around the esophageal branch of the left gastric artery in front of the right diaphragmatic pillar)
2	Left paracardials (including the esophageal branch of the left sub-phrenic artery)
3	Small curve
3a	The small curve along the arterial arch of the small curve between the sheets of the small omentum
3b	The small curve along the distal part of the right gastric artery and its second branch
4	Great curvature
4sa	The large curve along the short gastric arteries (perigastric area)
4sb	The large curve along the left gastro-epiploic artery (perigastric area)
4d	Large curve (II branch and distal portion of the right gastro-epiploic artery)
5	Suprapiloric (around the right gastric artery and its first branch in the hepatoduodenal ligament)
6	Octopiloric (in front of the pancreatic head around the origin and proximal tract of the right gastro-epiploic artery and near the trunk of Henle)
7	Left gastric artery (around the tract of the artery between its origin from the celiac trunk and the origin of its ascending branch, i.e., its entrance into the small omentum where it relates to the small gastric curve)
8a	Common hepatic artery, anterosuperior group
8b	Common hepatic artery, posterior group
9	Celiac trunk
10	Splenic hilum: lymph nodes associated with the splenic artery between the hilum of the spleen and pancreatic tail, lymph nodes at the root of the short gastric arteries, and lymph nodes along the left gastro-epiploic artery proximal to its first gastric branch
11p	Splenic artery, proximal (from its origin to half of its length between its origin and the end of the pancreatic tail)
11d	Splenic artery, distal (from the middle of its length between its origin and the end of the pancreatic tail to the pancreatic tail)
12a	Hepato-duodenal ligament, along the proper hepatic artery in the caudal half between the confluence of the hepatic ducts and the upper edge of the pancreas

Table 1. Position of lymph node station in D1/D1+/D2 lymphadenectomy for gastric cancer.

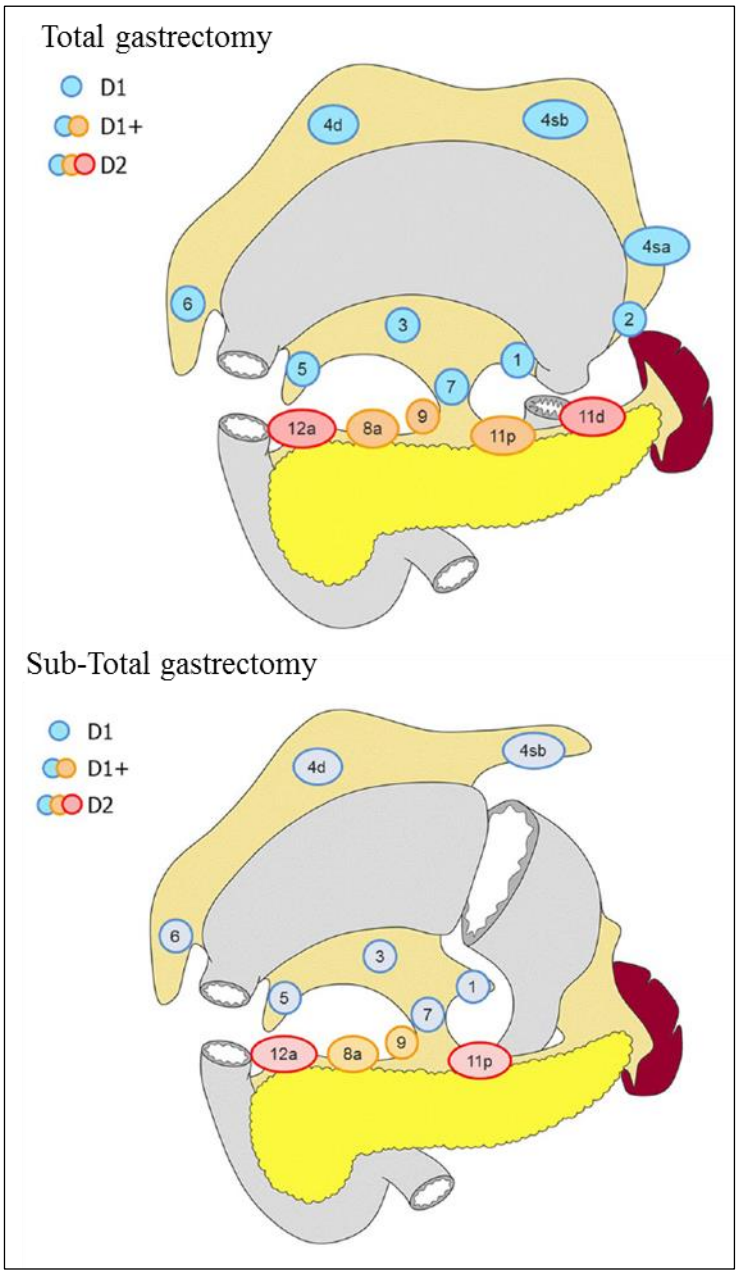

Figure 4. Lymph node dissection in total and sub-total gastrectomy. Lymph node stations in blue need to be dissected in D1 dissection. In addition, lymph node stations in orange need to be dissected in D1+ dissection and lymph node stations in red as well in D2 dissection.

1.4 The Western-Eastern difference in gastric cancer surgery and lymphadenectomy

The different treatment approaches reflect the variance in gastric cancer incidence between Eastern and Western countries.
For a long time in Europe, it has been debated which is the best extension of lymphadenectomy in surgery for gastric cancer with radical intent.

In Japan, where there was a high incidence of gastric cancer, surgeons performed an extended lymphadenectomy (D2) for decades, while in Western countries, limited nodal dissection was preferred. The Western approach gained temporary support by two European randomized controlled trials (RCTs) performed in the Nineties (41,42), which failed to detect any survival advantage when comparing dissection with extended procedures (D2) or limited procedures (D1). The RCTs outcome was probably influenced by the surgeons' limited experience with the D2 procedure, which requires a long learning curve. However, in the Dutch study (42), although there were no apparent differences for survival in the early follow-up of the study, tumor-related survival was improved in the D2 arm with a more extended follow-up period.
On the other hand, in the British study, a higher rate of post-operative mortality (13%) was observed in patients operated on with D2 lymphadenectomy, which was partly attributed to the removal of the pancreas and spleen.

A recent European study comparing D1 vs. D2 conducted by experienced surgeons showed no advantage for the D2 procedure (43). However, the number of removed nodes did not markedly differ between the study's two arms. On the other hand, one of the positive aspects of the study was that it showed better operative quality control and reduced morbidity and mortality. However, subgroup analysis showed better survival for D2 dissection in cases with positive lymph nodes (43).

In the last two decades, D2 lymphadenectomy has routinely performed in European high volume centres, becoming the standard surgical treatment with curative intent in several guidelines as British and German guidelines, European Society of Medical Oncology (ESMO), the joint ESMO-ESSO (European Society of Surgical Oncology), ESTRO (European Society of Radiotherapy and Oncology).

The current European consensus guidelines (ESMO, UK, Germany S-1) (44–51) recommend that specialized centres perform the D2 procedure in patients with moderate comorbidity.

However, there does not appear to be clear compliance with the guidelines as the gold standard in recent randomized controlled trials was a D1+ or "surgeon's discretion" procedure (52,53).

In a recent overview, outcomes of gastric cancer surgery showed a significant relationship between volume and operative mortality, but it was also suggested there might be other essential variables affecting the outcome, including the extent of lymph node dissection.

2 AIM

This study aimed to evaluate the current practice of D2 lymphadenectomy (in terms of choice and execution of the procedure) in Europe to determine any variations in training to develop a standard approach to be included in future guidelines.

In detail, this study was divided into two parts:

1. The first objective was to assess adherence to guidelines for selecting and performing the D2 lymphadenectomy procedure among experienced European surgeons.
2. In the second part of the study, the same surgeons were asked to retrospectively collect data from surgeries performed in a year for comparative analysis.

2.1 Methods

The study is divided into two parts: the first was a survey of surgeon preferences for lymph node dissection in various clinical scenarios. The second part was a retrospective review of all gastrectomy cases performed in European centres in 2015 by the same surgeons who answered the questionnaire.

In detail, a questionnaire based on 14 hypothetical clinical scenarios was designed and circulated among European experts in gastric surgery belonging to the European Chapter of the International Gastric Cancer Association (IGCA). A web link based on a secure online platform was used to evaluate the lymphadenectomy approach. (54).

The hypothetical clinical scenarios were centered on the depth of tumor invasion, positive lymph nodes, tumor site, and histotype (**Figure 5**) (54).

In the second part of the study, the same group of surgeons was asked to retrospectively collect data of all gastrectomies performed in 2015 from January to December and to report the clinical-pathological characteristics of the tumor, the surgery performed (sub-total or total gastrectomy), the extension of lymphadenectomy (D1, D1 + or D2), which and how many lymph node stations were removed and retrieved lymph nodes for each patient. The presence of positive lymph nodes was also recorded. The collected case data were used to compare theoretical and practical approaches.

Twenty-one surgeons (IGCA members) from 13 European high-volume gastric cancer centers were invited to participate in the study. Eighteen surgeons completed the questionnaire, and 14 surgeons in 12 of the participating centres provided information on 381 cases which were retrospectively collected in a centralized database with the specific information required.

In both parts of the study, the observed data were compared with the 3rd and 4th edition of Japanese guidelines (55,56), which recommend D1+ for early tumors (T1a/T1b cN0) and D2 for all other cases.

1	cT1 N0 gastric adenocarcinoma located in the gastric antrum
2	cT1N0 with intestinal Laurèn type located in the middle-upper part of the stomach
3	cT1N0 cardia Siewert type III adenocarcinoma
4	cT1 N+ gastric adenocarcinoma with intestinal Laurèn histology located in the middle-upper part of the stomach
5	cT1 N0 gastric adenocarcinoma with diffuse Laurèn histology located in the the middle-upper part of the stomach
6	cT1 N+ gastric adenocarcinoma located in the middle-upper part of the stomach in a high-morbidity patient with Charlson Comorbidity Score (CCS) >5
7	cT2-T3 N0 gastric adenocarcinoma located in gastric antrum
8	cT2-T3 N+ gastric adenocarcinoma located in gastric antrum
9	cT2-T3 N0 gastric adenocarcinoma located in gastric body along the greater curvature. In the previous case would you perform a splenectomy? ☐ Yes ☐ Not
10	cT2-T3 N+ gastric adenocarcinoma located in gastric body along the greater curvature with positive lymphnodes at the splenic hilum. In the previous case would you perform a splenectomy? ☐ Yes ☐ Not
11	cT4a N+ gastric adenocarcinoma with intestinal hystology located in gastric antrum.
12	cT4a N+ gastric adenocarcinoma with diffuse Laurèn hystology located in gastric antrum.
13	cT4a N+ gastric adenocarcinoma with intestinal hystology located in gastric body along the greater curvature. In the previous case would you perform a splenectomy? ☐ Yes ☐ Not
14	gastric *linitis plastica.*
15	At your hospital do you perform splenectomy: ☐ Routinely during D2 procedures ☐ In cases of positive lymphnodes at splenic hilum to perform a complete lymphadenectomy ☐ Only in cases of direct invasion of the spleen by the primary tumour or positive lymphnodes
16	At your hospital do you perform distal pancreatectomy: ☐ Routinely during D2 procedures ☐ Only in cases of direct invasion of the pancreas by the primary tumour or positive nodes
17	Do you extend lymphadenectomy for gastric cancer beyond the D2 dissection? ☐ Yes ☐ Not If yes, please describe the indications to lymphadenectomy extended beyond the D2 dissection and which are the nodal stations removed.
18	Do you usually dissect the surgical specimen after gastrectomy to separately send the removed lymph nodes for the pathological examination in numbered containers corresponding to the numerical system for lymph node identification reported by the Japanese Research Society for the study of Gastric Cancer? ☐ Yes ☐ Not
19	Do you usually record in a database the number of retrieved lymph nodes and the number of metastatic lymph nodes per each nodal station? ☐ Yes ☐ Not If yes, please fill in the attached file with the information regarding patients treated between January and December 2014.

Figure 5. Questionnaire based on the clinical scenarios.

2.2 Statistical analyses

Compliance of experienced surgeons with Japanese guidelines was expressed as compliant and non-compliant cases. In non-compliant cases, we recorded contaminated procedures ("more" lymph node station than D2 selected) and modified procedures ("less / more" than D2). We referred to the "Less" approach when the station to be removed in D2 lymphadenectomy was insufficient.

The distribution of the retrieved nodes in the reviewed cases was asymmetric with significant heteroscedasticity (unstable variance) across European centres. Hence the data were described by median and interquartile range. Nonparametric tests (Kruskal-Wallis test) were used to assess the significance of differences among groups (extent of lymphadenectomy D0, D1, D1+, D2).

Adequacy of different lymphadenectomies was evaluated by the percentage of procedures with at least 15 retrieved nodes according to the American Joint Committee on Cancer (AJCC) definition (57,58). It was also considered the percentage of the procedure with at least 25 retrieved nodes (59,60).

Quantile regression was used to evaluate predictors of retrieved nodes, whose distribution was skewed to the right.

Statistical analyses were performed using STATA 17 software (Stata Corp. College Station, TX, USA), and statistical significance was set at the 0.05 level.

2.3 Results

2.3.1 Survey on preferences of lymphadenectomy in different scenarios

Eighteen experienced surgeons from 12 European high-volume centres completed the questionnaire. As shown in **Figure 6**, the surgeons mostly agree on selecting the D2 procedure in the different clinical cases.

The surgical decision was affected mainly by tumor stage and, to some extent, site and histotype. In an initial overview, the choice of procedure D2 for both early and advanced cancers was evident (**Figure 6**).

In detail, in early gastric carcinoma of the middle/ upper third, the D2 procedure was influenced by tumor histology as D2 was recommended for 72% in cases of diffuse-type tumors and 44% in intestinal-type tumors, with no clinical evidence of positive lymph node.
In cases of lymph node metastases, D2 was the choice of most surgeons (83%) unless the patient had severe comorbidities (22% in Charlson Comorbidity Score>5) (**Figure 6**).

Even in locally advanced cancers, the choice of D2 was the preferred procedure for the most part. Depending on clinical cases location, the selection of D2 ranged between 72% and 83% of tumors arising from gastric antrum up to a maximum peak in *Linitis Plastica* (94%).
For tumors located along the great-upper curvature of the stomach, the preference of the D2 procedure is accompanied by the recommendation of removal of the spleen (splenectomy, 67%) only in cases of clinical evidence of metastatic disease in the specific lymph node station 10 (located in the Splenic hilum: lymph nodes associated with the splenic artery between the hilum of the spleen and pancreatic tail, **Table 1**). Splenectomy was not recommended for cases of advanced tumors, even with evidence of positive lymph nodes (**Figure 6**).

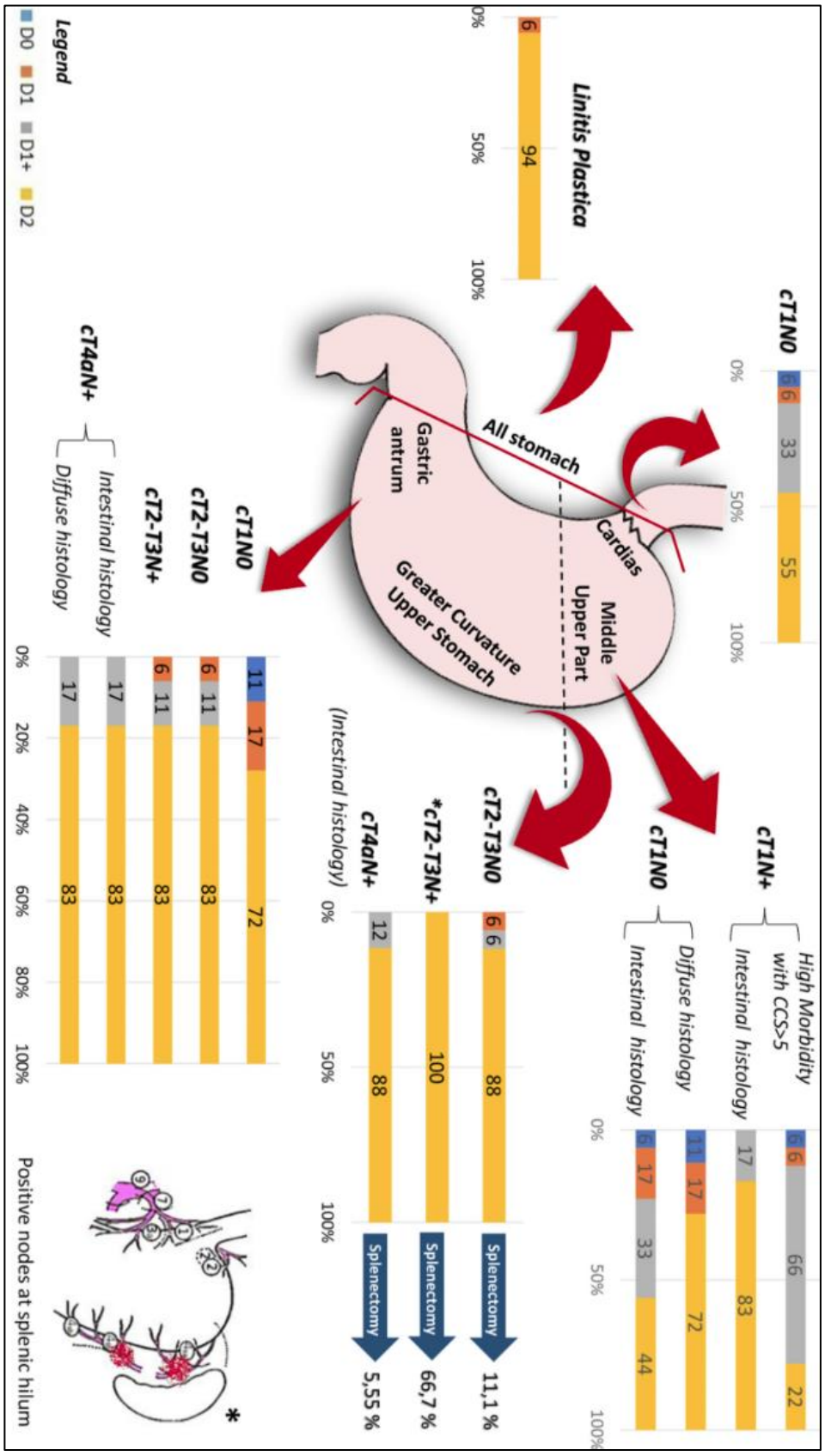

Figure 6. The extent of lymphadenectomy recommended by expert surgeons in paradigmatic clinical scenarios (Figure from Bencivenga et al. (61)).

However, although the choice of procedure appears to be clear, the described execution with related lymph node stations was rarely consistent with Japanese guidelines (16) (**Figure. 7**).

Indeed, surgeons tended to perform non-compliant dissections ("Less" than D2), especially in early tumors (cT1N0) with intestinal histology (63%).

In contrast, in cases of *Linitis Plastica* and cT2-T3-T4 tumors, the dissection was contaminated by choosing to remove additional lymph node stations to those required by the guidelines (referred to as "More" in **Figure 7**).
Furthermore, particular procedural choices resulted from the contaminated and non-compliant procedure, here defined as a modified procedure ("Less and more").
The modified procedure has been found mainly in early gastric cancer resulting from the upper-middle thirds.

During the analysis of the questionnaire responses relating to the selections of lymph node stations, it was possible to identify which stations were mainly involved in non-adherence to the guidelines. Furthermore, based on the choice of the different stations, it was possible to obtain the information "type of gastrectomy" to which the extension of the lymph node dissection was recommended.

Interestingly, in the spectrum of the different combinations of non-coherence with the guidelines, only some lymph node stations were involved in extending the D2 lymphadenectomy.
Specifically, stations 10, 11d, and 12a for total gastrectomy, while stations 4sb, 11p, 12a for sub-total gastrectomy.
In the contaminated procedures, however, the additional stations were, in most cases, the numbers 8p, 11d, 12b, and 12p.

As expected, sub-total gastrectomy was indicated in tumors located in the antrum, while total gastrectomy was recommended in the other tumor.

However, the choice of extent of gastric resection seemed to have had a strong influence on tumor histology. The recommended sub-total gastrectomy in antral tumors was replaced by total gastrectomy in advanced tumors with diffuse Laurèn histology compared to intestinal tumors (53% vs. 13% $p = 0.05$).

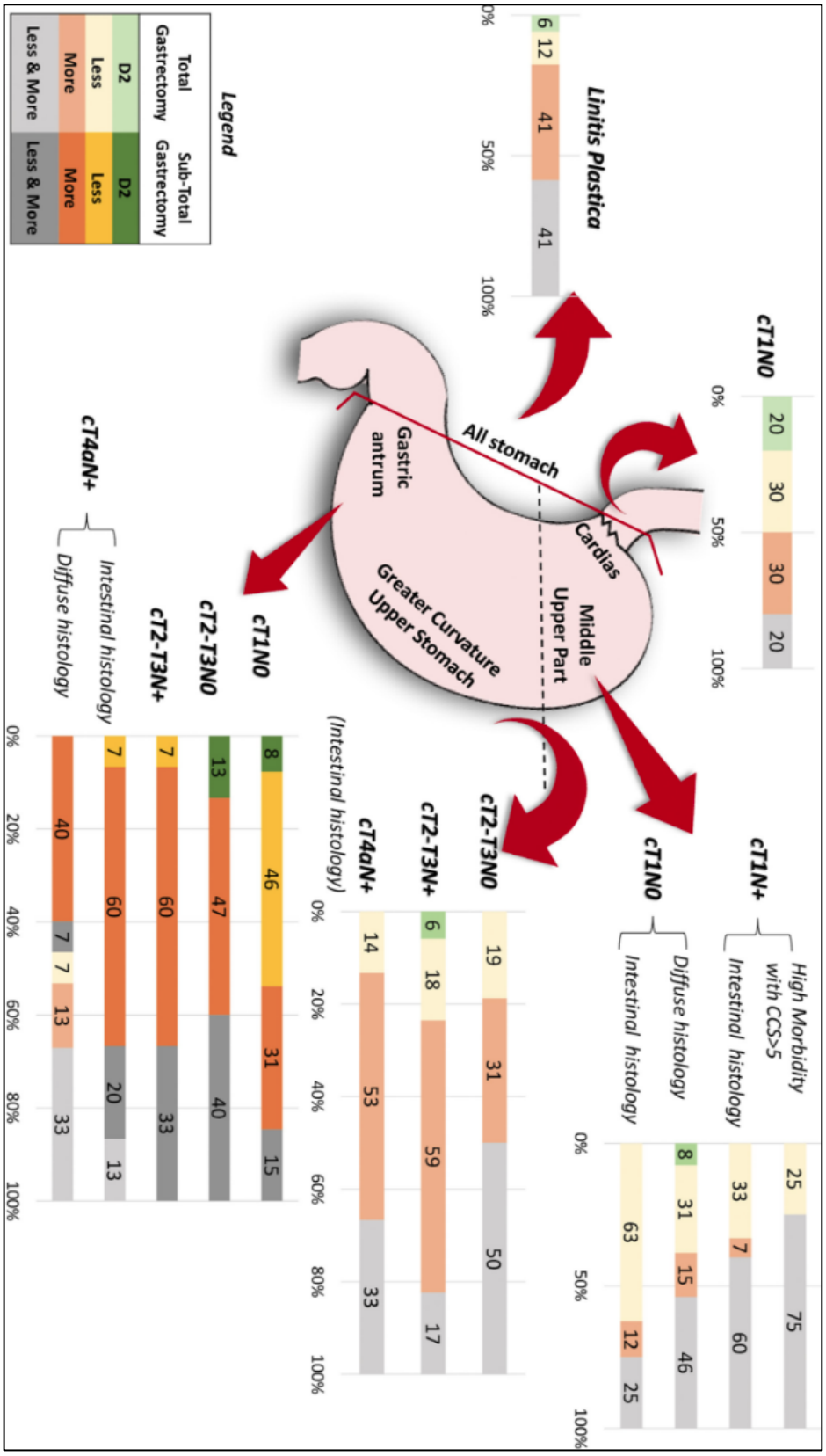

Figure 7. Compliance to and deviation from standard D2 lymphadenectomy, proposed by expert surgeons in paradigmatic clinical scenarios (Figure from Bencivenga et al. (61)).

2.3.2 Review of European gastrectomy practice

Fourteen out of 18 surgeons responding to the questionnaire provided data on gastrectomy cases performed from January to December 2015. Gastrectomy collected in the 12 European specialized centres amounted to 381 patients. As defined in the Japanese and ESMO (47,51,55,56) were treated with D2 lymphadenectomy (63%). **Table 2** summarizes the main clinical and pathologic characteristics of the European series.

The median number of retrieved nodes (25th percentile - 75th percentile) was 24 (17-39) after D1, 19 (17-27) after D1+, 32 (23.5-38) after D2, and 47 (32-51) after D2+ (**Figure 8**).

TNM nodal staging (15 or more retrieved lymph nodes (60)) was confirmed in 94.2% (358/380) cases. This rate increased progressively with the increasing extension of lymphadenectomy. Indeed, an increase was observed from 84% after D1, 89% after D1+, 96.7% after D2, and 100% after D2+. According to Maruyama et al. (59), 74% of D2 procedures had at least 25 retrieved nodes (**Table 3**).

	Frequencies (n = 381)	Percent
Tumor site		
Cardias	69	18.1
Upper	40	10.5
Middle	89	23.4
Lower	175	45.9
Linitis	8	2.1
Depth Invasion		
pT1	72	18.9
pT2	49	12.9
pT3	99	25.9
pT4a	112	29.4
pT4b	42	11
ypT0	7	1.8
pN		
N0	156	40.9
N1	49	12.9
N2	55	44.4
N3a	57	14.9
N3b	64	16.8
Histology (Laurén)		
Intestinal	224	58.8
Diffuse	103	27
Mixed	54	14.2
Gastrectomy		
Sub-Total	156	40.9
Total	193	55.7
Other	32	8.4
Surgery		
Laparotomy	371	97.4
Laparoscopy	10	2.6
Extension of lymphadenectomy		
D1	49	12.9
D1+	54	14.2
D2	240	63
D2+	38	10
Neoadjuvant		
Yes	187	49.1
No	194	51

Table 2. Main clinical and pathologic characteristics of the European series. ypTx were considered together with pTx

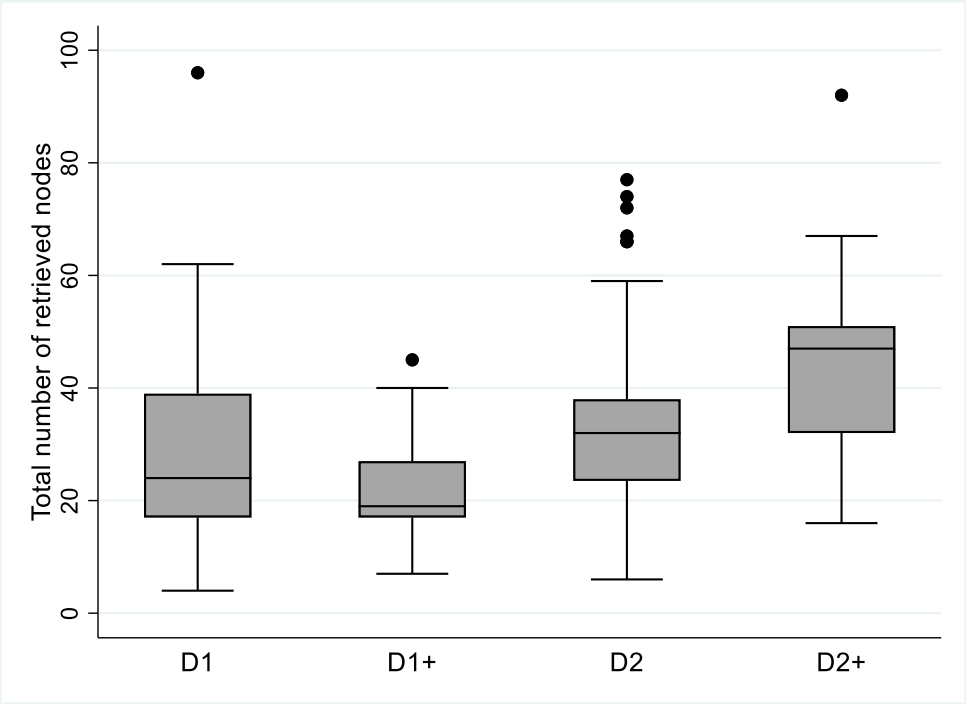

Figure. 8. Retrieved lymph nodes as a function of lymphadenectomy extension in gastric cancer series, treated at twelve high-volume European centres in 2015.

	n	At least 15 lymph nodes retrieved n (%)	At least 25 lymph nodes retrieved n (%)
D1	**49**	41 (83,7)	24 (49,0)
D1+	**54**	48 (88,9)	17 (31,5)
D2	**240**	232 (96,7)	172 (74,1)
D2+	**38**	37 (97,4)	34 (89,5)
Total	**381**	**358 (94.0)**	**247 (64.8)**

Table 3. According to adequate disease staging, the number of lymph nodes recovered at the pathological examination (≥15 or ≥25 nodes retrieved).

There was a considerable variation in the number of nodes retrieved across the centres, with median values ranging from 18 to 38 (p<0.001). Also, the intra-centre variability differed among centres (Bartlett's test for equal variances: p <0.001), with the IQR (interquartile range) varying from 6 to 22 (**Figure 9A**). The variability across centres did not substantially decrease when considering only D2 procedures (**Figure 9B**), with the median number of retrieved nodes varying from 6 to 17 (Kruskal-Wallis test: p =0.0002).

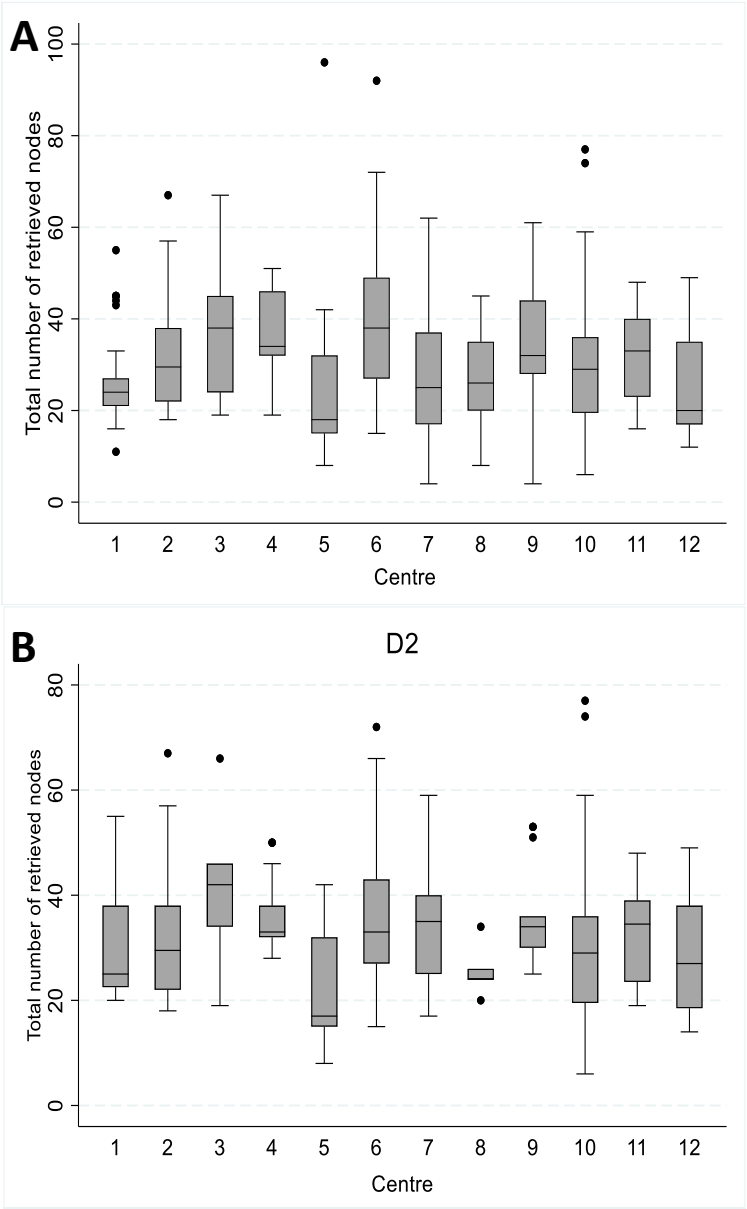

Figure. 9. Retrieved nodes in the whole series (A) and patients undergoing D2 procedures (B) in twelve high-volume European centres.

The D2 lymphadenectomy was the most used procedure in all T stages, except for pT1a cases treated with D1/D1+ in 60.9% of patients (**Figure 10A**), while D2+ was limited to advanced cancers as pT3-pT4 cases.

Also, D2 lymphadenectomy was the most common procedure chosen in all Laurèn histotypes, peaking at 74% of subjects in mixed histotypes (**Figure 10B**). Nearly one-third (31%) of cases with intestinal histotype underwent less than D2 (D1/D1+), while no negligible proportions (18.5%) of patients with diffuse histotype underwent more than D2 (D2+) (p= 0.028).

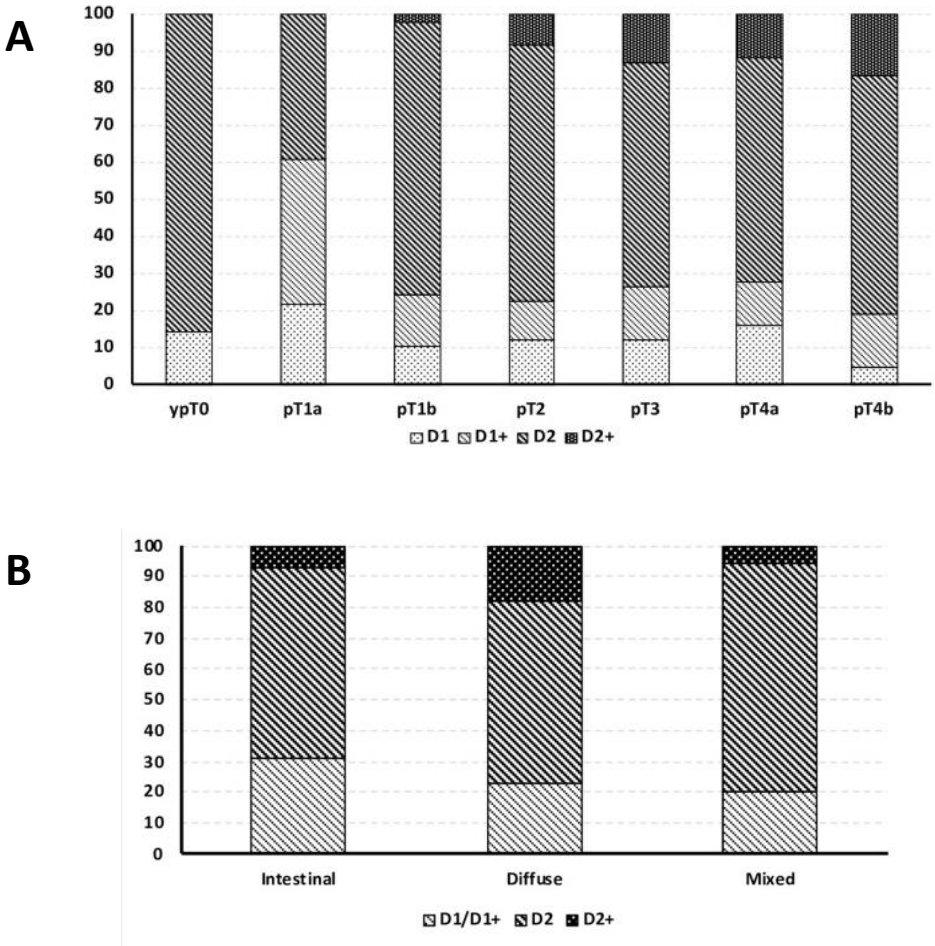

Figure 10. Lymphadenectomy as a function of T stage (A) and Laurèn histology (B)

3 DISCUSSION

Although in Europe D2 lymphadenectomy is currently considered the standard of care for intentionally curative treatment of gastric cancer patients (44–51), guideline adherence and compliance with D2 dissection by real-life European surgeons are mainly unknown.

After a few years of auditing and data control (62,63), many European countries have registered an improvement in surgical quality at a national level with greater compliance with guidelines. However, despite this improvement, this study highlighted a significant variability between high-volume centers, demonstrating the need to offer a much more consistent approach with international guidelines to improve patient outcomes.

A remarkable result in this study was that highly-trained European surgeons only partly follow international guidelines on lymphadenectomy. Although the present study shows that the quality of lymphadenectomy for gastric cancer in Europe reached a high standard, with at least 15 nodes retrieved at pathologic examination, there was still variability both between and within centres when evaluating the number of nodes removed. This variability was even higher when considering the stations removed.

It seems that guidelines represent a general framework where each surgeon develops their preferred procedure.

In detail, significant variability in the extent of lymphadenectomy was observed in cases of early cancer, where tumor histology and patient weakness are the main determining factors.

European guidelines (44–51) recommend D1 or D1 + dissection in early gastric cancer unsuitable for endoscopic resection or weak patients.

European surgeons observed these recommendations wherein patients with significant comorbidities, a limited dissection was preferred even in cases with positive lymph nodes. A more extensive lymphadenectomy was chosen in

tumors with diffuse Laurèn histology, even if no metastases were detected clinically.

However, it would appear from these findings that more tailored treatment recommendations should be based on tumor and patient characteristics in early-stage gastric cancer.
Specifically, concerning tumor histology, on one side, it is necessary to take into account preoperative histological assessment to tailor surgery to patient's characteristics; on the other side, preoperative histological evaluation may be inaccurate and differ from the final pathological review.

In locally advanced gastric cancer, D2 is generally preferred, but experienced surgeons also consider a high rate of non-compliant or contaminated procedures.
A specific group of lymph node stations was primarily involved in the non-compliance and modified lymphadenectomy.
Specifically, the significant non-compliance was with station "10", which was selected when lymph node metastases were clinically present at the level of the splenic hilum.
The most common contaminations in D2 lymphadenectomy compared to the Japanese guidelines (55,56) involved stations "8p", "12b", and "12p" in total gastrectomy, with the addition of station 11d if distal gastrectomy was performed.
In the 3rd and 4th versions of the Japanese guidelines (55,56), station "10" was included in the D2 standard for total gastrectomy.

In the recent 5th version, station "10" was instead excluded from D2 for total gastrectomy unless the tumor is in the upper third along the greater curvature. This change was due to a randomized controlled trial, which concluded that a splenectomy, with complete removal of the lymph nodes at the splenic hilum, should be avoided in total gastrectomy for proximal gastric cancer that does not invade the greater curvature.

The study found that European surgeons did not remove station "10" as a routine procedure for total gastrectomy even before the new version of the Japanese guidelines was published.

For locally advanced tumors located in the upper third along the greater curvature, the lymph nodes at the splenic hilum are removed by European surgeons only when a lymph node invasion is clinically detected.

It is interesting to note that more than half of the European expert surgeons participating in the study found splenectomy necessary to remove the lymph nodes at the splenic hilum adequately. This choice most likely reflects the technical difficulty of removing station "10" while maintaining the blood supply to the spleen, particularly in obese patients.

Finally, Japanese guidelines (3rd version (55)) do not include "posterior lymph node stations," "8p," and "12p" for standard dissection of D2 lymphadenectomy. These stations were required in the previous version (2^{nd}) for the D3 extension (64); however, they were excluded from standard dissections because of the lack of data to support the oncological benefit of removing these lymph node stations.

4 CONCLUSION

One of the aspects highlighted by the questionnaires' analysis for the choice of lymphadenectomy was the consideration of the tumor site. Moreover, interesting evidence (based on both survey and real-life practice) shows that experienced European surgeons also consider tumor histology to choose the most suitable lymphadenectomy procedure.
In contrast, according to the guidelines (48), histology is a factor that is slightly considered, occupying only a marginal but not decisive role in the choice of lymphadenectomy.

Previous observational studies found that in locoregional relapses (65) of advanced cancer with diffuse histology, patients operated with D3 lymphadenectomy had better outcomes than D2. However, no such evidence was found for survival (66). Therefore, further studies should explore the consideration of histology as part of the optimal surgical choice for patients with gastric cancer.

Although the present study shows that the quality of lymphadenectomy for gastric cancer in Europe reached a high standard, there was still variability between and within centres when evaluating the number of lymph nodes removed. The observed variability did not decrease even when the analysis was limited to D2 lymphadenectomy.
Since experienced European surgeons performed the surgical procedures, high surgical quality is attributed, confirming the guidelines according to UICC / AJCC TNM 8th edition, with at least 15 lymph nodes recovered at the pathological examination.

Excluding differences due to the operator's skill, the variability could be explained by the intention of the experienced surgeons to choose the best treatment for the patient, which is in some way tailored and based on the surgeons' knowledge, experience, and physical condition of the patient.

To a lesser extent, the variability could be influenced by the different training of the surgeons themselves and the use of other surgical techniques.

In conclusion, this study highlighted that the level of standardization for extended lymphadenectomy D2 should be improved to provide all European patients with adequate and high-quality treatment.

5 LIMITATIONS AND BIASES

Despite the significant results of the study, some limitations should be recognized regarding auditing among European surgeons.
First, no information was collected on long-term outcomes, particularly survival. Second, the actual number of lymph nodes recovered at each station was collected in approximately half of the centres, so this information could not be addressed.
Furthermore, the selection in the study of only high-volume European centres, if on the one hand guarantees the observation of the variability execution of the interventions in the specialized centres, on the other hand, it does not consider the real variability including also the smaller centres with fewer cases and less experienced surgeons.

6 FUTURE PROSPECTS

It is well known that the most appropriate extension of lymphadenectomy has been a hot topic for several decades.

In the Nineties, two randomized clinical trials, performed in the UK and the Netherlands found no survival advantage after extended (D2) lymphadenectomy with respect to limited (D1) lymphadenectomy. D2, on the other hand, was burdened by a very high post-operative mortality. However, eastern surgeons and the Italian Research Group for Gastric Cancer (GIRCG) (48) supported the routine use of D2 lymphadenectomy. The latter view was progressively adopted by most international and national guidelines (35,47,48,61,67). Only the National Comprehensive Cancer Network guidelines, produced in the US, just mention three different types of lymphadenectomies (D0 (very limited), D1, D2), with the only recommendation to remove at least 15 lymph nodes.

The future developments of this thesis consist of updating, through a systematic review and a possible meta-analysis, the current evidence on the extent of lymphadenectomy and the most recommended lymphadenectomy according to international guidelines.

Initial research results show no new RCT comparing D1 and D2 was found in the last ten years. Only two articles reported the late results of the Dutch (68) and Italian (69) trials. No difference emerged between D1 and D2 treatments as regards overall survival (OS) (RR of D2 vs D1=0.98, 95% CI 0.82-1.16; p=0.808) while D2 treatment was significantly favored as regards recurrence-related survival (RR=0.81, 95% CI 0.69-0.95; p=0.008) (**Figure 11**.), i.e. when neglecting post-operative mortality and other causes of death. Interestingly the Italian trial found that OS and Disease-Specific Survival (DSS) was better after D1 in elderly patients and early stages, while DSS was better after D2 in advance stages (pT>1 N+).

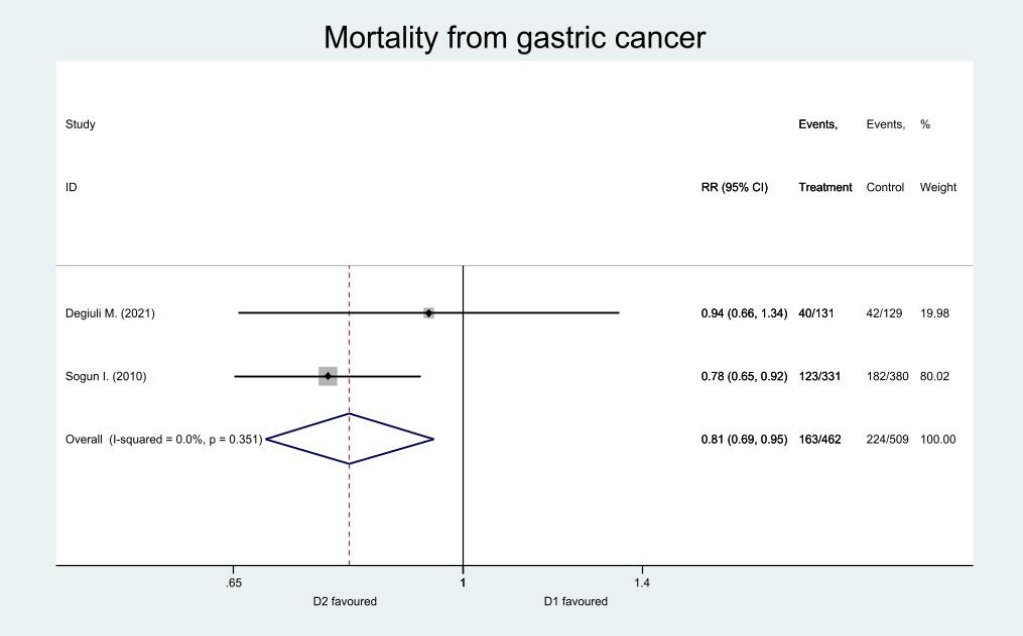

Figure 11. D1 vs. D2 lymphadenectomy

New RCTs comparing D1 or D2 have been lacking during the last ten years, and this likely reflects the absence of equipoise concerning the two procedures according to most international guidelines (ESSO-ESMO-ESTRO) (47). Only 15-year results of previously performed trials were published as an update, and they support an advantage of D2 over D1 if performed with no or minimal post-operative mortality. In addition, the need to tailor treatment to patient and tumor characteristics emerged. The scientific surgical community moves from an Eastern-Western confrontation about D1/D2 to a more sensible tailored approach.

According to Archie Cochrane, the founder of evidence-based medicine, "between measurements based on randomized controlled trials and benefit in the community, there is a gulf which has been much under-estimated" (70).

So far, the debate over lymphadenectomy extension aimed to identify the optimal treatment for the bulk of gastric cancer patients. In recent years, the need to taiolor treatment to individual cancer patients has emerged. In line with this trend, D1 lymphadenectomy has started to be used again in subgroups of patients, especially in elderly patients with early disease stages.

Recent observational studies have shown that both overall survival and disease-specific survival were similar after D1+ or D2 in Japanese patients with early gastric cancer (71). D1, however, was associated with lower incidence of post-operative complications with respect to D2 (10.0% versus 26.8%) (71). On the other hand, D2 was associated with better prognosis with respect to D1 in advanced cases, such as patients with positive peritoneal cytology (72) or patients with SRC cancer (73).

In Eastern countries (Japan and South Korea), where most gastric cancers are detected early through extensive screening programs and new tumor detection methods, D1 has become a rather standard procedure, especially in laparoscopic surgery (74). Indeed, given these new findings, an operation with extensive surgical resections would appear unnecessary, revealing D1 lymphadenectomy sufficient for these cases (71).

Western scientific literature still highlights a high incidence of post-operative complications (up to 48.2%) after D2 when performed by untrained surgeons and underlines the need for specific training in specialized institutions (75).

Therefore, the future systematic review and meta-analysis will consider these new strategies, their effect, ad benefits on patient outcomes.

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