# Overview on Gastric Cancer

**Chapter 4**

# Lymphadenectomy in Gastric Cancer Surgery

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## Abstract

Gastric cancer is the sixth most common cancer worldwide, with higher mortality and morbidity. Surgery is an essential part of the multidisciplinary treatment of stomach cancer. The extent of lymphadenectomy that should accompany the resection of the primary tumor has been a controversial issue between Eastern and Western upper gastrointestinal surgeons in the surgical management of gastric cancer. East-Asian surgeons believe that quality-controlled extended lymphadenectomy improves loco-regional control and leads to better survival in gastric cancer. However, many western surgeons believed that extended lymphadenectomy only increases postoperative morbidity and mortality without significantly improving overall survival. Furthermore, the Dutch trial, 15 years after this con¬clusion, found a substantial drop in recurrence rates following the D2 treatment. The spleno-pancreatectomy done in the D2 arm of the research was shown to be responsible for the related morbidity and mortality. For patients with resectable gastric cancer, the D2 lymphadenectomy is the preferred procedure due to its safety and capability to preserve the spleen and/or pancreas.

We present a comprehensive review of the lymphadenectomy in the gastric cancer surgery based on the previously published data.

*Citation: Golubovic I, (2024) Lymphadenectomy in Gastric Cancer Surgery, Vol. 4, Chapter 1, pp. 1-27.*

**Keywords:** Lymphadenectomy; Gastric cancer; Surgery; Gastrectomy; Treatment; Lymph node stations.



## Introduction

Gastric cancer is the sixth most common cancer worldwide, with a documented mortality of 8.9 per 100,000 people [1]. The highest incidence rates are found in South America, Japan, and Korea, whereas the lowest incidence rates are found in North America, Europe, and South and West Asia [2]. In Western countries, gastric cancers are typically identified at a later stage with a bad prognosis; but, in Japan, mass screening programs have made gastric cancer detections occur significantly earlier [3]. This has been cited as one of the causes of Asian countries' higher survival rates than those of Western countries [4].

Although multimodality management of gastric cancer has gradually become the standard of care, surgery remains at the center of it [5]. Complete surgical excision is the only potentially curative therapy option for an operable non-metastatic gastric cancer. However, there has been much dispute about the most appropriate lymph node dissection extent. In general, Eastern Asian surgeons supported the extended lymphadenectomy. This method was motivated mostly by the better locoregional control of the disease. Conversely, surgeons in Western centers used to think that prolonged lymphadenectomy was linked to significant morbidity and mortality failing however to counterbalance these limitations by significant survival benefits [6]. While extended lymphadenectomy has been accepted as standard in Asian countries since the Japanese Research Society for the Study of Gastric Cancer (JRSGC) established guidelines in 1981, extended lymph node dissection has only recently been included in treatment guidelines in Western countries [7,8].

We present a comprehensive review of the lymphadenectomy in the gastric cancer surgery based on the previously published data with the purpose to provide answers on this longstanding issue.

## Gastric lymph node stations

### Lymph nodal groups according to TMN and the Japanese Classification of Gastric Cancer

Lymph node metastasis in gastric cancer is widespread, and the incidence grows with advanced stages of tumor invasion [9]. The stomach's lymphatic drainage includes both intrinsic and extrinsic systems. The intrinsic system consists of intramural submucosal and subserosal networks, whereas the extrinsic system forms lymphatic vessels outside the stomach and generally follows the path of the arteries in various peritoneal ligaments surrounding the stomach. These lymphatic vessels drain into the lymph nodes at nodal stations in the appropriate ligaments and then into the central collecting nodes at the base of the celiac axis and the superior mesenteric artery [10].

The extent of nodal metastasis as measured by pathologic staging on surgical specimens have been utilized as prognostic markers depending on the number of positive nodes [11].

To determine the N status, the total number of lymph nodes and the number of involved lymph nodes at each nodal station are counted. When a malignant nodule without histological evidence of lymph node structure is discovered in the primary tumor's lymphatic drainage location, it is documented and counted as a metastatic lymph node in the N status determination [6].

Therefore, lymph node metastasis (N status) is classified as follows:

1. NX: Regional lymph nodes cannot be assessed;

2. N0: No regional lymph node metastasis;

3. N1: Metastasis in 1-2 regional lymph nodes;

4. N2: Metastasis in 3-6 regional lymph nodes;

5. N3: Metastasis in 7 or more regional lymph nodes, N3a: Metastasis in 7-15 regional lymph nodes, N3b: Metastasis in 16 or more regional lymph nodes.

To properly determine N status, it is recommended to examine 16 or more regional lymph nodes [12].

The extent of systematic lymphadenectomy is defined below, and depends on the type of gastrectomy conducted **(Table 1).**

**Table 1:** Types and definitions of gastric surgery according to the Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition) [13].

| **Types of gastric surgery** | | | **Definition** |
|---|---|---|---|
| Curative surgery | Standard gastrectomy | | Resection of at least two-thirds of the stomach with a D2 lymph node dissection |
| | Non-standard gastrectomy | Modified surgery | Resection and/or lymphadenectomy is reduced (D1, D1+ , etc.) compared to standard surgery |
| | | Extended surgery | Gastrectomy with combined resection of adjacent involved organs, or with extended lymphadenectomy exceeding D2 |
| Non-curative surgery | Palliative surgery | | Surgery to relieve imminent symptoms: Palliative gastrectomy or gastrojejunostomy is selected depending on the resectability of the primary tumor and/or surgical risks |
| | Reduction surgery | | Gastrectomy performed for patients with incurable factors (unresectable liver metastasis and peritoneal metastasis), while suffering from no tumor-associated symptoms such as bleeding, obstruction, and pain |

However, the nodal groups mentioned in this section are based on anatomical locations as defined by the Japanese Classification of Gastric Cancer (JCGC) [11].

The JCGC classified the nodes into three groups:

• The lymph nodes around the stomach, known as **Group 1 (N1),** include the left and right cardiac, greater and lesser curvature, and supra- and infrapyloric nodes. Resection of these nodes is categorized as D1.

• Lymph nodes outside of the perigastric lymph nodes are classified as **Group 2 (N2).** They consist of the left gastric, common hepatic, splenic artery, splenic hilum, proper hepatic, and celiac nodes. Resection of nodes in groups 1 and 2 is categorized as D2.

• Lymph nodes in the hepatoduodenal ligament, posterior pancreas, root of the mesentery, paraesophageal, and diaphragmatic regions are classified as **Group 3 (N3).** D3 refers to the resection of the three nodal groups and the paraaortic nodes [11,14].

*Distant lymph nodes located beyond Group 3 (N3) are referred to as **N4** [15].

Lymph node groups **(Compartments 1- 3)** depend on the location of the gastric cancer (in this paper, only the case with a dominantly central localization of the gastric cancer is shown- **Figure 1 and 2)**. For other cases (eg, a cancer extending to the duodenum or esophagus), a detailed tabular presentation can be found in a paper published by the Japanese Gastric Cancer Association in 1998 [14]. Depending on the localization of the tumor, the same lymph node may belong to Compartment 1 or 2, or be interpreted as a distant metastasis.


| | |
|---|---|
| 1 | Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery |
| 2 | Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery |
| 3a | Lesser curvature LNs along the branches of the left gastric artery |
| 3b | Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery |
| 4sa | Left greater curvature LNs along the short gastric arteries (perigastric area) |
| 4sb | Left greater curvature LNs along the left gastroepiploic artery (perigastric area) |
| 4d | Rt. greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery |
| 5 | Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery |
| 6 | Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein |

***Figure 1:*** Lymph node groups (Compartments 1) - a case with a dominantly central localization of the gastric cancer [14], as well as the lymph nodes stations of the stomach that are categorized anatomically and identified numerically by the Japanese Gastric Cancer Association (JGCA) (published in the paper: Japanese classification of gastric carcinoma - 3rd edition in 2011) [16].


| | |
|---|---|
| 7 | LNs along the trunk of left gastric artery between its root and the origin of its ascending branch |
| 8a | Anterosuperior LNs along the common hepatic artery |
| 8p | Posterior LNs along the common hepatic artery |
| 9 | Celiac artery LNs |
| 10 | Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch |
| 11p | Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end |
| 11d | Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail |
| 12a | Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas |
| 12b | Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas |
| 12p | Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas |
| 13 | LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla |
| 14v | LNs along the superior mesenteric vein |

***Figure 2:*** Lymph node groups (Compartments 2) - a case with a dominantly central localization of the gastric cancer [14], as well as the lymph nodes stations of the stomach that are categorized anatomically and identified numerically by the Japanese Gastric Cancer Association (JGCA) (published in the paper: Japanese classification of gastric carcinoma - 3rd edition in 2011) [16].

**Note:** Other Lymph Nodes (LNs), but only for this case shown, are designated as Group 3 (Compartments 3) as well as distant Metastases (M) [14, 16]: No. 8p (see description in Figure 2) (Compartments 3), 12b (see description in Figure 2) (Compartments 3), 12p (see description in Figure 2) (Compartments 3), 13 (see description in Figure 2) (Compartments 3), 14a (LNs along the superior mesenteric artery) (M), 15 (LNs along the middle colic vessels) (M), 16a1 (Paraaortic LNs in the diaphragmatic aortic hiatus) (M), 16a2 (Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein) (Compartments 3), 16b1 (Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery) (Compartments 3), 16b2 (Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation) (M), 17 (LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath) (M), 18 (LNs along the inferior border of the pancreatic body) (M), 19 (Infradiaphragmatic LNs predominantly along the subphrenic artery) (Compartments 3), 20 (Paraesophageal LNs in the diaphragmatic esophageal hiatus) (Compartments 3), 110 (Paraesophageal LNs in the lower thorax) (M), 111 (Supradiaphragmatic LNs separate from the esophagus) (M), 112 (Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus) (M).

According to this classification, the stomach's lymphatic drainage is filtered through lymph nodes numbered 1-20, including stations 110, 111, and 112. Lymph node stations 1–12 and 14v have been marked as **regional stations**, while the remaining lymph node stations are categorized as **distant stations**. Metastasis within a different node is recognized as **M1.**

Lymph node stations Nos. 19, 20, 110, and 111 represent regional lymph nodes in the setting of an esophageal tumor invasion. Similarly, for carcinomas that occur in the remaining stomach following a gastrojejunostomy, the jejunal lymph nodes immediately next to the anastomosis are included in the regional lymph node group [16].

## Lymphatic Drainage Pathways and Lymph Nodes

The lymph nodal drainage pattern is described here and accompanied by Computed Tomography (CT) images. Furthermore, it is important to mention several conclusions. First, the existence of lymph node metastases precludes endoscopic resection in cases of T1 tumors that would otherwise be eligible [17]. Second, the involvement of regional nodes influences the extent of lymphadenectomy and the requirement for treatment. Third, patients who have group one nodal involvement are not eligible for laparoscopic gastrectomy because it suggests subserosal disease spread. [17,18]. At the end it should be mentioned that the presence of metastatic disease in nodes of normal size and the variety of nodal drainage pattern with skip metastases, however, continue to be challenging [18].

The most frequently advised diagnostic imaging procedure for preoperative staging of gastric cancer is CT, with sensitivity ranges of roughly 63% to 92% for lymph node staging [19]. Magnetic Resonance Imaging (MRI) is thought to be less reliable than CT for assessing lymph node involvement, but it may be more accurate for non-nodal metastatic disease [20]. Further diagnostic imaging with 18 F-Fluoro-Deoxy-D-Glucose (FDG) PET is not a replacement for CT in gastric cancer cases, but it can supplement CT for staging and prognosis [21].

## Paracardiac and Paraesophageal Lymph Nodes

The paraesophageal lymph nodes, which are located above the diaphragm and the

paracardiac nodes below the diaphragm, receive lymph from the distal esophagus and the stomach's cardiac orifice.

Furthermore, lymph may extend downward along the esophageal branches of the left gastric artery to the left gastric nodes and the celiac nodes (**see Figure 3**), or upward along the esophagus to the mediastinal lymph nodes and along the thoracic duct to the left or right supraclavicular nodes [10,11].

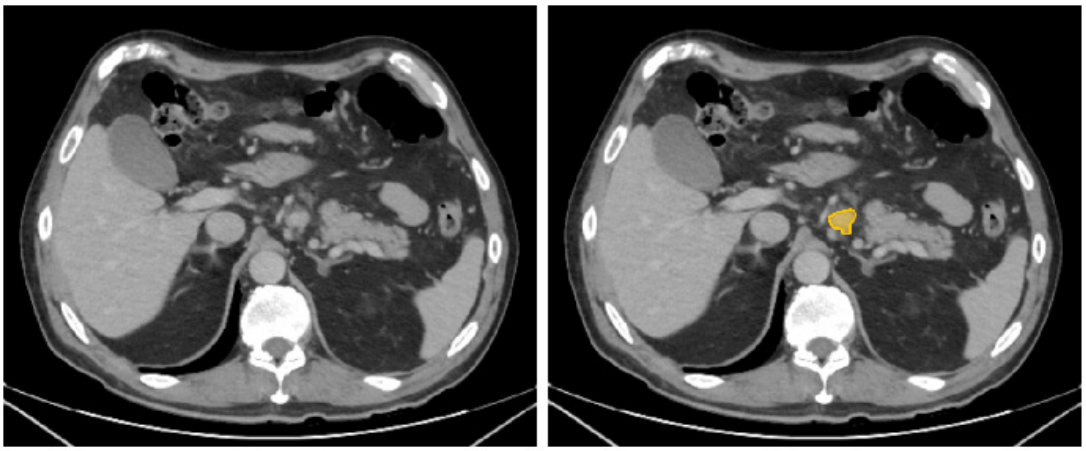

***Figure 3:*** Axial computed tomography image of the abdomen in a patient with gastric cancer shows enlarged celiac lymph node (yellow).

## Lymph Nodes Metastases in the Gastrohepatic Ligament

Tumors that arise from the stomach along the lesser curvature and the esophagogastric junction, supplied by the left gastric artery, often metastasis to the lymph nodes in the gastrohepatic ligament (**see Figure 4**).

The perigastric nodes and the suprapyloric nodes close to the pylorus receive metastases of tumors that originate from the stomach region in the right gastric artery's distribution along the lesser curvature of the gastric antrum (group 1). They subsequently drain into the nodes of the common hepatic artery (group 2), which is where the right gastric artery begins or where the right gastric vein drains into the portal vein. Drainage from these nodes continues along the hepatic artery to the celiac axis (group 2).

The lymphatic anastomoses in the gastrohepatic ligament along the lesser curvature provide additional drainage channels for malignancies that arise in this region. They are less commonly involved in pancreatic cancer because of retrograde tumor migration from the celiac nodes [10,11].

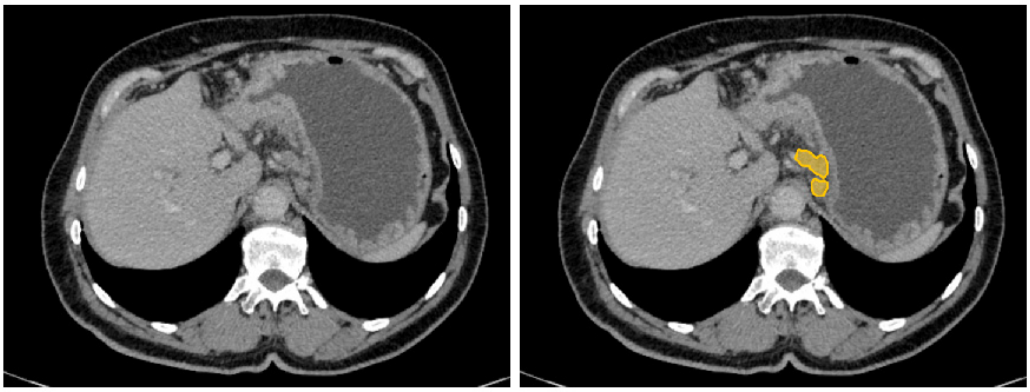

***Figure 4:*** Axial computed tomography image of the abdomen in a patient with gastric cancer shows enlarged gastrohepatic ligament lymph nodes along the lesser curvature (yellow).

## Lymph Nodes Metastases in the in the Gastrosplenic Ligament

Tumors at the posterior wall and the greater curvature of the gastric fundus have lymphatic drainage that flows to the perigastric nodes (group 1) in the superior segment of the gastrosplenic ligament (**see Figure 5**). It then continues along the short gastric artery's branches to the spleen's hilum nodes (group 2).

The tumors originating from the stomach's greater curvature similarly progress to the perigastric nodes (group 1), follow the left gastroepiploic vessels, and subsequently drain into the lymph nodes located in the splenic hilum (group 2). From the splenic hilum, metastases may spread to the nodes along the splenic artery to the nodes at the celiac axis (group 2).

Additionally, tumors from the upper segment of the body and the posterior wall of the gastric fundus may drain along the posterior gastric artery to the nodes along the splenic artery (known as the suprapancreatic nodes or the nodes in the splenorenal ligament) and then to the nodes at the celiac axis [10,11].

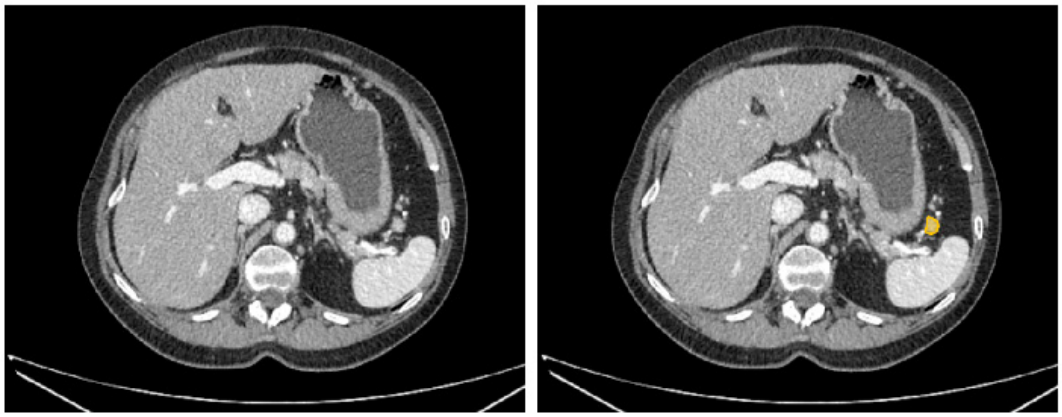

***Figure 5:*** Axial computed tomography image of the abdomen in a patient with gastric cancer shows enlarged gastrosplenic ligament lymph node (yellow).

## Lymph Nodal Metastases in the Gastrocolic Ligament

Primary tumors involving the greater curvature of the antrum of the stomach in the distribution of the right gastroepiploic artery disseminate to the perigastric nodes (group 1) that accompany the right gastroepiploic vessels that are located along the stomach's greater curvature. The nodes at the origin of the right gastroepiploic artery, the nodes at the gastrocolic trunk (group 2), and the nodes along the gastroduodenal artery (the subpyloric or infrapyloric node) are where they drain into. From there, metastases can advance to the superior mesenteric artery's root or the celiac axis [10,11].

## Lymphatic Drainage Pathways through Inferior Phrenic Lymph Nodes

Tumors involving the esophagogastric junction or the gastric cardia may penetrate beyond the diaphragm's wall. The lymphatic drainage of the peritoneal surface of the diaphragm occurs via nodes along the inferior phrenic artery and veins that go along the diaphragm's left crus toward the celiac axis or the left renal vein [10,11].

## Extent of lymph node dissection

Based on the type of gastrectomy performed, the extent of lymphadenectomy is described as follows and is classified by the D-level criteria into D1, D1+, or D2.

The lymph node station that has been extra resected or left in situ may be documented as follows when the extent of the lymphadenectomy performed does not entirely meet the D-level criteria: D1 (+ No. 8a), D2 (− No. 12a). But when entering data into the nationwide database, the D levels must be precisely defined, and they must be decremented when any lymph node station that should have been resected to meet the requirements for a particular D level is not removed (e.g., D2 (− No. 12a) should be entered as D1 +) [13].

## Extent of the lymphadenectomy according to the type of gastrectomy

The Japanese Gastric Cancer Association released version 6 of their most recent update to their treatment guidelines for gastric cancer in 2021, based on this classification. These guidelines provide a detailed explanation of the extent of the lymphadenectomy required based on the type of indicated gastrectomy [13].

Illustrative images for each of the following cases are published in the Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition) [13].

**For total gastrectomy**, the lymph node stations to be dissected in D1 lymphadenectomy are stations 1-7; D1+ includes D1 + No.8a, 9, and 11p; D2 includes D1 + No.8a, 9, 10, 11p, 11d, and 12a. Resection of Nos. 19, 20, and 110 should be added to D2 for esophageal tumors.

The lower thoracic para-esophageal nodes, or No. 110 lymph nodes, are those that are connected to the lower portion of the esophagus and are removed in order to provide an adequate resection margin in cases of gastric cancer invading the esophagus [13].

**For distal gastrectomy**, the lymph node stations to be dissected in D1 lymphadenectomy are stations: No.1, 3, 4sb, 4d, 5, 6 and 7; D1+ includes D1 + No.8a, and 9; D2 includes D1 + No.8a, 9, 11p, and 12a [13].

**For pylorus-preserving gastrectomy**, the lymph node stations to be dissected in D1 lymphadenectomy are stations: No.1, 3, 4sb, 4d, 5, 6 and 7; D1+ includes D1 + No.8a, and 9. When doing a pylorus-preserving gastrectomy and No. 6 was not fully dissected, the D level shouldn't be altered [13].

**For proximal gastrectomy**, the lymph node stations to be dissected in D1 lymphadenectomy are stations: No.1, 2, 3a, 4sa, 4sb and 7; D1+ includes D1 + No.8a, 9 and 11p, and D2 includes D1 + No.8a, 9, 11p, and 11d. Resection of Nos. 19, 20, and 110 should be added to D2 for esophageal tumors. The lower thoracic para-esophageal nodes, or No. 110 lymph nodes, are those that are connected to the lower portion of the esophagus and are removed in order to provide an adequate resection margin in cases of gastric cancer invading the esophagus [13].

**Indications for lymph node dissection (Table 2).**

In general, cT1N0 tumors should be treated with a D1 or D1 + lymphadenectomy, and cN + or ≥ cT2 tumors with a D2 lymphadenectomy (clinical stage /cTNM/ to be established based on preoperative imaging, staging laparoscopy findings and intraoperative findings). Because pre- and intraoperative assessments of tumor invasion depth and nodal involvement are still unreliable, D2 lymphadenectomy should be performed whenever nodal involvement is suspected [13].

**Table 2:** Indications for lymph node dissection in gastric cancer surgery according to the Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition) [13].

| | |
|---|---|
| D1 lymphadenectomy | cT1a tumors that do not meet the criteria for Endoscopic mucosal resection (EMR) or Endoscopic submucosal dissection (ESD)** |
| D1 + lymphadenectomy | cT1N0 tumors other than the above |
| D2 lymphadenectomy | Potentially curable cT2–T4 tumors, as well as cT1N + tumors (The spleen should be preserved in total gastrectomy for advanced cancer of the proximal stomach provided the tumor does not involve the greater curvature) |
| D2 + lymphadenectomy* | Classified as a non-standard gastrectomy, and could be considered for the following cases:<br>1) D2 + No. 10 (for cancer of the proximal stomach invading the greater curvature)<br>2) D2 + No. 14v (for cancer of the distal stomach with metastasis to the No. 6 lymph nodes)<br>3) D2 + No. 13*** (for cancer invading the duodenum)<br>4) D2 + No. 16 (after neoadjuvant chemotherapy for cancer with extensive lymph node involvement) |

** Hard evidence is lacking*
*** Criteria for Endoscopic Mucosal Resection (EMR) or Endoscopic submucosal dissection (ESD) are described in detail in the paper Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition) [13].*
**** The No. 13 nodes are not included in the regional lymph nodes for gastric cancer, hence metastases to these nodes are typically categorized as M1. However, because the No. 13 nodes are among the regional lymph nodes for cancer of the duodenum according to the TNM classification and the Japanese Classification of Gastric Carcinoma 15th edition, these should be considered as regional lymph nodes once gastric cancer invades the duodenum*

## Esophagogastric junctional cancer and extent of lymphadenectomy

Esophagogastric junctional cancer is treated using one of the following procedures:

1) Proximal gastrectomy with or without lower esophageal resection;

2) Total gastrectomy with or without lower esophageal resection;

3) Esophageal resection and proximal gastrectomy [13].

Regardless of the location of the tumor, the most recent edition of the Japanese Gastric Cancer Treatment Guidelines specifies the extent of lymphadenectomy based on the type of gastrectomy.

As a standard of treatment, there is no consensus on the type of resection or degree of lymphadenectomy for esophagogastric junctional cancer, which is specified as adenocarcinoma or squamous cell carcinoma with a center located within 2 cm of the esophagogastric junction. Together, the Japan Esophageal Society and the Japanese Gastric carcinoma Association carried out a prospective research of esophagogastric junctional carcinoma of cT2-T4, looking at the incidences of lymph node metastasis [22].

Although long-term outcomes for the survival advantage of lymphadenectomy for this group have yet to be obtained, it appears appropriate to follow **Table 3**, which summarized lymphadenectomy for the treatment of esophagogastric junctional cancer of cT2 or deeper [13].

**Table 3:** Lymphadenectomy for the treatment of esophagogastric junctional cancer of cT2 or deeper according to algorithm of the surgical approach and lymph node dissection for esophagogastric junctional carcinoma of the Japanese Gastric Cancer Association and Japan Esophageal Society [13].

| | | |
|---|---|---|
| ***cT2-T4* esophagogastric junctional cancer** | tumors with esophageal invasion shorter than 2 cm | *1, 2, 3a, 7, 8a, 9, 11p, 19* |
| | tumors with esophageal invasion of 2.1–4.0 cm | *1, 2, 3a, 7, 8a, 9, 11p, 19,* 110 |
| | with esophageal invasion greater than 4 cm, or clinically positive upper and middle mediastinum lymph nodes | *1, 2, 3a, 7, 8a, 9, 11p, 19, 106 right recurrent laryngeal nerve lymph node, 107,* 108, 109, 110, 111, 112 |

## Various extents of lymph node dissection in the gastric cancer surgery: For early as well as advanced gastric cancer

Western surgeons generally believed that malignant lymph nodes serve as indications rather than predictors of survival [23,24]. In contrast, Japanese surgeons have shown that improved loco-regional control achieved by carefully planned radical resections combined with extensive lymphadenectomy improves survival by decreasing distant metastasis and preventing loco-regional recurrences [6]. A few Randomized Controlled Trials (RCTs) that compare different degrees of lymphadenectomy in gastric cancer surgery to evaluate the associated postoperative morbidity and mortality and their effect on survival have been published in the past 20 years. These RCTs are discussed later in the text.

## Lymph node dissection for Early Gastric Cancers (EGC)

Established in 1971 by the Japanese Society of Gastroenterology and Endoscopy, the term Early Gastric Cancer (ECG) refers to cancer restricted to the gastric mucosa and/or submucosa, regardless of the status of lymph nodes [25]. In general, EGC was assumed to have a good prognosis because the likelihood of lymph node involvement is nearly zero. However, there are tumors that demonstrate excellent clinical behavior with survival rates of 98-100% following treatment, but there are also worrisome subgroups of EGC with elevated lymph node metastases incidence (14-20%) and survival rates as low as 70% [26].

As a result, it is clear that additional classification of EGC is required in order to distinguish more aggressive types, i.e. tumors with a higher probability of lymph node involvement and treatment failure. Risk factors for lymph node metastases in EGC include submucosal invasion, differentiation grade, lesion size and macroscopic appearance, and lymphatic and/or vascular invasion [26]. More specifically, one of the most critical parameters impacting the probability of lymph node involvement in EGC appeared to be the depth of invasion of the gastric According to Inoue et al., patients with mucosal lesions had a 5-year survival rate of 100%, whereas those with submucosal lesions had a rate of 90%. They also found that lymph node metastases have a direct impact on survival, with an overall survival rate of 99% for N0 patients and 73% for N1 [27]. Other authors have also agreed these results [28].

The morphological growth patterns of the lesions are another factor that influences prognosis. In 1983, **Kodama et al.** categorized EGC's morphological growth patterns into categories, each with its own risk of lymph node involvement [23]. Other major prognostic indicators include lymphovascular invasion status and grade of tumor differentiation. In the absence of lymphovascular invasion, the average rate of lymph node metastases is 9%, compared to 53% in the opposite scenario. Lymph node involvement is higher in well-differentiated tumors (13% vs. 34% for poorly differentiated tumors). Furthermore, the risk of lymph node involvement is markedly increased by tumor size greater than 2 cm and diffuse

histologic type as classified by **the Lauren classification** [24,29-31]. The probability of lymph node metastases is up to 2.3 times higher for depressed lesions compared with elevated in morphology EGCs, based on the macroscopic types as determined by the Paris classification [32].

Through this view, there is a rationale for the rigorously defined indications of the two endoscopic procedures used to treat EGC: Endoscopic Mucosal Resection (EMR) And Endoscopic Submucosal Dissection (ESD). Therefore, when all of the following criteria are met - complete resection, tumor size less than 2 cm in diameter, absence of neoplastic ulcer, intestinal histologic type, pT1a, negative lateral and vertical margin, and absence of lymphovascular invasion - endoscopic resection can be recognized curative, according to the Japanese Gastric Cancer Association. Without meeting the previously stated criteria, every other early case of gastric cancer requires a D1 or D1 + lymphadenectomy if no clinically positive nodes are found. The latter situation, in which patients have nodes that are clinically positive, requires a correct D2 lymphadenectomy [17].

**Ishikawa et al.** [33] presented optimized lymphadenectomy for EGC based on the analysis of 1141 cases from a single institution. They analyzed 678 T1a and 463 T1b cancers. There were 11 cases of lymph node metastasis positive T1a cancer. All of them were undifferentiated, and the metastasis-positive lymph nodes were all limited to the D1 region. There were 82 cases of T1b cancer with lymph node metastases. Of them, 70 cases fell into the D1 area, 77 into the D1+ area, and 79 into the D2 area. Beyond the D2 area, the lymph nodes in the other three cases showed evidence of metastases. Ishikawa et al. [33] concluded that D1 lymphadenectomy is enough for T1a EGC that is out of indication of endoscopic resection and D1+ lymphadenectomy is reasonable for T1b EGC. They advise that this cases are good indication of laparoscopic surgery, and emphasize that D2 lymphadenectomy is required for T1b undifferentiated cancers which size is larger than 4 cm.

**In the Western world,** however, things are not so simple. Epidemiological data shows a decrease in the incidence of intestinal type tumors of the distal stomach, while proximal and tumors of the diffuse type are becoming more common [34]. Due to the epidemiological shift in the characteristics of gastric cancer, Western surgeons are now treating increasingly aggressive types of the disease. Moreover, endoscopic resection is still not widely used in Western institutions for either therapy or diagnostic/staging purposes [35]. The guidelines of the Italian Gastric Cancer Study Group **recommend a D2 lymphadenectomy** in cases of clinically early forms that are not suited for endoscopic treatment, due to the potential risk of understaging and consequent undertreatment [36]. Nowadays, when done in specialized settings avoiding unnecessary splenectomy and/or pancreatectomy, the D2 lymphadenectomy is a technique with minimal associated morbidity and mortality [36-37]. In patients who are not eligible for endoscopic treatment due to co-morbidities, a more limited lymphadenectomy

would be a compromise between the risks associated with an extensive surgery on a fragile patient and an optimal oncological outcome [37].

**Lymph node dissection for advanced gastric cancers (AGC)**

It is difficult to define advanced gastric cancer because of its complexity and variety. Although there are a number of different categorization systems, including **TNM staging and the Japanese Gastric Cancer Association (JGCA) classifications**, there isn't a single, widely recognized definition since tumor size, lymph node involvement, and other prognostic variables vary [38]. For all gastric cancers that can be surgically removed, surgery is the standard of care. At this time, a radical gastrectomy combined with a lymphadenectomy is seen to be the most appropriate strategy for treatment [39]. While the diagnosis of gastric cancer is frequently made later in the course of the disease in Western nations, well-organized screening programs operating in Eastern countries result in an earlier diagnosis [40]. Nodal involvement has significant prognostic significance for gastric cancer because, like other gastrointestinal malignancies, it spreads via lymphatics to the regional lymph nodes [6].

During the 1990s, one of the main points of contention **between Japanese and Western surgeons** was the extent of lymphadenectomy [41].

Since it has been shown that an extensive lymphadenectomy is linked to better outcomes in terms of survival and optimal locoregional control of the disease, the D2 lymphadenectomy has been accepted as the standard procedure in **Eastern nations** [42]. This technique may be explained, at least in part, by the experience Asian surgeons have obtained by doing routine radical lymphadenectomies for gastric cancer at high-volume clinics. Furthermore, from a technological point of view, the surgery is made easier and more practicable by the specific epidemiological characteristics of the gastric cancer patient pool seen in Eastern nations, such as younger patients with fewer co-morbidities and less abdominal obesity [43].

Conversely, the D2 lymphadenectomy was historically viewed as an excessive treatment for patients with gastric cancer in **Western nations** [44]. Higher perioperative morbidity and mortality have been linked to D2 lymphadenectomy in Western Randomized Clinical Trials (RCTs), with no obvious benefit to survival [45-47]. Within this context, a more restricted lymphadenectomy than the D2 was performed in conjunction with the proper gastrectomy, either total or distal, by Western surgeons [6].

**Three important RCTs** compared **D1 and D2 lymphadenectomy** in gastric cancer surgery, significantly influencing surgical treatment guidelines.

From August 1989 to July 1993, **the Dutch Gastric Cancer Group** performed the well-known Dutch trial [43]. They randomly assigned 711 patients to two groups. The first group

got a D1 lymphadenectomy, whereas the second group underwent a D2 lymphadenectomy. The D1 dissection involved clearing lymph node stations 1-6, whereas the D2 group additionally cleared stations 7-11. Distal pancreatectomy along with splenectomy were regularly performed on all D2 patients. But only the D1 patient group had pancreatectomy and splenectomy since there was tumor involvement in these organs [6].

When comparing the D2 group to the D1 group, they found a statistically significant increase in postoperative morbidity (43 vs. 4%) and mortality (10 vs. 4%). The 5-year survival rates for the two groups were similar. The authors concluded that their findings did not justify regular D2 lymphadenectomy in individuals with gastric cancer. On the other hand, this trial has drawn a lot of criticism. The research included low volume centers for gastric resection, while the participating surgeons had no prior training or experience with D2 lymphadenectomy [6].

The 11-year follow-up data of this trial (reported in 2004) showed similar survival in both groups (30% for D1 vs 35% for D2, P = 0.53) [9]. The 15-year survival results from the Dutch trial (released in 2010) elevated the evidence toward the D2 dissection. Loco-regional recurrences were higher in the D1 group than the D2 group (40.7 vs. 21.8%). The 15-year overall survival rate for patients who underwent curative resections was 21% for the D1 group and 29% for the D2 group; however, the difference in survival (25 vs. 35%) between the two groups became more apparent if the postoperative mortality were eliminated (4 vs. 10%). Subgroup analysis revealed that pancreatectomy and splenectomy, which were performed routinely in the D2 group, significantly reduced overall survival. The authors' recommendation for spleen-preserving D2 dissection in patients with resectable gastric cancer was prompted by these findings [39].

The MRC trial, conducted by Cuschieri et al., was the second important trial on this subject that was published in 1999 [45]. Two groups of 400 patients were randomly assigned. The term "D1 dissection" refers to the removal of lymph nodes from within 3.0 cm of the tumor in 200 patients in one group; additional removal of the omental bursa, hepatoduodenal and retroduodenal nodes (antral lesions), splenic artery/splenic hilar nodes, and retropancreatic nodes by distal hemipancreaticosplenectomy for middle and upper third lesions was included in the D2 dissection procedure for 200 patients in the other group.

According to the authors, D2 lymphadenectomy was linked to significantly higher postoperative complications as well as mortality [48]. After a median follow-up of 6.5 years, the authors demonstrated that there was no statistically significant difference in total 5-year survival between these two groups. Both recurrence-free survival and gastric cancer-specific survival were comparable between the D1 and D2 groups. The trial's results led the authors to conclude that there was no survival benefit to traditional Japanese D2 resection over D1

resection [48].

Nevertheless, given that the group having splenectomy with distal pancreatectomy had a substantial survival disadvantage, they did not rule out the potential that the D2 resection without pancreatico-splenectomy would be superior to the usual D1 resection. This fact may also have influenced the findings, as 57% of the D2 group got distal pancreatectomy and splenectomy against 4% in the D1 group. There was a little variation in the median number of nodes examined, with a mean of 13 in the D1 group vs. 17 in the D2 group, despite the fact that the D2 lymphadenectomy involved a more extensive dissection of lymph nodes than the D1 [48].

The Italian Gastric Cancer Study Group (IGCSG) carried out the third study [49]. The authors sought to evaluate the short-term outcomes and potential survival advantages of the D2 lymphadenectomy in light of the higher rates of postoperative morbidity and mortality reported by the MRC and the Dutch study in the D2 lymphadenectomy groups. 267 participants were randomly assigned to get D1 or D2 lymphadenectomy.

According to the authors [49], there was no difference in the overall morbidity as well as the postoperative mortality rates between the two groups. They came to the conclusion that, in appropriate circumstances, the D2 lymphadenectomy should be considered a safe option for the treatment of gastric cancer in Western patients because the postoperative complications in this group of patients were not as high as previously described [49]. Long-term findings (i.e. 5-year survival) showed no difference between the two treatment groups after a median follow-up of 8.8 years for survivors and 2.4 years for those who died [50]. Subgroup analysis revealed that patients with T1 tumors in the D1 lymphadenectomy group had a significant 5-year disease-specific survival advantage compared to the D2 group. In the D2 lymphadenectomy group, patients with positive lymph nodes and pathologic T2-4 status had higher survival ratings. The authors came to the conclusion that patients with lymph node metastases and advanced disease (pT2-4) could benefit more from a D2 lymphadenectomy.

**Lymphadenectomy beyond the standard D2 dissection**

The question of whether extended lymphadenectomy beyond the conventional D2 dissection would be beneficial in the treatment of advanced gastric cancer is disputed. Following the publication of **the Japan Clinical Oncology Group (JCOG) 9501 trial** results, routine lymphadenectomy of para-aortic nodes (station No. 16) is presently no longer suggested. In fact, in advanced gastric cancer patients without a clinical suspicion of para-aortic node metastases, the Japanese trial's findings indicated no survival advantage following **D2 + para-aortic node dissection** as opposed to D2 lymphadenectomy alone [51].

## D2 vs extended D2 lymphadenectomy

The question of D2 vs. expanded D2 (which include para-aortic lymph node dissection) has been the subject of three reported RCTs. There has always been considerable concern about significant postoperative morbidity and mortality after substantial lymphadenectomy, particularly among surgeons in the West [41].

**The Polish Gastric Cancer Study Group** released the interim analysis of their multicenter, randomized clinical trial, which was started to assess the potential advantages of extended D2 (D2+) lymphadenectomy following potentially curative resection of gastric cancer, in order to address the safety concerns of extensive D2 dissection [52]. **The JGCA** categorization was used to define standard D2 lymphadenectomy; additional para-aortic node removal was included in D2+ lymphadenectomy. 275 individuals were divided into two groups at random: 141 had a standard D2, and 134 had a D2+ lymphadenectomy. Both the postoperative mortality rates and the total morbidity rates were similar between the two groups. They came to the conclusion that two groups would have identical surgical outcomes based on the interim safety analysis [41].

**The JCOG 9501 trial** was unable to demonstrate the **oncological advantage** of D2 prolonged dissection, despite the POLAND trial having demonstrated the safety of this procedure [51]. The surgical question of whether Para-Aortic Nodal Dissection (PAND) added to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival was investigated in the JCOG 9501 trial. In order to compare D2 lymphadenectomy alone with D2 lymphadenectomy with PAND in patients having gastrectomy for curable gastric cancer, a multi-centric (24 hospitals in Japan) randomized controlled trial was carried out. After surgery, none of the patients received any prescriptions for adjuvant care. There was no difference in 5-year overall survival rates between the two groups. Furthermore, the results indicated no significant differences in recurrence-free survival between the two groups, and the authors reported that D2 lymphadenectomy + PAND did not increase the survival rate in curable gastric cancer in comparison with D2 lymphadenectomy alone.

**The East Asia Surgical Oncology (EASO) group** carried out the third RCT to assess the survival benefit of para-aortic dissection in addition to D2 lymphadenectomy in patients with gastric adenocarcinoma that may be curable [53]. Patients were randomly assigned to two groups: 135 patients were allocated to participate in the D2 group, and 134 patients in the D2 + para-aortic lymphadenectomy group (D2+; the authors also refer to this group as D4). The researchers came to the conclusion that patients with advanced gastric cancer who may be curable should not have preventive para-aortic dissection since there was no statistically significant difference in survival between the two groups. It is noteworthy to emphasize that three of the twelve patients with pathologically positive station 16 nodes lived longer than five

years (median survival 2.8 years).

**D1 vs D3 lymphadenectomy**

While most surgical societies support D2 level of lymph node dissection in their treatment guidelines for gastric cancer, extended D3 dissection has also been tried to enhance oncologic results.

In their mini review, Douridas et Pierrakakis (2018) [54] studied five meta-analyses [46,55-58], three randomized trials [51-53], and seven non-randomized comparisons [59-65] that were almost exclusively Asian in origin. According to their findings, D3 lymphadenectomy was consistently and significantly linked to "heavier" iatrogenic surgical trauma, which was characterized by increased blood loss, longer operating times, a higher likelihood of relaparotomies, and post-procedural surgical and non-surgical morbidity. Surprisingly, mortality in the majority of these series did not achieve statistical significance, which is most likely due to Asian surgical competence and/or methodologic drawbacks. They discovered that all available data, including meta-analyses and a well-designed RCT from Japan (JCOG), failed to establish a clear overall survival advantage associated with D3 dissection, therefore eliminating the technique from current therapy protocols [54].

Wu et al. [66] conducted a randomized controlled trial of nodal dissection for patients with advanced gastric cancer in Taiwan, randomly assigning 221 patients to either D1 lymphadenectomy or D3 lymphadenectomy. According to the intention-to-treat analysis, the 5-year overall survival was 59.5% in the D3 group and 53.6% in the D1 group (difference between groups 5.9%, 95%CI: -7.3 to 19.1, log-rank P = 0.041). However, within this R0 resection group, the D3 group had significantly higher 5-year overall survival than the D1 group. The authors found that D3 nodal dissection performed by well-trained and experienced surgeons provides a survival benefit over D1 in gastric cancer. However, this study had its limitations.

The extent and post-treatment impact of gastric cancer lymphadenectomy in combination with modern chemotherapeutic drugs in multimodal therapies should be investigated in future multicenter randomized studies [54].

**General overview of the mentioned trials**

Although D2 dissection has been linked to significantly higher postoperative morbidity in terms of anastomotic leakage, pancreatic leakage, reoperation rates, wound infection, and pulmonary complications, according to **the MRC** [48] and **Dutch trial** [43], it appears that the higher postoperative risk associated with D2 dissection in these trials is primarily due to splenectomy and pancreatectomy rather than D2. Second, poor surgical training in

the D2 dissection, as well as suboptimal quality control, might explain the higher levels of postoperative morbidity and mortality seen in previous studies. **The IGCSG trial** demonstrated that D2 dissection may be done safely without splenectomy or distal pancreatectomy, with mortality and morbidity rates comparable to those of D1 dissection [49]. Splenectomy or distal pancreatectomy may be considered useful if the primary tumor or metastatic lymph nodes directly infiltrate these organs. Routine resection of the spleen and pancreatic tail is no longer considered a required component of current D2 dissection [67].

Though the initial findings of the Dutch and MRC trials did not reveal a survival benefit from D2 lymphadenectomy, the Dutch trial's 15-year follow-up data decisively changed the evidence in favor of spleen-preserving D2 lymphadenectomy [41].

Furthermore, after **the Japan Clinical Oncology Group (JCOG) 9501 study** was published, the routine lymphadenectomy of para-aortic nodes (station No. 16) is no longer recommended [51]. Although there is optimism for this patient cohort due to the 25% 5-year survival rate among patients with pathologically positive para-aortic nodes (**the EASO group study**), prophylactic dissection of station 16 does not offer any substantial advantage over routine D2 lymphadenectomy [53].

The underlying question remains: what is the best lymphadenectomy for a specific patient to enhance survival while avoiding significant postoperative complications? A personalized surgical approach may be beneficial in determining whether to perform a D1 or D2 lymphadenectomy in a given patient - a D2 lymphadenectomy may not benefit a patient with early gastric cancer and may even lead to increased complications; On the opposing side, patients with advanced disease may benefit from an extensive lymphadenectomy [68].

**In general,** the global consensus on D2 lymphadenectomy has increased substantially due to well-documented survival improvement [69-72].

**Interesting approaches for the future**

**Maruyama Index** [73]

After carefully examining every resected lymph node station in 3,843 patients, Prof. Maruyama developed **the Maruyama Index (MI) of unresected disease** to enable more tailored lymph node dissections [42,74]. **The Maruyama Computer Program** can determine the likelihood of nodal involvement of each lymph node station based on seven input variables (age, sex, Borrmann type, tumor size, tumor location and histology) [73].

The MI of unresected disease was then defined as the total of regional nodal disease percentages for stations (1-12) that were not surgically removed. It was created to estimate the survival of patients with gastric cancer following surgery through patient and tumor

characteristics as well as information from the removed lymph node stations [73].

Compared to patients who scored five or above, those with a MI of less than five had a considerably higher likelihood of survival and a smaller likelihood of recurrence [75]. In the Intergroup 0116 trial, this indicator also showed promise as a significant predictor of survival on univariate and multivariate analysis [76]. In Western nations, the MI is not frequently used during surgery because of its complexity for use in the operating room [73].

**A modular approach for the radical resection of advanced gastric cancer called the three-step method for modular lymphadenectomy (TSMML)** [77]

The most crucial component of curative resection is systematic lymphadenectomy for the removal of sufficient lymph nodes. However, retrieving adequate lymph nodes is the major issue for surgeons [78]. The technique and intensity of the lymph node retrieval, in addition to the extent of the lymphadenectomy, influence the number of lymph nodes that are retrieved [79-81].

In 2011, Li et al. [77] given a modular strategy for radical resection of advanced gastric cancer known as **the three-step method for modular lymphadenectomy (TSMML)** [82], which targeted at **a sufficient number of retrieved Lymph Nodes (rLNs) and improved survival.** This paper aimed to compare the treatment outcomes of individuals who had TSMML with those who underwent the Conventional Method for Lymphadenectomy (CML) [77].

As previously mentioned, there were three steps in the TSMML technique **(Table 4)** [82]. Four principles guided the main procedure: from right to left, in the caudal to cranial direction, en-bloc removal and lymphadenectomy in order [77].

**Table 4:** The TSMML procedure.

| | | |
|---|---|---|
| **Step A** | The Kocher maneuver and the dissection of the greater omentum, the anterior sheet of the mesocolon and the pancreatic capsule | The lymph node stations to be dissected: 6, 4d and 4sb |
| **Step B** | Early division of the duodenum and the dissection of tissue in the hepatoduodenal ligament and the lesser omentum | The lymph node stations to be dissected: 12a, 5, 1 and 3 |
| **Step C*** | A lymphadenectomy along the main vessels | The lymph node stations to be dissected: 8a, 7, 9, 11p. |

**Lymph node stations 11d, 10, 4sa and 2 were included in this step when the tumor involved the upper or middle third of the stomach.*

Li et al. [77] reported that patients in **the TSMML group** had a significantly higher median number of retrieved Lymph Nodes (rLNs), lower median Metastatic Lymph Node Ratios (MLRs), and more favorable 5-year Relapse-Free Survival (RFS) than **the CML group**. Furthermore, using the TSMML technique was an independent protective factor for RFS. In these two groups, there were not significant intergroup differences in morbidity or mortality. The TSMML technique was shown to be safe, effective, and easy to learn.

**Laparoscopic as well as robot-assisted lymph node dissection**

**Laparoscopic-assisted lymph node dissection**

Many surgeons are using laparoscopic-assisted gastrectomy for gastric cancer because of its many benefits over traditional open surgery, including less postoperative pain, better cosmetic results, less blood loss, quicker recovery, and shorter hospital stays. However, concerns about the technique's oncological radicality have prompted the need to thoroughly examine it in well-designed studies [6].

Few studies have reported the outcomes of laparoscopic D2 gastrectomy, despite the fact that many have compared laparoscopy-assisted gastrectomy with conventional open surgery. The three most important trials are the JCOG0912 trial, which was carried out in Japan [83], the CLASS-01 trial from China [84], and the KLASS-02 trial, which was carried out in Korea [85].

According to the results of these investigations, laparoscopy-assisted D2 gastrectomy is a safe, practical procedure that offers comparable short-term results to open surgery. In comparison to open surgery, many questions have been raised regarding the quality and oncologic safety of laparoscopic D2 lymph dissection despite these encouraging outcomes [86].

Additionally, the results of 25 consecutive patients with gastric cancer who underwent laparoscopic D2 gastrectomy were reported by Abdelhamed et al. (2020): Patients had distal gastrectomy performed on 72% of them, total gastrectomy on 16%, and proximal gastrectomy on 12% of them [86]. According to their research, the median number of extracted lymph nodes was 18 (5-35), and two cases (8%), had a positive proximal margin. Seven patients (28%) had their procedures converted to open, and postoperative complications were detected in 16% of patients. They came to the conclusion that laparoscopic D2 gastrectomy is a safe and feasible procedure that can be carried out by skilled surgeons to get the optimal short-term oncological results. To examine long-term results, additional cases with an adequate follow-up period are however required [86].

Furthermore, investigations on laparoscopic gastrectomy are showing a steady increase

in lymph node harvest rate, reaching levels comparable to those seen during open surgery [87]. There is not an evident difference in the amount of lymph nodes removed between laparoscopic distal gastrectomy and the open procedure, according to a recent meta-analysis of eight case-control studies. Nonetheless, compared to an open distal gastrectomy, the mean operating time for a laparoscopic distal gastrectomy is noticeably longer [87].

## Robot-assisted surgery for gastric cancer

Robot-assisted surgery for gastric cancer was approved for health insurance coverage in 2018, and it is now widely used in many institutions as a method that allows for more advanced surgery. In Japan, it has been found that robot-assisted surgery reduces postoperative complications when compared to laparoscopic surgery [13].

However, because the studies done by Uyama et al. and Hikage et al. were single-arm trials or retrospective comparisons, respectively, no evident advantage of robot-assisted gastrectomy has been demonstrated [88, 89]. A randomized, controlled research (JCOG1907) is now being conducted to confirm the advantages of robot-assisted gastrectomy over laparoscopic gastrectomy in terms of morbidity reduction for clinical T1-2 N0-2 gastric cancer. Currently, there is a weak recommendation for robot-assisted surgery for gastric cancer at clinical stage I. In order to perform a robot-assisted gastrectomy, the surgeon and the facility must meet the required quality criteria [13].

**Finally,** we want to point out that in order to enhance surgical care for gastric cancer in the West, Giacopuzzi et al. published **the technical details** of the D2 dissection in both open and laparoscopic gastrectomy. We recommend that paper for details on performing lymphadenectomy in gastric cancer surgery [90].

## Conclusion

In conclusion, the standard course of treatment for a gastric cancer that is operable is a D2 lymphadenectomy. Routine excision of the spleen and pancreatic tail is not recommended since it raises the risk of complications following surgery without significantly improving overall survival.

**Conflict of interests:** The authors declare no conflict of interests.

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