# Lymphadenectomy for Gastric Cancer

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**KEYWORDS**

• Gastric cancer • Lymph node dissection • D2 lymph node dissection
• NCCN guidelines

**KEY POINTS**

- Lymph node dissection for gastric cancer has fluctuated over the past several decades.
- Studies conducted in Japan and Western countries have sometimes demonstrated conflicting results regarding the need for an extended lymph node dissection.
- Current guidelines dictate the need for a lymph node harvest of 16 nodes regardless of the location of these nodes.

## INTRODUCTION

While the incidence and mortality of gastric cancer have declined over the past few decades, the disease continues to remain one of the top 5 causes of cancer-related deaths worldwide.[1–3] In 2020, gastric cancer accounted for about 1 in every 13 deaths globally with more than one million new cases reported and greater than 750,000 deaths.[4] Population screening programs in Japan and South Korea have resulted in improved outcomes due to early detection with a 5 year survival up to 75%.[5] In the United States, the 5 year survival is about 20% to 30%,[3,5] partly due to detection at later stages.

Gastric cancer is highly associated with environmental, dietary, and hereditary risk factors, including *Helicobacter pylori* infection, tobacco smoking, nitrates in processed meals, dairy, and heavy alcohol use.[2] Although most cases of gastric cancer are sporadic, several inherited cancer predisposition syndromes increase the risk of gastric cancer. These include hereditary diffuse gastric cancer, Lynch syndrome, juvenile polyposis syndrome, Peutz–Jeghers syndrome, and familial adenomatous polyposis. Over half of gastric cancer cases that are linked to gene mutations involve the TP53 gene.[3] Other mutations involve KRAS, APC, and SMAD4.[3]

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Staging of gastric cancer follows the tumor (T), node (N), and metastasis (M) system as outlined in the eighth edition of the *AJCC Cancer Staging Manual*.[6] The major changes to staging reflected in the eighth edition (published in 2016) included the division of the pN3 stage into pN3a and pN3b, the introduction of staging for patients who have received neoadjuvant chemotherapy (ypTNM), the introduction of clinical TNM staging for patients who are newly diagnosed and not yet treated (cTNM), and redefinition of the esophagogastric junction (EGJ) and cardia cancer staging systems.[6,7] The classification of EGJ tumors dictated that only tumors in which the epicenter was greater than 2 cm in size from the junction be treated as gastric cancer.[6] Kim and colleagues studied whether the changes in the eighth edition were associated with improvements in prognostic performance.[8] They reviewed 5507 patients with gastric cancer in a single South Korean institute who underwent treatment between January 1989 and December 2013, and found stage migration in 6.4% of patients. Comparison of 5 year overall survival rates between staging per the seventh and eighth edition guidelines yielded a statistically significant improvement in survival discrimination, especially in the stage III group of primarily lymph node-positive patients.

## LYMPH NODE DISSECTION

Because lymph node status has been shown to correlate with prognosis, the extent of lymph node dissection (LND) during curative resection has been highly debated.[9] These debates have been framed by a classification system published by the Japanese Research Society for Gastric Cancer in 1973.[8] The Society divided the perigastric lymph nodes into 16 stations based on their anatomic location along the lymph drainage pattern of the stomach.[7] The nodal stations were further divided into nodal groups (N1–3) based on the tumor location.[10] LND classification was further simplified into dissection or "D" levels, which is the classification widely used today (**Fig. 1**).[8]

Proponents of more extensive dissection argue that insufficient harvest may result in under-staging and undertreatment, while others argue that unnecessary dissection may increase postoperative complications[7] and may not affect recurrence or survival outcomes.[11–16] In Japan, D2 lymphadenectomy has been the standard of care for over 50 years because it has been shown to increase survival outcomes and lower local recurrence rates in the Japanese population.[17–21]

An early study by Sue-ling and colleagues[18] investigated 207 patients who underwent potentially curative resection for gastric cancer at a single university hospital between 1970 and 1989. Dissection of N1 and N2 lymph nodes, referred to as radical (R2) lymphadenectomy, was the standard of care at this institution by 1980. When comparing the 1980s with the 1970s, there was a statistically significant decrease in surgical mortality and morbidity and a significant increase in 5 year survival rates favoring R2 lymphadenectomy. Part of this improvement in 5 year survival was attributed to the detection of gastric cancer at earlier stages due to advancements in endoscopy, and the sample size was too small to allow comparison of R1 and R2 dissections in each pathologic stage. However, the findings did support the safety of R2 lymphadenectomy and its prognostic significance.

Similar findings were published by Smith and colleagues,[19] who performed a retrospective review of 683 patients with gastric cancer treated at Memorial Sloan-Kettering Cancer Center between July 1985 and July 1989. Patients were divided into 2 groups based on the extent of LND performed: the radical lymph node dissection (RLND) group underwent removal of N1 and N2 lymph nodes ($n = 123$) and the others were included in the R<2 group ($n = 62$). Like the Japanese study, the RLND

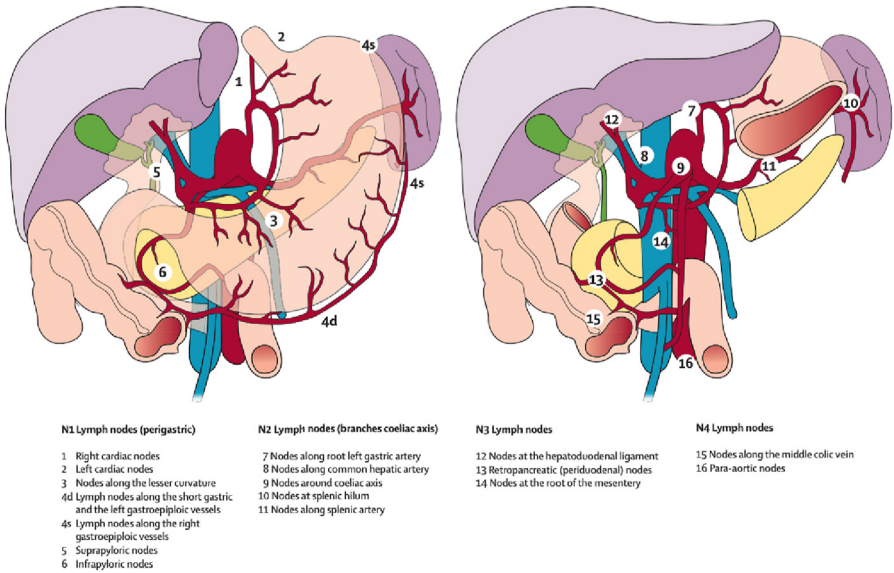


**Fig. 1.** Location and grouping of the lymph nodes. D1 resection: removal of the N1 lymph nodes. D2 resection: removal of the N1 and N2 lymph nodes. D0: incomplete LND less than D1. D1: N1 lymph nodes. D2: D1 + N2. D3: D2 + N3 + N4. (*With permission from* Prof. Cornelis JH van de Velde, MD.)

group did not experience an increase in operative mortality or morbidity. The RLND group demonstrated a survival benefit, especially in those patients with lymph node metastases.

Extended LND was further supported by a prospective analysis conducted by the German Gastric Cancer Study group, which analyzed 1654 patients with resected gastric cancer across 19 hospitals in Germany and Austria.[20] A total of 558 patients with less than 25 lymph nodes removed were included in the standard lymphadenectomy group, while 1096 patients with 26 or more lymph nodes removed were included in the radical lymphadenectomy group. In this study, there was a significant improvement in survival in the radical lymphadenectomy group, particularly in stage II and III patients, without an increase in morbidity.

Despite these positive studies, resection of N1 + N2 lymph nodes ("D2" lymphadenectomy) was not widely practiced in Western countries, largely because extended lymphadenectomy was linked to higher postoperative morbidity and mortality without a significant oncological impact.[13–15] The details of these studies, however, revealed that most centers included distal pancreatectomy and splenectomy in the D2 lymphadenectomy in order to maximize lymph node harvest.[11,13–15,21,22] Studies that included this element of the procedure were unable to replicate the survival benefits of the early Japanese and German studies.

One such study was the Medical Research Council (MRC) Gastric Cancer Surgical Trial (ST01), a prospective study launched in 1986 that examined the benefit of D2 over D1 resections. Four hundred patients were randomized into 2 equal arms: D1 versus D2 resection. The surgical procedure in patients with D2 resection included a pancreatico-splenectomy, except in antral cancers. Short-term analysis failed to show survival benefits in patients with D2, and these patients carried a higher morbidity and prolonged hospitalization.[16] A later analysis of the study concluded

that the increased postoperative morbidity and mortality and reduction in long-term survival may be attributed to the pancreatico-splenectomy.[23]

The Dutch Gastric Cancer Group D1D2 trial also compared D1 versus D2 lymphadenectomy in resectable gastric adenocarcinoma between 1989 and 1993.[11] In this prospective study, 711 patients were randomly assigned to D1 versus D2 lymphadenectomy. Short-term analysis showed no difference in 5 year survival, but the patients with D2 lymphadenectomy demonstrated higher postoperative morbidity and mortality, prolonged hospitalization, and higher reoperation rates. On 15 year follow-up analysis, however, there were lower locoregional recurrence and fewer disease-specific deaths with D2 lymphadenectomy than with D1. Similar to the conclusion from long-term analysis of the MRC ST01 study, the Dutch D1D2 trial also attributed the increased postoperative morbidity and mortality to pancreatico-splenectomy. This trial also supported pancreas-preserving and spleen-preserving D2 resection as the standard surgical approach as it provided improved locoregional control and disease-specific survival when compared to D1 resection.[11,22,24]

Finally, the Italian Gastric Cancer Study Group performed a randomized controlled trial to compare D1 versus D2 lymphadenectomy in 267 patients between 1998 and 2006 and demonstrated findings similar to that of the British and Dutch studies.[13] Initially, there were no statistical significant differences in morbidity, mortality, 5 year survival, and disease-specific survival between the D1 and D2 treatment arms. However, the 15 year follow-up analysis showed improvement in disease-specific survival and gastric cancer-related mortality in patients with lymph node metastasis who underwent D2 lymphadenectomy. This study focused less on a true D1 versus D2 resection and stressed the benefit of retrieving a high number of lymph nodes.[12–15,25]

## CURRENT GUIDELINES

While the studies illustrated earlier potentially disparate findings among randomized, prospective, and retrospective studies, the National Comprehensive Cancer Network (NCCN) guidelines recommend examining 16 or more lymph nodes. This is largely based upon the long-term follow-up results of the Dutch D1D2 trial and the Italian Gastric Center Study, which demonstrated that pancreas and spleen-sparing D2 lymphadenectomy exhibits superior survival.[11,25] These recommendations are also supported by later studies conducted by Karpeh and colleagues and Schwarz and colleagues, which both demonstrated that the total number of lymph nodes retrieved was likely more important than their specific location.

Karpeh and colleagues evaluated whether the location of positive lymph nodes affected survival in 1038 patients. Interestingly, though the recommended number of examined lymph nodes was 15 or more, 27% of the included patients did not meet this minimum. The study demonstrated that the number of positive lymph nodes positively influenced survival, whereas location of positive nodes had no effect.[26] Schwarz and colleagues utilized the Surveillance, Epidemiology, and End Results Program (SEER) database to retrospectively analyze 1377 patients with node positive gastric cancer.[27] The median number of examined lymph nodes was 17 and ranged from 7 to 94. The authors concluded that survival is positively influenced by a higher number of resected lymph nodes, as they showed favorable outcomes when the number of examined lymph nodes exceeded the number of positive lymph nodes by at least 10.

In addition to these lymph node-specific trials, The NCCN guidelines are also shaped by randomized trials that examine the total treatment of gastric cancer, including surgical, local, and systemic therapies. For example, the CLASSIC trial

examined 1,035 patients with stage II or IIIB gastric cancer in South Korea, China, and Taiwan who underwent R0 resection with D2 lymphadenectomy and retrieval of at least 15 nodes.[28] Patients were randomized into surgery-only or surgery plus adjuvant chemotherapy, and patients in the adjuvant chemotherapy group demonstrated increased 3 year disease-free survival (68%) when compared to the surgery-only group (53%). The ARTIST and ARTIST II trials randomly assigned patients who underwent gastrectomy with D2 lymphadenectomy to adjuvant chemoradiation or adjuvant chemotherapy without radiation.[28,29] Neither trial showed that the addition of radiation to adjuvant chemotherapy resulted in lower recurrence rates.

Since the inclusion criteria of these trials dictated that patients must have undergone D2 lymphadenectomy in order to be included, these trials can be applied only to patients who have undergone D2 lymphadenectomy. Thus, D2 lymphadenectomy is critical for guiding adjuvant therapy. Indeed, guidelines still suggest consideration of adjuvant chemoradiation for patients who have undergone less than a D2 lymphadenectomy.

## ADDITIONAL CONSIDERATIONS

Other considerations for the extent of lymphadenectomy include the volume of cases performed at each surgical center, and the emergence of biomarker data in guiding therapy. Data have shown improved overall survival when gastric cancer surgery is performed at moderate to high volume centers.[25,30–32] Parikh and colleagues[30] have suggested that a D2 lymphadenectomy has a learning curve of about 15 to 25 procedures within an 18 to 24 month timeframe. Yu and colleagues[31] further explored the effects on 30 day mortality and long-term survival when comparing gastric cancer surgeries performed by a specialized surgeon versus a general surgeon. Based on this study, a surgeon with 2 or more consecutive years of practice with at least 50 new cases per year should be considered a specialized gastric cancer surgeon, but by the fourth consecutive year in practice, 10 or more annual cases also yielded improved 5 year survival rates. Ju found that high-volume centers performed at least 17 cases per year and yielded a significant decrease in postoperative mortality within a 30 day and 90 day period, largely attributed to manipulation during D2 dissection.[32]

An interesting study conducted in November 2013 examined 2 surgeons from the same institution in Canada who traveled to Japan to participate in a 1 month course for training in the Japanese D2 lymphadenectomy technique.[33] The 2 surgeons implemented the teachings from the course into their practice and continued to assist each other whenever possible after their return. The differences in outcomes before and after the course are impressive: complication rates of both surgeons decreased to 15% from 48%, the 5 year survival increased from 19% to 48%, and adequate LND of 16 or more lymph nodes increased from 37% to 91.1%. Similar trends were noted by Luna and colleagues[34] when 3 surgeons traveled to Japan for similar training courses. The improvements in outcomes after a short training course question the role of further specialized training in these subsets of oncological surgeries and whether they can be incorporated into the current surgical training curricula.

The role of biomarker testing is unclear at this time and is the topic of ongoing research. HER2 overexpression is associated with gastric cancer, but its exact relationship remains undefined. In a retrospective study of 727 patients who underwent surgical treatment for gastric cancer between October 2010 and August 2017, HER2 overexpression was associated with lymphovascular invasion and presence of lymph node metastases in patients with poorly differentiated gastric cancer, but these differences were not seen in well-differentiated patients.[35] This suggests that

while endoscopic treatment may be an option for T1a patients, those with poorly differentiated histology may benefit from testing for HER2 testing and lymph node sampling. Choi and colleagues performed a post hoc analysis of the CLASSIC trial data to explore the roles of microsatellite instability (MSI) and PD-L1 in gastric cancer.[36] A total of 40 patients had MSI-high (MSI-H) tumors; these patients did not experience a statistically significant benefit from adjuvant chemotherapy regardless of their PD-L1 status. But patients with microsatellite-stable tumors demonstrated a response to adjuvant chemotherapy that varied with PD-L1 expression. While the precise role of biomarkers in the treatment of gastric cancer remains unclear, these studies suggest that gene expression may ultimately play a greater role in dictating systemic therapy than lymph node status.

## SUMMARY

The incidence and mortality of gastric cancer have declined over the past few decades, but the disease remains one of the top five causes of cancer-related deaths worldwide.[1–3] The role of lymph node dissection in the treatment of gastric cancer has been studied extensively with retrospective, prospective, and randomized approaches. Current NCCN guidelines dictate a retrieval of 16 lymph nodes for accurate staging, regardless of the specific location of these nodes.

## CLINICS CARE POINTS

- NCCN guidelines recommend a node retrieval of 16 nodes during gastrectomy for gastric cancer in order to accurately stage patients.
- Several modern clinical trials utilized for the multimodal treatment of gastric cancer cannot be applied in the absence of an adequate node harvest.
- Pancreas-sparing and spleen-sparing D2 lymphadenectomy does not increase the morbidity associated with gastrectomy for gastric cancer.

## DISCLOSURE

The authors have nothing to disclose.

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