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REVIEW ARTICLE

Current role of lymphadenectomy in gastric cancer surgery

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Summary

Gastric cancer is the sixth most common cancer worldwide with increased associated morbidity and mortality. Although a multimodality treatment approach is necessary, surgery is still considered as the standard of care. There is a longstanding intercontinental debate between Eastern and Western upper GI surgeons in regards to the proper type of lymphadenectomy that should accompany the resection of the primary tumor. While D2 gastrectomy was performed as the standard procedure in eastern countries, the increased morbidity and mortality attributed initially to the D2 lymphadenectomy by the Medical Research Council (MRC), the Dutch and the Italian randomized control trial without respective survival benefits had led Western surgeons towards a more limited lymphadenectomy. Only 15 years after the conclusion of its accrual, the Dutch trial reported a significant decrease in recurrence rate after D2 procedure and attributed the D2-associated morbidity and mortality to the splenopancreatectomy that was routinely performed in the D2 arm of the study. As the D2 lymphadenectomy can be safely and adequately performed while preserving the spleen and/or the pancreas, it has been suggested as the recommended procedure for patients with resectable gastric cancer.

Key words: *gastric cancer, lymphadenectomy, radical gastrectomy*

Introduction

Gastric cancer is the sixth most common cancer worldwide with a reported mortality of 8.9/100000 population [1]. Surgery with curative intent is currently the only potentially curable treatment available. Though the complete surgical excision of the affected area of the stomach, in the form of either total or distal gastrectomy, is commonplace, there has been an extensive debate in regards to the most proper lymph node dissection extent. In general, Eastern Asian surgeons stated in favor of the extended lymphadenectomy. The better locoregional control of the disease was the main rationale behind this approach. On the other hand, Western centers surgeons used to believe that the extended lymphadenectomy is associated with significant morbidity and mortality, failing however to counterbalance these limitations by significant survival benefits.

The purpose of the present review is to provide answers on this longstanding issue based on the most recent available literature on the subject.

Gastric lymph node stations

In 1973, the Japanese Research Society for the study of gastric cancer published a manual standardizing lymph node dissection in gastric cancer by recognizing 16 distinct anatomic lymph node stations (Table 1) [2]. This initial classification has been thoroughly revised until the latest Japanese Gastric Cancer Association classification published in 2011 where a detailed description of the regional lymph nodes of the stomach is provided (Table 2) [3].

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According to this classification, the lymphatic drainage of the stomach is drained via lymphatics and filtered through lymph nodes which are classified into stations numbered from 1 to 20 plus stations 110,111 and 112. Lymph node stations 1-12 and station 14v are defined as regional stations, the rest of the lymph node stations are considered as distant stations. Metastasis to any other node is classified as M1. Lymph node stations No. 19, 20, 110 and 111 represent regional lymph nodes in case of tumor invading the esophagus. Similarly, for carcinomas arising in the remnant stomach with a gastrojejunostomy, the jejunal lymph nodes, just adjacent to the anastomosis, are included in the regional lymph node group. In regards to determining the N status, the total number of lymph nodes and the number of involved lymph nodes at each nodal station are recorded. When a malignant nodule without histological evidence of lymph node structure is found in the lymphatic drainage area of the primary tumor, it is recorded and counted as a metastatic lymph node in the N status determination.

So, 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.

The examination of 16 or more regional lymph nodes is recommended for a proper N status determination [3].

Table 1. Anatomic location of gastric lymph node stations (LN stations)

LN stations	*Anatomic location*
1	Right cardia
2	Left cardia
3	Lesser curvature
4	Greater curvature
4a	Short gastric vessels
4b	Left gastroepiploic vessels
4c	Right gastroepiploic vessels
5	Suprapyloric
6	Infrapyloric
7	Left gastric artery
8	Common hepatic artery
9	Celiac trunk
10	Splenic hilus
11	Splenic artery
12	Hepatoduodenal ligament
13	Posterior surface of the head of the pancreas
14	Root of the mesentery
14A	Superior mesenteric artery
14V	Superior mesenteric vein
15	Paracolic
16	Para-aortic

Table 2. Anatomical definitions of lymph node stations (LN: lymph nodes stations)

LN stations	*Definition*
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
7	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

Continued on the next page

LN stations	*Definition*
13	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla
14v	LNs along the superior mesenteric vein
15	LNs along the middle colic vessels
16a1	Paraaortic LNs in the diaphragmatic aortic hiatus
16a2	Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein
16b1	Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery
16b2	Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	LNs along the inferior border of the pancreatic body
19	Infradiaphragmatic LNs predominantly along the subphrenic artery
20	Paraesophageal LNs in the diaphragmatic esophageal hiatus
110	Paraesophageal LNs in the lower thorax
111	Supradiaphragmatic LNs separate from the esophagus
112	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus

LNs: lymph nodes

Table 3. Kodama's classification

Kodama's types	*Description*
Small mucosal	
Mucosal (M)	Intramucosal EGCs measuring less than 4 cm
Submucosal (SM)	Intramucosal EGCs minimally invading submucosa measuring less than 4 cm
Super mucosal	
Mucosal (M)	Intramucosal EGCs measuring more than 4 cm
Submucosal (SM)	Intramucosal EGCs minimally invading submucosa measuring more than 4 cm
Pen (penetrating)	
A	EGCs massively invading submucosa with nodular pattern measuring less than 4 cm
B	EGCs massively invading submucosa with saw teeth pattern measuring less than 4 cm
Mixed	Penetrating types (A or B) measuring more than 4 cm

Based on this classification the Japanese Gastric Cancer Association published in 2017 the latest update (version 4) of the gastric cancer treatment guidelines [4]. A comprehensive description of the extent of the lymphadenectomy required according to the type of the indicated gastrectomy is provided in these guidelines. For total gastrectomy, the lymph nodes stations to be dissected in D1 lymphadenectomy are stations from No.1 to 7; D1+ includes D1 stations plus stations No.8a, 9, and 11p, and D2 includes D1 stations plus stations No.8a, 9, 10, 11p, 11d, and 12a. For tumors invading the esophagus, D1+ includes No. 110 and D2 includes No. 19, 20, 110 and 111. For distal gastrectomy, the lymph nodes stations to be dissected in D1 lymphadenectomy are stations No.1, 3, 4sb, 4d, 5, 6 and 7; D1+ includes D1 stations plus stations No.8a, and 9, and D2 includes D1 stations plus stations No.8a, 9, 11p, and 12a [4].

Lymph node dissection for early gastric cancers (EGC)

The definition of ECG as carcinoma confined to the gastric mucosa and/or the submucosa regardless of the lymph node status has its roots back in 1971 when the Japanese Society of Gastroenterology and Endoscopy first introduced this term [5]. In general, EGC was thought to have an excellent prognosis based on the fact that the risk of lymph node involvement is virtually zero. However, there are indeed tumors that exhibit optimal clinical behavior with survival rates of 98-100% after treatment, but there are also threatening subgroups of EGC that have increased lymph node metastases incidence (14-20%) and survival rates as low as 70% [6].

Consequently, the need to further classify EGC in an attempt to distinguish the more aggressive forms, i.e. tumors of increased risk of lymph node involvement and treatment failure, is more than obvious. Invasion of the submucosa, the grade of differentiation, the size and the macroscopic appearance of the lesion and the presence of lymphatic and/or vascular invasion are all risk factors for lymph node metastases in EGC [6]. More specifically, one of the most important factors influencing the risk of lymph node involvement in EGC seemed to be the depth of invasion in the gastric wall. Inoue et al reported that the 5-year survival rate is 100% in patients with mucosal lesions and 90% in those with lesions penetrating into the submucosa. They also demonstrated that lymph node metastases directly affect survival, documenting an overall survival rate of 99% for N0 patients and 73% for N1 [7]. These results have been confirmed by other authors as well [8].

The morphological growth patterns of the lesions are another feature of prognostic significance. Kodama et al first described and classified into groups the morphological growth patterns of EGC in 1983 assigning in each group a unique lymph node involvement risk (Table 3) [9]. In particular, Kodama penetrating A type is associated with lymph node metastases incidence of 31.7%. Other important prognostic factors include the lymphovascular invasion status and the grade of tumor differentiation. In particular, the mean incidence

Table 4. Macroscopic classification of EGC

Macroscopic types	*Description*
Type I	Protruded
Type IIa	Elevated
Type IIb	Flat
Type IIc	Depressed
Type III	Excavated

of lymph node metastases is 9% in the absence of lymphovascular invasion compared to the 53% observed in the opposite scenario. In regards to tumor grade, well-differentiated tumors have lymph node involvement in 13% of the cases compared to 34% when a poorly differentiated tumor is the case. Moreover, the diffuse histologic type according to the Lauren classification and tumor size larger than 2 cm significantly increases the risk of lymph node involvement [10-13]. According to the macroscopic types as defined by the Paris classification, the probability of lymph node metastases is up to 2.3 times higher for depressed lesions compared with the elevated in morphology EGCs (Table 4) [14].

Under this prism, strictly defined indications for the two forms of endoscopic treatment for EGC, the Endoscopic Mucosal Resection (EMR) and the Endoscopic Submucosal Dissection (ESD) are a warrant. Thus, according to the Japanese Gastric Cancer Association, the endoscopic resection can be considered as curative when the following conditions are fulfilled: 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. Recently, the Japanese Gastric Cancer Association expanded, for investigative however purposes, the eligibility criteria for ESD [4]. All the other early gastric cancer cases, not fulfilling the above mentioned criteria, require a D1 or a D1 plus lymphadenectomy, given that no clinically positive nodes are identified. The latter scenario i.e. patients with clinically positive nodes require a proper D2 lymphadenectomy [4].

In the Western setting, however, things are not as straightforward. From the epidemiological point of view, we are witnessing a gradual decrease in the incidence of intestinal type tumors of the distal stomach while proximal tumors as well as tumors of the diffuse type, are diagnosed with increased frequency [15]. This epidemiological shift of gastric cancer characteristics leads Western surgeons dealing with more aggressive forms of the disease. Furthermore, the penetration of endoscopic resection in Western institutions either as a form of treatment or for diagnostic/staging purposes remains particularly low [16]. Having in mind the risk of under-staging and the subsequent under-treatment, the Italian Gastric Cancer Study Group guidelines recommend a D2 lymphadenectomy in clinically early forms not suitable for endoscopic treatment [17]. Currently, the D2 lymphadenectomy is a procedure with low associated morbidity and mortality when performed in specialized centers and when avoiding unnecessary splenectomy and/or pancreatectomy [17-18]. A more limited lymphadenectomy in patients with co-morbidities, not eligible for endoscopic treatment, would be a compromise between the optimal oncological results and the risks of an extensive operation in a fragile patient [18].

Lymph node dissection in advanced gastric cancer

According to GLOBOCAN 2012 data, gastric cancer is the sixth most common cancer worldwide with an age-standardized mortality of 8.9/100000 population [1]. Surgery is the standard of treatment for all resectable gastric cancers. Radical gastrectomy with some form of lymphadenectomy is currently considered the appropriate treatment [19]. The well-organized screening programs running in Eastern countries lead to an earlier gastric cancer diagnosis while the diagnosis in Western countries is often established later in the course of disease [20]. Similarly to other gastrointestinal malignancies, gastric cancer spreads via lymphatics to the regional lymph nodes, giving the nodal involvement significant prognostic value [21].

The extent of lymph node dissection in gastric cancer surgery has been a field of constant intercontinental debate. In Eastern countries, the D2 lymphadenectomy has been considered the standard of care as it was suggested that an extensive lymphadenectomy is associated with superior results in terms of survival and optimal loco-regional control of the disease [23]. The expertise Asian Surgeons gained by performing routinely radical lymphadenectomies for gastric cancer in high volume centres could at least in part explain this approach. In addition, the certain gastric cancer patient pool epidiomiological characteristics in Eastern countries i.e. patients of younger age with fewer co-morbidities and less abdominal fat render the procedure easier and feasible from the technical viewpoint [24].

On the contrary, in Western countries, the D2 lymphadenectomy was traditionally considered as an over-treatment for gastric cancer patients [25]. Western randomized clinical trials (RCTs) have attached to the D2 lymphadenectomy the labels of higher perioperative morbidity and mortality, without obvious survival benefits [26-30].Within this framework, Western surgeons were used to accompany the appropriate gastrectomy, either total or distal, with a more limited than the D2, lymphadenectomy.

There are three major randomized controlled studies which have compared the D1 and D2 lymphadenectomy in the gastric cancer surgery and have influenced dramatically the surgical treatment guidelines on gastric cancer. The Dutch Gastric Cancer Group conducted from August 1989 till July 1993 the famous in the literature Dutch trial [24]. They randomized a total of 711 patients into two groups. The first group had a D1 lymphadenectomy while a D2 dissection was performed in the second group. The D1 dissection was defined as the clearance of lymph node stations 1-6 while in the D2 group the additional clearance of stations 7-11 was conducted. Distal pancreatectomy along with splenectomy was routinely

performed in all D2 patients. The adequacy of a proper D2 lymphadenectomy was the rationale behind this approach. On the other hand, pancreatectomy and splenectomy were performed only selectively in the D1 patient group given that these organs were directly involved by the tumor. The quality control was confirmed by the pathological confirmation of lymph nodes in each particular station.

The term "contamination" was used to dictate overtreatment in a certain group, i.e. when a surgeon dissected two or more lymph node stations which he should not have. On the other hand, the term "non-compliance" was used to underline under-treatment, i.e. when a surgeon did not dissect two or more lymph node stations which should have. They reported a statistically significant high postoperative morbidity (43 vs. 4%) and mortality (10 vs. 4%) in the D2 group as compared to the D1 group. No differences in the 5-year survival in between the two groups were recorded. The authors concluded that their data did not support routine D2 lymphadenectomy in gastric cancer patients. However, there has been a lot of criticism on this trial. The participating surgeons had no previous experience and previous training on D2 lymphadenectomy, while low volume, for gastric resection, centers were included in the study. The non-compliance was very high in the D2 group, up to 51%.

While the 11-year follow-up data of this trial indicated similar survival and risk of relapse in between the two groups, the 15-year survival data of the Dutch trial pointed out on the superiority of the D2 dissection. Gastric cancer-related deaths were significantly higher in the D1 group compared with the D2 group, whereas death due to other causes was not different. Locoregional recurrences were higher in the D1 group compared to the D2 group (40.7 vs. 21.8%). The 15-year overall survival for patients who had curative resections was 21% for the D1 and 29% for the D2 group, however, the difference in survival (25 vs. 35%) in the two groups became more evident if the postoperative deaths in the two groups were excluded (4 vs.10%). Subgroup analysis showed that the pancreatectomy and the splenectomy, which were routinely done in the D2 group, significantly lowered the overall survival. These findings led the authors to recommend spleen-preserving D2 dissection in patients with resectable gastric cancer [19].

The second very important trial on the subject was the MRC trial performed by Cuschieri et al [26]. In this trial, a total of 400 patients were randomized into two groups, 200 patients underwent D1 dissection which was defined as removal of lymph nodes within 3.0 cm of the tumor while another 200 patients had a D2 dissection with the additional removal of omental bursa, the hepatoduodenal and retroduodenal nodes, and the splenic artery/splenic hilar nodes and retropancreatic nodes by distal hemipancreatico-splenectomy for middle and upper third lesions.

According to the results of the study, the D2 lymphadenectomy was associated with significantly higher postoperative complications (46 vs. 28%) and postoperative mortality (13 vs. 6.5%) [22]. There was no statistically significant difference in overall 5-year survival between the two arms after a median follow-up of 6.5 years. Gastric cancer-specific survival and recurrence-free survival were also similar in the two groups. Thus, the authors concluded that the D2 resection offered no survival advantage over the D1 resection. However, they did underline the possibility that the D2 resection without pancreatectomy and/or splenectomy might be superior to the standard D1 resection as there was a statistically significant survival disadvantage in the group undergoing splenectomy along with distal pancreatectomy.

The third trial was conducted by the Italian Gastric Cancer Study Group (IGCSG) [31]. As the MRC and the Dutch trial reported higher postoperative morbidity and mortality in the D2 lymphadenectomy arms, the authors aimed to assess the short-term results and the possible survival benefits of the D2 lymphadenectomy. They randomized 267 patients into D1 and D2 lymphadenectomy. This trial in an attempt to eliminate bias had a strict quality control i.e. only surgeons with adequate expertise in D2 lymphadenectomy were asked to participate. Despite this, the trial had a contamination and non-compliance incidence of 17.3% and 33.6% respectively.

The authors reported that the overall morbidity rate was comparable in the two groups and there was also no difference in the postoperative mortality rates. They concluded that the postoperative complications in the D2 arm were not as high as previously reported and it should be considered a safe option for the management of gastric cancer in Western patients in an appropriate setting [31]. Regarding the long-term results i.e. 5-year survival, on a median follow-up of 8.8 years for the surviving patients and of 2.4 years for those who died there were no differences in the two treatment arms [32]. Subgroup analyses showed a significant 5-year disease-specific survival benefit for patients with T1 tumors in the D1 lymphadenectomy group as compared to the D2 (98 vs. 83 %). Similarly, patients with pathologic T2-4 status and positive lymph nodes yielded better survival scores in the D2 lymphadenectomy arm (59 vs. 38%). The authors concluded that D2 lymphadenectomy might be a better choice in patients with advanced disease (pT2-4) and lymph node metastases.

It is now clear that the higher rate of the D2 lymphadenectomy associated morbidity and mortality are mostly related to distal pancreatectomy and/or splenectomy which were integral parts of a previously proper D2 lymphadenectomy [32-35]. Studies have shown that proper training can have a significant impact on the prognosis [32-35]. Adequately trained surgeons can indeed perform safely a radical gastrectomy and a D2 lymphadenectomy and preserving the spleen and the pancreas at the same time. The advantages in terms of lower morbidity and mortality rates are becoming obvious in recent studies [35-36]. On top of all, the 15 years follow up of the famous Dutch study has demonstrated that the loco-regional recurrence rate is significantly lower in patients treated with D2 lymphadenectomy compared with patients who underwent D1 dissection, showing a survival benefit in this treatment arm [19].

In general, the global consensus on D2 lymphadenectomy has substantially increased as the survival benefit has been well documented [37-41]. Whether the extension of lymphadenectomy beyond the standard

D2 dissection could add any benefit in the treatment of advanced gastric cancer, is a controversial issue. The routine lymphadenectomy of para-aortic nodes (station No 16) is currently no more indicated after the publication of the Japan Clinical Oncology Group (JCOG) 9501 trial. Indeed, the results of the Japanese trial showed no survival benefit after D2 plus the para-aortic nodes dissection compared to D2 lymphadenectomy alone in advanced gastric cancer without clinical suspicion of para-aortic node metastases [42].

Laparoscopic lymph node dissection

The several advantages of laparoscopic surgery over conventional open surgery such as less postoperative pain, superior cosmetic result, less blood loss, faster recovery, and shorter hospital stay have led several surgeons in applying laparoscopic-assisted gastrectomy for gastric cancer. However, concerns in regards to the oncological radicality of the technique have raised the need to properly test the technique within well-designed studies. Two prospective trials, the KLASS 01 and the JCOG 0703 documented the safety and efficacy of the procedure without compromising the basic oncological principles [43,44].

In addition, lymph node harvest rate is steadily increasing in laparoscopic gastrectomy studies to as high as to the numbers observed in open surgery [45]. A recent meta-analysis of eight case-control studies has revealed that there is no evident difference in the number of lymph nodes dissected, between laparoscopic distal gastrectomy and the traditional open technique. However, the mean operative time for the laparoscopic distal gastrectomy is significantly higher than the open distal gastrectomy [45]. Recently, in the latest edition of the Japanese Gastric Cancer Treatment Guidelines 2014 (vers. 4) published by the Japanese Gastric Cancer Association, laparoscopic distal gastrectomy for clinical stage I cancer was upgraded from an investigational treatment to an option in general practice [4].

Conclusions

In conclusion, the D2 lymphadenectomy is the standard of care in an operable gastric cancer. Routine excision of the spleen and pancreatic tail should not be undertaken as it increases the postoperative complications without adding significantly to overall survival.

Conflict of interests

The authors declare no conflict of interests.

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