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Lymph Node Dissection

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1. Introduction

Gastric cancer remains as one of the leading causes of death worldwide (Yoshida et al., 2004). Middle third and distal cancers tend to decline worldwide. However, in the western populations proximal gastric cancers tend to increase even though the incidence of those cancers stays the same in Japan. Today, the incidence of early gastric cancer has reached above 50% in Japan while in the west two thirds of gastric cancers are at an advanced stage at the time of diagnosis (Biondi, 2010). This problem is complicated further by a recurrence rate of 40% to 65% in patients resected with curative intent (Dicken, 2005). Currently, the only potentially curative option for gastric cancer is surgery which may promise complete resection, although the extent of regional lymphadenectomy (LND) has been a matter of considerable debate.

2. Surgery of the stomach

Radical resection of stomach and the related lymphatic drainage has been the way of treatment of gastric cancer (GC) in west and Japan. The debate has been carried out on what extent the resection must be carried out. Japanese investigators assert that the extended LND (D2) removes tumor in the regional lymph nodes (LNs) before it can metastasize. In addition, it is argued that extended LND improves staging accuracy. On the other hand, western surgeons have argued that the benefits promised by extended lymphadenectomy may be reversed by the high complication rate even if they have any. Theoretically, the removal of a wider range of LNs by extended LN dissection increases the chances for cure. In fact, the pattern of recurrence after extended surgery is completely different from that after limited surgery and involves locoregional recurrence in the majority of cases (Gunderson & Sosin, 1982). An extended LN dissection might have an influence on the locoregional recurrence rate. However, if the patients have already developed micrometastases or if no LNs are affected, such resection might be irrelevant and harmful, in terms of increased morbidity and mortality (Tanizawa & Terashima, 2010).

2.1 The classification of lymph node tiers

The Japanese Research Society for the study of gastric cancer published a manual in 1963 standardizing LND and pathologic evaluations for GC; these guidelines recognized 16 different LN stations that surround the stomach. These 16 nodal stations are grouped according to the location and extension of the primary tumor (N0-N4) and the extent of

lymphadenectomy is classified according the level of LND (D1-D4). In D1 dissections, only the perigastric nodes directly attached along the lesser curvature and greater curvatures of the stomach are removed (stations 1-6, N1 level). An incomplete N1 dissection is labelled a D0 lymphadenectomy. D2 dissections (N2 level) add the removal of nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac trunk (station 9), splenic hilus, and splenic artery (station 10 and 11). D3 dissections include the dissection of lymph nodes at stations 12 through 14, along the hepatoduodenal ligament and the root of the mesentery (N3 level). Finally D4 resections add the stations 15 and 16 in the paraaortic and the paracolic region (N4 level). The incidence of metastasis to any perigastric station is highest when the tumor location is close to it. There is little variation in the metastatic pattern along the lesser curvature between tumors of different thirds. For tumors of antrum right paracardiac lymph nodes are staged as second tier while left paracardiac lymph nodes are N3. For tumors of cardia the 5th and 6th lymph node stations are in the second tier (Kim et al., 2001) .

2.2 The regional lymph nodes

No. 1 Right paracardial LN

No. 2 Left paracardial LN

No. 3 LN along the lesser curvature

No. 4sa LN along the short gastric vessels

No. 4sb LN along the left gastroepiploic vessels

No. 4d LN along the right gastroepiploic vessels

No. 5 Suprapyloric LN

No. 6 Infrapyloric LN

No. 7 LN along the left gastric artery

No. 8a LN along the common hepatic artery (Anterosuperior group)

No. 8p LN along the common hepatic artery (Posterior group)

No. 9 LN around the celiac artery

No. 10 LN at the splenic hilum

No. 11p LN along the proximal splenic artery

No. 11d LN along the distal splenic artery

No. 12a LN in the hepatoduodenal ligament (along the hepatic artery)

No. 12b LN in the hepatoduodenal ligament (along the bile duct)

No. 12p LN in the hepatoduodenal ligament (behind the portal vein)

No. 13 LN on the posterior surface of the pancreatic head

No. 14v LN along the superior mesenteric vein

No. 14a LN along the superior mesenteric artery

No. 15 LN along the middle colic vessels

No. 16a1 LN in the aortic hiatus

No. 16a2 LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)

No. 16b1 LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)

No. 16b2 LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)

No. 17 LN on the anterior surface of the pancreatic head

- No. 18 LN along the inferior margin of the pancreas
- No. 19 Infradiaphragmatic LN
- No. 20 LN in the esophageal hiatus of the diaphragm
- No. 110 Paraesophageal LN in the lower thorax
- No. 111 Supradiaphragmatic LN
- No. 112 Posterior mediastinal LN

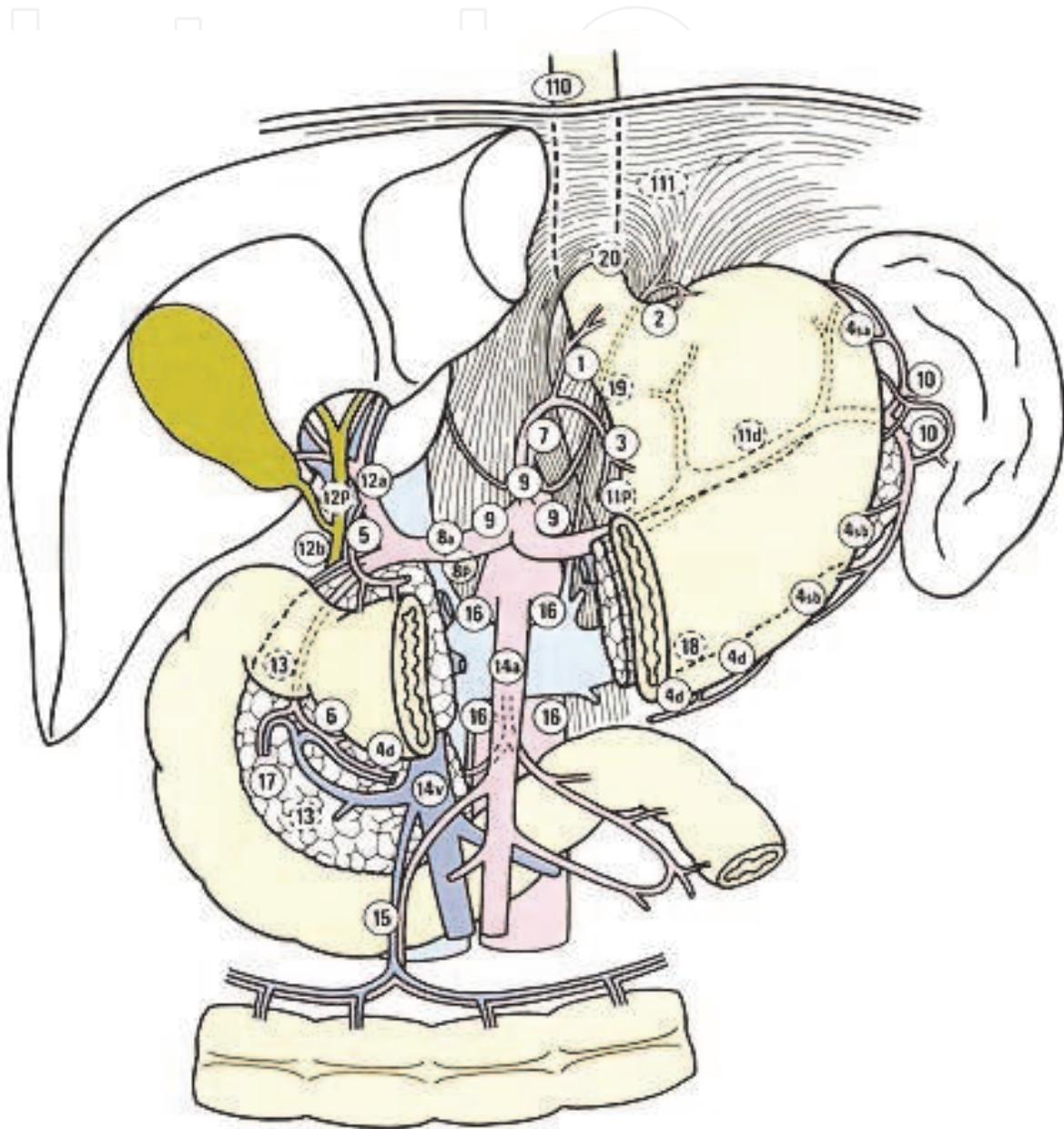


Fig. 1. The lymph node stations according to the Japanese classification

R0 resection indicates a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed. R1 resection indicates the removal of all macroscopic disease but microscopic margins are positive for tumors. R2 indicates gross residual disease with gross residual tumor that was not resected (primary tumor, regional nodes and macroscopic margin involvement). Resection in the eastern world is a little more

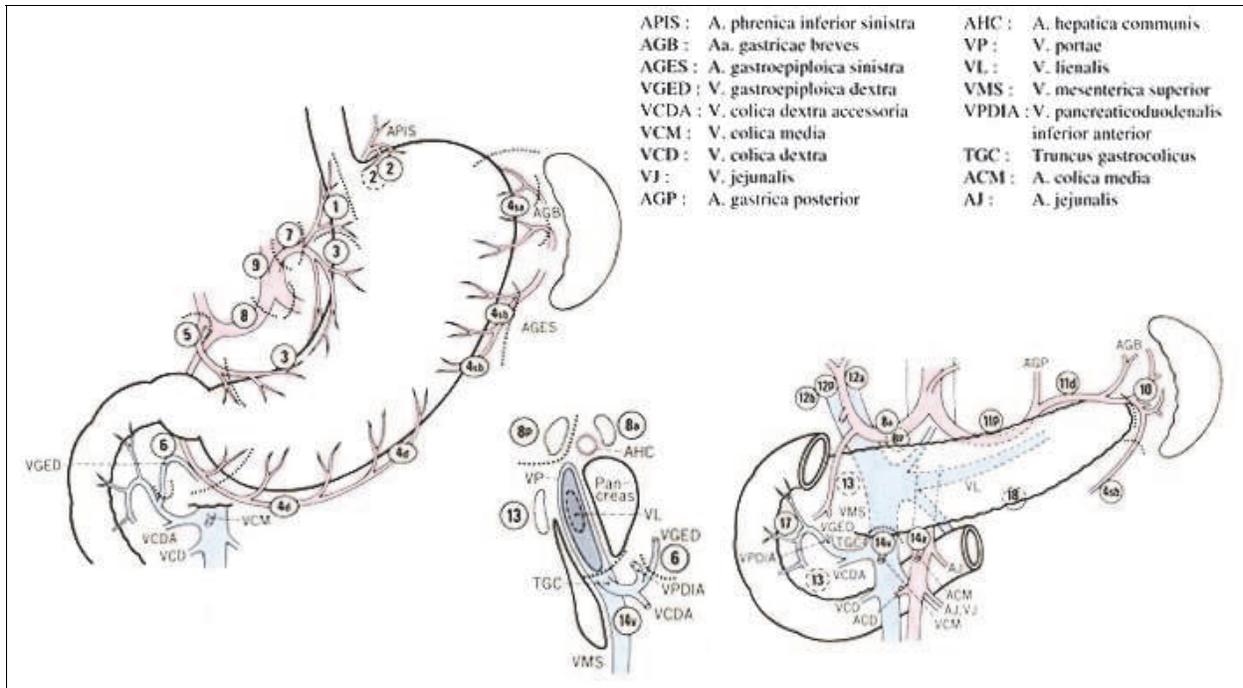


Fig. 2. Location of lymph nodes around abdominal aorta.

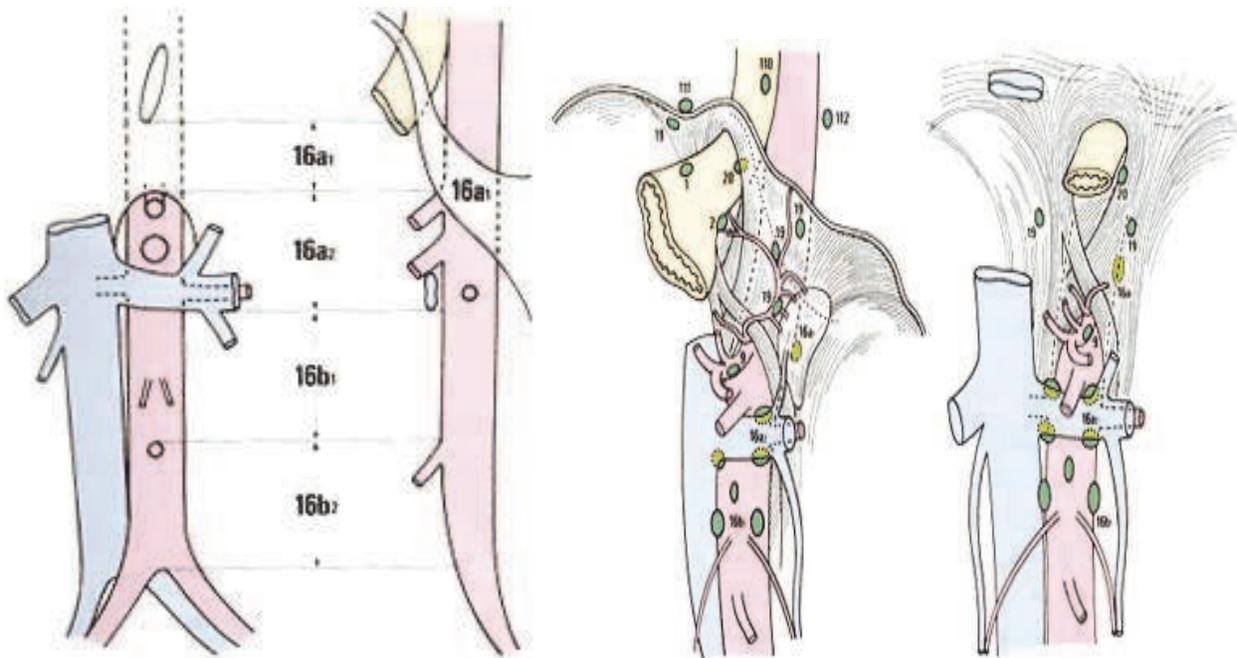


Fig. 3. Location of lymph nodes in the esophageal hiatus, and infradiaphragmatic and paraaortic regions.

complicated: Resection A: no residual disease, with a high cure probability. It implies resections satisfying all of the following conditions: tumor without serosal invasion; N0 treated by D1, D2, or D3 lymph node dissections, or tumor with first-level lymph node treated by D2 or D3 resection; no distant, peritoneal or liver metastases, negative cytological examination of peritoneal fluid and proximal and distal margins > 10 mm. Resection B: no

histopathologic residual disease but not fulfilling criteria for resection A. Resection C: definite residual disease (Biondi, 2010).

The groups of lymph node stations used to define the extent of lymph node dissection
Location of the tumor

Station Number	A, AM	M, MA, MC	C,CM	AMC,MAC, MCA,CMA
1	N2	N1	N1	N1
2	N3	N2	N1	N1
3,4	N1	N1	N1	N1
5,6	N1	N1	N2	N1
7,8,9	N2	N2	N2	N2
10,11	N3	N2	N2	N2
12,13,14	N3	N3	N3	N3
15,16	N4	N4	N4	N4

A: Antrum, M: Middle, C: Cardia

Table 1. Groups of lymph node stations used to define the extent of lymph node dissection.

The Union Internationale Contrale Cancer (UICC)/American Joint Committee on Cancer (AJCC) classification, which is most widely used for the staging of gastric cancer, suggests that at least 15 lymph nodes should be examined for a correct assessment of N staging. Lymph node dissemination is in an orderly fashion through lymphatic channels in gastric cancer (Shi & Zou, 2010). However, the type of fixative and clearance solution used by a pathology department may influence the number of nodes examined. One study found that 78% of nodes <5 mm are missed by the routine formalin fixation that is used in most Western countries, whereas clearance solutions allow detection of nodes 1 mm in diameter (Herrera & Villareal, 1992). Studies estimate that LNs will be involved with tumors for 3–5% of cases of gastric adenocarcinoma limited to the mucosa; 11–25% of cases for those limited to the sub-mucosa; 50% for T2; and 83% for T3 tumors (Coburn, 2009).

The 7th editon has brought some changes.

N0 (N plus zero): The cancer has not spread into the regional lymph nodes.

N1: The cancer has spread to one to two regional lymph nodes.

N2: The cancer has spread to three to six regional lymph nodes.

N3: The cancer has spread to seven or more regional lymph nodes.

N3a: The cancer has spread to seven to 15 regional lymph nodes.

N3b: The cancer has spread to more than 16 regional lymph nodes.

As a critics to TNM classification, it is difficult to directly correlate the number of lymph nodes assessed with the extent of lymphadenectomy. Autopsy studies have shown that an average of 15 nodes can be harvested from a D1 lymphadenectomy, 27 nodes from a D2 lymphadenectomy, and 43 nodes from a D3 lymphadenectomy (Wagner et al., 1991). But studies have shown the TNM classification to be an easier way with a more accurate prognostic value. But since the fifth edition prior to 1997 AJCG system was based on anatomic location of involved nodes rather than their number. Positive nodes >3 cm from the primary tumor or nodes associated with celiac or celiac based arteries were deemed N2 nodes. However, this anatomic scheme caused some problems undermining the concept of

anatomical staging. For example, following surgical resection some surgeon-pathologist teams harvested nodes on fresh specimens whereas others would harvest nodes only after fixation and substantial contraction of the specimen, the alterations that resulted from these different techniques compromised the staging accuracy. Besides, many surgeons in the west excluded the N2 node dissection and that also impaired the quality of accurate staging when a higher number of lymph nodes were extracted from a D2 resection. Thus, interpretation was harder as Japanese and German surgeons performed mainly D2 resection while at that time many surgeons in other countries in west ignored D2 resection and thus stage migration effect again vitiated the accurate staging. Therefore, in the western world the TNM classification has gained wider ground because of better prognostic predictions it has offered as justified by Japanese surgeons.

A number of investigators have observed progressive decrease in survival with the increasing number of involved lymph nodes, with an apparent drop off in survival when 3 or more nodes are involved. Another drop off has been reported when more than 6 nodes are involved. Involvement beyond 15 or 16 nodes has been observed to be largely incompetent with long term survival (Hundahl, 2002). As a prognostic tool, ratio between metastatic lymph nodes and the total number of lymph nodes examined was proposed (Marchet, 2007). Several cutoffs were studied increasing in pentathonic or decimal scale starting from zero to mostly >30 %; the survival decreases as the involved lymph node ratio increases. In a study by Xu et al. it is proposed that this scheme may also be useful for patients who had lower than 15 lymph nodes dissected (Xu et al., 2009).

2.2 Patterns of relapse and metastasis

In striving to achieve cure for gastric cancer it is essential to understand the modes of spread and patterns of relapse. Only then an optimum treatment with reasonable expectations are possible. The metastatic pathways are:

2.2.1 Direct extension

Into neighbouring organs and structures generally resected en-bloc with the stomach. Once a lesion has extended beyond the gastric wall, a multitude of organs and structures can be involved, dependent on lesion location within the stomach. For proximal lesions, organs or structures that may be involved with superior or anterior extragastric extension include the left diaphragm, anterior abdominal wall, or undersurface of the liver, while with posterior extension, the celiac artery, body of pancreas (anterior, superior), aorta, or diaphragmatic crura may be involved. For body of stomach lesions, anterior extension may involve the anterior abdominal wall or liver; lateral extension--the gastrosplenic ligament or spleen; posterior extension--the pancreas (tail, body); superior extension--the gastrohepatic ligament or lesser omentum; and inferior extension--the transverse colon or mesocolon, or greater omentum. With distal gastric lesions, posterior extension may involve the head of pancreas or porta hepatis structures; inferior extension--the transverse mesocolon and colon. Adherence from inflammatory conditions can mimic direct extension of tumor, but all adhesions between a gastric carcinoma and adjacent structures must be regarded as malignant (Gunderson, 2002).

2.2.2 Lymphatic route

Lymphatic spread occurs via subserosal and submucosal lymphatic plexuses depending on the depth of invasion. The lymphatic drainage of the stomach follows the arterial supply.

Although most lymphatics ultimately drain into the celiac nodal area, lymph drainage sites can include the splenic hilum, suprapancreatic nodal groups, porta hepatis, and gastroduodenal areas. Abundant lymphatic channels are present within both the submucosal and subserosal layers of the gastric wall. Microscopic or subclinical spread well beyond the visible gross lesion occurs via these lymphatic channels (intramural spread), and the surgeon can be misled into thinking that resection margins are free of tumor. Accordingly, frozen sections of the gastric resection margins should be obtained intraoperatively to ensure that margins of resection are microscopically uninvolved. The submucosal lymphatic plexus is also prominent in the esophagus and the subserosal plexus in the duodenum, allowing both proximal and distal intramural tumor spread. Although a so-called "duodenal block" occurs with the mucosa scarcely ever being involved for more than 1-2 mm beyond the pylorus, the existence of a prominent subserosal plexus allows distal spread in as high as 30% to 40% of patients (Gunderson, 2002). In the stomach, as in other organs, the very presence of cancer can alter the normal lymphatic drainage. Obstructed vessels can divert the drainage so that metastases appear in unexpected nodes. Collateral lymphatics can form, producing a shift in the drainage pattern. The possibly multicentric origin of gastric cancer further complicates a simple approach to the proposed resection (Fischer & Bland, 2007).

2.2.3 Peritoneal disease

Because stomach is a peritoneal organ once the tumor cells have extended beyond the gastric wall to the serosal surface peritoneal spread may happen. Peritoneal spread may initially be a localized process confined to the surrounding ligaments (Gunderson, 1982).

2.2.4 Hematogenous spread

For malignancies confined to the stomach the venous drainage is primarily to liver which proves an effective filter. As neoplastic cells invade beyond the stomach wall into adjacent organs, hematogenous spread through the lymphatics and venous system of the involved organ happens and metastasis to lungs and other organs may happen (Smalley et al., 2002).

2.3 Patterns of relapse

There are 5 ways recurrence following surgical removal of gastric carcinoma: lymph node, remnant stomach, local, peritoneal and hematogenous recurrence. Sixty percent to 72% of gastric cancer patients succumb to recurrences within the first 2 years. Hematogenous or lymphatic spreads without intraabdominal metastases occur rarely. It may be postulated that gastric cancer prefers to spread intraabdominally, and that locoregional control is therefore an important issue in treatment strategy years (Wu, 2003). Locoregional recurrence rates varies from 25% to 96% depending on different detection methods and study populations.

2.4 Histology and recurrence

Gastric cancer can recur in different pathways. The possibility of predicting the risk and type of recurrence in patients with resectable gastric cancer could have important implications for therapy, both in the surgical approach (extent of lymphadenectomy, partial or total resection) and in complementary therapies. Marelli et al. found out that the main difference was found on the onset of peritoneal recurrence in a study of 412 patients in

which they compared the recurrence patterns of intestinal type and diffuse type years (Marelli et al., 2002). Shiriashi et al. confirmed that most recurrences were within the first two years after surgery and rare after 5 years (Shiriashi et al., 2000).

For intestinal type of the tumor lymph node positivity, depth of invasion, advanced age and male gender significantly increases the risk of recurrence. The patterns of relapse were mainly locoregional or hematogenous and peritoneal recurrence was limited. For diffuse type of tumors very high rates of peritoneal recurrence were observed in neoplasms with infiltration of the serosa, involvement of second level lymph nodes, and large tumor size. Locoregional recurrences were frequent in advanced forms, lymph node-positive cases, and tumors larger than 4 cm. The rate of hematogenous recurrence was generally smaller than that of peritoneal or locoregional disease. Early forms and tumors smaller than 4 cm recurred primarily via hematogenous route.

The main difference was found in the onset of peritoneal recurrence; this was observed in 34% of diffuse-type cases compared to 9% of intestinal-type cases, and was the main pathway of spread in the former. Compared to intestinal-type cells, the diffuse type showed a greater predisposition to proliferate in the peritoneum, considering that 50% of the cases with infiltration of the serosa led to peritoneal carcinomatosis, which was observed in only 16% of T3 and T4 intestinal-type cases. On the contrary, recurrences of intestinal-type tumors were mainly locoregional or hematogenous. The incidence of hematogenous recurrence did not show significant differences between the intestinal and the diffuse types; in both groups of patients, they observed a higher frequency of this recurrence in lymph node-positive cases, a finding in accord with other reports. However, the degree of involvement in the various organs was different, because the intestinal type metastasized primarily to the liver, whereas in the diffuse type the liver was involved in only half of the cases; in the other cases, hematogenous metastases involved distant organs. The data may suggest that in the diffuse type, but not in the intestinal type, superextended lymphadenectomy may play a more important role in reducing the risk of recurrence. The diffuse type may show a greater propensity than the intestinal type to metastasize to third- and fourth-level lymph nodes (Marelli et al., 2002).

In a large series Nakamura et al. demonstrated that there is some correlation between the tumor histological type and the gross type. Seventy nine percent of diffusely infiltrating tumors and 69% of ulcerative infiltrating tumors were poorly differentiated and 60% of polypoid tumors were well differentiated in advanced carcinomas. In early carcinomas 89% of Type I and 77% of Type IIa lesions were well differentiated. Type IIc tumors were either well (31%), moderate(19%) or poorly differentiated (50%). In their large series of 10 thousand patients the most frequently encountered macroscopic type of advanced carcinoma was the ulcerative infiltrating tumor (41%), followed by ulcerating circumscribed type(31%). In early carcinomas type IIc (70%) was the most frequently encountered type, followed by Type II a. In advanced forms well differentiated types showed fairer prognosis (Nakamura et al., 1992).

Adachi et al. demonstrated that patients with poorly differentiated type show a poorer prognosis especially when the tumor is bigger than 10 cm or serosal involvement is positive. If the tumor did not invade serosa but had lymph node metastasis, survival rate was significantly lower in the well differentiated group. Moriguchi et al. also demonstrated that when the tumor invasion was restricted within mucosa or submucosa the well differentiated type of tumor were associated with poorer prognosis. This difference can be explained by the

characteristics of well differentiated type which readily develops blood-borne metastases irrespective of the degree of penetration by tumor cells (Adachi et al., 1997).

2.5 Lymph nodes and tumors of cardia

Tumors of cardia are generally larger than the tumors of other parts of the stomach. The incidence of serosal invasion, lymph node metastasis and lymphatic and blood vessel invasion are higher. With regards to the site of recurrence both lymph node and hematogenous recurrence were observed more frequently in the cardia than remaining parts of the stomach. The adenocarcinoma of gastric cardia shows involvement of left and right paracardial section and the lesser curvature as the predominating areas, then the lower posterior mediastinum and left gastric artery and abdominal aorta (Saito et al., 2006). The incidence of lymph nodes at the splenic hilum and splenic artery are less, between 9% and 20%. The splenic hilar lymph node metastasis increases with the advanced stage (Shin et al., 2009). In a review of literature by Ashikaga et al. the incidence of hilar lymph node positivity for T1 tumors of cardia is 0.3%, for subserosal involvement the incidence is 13% and 26% when the tumor has infiltrated serosa. The involvement of the hilar lymph node is associated with ominous prognosis (Shin et al., 2009).

For tumors of cardia in order to decide the necessity of dissection No 10 lymph nodes, evaluation of the 4d lymph node metastasis has been proposed. If the 4d lymph nodes are uninvolved it is unlikely for the splenic hilus lymph nodes to be involved (Ishikawa et al., 2009).

2.6 Lymphadenectomy and pancreaticosplenectomy

Tumors of the upper and middle stomach are known to metastasize to the splenic artery (station 11) and splenic hilar (station 10) lymph nodes, and distal pancreatectomy and splenectomy were historically routinely performed to clear these nodal stations. Pancreatic fistula rates were high, thus significantly increasing the morbidity of the D2 lymphadenectomy procedure (Yoon et al., 2009). Maruyama et al. described a pancreas-preserving D2 lymphadenectomy that resected the spleen and splenic artery along with the station 10 and 11 lymph nodes (Maruyama et al., 1995). A retrospective study from Japan of nearly 400 patients found that there was no survival benefit in patients undergoing total gastrectomy combined with distal pancreatectomy and splenectomy over patients undergoing total gastrectomy with splenectomy only (Kitamura et al., 1999). Distal pancreatectomy is now generally considered to be unwarranted in the routine performance of a D2 lymphadenectomy until there is direct extension of the tumor. A retrospective Japanese study of 224 patients with proximal gastric cancer found no survival benefit in patients who received pancreaticosplenectomy or splenectomy over pancreas and spleen preservation, but morbidity was significantly greater in the pancreaticosplenectomy group (Kodera et al., 1997). Sasako et al. estimated the benefit of dissecting the station 10 and 11 lymph nodes for a proximal gastric cancer at 5.6% (Sasako et al., 1995). Hartgrink et al. analyzed the patients in the Dutch Gastric Cancer Trial who had lymph node metastases at stations 10 and 11. Of the 18 patients with station 10 metastases, the 11-year survival rate was 11%. Of the 24 patients with station 11 metastases, the 11-year survival rate was 8%. The authors concluded that "the relevance of the dissection of these nodes has to be questioned as the survival benefit is small and morbidity and hospital mortality are significantly increased" (Hartgrink et al., 2005)

Although most expert gastric cancer surgeons no longer resect the distal pancreas as part of a D2 lymphadenectomy unless there is direct tumor extension, the resection of the spleen continues to be controversial (Yoon et al., 2009). Two prospective randomized trials of total gastrectomy and lymphadenectomy with or without splenectomy have been performed in Chile and South Korea. Both studies found no difference in overall survival, and the Chilean study found a significantly higher rate of infectious complications in the splenectomy group. However, the number of patients in these studies was between 187–207, and thus the power of these studies to determine a modest improvement in survival for splenectomy is limited (Csendes et al., 2002, Yu et al., 2006).

3. Scientific basis of lymph node dissection

3.1 The Japanese evidence

In the western world the over-all 5-year survival rate among patients with resectable gastric cancers range from 10%-30%, while in Japan the survival for the same subgroup of patients is between 50% and 62% largely attributable to the lymph node dissection known as D2 which was introduced in 1960s. In Japan standard resection refers to total or subtotal gastrectomy with D2 resection. The 5 year survival rate following D2 lymphadenectomy is 63,8% and is superior to survival after D1 or D0 lymphadenectomy (41,2% and 20,3% respectively) according to the Japanese Nationwide Registry for Gastric Cancer. The major effect of systemic lymph node dissection is the reduction in locoregional recurrence. The proportions of local recurrences were decreased by the introduction of this procedure, 38% in 1967-1971, 12% in 1982-1986. Operative mortality rate is very low in Japanese series and no different from D1/D0 patients. According to the Japanese Nationwide registry reports the 30 days postoperative mortality is 1,7% (Maruyama et al., 1998).

3.2 The evidence for D2 resection in western world

The National Comprehensive Cancer Network (NCCN), an alliance of 21 of the world's leading cancer center has released a latest guideline in 2010. According to this guideline gastric resection should include the regional lymphatics, the perigastric lymph nodes as well as those along the celiac axis with at least 15 lymph nodes. Splenectomy is acceptable only when spleen or hilus is involved. The guideline points out several studies the guideline is based on.

Schwarz et al. reviewed relationships between the number of LNs examined and survival among the patients in SEER (Surveillance, Epidemiology and End Results) database. Outcomes were analyzed only for the stage subgroups characterized by the N categories N2 or N3, and transmural tumor extension (T categories T2b or T3). Advanced but potentially still curable gastric cancer (stages IIIA, IIIB, or stage IV M0) is associated with very high recurrence rates after gastrectomy. For every ten extra LNs added to the total LN count, the calculated overall survival increased by: 5.7% (T2b-3N2), 4.6% (T2b-3N3), or 5.9%. Despite the small incremental increases in survival, benefits based on increasing LN counts were obvious for all groups analyzed, but reached statistically significant differences only for the N3 subgroup. The findings demonstrate that even in transmural or serosa-positive gastric cancer with advanced nodal involvement, more extensive LN dissection and analysis influences survival. Stage-based survival prediction of advanced gastric cancer without distant metastases depends on total LN number and number of negative LNs. For the curative-intent gastrectomy of locoregionally advanced gastric cancer, retrieval and

examination of larger numbers of LNs are suggested. It is criticized that recommended minimum goal of 15 LNs to satisfy current (6th edition at the time the study was made) AJCC staging criteria appears insufficient. Especially for N3 categories, the minimum goal theoretically should be set to at least ten LNs above the number of positive nodes. Practically, this would require at least 25 LNs although counts of 40 or more total LNs appear even yet superior. As long as operative morbidity is not affected negatively, extended lymphadenectomy (ELND) during potentially curative gastrectomy is recommended even for advanced gastric cancer. The NCNN guideline excerpts that patients who had more than 15 D2 lymph nodes and patients with more than 20 N3 lymph nodes dissected had the best survival outcome (Schwarz & Smith, 2007). As a result the NCNN guide has increased the number of lymph nodes necessarily dissected for better staging and curativeness in the seventh edition. There is now a category of N3b with metastases to 16 or more lymph nodes

3.2.1 The Dutch study from the beginning to now

The Dutch gastric cancer group randomized 711 patients to go under resection with curative intent, and randomly assigned them into D1 (380 patients) and D2 (311 patients) resection groups. The results of this study is extensively evaluated. They demonstrated that patients in D2 group suffered from a higher rate of postoperative complications than did those in D1 group (43% vs 25%), higher postoperative mortality rates (10% vs 4%) and longer hospital stay (Bonenkamp et al., 1995). Nevertheless, they found out that the 5-year survival rate did not significantly differ between the two groups; 45% in D1 group and 47% in D2 group (Bonenkamp et al., 1999). After a median follow up period of 11 years no statistically survival difference was encountered between the two groups (D1 30% vs D2 35%) (Hartgrink, 2004). Noncompliance, which is inadequate removal of 2nd echelon and contamination, which is unnecessary removal of the second tier lymph nodes were encountered. In Dutch trial while 6% of the patients who were supposedly to go under D1 resection had additional lymph node dissections, 51% of the patients with D2 resection had one or more node stations left undissected (Bonenkamp et al., 1998).

The learning curve for D2 resection is steep and it has been proposed that it may entail as much as 25 operations. The higher complication rates maybe attributed to the lack of experience of the participating surgeons with D2 resection but in subgroup analysis higher morbidity and mortality rates are associated with pancreaticosplenectomy carried out in the D2 group, which was regarded as a part of the R0 surgery especially for proximal cancers at the time of the study (de Gara et al., 2003).

The Dutch gastric study revealed a 30% stage migration when a higher number of lymph nodes were examined. The most prominent feature is that patients with N2 disease in the D2 group showed significantly improved survival rates than those in D1 group (19% vs 0%) in consistence with that in the subgroup analysis Siewart et al. had demonstrated a significant difference in patients with stages II and IIIa in the German study. In the long term follow up the results of the Dutch study confers a lower risk of recurrence in patients who underwent D2 resection and higher survival rates.

In the final analysis of 15 years follow up which was evaluated in a 2010 article gastric-cancer-related death rate was significantly higher in the D2 group (48%, 182 patients) compared with the D1 group (37%, 123 patients), whereas death due to other diseases was similar in both groups. Local recurrence was 22% (82 patients) in the D1 group versus 12%

(40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2.

Even though the initial conclusions from the Dutch gastric cancer study were discouraging especially when a high mortality rate was observed without any significant survival improvement, on the final conclusion D2 lymphadenectomy is the recommended surgical approach for patients with resectable (curable) gastric cancer while especially a spleen preserving technique is available (Songun et al., 2010)

3.2.2 The German study

A total of 1654 patients treated for gastric cancer between 1986 and 1989 at 19 centers in Germany and Austria were included. The resected specimen were evaluated histopathologically according to a standardized protocol. The extent of lymphadenectomy was classified after surgery based on the number of removed lymph nodes on histopathologic assessment (25 or fewer removed nodes, D1 or standard lymphadenectomy; >25 removed nodes, D2 or extended lymphadenectomy). Endpoint of the study was death. Median follow-up of the surviving patients was 8.4 years. There was no difference in the postsurgical morbidity and mortality rates between patients with standard and extended lymph node dissection, even though they were worse when compared to Japanese statistics. The 30- and 90-day mortality rates in the total patient population were 5.1% and 10.6%, respectively.

Calculated 10-year survival rate was $26.3\% \pm 4.7\%$ in the total patient population and $36.1\% \pm 1.6\%$ in those with an R0 resection. Extended lymph node dissection significantly increased the 10-year survival rate and median survival time in patients with UICC stage II tumors. In this patient subgroup, extended lymphadenectomy resulted in a marked improvement of the 10-year survival rate from 19.9% with standard lymphadenectomy to 49.2% with extended lymphadenectomy (Siewart et al., 1998).

3.2.3 The British study

In 1986 the Medical Research Council of Great Britain initiated a nationwide, multicenter randomized controlled trial (RCT) comparing D1 dissection to D2 dissection of 200 patients randomized at each limb. Postoperative mortality was significantly higher in the D2 group than D1 (13,1% vs 6,5%). postoperative complications were also higher in the D2 group reaching 46%. However, in this trial many surgeons thought that D2 dissection included splenectomy and splenectomy was carried out in many distal gastrectomy cases (Cushieri et al., 1999) Pancreaticosplenectomy was carried out in 56% of the cases in D2 group. Splenectomy with subtotal gastrectomy causes serious ischemia of the remnant stomach causing anastomotic leakage or necrosis. The five year overall survival did not differ in either limb (Tanizawa & Terashima, 2010).

3.2.4 Italian study

The majority of complications in the Dutch and British trials are associated with pancreaticosplenectomy. Deguili et al. have shown the safety of D2 dissection with pancreas preservation. In their studies postoperative morbidity is as low as 13-17% with mortality rates 0,6-3% without significant difference in mortality and morbidity between D1 and D2 results. In their IGCSG-R01 trial splenopancreatectomy was not considered as a routine part of the D2 total gastrectomy. The spleen was removed according to the Maruyama technique only when the tumour was in the left part of the upper stomach or located close to the

greater curvature, beyond Demel's point. The spleen was also preserved in patients with clinical T1 tumours. The pancreas was removed only when tumour involvement was suspected. As a consequence the overall morbidity rate after D2 and D1 dissections was 17.9% and 12.0%. The postoperative 30-day mortality rate was 3.0% after D1 and 2.2% after D2 gastrectomy. In specialized centres the rate of complications following D2 dissection is much lower than in published randomized Western trials. D2 dissection, in an appropriate setting, can therefore be considered a safe option for the radical management of gastric cancer in Western patients (Deguili et al., 2004).

3.2.5 Additional information

Diaz et al. studied prospectively 126 consecutive patients operated upon for gastric cancer, with gastrectomy and D2 lymphadenectomy. Hospital morbidity and mortality, relapses, and patient survival after 5 years were studied. The overall hospital mortality rate was 1.6%, with a mortality of 2.1% in the patients submitted to total gastrectomy. The overall morbidity rate was 29.4% with a 5-year survival of more than 50%. Dehiscence of the esophagojejunal anastomosis was recorded in 1.6%. The median follow-up was 73.6 months. Relapses were observed in 37% of the patients (76% in the first 2 years). Overall actuarial survival after 5 years was 52.3%, and 5-year survival in the patients with R0 resection with positive N2 lymph nodes according to the Japanese classification was 26.5% (Diaz et al., 2008).

Other reports from Spain reveal results comparable to Japanese practice applying the D2 resection. Sierra et al. (2003) found no significant difference in the length of hospital stay (median, 12.1 and 13.1 days), overall morbidity (48.2% and 53.5%), or operative mortality (2.3% and 0%) between D1 and D2, respectively. Five-year survival in the D2 group was longer (50.6%) than in the D1 group (41.4%) for tumor stages (tumor-node-metastasis) greater than I.

An RCT performed in the USA investigated the role of post-operative chemoradiotherapy and also showed significant survival benefit. However, only 10% of the patients underwent D2 dissection, there was a very high rate of local recurrence, and the surgery was not standardized among the participating hospitals. Subgroup analysis found survival benefit only in D0 or D1, but not in the D2-dissected group (Mac Donald et al., 2001). The study thus showed that D0/D1 dissection was insufficient treatment.

There are reports about low mortality and morbidity for D2 dissection from various European countries. For example, the Latvian Oncology Center in a series of 468 patients has in hospital mortality 3.3% and morbidity 16.3% with a five year overall survival of 52.5%. The 5 year survival rates according to pT category are 86% for pT1, 65% for pT2 and 43% for pT3, 27% for pT4 (Sivins et al., 2009).

3.3 D2 vs D3

In a review by Tanizawa and Terashima three major studies comparing D2 lymphadenectomy with D3 are discussed. In advanced gastric cancer the incidence of microscopic metastases in the paraaortic lymph nodes is 6% to 33% (Takashima & Kosaka, 2005). Since 1980s superextended lymph node dissection is carried out in specialized centers in Japan. The Japanese Clinical Oncology Group conducted a randomized trial comparing D2 and D2 plus paraaortic lymphadenectomy among patients with curable gastric cancer (Sasako et al., 2008). The overall morbidity was 24% and even though the morbidity was higher in the D2 plus

group it did not significantly differ. (28% vs 21%). There was no difference in hospital mortality between the two groups as well overall survival after 5 years. The blood loss and operation time are significantly increased in the D2 plus paraaortic lymph node dissection group (Sano et al., 2004).

The rationale behind D4 resection is that to obtain a safe dissection margin for the lymph node involvement in the N2 and N3 stations. It is proposed that when the D-number is greater than the N-number, recurrence can be decreased. Accordingly, D2 gastrectomy is effective for N1 patients. In this sense, D4 dissection has been considered to improve the survival of patients with N2 or N3 involvement. D4 dissection had been practiced at many Asian institutions and Asian surgeons have proposed D4 dissection as a surgical technique to remove micrometastasis in the No. 16 lymph node. Micrometastasis in No. 16 lymph nodes was detected in 20% to 31% of patients with advanced gastric cancer, who underwent curative gastrectomy (Yonemura et al., 2008).

The major lymphatic channels from the upper half of the stomach run along the left gastric artery (No. 7), posterior gastric artery (No. 11), and splenic artery. In contrast, lymphatic channels from the lower half of the stomach run along not only the common hepatic artery (No. 8) but also along the root of the superior mesenteric artery (No. 14). Efferent lymphatic channels from these nodes drain into the No. 16 nodes, which are named No. 16 a2 and No. 16 b1. Accordingly, No. 16 a2 and No. 16 b1 are considered as the terminal nodes of the stomach. Cancer cells released from the N2 or N3 lymph node stations are trapped in the lymph nodes located in the bilateral space around the aorta (No. 16 a2-lateral, -pre, and -inter), before the systemic spreading of cancer cells through the thoracic duct. According to the literature, the 5-year survival rates of N4 patients who underwent D4 resection ranged from 14% to 30% (Yonemura et al., 2008). Neither JCOG trial and another east asian trial did not reveal any significant difference in survival between two groups (Sano et al., 2004; Yonemura et al., 2008). There has been a recent study from Poland that compares the two methods revealing that there was no difference in morbidity and mortality but survival yet remains to be analysed (Kulig et al. 2007).

However, a study from Italy on superextended lymphadenectomy with a population of 286 patients, even though it is not a randomized study but a review of cases between 1993 and 2007, reveal some long term survival chance for both pN3 and M1a patients, 31% and 17% respectively. There is also remarkably high survival rate in pN2 and pN3 subsets when no serosal invasion was demonstrated, reaching up to 60%. The authors of this study, (Roviello et al.) has some points on the previous studies carried out in Japan. The overall survival rates (5-year survival: 70%) in east asian studies are at least better by one third than those reported by specialized Western centres in advanced forms. The adopted lymphadenectomy in D2 group included third level nodes (posterior hepatic artery nodes, posterior hepatoduodenal ligament nodes, etc.) in tumour with antral location that lead to a 'D3 lymphadenectomy minus paraaortic nodes (PAN) dissection'. The extent of lymphadenectomy is indeed demonstrated by the extremely high number of removed nodes (mean: 53 for D2 and 73 for D2 plus paraaortic). Cases in which macroscopic involvement of PANs was evident at surgery were excluded from the study. As stated by the authors themselves, the percentage of involvement was lower than expected (8%) and the potential survival benefit possibly weakened. Furthermore, the post hoc subgroup analysis based on pathologic N and T stages showed a better survival rate in the D2 plus para-aortic group for patients without nodal involvement and for patients with tumour invasion limited to the

subserosal layer (less than pT3). An extremely high chance of cure was observed in patients with tumors not involving the serosa (pT2) or absence of nodal metastases (pN0), even if survival probability did not reach the results of the Japanese trial. Particularly, long-term results were remarkable in pT2 N2 and N3 patients. One could speculate that in these particular subsets of patients, where the local control of the disease is essential, D3 lymphadenectomy may be of value in improving long-term results. On the contrary, in serosally exposed neoplasms, which are particularly prone to peritoneal dissemination, the extent of lymphadenectomy might not provide a survival advantage with respect to more limited dissection (Roviello et al., 2010).

As a consequence the NCCN guide does not recommend D2 plus paraaortic lymph node dissection for patients with curable gastric cancer (T2b, T3 or T4).

3.4 Conclusion

The NCCN 2010 guideline states that in west the D2 resection is a recommended but not a required operation. Modified lymphadectomy without pancreaticosplenectomy is associated with low mortality and morbidity as well as with reasonable survival times when performed in institutions with sufficient experience in operative and postoperative management. While in the east standard surgery is D2 lymphadenectomy and so far has proved longer 5 year survival and less locoregional recurrence rates. Finally, in our study although extensive dissection had an increased morbidity, there was no significant statistical difference between the D1 and D2 procedures (Yuksel et al., 2009). As a conclusion, we think that D2 dissection can be carried out with safety in centers with experience.

4. Sentinel lymph node dissection

Sentinel node is the first lymph node that receives the drainage from primary tumor. A sentinel biopsy for gastric cancer is an intra operative diagnostic tool to detect lymph node metastasis (Ishii et al., 2008). The sentinel node hypothesis states that the histopathologic status of the first node on the lymphatic drainage pathway from a primary tumor reflects the tumor status of the entire lymphatic drainage basin. Underlying this hypothesis is the assumption that the surgeon can correctly and consistently identify this node (Hsueh et al., 2001).

The history of sentinel lymph node mapping dates back to 1977. Cabanas described and used the technique of lymphangiograms in patients with penile carcinoma (Cabanas, 1977). Later it gained more common use in the treatment of malignant melanoma and breast cancer. For epithelial tumors lymphatic spread is a common route of metastasis and the nodal status is important for staging and therefore in planning the surgical and adjuvant therapies. Nodal involvement in gastric cancer depends on the depth of invasion and it is between 2-18% for tumors limited with mucosa or submucosa, and around 50% for tumors which has invaded muscularis propria or subserosa, T1 and T2 respectively. Therefore in some cases there is a chance of resecting more tissue than what may be required. Given the high morbidity rates associated with extended dissections in elderly population and in general, especially in western countries, when compared to more limited dissections, alternative treatments to avoid the risks associated with this procedure has been discussed among surgeons. D2 lymph node dissection may be unnecessary for patients without lymph node metastasis (Cozzaglio et al., 2011). To decrease the perioperative morbidity and

mortality and to improve the quality of life, less invasive surgery has been employed on patients with node-negative gastric cancer. However, it is difficult to precisely diagnose lymph node metastasis using preoperative examinations such as endoscopic ultrasonography and computed tomography (Li et al., 2008).

Miwa et al. (2001) demonstrated that extended lymphadenectomy in patients with early gastric cancer (EGC) resulted in a significantly lower 10-year recurrence rate than limited lymph node dissection (D1). Among node-positive patients, the recurrence rate following D2 was significantly lower than that after D1. Among node-negative patients, there was no difference in recurrence rate between two groups. Based on these observations he suggested that there are two optimal methods of node dissections in EGC surgery based on nodal status. He further stated that sentinel node concept is important to understand nodal status and introduced the sentinel node concept to gastric area. In 34 of 35 patients, metastatic nodes were located along the lymphatic basins. Among them, 15 patients had metastasis only in the sentinel lymph nodes. Of 5 gastric lymphatic basins, 42% of the patients had involvement of one, 47% 2, and 12% 3. These results show that each EGC has its own lymphatic basins in which metastasis can develop. The more numbers of the sections there are, the higher the likelihood of nodal metastasis. This means that each frozen section slice carries the risk of being false negative. Therefore we should always dissect the lymphatic basins even in cases with no sentinel node metastasis. In addition, patients with sentinel nodes containing metastasis should be treated with the D2 procedure (Miwa et al., 2001).

The current Japanese guideline recommendations for early cancers that are seemingly lymph node negative are as follows:

For Stage IA (T1N0) tumors Endoscopic Mucosal Resection EMR or modified gastrectomy (MG) is indicated according to the following instruction.

Depth of invasion	Histology	Size	Indication
Mucosa(M)	differentiated	2cm	EMR
Mucosa(M)	else		MG A
Submucosa(SM)	differentiated	1.5cm	MG A
Submucosa(SM)	else		MG B

Table 2. Treatment indication for Stage IA

EMR should be indicated to patients with small mucosal cancer with no lymph node metastasis. The JGSA database suggests that intestinal type mucosal cancer less than 2cm in diameter has no lymph node metastasis. En-bloc resection is preferable because of risk of residual cancer left behind EMR, and 2cm is the upper limit of en-bloc resection. Then, accurate assessment of the depth of wall invasion, histological type and size of tumor is mandatory before carrying out EMR. Mucosal cancer that does not meet this condition should be treated by MG A. MG A is also indicated to the differentiated submucosal cancer less than 1.5 cm in diameter. Submucosal cancer that does not meet this condition should be treated by MG B. Type of gastrectomy is shown in Table 3.

The lymphatic basins are defined as the area containing the stained or radiologically marked lymphatic vessels and are divided into five categories according to the directions of arteries that surrounds the stomach as follows: the left gastric area, the right gastric area, the right gastroepiploic area, the left gastroepiploic are and the posterior gastric artery area.

Gastrectomy	Range of Resection	Dissection	Option
Modified A	< 2/3	D1 + No.7*	Vagus preserving
Modified B	< 2/3	D1 + No.7,8a,9	Pylorus preserving Laparoscopic
Standard	2/3	D2	
Extended	2/3	D2	D3
Combined resection			

*In case of lower third cancer, No.8a nodes should be dissected.

Standard gastrectomy includes proximal, distal or total gastrectomy associated with D2 dissection according to the size and location of the tumor.

The differentiated type: papillary, well and moderately differentiated tubular adenocarcinomas.

The undifferentiated type: poorly differentiated adenocarcinoma, mucinous adenocarcinoma and signet-ring cell adeno-carcinoma.

Table 3. Type of gastrectomy

A preoperative endoscopic injection of dye or radioactive tracer followed by intraoperative mapping, intraoperative endoscopic injection, intraoperative subserosal injection of dye are the usual ways of defining the lymphatic basin. The injections are carried out in four quadrants of the tumor either by endoscopy or by open surgery. The dye guided method is safe convenient and cost-effective. The radioguided method is more costly and may confront legal issues (Miyashiro et al., 2010).

The sentinel node (SN) concept has revolutionized the approach to the surgical staging of both melanoma and breast cancer, and these techniques can yield patient benefit by avoiding various complications due to unnecessary prophylactic regional lymph node dissection in cases with negative SN for cancer metastasis. Clinical application of SN mapping for early gastric cancer had been controversial for years. However, single institutional results of SN mapping for early gastric cancer are almost acceptable results in terms of detection rate and accuracy to determine lymph node status. Hypothesizing that SN mapping plays a key role to obtain individual information and allows modification of the surgical procedure for early gastric cancer, The Japan Society of Sentinel Node Navigation Surgery (JSNNS) has conducted a prospective multicenter trial of SN mapping by a dual tracer method with radioactive colloid and blue dye. Between September 2004 and March 2008, 433 patients with early gastric cancer were accrued at 12 comprehensive hospitals. Patients were enrolled under JSNNS and each institutional review board-approved protocols. Eligibility criteria were that patients had clinically T1N0M0 or T2N0M0 single tumor with diameter of primary lesion less than 4cm without any previous treatments. Technetium-99m tin colloid and isosulfan blue were utilized as dual tracers for SN mapping. SN mapping was performed for 397 patients with early gastric cancer. Detection rate of hot and/or blue node using their procedure was 97.5% (387/397). The mean number of sentinel nodes per case was 5.6. Fifty-three of 57 cases with lymph node metastasis showed positive sentinel nodes. The sensitivity to detect metastasis based on SN status was therefore 93% in their experience. Accuracy of metastatic status based on SN was 99% (383/387). In two of the four SN false-negative cases, the tumor involved to pT2, and only one case showed the metastatic lymph node beyond the SN basin (Kitagawa et al., 2009). Reviewing the relevant data, it becomes evident that the success rate of SLN mapping varies from as high as 99% in the Hiratsuka et al. series or 95% in the Aikou et al. series to as low as 74% in other series.

4.1 Pertinent issues

Skip metastasis is defined as the detection of metastatically infiltrated extragastric lymph nodes (level 2) in the absence of perigastric lymph node (level 1) involvement (Lee et al., 2009). However, the existence of skip metastases maybe as high as 17% and because of the complex and multi directional status of the gastric lymphatic drainage and the alteration of lymphatic pathways in advanced tumors because of the obstruction caused by tumor deposits (Griniatsos et al., 2009). There are also concerns about the negative predictivity of the technique. In patients with histologically classified as level one lymph node negative early gastric cancer, micrometastatically infiltrated level 2 lymph nodes are detected in 10 % (Morgagni et al., 2003). The lymphatic drainage route is patient-specific and lesion-specific in gastric cancer due to complicated lymphatic streams from the stomach. The most common channel for metastasis has been analyzed by subdividing the location of the tumor. For upper-thirds, the left gastric artery channel (Nos. 1, 3, 7) is the most common route. For the lower- and middle-third tumors, the left gastric artery channel and right gastroepiploic artery channel (No. 4 and No. 6) are equally frequent routes. The following factors could play some role in the pathogenesis of skip metastasis: (1) Occult metastasis or micrometastasis to N1 nodes may have been missed during the dissection or routine histopathologic examination; (2) There may have been some aberrant lymphatic drainage patterns in patients with gastric cancer through which metastasis bypassed the lymphatic vessels; (3) Lymphatic flows to the N1 nodes may have been blocked by cancer tissue; (4) Free cancer cells may diffuse through regional nodes to distant nodes because the microenvironment in N1 nodes is unfit for the development of metastasis (Li et al., 2008)

In overweight patients when the cancer is located in the upper third of the stomach dense fat can conceal the visualization of SNL. When harvested lymph nodes are smaller than 3 false negativity increases. So maybe instead of lymph node biopsy, limited lymphadenectomy or lymphatic basin dissection may lead to better results. This is not actually a sentinel node biopsy because it is not a single pick biopsy but a limited resection. However if there are too many lymph nodes in the sentinel piece it will be hard to examine by frozen section.

When a lymph node micrometastasis is identified, routine extended resection is indicated but currently it is hard to detect micrometastasis in a short time during the operation. Another shortcoming is that in cases where SNs dont contain metastasis how to determine the extent of dissection.

The presence of micrometastasis in a lymph node is a critical issue for the clinical application of sentinel node biopsy for gastric cancer. There has been found micrometastases among patients who had been classified as tumor-free in routine histological examination.

Micrometastases may be found by using step sectioning, immunohistochemical (IHC) staining and reverse transcriptase-polymerase chain reaction. Matsumoto et al. (2002) demonstrated that the reverse transcriptase chain reaction is more sensitive than IHC for detection of micrometastases. However Yamamoto et al. (2001) suggested that positive results with a molecular array may not be indicative of the presence of viable tumor cells but rather the presence of tumor dna thus may be associated with an increase rate of false positivity. The serial sectioning with IHC is thought to be the most accurate method for detection of lymph node micrometastases. In a study by Ishii et al. (2008) they demonstrated that the the sentinel nodes were the first to receive micrometastases and they found no micrometastasis without the sentinel lymph node metastasis. They also suggested

that it is sufficient to examine the sentinel lymph node for micrometastasis to determine whether or not there are lymph node micrometastases in patients with gastric cancer. Ajisaka et al. have proposed that dissection of the lymph nodes in the same lymphatic basin with the SN maybe mandatory even if the SN does not contain metastasis. After they found out that metastatic nonsentinel nodes lie within the same basin with micrometastatic SNs, they proposed that the dissection of lymphatic basin containing SNs is minimal requirement for early stage gastric cancer even for patients without histologically detectable metastases in SNs (Ajisaka et al., 2003).

Another issue is that the reports from far Asia yields and accuracy rate of 98%, whereas in Europe the false negativity increases as well as accuracy drops to 80%. In a study from Tel Aviv University they concluded that while in T1 and T2 tumors sentinel node mapping may be of assistance in decision making process regarding the extent of lymphadenectomy, SLN mapping in patients with T3 tumors maybe misleading in a third of the patients and therefore is not advised (Rabin et al., 2010).

5. Micrometastases and early gastric cancer

While the presence of lymph node metastases in early gastric cancer (EGC) is the most significant prognostic factor, the relevance of lymph node micrometastases (MM) remains uncertain. In 1996 Maehara noticed that even after curative resection of an early gastric cancer, some patients die of a recurrence. It is thought that patients with early gastric cancer who died of their disease had occult micrometastases in perigastric lymph nodes at the time of the original diagnosis.

Saito et al. (2007) studied seven hundred and sixty-five patients with early gastric cancer who underwent curative gastrectomy and analyzed them to identify the prognostic factor. The recurrence was observed in 17 patients. Hematogenous recurrence was observed most frequently (47.1%), followed by peritoneal recurrence (23.5%). Of 17 patients with recurrence, 6 (35.3%) patients died more than 5 years after operation. The prognosis was poorer when the patients were older, and the depth of invasion was greater, lymph node metastasis, lymphatic involvement, and vascular involvement were present, and lymph node dissection was limited. The independent prognostic factors were lymph node metastasis, lymph node dissection, and age by multivariate analysis using Cox proportional hazards. Micrometastases within lymph nodes were confirmed in 3 of 6 node-negative patients with recurrence (Saito et al., 2007). Several other studies have also supported the poorer prognosis of occult metastasis in early gastric cancer patients. In retrospective studies the frequency of micrometastasis in early gastric cancer can be as high as 20% and in most studies they are associated with poorer survival and more recurrence.

In a study by Liang Cao et al. MM was significantly associated with tumor size and lymphatic invasion. The statistically significant prognostic factors affecting 5-year survival rates were depth of tumor invasion, tumor size, lymphatic invasion, MM, and type of MM. The presence of MM, and particularly the cluster-type MM ($P < 0.001$), were independent prognostic factors in pN0 early gastric cancer patients: The incidence of lymph node MM in patients with node negative early gastric cancer was 21.3%, and cancer cell cluster type of MM proved a primary independent prognostic factor for pN0 early gastric cancer patients (Cao et al., 2011)

Many studies have proved that there are two types micrometastases in lymph nodes: single-cell type and clustered-cell type. This can be explained by invoking the concept of tumor

cell dormancy. Studies report that single cancer cells in lymph nodes may be associated with cells either under cell-cycle arrest or approaching apoptosis. According to cancer stem cell theory, an alternative explanation is that the disseminated cancer cells in some of the patients arose from the spread of nontumorigenic cells and only when cancer stem cells disseminate, and subsequently self-renew, will metastatic tumors form. Cancer stem cell can proliferate and form clusters of tumor cells, and nontumorigenic cells form single cells lymph node MM. Only when cancer stem cells disseminate and self-renew will the cluster type of MM form. Cancer stem cell theory predicts that the prognosis of clustered-cell MM should be worse compared to single-cell MM. The 5-year survival rate for the group of patients with cluster-type MM (45.8%) was significantly lower than that for the group with negative (92.9%) or single-cell MM (80%). Cluster type of MM was proved a major independent prognostic factor for histologically node negative gastric cancer patients. This phenomenon can be explained by the association of clustering with the presence true cancer stem cells (Cao et al., 2011). Cai describes that a high incidence of nodal involvement is found in submucosal cancers of large size (>2 cm; 43%), a depressed type (48%) and lymphatic invasion. A higher incidence of microinvasion is found with the diffuse-type carcinoma (33%) (Cai et al., 2000).

Morgagni et al. studied 5400 lymph nodes dissected from 300 patients treated surgically for EGC between 1976 and 1999, all of whom were histologically pN0. Micrometastases were defined as single or small clusters of neoplastic cells identifiable only by immunohistochemical methods. Lymph node micrometastases were observed in 30 of the 300 patients (10%). No significant correlation was observed between micrometastases and other clinicopathological characteristics. Analysis of overall survival showed no significant difference between positive or negative micrometastasis groups. The results of their study show that the presence of lymph node micrometastases in EGC does not influence patient prognosis (Morgagni et al., 2003).

6. Micrometastasis in locally advanced and advanced tumors

Giuli reviewed micrometastasis in gastric cancer in 2003. Nakajo et al. (2001) reported that lymph node micrometastasis was correlated with a significantly worse survival rate in patients with T1 or T2 tumors. Cai et al. (1999) also found a significant relationship between lymph node micrometastasis and poor prognosis in patients with T3 gastric cancer. However, Fukagawa et al. found that the presence of lymph node micrometastasis did not affect the survival in large numbers of patients with T2 cancer (Fukagawa et al., 2001). To clarify the prognostic importance of lymph node micrometastasis in patients with gastric cancer, histologically node-negative gastric cancers invading the muscularis propria or deeper (T2 and T3) were selected by Yasuda. The author's results indicate that lymph node micrometastasis is an independent prognostic indicator for patients with histologically node-negative gastric cancer invading the muscularis propria or deeper (T2 or T3). Micrometastasis of four or more lymph nodes or micrometastasis of level 2 nodes was significantly associated with a poor outcome. Lymph node metastasis is linked to tumor progression. Lymph node micrometastasis in gastric cancer is also associated with deep invasion through the gastric wall, large tumor size, and positive lymphatic or venous invasion. In this study, although no relationship was found between the presence of lymph node micrometastasis and clinico-pathologic characteristics, a weak association was found between lymph node micrometastasis and depth of wall invasion. In this series, the most

common pattern of recurrence was peritoneal and lung metastasis. Similar to these results, previous studies reported that lymph node micrometastasis was strongly associated with subsequent development of hematogenous and peritoneal metastases, but not locoregional lymph node recurrence (Yasuda et al., 2002). Cai et al. studied cases of pT3 gastric cancer and found out even when standard histological staining reveals no evidence of metastases in the regional lymph nodes, patients still may die of postoperative recurrence of the tumor. Evidence of occult involvement was found in 299 of 2310 (13%) lymph nodes and in 54 of 83 (65%) patients with pT3 gastric cancer. An analysis of survival demonstrated the limited 5-year survival of patients with occult involvement in their resected lymph nodes, as compared with that of patients without involvement. Moreover, the patients in whom group 2 lymph nodes had occult cancer cells had a significantly poorer prognosis than those in whom occult involvement was limited to group 1 lymph nodes (Cai et al., 1999).

Lee et al. studied the overall 5-year survival rate of patients in the MM negative group (76%) was higher compared with the rate of patients in the MM positive group (49%) for both patients with EGC and patients with AGC (Table 4). The effect of MM was most pronounced among patients in the Stage I and LNM negative group. There was a significant correlation between MM and depth of tumor invasion. Patients with MM had a decreased 5-year survival rate (49%) compared with patients without MM (76%) for both early and advanced gastric carcinoma. The effect of MM on survival was most pronounced for patients in the Stage I and LNM negative group (Lee et al., 2002).

7. Early gastric cancer and lymphadenectomy

Early gastric cancer is a more common entity in the east where screening programs are active, In the west most of the cancers are locally advanced or advanced at the time of diagnosis at present. The outcome of surgical treatment for early gastric cancer is satisfactory. Early gastric cancer is limited to mucosa or submucosa with or without lymph node metastasis. Even though the surgical treatment has excellent results in the management of early gastric cancer, the presence of lymph node metastasis is the most important prognostic factor.

For intramucosal cancer lesions with a differentiated histological type and without lymphatic-vascular involvement or ulcerative findings within the cancerous lesion there is a minimal risk for lymph node invasion. The surgical treatment is excellent even in lymph node positive disease. In a study by Sano et al. in which they summarized their findings in 1475 patients and reviewed 20 other articles in Japan about early gastric cancer, they pointed out that recurrence was higher in submucosal group (2,6%) than in mucosal group (0,4%) and in lymph node positive group (7,3%) than the node free group (0,7%). In addition to this, histologically well differentiated tumors tended to recur more. The modes of recurrence were lymphatic, hematogenous, local peritoneal or a combination of these (Sano et al., 1993). In their literature review they found out the overall recurrence rate was between 0,25% and 4,18% with a mean of 1,9%. The principal route of recurrence which led to death was hematogenous route in 59,3% of the patients and 68% of these recurrent tumors were well differentiated. Nevertheless, all the papillary carcinomas and five out of six poorly differentiated adenocarcinomas that recurred had positive lymph nodes at the time of diagnosis. The recurrence modes were almost similar for both nodal and node-free diseases, hematogenous recurrence being the most prominent one. As a conclusion, submucosal invasion, node positivity, histologically differentiated tumors and type 2a and 2c are high

risk group. Traditional surgical resection is associated with 90% survival over 10 years (Sano et al., 1993).

Although there was a controversy on the extent of lymph node dissection in the past, today there is a consensus that limited D1 dissection is suitable for most of the cases. The reason for a minimally invasive treatment is the low incidence of lymph node metastasis. Only 2% (range 0-4,8%) of patients with mucosal cancer will have positive lymph nodes. However when the tumor invades the submucosa this rate is about %20 (range 15-25%) and this metastasis is not confined to the first lymphatic echelon, especially when the submucosal lesion is bigger than 2 cms in diameter (Roukos et al., 2002).

For tumors which have exceeded the mucosa the risk factors for lymph node metastasis are tumor size larger than 30 mm, undifferentiated histological type, lymphatic vascular involvement and submucosal invasion more than 0,5 mm. Additional surgery with lymph node dissection is of little benefit for tumors that satisfy the following conditions. No lymphovascular involvement, tumor size smaller than 2 cm, differentiated histological type and depth of submucosal penetrations smaller than 0,5mm.

According to the Japanese guideline 2004 for macroscopic mucosal cancer of differentiated type (papillary, tubular carcinoma grade 1, tubular carcinoma grade 2) less than 2 cm in diameter with no ulceration or scar in cases of depressed type, irrespective of macroscopic type, no lymph node dissection is recommended. In such cases local excision of tumor with endoscopic procedures are considered sufficient if the procedure is carried out in a specialized center. For T1 cancers which are not indicated for EMR and which are with little possibility of lymph node metastasis, are expected to be cured with D1+ α dissection. Such conditions are macroscopic mucosal cancer (more than 21 mm) without lymph node metastasis and macroscopic submucosal cancer of differentiated type less than 1.5 cm in diameter without lymph node metastasis. An α dissection refers to dissection of first echelon lymph nodes and the 7th lymph node station in the second tier with addition of the 8th nodal station in cancers of the lower third with standard gastrectomy that is removal of two thirds of stomach. If that the cancer is differentiated type, \leq 2.0 cm in diameter, no ulceration in cases of depressed-type and there is involvement of the first tier of lymph nodes modified or if the submucosal cancer is differentiated type but more than 1,5 cms without lymph node involvement surgery-B (subtotal gastrectomy with the removal of first tier lymph nodes as well as lymph node stations 7, 8a, 9) is recommended. For other T1 tumors up to N2 nodal involvement standard surgery that is subtotal gastrectomy with the removal of second tiers of nodes is recommended. A very careful pre and intraoperative assessment of lymph nodes are mandatory and in case of any suspicion standard gastrectomy should be carried out.

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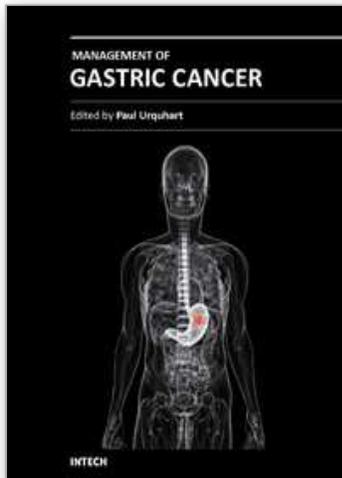
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Gastric cancer is the fifth most common cancer and the second most common cause of cancer death worldwide. More than 50% of the patients have advanced disease at diagnosis and in this case the disease has a poor outcome. The staging of gastric cancers is based on endoscopic ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography, in addition to the laparoscopic staging. Many improvements in the surgical techniques have been seen in the last decade. Laparoscopic surgery is an emerging approach which offers important advantages: less blood loss, reduced postoperative pain, accelerated recovery, early return to normal bowel function and reduced hospital stay. D1 lymphadenectomy, with a goal of examining 15 or greater lymph nodes is a standard. D2 dissection is considered as a standard in several institutions especially in eastern Asia. Perioperative chemotherapy and adjuvant concurrent radiochemotherapy are recognized as standards treatments. Palliative chemotherapy is the mainstay treatment of advanced stages of the disease (metastatic and non-operable tumors). Despite these treatment advances, the prognosis of gastric cancer remains poor with a 5-year survival ranging from 10 to 15% in all stages combined.

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