Review Article

Significance of nodal dissection and nodal positivity in gastric cancer

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Abstract: Lymphadenectomy is a central component of surgery for gastric cancer. However, controversies over the optimal extent of lymphadenectomy in gastric cancer surgery have persisted for several decades. In Eastern countries where the incidence of gastric cancer is high, surgeons have performed extensive lymphadenectomy (D2 lymphadenectomy) with low morbidity and mortality, while most Western surgeons have advocated for more limited lymphadenectomies according to the results of Dutch trial and MRC trial. Initially, these trials had failed to show survival benefit of D2 procedure and instead, found pancreaticosplenectomy performed as part of the D2 procedure associated with high incidence of morbidity and mortality. Subsequently, superiority of D2 lymphadenectomy on survival was demonstrated based on updated results. Moreover, spleen and pancreas preserving D2 lymphadenectomy are being performed safely in Western countries. Today, there is an international consensus on performing D2 lymphadenectomy as the standard procedure for advanced gastric cancer and is widely accepted as the standard procedure for gastric cancer surgery. The significance of the extent of lymphadenectomy is intimately associated with the prognostic importance of nodal metastases as the most powerful indicator of recurrence and survival for patients after curative gastrectomy. Maruyama computer program could be used to estimate the risk of lymph node metastasis in each nodal station. The Maruyama Index could be used to assess the adequacy of lymphadenectomy in gastric cancer. Positive lymph node ratio is calculated as the ratio of positive lymph nodes to all harvested lymph nodes, which might be a more precise predictor of prognosis than the absolute number of positive lymph nodes. While D2 lymphadenectomy enables the accurate staging of the disease, reduces the incidence of locoregional recurrences and thus contribute to an improved overall survival; performing lymphadenectomy beyond D2 is unlikely to improve survival. Therapeutic D2+ lymphadenectomy for advanced gastric cancer requires further evaluations, especially for patients receiving neo-adjuvant or conversion treatments.

Keywords: Gastric cancer; surgery; lymph node dissection; lymph node metastasis

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Introduction

Gastric cancer is a global health problem with significant geographical variability. The burden of gastric cancer is especially high in East Asia where more than half the incidence of gastric cancer occurs (1,2). Since lymph node metastasis is the most frequent metastatic route and the most important prognostic factor in gastric cancer (3), curative gastrectomy with lymphadenectomy is at the core of a comprehensive treatment strategy for gastric cancer.

The standard operation for gastric cancer was defined by the Japanese Research Society for Gastric Cancer (JRSGC) in 1962 (4). After studying lymphatic flow, risk of metastasis and survival benefit, Japanese surgeons proposed several fundamental concepts concerning lymphadenectomy techniques (5). In order to systematically dissect the lymph nodes, the lymph nodes surrounding the stomach were defined and categorized by the JRSGC into four groups: N1, N2, N3 and N4. The D level of lymphadenectomy, which was formerly known as the R level, was then put forward in accordance with this classification of lymph node stations (6).

D1 lymphadenectomy included removal of the lymph nodes in N1 station, while D2 lymph nodes dissection, which included removal of all N1 and N2 lymph nodes, has been the standard lymphadenectomy among Japanese surgeons since the 1960s, However, at the same time, lymphadenectomy beyond D2 was performed in Japan as well. The designation of N1–N4 nodes was based upon the location of the tumor, which was divided into upper, middle, and lower third of the stomach. Nevertheless, No.15 (lymph nodes along the middle colic artery) and No.16 (para-aortic lymph nodes) lymph nodes were defined as N4 despite the location.

In 1998, the second English edition of the Japanese Classification of Gastric Carcinoma was published (7), in which regional lymph nodes were categorized into three levels based on the site of the primary tumor. Tumors of different locations had different definitions of the three levels. D2 lymphadenectomy included removal of all lymph nodes at the first and second levels. The N stage (lymph node metastasis) was graded according to the level of lymph nodes involved.

In 2010, the third English edition of the Japanese Classification of Gastric Carcinoma and Japanese gastric cancer treatment guidelines was published (8,9), in which the N stage was classified based on the number of metastatic lymph nodes, which was identical to that in the 7th edition of The Union for International Cancer Control (UICC) TNM staging system as well as the T stage and M stage (10). As a result, grading lymph node metastasis based on anatomic stations was no longer feasible, and the extent of lymph nodes dissection was also revised and obviously simplified.

The extent of D1, D1+ and D2 lymphadenectomy were defined according to the extent of gastrectomy, despite the location of the primary tumor. Indications for lymphadenectomy were also clarified with D2 lymphadenectomy being the standard procedure. However, D3 lymphadenectomy was abandoned in the 2010 guideline due to the lack of additional survival benefit. In the fourth and fifth edition of guideline, the extent of D1, D1+ and D2 lymphadenectomy were almost the same as that in the third edition (11), with the only difference being No.10 lymph nodes removed from D2 lymphadenectomy for total gastrectomy in the fifth edition (12).

Significance of nodal dissection in gastric cancer

The justification behind lymphadenectomy is based on the lymphatic spread of cancer. However, controversy over the optimal extent of lymphadenectomy in gastric cancer surgery has persisted for several decades. There were significant differences in terms of the extent of lymphadenectomy in different regions. In the Eastern countries where the high incidence of gastric cancer has always attracted attentions, surgeons always considered D2 lymphadenectomy as the standard operation since 1960s, and refused to conduct the "deemed unethical" studies comparing D1 with D2 dissection, especially in Japan (13,14). Superior results of overall survival and recurrence-free survival after extended lymphadenectomy have been reported by Eastern surgeons (15-18). Not only the prognosis of surgery-only group but also surgery with chemotherapy group from Western trials was significantly poorer compared with that of surgery-only group from Eastern trials where more extensive lymphadenectomy (D2) has been a standard; those difference partly caused by the insufficient lymphadenectomy in Western trials (15-17). However, these results have often been criticized by the Western surgeons for their retrospective and non-randomized nature (13). In the late 1990s, western countries including the Netherlands and the United Kingdom conducted two large prospective randomized controlled

trials to address the extent of lymphadenectomy for gastric cancer patients (19,20).

The early result of Dutch Gastric Cancer Trial was published in 1995 (19), while those of Medical Research Council (MRC) Trial in 1996 (20). Results of both trials revealed that D2 lymphadenectomy was in strong correlation with postoperative morbidity and mortality. The long-term results of these two trials were further published in 1999 (21,22), from which no long-term survival benefit of D2 over D1 lymphadenectomy was demonstrated in terms of overall and disease-free survival. Therefore, most Western surgeons did not consider D2 lymphadenectomy as a standard operation in clinical practice and preferred to perform lymphadenectomies such as D1 or less, even though they are more limited. However, one thing should be noted that patients with N2 lymph nodes metastasis had a significantly higher survival benefit after having undergone D2 lymphadenectomy if the in-hospital dead patients were excluded in the Dutch trial (23).

Actually, there were also several problems of these two large trials that were criticized by Eastern surgeons. Firstly, high morbidity (43–46%) and mortality (10–13%) rates were found in the D2 group, mainly due to frequent performance of a distal pancreatectomy and splenectomy during dissection of No.10 and 11 nodes as a part of D2 dissection for middle and upper tumors, which was considered unnecessary nowadays (24). Furthermore, D2 lymphadenectomy is more complicated and requires challenging surgical techniques, for which a proper training is essential. Lower incidence of gastric cancer and inadequate surgical training for D2 lymphadenectomy in Western surgeons also contributed to high morbidity and mortality at that time, although there have been reports that D2 lymphadenectomy can be associated with low morbidity and mortality, thus be routinely performed, even in small hospitals in the East (25,26). Currently, Western surgeons can perform a spleen and pancreas preserving D2 lymphadenectomy safely after adequate training, with low morbidity and mortality rates similar to those of high-volume Eastern centers (27). Secondly, standardize D2 operation and detailed surgical techniques for centers with a low volume of participants were also in dispute.

In 2006, a randomized trial was conducted in Taiwan and has demonstrated that low morbidity and mortality could be achieved by well trained, experienced surgeons even though an extensive lymphadenectomy was performed, which could offer survival benefit for patients with gastric cancer when compared with D1 lymphadenectomy, with overall 5-year survival rates of 59.5% and 53.6% respectively (P<0.05) (28).

In 2010, the 15-year follow-up results of the Dutch trial were published (29), which indicated that D2 lymphadenectomy could decrease the locoregional recurrence (12% *vs.* 22%) and death related to gastric cancer (37% *vs.* 48%), and had a relatively higher overall survival rate (29% *vs.* 21%) when compared with D1 lymphadenectomy. In addition, the survival rate was significantly higher in D2 group than in D1 group (35% *vs.* 22%) among patients without pancreaticosplenectomy. Therefore, Dutch study has confirmed the survival benefit of D2 lymphadenectomy and recommended D2 lymphadenectomy for resectable gastric cancer in the context that spleen-preserving D2 dissection was safe to be done in high-volume centers.

In 2016, we performed a study to compare tumor characteristics, treatment parameters, and survival outcomes among patients with gastric cancer from Korea and China based on data of two high-volume hospitals, with the aim to identify prognostic indicators for gastric cancer patients (30). The results showed that for patients with stage II or III gastric cancer, D2 lymphadenectomy was a positive prognostic factor, which can even cure some stage II patients. However, the survival of patients with stage II or III cancer significantly varied between the two countries. In addition, we found no more than 50% of Chinese patients with stage II or III cancer have undergone D2 lymphadenectomy, whereas over 80% of Korean patients with the same tumor stage underwent this surgery. Patients' survival was similar when the analyses were confined to patients who underwent D2/D2+ lymphadenectomy. These findings emphasized importance and necessity of D2 lymphadenectomy.

In regard with lymphadenectomy beyond D2, Japanese surgeons have performed D3 (or D2 with para-aortic nodal dissection) lymphadenectomy for patients with tumors invading the serosa or adjacent structures since 1980s, in order to stage the gastric cancer accurately, reduce the risk of locoregional recurrence and improve survival (4). However, performing lymphadenectomy beyond D2 (D2+ lymphadenectomy) is not likely to improve patients' survival, due to the fact that metastasis to such distant nodes can hardly be cured simply by operation alone (14).

The effectiveness of D2 plus para-aortic nodes (No.16 lymph nodes) dissection was investigated in a prospective multicenter randomized controlled trial in Japan (JCOG 9501 trial) (31). In this trial, 523 patients were randomly allocated into D2 plus para-aortic nodes lymphadenectomy

group and D2 lymphadenectomy alone group. The results showed the mortality rates were same in the two groups (0.8%), while the morbidity rate was 28.1% in D2 plus para-aortic nodes group, which was slightly higher than 24.5% in the D2 group. However, the 5-year overall survival rates were approximately 70% in both groups without any significant difference. The authors drew a conclusion that treatment with D2 lymphadenectomy plus prophylactic para-aortic nodes dissection could not improve survival rate in curable gastric cancer and thus it should not be recommended.

However, some studies have shown that incidence of metastasis to para-aortic lymph node could be around 20% (32), and the 5-year survival rate for patients with para-aortic node metastasis who had undergone para-aortic node dissection could be up to about 20%. Therefore, the rationale of therapeutic para-aortic lymphadenectomy for advanced gastric cancer is suggested for further evaluations (33,34). D2 plus para-aortic lymphadenectomy after neo-adjuvant or conversion chemotherapy could be considered as a promising treatment for patients with para-aortic lymph nodes involved (35).

Although the No.8p, 12p, 13 lymph nodes were removed during a super-extensive lymphadenectomy (D3 lymphadenectomy) previously, it was no longer considered routinely (11). Only in some special situations (e.g., in a potentially curative gastrectomy for tumors invading the duodenum), the additional dissection of No.13 lymph nodes may be an option (11). However, an observational study has showed that a super-extensive lymphadenectomy including dissection of No. 8p, 12p, 13, 16a2 and 16b1 lymph nodes was in correlation with a significantly lower incidence of locoregional recurrence than the standard D2 dissection for advanced gastric cancer with mixed-diffuse histology (36), which may indicate a possible therapeutic role of the No.8p, 12p. 13 lymph nodes dissection. In the future, specific evidences are needed to be collected in well-designed, large scale prospective randomized trials with the aim to reasonably expand the extent of lymphadenectomy and the indications of D2+ lymphadenectomy in advanced gastric cancer, especially for patients receiving neo-adjuvant or conversion treatments (13).

Based on the updated results, the consensus on D2 lymphadenectomy has increased worldwide, provided that the spleen and pancreas preserving D2 lymphadenectomy could be performed safely as the improvement of surgical skill and experience in the latest years. Trends are that the extent of lymphadenectomy in the East and West has been approaching each other. In other words, the extent of lymphadenectomies are much more similar between the East and West and D2 dissection is becoming widely accepted as the standard procedure for gastric cancer surgery (4). There is no longer dispute against performing D2 gastrectomy for invasive gastric cancer as a standard procedure in modern days (11,37), except in early cases where endoscopic treatment is not suitable, thus a D1 or D1+ lymphadenectomy could be considered according to the Japanese guidelines (11). Nonetheless, it needs to be addressed that proper training for D2 gastrectomy and quality control of its performance remain challenging (30).

When D2 lymphadenectomy of high quality is performed with low morbidity and mortality, it could enable an accurate staging of the disease, reduce the incidence of locoregional recurrence and thus contribute to an improved overall survival (38).

Enable an accurate staging

Many Western gastric cancer patients were actually understaged because of inadequate lymph node sampling after gastrectomy. It has been reported that only 40% of 6,000 gastric cancer patients from 691 American hospitals had 15 lymph nodes checked after the operation (39), which is the minimum number of examined lymph nodes necessary for accurate staging of gastric cancer suggested by National Comprehensive Cancer Network gastric cancer guidelines (37). The data of Surveillance, Epidemiology, and End Results (SEER) database showed that only 29% of 10,807 patients who had undergone resected gastric cancer had 15 lymph nodes examined (40). There would be a possibility of false negative lymph node metastasis if less than 15 lymph nodes were harvested (14,41), and also unable to identify the N3b disease. However, the more lymph nodes retrieved, the more likely a stage migration of cancer to be caused. It is very easy for N0 tumors to upstage to N1, and N1 tumors to upstage to N2 as the number of resected lymph nodes increase. Consequently, extensive lymphadenectomy (D2 lymphadenectomy) can improve the accuracy of staging for gastric cancer patients. Some studies have demonstrated that more than 30 lymph nodes examined could improve staging accuracy for patients with T3 disease (42). Therefore, the 8th American Joint Committee on Cancer (AJCC) staging system of stomach indicates that although it is suggested at least 16 regional lymph nodes to be removed or assessed pathologically, removal and evaluation of more nodes (≥30) is desirable (43).

Evaluation of over 15 lymph nodes have been proven to facilitate the prediction of prognosis for patients with gastric cancer (44).

Decrease recurrence

Locoregional recurrence after curative gastrectomy for gastric cancer can be quite high. Both lymph nodes and anastomosis are frequent sites of first recurrence after gastrectomy for patients with locoregional gastric cancer (14). In the Japanese ACTS-GC randomized trial (45), it has been reported that 35.5% patients (N=188) suffered the recurrence after gastrectomy, while lymph nodes and local recurrence as the site of first recurrence accounted for 24.5% and 7.9% respectively. Therefore, an extensive lymphadenectomy is very important to decrease the recurrence through an effective and thorough clearance of potential metastatic nodes (46). Data from the Dutch trial confirmed that D1 group had more local recurrences than D2 group (41% *vs.* 30%; P<0.05) (29). There is also indirect evidence that extensive lymphadenectomy could decrease the locoregional recurrence. Rates of locoregional recurrence were generally lower in cases that undergone more extensive lymphadenectomy from both Western and Eastern hospitals (15-17,31). The reported recurrence rates from Western trials with limited lymphadenectomy was significantly higher compared with those from Eastern trials where more extensive lymphadenectomy (D2 lymphadenectomy) has been the standard procedure.

Improve survival

Performing a D0, D1 or D1+ lymphadenectomy may result in the positive lymph nodes being left out in the abdomen, which could cause an early recurrence and consequently a poor long-term survival. Morgan *et al.* found that, in the United States, the number of harvested lymph node being over 15 could lead to a better survival outcome (47). An analysis of 3,814 patients from the SEER database showed that the calculated overall survival increased by 7.6% (for T1/2N0), 5.7% (for T1/2N1), 11% (for T3N0), or 7% (for T3N1) for every additional 10 lymph nodes dissected, which could be up to a cut points at 40 dissected lymph nodes (48). Our team found that among patients with stage N2-N3 gastric cancer, resecting at least 25 lymph nodes may manifest a superior cutoff for radical gastrectomy and thus presenting better survival outcomes (49). There have also been reports that retrieval of more than 25 lymph nodes could associate with an overall survival benefit for patients with advanced node-negative gastric cancer (50).

Significance of nodal positivity in gastric cancer

Lymph node metastasis is the most frequent route of metastasis in patients with gastric cancer. Over half of the patients already have lymph nodes metastasis when they were first admitted to the hospital for surgical resection of the tumor (51). As the invasion of the tumor get deeper, the patient has greater risk of lymph node metastasis. For T1 lesions invading submucosa, the rate of lymph node involvement may be around 20% (52). For tumors invading the muscularis propria (T2 lesions), the rate of positive lymph nodes metastasis may increase to over 50% (4,14). If serosa or adjacent organs are invaded, the metastatic rate of lymph nodes could exceed to as high as 80% (53). Perigastric lymph nodes (No.1-6) are more frequently metastasized, followed by extra-perigastric nodes (No.7, 8a, 9, 11p). Among extra-perigastric nodes, No.7 and 9 are more frequently involved (54,55).

The incidence of lymph node metastasis varied from 2% to 50% for early gastric cancer located at the upper third, while 65–89% for advanced cancer (55,56). Specifically, in the upper third of the advanced gastric adenocarcinomas, the para-aortic (No.16) lymph nodes had a relative high positive rate, varying from 16% to 38% (34). In the middle third of the early gastric adenocarcinomas, the incidence of lymph node metastasis ranged from 0% to 31%, while that of advanced gastric cancer varied from 62% to 90% (53). No.16 lymph nodes were less frequently involved in middle third than in upper third gastric cancer. Lymph nodes metastasis in lower third gastric cancer was detected in 50–59% of all the cases (55), with No.6 lymph nodes involved most frequently. Lymph nodes metastasis is the most important prognosis indicator for gastric cancer patients after curative gastrectomy, and the survival rates sharply declines as the number of positive lymph nodes increases (40,57).

In 1989, the Maruyama computer program was created based on the data of 3,843 cases from Japanese National Cancer Center database (58). Eight variables including age, gender, Borrmann type, invasion depth, maximal diameter, longitudinal and circumferential tumor location as well as histological classification were used to estimate the risk of lymph node metastasis in each nodal station by matching the input variables to the database of Maruyama computer program. Sasako *et al.* has reported that it was possible to

predict the 5-year survival rate and calculate the estimated benefit from lymph node dissection of each station based on tumor location and positive lymph node stations, besides estimating the possibility of lymph node metastasis for each nodal station (59). Then, the Maruyama Index (MI) of residual disease was proposed, which was the sum of the estimated percentage of likelihood by the Maruyama program in the No.1-12 nodal disease without being removed in the operation (60). An opposite relationship has been found between MI and long-term overall survival rate and recurrence-free survival rate. Therefore, MI could be used as a quantitative yardstick to assess the adequacy of lymphadenectomy in gastric cancer (61).

Positive lymph node ratio is calculated as the ratio of positive lymph nodes to all resected lymph nodes, which could contribute to predicting the prognosis and alleviating the stage migration effect. The positive lymph node ratio was found to be a more precise predictor of prognosis than the absolute number of positive lymph nodes for patients undergone resection for gastric cancer (62,63). One study, which analyzed 1,069 consecutive gastric cancer patients with curative gastrectomy and radical lymphadenectomy, demonstrated that the positive lymph node ratio ≥0.2 was an independent poor prognostic factor, being associated with higher incidence of pT3-4 and pN2-3 stage, lymphovascular invasion and undifferentiated cancer (64).

Summary

Lymphadenectomy is the core of surgery for gastric cancer. However, there have been constant controversies over the optimal extent of lymphadenectomy in gastric cancer surgery for several decades. In Eastern countries where the incidence of gastric cancer is high, surgeons performed extensive lymphadenectomy (D2 lymphadenectomy) with low morbidity and mortality, while most Western surgeons preferred more limited lymphadenectomies according to the results of Dutch trial and MRC trial, which failed to show survival benefit of D2 procedure and instead, found pancreaticosplenectomy associating with high incidence of morbidity and mortality. As spleen and pancreas preserving D2 lymphadenectomy could be performed safely in western countries as well, and superiority of D2 lymphadenectomy on survival has been demonstrated based on updated results, performing D2 lymphadenectomy as the standard procedure for gastric cancer surgery is widely approved. D2 lymphadenectomy could enable an accurate staging of the disease, reduce the incidence of locoregional recurrences and thus contribute to an improved overall survival. Performing lymphadenectomy beyond D2 is not likely to improve survival. Therapeutic D2+ lymphadenectomy for advanced gastric cancer is suggested for further evaluations, especially for patients receiving neo-adjuvant or conversion treatments. Lymph node metastasis is the most important prognosis indicator for patients after curative gastrectomy. Maruyama computer program could be used to estimate the risk of lymph node metastasis in each nodal station. The Maruyama Index could be used to assess the adequacy of lymphadenectomy in gastric cancer. Positive lymph node ratio is calculated as the ratio of positive lymph nodes to all harvested lymph nodes, which might be a more precise predictor of prognosis than the absolute number of positive lymph nodes.

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Footnote

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