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Role of Extended Lymphadenectomy for Gastric Cancer

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Abstract Significant variability exists throughout the world in the extent of lymphadenectomy that is performed for gastric adenocarcinoma. D2 lymphadenectomy is the standard lymphadenectomy performed in high incidence countries such as Japan and South Korea, and less extensive lymphadenectomies are often performed in lower incidence countries such as the Unites States. This article reviews the evidence on the extent of lymphadenectomy that should be performed for gastric adenocarcinoma.

Keywords gastric adenocarcinoma, lymphadenectomy, surgery, stage, survival

Introduction

There has been intense debate over the extent of lymphadenectomy in the treatment of gastric adenocarcinoma for decades. This controversy is due to the differences in the global epidemiology of gastric cancer, and thus differences in experience and outcomes between centers in the Eastern and Western part of the world. Extent of lymphadenectomy involves at least two important issues: (1) adequate staging in terms of number of lymph nodes resected surgically and examined pathologically, and (2) adequate therapy (i.e., do some forms of lymphadenectomy result in better outcomes?). There is little disagreement among gastric cancer experts that the minimum lymphadenectomy that should be performed for gastric adenocarcinoma beyond an early mucosal or submucosal tumor should be at least a D1 lymphadenectomy. The majority of Japanese and South Korean surgeons believe that D2 lymphadenectomy improves outcomes to the extent that they would not consider a randomized trial of D1 versus D2 lymphadenectomy. Two large, prospective randomized trial performed in the United Kingdom (Medical Research Council Trial) and the Netherlands (Dutch Gastric Cancer Trial) in the 1999 failed to demonstrate a survival benefit of D2 over D1 lymphadenectomy [1, 2], but on contrary showed high surgical morbidity and mortality rates in the D2 group. Several studies since those trials have suggested that more extensive lymphadenectomies may be beneficial in certain patients with gastric adenocarcinoma.

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Epidemiology

Gastric cancer is now second only to lung cancer as the leading worldwide cause of cancer death and the fourth most common cancer after lung cancer, breast cancer and colorectal cancer with over one million new cases estimated to occur each year [3]. Nearly three-quarters of cases occur in developing countries, and nearly half of cases occur in Eastern Asia. The incidence of gastric adenocarcinoma varies tremendously

throughout the world and country-by-country. Forty-two percent of gastric cancer cases occur in China due to its high incidence and large population [4]. The highest incidence of gastric cancer is found in South Korea at 66.5–72.5 per 100,000 males and 19.5–30.4 per 100,000 females [5]. The incidence in the United States is only one-tenth of this with 22,220 new cases and 10,990 deaths expected in 2014 [6].

As the incidence of gastric cancer has wide global variability, different countries have adopted different strategies for gastric cancer surveillance. In the United States, gastric cancer detection is still largely based on symptomatic presentation [7]. In Japan, radiographic gastric cancer screening was first performed in the early 1960s and became national policy for citizens over the age of 40 in 1983 [8]. In Japan census data reported that 13% of the population underwent screening in 2004. South Korea initiated a campaign in 1999 recommending either upper endoscopy or upper GI series every 2 years starting at age 40 [9]. These screening programs, combined with high social awareness, are responsible for a substantial number of gastric cancer patients presenting in early stages in Japan and South Korea, with nearly half of patients presenting with T1 disease (i.e., tumor invading lamina propria or submucosa) [10, 11]. *H. pylori* screening and eradication systems are also beginning to show effectiveness and hold promise for contributing to a global decline in gastric cancer in the future [12, 13].

Current Nodal Station and Lymphadenectomy Definitions

Japanese Gastric Cancer Association (JGCA) has precisely defined the lymph node stations surrounding the stomach [14]. Previously the JGCA divided these stations into four levels (N1 through N4) based on analysis of lymphatic flow and the likelihood of gastric cancer to metastasize to each station, and these designations change based on the primary location of the tumor (i.e., upper third, middle third, and lower third) [15]. The anatomic definitions of the lymph node stations have remained constant during further revisions of the classification system [16] but the N designation of the stations as a component of D1 or D2 resection has changed as guidelines have been revised. The JGCA recently abandoned their N designation of nodal stations in order to more closely adopt and avoid confusion with International Union against Cancer (UICC)/American Joint Committee on Cancer (AJCC) staging [17]. Nodal stations for a D1 and D2 are now defined by the operation performed rather than the location of the tumor [18]. D1 lymphadenectomy along with proximal gastrectomy and pylorus preserving gastrectomy are only recommended for T1N0 disease.

Regional Differences in Lymphadenectomy for Gastric Adenocarcinoma

Two-thirds of all gastric cancer surgeries in South Korea are performed at 16 high-volume institutions, performing at least 200 gastric cancer surgeries per year. Same is the situation in Japan where maximum gastric cancer surgeries are performed at high volume tertiary care centers. Thus gastric cancer surgeons at high-volume institutions in Korea and Japan gain tremendous experience in the surgical management of gastric cancer. In contrast, the majority of gastric cancer surgeries in the United States are performed at non-referral centers. A "high volume" institution in the United States has been defined in some studies as an institution performing more than 15–20 gastrectomies per year [19, 20].

Standard lymphadenectomy for gastric adenocarcinoma in Japan and South Korea for any tumor beyond a T1 tumor is a D2

lymphadenectomy. Lymphadenectomy in not standardized among United States surgeons. Despite the performance of less extensive lymphadenectomies in the United States, surgical morbidity and mortality rates for gastric adenocarcinoma are generally much higher in the United States than in South Korea and Japan. Seoul National University Hospital performs almost 1,000 gastric cancer operations per year, and recently reported a morbidity rate of 18% and mortality rate of 0.5% [21]. Similar mortality and morbidity rates were found in RCTs from 24 Japanese institutions [22]. In the United States, single institutions series have reported morbidity rates following gastrectomy of up to 40% [23].

Single institution reports suggest that the number of pathologically positive lymph nodes is of prognostic significance, and that removal and pathological analysis of atleast 15 lymph nodes is required for adequate pathologic staging [24]. Indeed the current AJCC staging system accounts for these issues and therefore requires analysis of $\geq$ 16 lymph nodes to assign a pathological N stage [24]. The possible therapeutic benefit of extended lymph node dissection D2 versus D1 has been the focus of randomized control trials. These trials were performed because retrospective and prospective nonrandomized evidence suggested that extended lymph node dissection may be associated with improved long term survival [24]. The RCTs tested the hypothesis that removal of additional pathologically positive lymph nodes improves survival. The larger RCTs attempted to follow what are referred to as the

"Japanese rules" for lymph node classification and dissection that govern the extent of nodal dissection required based on anatomic location of the primary tumor [24]. Using these Japanese definitions, the RCTs compared limited lymphadenectomy of perigastric lymph nodes (D1) to en bloc removal of second echelon lymph nodes (D2). At least two of the completed trials are underpowered for their primary end point, OS [24]. The trials from the Medical Research Council of United Kingdom [24] and the Dutch Gastric Cancer Group [24] have received the most attention and discussion.

Staging and Locoregional Recurrence after D1 versus D2 Lymphadenectomy

Generally lymphadenectomy serves three purposes: Staging of disease, prevention of loco-regional recurrence, and improvement in overall survival. To stage the cancer, additional lymph nodes examined generally provide additional information on extent of disease. The AJCC Cancer Staging Manual recommends a minimum of 16 lymph nodes be examined [25]. Various studies have shown that it is difficult to be confident that a gastric cancer is truly node negative if fewer than 10 lymph nodes are examined [26,27]. Tumors categorized as N1 (1–2 positive nodes) may truly be N2 (3–6 positive nodes) or even N3a (7–15 positive nodes) as more lymph nodes are harvested [26, 28]. It is impossible to be categorized as N3b if less than 16 lymph nodes are harvested.

In centers where less than D2 lymphadenectomies are generally performed, 16 lymph nodes are often not examined. An analysis of over 6,000 gastric cancer patients treated at 691 United States hospitals found that less than 40% of patients undergoing surgical resection had at least 15 lymph nodes examined [29]. In a study from the United Kingdom analyzing 18 hospitals, only 31% of the 699 surgical resections resulted in 15 or more lymph nodes analyzed [30]. The arguments favoring an extended lymphadenectomy (i.e. D2 or D3 vs D1) are that removing a larger number of nodes more accurately stages disease extent and that failure to remove these nodes leaves behind disease (which would be a potentially fatal

event) in as many as one-third of patients [18]. A consequence of more accurate staging is to minimize stage migration (the Okie phenomenon, as described by Will Rodgers). The resulting improvement in stage-specific survival may explain, in part, the better results in Asian patients [31]. Furthermore, the influence of total lymph node count on stage-specific survival has been extensively studied and also proved to be significantly better as more nodes were examined in every stage subgroup [32]. Some or possibly all of the differences in stage for stage overall survival in patients undergoing varying lymphadenectomies can be attributed to stage migration. With the routine performance of D2 lymphadenectomy, a greater number of nodes are examined. More extended lymphadenectomies may discover additional positive nodes, and thus a patient may be assigned a more advanced stage after undergoing D2 lymphadenectomy than would be assigned after D1 lymphadenectomy. A large comparison between Japanese and Western cohorts suggested that analysis of additional nodes as a result of D2 lymphadenectomy shifted nearly a third of patients from N1 to N2 disease [33]. A recent retrospective analysis of patients treated at Kaiser Permanente Los Angeles Medical Center over the last decade demonstrated that D2 lymphadenectomy discovered additional positive nodes beyond D1 boundaries in 39% of patients, altering nodal status (N0 vs. N+) in 20% of patients and resulting in a higher N stage in 16% by 7th edition AJCC standards [34].

Some indirect evidence points out that more extensive lymphadenectomies result in lower rates of loco-regional recurrence. Loco-regional recurrence after potentially curative surgery for gastric adenocarcinoma can be quite high. In series from the University of Minnesota in 1982, 80% of 107 patients who underwent second look laparotomy had a recurrence [35]. Among these recurrences, 88% were loco-regional, 54% were peritoneal, and 29% were distant. In Intergroup 0116 trial, 177 of 275 patients (64%) in the surgery only group developed recurrent disease [36]. In terms of the site of first relapse, 29% had local recurrence, 72% had regional recurrence, and only 18% had distant recurrence. Generally Rates of loco-regional recurrence are lower in reports from both Western and Asian institutions that perform more extensive lymphadenectomies.

Overall Survival Following D1 versus D2 Lymphadenectomy

Western opinion on D2 lymphadenectomy are often still based on two large randomized control trials conducted in the 1990s. A United Kingdom Medical Research Council (MRC) trial randomized patients with histologically proven gastric adenocarcinoma to D1 or D2 lymphadenectomy [2]. MRC trial registered 737 patients with gastric adenocarcinoma; 337(46%) patients were ineligible by staging laparotomy because of advanced disease, before 200 potentially curable patients were recruited to each arm to undergo D1 or D2 lymph node dissection. In hospital mortality was high in both groups compared to high volume Asian centers, and significantly higher in the D2 versus D1 arm (13 vs. 6.5%, P< 0.04). No adjuvant chemotherapy or radiation was provided. There was no significant difference in overall survival at 5 years (D1 35%; D2 33%;*P*= 0.43). Survival based on death from gastric cancer as the event was also similar in both the groups, as was recurrence free survival. Postoperative morbidity and in hospital mortality rates were also significantly higher in D2 group. The authors found that much of the additional mortality in the D2 group could be attributed to the performance of distal pancreatectomy and splenectomy (as part of the lymphadenectomy) for many patients the D2 group.

The Dutch Gastric Cancer Group conducted a larger RCT with optimal surgical quality control comparing D1 and D2 lymph node dissections that was updated in 2010 after 15-year follow up [24]. It was conducted at 80 different centers in the Netherlands randomized 711 patients from a pool of 996 undergoing laparotomy to receive D1 (n=380) or D2 (n= 331) lymphadenectomy [1]. An experienced Japanese surgeon was present for the first 4 months of the study to supervise operations. Patients undergoing D2 resection were over three times more likely to undergo splenectomy (37 vs. 11%) and over ten times more likely to undergo distal pancreatectomy (30 vs. 3%). Patients in the D2 group had significantly higher rates of complications (43 vs. 25%; $P< 0.001$) and post-operative death (10 vs. 4%$P= 0.004$). Overall survival at 5 years was not statistically different (45% for D1; 47% for D2). Initially the Dutch investigators concluded that there was no role for the routine use of D2 lymph node dissection in gastric cancer. But after 15 year follow up, authors concluded that D2 lymphadenectomy is associated with lower loco-regional recurrence and gastric cancer specific death rates than D1 lymphadenectomy. Examining the results after 15 year follow up and given the data regarding gastric cancer specific mortality, loco regional recurrence, the authors revised their original conclusion: "Because spleen-preserving D2 resection is safer in high volume centers, it is the recommended surgical approach for patients with potentially curable gastric cancer" [24].

Pancreas-preserving D2 lymphadenectomy has been shown to reduce peri-operative morbidity and mortality and improve overall survival in a large Japanese series published in 1995 [37]. Studies in both the East and West have shown that avoidance of routine splenectomy improves morbidity and mortality [38].

The effect of more extensive lymphadenectomies on overall survival for gastric cancer is still quite controversial. It is difficult to separate a true survival benefit from stage migration and possible differences in tumor biology, but a number of retrospective studies have shown a correlation between survival and extended lymphadenectomy. This seems particularly true for advanced disease. A study of 4,789 patients at Seoul National University Hospital found that for patients with stage IIIB disease, those who had more than 35 lymph nodes removed had better survival than those who had less than 20 nodes removed [39]. The total number of positive nodes was not statistically different between these two groups leading the authors to conclude that this improvement in survival was due to surgical control of disease rather than stage migration. The German Gastric Carcinoma Study Group found in an analysis of 1,654 patients that those patients who underwent a D2 lymphadenectomy (>25 lymph nodes) had a significantly improved survival rate compared to patients who had a standard lymph node dissection [40]. Despite the greater number of lymph nodes examined, there was no statistically significant difference in stage-distribution. The difference in 5-year survival was particularly dramatic for stage II disease. This survival benefit remained significant between D1 and D2 groups when the patients most likely to be under-staged (examined lymph nodes <15) were removed from the D1 group in analysis.

Partial Pancreatectomy and Splenectomy Resect or Preserve?

There is an evolving consensus that splenectomy should be performed only in cases with intraoperative evidence of direct tumor extension into the spleen, or its hilar vasculature, or when the primary tumor is located in the proximal stomach along greater curvature [24]. Partial pancreatectomy should

be performed only in cases of direct tumor extension to the pancreas. This organ preserving modification of classic D2 dissection allows for dissection of some station 11 and 12 lymph nodes without the potential adverse effects of pancreatectomy /or splenectomy. In a small single institution RCT recently reported from Chile 187 patients with localized proximal gastric adenocarcinoma were randomized to treatment by total gastrectomy with D2 lymph node dissection plus splenectomy or total gastrectomy with D2 dissection alone[24]. Operative mortality was similar in both groups; however septic complication rates were higher in splenectomy arm. There was no difference in 5 year OS. In the Japan Clinical Oncology Group (JCOG) 9501 study, pancreas-preserving splenectomy was generally performed with low surgical mortality. In this study, only 22 of 523 patients underwent pancreatico-splenectomy and 59% of them (13 of 22 cases) developed postoperative complications [41]. According to Yao and colleagues,[42] 5-year survival rates of patients underwent spleen-preserving versus splenectomy D2-gastrectomy are usually very similar, ranging from approximately 100% to 100% for stage I, 66.7% versus 70.0% for stage II, 27.8% versus 26.7% for stage III, and 17.4% versus 5.6%for stage IV, respectively; none of these differences were statistically significant. Furthermore, there is a significant difference in postoperative morbidity rate (11.5% vs 27.5%) favoring spleen-preserving D2-gastrectomy.

The JCOG is conducting a multi-institutional RCT (JCOG 0110-MF) comparing D2 dissection with and without splenectomy for patients diagnosed with proximal gastric cancer[24]. The hypothesis to be tested is that 5-year OS of patients treated by extended D2 dissection without splenectomy is 5% less than that of patients treated by D2 dissection with splenectomy. With a planned accrual of 500 patients, this design will provide 70% power to reject the null hypothesis when 5-year OS is 3% greater following splenic preservation compared with splenectomy. The results of this trial will better define the short and long term effects of splenectomy for patients with proximal gastric cancers undergoing extended lymphadenectomy.

On the other hand, total gastrectomy with splenectomy has still been recommended for patients with T3 proximal gastric cancer who have 10-station lymph node metastasis to improve their prognosis [43]. Similarly, the current Japanese gastric cancer treatment guidelines continues to include splenectomies as part of the definition of D2 lymphadenectomies in more than T2 proximal third tumors eligible for a total gastrectomy [44]. However, preliminary results of the ongoing JCOG 0110 trial confirmed greater blood loss and operative morbidity in the group who underwent splenectomies [45].

Is more radical lymph node dissection needed?

Asian surgeons have also proposed a more radical lymph node dissection in order to improve survival for patients with stage T2-4 tumors. In this extensive procedure, designated as D4 dissection, paraaortic lymph nodes are removed in combination with D2 dissection. Two Japanese trials rigorously explored this important issue [46] and concluded that treatment with D2 lymphadenectomy plus paraaortic lymph node dissection (PAND) does not improve the survival rate in curable gastric cancer when compared with standard D2 lymphadenectomy alone. Thus, systematic D4 dissection has not been recommended for treatment of stomach cancer because it failed to benefit overall survival in patients with potentially curable advanced gastric cancer [46]. Furthermore, although an extended dissection may be performed as safely as D2

dissection when performed by well-trained surgeons [47] and obviously offers a survival benefit for patients with gastric cancer when compared to D1 dissection [48], this extended lymphadenectomy is often significantly associated with higher surgical complication rates [49]. More recent studies may help reshape Western opinion regarding the question of long-survival benefit of D2 versus D1 lymphadenectomy. A recent prospective trial in Taiwan randomized 110 patients to D1 surgery and 111 to D3 surgery (additional dissection of the hepatoduodenal ligament, superior mesenteric vein and retro-pancreatic area) with preservation of the pancreas and spleen [50]. This study demonstrated an overall survival advantage of more extensive lymphadenectomy over D1 lymphadenectomy, with overall 5-year survival being 59.5% compared to 53.6%, respectively (P = 0.041). However, the clinical benefit of this statistical observation has been questioned by Western audiences [51].

Is difference in epidemiology and biology responsible for differences in D1 vs D2 outcome?

Differences in outcomes between centers performing D1 and D2 lymphadenectomy may also be in part due to global differences in epidemiology and biology. In terms of patient demographics, Western patients compared to Eastern patients are generally: (1) older; (2) have a higher body mass index; (3) have a lower incidence of H. pylori infection; (4) have more proximal tumors; (5) present with later stage disease; and (6) receive different adjuvant therapies [52]. Many of the factors more common in Western patients are negative prognostic factors for gastric adenocarcinoma. A recent comparison was performed between patients treated with R0 resection between 1995 and 2005 at Memorial-Sloan Kettering Cancer Center (MSKCC) in New York and Seoul St. Mary's Hospital [53]. The median age of United States patients was 10 years greater than that of Korean patients (69 vs. 59 years old). Thirty-nine percent of United States patients had upper third or GE junction tumors compared to only 9.4% of Korean patients, and 59% of United States patients had intestinal type tumors compared to 49% of Korean patients. D2 lymphadenectomy was performed in similar percentages of patients (84 and 89%), but there were more nodes examined in Korean patients than United States patients (97% of Korean patients with ≥15 nodes examined compared to 78% of United States patients). Overall survival of United States patients with middle or upper tumors was worse than that of Korean patients, but United States and Korean patients with distal tumors has similar overall survival. The investigators applied a previously validated nomogram designed to correct for differences in age, sex, tumor location, Lauren classification, number of lymph nodes resected (negative and positive), and depth of invasion [54]. After these adjustments, Korean patients still had a 30% better disease-specific survival than United States patients, suggesting that Asian patients generally may have more favorable tumor biology. One important confounding factor in this analysis was that it was necessary to exclude a significant fraction of United States patients who received chemotherapy, in order to compare them to patients in South Korea where adjuvant chemotherapy was not standard of care at the time of the study.

Summary

D2 lymphadenectomy is the standard lymphadenectomy performed in Japan and South Korea for all resectable tumors except for T1 tumors. Less extensive lymphadenectomies are generally performed in lower incidence countries such as the United States. Less extensive lymphadenectomies result in under staging of patients [33]. Less extensive

lymphadenectomies also likely result in increased loco-regional recurrence, and may affect decisions regarding adjuvant chemotherapy versus chemoradiation. In terms of overall survival, the effects of more extensive lymphadenectomy are difficult to discern. However, in order to improve outcomes, the decision between D1 versus D2 lymph node dissection should be personalized after consideration of patient characteristics, tumor stage and surgical experience, especially because stomach cancers are now often comprehensively treated by a multimodal approach including perioperative chemotherapy or chemo-radiation. So, an aggressive nodal dissection should only be performed in selected centers where surgeons have demonstrated acceptably low operative morbidity and mortality rates with expected mortality rates of less than 2%. Besides, taking into account promising advances in these therapeutic options (including, for example, target therapy), the benefit of an extensive dissection may ultimately become more limited if some highly effective perioperative therapies are available. Whether these therapies may replace more extensive surgical procedure (possibly at a much higher cost), or if their benefit would also be extended to more extensive surgery remains unclear.

Authors' Contribution

SN: Contributions to conception, design, acquisition of data, analysis and interpretation of data.

HQ: Drafting the article, revising it critically for important intellectual content.

AA: Contribution to design, analysis and interpretation of data.

MP: Revising the article and correcting and analyzing it critically.

Conflict of Interests

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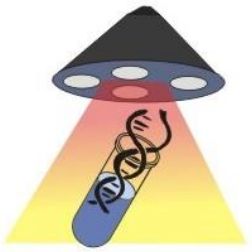

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