D2 Lymphadenectomy in Gastric Cancer Surgery

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ABSTRACT   Gastric cancer is one of the most common causes of cancer death worldwide. Surgery is the most widely utilized treatment for resectable gastric cancer. Evidence indicates that lymph node involvement and depth of invasion of the primary tumor are the most important prognostic factors for gastric cancer patients. Therefore, lymph node clearance is deemed a key procedure in gastric cancer surgery for the prognostic value to patients. Although the appropriate lymphadenectomy during gastrectomy for cancer still remains controversial, extended lymph node dissection (D2 lymphadenectomy) should be recommended in high volume hospitals.

KEY WORDS: gastric cancer, lymphadenectomy, lymph node metastasis, prognosis.

Introduction

Gastric cancer is the second most common cancer and deadliest malignancy, after lung cancer, despite the steady decline in its incidence worldwide[1]. This disease affects approximate 870,000 new cases a year, causing about 650,000 deaths annually[2]. Surgical resection remains the only potentially curative method of treatment for patients with gastric cancer. Whereas studies that investigate malignancies in other parts of the gastrointestinal tract pursue multimodality and less invasive therapeutic options, trials in gastric cancer focus on refinement and optimization of surgical therapy, especially with regard to the extent and the total number of lymph nodes removed[3]. Owing to the significance of lymph node metastasis, extended lymph node dissection (D2 lymphadenectomy) is still widely accepted and practiced as the standard procedure for gastric cancer[4-7]. Although the initial results of a prospectively randomized Dutch trial could not support the routine use of D2 lymph node dissection in gastric cancer patients[8], the final results of the Dutch trial[9] showed that patients with N2 stage disease might benefit from receiving D2 lymphadenectomy. In addition, Marubini et al.[10] in a randomized trial demonstrated that D2 lymphadenectomy should be recommended in surgical resections for gastric cancer. Likewise, Schwarz et al.[11] found that D2 lymphadenectomy might improve the survival of patients who presented with transmural or seropositive gastric cancer with advanced nodal involvement.

   In this review, we will discuss the superiority of the D2 lymphadenectomy in gastric cancer surgery for the prognosis of patients and will supply with the recent information gained from an investigation which is in favor of performance of D2 lymphadenectomy for gastric cancer patients.

Definition of D2 lymphadenectomy

Lymphatic drainage from the stomach flows to the perigastric nodes and then to the nodes around the celiac axis and its main branches. From there it enters the para-aortic nodes before joining the systemic circulation via the thoracic duct. Lymph node metastasis occurs during the early stages of this disease, and regional lymphadenectomy is recommended as part of radical gastrectomy. However, the extent of the lymphadenectomy to achieve the optimal result is controversial, and there is no worldwide consensus. The extended lymphadenectomy procedure, known today as D2, was first introduced by a Japanese surgeon in the 1960s[12]. This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches). Early studies have reported that between 30% and 40% of patients with lymph node metastasis including involvement of the second tier lymph nodes, have survived longer than 5 years with a D2 lymphadenectomy[13]. The D2 gastrectomy procedure is known as "extended lymphadenectomy" in Western countries, while Japanese surgeons employ the D2 as a standard technique and reserve the term "extended" for para-aortic dissection. The definition for D2 lymphadenectomy is based on the Japanese Classification of Gastric Carcinoma[14] and D2 lymphadenectomy signifies the dissection of all the first and the second tier lymph nodes. The first tier nodes consist of the perigastric lymph nodes, and the second tier nodes consist of the lymph nodes along the left gastric artery, the common hepatic artery and the splenic artery as well as those around the celiac axis. However, when the primary tumor is located in the lower third stomach, the lymph nodes along the superior mesenteric vein and the lymph nodes along the splenic artery are classified as being in the third tier. In contrast, when the primary tumor is located in upper third stomach, the suprapyloric and infrapyloric lymph nodes are classified as being in the third tier.

Survival significance of the D2 lymphadenectomy

For many years it has been debated whether an extended lymph node dissection for gastric cancer is beneficial. Theoretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for a curative outcome. Such resections, however, may be irrelevant if there are no lymph nodes affected, if the cancer has developed into systemic disease, or if the resection increases morbidity and mortality substantially. Reports from the Gastric Cancer Registry and other retrospective studies[15-17] have made radical gastrectomy with D2 lymphadenectomy the standard for the treatment of curable gastric cancer in Japan. Long-term follow-up of the largest European randomized studies of

D1 and D2 dissection clearly demonstrated that overall, no improved survival rate can be obtained by D2 lymphadenectomy[8,18]. However, lack of experience with the surgical procedure and with postoperative care was thought to account for the poor outcome of patients who underwent D2 lymphadenectomy[19-21]. The Dutch trial was conducted in 80 hospitals, including small community hospitals, by 11 surgeons who had little experience with D2 gastrectomy before the study. The limited experience of the surgeons made it difficult for them to learn how to perform the procedure safely and effectively, and the small volume of cases limited the ability of the hospitals to manage major surgical complications. Further, splenectomy and pancreatectomy are important risk factors for morbidity and hospital mortality after D2 dissection, with a significant adverse effect on survival as well[22-24]. Ultimately, Hartgrink et al. demonstrated that D2 lymphadenectomy may be curative for gastric cancer patients with N2 disease[25]. In 2001, the American Intergroup 0116 study showed that chemotherapy after limited lymphadenectomy (D0 or D1) decreased the local recurrence and increased long-term survival[26], the result suggesting that chemoradiotherapy eliminates the residual lymph node metastases that could be removed by D2 lymphadenectomy. In 2006, a randomized trial in Taiwan showed a significant benefit in overall survival for a D2 or D3 procedure as compared with D1 dissection, with no increase in operative mortality, which indicated that adequate local control is essential for the treatment of gastric cancer[27]. In this single institution trial comparing D1 gastrectomy with D2 or a more extensive gastrectomy, all the surgeons had performed at least 80 D2 procedures before participating in the study, and there were no deaths in either group.

D2 lymphadenectomy is adequate for resectable gastric cancer

Recently, Sasako et al.[28] reported remarkable survival results among patients undergoing D2 dissection, whereas more extended surgery did not improve the results. Similarly, Yonemura et al.[29] demonstrated a 5-year survival rate of 52.6% after D2 surgery and 55.0% after D4 gastrectomy in advanced gastric cancer patients ($P = 0.801$), and did not recommend the latter, more extensive lymphadenectomy for patients with potentially curable advanced gastric cancer.

D2 lymphadenectomy is an imperative procedure for the control of local relapse

The main types of recurrence of gastric cancer after curative resection include local relapse, lymph node metastasis, peritoneal dissemination, and distant metastasis. The extent of surgery is especially influential on locoregional control. Relapse after curative surgery because

of local recurrence or regional lymph node metastasis has been shown in up to 87.5% of patients[30]. In the Dutch trial, loco-regional recurrence was recorded 58% in the D1 group and 45% in the D2 group. However, the Japan Clinical Oncology Group 9206-1 Trial demonstrated that the local relapse rate was only less than 1% following curative gastrectomy with D2 or more extensive surgery[31]. Yoshikawa et al.[32] analyzed 1,041 early gastric cancer patients who underwent D2 lymphadenectomy with curative intent, and found that 129 cases had died at last follow-up. Of these 129 patients, 15 died of recurrence, 6 died of surgical complications, and 108 died of diseases other than the primary gastric cancer. In a recent meta-analysis of randomized clinical trials, Lustosa et al.[33] reported that overall, in 642 D2/D3 versus 690 D1 patients, a significantly higher recurrence rate was found in the D1 lymphadenectomy group (RR, 0.89; 95% CI: 0.80 to 0.98, $P < 0.02$) with significant statistical data heterogeneity ($P = 0.03$ and $I^2 = 71\%$) in the 3 randomized clinical trials analyzed[19,34,35].

Morbidity and mortality of the D2 lymphadenectomy

Major complications of gastric cancer surgery include anastomotic leakage or stenosis, bleeding, abscess formation, wound dehiscence, pancreatitis, and varied functional problems. High morbidity and mortality rates have been reported for those requiring extensive gastric resection[36]. D2 lymphadenectomy has a much lower morbidity and mortality in Japan than in the West, with the mortality rate being less than 3% in the former[37]. The lowest combined morbidity and mortality rates after D2 lymphadenectomy in the West have been reported from the Memorial Sloan-Kettering Cancer Center in the USA[38] and from Leeds in the UK[39], which are retrospective selective single-center series. Further a multicentre German study[40] also demonstrated a low mortality for D2 resections (5%), but, although prospective, it was not a randomized trial. In randomized clinical trials from Holland[35] and the UK[41], with 711 and 400 patients respectively, D2 patients had a higher operative mortality rate than D1 patients (10% *vs.* 4% and 13% *vs.* 6.5% respectively; $P = 0.04$). Accordingly, they also experienced more complications ($P < 0.001$). These unfavorable early postoperative outcomes have proven able to nullify any possible survival benefit of D2 lymphadenectomy. Subset analysis has clearly demonstrated that increased morbidity rate in the D2 arm of these studies was mainly due to caudal pancreatectomy and concomitant splenectomy, routinely performed during total gastrectomy[8,18,42]. The possible reasons for the adverse effects of pancreaticosplenectomy include subclinical leakage of pancreatic juice, vascular impairment of the stomach remnant following proximal ligature of the arterial pedicles, and extensive clearance of tissue

and lymph nodes in the gastric bed[41]. A large Norwegian trial first found a significantly higher complication rate with the use of splenectomy (42% *vs.* 27%)[43]. In a review of more than 300 patients, the 4-year survival rate was adversely affected by the use of "prophylactic" splenectomy[44]. The obligatory resection of the spleen and distal pancreas during total gastrectomy was specified in randomized controlled European trials (Dutch and MRC UK trials) protocols for D2 total gastrectomy, and was very strongly associated with mortality[36,41]. Many authors have emphasized that pancreatic resection should be done in gastric cancer cases with local involvement and that splenectomies be reserved only for proximal gastric cancer[5,16]. Recently, Biffi et al.[45] analyzed 250 gastric cancer patients in a single center to demonstrate that D2 gastrectomy with routine preservation of the spleen and pancreas can be considered a safe treatment for gastric cancer in Western patients, at least in experienced centers. In the Japan Clinical Oncology Group Study 9501, the hospital mortality was reported that only 0.80% which is significantly low compared with that reported in the West[4]. In that study, pancreatectomy was avoided whenever possible (4.2% of all patients), while splenectomy accompanied total gastrectomy in many cases (36.5% of all patients). In actuality, pancreatectomy is not performed as a standard procedure in Japan or in the West because the assessed increased morbidity is well known. Maruyama et al.[46] have shown that pancreatectomy does not constitute a more radical procedure because the lymph nodes are not located within the pancreatic parenchyma but only at the pancreatic surface.

Another key factor which can affect the morbidity and mortality of D2 lymphadenectomy is the level of surgical skill. D2 lymphadenectomy is the standard treatment of curable gastric cancer in Japan. Although two randomized controlled European trials that compared the less extensive D1 dissection with the D2 procedure failed to show a survival benefit for the patients with D2 dissection, lack of experience with the surgical procedure and with postoperative care were thought to account for the poor outcome of the patients who underwent D2 lymphadenectomy[19-21]. It has been shown that surgical morbidity and mortality rates has been decreased after the performance of 200 D2 procedures[47]. This implies that the 11 surgeons in the Dutch study were in the learning period throughout the trial. Consequently, they could not detect a learning curve for any of the participating surgeons[48] who did only an average of one curative D2 resection per year[49]. In 2006, a randomized trial in Taiwan showed a significant benefit in overall survival for a D2 or D3 procedure in comparison to a D1 dissection with no increase in operative mortality[19,27]. Furthermore, Sasako et al.[28] demonstrated that the hospital mortality of extended D2 or D2 plus paraaortic nodal dissection was only 0.8% in Japan, whereas the mortality rates in patients treated with D2 gastrec-

tomy reached 10% or higher[35,41]. The excessive number of early deaths in these studies may have obscured any potential difference in long-term survival between patients undergoing D1 and D2 gastrectomies. The Dutch trial was conducted in 80 hospitals, including small community hospitals, by 11 surgeons who had little experience with D2 gastrectomy before the study began. The limited experience of the surgeons kept them from performing the procedure safely and effectively, and the small volume of cases limited the ability of the hospitals to manage major surgical complications. By contrast, in the Taiwan trial comparing the D1 gastrectomy with the D2 or a more extensive gastrectomy, all the surgeons had performed at least 80 D2 procedures before participating in the study, and there were no deaths in either group[27].

Recently, body mass index (BMI) has been considered a significant factor leading to technical difficulties in D2 lymphadenectomy despite some authors maintaining the opposing opinion[50-54]. The incidence of the overweight and of the obese is steadily increasing in the general population and compared to the Japanese, the US and European populations have a much higher average BMI[55-58]. Interestingly, Tsujinaka et al.[59] demonstrated that BMI had a direct effect on surgical complications other than the indirect effects related to operation time and blood loss. The presence of a large amount of viscera may disturb drainage of exudates and coagula, and excess fatty tissue may become necrotic more easily as a result of surgical manipulation. In addition, the demarcation between pancreas and adipose tissue in overweight individuals may be obscured during surgery, owing to greater fat deposition[60]. Collectively, these factors may contribute to the increased occurrence of abdominal abscess and pancreatic fistula in overweight patients with surgery.

D2 lymphadenectomy decreases the stage migration

The number of metastatic lymph nodes, which is the most important predictor of survival for gastric cancer patients following curative resection[61-64], was identified to be significantly associated with the number of total harvested lymph nodes[65,66]. Theoretically, the greater the number of dissected lymph nodes, the more credible the curative resection is. Conversely, if fewer lymph nodes are dissected, the lymphadenectomy is regarded as insufficient. Schwarz et al.[11] reported that higher lymph node counts resulted in the better survival of gastric cancer patients after curative resection. The current UICC/AJCC manual requires that a minimum of 15 lymph nodes should be examined for accurate assignment of the lymph node metastatic category[67]. This implies that D1 lymph node dissection, which is limited to the perigastric lymph nodes, might not guarantee an accurate staging[68]. When a quantitative classification, based on the number of metastatic lymph nodes was used, in accordance with the UICC/AJCC 5th edition TNM system, the phenomenon of stage migration, the so-called Will Rogers phenomenon, was observed in 10% to 15% of gastric cancer patients[69,70]. However, a different study maintained that the number of metastatic lymph nodes could not increase further when more than 15 lymph nodes were harvested[40]. Stage migration, due to inappropriately understaging the disease, was suggested to be a dominant factor in early-stage gastric cancer survival when fewer than 10-15 lymph nodes were dissected in order to assign an N category[69,71]. Bando et al.[72] reported that stage migration of lymph node metastases, which could be produced from an anatomical location based classification of metastatic lymph nodes, was significantly associated with the extent of lymph node dissection. Sano et al.[4] reported that patients who underwent D2 lymphadenectomy in Japan had an average of 54 nodes evaluated. This is in comparison to the findings in the United States, where, in the retrospective study by Wanebo et al.[73], more than 1/3 of patients had no nodes reported in the pathologic specimen. Schwarz et al.[11] reported that D2 lymphadenectomy could produce significantly superior survival results in N3 gastric cancer with more than 40 total lymph nodes harvested or with more than 20 negative lymph nodes obtained. This must be explained by mechanisms which are most likely different from stage migration. D2 lymphadenectomy improving the survival of gastric cancer patients is not only due to decreased the stage migration, but also to the inherent therapeutic benefit[74].

D2 lymphadenectomy for early gastric cancer

Early gastric cancer is defined as adenocarcinoma of the stomach in which the depth of invasion is limited to the mucosa and/or submucosa, regardless of the status of lymph node metastasis[75]. Although the characteristics of early gastric cancer with lymph node metastasis have been reported in many institutions[76,77], the controversy remains as to the appropriate gastric resection and extent of lymph node dissection for early gastric cancer. Borie et al.[71] analyzed the clinicopathological and follow-up data of 332 early gastric cancer patients and demonstrated that 10% of patients had multiple cancers, which might be prohibitive in achieving a safe margin of resection. Although the incidence of nodal metastasis in early gastric cancer is 10% to 20%[78-81], the incidence of second tier lymph node involvement was reported from 10% to 19% in early gastric cancer patients who had positive lymph nodes[82,83]. Many reports have concluded that radical lymphadenectomy is necessary because early gastric cancer does metastasize to second tier lymph nodes[84-88]. The most widely applied treatment for early gastric cancer in Japan and in some European

countries has been total or subtotal gastrectomy with D2 lymphadenectomy. However, other investigators have demonstrated that hematogenous spread is the major mode of recurrence in early gastric cancer patients with second tier positive lymph nodes following curative gastrectomy[32,89,90]. Therefore, there is not a consensus as to whether D2 lymphadenectomies are essential for early gastric cancer.

Borie et al.[91] analyzed 332 patients with early gastric cancer following curative surgery and concluded that the rate of lymph node involvement correlated significantly with submucosal invasion and lack of histologic differentiation. Although extended lymphadenectomy in these early gastric cancer patients does not alter prognosis, lymphdenectomy in early gastric cancer is important in identifying the high-risk population for whom prognosis is worse.

Conclusion

The D2 lymphadenectomy is considered a safe and standard treatment for resectable gastric cancer. Surgeons much experienced with D2 procedures can control and significantly lower the incidence rate of morbidity and mortality. D2 lymphadenectomy can provide both more accurate nodal staging and better prognosis for gastric cancer patients, compared to D1 lymphadenectomies. In addition, D2 lymphadenectomy should be strongly recommended for some early gastric cancer patients who present with submucosal involvement or with undifferentiated adenocarcinoma.

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