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The Type of Complications Following Gastric Cancer Surgery

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Abstract: ***The incidence of postoperative complications after radical gastrectomy remains high, and the estimated incidence is 12.8 to 14%. Given the prevalence of postoperative complications after radical gastrectomy, it is important to determine whether a correlation exists between postoperative complications and poor prognosis. The existence of that correlation may not only lead to a consideration of shortening follow-up interval and enforcing adjuvant chemotherapy in patient who have developed postoperative complications, but may also underline the necessity of neoadjuvant chemotherapy and stress control management in patients with high risk of developing postoperative complications to reduce the hazard for long term prognosis. [4] In the meta-analysis, the correlations between postoperative complications and prognosis after radical gastrectomy were assessed. Although etiologic and pathologic differences exist in the presentation of gastric cancer treated in the West versus the East, surgical techniques developed in countries of high-incidence have become more universal. It is widely accepted that gastrectomy with a modified D2 lymphadenectomy (sparing the distal pancreas and spleen) confers adequate staging information, with the goal of obtaining a minimum of 15 lymph nodes.***

Keywords: complications, prognosis, radical gastrectomy, stomach neoplasms

1. Introduction

The incidence of postoperative complications after radical gastrectomy remains high [1], and the estimated incidence is 12.8 to 14% [2]. In addition to undermining the short-term survival, postoperative complications may also be correlated with long term prognosis. Currently, increasing numbers of observational studies have investigated the correlation between postoperative complications and long-term prognosis after radical gastrectomy. Although some reports have negative findings, other studies have demonstrated that overall postoperative complications, infectious complications, and gastrointestinal leakages are all correlated with poor overall survival (OS) and/or recurrence-free survival [RFS] [3]. Additionally, the correlations between postoperative complications and long-term prognosis in different stages are controversial and are based on subgroup analyses with small sample sizes. [4]

Given the prevalence of postoperative complications after radical gastrectomy, it is important to determine whether a correlation exists between postoperative complications and poor prognosis. The existence of that correlation may not only lead to a consideration of shortening follow-up interval and enforcing adjuvant chemotherapy in patient who have developed postoperative complications, but may also underline the necessity of neoadjuvant chemotherapy and stress control management in patients with high risk of developing postoperative complications to reduce the hazard for long term prognosis. [4] In the meta-analysis, the correlations between postoperative complications and prognosis after radical gastrectomy were assessed.

2. Material and Methods

Search strategy and eligibility criteria The PubMed, EMBASE, and Cochrane Library databases were searched for studies that assessed the relationship between postoperative complications and prognosis after radical gastrectomy up to year 2019. The following medical subject heading [MeSH] terms and keywords were used: "Stomach Neoplasms", "Gastrectomy", "Postoperative Complications", and "Prognosis". The search was restricted to studies on humans and to those that were published in the English language. The titles and abstracts were screened by two authors independently. The inclusion criterion was as follows: any study that compared the long-term prognosis between patients with and without postoperative complications after radical gastrectomy for gastric cancer. The exclusion criteria were as follows: (1) data of other neoplasms other than gastric cancer were included in the survival analysis; (2) data of palliative surgery were included in the survival analysis; (3) studies that describe the same patient population; (4) hazard ratio (HR) cannot be estimated; (5) describing complications without precise definitions; (6) letters, comments, or conference abstracts. When multiple studies describing the same patient population were identified, the most recent publication was used unless additional data were provided in the earlier work.

3. Results

For advanced gastric cancer and most early-stage gastric cancer, gastrectomy with D2 lymphadenectomy (resection of perigastric lymph nodes and nodes along the named branches of the celiac axis) is considered standard surgical therapy. However, with advancement in techniques for local evaluation of gastric tumors with endoscopic ultrasound, as well as endoscopic resection techniques, endoscopic submucosal dissection [ESD] has become well-recognized as a treatment for early gastric cancers that are at low risk for lymph node metastases. Initial indications for endoscopic resection for early gastric cancer were differentiated histology, <2 cm in diameter, lack of ulceration or scarring, mucosal involvement only, with no lymphatic or vascular

involvement. [5] More recently, extended indications for ESD are differentiated tumors, without evidence of venous or lymphatic involvement, <3 cm in diameter, and confined to the mucosa or submucosa. Expanded criteria to include undifferentiated tumors has yielded excellent long-term survival rates [16, 17]; ESD is now considered a therapy that could be offered to patients who have early gastric cancer, particularly those limited to the mucosa, without adverse histologic features. Caution must be exercised for tumors with submucosal involvement due to the increased risk for occult lymph node metastases. Lymph node metastases may be present in as many as 20% of patients with early stage gastric cancer, particularly in those patients with lymphovascular invasion and larger tumor size (≥2 cm). [6] Therefore, in patients with submucosal disease, gastrectomy with associated lymphadenectomy should be considered standard of care. For patients at high-risk for surgery, ESD can be considered an option.

Surgery is the mainstay treatment for early stage gastric cancer and is paramount for achieving cure in patients with gastric adenocarcinoma. Barring an early T1a or *in situ* tumor, gastrectomy including resection of the regional lymph nodes remains the standard surgical procedure. The extent of lymphadenectomy, however, has been a greatly debated topic of controversy throughout the last few decades. The majority of Japanese and Korean (i. e., Eastern) surgeons would agree that an extended lymphadenectomy (D2) leads to improved outcomes and survival. Certainly, multiple large retrospective studies from those groups have illustrated an impressive overall survival that has not been replicated in Western series. [7]

The Japanese Gastric Cancer Association (JGCA) published guidelines for surgical treatment and pathologic evaluation that grouped the perigastric and distant draining lymph nodes into 16 stations. These stations were then categorized into 4 levels [N1 to 4] based on the likely lymphatic drainage from the respective primary tumor location. [8]. The nodes along the lesser and greater curvatures are included in the perigastric lymph node level [N1]. The more distant draining lymph node stations follow the left gastric artery, common hepatic artery, celiac artery splenic hilum and artery (stations 10 and 11] and are grouped in the N2 level. The most distant, or para-aortic, nodes (N3 or N4) are usually considered distant metastatic disease and are not traditionally included with gastric resections. However, these four categorization levels have recently been abandoned to prevent confusion with the TNM staging systems.

The extent of lymphadenectomy is dependent on the extent of gastrectomy being performed [i. e., total, subtotal/distal, or proximal gastrectomy]. For example, historically, a D2 dissection for a total gastrectomy would involve retrieval of lymph node stations 1-12 with a concomitant distal pancreatectomy and splenectomy while a D1 dissection would only require the perigastric nodes at stations. More recently, proponents have advocated a modified approach to a D2 dissection by sparing the spleen and pancreas unless directly involved with the primary tumor. This approach of sparing the pancreas and spleen has shown adequate retrieval of lymph nodes without the morbidity associated with multi-visceral resection. [9, 10].

A recent retrospective study evaluating 1, 377 patients from the Surveillance, Epidemiology, and End-Results (SEER) database looked at the impact of the number of nodes examined and its relationship with survival as a surrogate for accurate staging. Total lymph node count and number of positive lymph nodes were two of the independent factors associated with survival. Significant survival benefit was observed for patients who had more than 15 N2 nodes and 20 N3 nodes examined. Although there is no consensus on the level of dissection required (D1 *vs.* D2) in the U. S., pathologic assessment of at least 15 nodes is considered standard of care, and D2 lymphadenectomy is recommended. [11]

Japanese and South Korean surgeons routinely perform D2 lymphadenectomy for patients with gastric adenocarcinoma. The surgeon will then meticulously dissect out each lymph node station prior to sending tissue for pathologic evaluation, unlike in the U. S., where surgeons submit the gastrectomy specimen *en bloc* with the lymphadenectomy. Based on the extensive gastric cancer database of 3, 843 patients from the experience by the National Cancer Center in Japan, the Maruyama index (MI) was created in order to create estimates for the likelihood of metastases for each lymph node station not removed by the surgeon. The index is based on 8 variables: age, sex, Borrmann classification, depth of invasion, diameter, location, position and histology. [12] Studies of gastric cancer patients undergoing gastrectomy with a MI <5 versus those ≥5, had an improved median overall and relapse-free survival on univariate and multivariate analysis. Due to the complexity, however, it is infrequently utilized in the West.

Western proponents for a limited D1 resection cite two large randomized controlled trials published in the 1990s from the Netherlands and United Kingdom that were unable to show a survival benefit with extended lymphadenectomy. The Dutch Gastric Cancer Group Trial randomized 711 patients undergoing surgery for curative intent to either D1 or D2 lymphadenectomy in 80 centers throughout the Netherlands. [13] Participating surgeons were provided an instruction booklet and videotape on how to perform D2 lymphadenectomy, and an experienced Japanese gastric cancer surgeon was present for the first 6 months of the study for instruction. Patients undergoing D2 resections were more likely to have a higher operative mortality (10% *vs.4*%, P=0.004) and morbidity (43% *vs.*25%, P<0.001). Mature, 15-year follow-up data showed no overall survival benefit with a D2 lymphadenectomy. A subset analysis, however, showed a lower locoregional recurrence rate and fewer gastric cancer related deaths with D2 lymphadenectomy. Similar to the Dutch trial, the United Kingdom Medical Research Council (MRC) Gastric Cancer Surgical Trial (ST01) randomized 400 gastric adenocarcinoma patients to D1 or D2 lymphadenectomy. [14] The operating surgeons were provided with a booklet and instructional video to ensure standardization of the two procedures. Again, this Western study demonstrated higher post-operative mortality (13% *vs.*6.5%, P=0.04) and morbidity rates (46% *vs.*28%, P<0.01) in the D2

lymphadenectomy group as well as a higher chance of undergoing concomitant pancreatectomy and splenectomy. Most notably was the significantly higher rate of anastomotic complications in the D2 dissection group, also including severe pancreatitis, pancreatic fistula, and gastric remnant necrosis. Long-term results showed no difference in overall survival, gastric cancer related deaths, or recurrence-free survival.

4. Discussion

These trials may now be less relevant as more recent studies have shown that routine resection of the spleen and pancreatic tail for middle and proximal gastric tumors increases morbidity and perioperative mortality without long term overall survival benefit. The traditional D2 resection involves a distal pancreatectomy and splenectomy for all tumors except in the antral location, in order to adequately resect lymph node stations 10 and 11 surrounding the splenic artery and hilum. In the UK MRC trial, subset analysis of patients undergoing pancreatico-splenectomy, splenectomy alone, or preservation of both organs showed survival difference, with the poorest survival in those undergoing multi-visceral resection. [15]. Similarly, the Dutch trial performed a multivariate analysis and showed increased mortality associated with splenic or pancreatic resections. This likely contributed to the lack of survival difference between D1 and D2 resections.

More recently, however, studies from the East and West have shown improved morbidity and mortality with avoidance of routine splenectomy and pancreatectomy compared to traditional D2 resection. [16] The Italian Gastric Cancer Study group randomized 267 patients with gastric adenocarcinoma to a D1 or modified D2 resection. [17] Routine splenectomy and pancreatectomy were not performed unless direct extension by the primary tumor [T4] was noted. No statistically significant difference was noted between the groups in regards to morbidity or in-hospital mortality. Due to this most recent data, surgeons in the Eastern hemisphere are routinely adopting a modified technique for D2 resections and preserving the pancreas and spleen.

The difference in survival and results between Eastern and Western surgeons is likely multi-factorial. Some have pointed to the theory of stage migration as the etiology for improved survival with D2 resection with Eastern surgeons. With an extended lymphadenectomy, a greater number of lymph nodes are retrieved with a higher chance of detecting a positive node. A recent retrospective analysis of 79 patients undergoing D2 *vs*. D1 lymphadenectomy from Kaiser Permanente Los Angeles showed a significantly greater number of nodes retrieved with a D2 lymphadenectomy (mean, 26 *vs*.9 nodes, P<0.0001). [18] Within the D2 lymphadenectomy group, 39% showed additional lymph node metastases in the extended portion of the dissection, altering 16% of the TNM staging. Additional lymph node dissection beyond a D2 is traditionally not recommended. A prospective trial spearheaded by the Japanese Clinical Oncology Group randomized 523 patients with gastric cancer to D2 or D2 plus para-aortic lymph node dissection. [19] Although, as expected, the operative time and estimated blood loss were increased with the extended dissection, the overall and recurrence-free survival showed no significant difference.

Although both the East and West utilize the American Joint Committee on Cancer (AJCC) staging system for determination of prognosis, relative survival differs markedly even when matched by stage. For example, when comparing Korean and U. S. high-volume centers, disease specific survival after R0 resection was greater in Korea, with a 5-year gastric-cancer-related probability of death of 17% versus 32% in the U. S. [20] Interestingly, a subset analysis of a T1N0 cohort at the same institutions demonstrated no difference in rates of death due to gastric cancer. [21] A meta-analysis addressing this question, comparing published disease specific survival rates in randomized control trials, demonstrated improved relative 5-year survival in the East with an adjusted odds ratio of 3.22 [95% confidence interval: 1.85-5.58]. [22] These results were demonstrated even after adjusting for patient age, chemotherapy, gender, and tumor size, factors historically attributed as reasons for differences in survival outcomes between East and West.

Other than the differences in surgical treatment as discussed above, there are also important differences between East and West in perioperative therapy to consider. Lesions T2 or greater, or with evidence of lymph node disease, are typically treated first with systemic therapy in the West, unlike in the East where surgical resection is typically performed, even for advanced gastric cancer. [23] Theoretical advantages for pre-operative therapy include: demonstration of an *in vivo* response to therapy, treatment of occult micrometastatic disease, better health of patients who may subsequently receive the full chemotherapy regimen, and increased likelihood of margin-negative surgical resection of tumor.

The British medical research council adjuvant gastric cancer infusional chemotherapy (MAGIC) trial introduced neoadjuvant chemotherapy as standard of care in the West. The trial demonstrated that patients with operable gastric, esophageal, and gastroesophageal cancer had improved survival when treated with preoperative and postoperative chemotherapy, 23% with surgery-alone versus 36% with surgery and chemotherapy. [24] In addition, the authors illustrated a higher curative resection rate (79% *vs*.70%, P=0.03) for patients who underwent neoadjuvant therapy. This increase in curative resection rate [R0 resection] for neoadjuvant therapy is mirrored in other studies as well. [25] While this approach reflects the treatment philosophy in the West, in the East the results were criticized because of the inclusion of esophageal cancers and the limited extent of lymphadenectomy in surgical treatment. It should be noted, however, that phase II and phase III trials of preoperative S-1 and cisplatin in Japanese series, including the extended lymphadenectomy, demonstrated improved survival compared to historical controls. [26] For patients with bulky nodal or para-aortic nodal disease, improved overall survival was also observed when randomized to neoadjuvant S-1 and cisplatin followed by surgery with an extended lymphadenectomy, but further trials are under way [27].

5. Conclusions

Although etiologic and pathologic differences exist in the presentation of gastric cancer treated in the West versus the East, surgical techniques developed in countries of high-incidence have become more universal. It is widely accepted that gastrectomy with a modified D2 lymphadenectomy (sparing the distal pancreas and spleen) confers adequate staging information, with the goal of obtaining a minimum of 15 lymph nodes. As minimally-invasive techniques continue to be developed, oncologic safety and equivalence to the standard open gastrectomy remains to be seen. With better efficacy of systemic chemotherapy, more aggressive approaches to surgical resection, including cytoreduction and HIPEC, can also be considered in selected patients. These techniques appear to be applicable to patients in both the Eastern and Western hemispheres.

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