



The role of surgery in the current treatment of gastric carcinoma

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Abstract

Surgery currently is the only curative option in the treatment of gastric cancer. For early gastric cancer, an endoscopic mucosal resection (EMR) is adequate for intramucosal cancer less than 2 cm in diameter without ulcer. For early cancers ineligible for EMR, limited surgical operation (proximal gastrectomy, segmental resection, and pylorus-preserving distal gastrectomy) can be recommended to reduce surgical risk and achieve improvements in quality of life without decreasing survival. Subtotal/total gastrectomy plus D2 lymph node dissection is the standard surgery for advanced gastric cancer in Japan. Pancreas-preserving total gastrectomy is recommended due to the reduced risk of pancreatic fistula and post-operative diabetes. Regarding extended surgery, results of a phase III study to evaluate the role of paraaortic node dissection will be analyzed in a few years' time after the accrual of more than 500 patients in a Japan Clinical Oncology Group (JCOG) study. For scirrhous gastric cancer, left upper abdominal exenteration appears to be associated with improved survival and should be tested in another controlled trial.

Key words Gastric carcinoma · EMR · Proximal gastrectomy · Segmental resection · Left upper abdominal exenteration

Introduction

As with other tumors, the prognosis in gastric cancer is clearly related to stage. In Japan, where extended lymph node dissection had been practiced nationwide for several years, exemplary clinical data in terms of accurate clinical staging and case volume have been available. According to these data, 5-year survival rates following surgical resection may exceed 90% in stage-I

patients, while in patients with the most advanced disease, the corresponding figure is less than 20% [1].

Early gastric cancer

Natural history

Five-year survival rate and median survival time in a case series consisting of 56 patients who refused treatment following endoscopic diagnosis of early gastric cancer were 66% and 77 months, respectively [2]. However, in a small proportion of patients, advanced gastric cancer did not develop even after 10 years. This may reflect the fact that interpretation of histologic findings of certain mucosal lesions could vary among pathologists [3]. Consequently, the diagnosis of a single lesion could range from severe dysplasia to mucosal cancer of the intestinal type, depending on the diagnostic criteria of the pathologists. In general, a Japanese pathologist is more inclined to diagnose these controversial lesions as malignant.

Limited surgery

Endoscopic mucosal resection (EMR) has been performed as a standard procedure for a well-differentiated cancer of less than 2.0 cm diameter without ulcer, based on a general agreement that lymph node metastases are not found in cancers that satisfy these criteria [4]. Early-stage cancers that, nevertheless, do not satisfy these strict criteria may suffer from nodal spread, and the recommended procedure for these lesions is gastrectomy with co-resection of perigastric lymph nodes and lymph nodes at the base of the left gastric artery (no. 7 by the *Japanese classification of gastric carcinoma* [5]). This procedure is defined as “modified A or D1+alpha” by the gastric cancer treatment guidelines compiled by the Japan Gastric Cancer Association in 2001. Recently,

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improvements in postoperative gastric function have been explored through the preservation of various structures, such as the pyloric ring and hepatic and celiac branches of the vagal nerve, and pylorus-preserving gastrectomy has been preferred by some surgeons for lesions in the lower and middle-third of the stomach [6–9]. An even less aggressive approach that consists of a minimal resection of the stomach plus co-resection of the neighboring lymph nodes (limited surgery) could be proposed. Limited surgery in this context would include proximal gastrectomy for cancers in the upper stomach and segmental resection for cancers in the middle-third [10].

We conducted a single-institutional clinical phase II trial of proximal gastrectomy with limited lymphadenectomy for cancer that met the following criteria: preoperative diagnosis of T1 stage, less than 5 cm diameter, located in the upper third of the stomach, and ineligible for EMR [6]. Thirty-four patients were accrued, and proximal gastrectomy of one-third to one-half of the upper stomach was performed, together with D0–1 lymph node dissection. The hepatic branch of the vagal nerve was preserved. Reconstruction was performed with jejunum interposition in 21 patients and interposition of the jejunal pouch in 13 patients. Compared with a historical control consisting of 40 patients who underwent total gastrectomy, blood loss during surgery was smaller in the proximal gastrectomy group (300 ml vs 555 ml; $P < 0.05$). Among the patients treated with proximal gastrectomy, anastomotic failure occurred in only 1 patient, whereas pancreatic fistula, various types of abdominal infection, anastomotic stenosis, and anastomotic dehiscence occurred in 6, 4, 3, and 2 patients, respectively, among the patients treated with total gastrectomy. Thus, the incidence of postoperative complications was significantly lower in patients treated with limited surgery ($P < 0.05$) [11].

A phase II study of segmental resection also was carried out. T1 stage cancer with a diameter of less than 5 cm and located in the middle third of the stomach was eligible, and 50 patients were accrued. The lesion was resected segmentally, accompanied by D0–1 lymph node dissection, while the omentum and hepatic and celiac branches of the vagal nerve were preserved. A comparison was undertaken between these patients and 50 patients who underwent distal gastrectomy. Operative blood loss was significantly smaller in the segmental gastrectomy group (239 ml vs 342 ml; $P < 0.05$). Among patients who underwent distal gastrectomy, postsurgical complications (anastomotic failure, stenosis, infection, and pancreatic fistula) were observed in 7 patients (14%) and cholelithiasis in 8 patients (16%). In the group treated with segmental gastrectomy, postoperative complication and cholelithiasis were each observed

in 1 patient (2%), and the incidences were significantly lower in this group ($P < 0.05$) [12].

Advanced gastric cancer

Standard operation

In more advanced cases (T2–T3), subtotal or total gastrectomy with D2 lymph node dissection is the standard treatment in Japan. The standard operation has been recommended when potentially curative resection is considered possible without apparent need for resection of the adjacent organs or paraaortic lymph nodes. The stage-stratified survival rates following this procedure appear to be better than those in Western countries, although the data may be biased by stage migration [13].

Pancreas-preserving total gastrectomy

The role of pancreato-splenectomy in systemic dissection of lymph nodes at the splenic hilus and along the splenic artery (lymph node stations nos. 10 and 11) remains ambiguous, despite it being recommended by earlier versions of the *Japanese classification of gastric carcinoma*. We conducted a phase III study that compared the postoperative outcome of patients treated with total gastrectomy and pancreatoco-splenectomy with that of those treated with pancreas-preserving total gastrectomy [14]. Eligibility criteria included gastric cancer which invades as far as or beyond the muscularis propria (T2, T3) but does not involve the pancreas, location in the upper or middle third of the stomach, patient age less than 70 years, and absence of gross metastasis to the no. 11 lymph nodes. Pancreas-preserving total gastrectomy, also known as Maruyama's procedure [15], necessitates resection of the splenic artery and spleen en bloc with the lymph nodes without resection of the distal pancreas. The splenic artery in this case is dissected distal to the dorsal pancreatic artery. There was no difference between the two procedures in terms of the amount of operative blood loss and the incidence of postoperative complications. The number of resected lymph nodes at station no. 11 also was similar between the two groups. The incidence of diabetes mellitus or impaired glucose tolerance was higher in the patients treated with pancreatoco-splenectomy, at 1 year after surgery. Our results, together with findings by the European D1 vs D2 trials [16], suggest that resection of the distal pancreas should not be a part of standard treatment for T2–T3 gastric cancer. Whether or not to routinely perform splenectomy should be the next issue to be tested in a trial. Such a trial has been prepared as a multi-institutional phase III study by the Japan Clinical Oncology Group (JCOG), and the patient accrual started in 2002.

Thoracotomy vs transhiatal approach for treatment of cancer of the cardia

Another issue that has been debated is whether left thoracotomy is necessary for the treatment of advanced cancer invading the esophagus in order to perform sufficient mediastinal lymphadenectomy. In 1995, the JCOG launched a trial in which patients with carcinoma of the cardia with esophageal invasion less than 3 cm are randomized into a left-thoracotomy group or a group treated with the transhiatal approach. The primary endpoint of this phase III study is the overall survival rate. The study is still ongoing because of poor patient accrual, due in part to the relative rarity of cancer of the cardia in Japan [17]. In the meantime, no apparent breakthrough in terms of surgical technique has been reported for this population.

Extended operation

An unsolved problem that continues to attract the interest of surgeons in Japan is the role of super-extended lymph node dissection that involves systemic resection of the paraaortic lymph node. Another important topic is the benefit of performing left upper abdominal exenteration (LUAE), an extended total gastrectomy with co-resection of the pancreas, spleen, transverse colon, gallbladder, and left adrenal gland, for scirrhous type gastric carcinoma. The LUAE has been associated with improved survival rates in stage III scirrhous type cancer in a phase II setting [18].

The role of paraaortic node dissection

A phase III study comparing paraaortic node dissection (D3 dissection) with D2 dissection was launched by the JCOG in 1995. Patients with advanced cancer that invades as far as or beyond the subserosa, with no evidence of distant metastasis, with negative findings for peritoneal washing cytology, and with potential for curative resection were registered during surgery. The primary endpoint was the overall survival. Patient accrual was completed in 2001 with over 500 patients randomized into the two groups to detect a difference in 5-year survival rate of more than 8%. There were significant increases in the operative blood loss and duration of the operation among the D3 group patients, but no increase in the operative mortality was observed [19]. A few more years of follow-up are needed before the final survival analysis.

Extended surgery for scirrhous gastric cancer

A phase II study had been carried out on the extended operation for patients with scirrhous or linitis plastica-type gastric cancer. The extended surgical procedure tested in this trial was LUAE plus Appleby's procedure. LUAE was performed with intent to remove micro-

scopic invasion to the retroperitoneum [20]. Thirty patients with scirrhous-type gastric cancer with a potential for curative operation were registered and underwent LUAE. Two cases of postoperative death were observed, along with a high incidence of pancreatic fistula. One of the operative deaths was due to severe liver dysfunction and the other was due to multiple organ failure secondary to severe pancreatitis. Appleby's procedure, presumably, reduced blood supply to the liver and the pancreas. We abandoned Appleby's procedure after this trial, and no more surgical deaths were observed. Before 1983, the year the phase II study started, the 5-year survival rates of the patients with stage III scirrhous cancer treated with total gastrectomy and pancreatico-splenectomy were between 15% and 20%. During the phase II study of LUAE, the 5-year survival of the similar patient population reached 40%. Various adjuvant chemotherapies had been conducted for patients with scirrhous cancer before and after 1983, but they were considered to have had little, if any, influence on the survival of the patients, because no chemotherapeutic regimen has been found to improve the survival of scirrhous cancer significantly. A phase III study is now needed to confirm the survival benefit of LUAE demonstrated in our phase II study [20].

Conclusion

Curative surgery is the only treatment modality for gastric carcinoma with potential for cure. In Japan, D2 resection had long been a standard procedure for all patients with gastric carcinoma, resulting in superior stage-by-stage survival results compared with Western counterparts. Recently, several Japanese investigators have attempted a more extensive surgical approach with wider lymph node dissection and co-resection of adjacent organs for locally advanced cancer, because locoregional failures occur even after the D2 resection. In the meantime, formal D2 resection was discreetly abandoned, and various types of limited surgery have been introduced for early-stage cancer, for which a 5-year survival rate of over 90% had been obtained by the D2 resection. Several phase II studies suggest the potential benefits of limited surgery for patients with early-stage disease in terms of a decrease in surgical complications, while a survival benefit of extended surgery for advanced cancer also has been suggested. Multi-institutional phase III studies to confirm the benefits associated with these novel procedures, however, have been lacking. A nationwide phase III study to evaluate the survival benefit of paraaortic lymph node dissection for locally advanced cancer became the first Japanese phase III study testing a surgical tech-

nique to complete patient accrual, and the results of final survival analyses are eagerly awaited.

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