EXTENT OF RESECTION, CONSEQUENT DUODENAL FOOD PASSAGE RECONSTRUCTION, AND POSTOPERATIVE ADJUVANT THERAPY FOR RESECTABLE MIDDLE GASTRIC CARCINOMA WITH D2 LYMPH NODE DISSECTION

Kazuhito Nabeshima, Kyoji Ogoshi, Yuichi Okamoto, Mari Morita, Kenji Nakamura, Kunihiro Iwata, Yasumasa Kondoh, and Hiroyasu Makuuchi

Department of Surgery, Tokai University School of Medicine, Kanagawa, Japan

Key Words: Duodenal food passage reconstruction, gastric resection, middle gastric cancer, postoperative adjuvant therapy, stages of cancer

Abstract

A consecutive series of 570 patients with middle gastric cancer were evaluated in order to assess their prognosis, focusing on the relationship among the extent of gastric resection, consequent duodenal passage reconstruction, and postoperative adjuvant therapy.

These patients underwent total, subtotal (distal or proximal) gastrectomy between Aug. 1974 and May 1997. Patients receiving subtotal gastrectomy had significantly better survival than those receiving total gastrectomy in stage 1A and 3A gastric cancer. On the other hand, patients with duodenal food passage (DFP)
reconstruction had better survival than those without DFP reconstruction, though the difference between these groups was not significant.

Multivariate analysis revealed that the duodenal food passage and the extent of the gastric resection were independent prognostic variables; in patients who underwent only gastrectomy, the extent of resection and DFP were independent prognostic variables, whereas in patients who underwent gastrectomy with postoperative adjuvant therapy, these two factors were not independent prognostic variables. Though the actual mechanism behind this difference is unclear, our findings indicate that gastric surgeons must carefully consider among the surgical resection procedures when treating adenocarcinoma of the middle gastric cancer.

Introduction

Since the first gastric resection performed by Theodor Billroth in 1881, several different surgical techniques have been developed, and much discussion has arisen over the treatment of choice for middle gastric cancer; namely, what is the suitable extent of resection (distal, proximal, or total gastrectomy). However, many controlled studies have failed to confirm the theoretical advantage of retaining the minimal amount of the stomach (Espat and Karpeh 1998). The end points of many studies were operation time, intra- and postoperative complications, patient body weight, functional assessment, and quality of life. To our knowledge, from the viewpoint of long-term survival in carcinoma of the middle stomach, previous reports have failed to determine the best method of surgical therapy. This study analyzed the experience of a single institution in the treatment of carcinoma of the middle stomach with the aim of assessing the best principal method of surgical therapy and its long-term outcome, and supposing that patients receiving partial or subtotal (distal or proximal) gastrectomy (DG or PG, respectively) with DFP reconstruction might show better survival rates than those who received total gastrectomy (TG) without DFP reconstruction.
Patients

The study group consisted of a consecutive series of 570 patients who underwent DG, PG, or TG with D2 lymph node dissection for adenocarcinoma of the middle stomach with or without DFP reconstruction between Aug. 1974 and May 1997. The use of postoperative adjuvant therapy was made based on discussion between patients and attending doctors, or on the chief surgeon’s decision.

The clinicopathological variables we analyzed included age at time of operation, gender, location of cancer, histology, lymph node metastasis, and depth of cancer. Patient age ranged from 21 to 88 years (median: 56 years), and 70.7% were men. Pathological diagnosis and classification of resected gastric cancer tissue and removed lymph nodes were carried out according to the general rules for gastric cancer study in surgery and pathology in Japan (Japanese Research Society for Gastric Cancer, 1984) and staging by pTNM classification (UICC 1987).

Surgical techniques

In proximal gastrectomy, the stomach was transected 1.0 cm orally from the fundic ring to the line that connected 1.0 to 2.0 cm distal from the pyloric ring in the lesser curvature, and 10 cm distal from the pyloric ring, thereby preserving two or three marginal branches of the right gastroepiploic artery and vein in the greater curvature. These operations include a resection of the lesser and greater omentum. The amount of remaining stomach is almost similar in distal and proximal gastrectomies.

Extent of lymph node dissection

In PG with D2, lymph nodes along the right gastroepiploic artery and infrapyloric lymph nodes (No.4d and 6) were removed skeletally, preserving two or three branches of the right gastroepiploic artery and vein. The grade of the extent of lymph
node dissection was similar among total gastrectomy procedures, and included the removal of the lymph nodes around the stomach. When we preserved the spleen in cases of D2, the lymph nodes at the splenic hilum (No.10) and along the splenic artery (No.11) were also removed skeletally.

**Adjuvant therapy**

One hundred and thirty-two patients received adjuvant postoperative chemotherapy, 177 patients received adjuvant immunochemotherapy, and 207 patients received only gastrectomy. In the chemotherapy group, various fluoropyrimidines, such as N1-(2'-primotetrahydrofuryl)-5-fluorouracil (Futraful; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) at 600 mg/day, 5-fluorouracil (Kyowa Hakko Kogyo Co. Ltd, Tokyo, Japan) at 150 mg/day, or UFT (a 1:4 mixture of tegafur and uracil) (Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) at 300 mg/day, were administered orally from day 14 after surgery. In the immunotherapy group, PSK (Krestin; Kureha Chemical Industry Co. Ltd., and Tokyo, Japan) was administered orally at a dose of 3.0 g/day from day 14 after gastrectomy. The nonspecific immunomodulator PSK is prepared from Coriolus vesicolor (Fr.) Quel, one of the Basidiomycetes. In Japanese clinical trials of PSK therapy in patients with gastric cancer, this agent was effective when combined with chemotherapy (Nakazato, Koike et al., 1994, Ogoshi, Satou et al., 1995).

**Statistical analysis**

Mean values were compared by Student’s t-test. The chi-square test was used to compare the prevalence of characteristics. Results were considered significant when the P value (2-tailed) was less than 0.05. Survival curves were calculated using the Kaplan-Meier product-limit estimate, and differences in survival were assessed by the log-rank test. P values of less than 0.05 were considered significant. In the Cox multivariate
logistic regression analysis, variables such as age at operation (under 64 years old vs. over 65 years old), sex (female vs male), depth of tumor (t1 and t2 vs. t3 and t4), histologic type (well differentiated vs. undifferentiated adenocarcinoma), lymph node metastasis (n (-) vs. n (+)), residual tumor (R1 and R2 vs. R0), postoperative adjuvant therapy (no adjuvant therapy vs. postoperative adjuvant therapy), condition of the duodenal food passage DFP(-) vs. DFP(+), and extent of gastric resection (subtotal (distal or proximal) vs. total gastrectomy) were evaluated to assess which prognostic independent factors were significant (significance level was set at .05), and 95% confidence intervals (CI) were calculated.

All statistical analyses were carried out using SPSS 10.0 software (SPSS Inc., Chicago, USA).

Results

Patient characteristics

Characteristics of the 570 gastric cancer patients are listed in Table I according to the operative procedures. One (0.2%) patient who underwent distal gastrectomy with Billroth I died within 30 days of surgery. Four hundred and thirty-one patients underwent DG, 37 PG, and 102 TG. Splenectomies were performed in 7/468 (1.5%) and in 47/102 (46.1%) patients who underwent DG and TG, respectively. Patients with a positive proximal margin of tumor were 2/468 (0.4%) and 2/102 (2.0%) of those receiving DG and TG, respectively, and patients with a positive distal margin were 3/468 (0.6%) and 1/102 (1.0%) of those receiving DG and TG, respectively.

Survival curves

The 10-year survival rates of patients who underwent DG with Billroth I (BI), Billroth II (BII), and double tract (DT) reconstructions were 78.6%, 70.7%, and 91.4%,
respectively, and those who underwent PG with interposition (IP) and DT reconstructions were 87.5% and 70.2%, respectively. The 10-year survival rates of patients who underwent TG with Roux-Y (RY), interposition (IP), and DT reconstructions were 35.3%, 60.0%, and 48.2%, respectively. Patients who underwent TG with RY showed a worse outcome than those who received other surgical procedures. Significant differences were observed among patients receiving DG with BII vs. those receiving DG with DT, those receiving TG with RY, and those receiving TG with DT (log rank test, p = 0.01, p = 0.0006, and p = 0.0411, respectively); those receiving DG with BI vs. those receiving TG with RY; and those receiving TG with DT (log rank test, p < 0.0001, and p < 0.0001, respectively), those receiving DG with DT vs those receiving TG with RY; those receiving TG with IP, and those receiving TG with DT (log rank test, p < 0.0001, p = 0.0003, and p < 0.0001, respectively), those receiving PG with DT vs those receiving TG with RY, and those receiving TG with DT (log-rank test, p = 0.0004, and p = 0.0106, respectively) and finally, those receiving PG with IP vs those receiving TG with RY (log-rank test, p = 0.0119).

**Extent of gastric resection and DFPR**

The 10-year survival rates of patients receiving DG, PG, and TG in stages 1A, 1B, 2, 3A, 3B, and 4 were 90.8%, 84.4%, and 69.8%; 80.5%, 66.7%, and 71.4%; 47.9%, 75.0%, and 47.6%; 56.5%, 50.0%, and 29.4%; 66.7%, 100%, and 27.3%; 22.9%, -, and 9.7%, respectively. Significant differences were observed between DG and TG in stages 1A and 3A (log-rank test, p = 0.001, and p = 0.01, respectively).

The 10-year survival rates of patients receiving gastrectomy with IP, DT, and RY in stages 1A, 1B, 2, 3A, 3B, and 4 were 90.8%, 85.1%, and 78.1%; 75.6%, 92.9%, and 76.2%; 53.9%, 36.4%, and 27.8%; 51.4%, 55.6%, and 27.3%; 71.4%, 50.0%, and
TABLE I

Characteristics of 570 patients with middle gastric cancer, arranged according to the surgical therapies.

<table>
<thead>
<tr>
<th>Age (range)</th>
<th>Distal Gastrectomy</th>
<th>Proximal Gastrectomy</th>
<th>Total Gastrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Billroth I (n=328)</td>
<td>Billroth II (n=42)</td>
<td>Double tract (n=83)</td>
</tr>
<tr>
<td>56 (27-80)</td>
<td>56</td>
<td>57 (34-80)</td>
<td>59(23-82)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female 93 15 14 8 4 23 6 4 167</th>
<th>Male 233 27 49 18 7 33 9 27 403</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTNM stage</td>
<td>1A 199 26 41 18 8 12 5 10 319</td>
<td>1B 57 6 13 3 0 8 1 3 91</td>
</tr>
<tr>
<td></td>
<td>2 32 3 4 3 1 6 2 4 55</td>
<td>3A 18 3 2 1 2 8 3 6 43</td>
</tr>
<tr>
<td></td>
<td>3B 6 0 0 1 3 7 1 3 18</td>
<td>4 14 4 3 0 0 15 3 5 44</td>
</tr>
<tr>
<td>Residual Tumor</td>
<td>R1-R2 21 4 5 1 0 18 3 5 57</td>
<td>R0 305 38 58 25 11 38 12 26 513</td>
</tr>
<tr>
<td>Histology</td>
<td>diff 154 19 28 11 7 15 4 12 250</td>
<td>undiff 172 23 35 15 4 41 11 19 320</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>n(-) 253 31 32 20 8 21 7 13 405</td>
<td>n(+) 73 11 11 6 3 35 8 18 165</td>
</tr>
<tr>
<td>Therapy</td>
<td>Gastrectomy alone 149 22 31 9 8 22 4 9 254</td>
<td>Gastrectomy+ChemoTX 70 17 14 9 0 20 4 11 145</td>
</tr>
<tr>
<td></td>
<td>Gastrectomy+ImmuoTX 107 3 18 8 3 14 7 11 171</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE II
Results of Cox’s multivariate analysis of 570 patients.

<table>
<thead>
<tr>
<th></th>
<th>Sig.</th>
<th>R.R.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>0.0021</td>
<td>1.527</td>
<td>1.166</td>
</tr>
<tr>
<td>Duodenal passage</td>
<td>0.0177</td>
<td>1.570</td>
<td>1.081</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>&lt;0.0001</td>
<td>1.821</td>
<td>1.392</td>
</tr>
<tr>
<td>Depth of tumor</td>
<td>&lt;0.0001</td>
<td>1.754</td>
<td>1.340</td>
</tr>
<tr>
<td>Histology</td>
<td>NS</td>
<td>1.102</td>
<td>0.810</td>
</tr>
<tr>
<td>Gender</td>
<td>0.0011</td>
<td>1.495</td>
<td>1.175</td>
</tr>
<tr>
<td>Therapy</td>
<td>NS</td>
<td>1.146</td>
<td>0.818</td>
</tr>
<tr>
<td>Residual tumor</td>
<td>&lt;0.0001</td>
<td>3.372</td>
<td>2.247</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>2.710</td>
<td>2.162</td>
</tr>
</tbody>
</table>

### TABLE III
Results of Cox’s multivariate analysis of patients, arranged according to the postoperative adjuvant therapy.

<table>
<thead>
<tr>
<th></th>
<th>Gastrectomy alone</th>
<th>Gastrectomy with postoperative adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sig.</td>
<td>R.R.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>0.0009</td>
<td>2.143</td>
</tr>
<tr>
<td>Duodenal passage</td>
<td>0.0383</td>
<td>1.885</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>&lt;0.0001</td>
<td>3.821</td>
</tr>
<tr>
<td>Depth of tumor</td>
<td>0.0488</td>
<td>1.824</td>
</tr>
<tr>
<td>Histology</td>
<td>NS</td>
<td>0.838</td>
</tr>
<tr>
<td>Gender</td>
<td>0.0103</td>
<td>1.728</td>
</tr>
<tr>
<td>Residual tumor</td>
<td>NS</td>
<td>2.406</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>4.077</td>
</tr>
</tbody>
</table>
Figure 1: Survival curves according to the operative procedures.
Figure 2: Survival curves of patients who underwent TG, DG, and PG according to the stages.
Figure 2: Survival curves of patients who underwent TG, DG, and PG according to the stages.
14.3%; 23.5%, 12.5%, and 12.0%, respectively. There were no significant differences among these groups. Table showed the 10-year survival rates of patients receiving DG and TG and those receiving DFP reconstruction (+) and DFP reconstruction (-) according to the pTNM stages.

**Multivariate analysis**

This multivariate analysis revealed that the strongest independent prognostic variable is residual tumor, and that age at operation, extent of gastric resection, duodenal food passage, depth of tumor, and lymph node metastasis were stronger significant independent prognostic factors in cases of 516 patients. The relative risk for these variables was 3.510, 2.196, 1.716, 1.655, 1.510, and 1.454, respectively (Table III).

In patients who underwent only gastrectomy, the extent of gastric resection and the duodenal food passage were independent prognostic variables, whereas in those who underwent gastrectomy with postoperative adjuvant therapy, extent of gastric resection and duodenal food passage were not significant prognostic factors (Table III).

**Discussion**

The choice of TG, DG, or PG for adenocarcinoma of the proximal stomach depends, in general, on tumor localization, and TG may theoretically provide a longer distal and proximal margin and a more complete lymphadenectomy, offering improved patient survival, whereas the clinical relevance of these factors is uncertain. The following three types of gastric resections for adenocarcinoma of the middle stomach are considered theoretically: 1) total gastrectomy, 2) subtotal proximal gastrectomy, and 3) subtotal distal gastrectomy with en bloc lymph node dissection. Most surgeons favor the use of subtotal distal gastrectomy because of its technical simplicity, reserving the other
procedures for lesions of the middle stomach, and the clinical importance of a TG is also probably related to the more complete staging afforded by the lymphadenectomy, rather than to provision of a survival advantage.

Shiu, Papacristou et al., (1980) failed to demonstrate that patients who underwent total gastrectomy showed better survival rates than those receiving subtotal gastrectomy in all TNM stages, though they did find that those who underwent total gastrectomy showed better survival rates than those who underwent subtotal gastrectomy in early-stage tumors (T1-4 N0 M0 and T1-4 N1 M0).

Several prospective controlled trials also failed to demonstrate that the extent of gastric resection was a significant predictor of long-term survival (Gouzi, Huguier et al., 1988; Haugstvedt, Viste et al., 1993; Bozzetti, Marubini et al., 1999). However, several retrospective studies demonstrated that DG offered a significantly better survival rate than TG (Gennari, Bozzetti et al., 1986; Robertson, Chung et al., 1994). On the other hand, a significantly better quality of life has been reported in patients who underwent DG in comparison with that of those who underwent subtotal gastrectomy (Davies, Johnston et al., 1998; Jentschura, Winkler, et al., 1997).

On the other hand, although gastro-duodenal anastomosis (Billroth I) after DG is in general regarded by many surgeons as more physiologic than gastro-jejunal anastomosis (Billroth II), diversion of the duodenal content via a Roux-en-Y end-to-side anastomosis is considered to be the standard procedure after TG, especially in Western countries. Chareton, Landen et al., (1996) and Fuchs, Thiede et al., (1995) also failed to demonstrate that the reconstruction of the duodenal passage was a significant predictor of long-term survival, although several studies have proposed that the theoretical advantages of this surgical procedure are that patients will have a significantly better quality of life,
higher body weight, and better physiologic regulation of gastrointestinal hormones (Del Gaudio, Marzo et al., 1991; Schwarz, Buchler, et al., 1996).

We previously reported that patients who underwent partial (distal or proximal) gastrectomy and those with duodenal passage showed higher CD4/8 ratio levels concomitant with higher levels of CD4+ cells and lower levels of CD8+ cells after gastrectomy, and that these patients had better outcomes than did patients who underwent TG. Consequently, the former also had better outcomes than those of patients who underwent gastrectomy without duodenal passage reconstructions (Iwata, Ogoshi et al., 2001). We also previously reported that when tumors were located in the lower third of the stomach, patients who underwent DG showed better outcome than those who underwent TG or DFP reconstruction, especially when they received postoperative adjuvant therapies after gastrectomy (Nakamura, Ogoshi 2002).

Several reports have analyzed the relationship among the extent of gastric resection, DFP reconstruction, and postoperative adjuvant therapy from the viewpoint of long-term survival in middle gastric cancer. The present study revealed that when tumors were located even in the middle third of the stomach, patients receiving PG showed better outcomes than those of patients receiving TG. It is well known that the upper part of the stomach contains predominantly mucin-secreting cells. The middle part (i.e., body) contains mucoid cells, chief cells, and parietal cells. The lower part (pyloric part) is composed of mucus-producing cells and endocrine cells. The findings we observed are probably related to cancer biology and carcinogenic factors as well as to surgical therapeutic responses. Though the actual mechanism behind our results is unclear, our findings indicate that the relationship among the extent of gastric resection, DFPR, and oral administration of chemotherapeutic agents potentially plays an important role in the
strategy for middle gastric cancer, depending on the carcinogenesis of the middle and
distal gastric cancer. Further studies should focus on the extent of gastric resection,
DFPR, postoperative adjuvant therapy, and carcinogenesis to determine the resection of
choice for middle gastric cancer.

In conclusion, gastric surgeons must exercise care in selecting among surgical
resection procedures and postoperative adjuvant therapy when treating adenocarcinoma
of middle gastric cancer.

References
Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a
multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group.
randomized trial comparing Billroth I and Billroth II procedures for carcinoma of
Davies, J., Johnston, D., Sue-Ling, H., Young, S., May, J., Griffith, J., Miller, G. and
Nakamura, K., Ogoshi, K., Okamoto, Y., Nabeshima, K., Morita, M., Iwata, K., Kondoh,
Y. and Makuuchi, H. (2002). Postoperative adjuvant therapy is an important
factor for surgical management in resectable distal gastric carcinoma with D2
Gennari, L., Bozzetti, F., Bonfanti, G., Morabito, A., Bufalino, R., Doci, R. and
Andreola, S. (1986). Subtotal versus total gastrectomy for cancer of the lower
two-thirds of the stomach: a new approach to an old problem. Br. J. Surg. 73:534-
538.


