Four Hundred Consecutive Total Gastrectomies for Gastric Cancer

A Single-Institution Experience

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Hypothesis: Although total gastrectomy (TG) has been generally accepted as the treatment of choice for upper and middle gastric cancers, some issues are still debated. The objective of this retrospective study was to analyze short- and long-term results of TG (radical and palliative) in a series of 400 patients consecutively admitted to our surgical unit.

Design: Retrospective cohort study.

Setting: Primary and referral hospital care.

Patients: Hospital records of 400 patients who consecutively underwent TG between January 1981 and June 2005 were reviewed.

Main Outcome Measures: Surgical complications and survival.

Results: Three hundred twelve patients underwent radical procedures, and 88 patients underwent palliative procedures. The incidence of postoperative complications was higher among patients who underwent palliative TG (33 of 88 [37.5%]) compared with patients who underwent curative TG (75 of 312 [24.0%]) (P=.01). Mortality was higher among patients who underwent palliative TG (6 of 88 [6.8%]) compared with patients who underwent curative TG (11 of 312 [3.5%]) (P=.18). Five-year survival was 61.8% after curative TG and 12.8% after palliative TG. Ten-year survival was 47.3% after curative TG and 0.0% after palliative TG.

Conclusions: This study among 400 consecutive patients who underwent TG at the same surgical unit shows that this surgical procedure in experienced hands can lead to excellent short- and long-term results.

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TOTAL GASTRECTOMY (TG) has been generally accepted as the treatment of choice for upper and middle gastric cancers. It remains the sole surgical option for patients with linitis plastica-type lesions involving most of the stomach. However, many issues are still a matter of debate. These include the need for pancreaticosplenectomy to achieve complete D2 lymph node dissection, the opportunity to perform TG whenever feasible in patients with stage IV gastric cancer, and the extent of nodal dissection (limited D1 vs extended D2/D3) to obtain a curative (R0) resection.1

To answer these questions, we performed a retrospective study among a series of 400 patients who consecutively underwent TG (radical and palliative) for gastric cancer at our surgical unit. We analyzed short- and long-term results of these surgical procedures.

METHODS

A review of the prospective database of gastric adenocarcinomas at the Digestive Surgery Unit, Department of Surgery, Catholic University School of Medicine, Rome, Italy, identified 426 patients who consecutively underwent TG between January 1981 and June 2005. Institutional review board approval was obtained before review of the patients’ medical records. All surgical procedures were performed by the same surgical group (F.P. and G.B.D.). To obtain a homogeneous population for the analysis relative to the type of reconstruction performed during the first operation, 26 patients who underwent resection of the gastric stump were excluded from the study. Therefore, the study population consisted of 400 of 1046 patients (38.2%) with primary gastric cancer observed in our unit during the study period.

We recorded hospital morbidity and mortality, type of treatment (curative vs palliative), histologic type according to Lauren,2 and...
The disease was staged according to the 2002 TNM classification. Based on categories established by the Japanese Gastric Cancer Association, the regional extent of nodal involvement after radical procedures was also recorded. Tumors located proximally were classified according to Siewert and Stein. Because type I tumors were treated by abdominal and thoracic approaches using proximal gastrectomy and subtotal esophagectomy with esophagogastrectomy, only patients with type II and type III tumors were included in the study.

All patients were operated on according to the intent-to-treat method. Those with potentially curable lesions were treated by TG and extended (D2-D3) lymphadenectomy. Patients with stage IV disease and noncurable lesions (distant metastases, peritoneal carcinomatosis, and N4 nodal involvement) at the preoperative evaluation were treated by TG and peri gastric (D1) lymphadenectomy with the intent to control specific symptoms and to obtain survival advantage.

Based on definitive pathologic findings, the potentially curative operations were classified as radical (R0 [microscopic residual disease]) according to the presence or absence of residual tumor. Palliative resection (among patients with stage IV disease) was classified based on R2 macroscopic disease left behind. All patients who underwent TG with curative intent were treated using a pancreas-preserving procedure based on surgeon preference, and only patients with macroscopic infiltration of the pancreatic gland underwent en bloc pancreatic body and tail resection. The pancreas-preserving procedure involved dissection of the entire greater omentum, the superior leaf of the mesocolon, and the serosa of the pancreatic surface. Node dissection was then performed in the infraduodenal and supraduodenal areas and along the retropancreatic region (node region 13 according to the Japanese Gastric Cancer Association), the hepatic pedicle (node region 12), the mesenteric root (node region 14), and the common hepatic (node region 8) and celiac (node region 9) arteries. The left gastric artery (node region 7) was ligated at its origin, and node dissection (node region 11) was extended along the proximal third of the splenic artery, which was ligated distally approximately 5 cm from its origin. The maneuver by Jinnai was performed, and the spleen and the distal pancreas were mobilized and exposed. Finally, the splenic vein was ligated and divided at the splenic hilum, and the spleen (node region 10) and the middle and distal thirds of the splenic artery with the surrounding fatty connective tissue and nodes (node region 11) were removed en bloc with the stomach, gastric omentum, and perigastric nodes (node regions 1-6). At the end of the operation, the surgeon resected all lymph nodes from the surgical specimen and identified their distribution and tumor location according to the classification by the Japanese Gastric Cancer Association.

In most cases, Siewert type II and type III proximal cancers were treated by a subdiaphragmatic approach including the maneuver by Pinotti. The extent of esophageal resection was at least 6 cm (as measured in prefixed fresh specimens immediately after resection).

Intestinal continuity was restored by means of Roux-en-Y esogaugo jejunostomy in all cases. Esophagogjunal anastomosis was performed using a 2-layer manual technique with 3-0 catgut and 3-0 silk and, since 1988, using a 23-mm mechanical circular stapler with a row of external seromuscular sutures with interrupted absorbable stitches. The duodenal stump was closed, and the enteroenteroanastomosis of the Roux-en-Y limb was performed 60 cm distal to the esophagogjunal anastomosis. Duodenal closure and enteroenteroanastomosis were performed using a 2-layer manual technique in all cases.

Patient characteristics are given in Table 1. Three hundred twelve patients underwent potentially curative TG, and 88 patients underwent palliative TG. As expected, some characteristics differed between the 2 treatment groups. The total number of patients who received various schedules of adjuvant chemotherapy was 229 (57.3%) (168 of 312 patients [53.8%] in the curative group and 61 of 88 patients [69.3%] in the palliative group). The primary regimens used were fluorouracil, doxorubicin hydrochloride, and mitomycin C (FAM) in the 1980s and epirubicin hydrochloride, cisplatin, and fluorouracil (ECF) in the 1990s and 2000s, for a mean of 3 cycles after surgery, depending on clinical response or the occurrence of adverse effects.

Survival was calculated after curative and palliative treatment. Patient status was investigated by follow-up examination or by telephone contact. Statistical analysis was performed using commercially available software (SPSS for Windows version 6.01; BMDP Statistical Software, Inc, Los Angeles, California). Results are given as mean (SD). The statistical significance of the difference between mean values was evaluated using the t test. Categorical variables were assessed by the chi² test, using the Fisher exact test correction where appropriate. Survival was calculated according to the actuarial life-table method. Operative deaths were excluded from the survival analysis; therefore, overall survival was calculated in 301 patients after curative treatment and in 82 patients after palliative treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Curative (n=312)</th>
<th>Palliative (n=88)</th>
<th>P Value</th>
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<td>58.1 (12.7)</td>
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<td>53:33</td>
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<td>Tumor location, No. (%)</td>
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<td>Middle third</td>
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<td>24 (27.3)</td>
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<tr>
<td>Whole stomach</td>
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<td>I</td>
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<td>6 (6.8)</td>
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<tr>
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<td>14 (15.9)</td>
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<td>IV</td>
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<tr>
<td>Extensive surgery, No. (%)</td>
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<td>25 (28.4)</td>
<td>.007</td>
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</table>

RESULTS

Patient characteristics are given in Table 1. Three hundred twelve patients underwent potentially curative TG, and 88 patients underwent palliative TG. As expected, some characteristics differed between the 2 treatment groups.
groups. In particular, the numbers of patients with advanced cancer stage, Borrmann type IV tumors, need for extensive surgery, whole-stomach involvement, and diffuse forms according to the Lauren classification were significantly higher among patients undergoing palliative TG. In 74 patients (18.5%), TG was extended to other organs (Table 2). Among patients undergoing TG with curative intent, 296 were treated using a pancreas-preserving procedure, and 16 required a pancreatic body and tail resection. The in-hospital morbidity and mortality rates associated with curative and palliative TG are given in Table 3.

Among patients undergoing TG with curative intent, the incidence of postoperative complications after pancreas-preserving TG was lower than that observed after TG associated with pancreatic resection (69 of 296 [23.3%] vs 6 of 16 [37.5%], P = .20). Similarly, postoperative mortality after pancreas-preserving TG was lower than that observed after TG associated with pancreatic resection (9 of 296 [3.0%] vs 2 of 16 [12.5%], P = .10). No patient developed postoperative pancreatic necrosis after pancreas-preserving TG, and 5 patients (1.7%) experienced pancreatic fistula (output of >10 mL/d, with an amylase level 3 times the normal serum level at 7 days after surgery). In contrast, the incidence of pancreatic fistula was higher after TG associated with pancreatic resection (2 of 16 [12.5%] vs 5 of 296 [1.7%], P = .04), as was the incidence of esophagojejunostomy leak (2 of 16 [12.5%] vs 25 of 296 [8.4%], P = .40).

The incidence of postoperative complications was higher among patients who underwent palliative TG (33 of 88 [37.5%]) compared with patients who underwent potentially curative TG (75 of 312 [24.0%]) (P = .01). Mortality was higher among patients who underwent palliative TG (6 of 88 [6.8%]) compared with patients who underwent potentially curative TG (11 of 312 [3.5%]) (P = .18). During the last 5 years, the operative mortality was 0.0%.

Based on definitive pathologic findings, 14 patients among those who underwent TG with curative intent had microscopic infiltration of the esophageal resection margin (R1 resections). According to the intent-to-treat concept, these patients were included in the curative group for the survival analysis.

The mean number of dissected nodes per operative specimen after curative TG was 51.7 (25.2). Sixty-eight percent (212 of 312) of patients had nodal metastasis (37.2% [116 patients] had N1 involvement, 23.7% [74 patients] had N2 involvement, and 7.1% [22 patients] had N3 involvement). Table 4 gives the mean number of dissected nodes and the percentage of metastatic involvement relative to individual lymph node regions. Three hundred nineteen patients (79.8%) were followed up for at least 5 years after hospital discharge or until death, with an overall follow-up rate of 94.7%. The median follow-up was 30 months (range, 1-245 months) for all patients and 67 months (range, 1-245 months) for survivors.

Five-year survival was 61.8% after curative TG and 12.8% after palliative TG (Figure 1). Among patients who underwent curative resection, 5-year survival according to cancer stage was 100.0% for stage IA disease,
78.6% for stage IB disease, 71.1% for stage II disease, 45.3% for stage IIIA disease, and 31.1% for stage IIIB disease (Figure 2).

Ten-year survival was 47.3% after curative TG and 0.0% after palliative TG (Figure 3). Among patients who underwent curative resection, 10-year survival according to cancer stage was 93.6% for stage IA disease, 57.6% for stage IB disease, 59.3% for stage II disease, 34.6% for stage IIIA disease, and 10.3% for stage IIIB disease (Figure 4).

COMMENT

Results of randomized trials do not support TG for gastric cancer. However, it remains the only option for patients with linitis plastica–type lesions involving most of the stomach and is considered the treatment of choice for upper and middle gastric cancers by many digestive surgeons.

For curative (R0) TG, the need to perform complete D2 lymphadenectomy and the technique used to achieve such a dissection are matters of debate. In prospective randomized trials, extended nodal dissection has not improved overall survival and is associated with a high complication rate. A recent meta-analysis that examined extended vs limited lymph node dissection for adenocarcinoma of the stomach showed no survival benefit and increased postoperative mortality associated with extended node dissection. However, experienced groups from Japanese and Western institutions continue to perform complete D2 lymph node dissection, reporting low complication rates and survival advantages. Similar results have been obtained in recently published prospective studies.

Major criticism regarding Dutch and Medical Research Council prospective trials is that pancreatic resection was routinely performed in the D2 arm, leading to significant morbidity and mortality. The Medical Research Council trial reported significantly higher postoperative morbidity (56% vs 28%, P < .001) and mortality (18% vs 7%, P < .01) associated with pancreas removal. Based on univariate and multivariate analyses of postoperative risk factors, the Dutch Gastric Cancer Group found that distal pancreatectomy was associated with high relative risks of postoperative complications in the univariate model (relative risk, 5.04) and in the multivariate model (relative risk, 3.34).
tal pancreatectomy (performed only when necessary in patients with direct infiltration of the gland) negatively affected postoperative outcomes. Moreover, even in the absence of overt pancreatic fistula, subclinical pancreatic juice leakage after pancreatic resection accumulated near the proximal reconstructive anastomosis, affecting the healing process. To overcome this, authors have stressed that D2 TG should be performed, whenever possible, without distal pancreatectomy using pancreas-preserving techniques. The original technique as described by authors in Japan proposes ligation of the splenic artery at its origin. However, this technique carries the risk of pancreatic necrosis. In fact, the dorsal pancreatic artery usually arises from the proximal third of the splenic artery and joins the posterosuperior pancreaticoduodenal artery (so-called Kirk arcade) after the emergence of the transverse pancreatic artery. In the absence of Kirk arcade (about 40% of cases), the dorsal pancreatic artery is the sole blood supply to the left pancreas. Therefore, ligation of the splenic artery at its origin exposes some patients to risk of pancreatic necrosis.

For this reason, we preserve the proximal third of the splenic artery in all cases of pancreas-preserving TG by ligating the splenic artery approximately 5 cm distally from the root to preserve blood supply to the left pancreas through the dorsal pancreatic artery. Proximal splenic nodes are removed en bloc with those of the left gastric artery, and distal splenic nodes are removed together with the splenic artery, the surrounding fatty tissue, and the spleen (Figure 5). Relative to pancreatic resection, indications for splenectomy without distal pancreatectomy should also be considered. Although 2 recently published randomized studies do not support the use of prophylactic splenectomy to remove macroscopically negative lymph nodes at the splenic hilum in patients undergoing TG, the following should be emphasized: (1) for tumors located at the proximal and middle thirds of the stomach, lymph node regions 10 and 11 belong to compartment II (according to the Japanese Gastric Cancer Association) and may be dissected to obtain a complete D2 dissection and (2) metastases at region 10 and 11 lymph nodes occur in about 10% of cases and correlate with T stage. Given that spleen-preserving dissection of region 10 lymph nodes is technically difficult, it can be argued that splenectomy may be worthwhile, at least in patients with advanced proximal gastric cancer. In the future, indications for splenectomy in association with TG should be tailored to patient T stage.

N stage and R stage, especially for proximally located tumors, are variables that are likely to be affected by surgical technique. Achieving R0 resection for proximal gastric cancer can be challenging because of the propensity for intramural spread. The reported incidence of residual cancer at proximal resection margin ranges from 5% to 35%. Because palpation and gross inspection are unreliable methods to judge the adequacy of resection margin width and because intraoperative frozen section analysis seems inadequate (reported false-negative rates range from 9% to 21%) for T3-T4 tumors. In this context, a clear differentiation between the different types of proximal gastric cancers has fundamental technical implications. Siewert type I tumors always require subtotal esophagectomy, whereas types II and III do not require this procedure, which would compromise the ability to perform radical abdominal dissection to preserve the distal stomach and to restore the continuity of the alimentary tract.

The wide opening of the diaphragmatic hiatus as described by Pinotti facilitates intraoperative procedures (especially for T3 and T4 tumors) based on the esophageal width requirement, which may need to be considerably greater than that derived from examination of postresection specimens. It is well known that, as a consequence of specimen shrinkage, esophageal specimen margin width does not necessarily reflect corresponding intraoperative in situ width before completion of the resection.

With regard to palliative TG for patients with stage IV disease, the present study confirms that palliative resections carry high rates of morbidity and mortality. This is mainly because of the combination of a greater tumor load with invasion into surrounding tissues, often requiring extended resections, and the compromised nutritional status of patients. Regarding survival, it is well recognized that patients who undergo resection experience more favorable outcomes than those who do not undergo resection. Compared with bypass procedures or explorative laparotomy, the survival advantage associated with resectional surgery (including TG) has been demonstrated not only in patients with local tumor spread but also in patients with disseminated distant disease.
Moreover, palliative resections have a positive effect on the quality of life by preventing common complications such as bleeding, obstructions, or perforations. The present study shows that palliative TG, despite higher complication rates and mortality compared with curative TG, is a safe procedure. Therefore, we do not oppose palliative TG for proximal or extensive tumors.

The present study performed among 400 consecutive patients who underwent TG at the same surgical unit shows that this procedure in experienced hands can lead to excellent short- and long-term results. In general, many factors are responsible for recently observed significant decreases in hospital mortality. In patients with preoperative malnutrition, nutritional status can be improved by various parenteral or enteral means. Improvements in the field of anesthesia have reduced anesthetic death to a minimum, and support is readily available in the intensive care unit if postoperative organ failure occurs. Besides these general improvements in perioperative care, refinement of the surgical technique may have contributed to improve early results after TG. The use of the pancreas-preserving procedure and the evolution of anastomotic techniques have reduced the incidence of postoperative surgical complications. Moreover, it has been prospectively demonstrated that routine use of a nasojejunal tube after TG is unjustified and is potentially dangerous.

In our study, the increase in long-term survival after curative TG is probably related to our maximum effort to effect a surgical cure. N and R variables were addressed by routine extended lymphadenectomy and by wide esophageal resection where indicated. The mean number of dissected nodes per operative specimen was high, and the frequency of microscopically infiltrated esophageal margins was low. Finally, the study findings indicate that TG should be performed, whenever possible, in patients with incurable upper and middle gastric cancer, as resectional surgery provides considerable survival advantages. In the future, our improved knowledge of tumor biology, the introduction of tumor markers, and progress in neoadjuvant and adjuvant therapies should improve long-term survival.

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Author Contributions: Study concept and design: Pacelli, Papa, Bossola, and Doglietto. Acquisition of data: Rosa, Tortorelli, and Sanchez. Analysis and interpretation of data: Papa and Covino. Drafting of the manuscript: Rosa, Tortorelli, Sanchez, and Covino. Critical revision of the manuscript for important intellectual content: Pacelli, Papa, Bossola, and Doglietto. Statistical analysis: Covino and Bossola. Administrative, technical, and material support: Tortorelli. Study supervision: Pacelli, Papa, and Bossola. Financial Disclosure: None reported.

REFERENCES


INVITED CRITIQUE

The article by Pacelli et al highlights, once again, the role of high-volume experienced centers in performing complex operations with low morbidity and mortality. The authors are to be commended for their ability to perform TG and pancreas-preserving D2-D3 lymph node dissections with excellent long-term survival (61.8% at 5 years and 47.3% at 10 years). In this study, 95.5% (298 of 312) of patients underwent R0 resection. However, several points required careful attention.

Although TG is no longer considered the standard for gastric cancer, it may be needed in selected patients with proximal lesions or diffuse-type (linitis plastica) gastric cancer to obtain R0 resection. However, the extent of lymphadenectomy in gastric cancer remains controversial. The authors routinely performed pancreas-preserving D2-D3 lymphadenectomy for gastric cancer. Data from several randomized trials and meta-analysis have shown no survival benefit of extended lymphadenectomy. The Dutch Gastric Cancer Group has recently published long-term results with 11-year follow-up and confirmed no survival benefit of D2 vs D1 lymph node dissection except for N2 disease on subset analysis. Splenectomy and pancreatectomy were shown to be significant risk factors for morbidity and inhospital mortality after D2 lymph node dissections in randomized trials. Recent evidence supports the use of the so-called over-D1 lymphadenectomy to obtain adequate lymph nodes for appropriate staging, with selective resection of the pancreas and spleen to obtain R0 resection. In addition, the role for palliative TG seems small, given a recent series showing that most patients with distant metastasis do not require any surgical interventions for symptom control. In the study by Pacelli et al, palliative TG by experienced surgeons carried substantial mortality of 6.8% and morbidity of 37.3%, with unclear benefits. Most patients (69.3%) undergoing palliative TG received adjuvant chemotherapy, and the authors do not address the contribution of adjuvant therapy. Gastric cancer remains a lethal disease worldwide, and future progress will depend on the addition of adjuvant and neoadjuvant regimens such as the regimen used in the recent MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial; as well as better disease stratification with the use of genetic profiles.

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