

REVIEW

## Current role of surgical therapy in gastric cancer

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### Abstract

Surgery is currently the only potentially curative treatment for gastric cancer. Since the inception of the gastrectomy for cancer of the stomach, there has been debate over the bounds of surgical therapy, balancing potential long-term survival with perioperative morbidity and mortality. This review delineates the current role of surgery in preoperative staging, curative resection, and palliative treatment for gastric cancer.

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### INTRODUCTION

Gastric cancer is one of the most common malignancies in the world and is a leading cause of cancer death. Despite some recent advances in neoadjuvant therapy, studies generally have failed to show any improvement in overall or relapse-free survival following adjuvant therapy. Surgical therapy remains as the most effective modality in treating gastric cancer. The goal of this review is to evaluate the optimal role and impact of surgery in regards to staging, resection of primary, regional and locally advanced disease, and palliation of symptoms in patients with incurable gastric cancer.

### STAGING

Laparoscopy has emerged as an essential staging modality prior to gastric resection, identifying unresectable disease in a significant number of patients deemed resectable by current radiographic and endoscopic modalities. The

diagnostic yield of laparoscopy has been improved by the addition of laparoscopic ultrasound and peritoneal cytology.

Stell *et al*<sup>[1]</sup> compared 103 patients with gastric adenocarcinoma who underwent preoperative staging with ultrasound (US), computed tomography (CT), and laparoscopy. Histologic confirmation was obtained at laparotomy ( $n=65$ ) or with percutaneous liver biopsy during laparoscopy ( $n=27$ ). The sensitivity, specificity, and accuracy of laparoscopy in detecting hepatic metastases ( $n=27$ ) was 96%, 100%, and 99%, respectively. Laparoscopy had a sensitivity of 53%, a specificity of 100%, and an accuracy of 65% in detecting nodal metastasis ( $n=49$ ). Peritoneal metastases were histologically confirmed in 13 patients, and laparoscopy was 69% sensitive, 100% specific, and 94% accurate.

Burke *et al*<sup>[2]</sup> reviewed 103 patients who were deemed free from intra-abdominal metastases by CT scan and subsequently underwent laparoscopy. A control group who underwent laparotomy for possible gastric resection and subsequently found to have M1 disease was also reviewed. Laparoscopy accurately staged 94% of these patients. Histologic evidence of metastasis was obtained in 32 patients during laparoscopy. Of the 71 patients who were M0 by laparoscopy, 65 were confirmed by laparotomy. Of the six false negatives, three were missed peritoneal metastases, and three were missed distant nodal metastases, two of which were identified after resection. Of the 32 patients who were M1 on laparoscopy, 4 had chemotherapy followed by resection, 3 had further palliative procedures, and 1 had a mini-laparotomy for additional specimen. The remaining 24 patients went on to have no further operation. When comparing these 24 patients to the control group of 60 patients with M1 disease on laparotomy, the hospital stay was significantly shorter. There was one complication in the laparoscopy group and eight in the laparotomy group; however, this did not reach significance. The authors concluded that laparoscopy is a valuable staging tool that can spare patients with asymptomatic M1 disease a laparotomy, and identify those patients who may benefit from neoadjuvant therapy.

The addition of laparoscopic US has improved the yield of laparoscopy for staging gastric cancer. Hulscher *et al*<sup>[3]</sup> reviewed the utility of laparoscopic US in staging 48 patients with gastric carcinoma of the cardia and esophageal invasion. All of these patients were staged with endoscopic US, percutaneous US of the neck and abdomen, conventional chest radiograph and bronchoscopy if there was extensive proximal invasion. Metastatic

disease was detected and histologically confirmed in 11 patients (23%), 7 detected with laparoscopy alone, and an additional 4 detected by laparoscopic US. Of the patients who went on to laparotomy, two were found to have posterior liver metastases, and two to have unresectable lymph nodes at the base of the celiac axis. Three of these four lesions were detected laparoscopically, but were either not amenable to biopsy due to position, or were negative on laparoscopic biopsy. The authors concluded that laparoscopy is a valuable staging tool for gastric adenocarcinoma of the cardia, and that the addition of US increases the yield, avoiding laparotomy in 23% of patients.

Peritoneal cytology obtained at laparoscopy has proven to be a predictor of post-operative mortality in patients undergoing curative (R0) resection. Bentrem *et al*<sup>41</sup> reviewed 371 patients who underwent staging laparoscopy with peritoneal washings and subsequent R0 resection as a combined procedure. Twenty-four patients (6%) had positive cytology, defined as the presence of adenocarcinoma cells, regardless of quantity. Positive cytology without evidence of macroscopic M1 disease was associated with advanced preoperative T stage and advanced AJCC stage, but not preoperative N stage. The median survival for patients with positive cytology was 15 mo, compared to 98.5 mo for those with negative cytology. On multivariate analysis, preoperative T stage, preoperative N stage, primary tumor site, and peritoneal cytology were significant predictors of survival, with positive cytology showing the highest risk ratio. The authors have altered their practice in response to this information, performing staging laparoscopy as a separate procedure in patients considered high risk (T3/4 and AJCC stage II/III). Those patients found to have positive cytology were then referred for chemotherapy followed by possible resection with intraperitoneal chemotherapy.

Laparoscopy and laparoscopy US are currently accepted as standard pre-operative staging tools. Laparoscopy is significantly more accurate than US and CT in detecting hepatic, nodal and peritoneal metastases. Reports suggest minimal added morbidity and no mortality from laparoscopy. Peritoneal cytology is not widely accepted as a screening tool; however, this is a topic of growing research interest.

## EXTENT OF GASTRIC RESECTION

### *Distal gastric adenocarcinoma*

The extent of gastric resection for distal lesions had been debated, and the traditional view that total gastrectomy (TG) is required for all gastric lesions has been challenged. Gouzi *et al*<sup>51</sup> conducted a multicenter randomized trial comparing TG to subtotal gastrectomy (SG) enrolling 169 patients with resectable lesions of the gastric antrum. Patients with macroscopic lymph node involvement of the cardioesophageal or splenopancreatic region were excluded from the study. TG consisted of TG with Roux-en-Y esophagojejunostomy. Splenectomy was not routinely performed; however, the TG group had an unspecified higher splenectomy rate than the SG group. SG consisted of a distal gastrectomy and Billroth II gastrojejunostomy.

Both procedures included a total omentectomy, and lymph node dissection extended to the pyloric, left gastric, hepatic, and cardiac nodes. The groups were well matched for tumor size, extent of invasion, and lymph node stage. There was a post-operative mortality of 2.4%, with three deaths in the SG group and one death in the TG group. The non-lethal complication rate was 33% in the TG group and 34% in the SG group. Lymph node involvement and serosal extension were significantly associated with 5-year survival; however, extent of resection was not. The authors concluded that TG or SG could be performed with equal morbidity and mortality, but that TG offered no added survival benefit. A major criticism of this study was that it was underpowered to detect a difference between the groups, as 200 patients were originally calculated to show a difference of 20%.

In a larger trial, Bozzetti *et al*<sup>61</sup> also performed a randomized trial comparing TG to SG in 618 patients with resectable tumors at least 6 cm from the cardia. Patients were enrolled if they had tumors of the distal half of the stomach without evidence of metastatic disease, were under 75 years of age and in good health, and had no previous gastric resection or chemotherapy. Patients were further assessed at laparotomy for a minimum distance from the tumor to the cardia and no evidence of peritoneal, D3 lymph node metastasis or extension into adjacent organs. Patients were randomized intra-operatively to TG or SG. Both operations were performed with a D2 lymphadenectomy. Splenectomy was left to the discretion of the operating surgeon. Patients were then followed regularly for a median follow-up of 72 mo in the SG group and 75 mo in the TG group. Five-year survival was 65.3% in the SG, and 62.5% in the TG group, suggesting that type of resection had no influence on the survival. Site of tumor, wall invasion, extension of surgery including splenectomy, and relative frequency of metastatic lymph nodes were significant predictors of survival. Given the lack of survival benefit, the authors concluded that SG was the preferred operation for distal gastric cancer, provided that a proximal margin of at least 6 cm could be obtained, because it is technically less demanding, results in a lower splenectomy rate, and is associated with better quality of life (QOL).

QOL is a very important outcome after gastrectomy. For tumors of the distal stomach, given the current data suggesting equivalent morbidity and survival for TG and SG, the procedure with the best QOL profile is preferred. Davies *et al*<sup>71</sup> compared the QOL of patients following TG to those after SG. These authors compared 46 patients who had undergone an R0 resection. Twenty-six underwent TG and 21 underwent SG. Five questionnaires were used: the Rotterdam symptoms checklist, the Trold index, the hospital anxiety and depression scale, the activities of daily living score, and the Visick grade. Patients were questioned before the operation and at 1, 3, 6, and 12 mo. There was no difference in QOL prior to the operation or at 1, 3 or 6 mo; however, patients undergoing SG had a significantly higher QOL at 1 year. The authors thus concluded that, given equivalent survival, SG is the operation of choice for tumors of the distal stomach.

Based on data that accrued in prospective, randomized

trials, it is now accepted that SG is an appropriate oncologic operation for distal adenocarcinoma.

### Proximal gastric adenocarcinoma

The extent of resection needed to achieve cure in tumors of the gastroesophageal junctions has been a topic of much debate. Ito *et al*<sup>[8]</sup> reviewed patients with Siewert type II or III carcinoma of the gastric cardia in an attempt to discern the optimal surgical approach. Eighty-two patients were included in the study, 59 with type II and 23 with type III lesions. The surgical approach varied, with 33% undergoing total esophagectomy, 29% undergoing extended gastrectomy with thoracotomy, and 38% undergoing extended gastrectomy without thoracotomy. There was no significant difference in the type of procedure between type II and III lesions. There was no significant difference in post-operative mortality; however, there was a higher post-operative morbidity associated with total esophagectomy as compared to extended gastrectomy with or without thoracotomy (33% *vs* 11%). The addition of a thoracotomy to extended gastrectomy did not have an impact on post-operative morbidity (13% *vs* 10%). There was a significantly higher incidence of microscopic residual disease at the proximal margin in the extended gastrectomy group with or without thoracotomy as compared to the total esophagectomy group (38% *vs* 7%). The mean follow-up was 34 mo and 5-year survival for the entire group was 33%. Multivariate analysis revealed that patient's age over 65, lymph node metastases, and absence of an R0 resection were adversely associated with survival. There was no survival difference between the different types of resection despite a higher incidence of positive proximal margins in the extended gastrectomy group. Based on these results, showing R0 status and nodal status to be predictors of survival, the authors made the following recommendations: (1) A minimum proximal margin of 6 cm and distal margin of 4 cm should be obtained. (2) A minimum of 15 lymph nodes should be sampled. The type of surgical approach should be tailored to fit the individual patient with these goals in mind.

TG is the traditional treatment for proximal gastric cancer; however, this has been recently challenged as well. Harrison *et al*<sup>[9]</sup> reviewed 98 patients with proximal gastric cancer who underwent gastric resection via an abdominal approach, excluding all patients who underwent esophagogastrectomy. Of these 98 patients, 65 underwent proximal gastrectomy (PG), and 33 underwent TG. There was no difference in post-operative mortality (6% *vs* 3%). Post-operative morbidity data was not analyzed; however, there was no difference in the length of hospital stay. There was no significant difference in time to recurrence or first site of recurrence. The 5-year survival rate was not significantly different between the TG and PG groups with a mean follow-up of 30 mo (43% for PG *vs* 41% for TG). The authors concluded that either procedure can be performed safely without sacrificing long-term survival.

The optimal approach for carcinoma of the gastroesophageal junction or gastric cardia is still a topic of debate. The over-riding factor, regardless of the type of resection, is the ability to obtain a margin-negative resection.

## EXTENT OF LYMPH NODE DISSECTION

The extent of lymphadenectomy is one of the most controversial topics in gastric cancer surgery. The Japanese developed an extensive classification system for the regional lymph nodes and a systematic method of dissection referred to now as the D2 resection. This method is described in detail by Maruyama *et al*<sup>[10]</sup>, who also reviewed the Japanese National Cancer Center experience with gastric resection over the period from 1963 to 1985. The authors reported an improvement over this time span in 5-year survival for resected patients from 44.3% to 61.6%. Most of this improvement was attributed to early gastric cancer screening established at a national level; however, they do report an increase in survival over this time period with respects to specific stage, T stage, and N stage.

Shiu *et al*<sup>[11]</sup> reviewed the results of gastric resection and lymphadenectomy for gastric cancer at Memorial Sloan Kettering Cancer Center over a 20-year period. They analyzed the outcomes of 210 patients and attempted to identify risk factors for mortality. On multivariate analysis, they identified non-pyloric tumor site and greater than three positive lymph nodes as pathologic risk factors. They also identified positive microscopic margins, inadequate lymphadenectomy, and TG as independent surgical risk factors for mortality. Adequate lymphadenectomy was defined as one and a half lymph node levels beyond the furthest level of lymph node disease. For example, patients with N0 disease would require a dissection including the N1 and part of N2 nodes.

This data from a Western center as well as the Japanese data were cited to justify extended lymphadenectomy, a practice which was not commonplace in the West. Multiple clinical trials were performed to look at the morbidity, mortality, and long term survival of a D2 dissection in Western centers.

The best known trial to evaluate lymphadenectomy was from the Dutch Gastric Cancer Group. Bonenkamp *et al*<sup>[12]</sup> published their results from a randomized controlled trial comparing D1 and D2 gastrectomy in 80 Dutch hospitals over 5 years. D1 resection was defined as containing only the N1 (perigastric) nodes. D2 resection was defined as encompassing the N2 nodes. The spleen and distal pancreas were resected in 11 (3%) of D1 resections and 30 (37%) of D2 resections. The type of gastrectomy, TG *vs* SG, as well as the method of reconstruction were left to the preference of the surgeon. Surgeons were instructed in the technique with video classes, and eight visiting Japanese surgeons were present to supervise all D2 resections. Seven hundred and seven patients underwent resection with intention to treat, and 632 were found to have an R0 resection, and thus followed for evidence of recurrence. These authors reported a statistically significant difference in post-operative mortality (4% *vs* 10%) and complication rate (25% *vs* 43%) for D1 *vs* D2 resection. The 5-year survival rate was 45% for the D1 group and 47% for the D2 group, which was not statistically significant. The 5-year risk of relapse was 43% in the D1 group and 37% in the D2 group, which also was not statistically significant. Subgroup analysis, however, showed that in patients who

did not require splenectomy or pancreatectomy, there was a significantly lower 5-year risk of relapse. The conclusions drawn from this article were that D2 lymphadenectomy was associated with a higher morbidity and mortality without offering a long-term survival benefit, and thus it was not recommended. The sub-group analysis also questioned the benefit of distal pancreatectomy or splenectomy.

A concomitant British trial was also performed over the same time period. Cuschieri *et al*<sup>[13]</sup> reported the results of a randomized study comparing D1 to D2 resections. Four hundred patients were randomized. In this trial a D1 resection consisted of the removal of all lymph nodes within 3 cm of the tumor and D2 resection consisted of the standard resection of the omental bursa, the hepatoduodenal nodes for antral lesions and the splenic artery, splenic hilar, and retropancreatic nodes by distal pancreatectomy for middle and upper third lesions. They reported similar post operative morbidity and mortality data to that of the Dutch study for the D2 resection group, and showed no difference in the 5-year survival (35% *vs* 33%) or risk of recurrence. As in the Dutch trial, the British trial showed that resection of the spleen and pancreas was independently associated with decreased survival.

Both of these large randomized studies showed no benefit from a D2 resection; however, each also raises the question: is there a role of D2 resection without pancreatico-splenectomy? Two current studies attempt to answer that question.

Edwards *et al*<sup>[14]</sup> compared D1 resection to D2 resection sparing the pancreas and spleen in a total of 118 patients. The study was not randomized, as one surgeon performed all the D1 resections ( $n=36$ ) at one hospital and the other surgeon performed all the D2 resections ( $n=82$ ) at another hospital in the same region of Wales. Splenectomy and pancreatectomy were performed only for evidence of direct invasion of tumor. They reported similar operative mortality (8.3% *vs* 7.3%) and a significant 5-year survival advantage for the D2 resection group (32% *vs* 59%), which was most evident in the patients with stage III disease (8% *vs* 33%). Extent of lymphadenectomy was independently associated with increased survival on multivariate analysis. The authors concluded that a modified D2 resection sparing resection of the pancreas and spleen offers a survival advantage over a D1 resection with no increase in short-term morbidity or mortality.

Recent phase II data from a multicenter trial conducted in Italy showed acceptable morbidity and mortality with good 5-year survival following pancreas-preserving D2 resection<sup>[15]</sup>. The Italian Gastric Cancer Study Group enrolled 191 patients, and pancreas-preserving D2 resection was performed with an operative mortality of 3.1%, morbidity of 20.9%, and 5-year survival rate of 55%. These numbers compare favorably to the Japanese experience, and suggest that pancreas-preserving D2 may offer a survival benefit; however, the randomized comparison to D1 resection has not yet been performed.

Data from Japan concerning mortality and 5-year survival after gastrectomy had been criticized for being retrospective in nature. A D1 gastrectomy is considered

as a non-curative operation in Japan; thus, it would not be performed in any randomized trial. Sano *et al*<sup>[16]</sup> are conducting a randomized trial comparing standard D2 resection to extended para-aortic lymphadenectomy. This is the first randomized prospective study to come from Japan. The selection criteria of the surgeons and the selected centers should be mentioned. Only surgeons with over 100 D2 gastrectomies, and only centers with over 80 gastrectomies a year were selected for the trial. This is in stark contrast to the Dutch and British trials which did not require a set training period to master the “learning curve” of the procedure. The spleen was resected in all the cases where TG was performed, and the pancreas was resected only in cases of direct invasion. The morbidity and mortality data for this trial have been released. The overall morbidity of a D2 resection was 20.9%, with a mortality of 0.8%. The conclusions that can be drawn from this study, pending the 5-year survival data, are that D2 resection can be performed at specialized centers by surgeons with ample experience with low morbidity and mortality.

Based on the current data, it appears that a modified D2 lymphadenectomy, sparing the spleen and pancreas when possible, can be performed safely and may offer the best chance for long-term survival; however, the randomized controlled data to support this argument is currently in progress.

## EXTENDING RESECTION TO ADJACENT ORGANS

D2 resection with splenectomy and distal pancreatectomy was performed by many centers in Japan to facilitate dissection of lymph nodes around the splenic artery with early reports suggesting improved survival<sup>[10]</sup>. The utility of extended resection was later called into question by many Japanese and Western surgeons. Otsuji *et al*<sup>[17]</sup> reviewed 128 patients who underwent TG for gastric adenocarcinoma of the middle or proximal stomach. Of these, 35.9% underwent pancreaticosplenectomy, 44.6% splenectomy, and 19.5% gastrectomy alone. Pancreaticosplenectomy increased the risk of pancreatic fistula significantly. Five-year survival for the pancreaticosplenectomy group, the splenectomy group and the gastrectomy alone group were 40.7%, 55.9%, and 54.2%, respectively; however, on multivariate analysis pancreaticosplenectomy and splenectomy alone were not independently associated with survival. The conclusions drawn from this study were that extension of TG to include pancreaticosplenectomy or splenectomy increases the risk of complications without improving survival.

Kasakura *et al*<sup>[18]</sup> reviewed 1 938 gastric resections over 18 years and also concluded that splenectomy and distal pancreatectomy do not have an impact on survival and are associated with an increased incidence of complications. Of these 1 938 patients, 78 underwent splenectomy (S), 105 underwent splenectomy/pancreatectomy (PS), and 1 755 underwent gastrectomy alone. The PS and S groups were associated with a higher percentage of proximal tumors and TG, higher T stage, higher N stage, and worse histologic grade. There were more severe post-operative

complications in the PS and S groups over the gastrectomy alone group, with a higher rate of pancreatic fistula, intra-abdominal abscess, and anastomotic leak. There was also a higher rate of local recurrence in the S and PS groups. When analyzed by UICC stage; however, no difference in 5-year survival for stage II, III, or IV tumors was detected. Gastrectomy alone was found to have higher 5-year survival for T2 tumors; however, for T3 and T4 tumors, there was no difference. Conclusions from this study were that long-term survival is not affected by splenectomy or pancreatectomy and these procedures should not be performed solely to aid in lymph node dissection. The spleen should only be resected when there are clearly positive lymph nodes in the splenic hilum and around the splenic artery, and the pancreas should only be resected when there is direct invasion of tumor.

Resection of adjacent organs for local invasion was advocated in the early Japanese literature<sup>[10]</sup>; however, this practice also has been analyzed extensively in the past decade. Shchepotin *et al*<sup>[19]</sup> reviewed 353 patients with T4 gastric cancer who underwent gastrectomy combined with resection of adjacent organs. Of these patients, 89% had histologically confirmed invasion. TG was performed in 32.9% of patients and SG in 67.1%. The extent of lymph node dissection was the same in all patients, consisting of dissection of all perigastric nodes, nodes along the celiac axis, hepatic artery, and proximal splenic artery. The transverse colon was resected in 45%, the tail of the pancreas and spleen in 42.5%, the left hepatic lobe in 28.5% and the head of the pancreas in 10.5%. The complication rate was 31.2%, and mortality rate was 13.6%. Combined 5-year survival was 25%; however, when this was broken down into node positive or node negative T4 lesions, 5-year survival changed significantly. Node negative T4 patients had a 37% 5-year survival, whereas node positive T4 patients had only a 15% survival. From these data, the authors continued to advocate extended resection of adjacent organs in the resection of gastric cancer for cure.

Martin *et al*<sup>[20]</sup> showed that extended organ resection could be performed with acceptable morbidity (4%) and 5-year survival (32%). Two hundred and sixty-eight patients with locally advanced gastric cancer underwent gastrectomy with adjacent organ resection and D2 lymphadenectomy. The type of gastrectomy was variable; however, there was a higher incidence of adjacent organ resection in the TG group. Spleen alone was the most common resection ( $n=123$ ), followed by spleen/pancreas ( $n=38$ ), spleen/colon ( $n=18$ ), pancreas alone ( $n=12$ ), and colon alone ( $n=16$ ). As would be expected, there was a higher percentage of T3/T4 tumors and N2/N3 lymph node metastases in the organ resection group. Perioperative mortality was not significantly different, 3.6% in the gastrectomy group and 3.7% in the gastrectomy with organ resection group. There was a higher rate of recurrence in the gastrectomy with organ resection group (52% *vs* 42% at 24 mo follow-up), and significantly lower median survival (32 mo *vs* 63 mo) on univariate analysis. On multivariate analysis, however, only T-stage, N-stage and overall stage were predictors of survival. The authors concluded that resection of adjacent organs is important

to achieve an R0 resection and can be done with minimal morbidity; however, careful selection of clinically T4 tumors should be performed to limit unnecessary organ resection in early stage gastric cancer.

Resection of adjacent organs in conjunction with gastrectomy can increase survival with minimal additional morbidity in a highly selected patient population.

## POSITIVE MARGINS

Patients with recurrence after resection of gastric cancer uniformly have a rapid decline. The risk factors for recurrence, and the rate and pattern of recurrence has been examined. In a recent retrospective review of 367 patients who underwent an R0 resection with subsequent recurrence, the rate and pattern of recurrence was examined<sup>[21]</sup>. The majority of the patients (65%) had T3 lesions, 46% had N1 nodal disease, and 54% were AJCC stage III. The type of gastric resection was highly variable, with the highest percent being esophago-proximal resections (45%). The extent of lymphadenectomy was also variable, with the majority being D2 (68%). The rate of locoregional, peritoneal, and distant metastases was 54%, 51%, and 29% respectively, with significant overlap of these three. Seventy-nine percent had recurred within two years and 94% by four years. The median time to death from diagnosis of recurrence was 6 mo. The pattern of recurrence was not associated with survival time; however, T stage, N stage, age and presentation with symptoms were all predictors of decreased survival. Advanced T stage, distal location, diffuse Lauren's subtype, and female gender were significantly associated with peritoneal metastases. Proximal location and male gender were associated with locoregional recurrence. Proximal location, early T stage, and intestinal Lauren's subtype were associated with distal recurrence. There was no significant pattern of recurrence associated with overall stage, extent of lymphadenectomy, nodal status, or extension of resection to adjacent organs.

There is no surgical therapy for recurrent gastric cancer; however, the question of re-excision for positive margins at primary resection has been raised. Survival for patients with microscopically positive margins has been shown to be significantly shorter than those with clear margins<sup>[25]</sup>. In a recent review of 259 patients who underwent gastrectomy with curative intent, 22 had microscopically positive resection line margins<sup>[22]</sup>. Positive margins were associated with tumor location and differentiation. There was a significantly lower 5-year survival for the patients with positive margins (18% *vs* 45%); however, when this was stratified for lymph node status, the patients with positive lymph nodes had a significantly lower survival. The authors concluded that, given the very poor prognosis associated with positive margins, re-laparotomy may be justified in those patients with node-negative disease.

## PALLIATIVE SURGERY FOR GASTRIC CANCER

Despite improved clinical outcomes associated with earlier diagnosis, more accurate staging, and decreased surgical morbidity and mortality, the overall prognosis of gastric

cancer remains poor because many patients are incurable at presentation. A complete R0 resection remains the most powerful indicator of survival, but is obtained in only 50% of those presenting for resection of a primary gastric cancer<sup>[20,23]</sup>. For those patients who present with stage IV disease, cure measured by 5-year survival is exceedingly rare and is not a realistic treatment goal<sup>[2,24-32]</sup>. Because of the low cure rate and the advanced stage at which many patients present, palliative strategies and symptom management remain an essential component in the total care of the patient with gastric cancer<sup>[33]</sup>.

Palliation of symptoms caused by any advanced cancer demands the highest level of surgical judgment. Although an important part of the surgical decision making process requires consideration of risk in terms of treatment-related toxicity, morbidity, and mortality, attention to this element should not be the predominant factor in making decisions about palliative therapy. Decisions are made best on endpoints such as the probability and durability of symptom resolution, the impact on overall QOL, and pain control. Deliberations must consider the medical condition and performance status of the patient, the extent and prognosis of the cancer, the availability and success of non-surgical management, cost effectiveness and the individual patient's quality and expectancy of life. Knowledge about the need to repeat a specific therapy or requirements to manage additional symptoms can give further information about the potential for symptom-free survival and what additional care will be needed. Therapy for symptoms must remain flexible and individualized to continually meet the patient's unique and ever changing needs<sup>[34,36]</sup>. Surgical palliation of advanced gastric cancer may include resection or bypass, alone or in combination with endoscopic or percutaneous interventions. Such interventions have been proposed not only to improve symptom control, but also to eliminate potential complications (bleeding, obstruction, pain, perforation, and debilitating ascites) caused by the primary tumor<sup>[37,38]</sup>.

In 1958, Lawrence and McNeer demonstrated that palliative gastric resections effectively relieve symptoms in patients with incurable gastric cancer. Because of high rates of associated perioperative morbidity and mortality and the brief period of anticipated survival, however, the authors suggested that a TG in patients with incurable gastric cancer was rarely a worthwhile palliative procedure<sup>[39]</sup>. This conclusion was supported by Remine in 1979 who also suggested that TG was not a satisfactory palliative operation<sup>[40]</sup>. Later series, however, showed improved symptom relief with gastrectomy compared to gastroenterostomy, without increasing complication rates<sup>[41,42]</sup>. Others have based their support for palliative gastric resections primarily on improved survival data and have proposed that it should be performed whenever technically possible<sup>[43,44]</sup>. Because of decreasing perioperative complications, some authors now suggest that total palliative gastrectomy and esophagogastrectomy is justified in selected patients<sup>[45-49]</sup>.

The effective and appropriate use of palliative surgical interventions in patients with gastric cancer remains controversial. Recommendations from the literature are contradictory and often based on the retrospective

evaluation of suboptimal data. A highly variable and imprecise understanding of the goals and indications of palliative surgery, poorly defined patient groups, and a reliance on inappropriate endpoints contributes to this confusion. The designation of patients as "palliative" is commonly based on the extent of disease (ranging from gross disease at operation to postoperative margin status) rather than a sound definition encompassing factors associated with good palliative therapy. Even though the value of a palliative procedure should be judged by its ability to control symptoms, reports often fail to utilize validated QOL or pain assessment instruments and rarely consider the durability of potential palliative benefits<sup>[25]</sup>. These factors limit useful interpretation of most prior studies on palliative procedures for gastric cancer. The impact of such deficiencies in the literature has been demonstrated by a recent analysis of the Memorial Sloan-Kettering Gastric Cancer Database. Important differences among the patients undergoing a non-curative gastric cancer were demonstrated when a sound and reproducible definition of palliative surgery was applied. Significant differences between overall survival, primary tumor sites, staging, degrees of nodal and metastatic disease, and the types of procedures performed support the differentiation between palliative and non-palliative designations<sup>[49]</sup>.

Conclusions over the effectiveness of palliative operations in the gastric cancer literature are often based, incorrectly, on incremental survival differences. Caution must be taken when evaluating survival data in patients following a palliative intervention. Palliative care ideally selects treatment that will maximize QOL and minimize complications. Consideration of anticipated survival helps to define a period during which the requirements of effective symptom control must be met and may be useful when considering the risk-benefit ratio for an individual patient<sup>[50,51]</sup>. Although increased survival may be a secondary goal of a palliative procedure, it is inappropriate to select a palliative procedure solely based on improved duration of survival<sup>[36]</sup>. Based on patients grouped by extent of disease rather than palliative intent, The Dutch Gastric Cancer Group has suggested that differences in overall survival following "palliative" gastric resections may be beneficial in patients with tumor load restricted to one metastatic site<sup>[52]</sup>. Such conclusions about the value of palliative gastrectomy are premature because they fail to consider the associated risks, benefits, and expected durability of the procedure<sup>[33,49]</sup>.

To compare the impact of potentially achievable gains associated with palliative surgery, non-curative gastrectomies were analyzed with a partitioned survival analysis<sup>[33,53]</sup>. The technique, which has been generally used to evaluate chemotherapy trials, analyzes treatment by defining relevant clinical health states and comparing their duration with regard to treatment, toxicity and relapse. The analysis provided by this methodology is well suited to evaluate surgical palliation, especially in conditions such as gastric cancer, in which treatment-related toxicity plays such an important role in both the literature and in clinical decision-making<sup>[33,54]</sup>. Palliative gastric resections previously have been associated with considerable operative morbidity (54%) and mortality (6%)<sup>[49]</sup>. Duration in the time without

symptoms or toxicity (TWiST) state was found to be significantly decreased (8.5 mo vs 2.1 mo,  $P=0.04$ ) in patients experiencing a major postoperative complication (requiring invasive interventions, unplanned ICU admission, or permanent disability). Complications have a considerable influence on the patients' limited survival by not only increasing time in a hospitalized setting but also by diminishing the QOL. Concerns about potential complications such as bleeding, obstruction or perforation have led some to propose prophylactic gastric resections in patients with advanced, asymptomatic gastric cancer. Sarela *et al* have shown in patients with known metastatic disease identified on laparoscopy; however, that complications requiring emergency or urgent palliative operations were rare in patients not receiving a prophylactic resection for incurable gastric cancer<sup>[55]</sup>.

Since palliative gastrectomies are associated with significant perioperative morbidity and mortality, the authors recommend deliberate palliative resection only in carefully selected patients with severe symptoms<sup>[34,50,54,55]</sup>.

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