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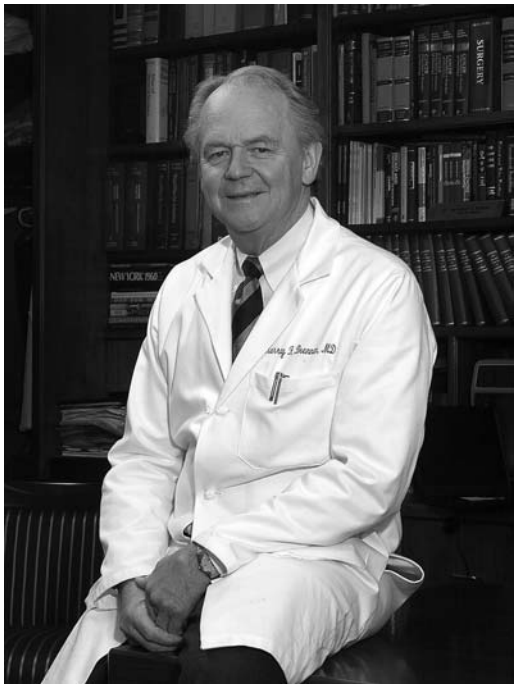
Special article

Current status of surgery for gastric cancer: a review

Murray F. Brennan

Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA



Murray F. Brennan
Department of Surgery
Memorial Sloan-Kettering Cancer Center

Abstract
In the last three decades, considerable progress has been made in the diagnosis and management of gastric cancer. This was initiated by the Japanese and taken up by other focus groups in Asia, the United States, and Europe. Exciting prospects have been identified with the molecular characterization of the mutated gene causative for familial gastric cancer, and new developments in endoscopy and laparoscopy for diagnosis, management, and treatment continue. It is now clear that the extent of the gastric resection requires only that an R0 resection be performed and that total gastrectomy is not necessary for all patients with gastric adenocarcinoma. The extent of nodal dissection is defined as a major factor in staging and can influence outcome by stage. The recent development of defining adequate staging based on at least 15 nodes being sampled is a clear example of a simple system that can make major differences in overall management. The role of extended node dissection has been studied in prospective randomized trials showing no overall survival benefit but perhaps benefit to selected subgroups. The importance of the hospital and surgical experience in improving mortality and long-term survival is established. The role of adjuvant therapy, both pre- and postoperative, continues to be evaluated with some frustration that a single trial, as yet unconfirmed by subsequent trials, is considered the "standard of care" in the United States. The international gastric cancer community can help define the important issues that need to be answered in the coming decades.

Key words Gastric adenocarcinoma · Management

Introduction

In the last three decades considerable progress has been made in the diagnosis and management of gastric cancer. Renewed interest in gastric cancer was led by the Japanese [1] and taken up by other focus groups in the West [2,3]. The evocative implications of careful retrospective reviews translated into meaningful prospective randomized trials of technical management

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[4–7]. This brief report summarizes the current status of several aspects of the management of gastric cancer.

Gastric cancer remains a major health hazard internationally. Approximately 800,000 patients will develop gastric cancer, and in the Untied States approximately 40% of the 25,000 patients who do develop cancer will die of the disease.

The etiology of gastric cancer remains imprecise, although *Helicobacter pylori* has been declared an official carcinogen by the World Health Organization. The identification of familial gastric cancer [8] due to mutations in the *E-cadherin* gene led to newer methods required for screening in the kindreds at risk. Chromoendoscopy appears to be a method that can improve the identification of early invasive cancer in high-risk groups [8,9].

Development of gastric stump cancer continues to follow prior gastric operations for benign disease. With decreasing operations for benign disease this should be an uncommon event [10].

Unfortunately, despite widespread application, no serum marker has accurately and precisely been proven valuable as a screening test. Utilization of gene microarray analysis has not yet translated into meaningful data to warrant uniform application.

Diagnosis has moved from conventional contrast imaging to endoscopy. Endoscopic identification and biopsy have been improved by the utilization of endoscopic ultrasound, with relatively good delineation of T stage and some improvement in the identification of N stage. Preoperative diagnostic tools combined with computerized tomography (CT) for the identification of systemic disease have allowed presurgical investigation of systemic therapy in an effort to improve long-term results. Early promising suggestions of the value of positron emission tomography (PET) scanning have not as yet been translated into precise and meaningful data that can be relied on. It would appear that PET information is currently more valuable in predicting likelihood of long-term outcome or response to treatment [11,12].

In a comparison of endoscopic ultrasound (EUS) and helical CT for preoperative staging, CT was correct in T staging in 76% of cases and N stage in 70%; EUS had correct T stage in 86% and correct N stage in 90% [13]. In a recent re-evaluation of our own experience, with 296 patients with EUS prior to R0 resection, we found overall T stage accuracy was only 17% and 50% for N stage (Bentrem et al., unpublished); however, for T3 lesions it remained 80+%.

Role of laparoscopy

Laparoscopy clearly has a significant role to play in the definition of those patients who have unsuspected M1 disease based on prior imaging. In essentially all studies [14] the utilization of laparoscopy in the patient with advanced gastric cancer, not identified to have extragastric extension or metastasis by imaging, has proven to yield 20%–30% of patients with microscopic peritoneal or liver disease not amenable to curative resection.

Surgical management

Endoscopic mucosal resection and limited minimally invasive procedures are progressively being applied and are described in the article by Drs. Kitagawa and Kitajima.

Open operations

Incision type has been studied in a randomized trial [15] suggesting that a transverse incision has less postoperative pain, less pneumonia, and less intestinal obstruction, not something this author expected and not readily explicable. Other studies have shown no difference [16,17]. Liberal use of the cautery has been shown to decrease wound blood loss and postoperative incisional pain [18]. Continuous mass wound closure has been shown to be superior to interrupted closure techniques in prevention of incisional hernia and is faster and more cost efficient [19].

Extent of resection

The extent of surgical resection required for curative (R0) resections is now defined. While total gastrectomy was the historic standard approach for gastric cancer, randomized trials show that total gastrectomy offers no value over complete gross resection either by distal gastrectomy or proximal gastrectomy [20,21]. The choice of operation, in terms of gastric resection, remains based no longer on the need for extended local resection for the control of malignancy, but rather on the potential complications, or lack thereof, of the primary operation. In general terms, distal subtotal gastrectomy is reserved for distal lesions and total gastrectomy/proximal gastrectomy for more proximal lesions. Total gastrectomy remains the only option for those patients with extensive linitis plastica type lesions involving the majority of the stomach.

The appropriate management of proximal gastric cancer remains a matter of debate. When done subdiaphragmatically [22], it appears that proximal gastrectomy has no greater late complications, particularly in terms of reflux, than the historical total gastrectomy. Debate continues, however, when the resection requires supra-diaphragmatic anastomosis, some groups favoring proximal gastrectomy, and others feeling that

either total gastrectomy or esophagectomy with proximal cervical anastomosis is the procedure of choice. In a recent study, the surgical approach, either total esophagectomy ($n = 27$), thoracic esophagogastrectomy ($n = 24$), and abdominal esophagogastrectomy ($n = 31$), did not influence 5-year survival. Operative mortality in the series was 2.1% and morbidity 20%. Morbidity was significantly higher in those having esophagectomy (33% vs 11%) [23].

More limited operations for gastric cancer, including pylorus-preserving gastrectomy, suggest that when possible, no difference in outcome was identified in a small randomized trial with limited procedures [24].

More extended resections, such as distal pancreaticosplenectomy, can no longer be justified in the absence of local invasion. The routine application of resection of distal pancreas and spleen translates into increased morbidity and mortality without survival benefit [25]. Conversely, in the patient with an extensive T4 lesion and limited or absent nodal disease, the more extended resection that provides an R0 resection can be justified and translate into long-term survival benefit [26].

Influence of positive resection margin

In our review of the influence of a positive microcopic resection margin, we looked at 46 patients with an otherwise R0 resection who had a positive micromargin, (R1) compared to 512 who had R0 resection. Only in patients with ≤ 5 nodes positive was a positive micromargin independently significant in survival outcome [27].

Reconstruction

The technique of anastomosis in gastric cancer has been examined in a number of studies [28], and despite the preference of this author, stapled anastomoses seem preferable—something already confirmed by a previous president of the IGCA, Dr. Siewert!

As has been known for a long period of time, bile reflux gastritis is best minimized by Roux-en-Y reconstruction when compared to Billroth I or II reconstruction [29]; however, in Western series this is often ignored as the majority of patients who have endoscopic gastritis identified have few or any symptoms.

Utilization of pouches, while theoretically attractive, has shown limited benefit, if any, in those studies that have carefully been conducted as to postoperative function and nutritional adequacy.

Interposition of a jejunal loop is favored by some [30] but has not received wide acceptance in the West. In North America most proximal gastrectomies do not have jejunal interposition, which is common in Japan [31].

More complicated reconstruction options, such as jejunal pouch interposition with esophageal preservation, have been proposed [32] but have limited application to early-stage disease, and rely on careful evaluation of long-term nutritional and reflux symptoms for justification.

Lymph node dissection

Extent of nodal dissection continues to be debated. In prospective randomized trials, extended nodal dissection has not been shown to improve overall survival [33,34]. The criticism of the Dutch trial because of the high complication rate has led to other studies designed to justify the more extended nodal dissection approach. In the Italian phase II study [35] with pancreas preservation, of 191 patients the overall morbidity was 21%, and in-hospital mortality 3.1%, with overall survival of 55%. Prospective comparisons by post code [36] of D2 and D1 dissection in 118 consecutive patients have shown similar operative mortality 8.3% vs 7.3% with improved survival at 5 years (32% vs 59%, $P = 0.03$) for the D2 group, with marked improvement for stage III patients. Multiple experienced groups [5,37–40] continue to practice extended or complete D2 nodal dissection; as in the hands of the experienced, complications are no greater, accuracy of staging is markedly improved, and some small survival benefit may be possible.

A recent Cochrane review [40] examined extended versus limited lymph node dissection for adenocarcinoma of the stomach. Meta-analysis did not show a survival benefit to extended node dissection, but did show increased postoperative mortality. Prespecified subgroup analysis suggested a benefit to extended node dissection in T3+ tumors (RR = 0.68, 95% CI 0.42–1.10).

Extended nodal dissection and nodal sampling markedly improve the accuracy of staging and the accuracy of prediction of outcome. The adoption of the concept of 15 nodes being removed and examined has provided a simple, readily available approach that can be applied by any experienced surgeon. Again, more extended local dissections, D4 dissections, or pancreaticosplenectomy for greater nodal yield have not shown improved survival and do increase morbidity significantly.

The randomized controlled trial examining D2 versus D2 extended lymphadenectomy has been completed [41] using 523 patients (only one patient died in either group) and only a slightly greater morbidity (28%) in the extended group compared with the standard group

(21%), confirming the capability of the experienced Japanese surgeon.

Age is no longer a barrier to successful resection [42,43].

Patterns of care

Very little attention has been paid to the remarkable differences in postoperative management in patients with gastric adenocarcinoma. This is most clearly reflected in the differences between hospital stay in various countries. Patients with early gastric cancer can stay in a Japanese hospital for 30 days [23], whereas conventional stays in North American hospitals are in the order of 10 days. Patients in Europe are often admitted 1 to 3 days ahead of operation, whereas patients in North America are admitted the day of the operation. Given the increased cost of hospitalized care in all nations, it can be expected that hospital stays will progressively fall, although they are highly influenced by the socioeconomic availability of support for patients undergoing early discharge.

The simple use of nasogastric suction, a common event in Japan and Europe, is relatively uncommon in the United States. The early removal of the nasogastric tube has not been shown to influence outcome. In my own department, nasogastric tubes are rarely used beyond 24 hours, while in others, even in early gastric cancer, they may be maintained for 2–4 days [24]. A prospective randomized trial of gastric suction after total gastrectomy confirms our practice that they are of no value and do not alter instances of esophagojejunal leak or complications [44].

The use of intraperitoneal drains has been examined in various situations, in major procedures [45] such as pancreaticoduodenectomy, and has not been demonstrated to favorably influence outcome. Conversely, in some societies they are widely utilized and deemed mandatory.

Prospective randomized trials of adjuvant nutritional support either by enteral or parenteral route have not shown to be beneficial when applied routinely [46,47].

Postoperative nutritional support using a nasojejunal feeding tube following total gastrectomy [44] has been studied in a prospective randomized trial, utilizing 237 patients, with no difference in esophagojejunal leak (6.9% vs 5.8%), or in major complication rates (26% and 22%) with similar low postoperative mortality of 0.9% and 0.8%.

The majority of patients can return to simple, regular small meals without adherence to complicated dietary formulation.

Postgastrectomy deficiency states continue to be defined. Following total gastrectomy, vitamin B12 and folate replacement are required. In subtotal gastrectomy iron deficiency is common, especially in the presence of gastritis [48].

Patterns of recurrence

Patterns of recurrence have been analyzed [50]. Of 1172 patients undergoing R0 resection, 42% recurred (n = 496). Complete data on 367 (74%), showed that 79% of the documented recurrences occurred within 2 years. Of those that recurred, local recurrence occurred in 54%, metastatic in 51%, and peritoneal in 29%. Median time to death after recurrence was 6 months.

Recurrence of a second primary tumor has been studied [50] after treatment for early gastric cancer. Examining 1070 patients, risk factors for recurrence were presence of lymph node metastases and older age.

Prediction of operative outcome

Operative morbidity and mortality is clearly related to institution and surgical experience. Results in high-volume centers in Asia have been translated to specialist centers in the West, and clear relationships between morbidity and outcome demonstrated depended upon volume [51].

In a review of the New York state-wide data sets, the overall mortality in patients undergoing gastrectomy was 6.1%, quite different from our own mortality of less than 3% and the mortality rate of <1% seen in experienced Asian and European centers. Review of these data suggests that when patients are grouped into volume percentiles both for institution and for surgeon, the observed mortality of the high-volume hospitals was increased from 2.85% to 11.16%, a risk-adjusted rate increase of 7.1. For surgeon volume the high-volume surgeon had an operative mortality of 2.76 whereas the low volume surgeon had an operative mortality of 8.83, or a relative risk-adjusted increase of 5.73 [51].

In a national study examining the national medicare database for 1994–1999, patients treated at the 51 national cancer centers in the United States were compared with patients from 51 controlled-volume hospitals with the highest volume for each procedure. The NCI Cancer Center had a lower adjusted surgical mortality rate than control hospitals for gastrectomy, 8% vs 12.2%, $P < 0.001$ [52], but still markedly higher than experienced centers.

The major difference between Japanese centers and experienced Western centers in outcome appears to be due to differences in site, greater frequency of early stage, and more precise staging [53]. The influence of obesity on operative outcome in Western patients com-

pared with Japanese [53] demonstrated a difference between BMI in Japanese and Western patients. More recently an analysis of 562 Japanese patients [54] using a definition of obesity of BMI >24.7, showed that 29% of Japanese patients were obese by this definition, but only 7% were obese by Western standards, i.e., BMI >27. Intra-abdominal infection, blood loss, complications, and length of stay were greater in the obese and lymph node yield was less, but no difference in long-term survival was found, consistent with the problems in the West.

Prediction of long-term outcome

Survival over the last 20 years has continued to improve, not only in Asia, but in the West. In a recent British experience [55] 5-year survival increased over a 20-year period from 15% to 41%. The number of curative resections increased from 33% to 73%, and similar results have been reported from Germany [2], the United States [3], with data beginning to approximate that of Asia.

Survival in our experience is related to both T and N stage. For T1 gastric cancers, survival in the Western world approximates that seen in the Japanese with 80+% patients alive in 10 years. For T2 lesions current North American figures are 55%, and for T3 and T4, 30%. N stage clearly affects outcome with patients having N0 having 10-year survival of approximately 70%, and N1 41%, and N2 or N3 less than 20%.

Multiple studies that have examined risk factors for outcome have been predominantly based on T, N, and M stage. Clearly, other factors beyond TNM can help predict outcome. Examining outcome following R0 resection in the absence of adjuvant therapy, we were able to take other factors potentially of meaning to outcome to validate their significance and use them in a nomogram. Such a nomogram contains information such as age, sex, primary site (distal one-third, middle one-third, gastroesophageal junction, proximal one-third), Lauren histotype (diffuse, intestinal, mixed), number of positive nodes, number of negative nodes, and depth of invasion. Given present databases, predictive nomograms [56] can now be utilized for the individual patient with some confidence, provided adequate staging information is available. Such nomograms have been developed in one institution and confirmed in another (Novothy et al., unpublished) [57].

The next challenge is to incorporate other histopathological features, such as lymphovascular invasion or molecular markers, e.g., expression of *E-cadherin* mutation into such nomograms to allow even more accurate prediction of outcome. Markers such as p53 and VEGF continue to be examined as to their relevance to outcome [58]; and for patients with node negative gastric cancer, vascular invasion can be an independent predictor of outcome [59]. Such nomograms can then be used in both a forward sense, i.e., only information obtainable preoperatively for risk prediction and use of neoadjuvant therapy, or in a backward sense, examining the effectiveness of prior adjuvant therapy. None of these observations would have been possible without the early commitment of the Japanese surgical community to accurate staging and diligent recording [1].

Role of chemotherapy and radiation therapy

Intensive prior studies as to the use of adjuvant chemoradiation therapy have all proven to be negative. More recently a randomized trial in the United States utilizing postoperative radiation and chemotherapy has demonstrated a survival benefit. The study has been appropriately criticized for the lack of surgical standardization and the lack of surgical quality control. Given the ability to apparently improve outcome statistics simply by increased nodal sampling (the stage migration phenomena), it is unfortunate that this study has been accepted as a standard of care in the absence of confirmatory studies. Potential morbidity of this approach, particularly in terms of the radiation dose of the kidneys, has been poorly elucidated and poorly described.

The initial British trial of adjuvant radiation or chemoradiation did not show a survival benefit [6,7]. The long-term results of the later British trial are soon to be published.

In the Dutch randomized control trial of preoperative FAMTX (5-Fluorouracil, doxorubicin and methotrexate) versus surgery alone, median survival for the 29 treated patients was 18 months and for surgery alone 30 months ($P = 0.17$). Based on this small negative trial, preoperative chemotherapy should remain an investigational regimen.

References

1. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H. Surgical treatment for gastric cancer: the Japanese approach. Semin Oncol 1996;23:360–8.
2. Siewert JR, Bottcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg 1998;228:449–61.
3. Brennan MF, Karpeh MS Jr. Surgery for gastric cancer: the American view. Semin Oncol 1996;23:352–9.
4. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ. Extended lymph node dissection for gastric cancer. N Engl J Med 1999;340:908–14.
5. Brennan MF. Lymph node dissection for gastric cancer (editorial). New Engl J Med 1999;340:956–8.

6. Yu CC, Levison DA, Dunn JA, Ward LC, Demonakou M, Allum WH, et al. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. Br J Cancer 1995; 71:1106–10.
7. Hallissey MT, Dunn JA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five year follow-up. Lancet 1994; 343:1309–12.
8. Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, et al. E-cadherin germline mutations in familial gastric cancer. Nature 1998;392:402–5.
9. Shaw D, Blair V, Martin IG. Chromoendoscopic surveillance in a Maori kindred genotypically predisposed to hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy. Gastrointest Endosc 2003;57:AB158.
10. Chen L, Tian H, Chen J, He ZG, Tao SF, Lokesh G, et al. Surgical management of gastric stump cancer: a report of 37 cases. J Zhejiang Univ Sci 2005;6(1):38–42.
11. Ott K, Fink U, Becker K, Stahl A, Dittler HJ, Busch R, et al. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. J Clin Oncol. 2003;21(24):4604–10.
12. Downey RJ, Akhurst T, Ilson D, Ginsberg R, Bains MS, Gonen M, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol. 2003;21(3):428–32.
13. Habermann CR, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, et al. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. Radiology 2004;230(2):465–71.
14. Burke EC, Karpeh MS, Conlon KC, Brennan MF. Laparoscopy in the management of gastric adenocarcinoma. Ann Surg 1997; 225:262–7.
15. Inaba T, Okinaga K, Fukushima R, Iinuma H, Ogihara T, Ogawa F, et al. Prospective randomized study of two laparotomy incisions for gastrectomy: midline incision versus transverse incision. Gastric Cancer 2004;7(3):167–71.
16. Brown SR, Goodfellow PJ, Adam IJ, Shorthouse AJ. A randomized controlled trial of transverse skin crease vs vertical midline incision for right hemicolectomy. Tech Coloproctol 2004;8(1):15–8.
17. Grantcharov TP, Rosenberg J. Vertical compared with transverse incisions in abdominal surgery. Eur J Surg 2001;167:260–7.
18. Kearns SR, Connolly EM, McNally S, McNamara DA, Deasy J. Randomized clinical trial of diathermy versus scalpel incision in elective midline laparotomy. Br J Surg 2001;88(1):41–4.
19. Colombo M, Maggioni A, Parma G, Scalambrino S, Milani R. A randomized comparison of continuous versus interrupted mass closure of midline incisions in patients with gynecologic cancer. Obstet Gynecol 1997;89:684–9.
20. Gouzi JL, Huguier M, Fagniez PL, Launois B, Flamant Y, Lacaine F, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum: a French prospective controlled study. Ann Surg 1989;209:162–6.
21. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five year survival rates in a multicenter randomized Italian trial. Ann Surg 1999;230:170–8.
22. Harrison LE, Karpeh MS, Brennan MF. Total gastrectomy is not necessary for proximal gastric cancer. Surgery 1998;123:127–30.
23. Ito H, Clancy TE, Osteen RT, Swanson RS, Bueno R, Sugarbaker DJ, et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg 2004;199(6):880–6.
24. Shibata C, Shiba K, Gunayama Y, Ishii S, Fukushima K, Mizoi T, et al. Outcomes after pylorus-preserving gastrectomy for early gastric cancer: a prospective multicenter trial. World J Surg 2004; 28:857–61.
25. van de Velde CJ, Sasako M. Surgical treatment of gastric cancer: anatomical borders and dissection of lymph nodes. Ann Chir Gynaecol 1998;87:89–98.
26. Martin RCG, Jaques DP, Brennan MF, Karpeh M. Extended local resection for advanced gastric cancer: increased survival vs increased morbidity. Ann Surg 2002;236:159–65.
27. Kim SH, Karpeh MS, Klimstra DS, Leung D, Brennan MF. Effect of microscopic resection line disease on gastric cancer survival. J Gastrointest Surg 1999;3:24–33.
28. Hori S, Ochiai T, Gunji Y, Hayashi H, Suzuki T. A prospective randomized trial of hand-sutured versus mechanically stapled anastomoses for gastroduodenostomy after distal gastrectomy. Gastric Cancer 2004;7(1):24–30.
29. Osugi H, Fukuhara K, Takada N, Takemura M, Kinoshita H. Reconstructive procedure after distal gastrectomy to prevent remnant gastritis. Hepatogastroenterology 2004;51(58):1215–8.
30. Nomura E, Shinohara H, Mabuchi H, Sang-Woong L, Sonoda T, Tanigawa N. Postoperative evaluation of the jejunal pouch reconstruction following proximal and distal gastrectomy for cancer. Hepatogastroenterology 2004;51(59):1561–6.
31. Shiraishi N, Hirose R, Morimoto A, Kawano K, Adachi Y, Kitano S. Gastric tube reconstruction prevented esophageal reflux after proximal gastrectomy. Gastric Cancer 1998;1:78–9.
32. Tomita R, Tanjoh K, Fujisaki S. Total gastrectomy reconstructed by interposition of a jejunal J pouch with preservation of hepatic vagus branch and lower esophageal sphincter for T2 gastric cancer without lymph node metastasis. Hepatogastroenterology 2004; 51(58):1233–40.
33. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ. Quality control of lymph node dissection in the Dutch randomized trial of D1 and D2 lymph node dissection for gastric cancer. Gastric Cancer 1998;1:152–9.
34. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC Randomized Surgical Trial, Surgical Cooperative Group. Br J Cancer 1999;79:1522–30.
35. Degiuli M, Sasako M, Calgaro M, Garino M, Rebecchi F, Mineccia M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol 2004;30(3):303–8.
36. Edwards P, Blackshaw GR, Lewis WG, Barry JD, Allison MC, Jones DR. Prospective comparison of D1 vs modified D2 gastrectomy for carcinoma. Br J Cancer 2004;90(10):1888–92.
37. Siewert JR, Kestlmeier R, Busch R, Bottcher K, Roder JK, Muller J. Benefits of D2 lymph node dissection for patients with gastric cancer and pN0 and pN1 lymph node metastases. Br J Surg 1996;83:1144–7.
38. Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. Br J Surg 1997;84:567–71.
39. Sasako M. Principles of surgical treatment for curable gastric cancer. J Clin Oncol 2003;21:274s–5s.
40. McCulloch P, Nita M, Kazi H, Gama-Rodrigues J. Extended versus limited lymph node dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev 2004;4: CD001964.
41. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501. J Clin Oncol 2004;22(14): 2767–73.
42. Katai H, Sasako M, Sano T, Fukagawa T. Gastric cancer surgery in the elderly without operative mortality. Surg Oncol 2004;13(4): 235–8.
43. Coniglio A, Tiberio GA, Busti M, Gaverini G, Baiocchi L, Piardi T, et al. Surgical treatment for gastric carcinoma in the elderly. J Surg Oncol 2004;88(4):201–5.

44. Doglietto GB, Papa V, Tortorelli AP, Bosssola M, Covino M, Pacelli F. Nasojejunal tube placement after total gastrectomy: a multicenter prospective randomized trial. Arch Surg 2004;139: 1309–13.
45. Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg 2001;234: 487–94.
46. Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PWT, et al. A prospective randomized trial of early enteral feeding after resection of upper GI malignancy. Ann Surg 1997; 226:567–80.
47. Brennan MF, Pisters PWT, Posner MC, Queseda O, Shike M. A prospective randomized trial of total parenteral nutrition following major pancreatic resection for malignancy. Ann Surg 1994;22: 436–44.
48. Roviello F, Fotia G, Marrelli D, De Stefano A, Macchiarelli R, Pinto E. Iron deficiency anemia after subtotal gastrectomy for gastric cancer. Hepatogastroenterology 2004;51(59):1510–4.
49. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 2004;240:808–16.
50. Ikeda Y, Saku M, Kishihara F, Maehara Y. Effective follow-up for recurrence or a second primary cancer in patients with early gastric cancer. Br J Surg 2005;92:235–9.
51. Hannan EL, Radzyner M, Rubin D, Dougherty J, Brennan MF. The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy and lung lobectomy in patients with cancer. Surgery 2002;131:6–15.
52. Birkmeyer NJ, Goodney PP, Stukel Ta, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer 2005;103:435–41.
53. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh M, Brennan MF. Is gastric cancer different between Japan and the United States? A comparison of patient survival among three institutions. Cancer 2000;89:2237–46.
54. Kodera Y, Ito S, Yamamura Y, Mochizuki Y, Fujiwara M, Hibi K, et al. Obesity and outcome of distal gastrectomy with D2 lymphadenectomy for carcinoma. Hepatogastroenterology 2004;51 (58):1225–8.
55. Desai AM, Pareek M, Nightingale PG, Fielding JW. Improving outcomes in gastric cancer over 20 years. Gastric Cancer 2004;7: 196–201.
56. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than number? An analysis of 1038 patients. Ann Surgery 2000;232:362–71.
57. Peeters KCMJ, Kattan MW, Hartgrink HH, Kranenbarg EK, Karpeh MS, Brennan MF, et al. Validation of a nomogram for predicting disease-specific survival following a R0 resection for gastric cancer. Cancer 2005;103:702–7.
58. Fondevila C, Metges JP, Fuster J, Grau JJ, Palacin A, Castells A, et al. p53 and VEGF expression are independent predictors of tumour recurrence and survival following curative resection of gastric cancer. Br J Cancer 2004;90(1):206–15.
59. Kooby DA, Suriawinata A, Klimstra DS, Brennan MF, Karpeh MS. Biologic predictors of survival in node-negative gastric cancer. Ann Surg 2003;237:828–35.