Controversies in the Surgical Management of Gastric Cancer

David A. Kooby, MD, and Daniel G. Coit, MD, New York, New York

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Stomach, neoplasms, gastrectomy, lymph node excision, splenectomy, adjuvant chemotherapy

Abstract
Although the incidence of gastric adenocarcinoma in the United States has declined steadily since the early 1900s, it remains a significant health problem, with more than 12,000 fatalities estimated in 2002. Overall survival is poor because the majority of cases are detected in advanced stages. Progress has been made during the past few decades, however, in the management of this disease. Lymph node staging has been refined. Perioperative mortality has fallen, and plausible adjuvant therapy has emerged. Even with these advances, complete surgical resection is the current mainstay of therapy because it is the only potentially curative option.

Although as many as 50% of patients with gastric cancer will undergo resection, the specifics of a surgical approach still generate considerable controversy. Seemingly basic concepts such as the optimal extent of gastric resection, the impact of removing neighboring organs (such as the spleen and distal pancreas) to improve surgical margins, and the role of extended lymph node clearance have not been clearly defined. Of these surgical issues, the most controversial is the importance of extended lymphadenectomy (ELND). Retrospective Japanese data support therapeutic benefit to this approach; however, four prospective, randomized trials performed in Western centers have failed to demonstrate a therapeutic value of more aggressive lymphadenectomy.

One area of agreement is the need for effective adjuvant therapy because relapse rates after surgical resection remain high. Unfortunately, little progress has been made in this direction despite many clinical trials. The recent Intergroup 0116 trial is the first to demonstrate a survival benefit associated with adjuvant chemoradiotherapy, which has become an accepted standard of care. Although the results of this trial are promising, issues of patient selection, treatment-related toxicity, and the lack of surgical standardization within the trial have raised as many questions as the study has answered.

This article examines 4 controversial issues in managing gastric cancer: the extent of gastric resection, the role of extended lymph node dissection, the value of elective splenectomy for proximal gastric lesions, and the current state of adjuvant therapy. We review pertinent retrospective and prospective studies to help readers formulate meaningful conclusions.
Extent of Gastric Resection

The goal of curative gastric resection is the removal of all gross and microscopic tumor. The stomach is an organ with an extensive submucosal plexus of lymphatics. As a result, tumors can exhibit extensive intramural spread even before reaching regional lymph nodes. Although a gross 5-cm proximal margin has been suggested, the use of intraoperative frozen-section margin analysis is imperative because 5 cm is an educated guess. The specific optimal margin has never been determined in a randomized trial.

To avoid potentially compromised resection margins, some surgeons advocate total gastrectomy (TG) in all cases, regardless of tumor size or location. This is based on the theory that, in addition to facilitating more extensive regional lymph node dissection, wider surgical margins may lead to fewer local recurrences, which should translate to fewer distant recurrences and prolonged survival. In fact, some older retrospective data suggest a survival advantage associated with this approach. However, other researchers believe that the morbidity associated with removing the cardia and fundus for distal antral cancers (ie, at laparotomy all macroscopic disease could be removed). At a median follow-up of 27 months, no survival advantage was associated with the more aggressive approach, although in this study, the TG + D3 group had a greater incidence of major complications (46% vs 0%, \( P < 0.5 \)).

A larger multicenter study re-examined this question. In this trial, 618 patients with macroscopically resectable disease were randomized during surgery to receive TG or SG, with both groups undergoing deliberate regional lymph node dissection. At a median follow-up of 73 months, no survival advantage was seen for either group (Table 1), and complication rates were similar. Again, this study shows that TG can be performed safely. However, the consistent conclusion from these studies is that routine use of TG for gastric adenocarcinoma does not improve survival for patients with distal gastric cancers.

Carcinomas arising in the proximal third of the stomach are associated with worse prognosis than their more distal counterparts. Although no prospective study has directly compared proximal SG (PSG) to TG for equivalent lesions of the proximal stomach, a retrospective analysis from the prospectively maintained Memorial Sloan-Kettering Gastric Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease Stages</th>
<th>Resection (n)</th>
<th>5-Yr Survival, %</th>
<th>Morbidity, n (%)</th>
<th>Mortality, n (%)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Gouzi et al</td>
<td>I–III</td>
<td>SG (93)</td>
<td>48</td>
<td>32 (34)</td>
<td>3 (3)</td>
<td>Multicenter</td>
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<td></td>
<td></td>
<td>TG (76)</td>
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<td>25 (32)</td>
<td>1 (1)</td>
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<td>0*</td>
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<td></td>
<td>TG (30)</td>
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<td>24</td>
<td>1 (3)</td>
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<td>TG (303)</td>
<td>62.4</td>
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<td>Multicenter</td>
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\( P = 0.05 \).

NA = data not available; SG = subtotal gastrectomy; TG = total gastrectomy.
Database compared PSG with TG for proximal lesions in 98 patients. No postoperative morbidity, mortality, or long-term survival difference was observed for either approach (5-year survival was 43% with PSG vs 41% with TG). This needs to be evaluated in a prospective fashion.

These studies demonstrate that tumor extent, rather than the limits of gastric resection, defines prognosis for patients with gastric cancer. Resection can only affect local disease directly; therefore, the local recurrence rate is the best measure of surgical success. However, quantifying local recurrence in gastric cancer is difficult because many left upper quadrant relapses stem from nodal basin ingrowth and new primary tumors. The premise that optimizing local control through more radical resection translates to a survival benefit has not been substantiated in other malignancies either. Therefore, although TG and SG are associated with similar morbidity and mortality in experienced hands, the optimal extent of gastric resection is that which achieves complete histologic negative margins with a reconstruction that yields optimal long-term functional outcome.

Extent of Lymph Node Dissection

The most controversial issue in surgical management of gastric cancer is the debate over optimal extent of regional lymphadenectomy. In the 1930s, Wangensteen et al reviewed their institution’s experience with gastric cancer and found no 5-year survivors. In an effort to improve results, they advocated a more aggressive surgical approach by adding ELND to gastric resection. Subsequently, techniques for curative gastrectomy with radical lymphadenectomy were standardized at Memorial Sloan-Kettering in the early 1950s. Several Japanese groups have improved our understanding of the complex patterns of gastric lymphatic drainage patterns with detailed pathologic analyses and activated carbon particle mapping.

Conservative lymphadenectomy (CLND), or D1 dissection, involves resection of only the perigastric nodes along the lesser and greater curvatures. A D0 dissection is anything less than a D1. D2 to D4 dissections are classified as ELND. D2 involves a D1 dissection plus nodes along the left gastric artery, common hepatic artery, celiac trunk, and splenic artery. D3 adds dissection of nodes along the hepatoduodenal ligament and root of the mesentery. D4 dissection extends to include para-aortic and paracolic nodes. The majority of Western surgeons perform either a D1 or D2 lymphadenectomy. Proponents of CLND (D1) believe that the potential for increased morbidity associated with ELND (D2) is unwarranted given the lack of prospective data showing a survival advantage with this more aggressive approach. Advocates of D2 lymphadenectomy assert that ELND can be performed safely in experienced hands and that there may be a therapeutic benefit for some patients.

Numerous retrospective studies report the association between improved survival and ELND. Several series in the 1970s and 1980s, primarily from Japanese centers, associated improved survival with greater lymph node clearance. In 1981, Kodama et al found a significant 5-year survival benefit for patients undergoing D2 or D3 resection over historical controls who had undergone D1 LND or less (39% vs 18%). More recently, Maruyama et al reported even better 5-year results (63.8%) for D2 dissection in a study of over 6000 patients; however, this study included a high proportion of patients with early gastric cancer, which may have contributed to improved survival. Because of these and similar results, ELND has become the standard of care in the Far East. Recently, retrospective reports from countries other than Japan have shown similar benefits associated with ELND.

Retrospective reports have obvious limitations. The results of radical surgery in the Far East have been attributed to factors such as stage migration, a higher incidence of early gastric cancers, and asthenic body habitus, facilitating low-morbidity ELND. Because nodal metastases are more likely to be discovered after careful pathologic study of an ELND specimen, many Western patients may be inadequately staged after CLND. For example, a patient with 3 positive nodes of 7 resected may be found to have 7 positive nodes if 20 had been removed and examined, which changes the patient’s TNM staging. Standardization of resection techniques, pathologic analysis, and staging systems are necessary to eliminate this stage migration. Current American Joint Commission on Cancer (AJCC) guidelines account for this issue, requiring examination of 15 or more nodes for adequate staging. Karpeh et al’s results confirmed the importance of this staging requirement. The major limitation of retrospective analyses is that they are heavily governed by patient selection and tumor biology rather than by treatment effect.
To date, 4 prospective, randomized trials have been conducted to address the question of morbidity and survival after ELND (Table 2). Two early trials were limited by small sample sizes. Dent et al. randomized 43 patients to undergo D1 or D2 LND and found no survival advantage for the ELND group; however, this trial only randomized 11% of patients undergoing exploration, restricting its power. Reasons for poor accrual included strict eligibility criteria, such as excluding patients with serosal involvement and those with less than a 5-cm distal margin in the non-stretched stomach. The previously cited Robertson et al. trial, which addressed extent of gastrectomy, also randomized patients to D1 or D3 lymphadenectomy. At a median follow-up of 27 months, survival was better in the D1 group than in the D3 group (45% vs 35% at 5 years). The high morbidity and mortality associated with ELND (57%) were attributed, in part, to complications associated with pancreatectomy and splenectomy.

The Dutch Gastric Cancer Group conducted the first large prospective, randomized controlled trial addressing impact of ELND on survival in gastric cancer. A tremendous effort was made to standardize procedures and to teach surgeons proper technique for participation. In this study, 711 patients (with stages I through IV disease) in 80 centers were randomized to undergo gastrectomy plus D1 or D2 LND. Morbidity and mortality were significantly greater in the D2 group than in the D1 group (morbidity, 43% vs 25%; mortality, 10% vs 4%). At a median follow-up of 72 months, no survival advantage was seen in the ELND group. Despite efforts to standardize both the operative procedure and pathologic evaluation, more than 50% of specimens in the D2 group lacked nodes in at least 2 of the lymph node stations required to complete this procedure (“noncompliance”). Furthermore, 42% of D1 specimens had too many nodal stations included (“contamination”).

Unfortunately, this impressive endeavor was plagued by too many variables and insufficient gastric cancer experience among the many participating surgeons. Recent subset analysis using current AJCC TNM staging demonstrated a survival benefit for patients who were under 70 years of age with N2 disease who underwent D2 LND without pancreatecospplenectomy (Van de Velde C, personal communications, 2002). Unfortunately, the clinical application of these important results is limited at this point because patients with N2 disease cannot consistently be identified preoperatively.

The most recent attempt to answer questions regarding ELND was reported by the Medical Research Council in the United Kingdom. In this trial, 400 patients with stage I to IIIB disease were randomized at time of laparotomy to receive D1 or D2 LND. Survival was equivalent for CLND and ELND at a median follow-up of 78 months; however, again, morbidity and mortality were significantly greater in the D2 group than in the D1 group (morbidity, 46% vs 28%; mortality, 13% vs 7%). Morbidity was strongly associated with concomitant distal pancreatectomy and splenectomy. Of note, 57% of D2 resections included distal pancreatectomy and splenectomy compared with only 4% of D1 resections. Furthermore, little difference was seen in lymph node harvests: a mean of 17 nodes per specimen in the D2 group and 13 nodes in the D1 group.

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease Stages</th>
<th>LND (n)</th>
<th>5-Yr Survival, %</th>
<th>Morbidity, n (%)</th>
<th>Mortality, n (%)</th>
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<tr>
<td>Dent et al.</td>
<td>I–IIIA</td>
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<td>D1 (25)</td>
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<tr>
<td>Bonenkamp et al.</td>
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<td>D1 (380)</td>
<td>45</td>
<td>94 (25)</td>
<td>15 (4)</td>
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<tr>
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<td>47</td>
<td>142 (43)*</td>
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<td>Cushieri et al.</td>
<td>I–IIIB</td>
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<td>35</td>
<td>55 (28)</td>
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<td></td>
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<td>D2 (200)</td>
<td>33</td>
<td>92 (46)*</td>
<td>26 (13)*</td>
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*P < .05.
In summary, retrospective data suggest improved survival for ELND, which prospective randomized controlled trials fail to confirm. Some patients may benefit from ELND, although we still cannot identify them preoperatively. Interestingly, the high perioperative mortality and morbidity reported in these multicenter prospective trials are not observed in single-center trials, in which experience appears to translate into better technique. Our current practice is to perform D2 lymphadenectomy without pancreaticosplenectomy, both to ensure adequate nodal staging (as required by the AJCC) and to provide possible therapeutic benefit for some patients, while minimizing morbidity of the procedure.

**Splenectomy**

Endoscopic lymphography has shown lymphatic drainage patterns running from the proximal left stomach to nodes in the splenic hilum, to splenic artery, and then into the celiac axis. Additionally, the rate of histologically proven cancer in the splenic hilum has been shown to approach 20% in some series, even when there is no obvious gross involvement. Proponents of elective splenectomy in curative resection of diffuse or proximal gastric cancers believe that this procedure is necessary to obtain proper clearance of lymph nodes at the splenic hilum and along the splenic artery. Physicians who do not advocate routine splenectomy quote retrospective data showing no survival advantage and increased morbidity for gastrectomy with elective splenectomy versus gastrectomy alone. Results from these reports are supported by prospective ELND trials, in which splenectomy and pancreaticosplenectomy were associated with most of the excess morbidity and mortality in the ELND group, without contributing to long-term survival (as discussed previously).

Clinical evidence supporting routine splenectomy for proximal gastric cancers is scant. One 1983 prospective, randomized trial of TG with or without splenectomy showed a survival benefit at 3 years for patients undergoing elective splenectomy (68.4% TG + splenectomy vs 50.8% TG alone; \( P = .05 \)), with particular improvement seen in the subset of patients with stage III or IV disease (51.3% vs 11.7%; \( P = .016 \)).

Csendes et al reported on a recent prospective, randomized trial that specifically addressed this controversy. Unlike the Medical Research Council and Dutch trials, this trial separated the question of elective splenectomy from that of ELND. In this study, 187 patients undergoing curative TG with D2 LND were randomized to receive or not receive elective splenectomy. Thus, splenectomy was the only variable. The study ran for 7 years with a minimum follow-up of 5 years. All patients with gross direct spleen involvement or gross adenopathy at the splenic hilum were excluded. Final randomization resulted in 97 patients in the TG, D2 + splenectomy group and 90 in the TG, D2 alone group. The 5-year survival rates were 42% for the splenectomy group and 36% for the nonsplenectomized group; this difference was not statistically significant. Operative mortality was similar for both groups, but the rate of septic complications was higher in the splenectomized cohort (pulmonary complications, 39% vs 24%; subphrenic abscess formation 11% vs 4%; \( P = .04 \)). This study concluded that splenectomy increases postoperative septic complications and should only be performed in patients with macroscopic disease invading the spleen or perisplenic nodes. The report does not state how many surgeons participated, only that surgical approach and pathological analysis were standardized. Therefore, the preponderance of data do not support the therapeutic benefit of elective splenectomy in curative resection of gastric cancer.

**Adjuvant Therapy for Gastric Cancer**

Because the majority of patients with gastric cancer present with advanced disease at diagnosis, recurrence after curative resection is common. Numerous clinical trials of adjuvant therapy have been conducted, but for the most part, results have been disappointing. More than 20 prospective randomized trials to date have evaluated the role of chemotherapy, immunotherapy, and radiation therapy (alone or in combination) as adjuvants to curative resection, 9 of which are particularly noteworthy based on study design (Table 3).  

The majority of trials show no survival advantage over surgery alone. However, 3 positive trials deserve mention. The first is a small study comparing surgery alone (n = 37) with surgery plus 4 cycles of mitomycin C (MMC, n = 33). Researchers observed 10-year survival rates of 48% (surgery alone) versus 84% (surgery and MMC). Interestingly, hepatic recurrences were less common in the treatment group (3 vs 11), while peritoneal recurrences were similar for both arms.
This finding suggests systemic therapy may have impacted distant relapse but not locoregional recurrence. Interpretation of these results, however, is limited by small sample size and lack of a confirmatory study. Larger prospective randomized trials of adjuvant MMC were negative, and no other gastric cancer trial to date has demonstrated an 84% 10-year survival. Therefore, adjuvant MMC cannot be recommended as standard of care.

The second trial investigated the role of adjuvant immunochemotherapy using 5-fluorouracil (5-FU) with MMC and picibanil (OK-432, *Streptococcus pyogenes* preparation) immunostimulant for patients with stage III disease. Two separate prospective single institution studies were performed. The first compared immunochemotherapy plus surgery (n = 74) to surgery alone (n = 64). At 5 years, a significant survival advantage was observed in the adjuvant group over

(13 vs 17). This finding suggests systemic therapy may have impacted distant relapse but not locoregional recurrence. Interpretation of these results, however, is limited by small sample size and lack of a confirmatory study. Larger prospective randomized trials of adjuvant MMC were negative, and no other gastric cancer trial to date has demonstrated an 84% 10-year survival. Therefore, adjuvant MMC cannot be recommended as standard of care.

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the surgery alone group (44.6% vs 23.4%; P < .05; results not shown in Table 3). A second study included a third arm (chemotherapy plus surgery) and confirmed the results of the first study. At 5 years, results from adjuvant immunochemotherapy plus surgery were superior to chemotherapy plus surgery or surgery alone (45.3% vs 29.8% vs 24.4%; P < .05; Table 3). Results of the second confirmatory trial suggested that it was the immunostimulation, rather than the chemotherapy per se, that contributed to improved outcome. These results are provocative and deserve further attention in subsequent trials.

The third positive trial is the most influential adjuvant gastric cancer trial to date; the Intergroup 0116 trial conducted by the Southwest Oncology Group. In this trial, 556 patients who had undergone curative resection for gastric adenocarcinoma (stages IB to IVM0) were randomized to observation (n = 275) or postoperative therapy with 5-FU, leucovorin, and 4500 cGy of fractionated radiotherapy (n = 281). Only patients with good performance scores and adequate oral intake were included. The majority of patients had T3 or higher tumors (68%) and node-positive disease (84%). Median survival was 36 months in the chemoradiotherapy group versus 27 months in the surgery alone group (P = .005), and 3-year survival rates were 50% and 41%, respectively (P = .005).

Overall relapses were higher in the surgery alone group (total relapses, 210) than in the adjuvant group (total relapses, 141). Interestingly, the rates of local and regional relapse were higher in the surgery alone group (178 vs 101), whereas the rates of distant failure were slightly higher in the adjuvant arm (40 vs 32). This pattern suggests that the benefit derived from this regimen may have been due to superior local control provided through radiation therapy rather than to the systemic effect of chemotherapy. Also, of note, a single investigator reviewed all radiation fields, and at least a third of the radiation fields had to be changed for significant protocol violations. The potential for radiation-induced renal toxicity was acknowledged in treatment planning, but the degree of postradiation renal impairment was not reported. Overall, only 64% of patients assigned to the chemoradiotherapy arm completed the planned treatment.

The Radiation Therapy Oncology Group is currently running a phase III trial of adjuvant chemoradiotherapy using 45 Gy of external beam radiation with cisplatin and paclitaxel plus or minus 5-FU. A phase III trial will ensue if the current trial provides promising results.

All adjuvant gastric cancer trials to date have essentially lacked surgical standardization, and the Intergroup trial is no exception. Patients were randomized after resection, and the only surgical requirement was a presumed R0 (curative) resection documented by the operating surgeon. Only 54 (10%) patients in this trial underwent D2 LND. The majority (54%) had less than D1 LND. If the survival advantage seen in the Intergroup trial resulted primarily from adjuvant radiation therapy, then the question becomes this: Does postoperative radiation therapy substitute for inadequate surgical resection? Although overall this is a well-conducted, properly powered study, it remains to be seen how adjuvant chemoradiotherapy will affect patients who undergo standardized, optimal surgical procedure.

Because many patients are not fit to undergo aggressive adjuvant therapy after gastric resection, neoadjuvant therapy is a possible strategy for reducing gastric cancer recurrence. Potential benefits of this approach are multiple. Systemic therapy can be initiated earlier and to more patients because this strategy does not rely on postoperative healing and performance status. Intact tumor blood supply could improve response to chemotherapy because distribution is not impaired by surgical scarring. Tumor responses can be measured objectively and may serve as an in vivo chemotherapy response assay.

Responses may be predictive of survival. If radiation therapy is used, the radiated tumor bed will be removed at surgery. This is in contrast to adjuvant strategies in which the radiation is directed at the intestinal reconstruction, potentially impairing long-term functional results. One possible limitation of neoadjuvant therapy is treating nontarget populations (ie, patients who might not benefit from additional therapy). This can result in excess morbidity and expense and theoretically delays surgery. Improvements in preoperative gastric cancer staging (eg, CT scanning, endoscopic ultrasound, laparoscopy, and laparoscopic ultrasonography) should help identify patients at high risk who are more likely to benefit from neoadjuvant therapy. Clinical neoadjuvant trials are being conducted in NCCN member institutions.

Currently, based on one report, postoperative chemoradiotherapy is an acceptable standard of care.
for patients with stage IB or higher gastric adenocarcinoma who undergo curative resection. The results of this trial clearly require confirmation in the setting of optimal consistent surgical resection and staging, both to define which component of treatment is important and to identify which patients are most likely to benefit.

Conclusions

Retrospective and prospective data have added to our current understanding and management of gastric cancer. Of the 4 controversies examined in this review, 2 appear to have been adequately addressed. The extent of gastric resection depends on tumor location and size, and distal SG is sufficient to treat antral tumors, provided adequate negative resection margins are obtained and have been confirmed by intraoperative frozen section. Elective splenectomy for proximal gastric cancers is not routinely recommended. Splenectomy should be reserved for direct tumor invasion of the spleen or splenic hilum.

Recommendations for the other 2 controversies are less precise. Extended lymph node dissection may benefit a select group of patients, but preoperative identification of these patients is not yet possible. Thus, our recommendation is perform a D2 lymphadenectomy to obtain sufficient nodal tissue for adequate staging, if it can be done with acceptable morbidity. Finally, based on the results of a single trial, the option of adjuvant chemoradiotherapy may be offered to fit patients with good performance status and adequate oral intake, who are at risk of recurrence.

Future trials evaluating both adjuvant and neoadjuvant therapy with surgical standardization are clearly needed. Prospective evaluations of both quality of care, comparing treatment in cancer centers with treatment in other institutions, and quality of life for gastric cancer patients will guide future practice. Finally, the ultimate goal will be to define each individual patient’s disease at the molecular level and tailor therapy accordingly.

References

Gastric Cancer Controversies


