

Review Article

Present and Future Status of Gastric Cancer Surgery

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The type of surgery and the role of adjuvant therapies in the treatment of gastric cancer have changed in recent times. The treatment of gastric cancer with curative intent is moving away from standard D2 or more extensive surgery to a tailored approach depending on the stage of the disease. Data collected from extensive lymphadenectomy for all stages of gastric cancer have confirmed that some subsets of early gastric cancer are very low risk for nodal metastasis. This group of patients may benefit from resection by endoscopic or laparoscopic techniques and may also be suitable for function-preserving procedures. The extent of resection for gastric cancer has always excited debate. D2 gastrectomy was criticized for its higher mortality in the early European Phase III trials, but recent studies from Taiwan and Italy have shown that the procedure is safe when performed by experienced surgeons and has a survival benefit over D1 gastrectomy. The role of para-aortic lymph node dissection for nodes without apparent metastasis in advanced gastric cancer was assessed by a Phase III Japanese trial and showed no additional benefit over D2 resection. Radical gastric resections, involving resection of adjacent organs for direct tumor invasion result in higher rates of complications, and the role of multi-visceral resections has also been reevaluated. Effective adjuvant therapies for gastric cancer have been reported since the early part of 2000. Development of more effective adjuvant therapy combined with D2 resection should continue to improve survival in the future.

Key words: gastric cancer – surgery – function-preserving gastrectomy – laparoscopic gastrectomy – adjuvant therapy

INTRODUCTION

Chemotherapy helps to prolong survival in cases of advanced disease, but surgery is still the mainstay of curative treatment for gastric cancer. From uniform use of D2 or more extensive surgery, surgical treatment has evolved to become more tailor-made depending on the stage of the disease.

Extensive operations have been reevaluated for advanced gastric cancer and the role of effective adjuvant therapies in this setting has expanded. More radical operations than D2 for gastric cancer have often been carried out without clear evidence until clinical trials have failed to show the survival benefit of these procedures over D2. For early gastric cancer,

less extensive resections and minimally invasive techniques have been developed, such as function-preserving procedures and laparoscopic surgery.

D2 LYMPHADENECTOMY

Total or subtotal gastrectomy with D2 lymphadenectomy is the gold standard surgical treatment for gastric cancer in eastern Asia. The procedure initially developed in Japan, has been safely performed and provided good survival outcomes for patients with gastric cancer regardless of disease stage (1,2). The use of this technique has been challenged by Western clinical trials since the 1990s.

RESULTS OF EARLY EUROPEAN TRIALS

Phase III trials on D2 dissection for curable gastric cancer were carried out by the Medical Research Council and the Dutch Gastric Cancer Group in the early 1990s (3,4). These trials failed to show a survival benefit for D2 over D1 dissection.

The British and Dutch trials demonstrated extremely high hospital mortality after D2, reaching 10 and 13%, respectively. In the British trial, the survival curve of D2 was never better than that of D1 until the end of the trial. In the Dutch trial, the survival curve of D2 caught up with that of D1 after 4 years and remained superior, but the difference between D1 and D2 survival never reached statistical significance.

DISCUSSION OF THE EARLY TRIALS

The lack of surgical training in the technique of D2 gastrectomy and sub-optimal quality control may explain the inferior outcomes of D2 versus D1 gastrectomy in these early trials. Both trials were carried out without pre-trial training or preliminary studies to confirm the safety of the procedure, and were concluded before many surgeons would have reached the plateau of their learning curve. The 80 hospitals contributing data to the Dutch trial were all relatively low volume units, with most performing only a few gastric resections per year. With such limited experience, it is almost impossible to maintain the quality of the technique and gain adequate experience in managing major complications such as anastomotic leakage, pancreatic fistula or intra-abdominal abscess, all of which can lead to an increase in morbidity and mortality.

Routine resection of the tail of the pancreas in total gastrectomy has been credited with disappointing results. Detailed analysis of the Dutch and British studies showed that splenectomy and distal pancreatectomy were more significant causes of morbidity and mortality than D2 itself (5). In the D2 arm of these trials, splenectomy and distal pancreatectomy were mandatory during total gastrectomy. Resection of the distal pancreas and spleen is no longer deemed a necessary component of modern D2.

Fifteen-year follow-up results of the Dutch trial were recently reported in 2010 (6). The authors reported that D2 was associated with lower loco-regional recurrence and gastric cancer-related death rates than D1. They concluded that D2 is the recommended surgical approach for patients with resectable gastric cancer.

RECENT TRIALS ON D2 DISSECTION

The Italian Gastric Cancer Study Group (IGCSG) started a prospective one-arm Phase II study in 1994 to confirm the safety and efficacy in increasing survival, using the D2 gastrectomy (7). Following concerns about the high mortality observed in the Dutch and British trials, with total

gastrectomy, they utilized the pancreas-preserving procedure according to the Maruyama technique instead of employing routine distal pancreatectomy (8). Furthermore, they implemented a strict quality control component consisting of pre-trial surgical training at a specialized center in Japan and intra-operative supervision by experienced surgeons. As a result, the Italian trial, including nine hospitals with a total of 191 patients, demonstrated 3% mortality. The survival results of this Phase II study were much better than that of the D2 arms in the Dutch and British trials (9).

Following the favorable results of the Phase II trial, the IGCSG conducted a Phase III trial comparing D1 ($n = 133$) with D2 ($n = 134$), including five specialized hospitals with a total of 267 patients. The post-operative 30-day mortality was 3% for D1 and 2.2% for D2 (10). The safety of D2 performed by experienced surgeons at specialized centers was confirmed in the Phase III study. The survival data from this study is eagerly awaited.

The results of a Phase III trial from Taiwan, comparing D1 ($n = 110$) with D3 ($n = 111$), were reported in 2006 (11). Their D3, according to the old Japanese Classification, in addition to D2, included lymph nodes within the hepato-duodenal ligament, on the superior mesenteric vein, behind the common hepatic artery and on the posterior pancreatic surface but not the para-aortic lymph nodes. This trial was conducted by three experienced surgeons at a single institution and showed statistically significant improvement in survival of D3 compared with D1, demonstrating 5-year survival rates of 59.5 and 53.6%, respectively ($P = 0.04$). This is the first Phase III trial in the world showing survival benefit of radical lymphadenectomy compared with the limited lymphadenectomy. However, this study cannot be considered as solid evidence for the superiority of D3 over D1 because of the rather small sample size and modest survival benefit.

IS SPLENECTOMY ESSENTIAL TO D2 TOTAL GASTRECTOMY?

Retrospective Japanese studies revealed that 20–30% of patients with advanced gastric cancer in the proximal stomach had nodal metastasis in the splenic hilum (12) and therefore pancreas-preserving splenectomy is part of the standard D2 total gastrectomy (8). After the British and Dutch trials on D2 showed that splenectomy was an important risk factor for post-operative morbidity and mortality, the Japan Clinical Oncology Group (JCOG) conducted a Phase III trial to evaluate the role of splenectomy in total gastrectomy (13). A total of 505 patients with advanced gastric cancer in the upper third of the stomach, without involvement of the greater curvature were randomly assigned to total gastrectomy with ($n = 254$) or without splenectomy ($n = 251$). Recruitment has been completed and final results are awaited. The trial is powered to evaluate the impact on overall survival. If the survival is approximately equivalent, splenic preservation will be the preferred treatment for patients with such tumors.

ADJUVANT THERAPY

A Phase III study comparing surgery alone to surgery plus post-operative adjuvant chemoradiotherapy (CRT), the INT0116/SWOG9008, showed a large survival benefit of the latter (14). The CRT arm included curative surgery and radiation therapy of 45 Gy with combination chemotherapy using fluorouracil and leucovorin. A total of 556 patients were randomly assigned to surgery alone ($n = 275$) or surgery plus CRT ($n = 281$). The median survival time of surgery alone and surgery plus CRT was 27 and 36 months, respectively ($P = 0.005$). In this trial, 90% of the patients underwent less extensive D0 or D1 surgery while only 10% underwent D2. Although the extent of lymphadenectomy failed to significantly correlate with survival due to the small patient population of D2, detailed analysis showed that inadequate surgery negatively affected survival (15). Sasako et al. (16) noted that the patient population in the CRT arm of this trial was quite similar to the population in a Japanese clinical trial comparing surgery alone to surgery plus adjuvant chemotherapy (17). Most of the prognostic factors, i.e. histological type, tumor location, age, tumor size, and, tumor depth were reasonably comparable between the groups. Nevertheless, the 5-year overall survival of the CRT arm of the INT0116 and the surgery alone arm of the Japanese trial were 42 and 61%, respectively. Sasako et al. strongly suggested that D2 surgery alone might produce better survival than D0/D1 surgery followed by CRT and that the effect of adjuvant CRT may not be so significant if D2 gastrectomy was performed as the standard operation.

The MAGIC trial, a Phase III trial comparing surgery alone to surgery plus peri-operative adjuvant chemotherapy, is the first study demonstrating a clear benefit of neoadjuvant chemotherapy (combined with post-operative chemotherapy) over surgery alone (18). The chemotherapy protocol consisted of three pre-operative and three post-operative cycles of intravenous epirubicin, cisplatin and fluorouracil. A total of 503 patients were randomly assigned to surgery alone ($n = 253$) or surgery plus peri-operative chemotherapy ($n = 250$). The 5-year survival rate of surgery alone and peri-operative chemotherapy group were 23 and 36%, respectively ($P = 0.009$). There was no hazard ratio analysis for the extent of surgery and therefore the benefit of peri-operative adjuvant chemotherapy in addition to D2 surgery remains unclear.

The results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC trial) comparing surgery alone to surgery plus adjuvant S-1 was reported in 2007 (19). Administration of S-1 was started within 6 weeks after curative D2 surgery and continued for 1 year. Patients treated with adjuvant S-1 ($n = 529$) demonstrated a significantly better 3-year survival than those who underwent surgery alone ($n = 530$) (80.5 versus 70.1%, $P = 0.003$). In Japan, adjuvant S-1 therapy has become the standard treatment of choice for Stages II and III gastric cancer patients after curative D2.

MORE EXTENSIVE SURGERY THAN D2

More extensive surgery than D2 was often carried out in the 1980s and the early 1990s, without any high-level evidence favoring these more extensive procedures. Japanese clinical trials of para-aortic lymph node dissection (PAND) for advanced tumor without apparent metastasis to the nodes and left thoraco-abdominal approach (LTA) for cardiac tumors have shown no survival benefit for patients who underwent such extensive procedures (20,21).

PARA-AORTIC LYMPH NODE DISSECTION

In advanced gastric cancer, the incidence of microscopic metastases in the para-aortic lymph nodes had been reported from 10 to 30% (22–24). Because the 5-year overall survival rate of patients with para-aortic nodal metastases could be as high as 20% after systematic dissection, PAND had been performed in Japan since the 1980s (25). JCOG conducted a Phase III trial at 24 hospitals in Japan comparing D2 alone ($n = 263$) to D2 plus PAND ($n = 260$) in the late 1990s (JCOG9501) (20). The 5-year overall survival rate was 69.2% for D2 alone and 70.3% for D2 plus PAND. The median operation time was 63 min longer and the median blood loss was 230 ml greater in the group assigned to D2 plus PAND. Treatment with D2 plus PAND did not significantly improve the survival rate in curable gastric cancer when compared with D2. The results may have been disappointing due to the low incidence of para-aortic node metastasis (8%) in this patient population. However, PAND is no longer routinely applied in patients without apparent para-aortic nodal metastases.

Along with para-aortic node metastasis, bulky nodal metastases surrounding the celiac artery and its branches usually suggest poor prognosis. A Phase II trial was carried out by JCOG to evaluate the efficacy and safety of pre-operative chemotherapy followed by D2 plus PAND for locally advanced gastric cancer with bulky celiac nodes and/or para-aortic node metastasis (JCOG0001) (26). The neoadjuvant chemotherapy consisted of irinotecan and cisplatin. This trial was terminated after 55 patients were enrolled because of three treatment-related deaths. The survival outcomes in these patients were promising, with the median survival time of 14.6 months and the 3-year survival rate of 27%.

Following the reasonable results of JCOG0001, JCOG conducted a Phase II trial of pre-operative S-1 plus cisplatin followed by D2 plus PAND for the same patient population as JCOG0001 (JCOG0405) (27). S-1 plus cisplatin is the Japanese standard chemotherapy regimen for unresectable or recurrent gastric cancer. Of 53 enrolled patients, 51 patients were eligible and resection rate and R0 rate were 92 and 82%, respectively. No treatment-related death was observed. Improvement in survival outcome is highly anticipated. The PAND procedure in this scenario is evaluated in combination with neoadjuvant chemotherapy for patients with apparent para-aortic node metastasis.

LTA APPROACH FOR CARDIAC TUMOR

The incidence of lower mediastinal lymph node metastasis from cardiac tumors is reported from 10 to 40% (28–32). Because of the inaccessibility of the mediastinal nodes, the LTA had often been used to treat gastric cancer in the cardia (28,29). A randomized Phase III trial was carried out by JCOG to compare the LTA to the abdominal–transhiatal (TH) approach in the treatment of gastric cancer of the cardia with esophageal invasion of <3 cm (JCOG9502) (21). A total of 167 patients were enrolled and randomly assigned to TH ($n = 82$) or the LTA ($n = 85$). At the first interim analysis, 5-year overall survival rate was 52.3% in the TH group and 37.9% in the LTA group. Mortality and morbidity were worse after the LTA (mortality 4%, morbidity 49%) compared with the TH group (0, 34%). The predicted probability of the LTA having a significantly better overall survival than TH group at the final analysis was only 3.65%, and the trial was closed before achieving the projected sample size ($n = 302$). These results do not support routine use of the LTA in treating such tumors.

MULTI-VISCERAL RESECTIONS FOR GASTRIC CANCER

For locally advanced gastric cancer with invasion of the head of the pancreas or duodenum, pancreato-duodenectomy may be required. This procedure was rarely performed due to the substantial associated morbidity and mortality until some favorable results were recently reported with a 5-year survival rate of 16–34% (33–36). Although the rate of morbidity after pancreato-duodenectomy is high, this procedure can be attempted by experienced surgeons at specialized hospitals in order to achieve an R0 resection. This may be attempted with the caveat that survival benefit is only likely for patients with a low burden of lymphatic disease (35,37).

For linitis plastica type gastric cancer, which is diffusely infiltrative and often incurable, wide resection such as the left upper abdominal evisceration with or without Appleby's procedure was sometimes attempted (38,39). However, many of these tumors were eventually incurable, and some curable tumors showed a very poor prognosis even after extensive surgery. Surgery alone is currently thought to be inadequate, and the addition of neoadjuvant chemotherapy has demonstrated interesting results for marginally resectable tumors (40).

LESS EXTENSIVE SURGERY FOR EARLY GASTRIC CANCER

Examination of lymph node status from extensive lymphadenectomy performed in all stages of gastric cancer has resulted in a vast amount of knowledge concerning the extent and pattern of nodal metastasis. We accordingly know that certain subsets of early gastric cancer have a rare chance of nodal metastasis and in this group extensive lymphadenectomy is unnecessary (41–44).

FUNCTION-PRESERVING GASTRECTOMY

Early gastric cancer has an excellent prognosis after surgical treatment, with 5-year survival rates of more than 90%. Since the early 1990s, function-preserving surgery has been introduced in the treatment of early gastric cancer to minimize post-gastrectomy syndromes with the intention of creating a better quality-of-life, while maintaining a high level of radicality (45–47).

PYLORUS-PRESERVING GASTRECTOMY

Pylorus-preserving gastrectomy (PPG) is a function-preserving procedure initially described for treatment of peptic ulcer disease by Maki et al. in 1967 (48). Early gastric cancer in the gastric body rarely spreads to the suprapyloric nodes, with an incidence of <1% (49). The pyloric branch of the vagal nerve running alongside the right gastric artery can be preserved by omitting the removal of the suprapyloric nodes so as to maintain the function of the pylorus. As a result, PPG is currently indicated for such tumors. A pyloric cuff of ~2–5 cm in length is preserved to prevent rapid gastric emptying and consequent dumping syndrome. Infrapyloric vessels are preserved to maintain the blood supply of the pyloric cuff. It has been reported that the incidence of the post-prandial dumping syndrome, biliary reflux and gallstone formation is decreased, and body weight recovery is as good as compared with Billroth I reconstruction (47,50–53). Survival outcome after PPG is comparable to that after conventional gastrectomy (49).

PROXIMAL GASTRECTOMY

Early gastric cancer located in the proximal third of the stomach rarely spreads to the distal peri-gastric lymph nodes (54). Proximal gastrectomy has been applied to these patients so as to maintain a gastric reservoir. Pylorus function is preserved with this method by preserving vagal nerves in a way similar to PPG. This procedure has clear advantages over total gastrectomy regarding short-term side effects and long-term survival (54,55). Reflux esophagitis is a common complication after proximal gastrectomy (56–58), and an anti-reflux procedure is usually combined with proximal gastrectomy (54,59).

LAPAROSCOPIC GASTRECTOMY

Since the early 1990s, laparoscopic surgery has been adopted as minimally invasive treatment for early gastric cancer. Laparoscopic wedge resection with a lesion-lifting method and intra-gastric mucosal resection were initially developed for the treatment of early gastric cancer without the risk of lymph node metastasis (60,61). Since Kitano et al. (62) first reported laparoscopic-assisted distal gastrectomy (LADG) with lymph node dissection, this procedure has been widely applied worldwide for early gastric cancer with a low risk of lymph node metastasis.

There have been four small randomized controlled trials, which reported that LADG has several advantages over open surgery, including early recovery, less pain and less impaired pulmonary function. At the same time, there appears to be no difference in morbidity and mortality when compared with open distal gastrectomy (ODG) (63–66). A recent multi-center retrospective study with 1294 patients conducted by the Japanese Laparoscopic Surgery Study Group reported morbidity and mortality rates after laparoscopic gastrectomy to be 14.8 and 0%, respectively, and showed a comparably good survival outcome to open gastrectomy (67).

A Phase II study estimating the feasibility of LADG in the treatment of Stage I gastric cancer patients was carried out by JCOG (JCOG0703). The results demonstrate that LADG can be performed safely with an acceptable morbidity by experienced surgeons (68). Following the result of this Phase II study, JCOG has initiated a large Phase III trial comparing LADG with ODG for Stage I cancer (JCOG0912).

The Korea Laparoscopic Gastrointestinal Surgery Study Group conducted a multi-institutional Phase III trial (KLASS trial) to assess the short- and long-term outcomes of LADG for early gastric cancer (69). A total of 342 patients were randomly assigned to LADG ($n = 179$) or ODG ($n = 161$) and the morbidity rates were 10.5 and 14.7%, respectively ($P = 0.137$). The mortality rates were 1.1 and 0% in the LADG and ODG groups ($P = 0.497$), respectively. Survival outcomes from this trial are still awaited.

CONCLUSION

D2 gastrectomy is still considered the gold standard surgical treatment for advanced gastric cancer but multi-modality treatments combined with surgery may further improve survival. There are now several surgical options for early gastric cancer depending on the risk of nodal metastasis. The efficacy of LADG for early gastric cancer is currently being assessed. If the results are favorable, then LADG may also be appropriate for more advanced disease. These specialist procedures will require good quality control achieved through supervision and training by experienced surgeons in high volume centers.

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Conflict of interest statement

None declared.

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