

Evidence Based Surgical Approach to Locally Advanced Gastric Cancer

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ABSTRACT

Gastric cancer is endemic in China, Japan, Korea, Brazil and Former Soviet Union. Patients are diagnosed usually in locally advanced stage. Endoscopy, Positron Emission Therapy- Computed Tomography, Endoscopic ultrasound and staging laparoscopy are the tools for proper evaluation of such patients. Locally advanced gastric cancer (T2-4N0 or TanyN+) requires multimodality treatment including surgery. Resection is the cornerstone of cure for gastric adenocarcinoma; however, several aspects of surgical intervention remain controversial or are suboptimally applied at a population level. Current evidence shows a D2 gastrectomy has got the best survival results. At least 15 lymph nodes should be assessed for adequate staging. Laparoscopic resections should be performed to the same standards as those for open resections, by surgeons who are experienced in both advanced laparoscopic surgery and gastric cancer management.

Keywords: Curative surgery; gastrectomy; stomach neoplasms.

INTRODUCTION

Gastric cancer though rampant in many countries around the world appears to be a serious health problem in East Asian countries. The incidence of gastric cancer is much higher in China than in any other country. In Japan, it remains the most common type of cancer among men. The incidence of gastric cancer, however, has been declining globally since World War II and it is one of the least common cancers in North America. According to GLOBOCAN 2018 data, gastric cancer is the third leading cause of cancer deaths worldwide, following only lung and colorectal cancer in overall mortality. Gastric cancer has the fifth highest incidence among cancers, with 5.7% of all new cases.¹ In 2018, an estimated 26240 people will be diagnosed and 10800 people will eventually die of their disease in the United States.² Non-cardia gastric cancer shows marked geographic variation with countries such as Japan, Korea, China, Taiwan, Costa Rica, Peru, Brazil, Chile, and the former Soviet Union.³

In Japan (and in a limited fashion in Korea) where screening is performed widely, early detection is often possible. In other parts of the world, it continues to pose a major challenge for health care professionals.

Therefore, patients are diagnosed mostly in locally

advanced stage. By definition, locally advanced cancer stands for T2-4N0 or N+ tumors.

Survival outcomes differ considerably between Eastern and Western populations, with better overall survival reported in Eastern series.⁴ Many authors have sought explanations for this finding based on the following: stage migration, differences in tumor biology, or differences in treatment.⁵ Surgical treatment differs in that extended lymph node dissection is routinely practiced in Asian countries,^{6,7} resulting in greater lymph node retrieval. Whether this leads to stage migration or to a direct therapeutic effect has yet to be resolved. Furthermore, adjuvant therapy differs between the two regions.

Junctional tumors have a various approach, therefore only the tumors, which are, located more than 2 cm distal to GE Junction (Siewert type - III/ body and antrum) will be discussed here.

WORK-UP AND STAGING

Clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound (EUS), CT, PET/ CT, MRI, and laparoscopic staging.⁸⁻¹⁰

EUS is indicated for assessing the depth of tumor

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invasion.¹¹ However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.¹² EUS is also helpful to identify T1 tumors for potential endoscopic approaches.

CT scan is routinely used for preoperative staging. It has an overall accuracy of 43% to 82% for T staging. Combined PET/CT imaging, on the other hand, has several potential advantages over PET scan alone.¹³ PET/CT has a significantly higher accuracy in preoperative staging (68%) than PET (47%) or CT (53%) alone.

Laparoscopic staging can detect occult metastases. In a study conducted by Memorial Sloan Kettering Cancer Center, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging over a period of 10 years.¹⁴ Distant metastatic disease (M1) was detected in 31% of the patients.

In summary, routine work up includes upper GI endoscopy, CT of chest/ abdomen/ pelvis, CT/ PET if no evidence of distant metastases and EUS.

SURGERY

In 2014, Japanese Gastric Cancer Association (JGCA)¹⁵ published Version 4 of the Japanese Gastric Cancer Treatment Guidelines. The English version was published in 2017. According to JGCA, surgery has been classified as curative and non-curative surgery. Curative surgery is further subclassified in standard gastrectomy (removal of at least two-thirds of stomach with a D2 nodal dissection), non-standard gastrectomy (resection is altered according to tumor stage), modified gastrectomy (only D1 or D1+ nodal dissection is performed) and extended gastrectomy (where adjacent involved organs are resected or a D2+ nodal dissection is performed). Non-curative gastrectomy stands for palliative surgery only (palliative gastrectomy or gastroenterostomy).

RESECTION MARGIN

A sufficient resection margin should be ensured when determining the resection line in gastrectomy with curative intent. Proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (types 1 and 2) and 5 cm for those with an infiltrative growth pattern (types 3 and 4). When these rules cannot be observed, it is advisable to examine the proximal resection margin by frozen section. For tumors invading the esophagus, a 5-cm margin is not necessarily required, but frozen section examination of the resection line is desirable to ensure an R0 resection.

Subtotal gastrectomy is the preferred approach for distal gastric cancers. This procedure has a similar surgical outcome compared to total gastrectomy although with significantly fewer complications.¹⁶ Adequate gastric resection (distal, subtotal, or total gastrectomy) to achieve negative microscopic margins (4 cm or greater from the gross tumor) is preferred for resectable T1b-T3 tumors.¹⁷ T4 tumors require en bloc resection of involved structures. Retrospective analyses have shown that more extensive lymph node dissection and analysis of 15 or more lymph nodes influences survival in patients with advanced gastric cancer.^{18,19} In the SEER database analysis that included 1377 patients diagnosed with advanced gastric cancer, patients who had more than 15 N2 nodes and more than 20 N3 nodes examined had the best long-term survival outcomes.¹⁸

EXTENT OF NODAL DISSECTION

Regional nodes for gastric cancer have been classified from levels 1-20, 110, 111 and 112.¹⁵

Lymph node dissection can be classified into D1, D1+, D2, D2+ and D3. For locally advanced gastric cancer,¹⁵ gastrectomy with D2 lymph node dissection is the standard treatment for curable gastric cancer in eastern Asia. In the West, D2 lymph node dissection is considered a recommended but not a required procedure. However, there is uniform consensus that removal of an adequate number of nodes (15 or greater) is beneficial for staging purposes.

Initial results from two large randomized trials performed in Western countries failed to demonstrate a significant survival benefit for D2 over D1 lymph node dissection.^{20,21} In the Dutch Gastric Cancer Group Trial, 711 patients who underwent surgical resection with curative intent were randomized to undergo either a D1 or D2 lymph node dissection.²⁰ The postoperative morbidity (25% vs. 43%, $P < .001$) and mortality (4% vs. 10%, $P = .004$) were higher for patients who underwent D2 lymph node dissection, with no difference in overall OS (30% vs. 35%, $P = .53$) between the two groups. In a subset analysis, patients with N2 cancer undergoing a D2 lymph node dissection showed a trend towards improved survival. Long-term follow-up data from the Dutch Gastric Cancer Group trial have confirmed a survival benefit for D2 lymph node dissection. The 15-year OS rates were 21% and 29%, respectively, for the D1 and D2 group ($P = .34$). D2 lymph node dissection was also associated with lower rates of local (12% vs. 22%) and regional recurrence (13% vs. 19%).²² More importantly, gastric cancer-related death rate was significantly lower in the D2 group compared to the D1 group (37% and 48%,

respectively).²²

The British Cooperative trial conducted by the Medical Research Council also failed to demonstrate a survival benefit for D2 over D1 lymph node dissection.²¹ The 5-year OS rates were 35% and 33%, respectively, for D1 and D2 lymph node dissections. In addition, the D2 lymph node dissection was associated with increased postoperative morbidity and mortality.

Both the Dutch and the MRC trials have been heavily criticized based on the following conditions: (1) poor quality control of both surgery and postoperative care, (2) high incidence of insufficient nodal dissection (noncompliance), and (3) adoption of a more aggressive D2 dissection by routine use of pancreaticosplenectomy.

In a randomized controlled trial (JCOG9501), Japanese investigators comparing D2 lymph node dissection alone with D2 lymph node dissection with para-aortic nodal dissection (PAND) in patients undergoing gastrectomy for curable gastric cancer (T2b, T3, or T4) reported a postoperative mortality rate of 0.8% in each arm.²³ The final results of this study showed that D2 lymph node dissection with PAND does not improve survival rate, compared to D2 lymph node dissection alone. The 5-year OS rates were 70.3% and 69.2%, respectively. There were also no significant differences in the relapse-free survival (RFS) rates between the two groups.²⁴ In a post-hoc subgroup analysis, among patients with pathologically negative nodes, the survival rates were better for patients who underwent D2 lymph node dissection plus PAND than those who were assigned to D2 lymph node dissection alone. In patients with metastatic nodes, the survival rates were worse for those assigned to D2 lymph node dissection plus PAND. However, the investigators of this study caution that these results from post-hoc analysis could be false positive due to multiple testing, and the survival benefit of D2 lymph node dissection with PAND in patients with node-negative disease needs to be clarified in further studies. The investigators concluded that D2 lymph node dissection plus PAND should not be used to treat patients with curable gastric cancer (T2b, T3, or T4).

In a randomized phase II trial of D1 vs. D2 lymph node dissection conducted by the Italian Gastric Cancer Study Group in 267 patients with gastric cancer (133 patients allocated to D1 lymph node dissection and 134 patients allocated to D2 lymph node dissection), the morbidity and postoperative mortality rate were not significantly different between the two groups.^{25,26} In this study, pancreatectomy and splenectomy were not considered as a routine part of the D2 resection; the spleen and

pancreas were removed only when indicated by the surgeon.

The overall mortality rate was 12% after D1 lymph node dissection vs. 17.9% after D2 lymph node dissection ($P = .183$). The corresponding postoperative 30-day mortality rates were 3% and 2.2%, respectively ($P = .722$). At the median follow-up of 8.8 years, the 5-year OS rates were 66.5% and 64.2% after D1 and D2 lymph node dissections, respectively ($P = .695$).²⁶ D2 lymph node dissection was associated with a trend towards improved DSS in patients with advanced gastric cancer (pT2-T4) and positive lymph nodes (59% vs. 38% for D1 lymph node dissection; $P = .055$).²⁶

Meta-analyses have confirmed that among patients who underwent D2 lymph node dissections, there was a trend toward improved survival and lower gastric cancer-related mortality for patients who did not undergo resection of the spleen or pancreas, as well as for patients with T3 or T4 cancers.²⁷⁻²⁹

The role of splenectomy for complete resection of lymph node stations 10 and 11 has long been a controversial issue. Recently, the final results of an RCT (JCOG 0110) that compared splenectomy and spleen preservation in total gastrectomy have been reported with survival analysis.³⁰ This is the largest RCT studying splenectomy in gastric cancer. It included 505 patients (splenectomy, 254; spleen preservation, 251) and demonstrated significant noninferiority of splenic preservation for the first time. The splenectomy group had higher morbidity ($P < .01$) and larger blood loss ($P = .025$) than the spleen-preserving group. The 5-year OS rates were 75.1% and 76.4% in the splenectomy and spleen preservation groups, respectively, and the noninferiority of spleen preservation was demonstrated ($P = .025$).

In total, gastrectomy for proximal gastric cancer that does not invade the greater curvature, prophylactic splenectomy should be avoided; this is true not only for surgical safety but also for survival benefit.

Therefore, the recent guidelines emphasize that D2 lymph node dissection should be performed by experienced surgeons in high-volume centers. Prophylactic pancreatectomy and splenectomy should be avoided with D2 lymph node dissection.^{31,32}

LAPAROSCOPIC RESECTION

A metaanalysis of 14 trials (1 RCT and 13 non-RCT) was performed. A total of 2596 patients (1328 - laparoscopic; 1268 - open) were included. Laparoscopic group showed

lower intraoperative blood loss, lower analgesic consumption, and shorter time to first ambulation, flatus and oral intake, shorter hospitalization and lower postoperative morbidities. Oncological outcome, three and five year overall survival were similar. However, laparoscopic group had longer operative time.³³

In a recent meta-analysis of seven randomized controlled trials totaling 390 patients comparing laparoscopic versus open distal gastrectomies, the laparoscopic approach was found to have longer operative time but was also associated with less blood loss, fewer analgesics administered, faster recovery, and shorter postoperative hospital stay.³⁴

POSTOPERATIVE CHEMORADIATION THERAPY

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effect of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of stomach or gastroesophageal junction.^{35,36} Median overall survival (OS) in the surgery only group was 27 months and was 36 months in the chemoradiation group ($P = .005$). The chemoradiation group had better 3-year OS (50% vs. 41%) and relapse free survival rates (48% vs. 31%) than the surgery only group. There was also a significant decrease in local failure as the first site of failure (19% vs. 29%) in the chemoradiation group. With more than 10 years of median follow-up, survival remains improved in patients with stage IB-IV (M0) gastric cancer or adenocarcinoma of gastroesophageal junction treated with postoperative chemoradiation.³⁶ In the INT-0116 trial, D2 lymph node dissection was not commonly performed and patients were not excluded on the basis of the extent of lymph node dissection. D0, D1, and D2 lymph node dissections were performed in 54%, 36%, and 10% of patients, respectively.

POSTOPERATIVE CHEMORADIATION VS. POSTOPERATIVE CHEMOTHERAPY

The results of a phase III trial (ARTIST trial) showed that postoperative chemoradiation with capecitabine and cisplatin did not significantly reduce recurrence after D2 lymph node dissection in patients with curatively resected gastric cancer ($n = 458$; stage IB-IV, M0).^{37,38} At a median follow-up of 53 months, the estimated three year disease free survival (DFS) rates were 78% and 74%, respectively, for postoperative chemoradiation and chemotherapy ($P = .0862$). After median follow-up duration of 7 years, the estimated 5-year OS rates were 73% and 75%, respectively, for postoperative chemotherapy and chemoradiation ($P = .484$).³⁸ In the

subgroup analysis of patients with positive pathologic lymph nodes, postoperative chemoradiation was associated with a statistically significant prolongation of 3-year DFS compared to chemotherapy alone (77.5% and 72%, respectively; $P = .0365$).³⁷ However, this study demonstrated that postoperative treatment with capecitabine and cisplatin is feasible following a D2 lymph node dissection.

PERIOPERATIVE CHEMOTHERAPY

The British Medical Research Council performed the first well-powered phase III trial (MAGIC trial) that evaluated perioperative chemotherapy for patients with resectable gastroesophageal cancer.³⁹ In this trial, 503 patients were randomized to receive either perioperative chemotherapy (preoperative and postoperative chemotherapy) with ECF and surgery or surgery alone. Patients were randomized prior to surgery (74% of patients had gastric cancer; 69% in the surgery plus chemotherapy group and 66% in the surgery only group had undergone R0 resection). The majority of patients had T2 or higher tumors (12% of patients had T1 tumors, 32% of patients had T2 tumors, and 56% of patients had T3-T4 tumors) and 71% of patients had node-positive disease. The perioperative chemotherapy group had a greater proportion of T1 and T2 tumors (51.7%) and less advanced nodal disease (N0 or N1; 84%) than the surgery group (36.8% and 70.5%, respectively). Perioperative chemotherapy significantly improved progression-free survival (PFS; $P < .001$) and OS ($P = .009$). The 5-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group but only 41% had D2 dissection and in 41%, lymphadenectomy status was unknown. Japanese surgeons would argue that perioperative chemotherapy or adjuvant chemoradiotherapy compensates for inadequate surgery.

POSTOPERATIVE CHEMOTHERAPY

Asian, randomized, phase III studies (ACTS GC trial and CLASSIC trial) have documented survival benefit for postoperative chemotherapy after curative D2 lymph node dissection in patients with gastric cancer.⁴⁰⁻⁴²

The objective of the Japanese ACTS-GC trial was to examine the efficacy of adjuvant S-1 (tegafur, gimeracil, and oteracil) in stage II and III gastric cancer where 1034 patients were randomized to 12 months of oral S-1 or surgery alone.^{40,41} The surgical quality control was excellent with all centers performing 100 cases annually; all but one patient underwent a D2 or D3 lymphadenectomy. The results of the trial

regarding chemotherapy and surgery demonstrated an improvement in 5-year overall survival of 71.1% versus 61.1%. This finding secured the place of postoperative chemotherapy with S-1 as a standard of care (recommendation category 1).

Additional evidence in support of postoperative chemotherapy was provided in 2012 by the CLASSIC trial conducted in South Korea, China, and Taiwan.⁴² In this trial, 1035 patients with stage II or III gastric cancer were randomized to XELOX (a combination of capecitabine and oxaliplatin) or surgery alone; significant prolongation of recurrence-free survival was shown in the XELOX arm.

SIGNIFICANCE OF PERITONEAL LAVAGE CYTOLOGY

Positive peritoneal lavage cytology carries poor prognosis similar to stage IV disease. Therefore, curative surgery is not recommended in such a clinical scenario. However, recently published guidelines suggested that cytology-positive status in the absence of other noncurative factors, that is, macroscopic disease, can be managed with D2 gastrectomy and perioperative chemotherapy.¹⁵

In a metaanalysis by Jamel et al,⁴³ it was found, patients with positive cytology may have good prognosis following neoadjuvant treatment if the cytology turns negative after treatment. They proposed repeat peritoneal lavage cytology after neoadjuvant chemotherapy and in case of negative cytology - to proceed for curative surgery.

SCENARIO IN NEPAL

The exact cancer prevalence rate in Nepal is unknown due to the lack of a population based national cancer registry. According to the present data from National Hospital based Cancer registry (analysis of 7212 cancer patients), gastric cancer is second most common cancer in males (7.3%) and 5th in females (3.8%).⁴⁴

Extent of gastric cancer resection and type of nodal dissection is also not known in Nepal. There are few data in literature that have highlighted the issue of surgery.

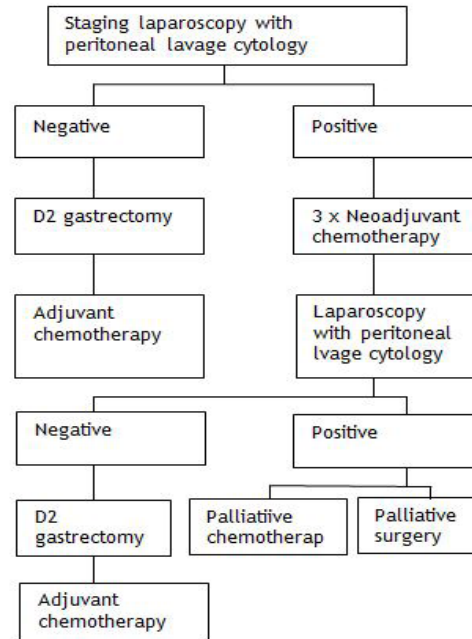
In a study of 397 cases of gastric cancer from Manipal Teaching Hospital, Nepal, 70% had the tumor located in antrum of stomach.⁴⁵

There have been several studies from Institute of Medicine, Nepal.⁴⁶⁻⁵⁰ In a retrospective review of 140 surgically treated patients at Tribhuvan Teaching

Hospital, Nepal, 61.5% had the tumors located in lower third of stomach. 96% had advanced carcinoma with only 4% having early gastric cancer. The overall 5 year survival was 8.3% only.⁴⁶

While looking particularly at the incidence of early gastric cancer, Ghimire et al found incidence of 4.3% in a retrospective analysis of 92 patients.⁴⁷ Authors emphasized the necessity of screening program in Nepal.

Based on the available evidences, the simple algorithm of management of locally advanced gastric cancer (excluding Siewert type II lesions), would be as follows:



CONCLUSIONS

At the time of diagnosis, patients are generally staged to have locally advanced disease except in the scenario of a National protocol for routine screening. In a resectable non metastatic disease, D2 gastrectomy not only stages the disease adequately but also improves overall and disease free survival. Therefore, D2 gastrectomy should be surgical procedure of choice. Extent of resection (distal vs. total gastrectomy) depends upon the location of tumor and if more than 4 cm of proximal tumor free margin can be achieved, distal gastrectomy has to be considered. Laparoscopic distal gastrectomy may be considered if the expertise is available. Laparoscopic total gastrectomy is technically more challenging and may not be recommended as a general rule. Besides, routine pancreaticosplenectomy should be avoided.

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