

## Review Article

## Surgical strategy for 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, PET-CT, Endoscopic ultrasound and staging laparoscopy are the tools for proper evaluation of such patients. Locally advanced gastric cancer (T2-4N0 or T any N+) requires multimodality treatment including surgery. Surgical strategy requires gastrectomy with D2 nodal dissection.

**Keywords:** Gastric cancer; D2 lymphadenectomy; Gastrectomy.

### Introduction:

Gastric cancer is rampant in many countries around the world. 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. By some estimates, it is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer worldwide. In 2017, an estimated 28,000 people will be diagnosed and 17,750 people will eventually die of their disease in the United States. 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.

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. Many authors have sought explanations for this finding based on the following: stage migration,<sup>5</sup> differences in tumor biology, or differences in treatment. Surgical treatment differs in that extended lymph node dissection is routinely practiced in Asian

countries,<sup>6,7</sup> 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.<sup>8-10</sup> EUS is indicated for assessing the depth of tumor invasion. However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.<sup>12</sup> 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. 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.<sup>14</sup> Distant metastatic disease (M1) was

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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)<sup>15</sup> 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 follows:

**Curative surgery**

**Standard gastrectomy:** Standard gastrectomy is the principal surgical procedure performed with curative intent. It involves resection of at least two-thirds of the stomach with a D2 lymph node dissection.

**Non-standard gastrectomy:** In non-standard gastrectomy, the extent of gastric resection and/or lymphadenectomy is altered according to tumor stages.

**Modified surgery:** The extent of gastric resection and/or lymphadenectomy is reduced (D1, D1+, etc.) compared to standard surgery.

**Extended surgery:** (1) Gastrectomy with combined resection of adjacent involved organs. (2) Gastrectomy with extended lymphadenectomy exceeding D2.

**Non-curative surgery**

Palliative surgery: Serious symptoms such as bleeding or obstruction may develop in a patient with advanced/metastatic gastric cancer. Surgery to relieve symptoms may then be considered an option, and palliative gastrectomy or gastrojejunostomy is selected depending on the resectability of the primary tumor and/or surgical risks.

Extent of gastric resection may vary from distal gastrectomy (Stomach resection including the pylorus. The cardia is preserved. In the standard gastrectomy, two-thirds of the stomach is resected) to total gastrectomy (Total resection of the stomach including the cardia and pylorus).

**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.

**Anatomical definitions of lymph node stations and concept of nodal dissection:**

Regional nodes for gastric cancer have been named as shown in Table 1.

Nr.	Definition
1	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery
2	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery
3a	Lesser curvature LNs along the branches of the left gastric artery
3b	Lesser curvature LNs along the 2 <sup>nd</sup> branch and distal part of the right gastric artery
4sa	Left greater curvature LNs along the short gastric arteries (perigastric area)
4sb	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)
4d	Rt. greater curvature LNs along the 2 <sup>nd</sup> branch and distal part of the right gastroepiploic artery
5	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery
6	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreaticoduodenal vein
7	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch
8a	Anterosuperior LNs along the common hepatic artery
8p	Posterior LNs along the common hepatic artery
9	Coeliac artery

Nr.	Definition
10	Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1 <sup>st</sup> gastric branch
11p	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end
11d	Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail
12a	Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
12b	Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
12p	Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
13	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla
14v	LNs along the superior mesenteric vein
15	LNs along the middle colic vessels
16a1	Paraaortic LNs in the diaphragmatic aortic hiatus
16a2	Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein
16b1	Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery
16b2	Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	LNs along the inferior border of the pancreatic body

Nr.	Definition
19	Infradiaphragmatic LNs predominantly along the subphrenic artery
20	Paraesophageal LNs in the diaphragmatic esophageal hiatus
110	Paraesophageal LNs in the lower thorax
111	Supradiaphragmatic LNs separate from the esophagus
112	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus

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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>18,19</sup> 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.<sup>18</sup>

#### Extent of nodal dissection:

Lymph node dissection can be classified into D1, D1+, D2, D2+ and D3. For locally advanced gastric cancer, 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.<sup>20,21</sup> 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.<sup>20</sup> 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 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%). More importantly, gastric cancer-related death rate was significantly lower in the D2 group compared to the D1 group (37% and 48%, respectively).

The British Cooperative trial conducted by the Medical Research Council also failed to demonstrate a survival benefit for D2 over D1 lymph node dissection. 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 pancreatico-splenectomy. 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. 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.<sup>24</sup> 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.<sup>25,26</sup> 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 ( $P = .695$ ).<sup>26</sup> 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;  $P = .055$ ).

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.<sup>27-29</sup>

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.<sup>30</sup> 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.<sup>31,32</sup>

For total gastrectomy with D2 nodal dissection, levels 1,2,3,4,5,6,7,8a, 9,10,11p, 11d, 12a should be excised (Fig1). For distal gastrectomy with D2 dissection, levels, 1,3,4,5,6,7,8a, 9,11p, 12a should be excised. (Fig 2).

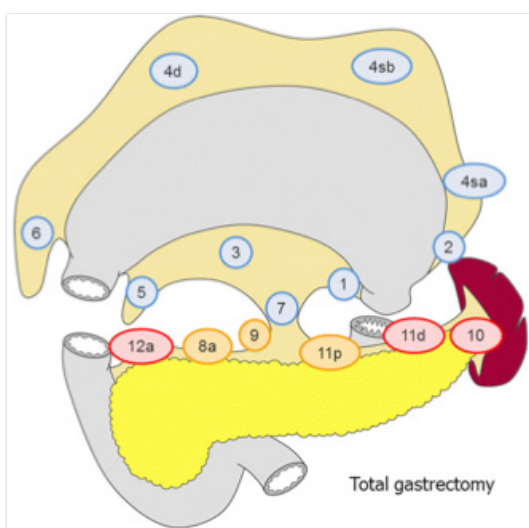


Fig. 1.

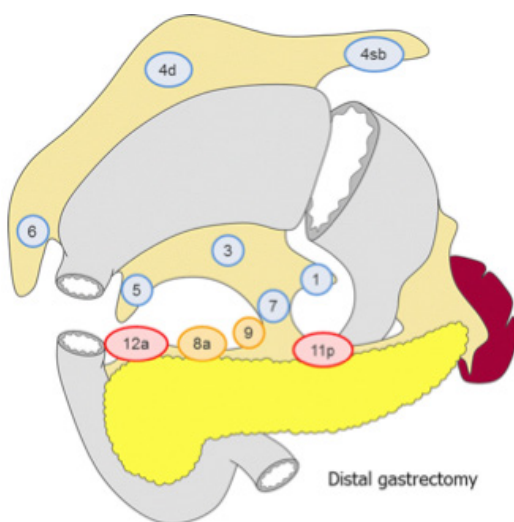


Fig 2.

### 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, 3 and 5-yr OS were similar. However, laparoscopic group had longer operative time.<sup>33</sup>

In a recent meta-analysis of 7 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.<sup>34</sup>

### 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 gastric or EGJ. Median 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 RFS 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 EGJ adenocarcinoma treated with postoperative chemoradiation.<sup>36</sup> 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).<sup>37,38</sup> At a median follow-up of 53 months, the estimated 3-year 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 ( $P = .484$ ).<sup>38</sup> 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;  $P = .0365$ ).<sup>37</sup> 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.<sup>39</sup> 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

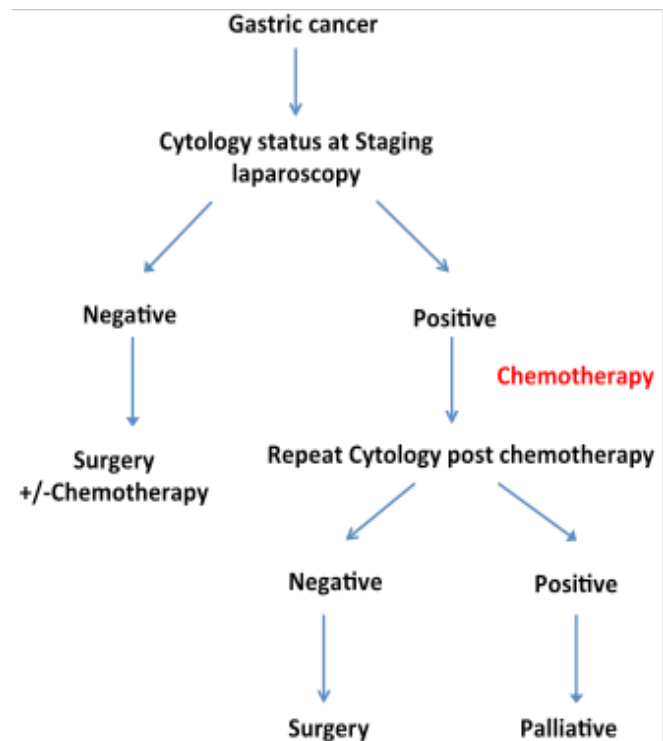
Asian, randomized, phase III studies (ACTS GC trial and CLASSIC trial) have documented survival benefit for postoperative chemotherapy after curative D2 lymph node dissection in patients with gastric cancer.<sup>40,41,42</sup>

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.<sup>40,41</sup> 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.<sup>42</sup> 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.

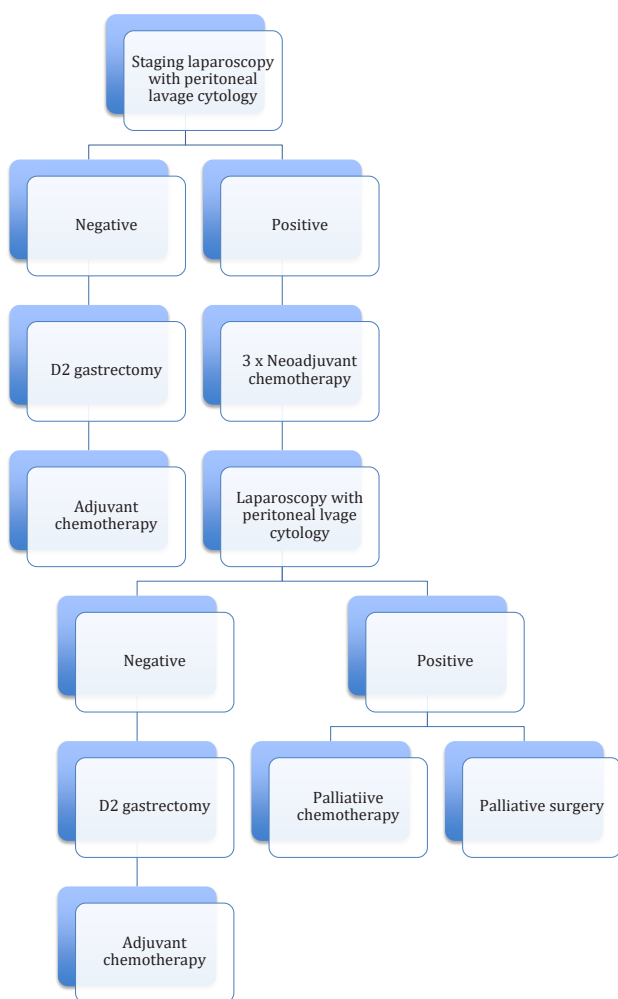
### Significance of peritoneal lavage cytology

In a metaanalysis by Jamel et al<sup>43</sup>, it was found, patients with positive cytology may have good prognosis following neoadjuvant treatment if the cytology turns negative after treatment. They proposed a guideline:



**Conclusion:**

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



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