Surgical Treatment of Gastric Cancer

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SURGICAL EXTENT

The curative treatment of gastric cancer can be divided into endoscopic and surgical. Endoscopic treatment is restricted to tumors with invasion until the mucosa **(T1a)**, well differentiated, non-ulcerated and up to 2.0 cm. For patients who do not meet these criteria, surgical treatment is proposed.

The extent of surgery depends primarily on the location of the tumor. Patients with tumors of the gastroesophageal transition (Siewert classification types II and III) are candidates for total gastrectomy + D2 lymphadenectomy + mediastinal lymphadenectomy, with mandatory intraoperative frozen section of the proximal

margin (esophageal margin). Patients with tumors Siewert I are candidates for esophagectomy + proximal gastrectomy + mediastinal lymphadenectomy and D1 plus lymphadenectomy.

For proximal gastric tumors, we recommend total gastrectomy (by the proximal oncologic margin - ideally 2.0cm for intestinal type tumors and 5.0cm for diffuse tumors) + D2 lymphadenectomy. For distal tumors, a subtotal gastrectomy can be performed as long as it respects margins of 2 cm for early tumors, 3 cm for advanced vegetative tumors and 5 cm for all others.

In 1999 Bozzetti et al. published a randomized multicentered retrospective study comparing total and subtotal gastrectomy (D2 lymphadenectomy and proximal surgical margin of 6 cm was used in both groups) with curative intent in patients with distal third gastric cancer in 31 Italian centers. That study concluded that the two procedures were equivalent when compared to 5-year survival, that is, there would be no advantage of total gastrectomy in relation to subtotal, especially when taking into account the greater degree of complexity of total gastrectomy, requiring greater surgical and hospitalization time, as well as being associated with higher rates of postoperative complications, however, without differences in survival outcome [1].

Squires et al. published in 2015 a retrospective study to assess whether the 5.0 cm margin obtained in subtotal gastrectomy is really necessary, as well as to evaluate its impact on recurrence and overall survival. As to survival, TNM clinical stage I patients with proximal margins between 3.1 and 5.0 cm had increased overall and disease-free survival when compared to patients with margins less than 3.0 cm. However, there was no gain in survival when the margin was greater than 5.0 cm. More advanced cases, TNM clinical stage II and III with margins between 3.0 and 5.0 cm are accepted because survival is impacted by other factors [2].

Another point of interest concerning the extent of the surgery is bursectomy and omentectomy. An omentectomy should be performed routinely and may be limited in tumors with infiltration up to the muscular layer - T2 (TNM, 2010). In these cases, a resection of omentum fat to approximately 3.0 cm from the arch of the gastro-epiploic vessels is performed. A bursectomy is the removal of the anterior leaflet of the mesocolon and pancreatic capsule in monobloc with gastrectomy and lymphadenectomy. It is agreed that a bursectomy should be performed in patients with posterior wall tumors infiltrating the serosa -T4a [3].

In 2015, Hirao et al. published a multicentered randomized prospective study that investigated the role of non-realization of prophylactic bursectomy. A bursectomy added in that sample an average of 27 minutes to the surgery and increased blood loss (475 ml in the bursectomy group vs. 350 ml in the group that bursectomy was not

performed). Despite the higher number of non-bursectomized patients, in multivariate analysis, bursectomy was a prognostic factor that improves survival and in sub-group analysis there was a trend for bursectomy to better results in middle third and distal tumors (5-year overall survival of 80.7% in patients undergoing bursectomy vs. 70.7% in non-bursectomized patients). Bursectomy was also superior in patients with stage T3/T4 [4].

LYMPHADENECTOMY EXTENT

Lymphadenectomy is a crucial part of the surgical treatment of gastric cancer. It is divided into D1, D1 plus and D2 according to the dissected lymph node chains. The extent of surgery as well as the location of the primary tumor may change the extent of lymphadenectomy.

Total Gastrectomy

D1 Lymphadenectomy

perigastric lymph nodes + left gastric artery; **D1 PLUS:** perigastric lymph nodes + left gastric artery + common hepatic artery + celiac trunk and proximal splenic territory; **D2:** perigastric lymph nodes + left gastric artery + common and proper hepatic artery + proximal/distal splenic artery + splenic hilum.

Subtotal Gastrectomy

D1 Lymphadenectomy

perigastric lymph nodes (small curvature dissection) + left gastric artery; **D1 PLUS:** perigastric lymph nodes + left gastric artery + common hepatic artery + celiac trunk; D2: perigastric lymph nodes + left gastric artery + common and proper hepatic artery + proximal splenic artery.

D1 lymphadenectomy should be performed on T1a tumors that are not candidates for endoscopic resection and T1b tumors up to 1.5 cm, well differentiated. A D1 plus in patients with lesions T1b that do not fit the requirements for D1 resection and D2 lymphadenectomy should be performed in all patients with lesions above T2 or with compromised lymph nodes.

In 2014, an Italian study comparing survival after D1 and D2 lymphadenectomy was published. In that study, the resection of the spleen and pancreas was not considered mandatory in D2 lymphadenectomy. In that sample, patients who underwent gastrectomy with D2 lymphadenectomy did not have greater overall survival than the group submitted to D1. Subgroup analysis suggests a survival benefit in patients with locally advanced tumors and positive lymph nodes. A criticism of this work is the excessive amount of lymph nodes resected in D1 and the amount of initial tumors in this group (T1 and T2). Usually the average of lymph nodes resected in D1 is 15, while in that study were 28 lymph nodes [5].

Another study conducted in Taiwan compared D1 and D3 lymphadenectomies. In that study, the overall survival at 5 years by intention to treat was 59.5% in the group that underwent D3 lymphadenectomy and 53.6% in the D1 group. Patients who underwent R0 resection with D3 lymphadenectomy had greater overall survival than those with D1 lymphadenectomy. In multivariate analysis, factors of worse prognosis were: positive lymph node, linitis, Borrmann type III and IV and D1 lymphadenectomy. That study did not show results of morbidity and mortality in the group that underwent D3 lymphadenectomy, but mentions that in experienced groups, morbidity and mortality is acceptable [6].

In both studies, none of the patients underwent neoadjuvant chemotherapy or adjuvant chemotherapy.

The D2 lymphadenectomy is performed mainly based on a randomized study conducted in Taiwan and the update from the “Dutch trial” published in 2010 that showed a gain of survival

with D2 lymphadenectomy, reduction of death from gastric cancer and decreased locoregional recurrence rate.

A para-aortic lymphadenectomy should not be routinely indicated because it increases surgical time, blood loss and postoperative complications without increasing overall and disease-free survival when compared to patients who underwent gastrectomy with D2 lymphadenectomy [7].

MULTIVISCERAL RESECTION

In many cases, resection of adjacent organs is necessary to obtain clear margins (R0 resection) and/or suitable lymphadenectomy. The organs most commonly resected in this setting are the spleen and the body and tail of the pancreas. In ultraselected cases, a gastroduodenopancreatectomy may be performed in patients with distal gastric cancer who underwent neoadjuvant treatment with good response and who have good prognostic factors. Surgery in these cases should be performed with curative intent.

Tran et al. published a retrospective study in 2015 investigating morbimortality and survival of patients undergoing multivisceral resection for gastric cancer. In those cases selected for study, the organs most commonly resected were the spleen (48%), pancreas (27%), the left lateral segment of the liver (14%) and colon (13%). Despite multivisceral resection increasing morbidity of surgery (longer operative and hospitalization time, greater blood loss, higher fistula rates and higher rates of Clavien- Dindo III and IV complications), no increase in postoperative mortality was observed in the first 30 and 60 days. The survival results were separated into three groups: gastrectomy; gastrectomy with multivisceral resection without pancreatectomy; gastrectomy with multivisceral resection with pancreatectomy. As expected, the cases in which multivisceral resection were performed had more advanced tumors and a higher incidence of perineural and lymphovascular invasion. The survival results were worse in the group who underwent pancreatectomy and overall survival at 5 years was only 6% [8].

In Japan and in some European trials, splenectomy and distal pancreatectomy were recommended for adequate D2 lymphadenectomy. When evaluating trials of multivisceral resection, it is necessary to evaluate the indication of pancreatectomy, since patients undergoing pancreatectomy with indication of complementary lymphadenectomy have better survival than those with direct invasion of the organ, which has low overall survival, consistent with that presented by Tran, 2015.

In summary, the treatment of gastric cancer, even with invasion of adjacent organs, is surgical and the goal should always be R0 resection. Patients undergoing pancreatectomy have a worse overall survival than those who undergo splenectomy, colectomy or hepatectomy. Nevertheless, morbidity and mortality rates are acceptable in the curative surgical setting.

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRA-ABDOMINAL CHEMOTHERAPY

In patients with peritoneal carcinomatosis as a single site of metastasis, cytoreduction with hyperthermic intra-abdominal chemotherapy is a therapeutic possibility in selected cases. Patients submitted to neoadjuvant chemotherapy with cytoreduction have a greater chance of complete surgery.

Chia, 2016 performed a retrospective study to evaluate the outcome of patients undergoing cytoreduction associated with hyperthermic intra-abdominal chemotherapy. That sample contained predictive factors of increased survival: complete cytoreduction, low peritoneal carcinomatous index, absence of signet ring cells and synchronous metastases. Patients submitted to complete cytoreduction **(CC0)** had an average survival of 22.1 months vs. 8.4 months of patients undergoing CC1 cytoreduction. There was a 11% rate of disease-free survival for patients after 5 years [9].

Coccolini, 2015 questioned the survival gain according to the value of the peritoneal disease index (PDI). In their sample with patients with PDI > 19, the mean survival at 1 year was 0%. In the patients with PDI between 0 and 6, the mean 1 year survival was 56% and 30% at 5 years [10].

MINIMALLY INVASIVE SURGERY

Laparoscopy for gastric tumors was described in the 1990s, especially for early tumors. Adequate lymphadenectomy was the greatest obstacle to the method; however, to gain global experience in advanced laparoscopy, the surgical indications were also expanded and thus increased the interest in the outcome of laparoscopy when compared to conventional surgery.

In 2014, a Korean retrospective study was published comparing the results of laparoscopic gastrectomy with conventional surgery. Two analyzes were performed: one case-control and another without matching cases. In the control case analysis, there was no statistical difference in overall survival at 5 years, except for stage Ia, which had better survival in the laparoscopic surgery group. In case-matched analysis, there was no difference in overall survival between groups. In both analyzes there was no difference in morbidity and mortality. In oncologic terms and long-term monitoring, there was no difference between open surgery and laparoscopy [11].

The KLASS-01 Trial is a phase 3 prospective/randomized multicentered study published by a Korean Group of Gastrointestinal Surgical Study to evaluate the morbidity of laparoscopic gastrectomy in patients with stage I gastric cancer. Laparoscopic gastrectomy is associated with longer surgical time, less blood loss, shorter hospital stay and lower rate of complications at 30 days. Nonetheless, it also showed a lower number of resected lymph nodes. The conversion rate was 0.9%. There was no statistical difference between the mortality rates of the two groups. Therefore, that study showed laparoscopy as a safe method for early gastric tumors, with less morbidity in the early postoperative period [12].

In addition to laparoscopy, robotic surgery has been gaining ground in the last decade. Despite this, its use for gastric neoplasms is still controversial and to our knowledge, there is no prospective study investigating the role of assisted robotic surgery.

In 2012, Xiong, et al. published a meta-analysis comparing laparoscopic and robotic gastrectomy in patients with gastric cancer. This meta-analysis had only three studies and those studies evidenced that robotics has longer surgical time and less bleeding. There was no difference in the number of lymph nodes resected, morbidity and mortality and/or hospital stay between the two groups [13].

As to minimally invasive surgery, more studies are needed comparing laparoscopy and robotics with conventional surgery, both short and long term, particularly for the oncological result.

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