Overview on Gastric Cancer

Chapter 2

Surgery of Localized Gastric Cancer

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1. Introduction

Gastric carcinoma is one of the most common cancers and one of the most frequent causes of cancer death worldwide. The first step for a correct treatment in gastric cancer is to stage correctly the tumor, based on the TNM classification, in accordance with the classification of the American Joint Committee on Cancer (AJCC) staging system [1].

The correct staging allows us to identify early or initial gastric tumors and choose the adequate treatment for each patient. This factor is one of the most important elements in the improvement of the results in the treatment of gastric cancer.

Once we have diagnosed our patient, through endoscopy and biopsy, we need to practice a TC scan in order to rule out the presence of metastasis. If we discard the presence of metastasis, we must assess the penetration of the tumor in the gastric wall (T) and the involvement of locoregional lymph nodes (N).

The endoscopic ultrasound (EUS) is the most common test for the determination of the T stage, even though its accuracy to distinguish the affectation of the mucosa and submucosa is low and its reliability decreases in case of ulcerated early gastric tumors [2,3,4]. However, it is the elected test in order to determine the T stage of the tumors.

As for the study of the T component, the most common test for the study of the N involvement is the endoscopic ultrasound. The EUS reaches a specificity of 80 % to determine affected or positive perigastric nodes [5].

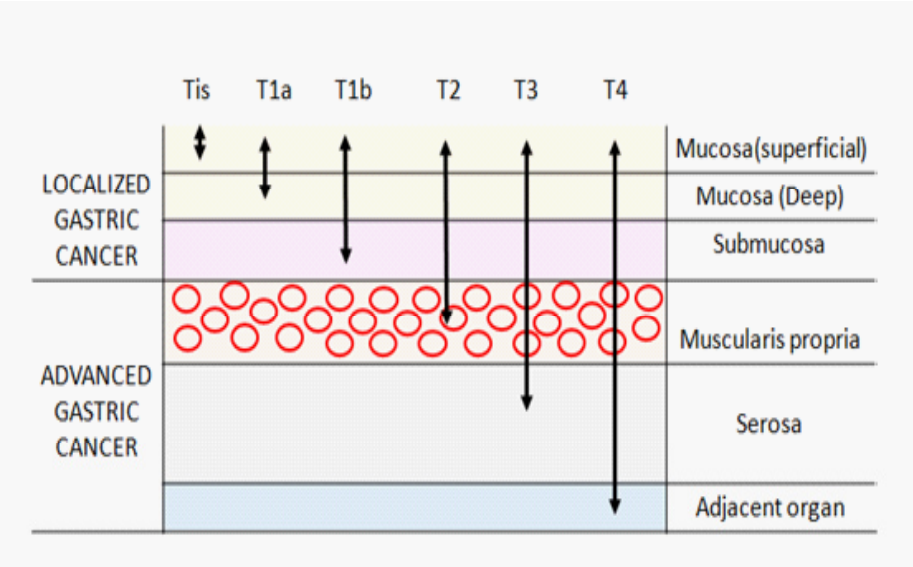
The presence of locoregional lymph nodes metastasis is one of the principle prognostic

factors in gastric cancer [6,7].

If the tumor is intraepithelial the probability of lymph node involvement is nearly absent. If the tumor affects only the mucosa the risk is <3 % but when the submucosa is affected, this risk arises up to 20 % approximately [8,9,10].

There are several characteristics of the tumors that allow us predict or determine the probability of presenting positive lymph nodes. Thus, tumors smaller than 3 cm, non-ulcerated, and without lymphatic infiltration have a minimal probability of lymph node involvement [11].

Grades of affectation on gastric wall



Once we have staged our tumor we define the localized gastric cancer (LGC) as the one that affects the mucosa or submucosa without evidence of involvement of locoregional lymph node metastasis. The involvement of the gastric wall in these cases corresponds to the stages Tis, T1 a, and T1 b.

Tumor staging for gastric cancer

Tis or in situ carcinoma or intraepithelial carcinoma: affects the mucosa without exceeding the lamina propria.

T1a: the tumor involves the lamina propria or the muscularis mucosae.

T1b: the tumor invades the submucosa.

Once classifying the tumor as a localized gastric cancer, the available treatment possibilities are reflected below. The choice of the best option will be based on the characteristics of each patient and tumor.

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Therapeutic Possibilities

- Conventional surgery or laparoscopic surgery
  - Total or partial gastrectomy
  - Pylorus-preserving gastrectomy
  - Atypical gastrectomy, local resection
- Endoscopic techniques
  - Endoscopic mucosal resection
  - Endoscopic submucosal dissection
  - Ablative mucosal techniques

2. Surgery Treatment

The main and curative treatment of gastric cancer is surgery [12,13,14]. The morbidity and mortality rates of gastrectomy for gastric cancer vary according to different regions of the world. In countries like Japan or Korea the morbidity and mortality rates round values over 17-20 % and 0.6-0.8 %, respectively, while in Western countries these rates reach values over 40 % and 10 % respectively [13]. This is due to the high incidence of this pathology in the Eastern countries (specially in Japan and Korea), where they have implemented screening programs, so the diagnosis is made at earlier stages increasing the chance of survival; the patients are younger with less comorbidities and the specialization of the surgeons in this pathology.

Surgery Options

- Conventional surgery or laparoscopic surgery
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The primary objective of surgery is to achieve the complete removal of the tumor with free disease margins to avoid relapse or local recurrences. In reference to the security disease margins to adopt there are different options. Although in the Japanese Gastric Cancer Treatment Guidelines they advocate in differentiating the security disease margins according to the stage of the patient, in T1 tumors they recommend a security disease margin of 2 cm and in ≥ T2 tumors they recommend a security disease margins of at least 3 cm. In addition, according

to the histological type of the tumor, in intestinal type tumors they support a security disease margin of at least 3 cm while in the diffuse histological type support a margin of 5 cm [15]. Other authors such as Griffin et al, state that a security disease margin of 5 cm is enough without making distinctions according to the histological type or the stage of the tumor [16].

2.1. Conventional Gastrectomy

The choice of the type of surgery is based on the location of the tumor, the characteristics of the tumor, and the characteristics of the patient. The standard worldwide accepted treatment is gastrectomy with D2 lymphadenectomy.

In tumors located in the third distal of the stomach, we must perform a partial gastrectomy with removal of the first duodenal portion.

In tumors located in middle third of the stomach, the therapeutic option will differ according to the remnant stomach on the upper third, being the total gastrectomy the most typical option.

Finally, for tumors located in the upper third the most common option is a total gastrectomy. To avoid performing a total gastrectomy, we can practice a partial gastrectomy with an esophageal-gastric reconstruction; this option has positive oncological results but poor results in terms of quality of life (high rate of gastroesophageal reflux and alkaline reflux). These complications can be offset with a jejunal isoperistaltic interposition [17] or with the performance of a duodenal switch [18].

Numerous authors have studied differences in quality of life, delayed gastric emptying, frequency of appearance of dumping syndrome, weight loss after surgery or symptoms of dysphagia between partial and total gastrectomy, with favorable results in all aspects for the partial gastrectomy group [19,20]. Some works report a higher incidence or local recurrence after a partial gastrectomy [21,22,23].

The improvement of the diagnosis tests that allows us to discard the presence of lymph node metastasis and the diagnosis in earlier stages have permitted the development of the function-preserving gastrectomy that offers a better postoperative quality of life [24]. The function-preserving gastrectomy includes the pylorus-preserving gastrectomy (PPG), proximal gastrectomy, and limited gastrectomy with sentinel node [25].

2.2. Pylorus-Preserving Gastrectomy

The pylorus-preserving gastrectomy was described in 1967 by Maki. It was a surgery indicated for ulcers that later extended to early gastric cancer. It has got some advantages as a decrease of gastric resection, preservation of the pylorus and preservation of the vagus nerve

[20].

The indications for this treatment modality are gastric tumors staged as T1 N0 M0 localized in the middle third with no evidence of lymph node involvement and localized at least 4 cm from the pylorus (despite the fact that it is still a controversial aspect) [27]. This technique is associated with a selective vagotomy, conserving the hepatic branch of the vagus nerve and preserving the infrapyloric and suprapyloric vessels [28].

When we compare the quality of life, frequency of appearance of dumping syndrome, weight loss after surgery or alkaline reflux between patients with pylorus-preserving gastrectomy and patients without preserving the pylorus we find better results in favor of the first group [26,29]. With respect to relapse and 5-overall survival rates, the results are excellent, with 5-year survival rate that reaches values over 96-98% [30,31,32].

2.3. Local Resections

The local resection under laparoscopy seems to be an ideal method to prevent postoperative symptoms caused by gastric resections. They can constitute an alternative to endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) when there are difficult techniques to carry out these procedures. The theoretical advantage over EMR is that local resection is able to achieve a resection of the entire lesion with free macroscopic margins with greater security. In the case of tumors located on the anterior gastric wall or in the curvatures, we can achieve the resection with conventional laparoscopy. In tumors located in posterior gastric wall, we should perform an intragastric laparoscopy or transgastric laparoscopy. A combined technique (laparoscopic endoscopic cooperative surgery) [33] can be helpful for achieving a complete resection of the tumor with adequate margins. The indications defined by Ohgami and colleagues are [34]:

1. Preoperatively diagnosed mucosal cancer.

2. <25 mm diameter elevated lesions.

3. <15 mm diameter depressed lesions without ulcer formation.

2.4. Lymphadenectomy

There is no evidence to prove that the implementation of more extended lymphadectomies in patients with gastric cancer improves survival rates. In fact, an aggressive surgery results in higher rates of postoperative complications [35,36]. The extent of the lymphadenectomy depends on the type of gastrectomy that has been done.

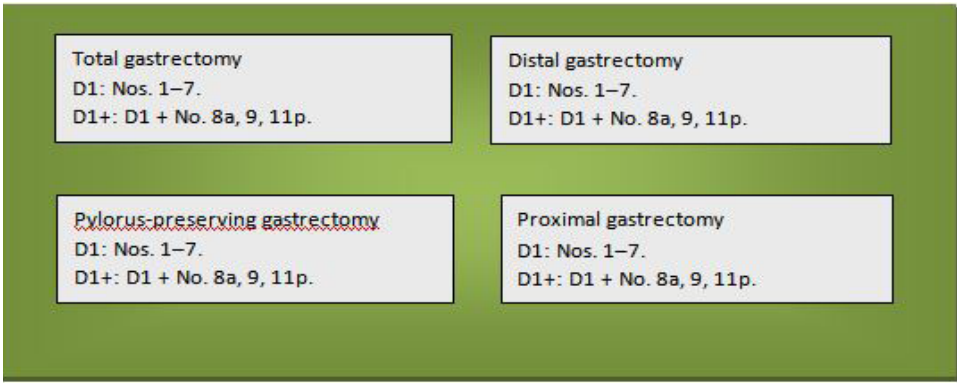
The indications for lymph node dissection according to the Japanese Gastric Cancer Association (JGCA) are the followings [15]:

- D1 lymphadenectomy:

• T1a tumors that do not meet the criteria for endoscopic treatment.
• T1b tumors classified as differentiated type with a diameter of 1.5 cm or less.

- D1+ lymphadenectomy:

• T1N0 tumors that do not meet the criteria for D1 lymphadenectomy.



Lymphadenectomy according to the type of gastrectomy conducted

2.5. Sentinel node

Nowadays, the procedure considered as curative for gastric cancer is gastrectomy associated with lymphadenectomy D2. This surgery has got excellent oncological outcomes but it is not exempt of mid-term and long-term complications. The main problems of the methods of function-preserving gastrectomy (endoscopic treatment or local resection) come from the non-assessment of lymph nodes [37].

The sentinel node technique has been established to avoid unnecessary lymphadenectomy and improve postoperative quality of life [38,39]. The sentinel node is defined as the first lymph node to receive cancer cell drainage. Negative metastasis in the sentinel node indicates no other lymph node metastasis, so it is not necessary to remove more lymph nodes.

Sentinel node mapping and biopsy is performed in patients with:

- T1-T2 tumors and

- Tumors less than 4 cm in diameter and

- N0 tumors.

In patients with positive lymph node metastasis by preoperative image (ultrasonography and tomography) sentinel node technique is not indicated [40]. Actually, sentinel node technique is the best method to evaluate the presence of metastasis in lymph nodes with a detection rate and an accuracy of 97.5% and 99% respectively [41].

We can use combined techniques as the endoscopic full-thickness resection (EFTR) associated to laparoscopic and sentinel node technique; endoscopic mucosal resection or endoscopic submucosal dissection also with the sentinel node technique by laparoscopy or partial resections with sentinel node technique [42,43]. It seems that sentinel node technique correlated with partial resections confer a better quality of life and less postoperative consequences than traditionally distal resections [44].

We dispose of a series of surgical techniques for SN mapping in gastric cancer. We can use a dye or radioisotope colloid (Patent blue, lymphazurin, indocyanine green ICG) to identify the sentinel node. It is injected around the primary tumor, and later, the stained lymph node is identified. Dye guided method is not suitable for patients with a dense adipose tissue [45]. ICG is less visible compared with blue, to overcome this problem, an infrared ray electronic endoscopy (IREE) combined with ICG has been developed with more sensitivity and accuracy [46]. There is also a radio-guided method that uses technetium 99m, for this technique it is necessary to use a gamma probe. This method is better to identify the nodes and can be used in laparoscopic surgery; however, it has got a higher cost.

As we can see, the radio guided method and the IREE have advantages and disadvantages, so a dual tracer method is the best method to obtain a precise identification rate of true sentinel node. Nowadays, SPECT-TC can be used to identify and locate the sentinel node before gastric cancer surgery.

There are two methods to inject the tracer:

- Inject the dye tracer into the submucosal layer around the tumor during an endoscopic examination

- Inject the tracer to the serosa membrane at the site of primary tumor during the surgical procedure.

In relation with the collection method, we can use:

- Picked up method to remove only hot node

- Lymphatic basin dissection (LBD)

There is still controversy about the application of SN mapping in gastric cancer. The results in the literature are divergent. Many authors from Asia report an accuracy of more than 98% in early stages (T1-T2), instead, in Western countries the accuracy is about 80%; this difference may be explained by the difference in the procedural technique. It is still necessary to resolve many issues before this method can be introduced in to daily practice.

2.6. Reconstruction

The modalities of reconstruction after a gastrectomy, whether it is partial or complete, are broad and depend on the initial technique performed. At the moment, there is no ideal technique of reconstruction free of complications or risks associated to surgery. If our initial technique is a total gastrectomy, the available options for reconstruction are Roux en Y reconstruction, double tract method, pouch and Roux en Y or a jejunal interposition. When we compare the different technical options we find that pouch and Roux en Y has got the best results with regard to percentage of intake of food, less incidence of sensation of epigastric fullness, nausea, vomiting, and improvement in nutritional parameters (serum proteins) [47,48].

If we aim for a partial gastrectomy the modality of reconstruction will depend if the resection has been distal or proximal. In the case of proximal resection we can perform an esophageal-gastric anastomosis or practice a jejunal interposition. In the case of a distal resection we dispose of more techniques: Roux en Y reconstruction, jejunal interposition, Billroth I or Billroth II techniques. Finally, if we perform a pylorus-preserving gastrectomy the reconstruction method will be a gastro-gastric anastomosis [15].

The approach method of the surgery may be via laparoscopic, open pathway, open pathway assisted by laparoscopy or robotic surgery. Laparoscopic surgery has a number of advantages over the open pathway such as reduced intraoperative blood less, less postoperative pain, less wound infection rate, lower postoperative ileus, less hospital stay and with equal results with a view to oncological results and number of lymph node dissected but at the expense of a longer operative time. It is considered a safe procedure for the treatment of gastric cancer [12, 49,50].

Robotic surgery permits a better visualization of the abdominal cavity and allows making more precise movements and with a better angle. It has got the same characteristics than the laparoscopic via over the open pathway: reduced intraoperative blood less, lower hospital stay, similar results in order of morbidity and mortality but with a much longer operative time. Long term oncological outcomes have to be determined, there are not randomized controlled trials showing this outcome [51,52].

3. Endoscopic Treatment

As previously mentioned, the indicated treatment for gastric cancer has been classically gastrectomy (either total or partial) associated with the removal of the perigastric lymph nodes. The gastrectomy conditions a serial of long-term alterations that include: dumping syndrome, diarrhea of the vagotomized, weight loss, nutritional alterations (anemia or hypocalcemia). As the majority of localized gastric cancer are presented at a stage without positive regional lymph nodes, new therapeutic modalities of treatment have been developed that are less inva-

sive or aggressive. On account of this, endoscopic techniques have been developed.

The Japanese Gastric Cancer Association (JGCA) established absolute indications for endoscopic treatment and refer to situations with a low probability to present positive lymph node metastasis and in which a tumor block resection can be achieved. These are [15,53]:

1. Differentiated type adenocarcinoma.

2. Absence of ulceration.

3. Diameter ≤ 2 cm.

4. Clinical diagnosis of T 1 a.

There are a number of extended criteria established by the Japanese Gastric Cancer Association that are actually in investigation, must be employed with care in daily clinical practice. These are , :

1. Clinical diagnosis of T 1 a, differentiated type, absence of ulceration, diameter > 2 cm.

2. Clinical diagnosis of T 1 a, differentiated type, presence of ulceration, diameter ≤ 3 cm.

3. Clinical diagnosis of T 1 a, undifferentiated type, absence of ulceration, diameter ≤ 2 cm.

Isomoto et al report that the 5-year survival and disease specific survival rates were 97.1% and 100% respectively in patients treated with ESD in patients meeting the extended criteria [56].

The basis of this therapeutic modality is to achieve an en bloc resection of the tumor, factor that allows us to perform a correct staging of the tumor (establish the degree of tumor invasion, presence of lymphovascular infiltration and determine the degree of tumor differentiation) and set up the necessity of a posterior treatment. Therefore, it has a double aspect: therapeutic and diagnostic, since it allows staging. [15,57,58].

We dispose of three principle endoscopic techniques: endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and ablative mucosal techniques.

The endoscopic mucosal resection is a procedure in where the lesion is removed until the mucosa layer; there are many technical variants such as the inject and cut, the inject, lift and cut, cap-assisted endoscopic mucosal resection, and endoscopic mucosal resection with ligation. The basis of this procedure consists on the injection of saline solution or serum with epinephrine (diluted 1:100,000) in the mucosa, to achieve a mucosal elevation and posterior removal. In the endoscopic submucosal dissection we make a label in the mucosa around the lesion with glycerol or serum with epinephrine (diluted 1:100.000) mixed with indigo carmin,

then we perform the removal of the lesion with devices that allows us coagulate until de submucosa layer [15,47,59,60,61].

The en bloc rate resection (75.8 % in EMR vs ≥95 % en ESD) and the complete excision of the lesion (73.9 % en EMR vs 90 % en ESD) are higher with the endoscopic submucosal dissection, while the rate of local recurrence is higher with the endoscopic mucosal resection. This depends on the number of histological pieces obtained during the procedure; the greater number of pieces, the greater risk of local recurrence [62,63]. When we compare the survival rates between both procedures there are not differences between EMR and ESD.

The main complications of the endoscopic mucosal resection and the endoscopic submucosal dissection are bleeding and perforation. The most common complication is bleeding (prevalence of 8 % after EMR and 7 % after ESD) that can be classified as early, occurred during the procedure, or delayed, exhibited as melena or hematemesis until the 30 day after the procedure. This complication is more common in tumors located in the distal third of the stomach. Generally it is conservatively managed by endoscopic treatment, coagulating or with endoclips, and surgery is not needed. The perforation rate rises up to 4% after ESD. As in the previous situation occurs, it is usually managed conservatively with placement of endoclips with endoscopy. In this case, the ulceration and the location in the middle third are risk factors [54,56,64].

When we bring into comparison endoscopic treatment (ESD and EMR) with surgery for the treatment of localized gastric cancer, we do not find statistically significant differences in 5-year survival rates (5-year survival rates of 95.7 % and 93.6 % respectively), according to a study published by Choi and colleagues , data that are similar to others published by different authors . Nevertheless, the chance of appearance of a metachronous gastric cancer (defined as the apparition of a new gastric cancer in a different location than the previous one, in an interval of at least one year from the first diagnosis) is higher in the endoscopic group treatment (2.9 – 14 % after endoscopic treatment versus 1.8 – 2.4 % after surgery) . The median hospital stay and the complication rates are higher in patients treated with surgery. [53,61].

The follow-up of these patients should be performed with blood tests (measuring hemogram, biochemistry, liver and kidney function tests, CA 19,9 and CEA), serial endoscopies (twice the first year and annually later) and imaging tests (TC scan) in order to detect relapses. In case of relapse, the treatment can be performed by a new endoscopy or by surgery [61].

Finally, the ablative therapies of the mucosa are a possibility of treatment in cases of tumors located in regions that are difficult to reach with endoscopy and in patients with surgery contraindications due to associated comorbidities [68].

The main disadvantage is the tissue destruction, with no possibility of obtaining a surgi-

cal specimen for an anatomopathologycal study, so the complete destruction of the lesion cannot be verified. Thus, the tumor response should be assessed by new endoscopy and biopsy.

There are many versions of this procedure, being the argon plasma coagulation the most performed, even though other modalities such as Nd:YAG laser and photodynamic therapy exist [69].

When we analyze the complications of the procedure, these are the same as for endoscopic mucosal resection and endoscopic submucosal dissection, bleeding and perforation. The surgical time is lower in comparison to endoscopic mucosal resection. However, the local recurrence rate is higher in patients treated with ablative mucosal techniques than with endoscopic submucosal dissection (3.8 % versus 0.4 % respectively) [62,70,71]. As for the subsequent relapses after this therapeutic option, this can be treated satisfactorily with a new procedure of mucosal ablation, other endoscopic technique or surgery.

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