Surgical Management of Gastric Cancer

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Published Date: September 17, 2016

INTRODUCTION

Currently, surgical treatment is the only modality that can offer a potential cure to gastric cancer, and should be performed in all cases whenever possible. Proper staging of the disease is imperative, as it allows the surgeon and oncologist to tailor treatment modalities around patient needs, instead of a pre-defined algorithm. Part of the process of staging is tumor resection in itself. The AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) 7th edition staging system was updated in 2010, and designated a minimum of 16 resected lymph nodes to perform a proper N staging of the disease [1]. The 3rd English edition of the JGCA (Japanese Gastric Cancer Association) followed suit in 2011 with an almost identical staging system [2]. This was intended to decrease the stage migration effect and correlate better with survival according to stage, although it is still a matter of controversy [3].

In countries with high prevalence (Eastern countries), extensive screening programs detect localized gastric cancer in 53% of cases, compared with only 27% of cases in Western countries, where incidence is lower [4]. This allows for the use of less invasive techniques such as endoscopic mucosal resection, which has yielded good results when patients are carefully selected. Locally advanced disease benefits from gastrectomy and lymphadenectomy combined with perioperative chemotherapy.

STAGING WORKUP

Typically, staging of gastric cancer involves several diagnostic tests. CT scan, endoscopic ultrasound, PET scan, and laparoscopy are the most commonly used methods. Each approach has its limitations, and the National Comprehensive Cancer Network **(NCCN)** does not recommend any fixed modality, but a combination of complementary tests for a proper work-up of each patient [5]. A number of tests such as sentinel lymph node mapping, magnetic resonance imaging, and contrast-enhanced ultrasound have shown promising results in preliminary studies, but are still in the experimental phase and have not been validated by regulatory organisms [5].

Early gastric cancers are tumors confined to the mucosa that can be removed completely by endoscopic means. Locally advanced tumors invade beyond the submucosa and/or have positive nodal status. Both of these benefit directly from surgery [3].

Endoscopic Ultrasound (EUS)

EUS is a superior method to CT in determining T status and specializes in differentiating T1-2 from T3-4 tumors [6]. This distinction is relevant because of the different management options. Tumors that don't extend beyond the submucosa are eligible for endoscopic resection [7] and locally advanced disease (T3-T4, or N1) is currently being treated with neoadjuvant therapy. EUS can visualize the 5 layers of the gastric mucosa clearly, and to some extent, adjacent organs and lymph nodes, although an obvious limitation is the inability to see distant nodes. A CT scan is useful to detect more distant metastasis [8]. Another application for EUS is to detect patients with high risk of distant nodal metastasis, making these patients prime candidates for staging laparoscopy and peritoneal lavage, or to avoid unnecessary testing in patients with low risk [9]. Both CT scan and EUS are insufficient by themselves to properly stage a patient preoperatively, and must be combined for maximum efficiency [10].

Staging laparoscopy and peritoneal lavage

Laparoscopy has been extensively used prior to treatment to evaluate the presence of metastatic disease (namely, peritoneal and/or hepatic implants). Patients with distant metastasis have poor survival with or without gastrectomy, which is reserved for palliative purposes (bleeding or obstruction) [14]. Staging laparoscopy is an effective, minimally invasive method of detecting peritoneal implants not otherwise seen on preoperative imaging. Minuscule implants, however, can still be missed with this technique. Peritoneal lavage can detect the presence of

cancer cells that cannot otherwise be seen [15]. A positive (P+) lavage is considered by both the NCCN [16] and the AICC1 to meet the criteria for M1 disease [14,17]. This enables patients to avoid unnecessary gastrectomies [15]. Evidence has shown that P+ correlates with poor survival with or without gastrectomy, justifying its designation as M1 [17,18].

About 30% of patients undergoing peritoneal lavage have P+. This raises questions as to the necessity of performing this in all cases of gastric cancer, due to a relatively low yield. It has been proposed that a careful selection of patients bearing certain clinical characteristics can increase the proportion of patients with P+. Tumor location (GE junction, large portions of the stomach), tumor extension (stages T3/T4), and lymph node positivity have all been associated with a higher yield of positive results [19]. Endoscopic ultrasound is a useful tool in the identification of ideal candidates for staging laparoscopy, as it can detect the extent of the tumor in the gastric wall and into adjacent organs and/or lymph nodes [9].

TREATMENT OF GASTRIC CANCER

Endoscopic Mucosal Resection (EMR)

EMR is a recent technique that has gained popularity among surgeons, especially in Eastern countries, since the incidence of early gastric cancer is much higher in that region. Tumors that have not invaded beyond the submucosa (early gastric cancer) are candidates for curative resection by endoscopic means. In the Japanese guidelines, EMR is the standard procedure for tumors that meet the absolute criteria (intramucosal, differentiated, ≤2cm in dimension) [11]. Given the success of this procedure in patients who met these criteria, authors have proposed extended criteria for more advanced tumors that might still benefit from EMR. A study by Gotoda et al. used SM1 invasion of less 500mcg, size ≤3 cm, differentiated tumor, no lymphovascular invasion, en bloc resection, and a negative margin as criteria for EMR. They reported no incidence of lymph node metastasis [12]. This study defined submucosal invasion of less 500 mcg as acceptable for EMR. Recently, studies have reported a higher incidence of lymph node metastasis, Eom et al. reported 3.9% incidence, and have question the suitability of the of less than 500 mcg limit for EMR [13].

Total *vs*. Subtotal Gastrectomy

Decades ago, the belief that a more extensive resection lowered rates of recurrence led surgeons to perform routine total gastrectomies in all cases of resectable gastric cancer. However, in 1999, an Italian trial found that after a 5-year follow up, subtotal and total gastrectomyhad similar survival outcomes, with subtotal gastrectomy resulting in a better nutritional status and quality of life [20]. Since then, subtotal gastrectomy has been the standard approach to middle-third or distal gastric tumors, so long as a 5cm margin with healthy tissue can be achieved. More recently, a multicenter study including 465 patients found that resection with greater than 3.1 to 5cm margins were equal in overall survival outcomes as patients with >5cm margins. This is meaningful as it can influence the decision to perform a total or subtotal gastrectomy and the

type of repair to be made, impacting the patient's morbidity and quality of life [21]. Proximal or lesser curve tumors still need a total gastrectomy in order to achieve negative margins and avoid postsurgical complications such as esophageal reflux [22]. A recent retrospective study found that recurrence rate after curative intent surgery was 30%, and that patients were at high risk of recurrence during the first two to three years after surgery. Patients who experienced recurrence had a median survival of five months after recurrence [23].

Multivisceral resection (MVR) in the setting of locally advanced gastric cancer is a controversial issue, as one of the strongest predictor for survival is achieving a microscopic R0 resection. As microscopic invasion into adjacent organs is difficult to anticipate with preoperative imaging, D2 resection routinely included splenectomy and distal pancreatectomy [24]. A study from the US Gastric Cancer Collaborative (USGC) showed that multivisceral resection (spleen, pancreas, liver, and/or colon) significantly increased patient morbidity (45% *vs*. 59%), but did not increase mortality (6% *vs*. 9%) [24]. The JGCA published a systematic review in which morbidity from MVR ranged from 11% to 90% and mortality from 0% to 15% [25]. Both studies conclude that carefully selected patients with locally advanced disease can benefit from MVR to achieve R0 resection, but caution should be taken, as survival remains low. To illustrate this, a comparison between patients who underwent routine splenectomy and those who did not, showed no additional benefit in resecting the spleen and thus did not recommend routine splenectomy [26].

After a gastrectomy, repair of the gastrointestinal tract must be undertaken. Three main procedures are used for this purpose: Roux-en-Y, Billroth I, and Billroth 2. There is a theoretical advantage to the Roux-en-Y procedure in avoiding esophageal biliary reflux due to an obtuse angle of His after Billroth I reconstruction [27,28]. Long-term outcomes in patients with Billroth I *vs*. Roux-en-Y reconstructionhave been found tobe no different in morbidity, mortality or quality of life, except for a lower incidence of esophageal reflux symptoms in patients with Roux-en-Y [29–31].

Minimally Invasive *vs.* Open Gastrectomy

Laparoscopic gastrectomy is an option surgeons are starting to take to thanks to improved surgical outcomes without any diminished oncologic results. A recent survey calculates an estimated 64% of distal gastrectomies and 9% of total gastrectomies are performed by laparoscopy in the setting of early gastric cancer. Asian correspondents report up to 82% of early cancer surgeries performed with minimally invasive techniques. In comparison, less than 40% of European surgeons preferred this approach. For advanced gastric cancer, 49% of distal surgeries and 6% of total gastrectomies were laparoscopic [22]. Advantages to minimally invasive surgery include shorter hospital stay, reduced intraoperative bleeding, less morbidity and better quality of life [32–34]. Relative disadvantages are a longer operative time. However, these studies are limited to short-term outcomes and further studies are needed to evaluate long-term oncologic and surgical effects [33].

Lymphadenectomy

One of the cornerstones of curative intent surgery for locally advanced gastric cancer is a proper lymphadenectomy. What this constitutes is still a matter of intense debate. As mentioned earlier, the AICC/UICC and the JGCA both recommend (but do not require) at least 16 lymph nodes resected at the time of surgery, be it subtotal or total gastrectomy. This is because the N stage categories have been modified to N0= 0 lymph nodes, N1= 1 to 2 lymph nodes, N2= 3 to 6 lymph nodes, N3a= 7-15 nodes and N3b= ≥16 nodes [1,2].

Lymph nodes that drain the stomach are classified by their approximate anatomical site in stations. These stations are grouped in D1, D2, and D3 locations. Traditionally, lymphadenectomy is described as D1 or D2 depending on the extent of resection. Which of the two dissections has better outcomes is still a matter of controversy. In the West, two classic randomized prospective studies in the 90's, one conducted in the UK, and one in the Netherlands, heavily influenced practice. The first, by Cuschieri et al., found no difference in survival between D1 and D2 approaches and a higher morbidity (46% *vs*. 28%) and mortality (13% *vs*. 6.5%), (although this could have been caused by the distal pancreatectomy and splenectomy) [35]. The second, by Bonenkamp et al., also reported significantly elevated complications rate in the D2 approach (43% *vs*. 25%) and elevated mortality (10% *vs*. 4%), while 5-year survival remained similar (34% *vs*. 33%) [36]. These two studies have been criticized by Eastern surgeons due to contamination and non-compliance, as the British study had a mean of 13 lymph nodes resected in the D1 arm and 17 in the D2 arm. Surgeons in the Dutch study were supervised by Japanese experts and still had a non-compliance of 36% in the D1 arm and 51% of D2 dissections [4].

On the other hand, high-volume countries such as Japan and Korea favor the more radical D2 approach, as they have demonstrated higher survival when performed, along with similar morbidity and mortality. The JCOG (Japanese Clinical Oncology Group) 9501 trial reported a mortality of 0.8% with a 5-year survival of 70% using a D2 approach [37]. Newer Western studies have also demonstrated an increased survival with D2 resection [38,39]. Another alternative whose usefulness is yet to be confirmed is the use of lymph node ratio to stage nodal status. This is thought to reduce stage migration effect with extended resections and to standardize staging when a smaller number of lymph nodes are examined [40].

These variations between the Eastern and Western experience exemplify the difficulties inherent in a classification system that relies on location rather than number of extracted lymph nodes. As such, modern staging systems have taken to using the latter to compare survival in patients.Irrespective of this, several studies have shown a survival benefit in patients with 16 or more lymph nodes resected [41–43]. A large, multicenter retrospective study in Italy included 1465 patients and compared gastrectomies with ≥16 lymph nodes resected with those with <16 nodes resected and found significant improvement in 5-year survival for patients in the first group (67.6% *vs*. 51.5%) [42]. Another large SEER-data base study divided patients in a group

that consisted in one lymph node resected, and then in groups for every 10 extra nodes resected. The greatest survival differenced was noted at 10 lymph nodes and then continued to increase for every extra 10 nodes up to 40 nodes examined [43].

Nasogastric or Nasojejunal Decompression

Surgical complications, such as anastomotic leakage, pulmonary aspiration, and wound dehiscence, are the main concern of the surgeon in the postoperative period. NG/NJ tubes were thought to improve bowel function and shorten hospital stay [44]. Recently, this practice has come into question, and several systematic reviews have been published on the issue. Pacelli et al, found no benefit in morbidity (including anastomotic leaks) or mortality, but did show shorter time to flatus in patients with Y-en-Roux who had NG/NJ tube placement [45].

Jejunostomy

A patient's postsurgical condition after a total gastrectomy (such as no oral intake) can diminish the patient's ability to receive adjuvant chemotherapy, which is now considered to be a key part of the multimodal treatment of gastric cancer [46,47]. Chemotherapy is also associated with severe gastrointestinal complications such as nausea or vomiting. In order to counter this difficulty, the NCCN guidelines recommend placing a jejunostomy feeding tube in selected patients at the time of surgery to improve patient nutrition, the effectiveness of chemotherapy and to reduce postsurgical infections associated with Total Parenteral Nutrition **(TPN)** [16,48]. In other oncologic conditions (such as pancreatic cancer), the placement of jejunal feeding tubes is associated with significantly increased morbidity [49]. In the case of gastric cancer, a single institution study found that jejunostomy tubes also increase morbidity and confer no advantage in the administration of chemotherapy or the nutritional status of the patient [50]. More recently, a multi-institution retrospective study found that the placement of a feeding tube did not in fact elevate morbidity or mortality, but they could not demonstrate a benefit in patient's tolerance of chemotherapy [51].

Fast Track Surgery

Fast track surgery refers to a multimodal approach to pre-, peri-, and postsurgical care that was proposed several years ago. It is geared towards a faster recovery of the patient by enforcing early feeding and mobilization, and a reduction of the surgical stress response [52]. These variations in traditional surgical care have been demonstrated to improve outcomes such as hospital stay, time to flatus and postoperative pain in several surgical branches. Recently, fast track protocols have been implemented in gastric cancer surgery to similar results. Systematic reviews have consistently found that fast track shortens hospital stay, time to first flatus and decreases medical costs (associated with a shorter hospital stay). It is also associated with an overall shorter recovery time [53-55]. General fast track surgery protocol can be found in Table 1.

Table 1: General Fast Track Surgery Protocol.

Perioperative interventions
Optimization of existing organ function
Ensuring of good nutritional status
Patient education regarding process
Minimal starvation (2 hours for liquids, 6 for solids)
No mechanical bowel preparation
Oral carbohydrate drink
Intraoperative interventions
Preoperative antibiotic, acid suppressor and prokinetic
Epidural anesthesia
Elective use of nasogastric decompression and abdominal drainage
Goal directed fluid administration
Temperature control
Postoperative interventions
Adequate analgesia
Nausea and vomiting prophylaxis
Early removal of drains and tubes
Early enteral feeding
Early ambulation
Ensure follow-up

Adapted from Nanavati et al. [52].

The Role of Palliative Surgery in Advanced Disease

The presence of distal metastasis is an ominous finding. Patients with stage IV disease have very low survival with a high rate of complications. Until recently, gastrectomy was considered to be the best available treatment for these patients, offering an increase of three to five months of survival [56]. Recently, advances in chemotherapy have increased the prognosis of metastatic disease, and is now the mainstay of treatment, with surgery being considered second line for selected patients for various complications. However, new reviews of the available evidence found that a combination of chemotherapy and gastrectomy further improves survival. It is also suggested that resection of liver metastasis is beneficial to the patient [57].

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