

Early esophageal and gastric cancers : surgery in the era of minimally invasive treatment

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Abstract

Surgery represents today the standard treatment of oesophageal and gastric cancer. Associated morbidity remain however significant in term of incisional access and functional sequels after organ resection and extended lymphadenectomy. Retrospective reviews of surgical series have defined indications for which more conservative treatment appears to provide similar survival without the need for lymph node resection. Endoscopic resection is now accepted for the treatment of well-differentiated tumors restricted to the mucosa. The expansion of this technique to deeper lesions or to lesions developed on a background of metaplasia is associated with an increased morbidity and significant risk of recurrence as well as a lifelong, close endoscopic surveillance. The role of surgery as primary treatment or rescue therapy to extend the resection will rely on an accurate preoperative and pathological staging of the lesion. Laparoscopy can play a central role in the management of early oesophageal and gastric cancer as it can permit from localized to extensive resection associated to lymph node dissection with the advantage of minimal invasive surgery. Its association to function-preserving operations awaits the demonstrated efficacy of targeted lymph node dissection. Those new techniques should be restricted to centres with extensive expertise and need to be validated in long-term controlled studies. (*Acta gastroenterol. belg.*, 2006, 69, 312-316).

Introduction

Surgery represents the standard treatment of oesogastric cancers without metastatic disease. Oncological surgical resection in cancer include wide resection of the tumor with frequent removal of the entire organ, associated to an extensive lymphadenectomy (1,2). It provides large security margins to obtain loco-regional control of the disease but also to give an accurate staging and prognosis. The R0 resection is the most powerful prognostic factor in multivariate analysis. By the resection of the organ on which the tumor arises, it definitely suppresses the risk of recurrence and the necessity of lifelong follow-up. Operative mortality and morbidity have decreased over time but remain significant especially for oesophagus surgery with reported 1-5% mortality and 18-57% morbidity (3-7). The quality of life after oesophagectomy or gastrectomy is also altered. The interest of less aggressive techniques is evident, but is only justified if they still respect the principles of oncology with an equivalent effect on patient survival. These techniques include endoscopic procedures of mucosal resection. Surgery also evolves as efforts are made towards function preserving operations (8-9). Progress in laparoscopy has allowed for some time limited partial

resections with or without lymphadenectomy with the advantages of minimal invasive surgery. In experienced centers, laparoscopy is now applied for total gastrectomy and oesophagectomy.

Early oesogastric cancer appears as a good candidate for more conservative resection techniques. It is defined as a tumor invasion limited to the mucosa or submucosa (Tis and T1 in the TNM classification (10)). This definition however does not take into account lymphatic node status and thus represents a spectrum of lesions with fundamentally opposed behaviors in the risk of locoregional or distant recurrence.

Early esogastric cancer - characteristics

Depth of invasion and lymphatic spread

Depth of parietal invasion is directly associated with lymph node invasion and patient survival. Endo *et al.* (11) reviewed a series of 236 patients who underwent surgical resection of thoracic esophagus for Tis or T1 lesions without adjuvant therapy. Lymphatic metastases were diagnosed in 3% of cancers limited to the mucosa and in 41% of cancers reaching the submucosa. Using the Japanese pathological subclassification for superficial cancer (12) (Table 1), lymphatic metastases ranged from 0% for M1 and M2 cases, 8% for M3 tumors to 61% for SM3 lesions. Furthermore, while metastases for M3 and SM1 lesions were regional, positive nodes were identified in the cervical and abdominal draining sites for deeper lesions. Similarly, Wang *et al.* (13) reported lymphatic metastasis for Tis, T1a and T1b, respectively in 0/76 patients, 2/126 patients and 34/218 patients operated for early squamous cancer of the esophagus. In the review of Van Sandick (14) the incidence of lymphatic metastases for early oesophageal squamous cell carcinoma were rare with T1a cancer (0-7%) but were reported in 16-53% of the patients with T1b tumors. The same behavior was observed for adenocarcinoma of the oesophagus and cardia. While T1a tumors were associated with 0-3% of lymphatic invasion, lymph node

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Table 1. — **Pathological subclassification of superficial esophageal cancer (12)**

M1 : tumor limited to the mucosal epithelium
M2 : Invasion limited to the lamina propria
M3 : Invasion in contact to or into the muscularis mucosae
SM1 : Invasion within upper third stratum of the submucosal layer
SM2 : Invasion to the middle third stratum of the submucosal layer
SM3 : Invasion to the lower third stratum of the submucosal layer

involvement was present in 16-36% of resected T1b cancer.

Similar evidence is reported for early gastric cancer. Gotoda *et al.* (15,16) reported on a 5265 patients series of early gastric cancers with a lymphatic invasion rate of 2.7% for T1a versus 18.6% for T1b lesions.

Tumor differentiation

Tumor differentiation is also an important prognostic factor for recurrence. Diffuse type adenocarcinoma has a higher risk of both loco-regional and peritoneal recurrence (17). Recommendations for gastric surgery independently of tumor depth invasion are 3 cm security margins for intestinal type lesions and 5-6 cm for diffuse type lesions. Diffuse type early gastric adenocarcinoma is associated with an increased risk of lymph node metastasis (RR 4.88) in a retrospective multicentric analysis of 652 cases (18). Isolated local resection is thus not recommended for poorly differentiated adenocarcinoma or signet-ring cell carcinoma. Abe *et al.* challenged this attitude after they reviewed their data from 175 patients operated for undifferentiated early gastric cancer (19). They identified size (> 2 cm) and lymphatic involvement as predictive factors for lymph node metastasis, with a rate of lymph node invasion of 60% if both factors were present. They suggested that a undifferentiated lesion < 1 cm without lymphatic invasion could be treated by endoscopic resection. Pathological determination of tumor margins in a small specimen is however difficult for those lesions and will increase the risk to recurrence.

Background

Aside the local characteristics of the tumor, another major prognostic factor is the background on which the tumor arises. Barrett's metaplasia is associated with a 0.2-3% annual risk of cancer (RR : 30-125) (20). While focal high-grade dysplasia (HGD) is associated with one- and 3-year incidence of cancer of 7% and 14%, diffuse HGD is associated with incidence of cancer of 38% and 56% for the same periods (21). Surgical series confirm that HGD is multifocal in 50% and that 33-50% of the patients operated for dysplasia have an occult cancer on the operative specimen (5,6,20).

Those facts are reflected in the literature related to local endoscopic therapy with 97% local remission for low-risk lesions – small (< 2 cm), well differentiated adenocarcinoma or high grade dysplasia – but with 59%

for high-risk lesions – > 2 cm lesions, limited to the mucosa, and/or macroscopically type III, and/or poorly differentiated and/or with submucosal invasion –. At 10 months follow-up, local recurrence with metachronous cancer was 10% for the high risk group (22).

Complete ablation of Barrett esophagus by chemical, thermal or mechanical techniques is a logical treatment but at this time its ability to completely eradicate the abnormal mucosa is not established by the reported studies (20,23). Furthermore the lifelong endoscopic surveillance after resection can be fooled by foci of intestinal metaplasia localized under the neosquamous epithelium (incidence of 19% reported by Van Sandick (14)).

Finally the compliance of the patient for regular – lifelong – investigation as well as the availability of a time-consuming thorough evaluation by the gastroenterologist has to be questioned.

Accuracy of preoperative staging and follow-up

Preoperative evaluation takes in «conservative» resection approach a paramount importance. Precise assessment of depth of invasion and identification of pathological adenopathy will define the possibility of local resection of a tumor. EUS appears as the most accurate investigation for T staging of gastric cancer in comparison to CT-Scan and peroperative assessment (24,25). Accuracy of EUS for gastric cancer however ranges from 64.8% to 92% in T staging and 50-90% in N staging (26). Similar disparity is emphasized in the review of Murata *et al.* (27), on the preoperative evaluation of lymph node metastasis in esophageal cancer. Sensitivity, specificity and accuracy for the diagnosis of malignant lymph nodes by EUS vary widely : 49-99%, 33-99%, 71-96%, being dependent on the judgment of subjective observers. EUS-FNA appears superior with respectively 81-97% sensitivity, 83-100% specificity, and 83-97% accuracy. The task will be further complicated for follow-up after local resection as postoperative changes will make differential diagnosis difficult.

Definitive diagnosis and staging of the lesion will thus ultimately depend on an accurate analysis by the pathologist (28-31). Analysis of the depth of invasion and margins of resection will depend on the quality of the specimen and hence of the resection.

Endoscopic resection

As discussed above, for adenocarcinoma of the esophagus, mucosal ablative therapy cannot currently be recommended as standard therapy until large size studies with sufficient follow-up are published. It is adequate for diagnosis and staging of a lesion but its role, as a treatment should reserve it to a selected group of non-surgical candidates or well-informed patients about the risk of recurrence.

Based on their large experience, the Japanese propose for squamous cell carcinoma of the esophagus and

gastric adenocarcinoma, an algorithm depending on the depth of the lesion, size of the tumor, differentiation, the presence of vascular or lymphatic invasion, or ulceration. Indication for EMR in squamous cell carcinoma, is well or moderately well differentiated cancer, < 2 cm, confined to the mucosa without vascular or lymphatic invasion (32). The accepted indications for EMR in gastric cancer include the resection of small intramucosal EGC of intestinal histology type, well differentiated elevated cancers less than 2 cm in size, and small < 1 cm depressed lesions without ulceration. However using a surgical database of patients who underwent gastrectomy with D2 lymph node dissection, Gotoda *et al.* (33) proposed extended criteria groups for whom resection could be performed with a low risk of lymph node invasion. It requires however the development of submucosal dissection (ESD) (34) with an associated increase in morbidity (up to 8% of bleeding and 4% of perforation).

If the tumor extends beyond those criteria, a surgical intervention is needed. These guidelines will have to be reviewed once mid and long-term studies have been published about the risk of recurrence and about long-term survival. Failing to perform an en-bloc resection of the tumor or to obtain negative margins exposes to high recurrence rate (2-35% in the EGC EMR series) (15). Even more importantly it can lead to lymphatic or systemic progression of the disease. Just as it is the case for cancers associated with Barrett's esophagus, the incidence of 14% metachronous multiple gastric cancers with a median follow-up of 57 months is also an issue that has to be studied to define surveillance guidelines – or question the validity of the technique (35).

Surgical resection

Efforts have also been made by surgical groups to increase quality of life after gastric surgery for early gastric cancers by a preservation of organ function. Segmental gastrectomy (36) and pylorus-preserving gastrectomy (36,37) decrease dumping syndrome and gallstones formation with a better weight recovery compared to Billroth I procedure but may be accompanied with higher emptying sequels. Proximal gastrectomy with jejunal pouch interposition is also evaluated in some centers (38).

Likewise, interventions have been designed to minimize post-esophagectomy sequels, principally dyspepsia associated with emptying delay and reflux. Vagus-preserving esophagectomy (39) improves functional results after surgery, and is associated with less complications and mortality (40). The more limited extent of lymphadenectomy reserves those procedures to indications of HGD or mucosal cancer with a low risk of lymphatic metastases. Their indications could be broadened if a precise definition of lymphatic drainage of the tumors could be obtained. The concept of sentinel node has been applied to esogastric surgery. As the obstruction of a lymphatic vessel by cancer can lead to false-

negative results, it appears that SN mapping has to be restricted for the detection of micrometastases in early esogastric cancer (cT1N0). Early reports emphasize the learning curve of a technique that is currently evaluated in prospective trials (8).

Laparoscopic resection

Laparoscopic surgery can be seen as taking the best of both worlds in many situations. Technological improvements associated with a growing experience in more complex operations can make patients with esogastric cancer benefit from the advantage of laparoscopy : reduction of postoperative pain and pulmonary complications, quicker recovery of gastrointestinal function, shorter hospital stays (41-44). Laparoscopic intragastric mucosal resection by insertion of trocars through the abdominal and gastric wall enables mucosal resections of lesions located in any part of the stomach but the anterior wall. Wedge resections offer for EGC with no risk of lymph node involvement, no mortality and a morbidity < 5%. It has the advantage over EMR to provide a complete specimen allowing the evaluation of a full-thickness wall but it however suffers from the limited reliability of preoperative assessment of lymphatic extension. Over the years, more extensive procedures of gastrectomy as well as esophagectomy, with lymphadenectomy have been performed worldwide in experienced centers. In the 2004 survey conducted by the Japanese Society of Endoscopic Surgery, among 7800 laparoscopic procedures for gastric cancer, laparoscopic assisted distal gastrectomy represented 83% of cases for 5% of wedge resections and 1.5% of intragastric resections (45).

In 2004, the Japanese Gastric Cancer Association recommended the laparoscopic technique for early gastric cancer with N0 or N1 lymphatic status (46). However several centers are currently reporting data for any tumor stage, performing D0 to D2 lymphadenectomy. Over the last years, accumulating reports suggest that laparoscopic gastrectomy is safe, associated with less pain, better respiratory function, a quicker recovery of gastrointestinal function and better postoperative quality of life and no negative influence of survival (47). A 5-year prospective randomized study comparing laparoscopy vs laparotomy for all stage distal gastrectomy in 59 patients was reported by Huscher *et al.* (48). Mortality was 3%, morbidity 27%, and cancer recurrence 38% for a 5-year recurrence free survival of 57%. There was no significant difference between the two groups.

Esophagectomy can also be performed in totality by laparoscopy (thoracic and abdominal, or abdominal with transhiatal dissection) or partially combining thoracoscopy and laparotomy.

Early results were disappointing with long operative time, high conversion rate and morbidity and mortality was not modified. With increased experience over the years and better surgical tools, surgical time has

decreased and conversion rate has become low. Akaichi *et al.* (49) performed en-bloc total esophagectomy by a combination of right thoracoscopy and laparotomy and demonstrated a better preservation of vital capacity compared to their open technique. Similar results (50, 51) were reported insisting on the importance of the learning curve for this demanding procedure. Reporting on 222 patients operated by totally laparoscopic transhiatal or three-stage approach, Luketich *et al.* (52) observed a 7% conversion rate, a median ICU stay of 1 day and an hospital stay of 7 days with a operative mortality of 1.4% and an anastomotic leak rate of 12% (39). Quality of lymphadenectomy appeared equivalent to the open technique in those experienced centers.

Those reports however emphasize the importance of the learning curve of these advanced techniques, e.g for an adequate lymphadenectomy and larger size series with long term follow-up are awaited. Many questions remain, concerning the quality of preoperative staging or the risk for peritoneal dissemination in more advanced disease.

Conclusion

With the advances in endoscopy and laparoscopic surgery we possess today a number of tools that have to be chosen or combined to offer the best treatment adapted to a specific lesion and patient. Endoscopic resection is now accepted for the treatment of differentiated mucosal cancer provided an en-bloc complete resection is performed (53). For deeper lesions, the risk for lymphatic metastases is exponential with the depth of invasion. The role of surgery as primary treatment or rescue therapy to extend the resection will thus depend on an accurate preoperative and pathological staging of the specimen. The risk for recurrence will also depend on the underlying disease on which tumor arises. A background of diffuse intestinal metaplasia not only exposes to recurrence but also to missing a synchronous lesion. The risk one is willing to accept will depend primarily on the patient. As progress in anesthesiology push back the limits to deny a patient for surgery, laparoscopy can fill in the gap between endoscopic treatment and classical open surgery. It permits to obtain the complete resection of a lesion with an adequate analysis of the entire wall and to associate a lymphadenectomy that will enable to obtain a complete staging of the lesion. In more advanced cases, it can be used alone or in combination with open surgery to perform gold standard surgery with a reduced morbidity. Nevertheless the less invasive is a technique for the patient, the more it is demanding for the physician from diagnosis to follow-up. All those techniques require an expertise that has to be reached by the entire team before it is offered to the patient. At the present time, "classical" surgery remains the standard therapy to which newer techniques have to be compared. All those techniques, from diagnosis to treatment, have to be assessed for in-house quality control. They have to be

conducted in multidisciplinary oncological concertation and in prospective trials in selected experienced centers.

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