Staging Laparoscopy in Gastric Cancer. Accuracy and Impact on Therapy

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Abstract

Background: Surgical therapy remains the most effective treatment modality in gastric cancer. The importance of multimodal treatment for advanced gastric cancer has contributed to the development of more accurate preoperative staging strategies. We examined the diagnostic accuracy of staging laparoscopy (SL) for abdominal metastases and the predictive value of SL for tumor resectability. **Material and method**: This is a prospective, cohort, observational study of 98 patients with primary gastric adenocarcinoma admitted at a tertiary referral hospital over a three year period. Extended SL, laparoscopic ultrasonography and peritoneal cytology were performed in 45 patients with gastric cancer without distant metastases on pre-therapeutic imaging staging. Of the 45 patients, 17 (37.8%) had distant metastases on SL and were offered palliative therapy and/or supportive care. Open laparotomy and gastrectomy was performed in the patients without distant metastases or with uncertain resectability on SL. **Results**: An unnecessary laparotomy was avoided in 17 (37.8%) patients. The overall SL sensitivity for distant metastases was 89%, specificity 100% and diagnostic accuracy 95.5%. The sensitivity for lymph node metastases was 54.5%, the specificity 100% and the diagnostic accuracy 64.3%. The SL positive predictive value for resectability was 96% and the negative predictive value was 50%. The morbidity of SL was 2.2% and the mortality 0. **Conclusion**: Staging laparoscopy is a safe and effective staging modality in patients with gastric carcinoma. It avoids unnecessary laparotomies in a significant number of patients and should be mandatory if neoadjuvant treatment is planned.

Key words

Gastric cancer – staging laparoscopy – laparoscopic ultrasonography – peritoneal cytology.

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Introduction

The therapy of gastrointestinal tumors is becoming more and more complex comprising surgical resection, investigational neoadjuvant, adjuvant or palliative chemotherapy or supportive care. The basis of optimized therapies is the correct evaluation of tumor spread and exact staging. Despite significant improvement in preoperative tumor staging due to sophisticated new imaging techniques (trans-abdominal and endoscopic ultrasound, CT scan, MRI and more recently PET-CT), peritoneal tumor spread and occult liver and lymph node metastases are only detected during surgery in many patients.

Laparoscopy has been proposed as an accurate staging modality in a variety of upper gastrointestinal malignancies. In gastric cancer, preoperative laparoscopy can avoid unhelpful surgical exploration in the case of peritoneal dissemination of tumor or liver metastases undetected by conventional staging [1, 2]. Laparoscopic ultrasound (L-US) represents an important technical improvement in diagnostic laparoscopy [3]. Moreover, laparoscopic approach offers surgical palliation in certain patient groups [4].

Although diagnostic laparoscopy has been used since the early 1990s and has been included in the diagnostic algorithm for gastric cancer in many hospitals [5, 6], surgical oncologists have been relatively slow to embrace this technology.

The aim of the present study is to evaluate the value of staging laparoscopy (SL) associated with L-US in gastric cancer patients (M0 cTNM) in predicting the presence of peritoneal and hepatic metastasis, the lymph node status and the resectability of the tumor.

Patients and methods

This is a prospective, cohort, observational study of 98 patients with primary gastric adenocarcioma on pathological examination (endoscopy and biopsy), admitted to two tertiary referral hospitals, participants in the DIASTAL Consortium

(Diagnosis and Staging Laparoscopy in Abdominal Cancers – Grant No.54/2005, CEEX Program), between January 2006 and December 2008. Laparotomy was performed for complications related to the cancer (obstruction, bleeding or perforation), and patients with distant metastases or medically unfit were referred for palliative therapy or supportive care. The remainder of the patients were prospectively enrolled in the DIASTAL study. The study protocol was approved by the Ethics Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.

All the patients received detailed information on diagnostic laparoscopy and only those who agreed to the study protocol were finally enrolled in the study. The pre-therapeutic imaging staging included conventional radiography of the thorax, abdominal ultrasonography, gastric hydrosonography or endosonography and abdominal CT, MRI or PET-CT. The T1 patients (cTNM) and those who refused laparoscopy or had medical contraindications for pneumoperitoneum were referred for open surgery. Patients with distant metastases M1 (cTNM) were offered chemotherapy or supportive care.

Extended SL and L-US of gastric cancer patients without distant metastases M0 (cTNM) was performed under general anesthesia, with a single-dose antibiotic cover, immediately before scheduled laparotomy. All surgical procedures were performed by the consultant surgeons involved in the preoperative staging workup.

The patient was positioned as for an open upper abdominal procedure and an angled 300 camera was used. The four trocar's position (one 10 mm for camera, one 12 mm for ultrasonographic probe 7.5-MHz, Aloka Co.Ltd,Tokyo, Japan, and two 5 mm for retracting the liver lobes of dissecting the lesser sac) depended on the tumor location. Open access to the abdomen was preferred using the open Hasson technique, with the first 10 mm trocar placed below or above the umbilicus, though special precautions were taken in patients with previous abdominal surgery.

A thorough inspection of the four quadrants of the peritoneal cavity was performed, with operating table repositioning according to the region inspected. Prior to any manipulation, ascites when present, or irrigation fluid (100 ml in the upper abdomen and 100 ml in the pelvis) was suctioned and immediately sent for centrifugation and cytological examination using Giemsa and Papanicolaou staining methods. A systematic inspection of the abdominal cavity was undertaken, with retraction of the organs and repositioning of the operating table as requird. Biopsies and frozen sections were performed if any suspicious abdominal lesions were evident.

The patient was then put in the Flower position and the US 7.5-MHz ultrasonographic probe was inserted through the 12 mm port. A thorough exploration of the stomach, to evaluate the extent of the primary tumor, of the regional lymph nodes and of the liver, for possible metastases, was undertaken. Lymph node and liver biopsies were performed under direct vision and US-guidance and sent for frozen sections.

The lesser sac was opened through the gastro-colic and/or gastro-hepatic ligaments, depending on tumor localization and extension. The lesser sac was then irrigated with 100 ml saline and the fluid was sent for immediate cytological examination. With gentle retraction of the stomach, the lesser sac inspection was completed, with appreciation of the tumor extension and posterior invasion, and biopsy and frozen section of suspicious peritoneal lesions. The lymph node biopsies were then performed from the enlarged nodes on inspection or ultrasonographic examination.

For cancers of the gastro-esophageal junction, the exploration of the diaphragmatic hiatus was achieved through incision of the esophago-cardial peritoneal fold and blunt dissection, with the retraction of the stomach to the patient's right.

The patients with M1 on frozen sections or unresectable because of local tumor extension were referred for palliative therapy, chemotherapy or chemoradiation and/or supportive care. Open laparotomy and gastrectomy was immediately performed in the M0 patients and those with uncertain resectability.

The specificity, sensitivity and diagnostic accuracy of SL for lymph node, peritoneal and hepatic metastases were assessed against the final pathological report, on permanent sections (pTNM). The SL positive and negative predictive value for tumor resectability was assessed against the findings on open surgery.

Results

Between January 2006 and December 2008, in both hospitals, 98 patients with gastric cancer on endoscopy and biopsy were admitted as participants in the study (Fig.1). Of the 98 patients, 24 had gastric cancer complications (10 with obstruction, 2 with perforation and 12 with active bleeding) and were referred for surgery. Palliative therapy was initiated in 13 patients with distant metastases (8 hepatic, 2 pulmonary and 3 massive ascites) and 4 patients were offered supportive care because of advanced disease, low performance score and/or serious medical conditions.

The 57 patients who met the inclusion criteria of the DIASTAL study underwent the staging pre-therapeutic protocol: conventional radiography of the thorax (57/57); abdominal ultrasonography (57/57); gastric hydro-sonography (34/57) or endo-sonography (17/57); abdominal CT (48/57), MRI (7/57) or PET-CT (2/57). In 8 patients the imaging tests evidenced distant metastases (6 hepatic, 1 pulmonary and 1 peritoneal carcinomatosis) and were offered palliative therapy (chemotherapy in 7 and supportive care in 1). Of the 49 M0 (cTNM) patients, 2 who refused the SL and 2 with T1 tumors were scheduled for open surgery (4 R0 gastric resections performed). The remaining 45 patients were scheduled for SL, just before the planned open surgical procedure.

During SL the inspection revealed unsuspected peritoneal lesions in 18 patients and in 14 the frozen sections were positive for adenocarcinoma (P1). Unsuspected liver lesions

were observed on inspection in 2 patients and revealed by L-US examination in another 4 patients. Five of the 6 patients had carcinoma on frozen sections (H1) (Fig. 1).

In the 45 patients with SL the peritoneal cytology was positive (CY1) in 19 (42%) patients and negative for malignant cells (CY0) in 26 (58%) patients. SL revealed a positive peritoneal cytology in 12 of the 17 M1 (frozen sections) patients and in 7 of the 28 M0 (frozen sections) patients. The peritoneal cytology was positive in 14 (73.6%) of the 19 M1 patients on final pathological examination (pTNM).

On inspection and L-US examination the gastric tumor was resectable in 39 patients (T1-T3 tumors), unresectable in 4 (T4 tumors) and the resectability remained uncertain in 2 patients (T4 tumors). In 12 patients there were no suspicious lymph nodes (N0). In the 33 patients with lymph node enlargement the biopsy and frozen sections revealed carcinoma in 25 patients (N1-N3).

The mean operative time of the SL was 54 minutes (range 35-90 min). The procedure is operator-dependent and has a learning curve. The SL morbidity was 2.2% (bleeding from short gastric vessels in one patient, controlled during open surgery) and SL mortality was 0. During the short study follow-up none of the 45 patients had port site metastases.

The SL was followed by open surgery in 28 patients, in whom we performed 22 R0 resections, 2 R1 resections, 2 R2 resections (P1 patients) and 2 bypass procedures (T4 patients). Staging laparoscopy correctly predicted resectability in 26 patients and failed in two cases (one false-positive and one false-negative). The SL positive predictive value for resectability was 96% and the negative predictive value for resectability was 50%.

In the 28 M0 patients on SL, open surgery revealed peritoneal metastases in 2 patients (P1, pTNM) and no hepatic metastases. The SL (inspection, L-US and frozen sections) diagnostic value for peritoneal and hepatic metastases was assessed against the final pathological report on permanent sections (pTNM). In the 45 patients with gastric cancer the overall SL sensitivity for distant metastases was 89%, the specificity 100% and the diagnostic accuracy 95.5%. The SL performance for peritoneal metastases was similar (Table I).

An unnecessary laparotomy was avoided in 17 out of the 45 gastric cancer patients with SL (37.8%).

The SL (inspection, L-US and frozen sections) diagnostic value for lymph node metastases was assessed against the final pathological report (permanent sections) in the 28 patients with open surgery. The SL sensitivity for lymph node metastases is shown in Table I.

Discussion

Indications of SL

For the SL utility in gastrointestinal cancer only prospective and retrospective observational studies are available, with an evidence-based level of grade B [7]. As a result of these trials laparoscopy has been recommended in

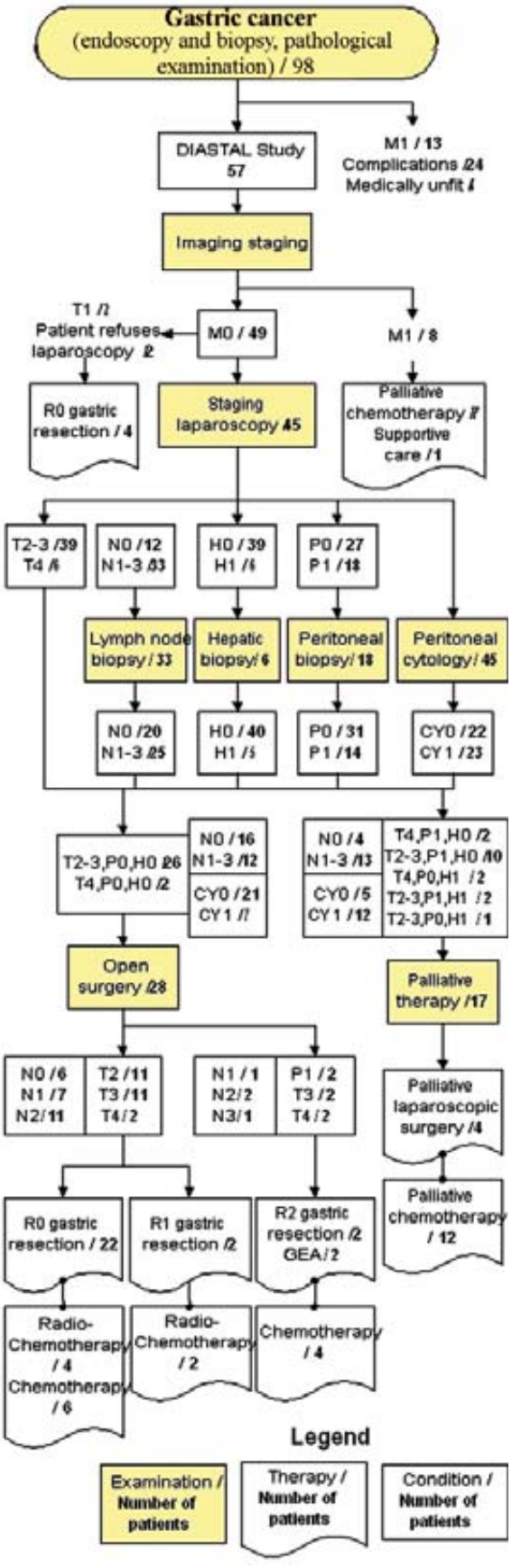

Fig 1. Staging laparoscopy in the 45 patients with gastric cancer.

Table I. The sensitivity, specificity and diagnostic accuracy of staging laparoscopy for distant metastases, peritoneal metastases and lymph node metastases

	Staging laparoscopy, biopsy and frozen sections						
	Number of patients				Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
	True positive	False positive	False negative	True negative			
Distant metastases	17	0	2	26	89%	100%	95.5%
Peritoneal metastases	14	0	2	29	87.5%	100%	95.5%
Lymph node metastases	12	0	10	6	54.5%	100%	64.3%

non-stenosing, non-bleeding patients with advanced (≥T2) gastric cancer. More than one third of these patients had unsuspected metastasis at time of operation. Laparoscopy is highly accurate in detecting occult metastases, avoiding unnecessary laparotomies and identifying patients who may benefit from chemotherapeutic approaches [5, 8].

Some authors recommend SL only for T4 gastric cancer (1) or in T3-T4 tumors [9, 10]. We performed SL in T2-T4 patients. In our experience it is quite difficult to accurately differentiate T2-T3 tumors and there is a certain risk, although small, of distant metastases in T2 (cTNM) patients.

In patients with early gastric cancer (T1), blue dye [11] or gamma mapping of the sentinel lymph node during SL might be useful for detecting lymph node metastases. In a recent study, the SL blue dye sentinel lymph node mapping accuracy was 100% [12].

The accuracy of laparoscopic staging has been documented, but its safety and impact on clinical decision making are less clear [13].

Peritoneal cytology

Peritoneal dissemination remains a frequent type of recurrence after surgical treatment. Positive peritoneal cytology (CY1) in the absence of overt peritoneal metastases (P0) is not uncommon in gastric adenocarcinoma and is a marker of poor prognosis [14].

In a recent retrospective study of patients with gastric cancer who underwent diagnostic laparoscopy for staging at the MD Anderson Cancer Center [15], 39 out of 381 patients were found to have positive peritoneal cytology (CY1) without gross peritoneal metastatic disease (P0). Median overall survival for CY1 patients (13 months) was no different from that of patients with gross metastatic disease at laparoscopy (10 months, P = 0.06). In 371 patients undergoing R0 resection for gastric adenocarcinoma at the Memorial Sloan-Kettering Cancer Center [16], median survival of patients with positive peritoneal cytology was 14.8 months vs. 98.5 months for patients with negative cytology. Multivariate analysis identified positive cytology as the preoperative factor most predictive of death from gastric cancer. Most previous studies [6, 17, 18] confirm these data.

The presence of CY1 is being considered a contraindication to attempted curative resection [17] and neoadjuvant chemotherapy should be seriously considered. Neoadjuvant chemotherapy induced downstaging of the disease in 11 of the 18 patients with positive cytology on SL (61.1%) [19]. In the study from the MD Anderson Cancer Center, in the CY1 P0 patients, the use of neoadjuvant therapy resulted in a 3-year overall survival rate of 12% versus 0% for patients who did not receive neoadjuvant therapy [15]. In another study, chemotherapy resulted in a slight survival advantage of CY1 P0 patients versus the P1 patients [20].

We found a positive CY in 7 of the 28 patients with open surgery and in 5 of the 26 M0 patients (19.2%) on the final pathology. This percentage is high when compared to retrospective series 10.2% [15]; 7.2% [20], but close to other reports - 29.0% [19], and can be explained by the prospective and systematic cytology (upper abdomen, Douglas pouch and lesser sac) performed in our study and the locally advanced cancer in most of the patients. None of our patients received chemotherapy prior to surgical resection. Adjuvant chemotherapy was given in 4 patients with R0 gastric resections, and palliative chemotherapy in another 3 patients, 2 with peritoneal metastases and R2 resection and one with a bypass procedure for local invasion (Fig.1).

Laparoscopic-US, hepatic and lymph node metastases

Diagnostic laparoscopy is limited in the assessment of solid abdominal organs, retroperitoneal structures and lymph-node metastasis. Laparoscopic US has been introduced as an adjunct to diagnostic laparoscopy for staging of tumors of the upper gastrointestinal tract, liver, biliary tree and pancreas. It has proved to be useful for detecting small liver metastases, lymph node metastases and for the assessment of the local extension of tumors of the stomach [21-24].

Laparoscopic-US was found to supply relevant clinical information and modify the surgical approach in a significant number of patients [25]. In 44 patients with gastro-esophageal tumors regarded as resectable by conventional staging, L-US found 7 irresectable tumors which were managed by palliative therapies [Flett, 2001 162 /id].

In our patients L-US revealed unsuspected liver metastases in 5 patients (100% sensitivity, versus 45.5% for preoperative imaging tests) and prevented unnecessary laparotomy in 3 of the 45 patients with SL. Most authors report similar figures [27-29], apart from one study [30]. We also found L-US a valuable tool in assessing lymph node status and guiding biopsies for frozen section.

In gastric cancer, depending on tumor location, some of the regional lymph nodes are classified as distant metastases

(e.g. lymph nodes in the splenic hilum or paracardial for antral tumors; middle colic lymph nodes for all gastric tumors) [31]. The detection of M1- lymph nodes might be facilitated by the use of laparoscopic ultrasound [32].

We did not diagnose M1-lymph nodes in any of the 45 patients with SL. In the 28 patients with open surgery, the SL (plus L-US and lymph node biopsy) sensitivity for lymph node metastases was 54.5%. The low sensitivity can be explained by the limited number and selective biopsies, only from enlarged lymph nodes on inspection and L-US examination. The high specificity is due to pathological intra-operative frozen sections confirmation of lymph node metastases.

Peritoneal and distant metastases

In the 45 patients with SL we found 17 (37.8%) unexpected distant metastases, a percentage close to some published series: 23% [33]; 33.7% [23]; 21% [9, 34]; 18.4% [35]; 37% [6]; 31% [36]. There were 14 unexpected peritoneal metastases (31.1%), similar to other studies, 40.6% [37]; 22.6% [19]. The high percentage of peritoneal metastases (62.5%) published by Song et al (10) can be explained by selective staging for T3-T4 tumors.

In a recent study the SL sensitivity and specificity for abdominal metastases was 97.6% and 98.5% respectively [38], and in another study, the accuracy was 94% [6]. The SL diagnostic accuracy for peritoneal metastases in our patients was 95.5%, close to other published series 91.7% [10]; 94% [37]. The 100% specificity of SL for peritoneal and visceral metastases in our study is due to histopatological intraoperative confirmation of metastases (frozen sections) in all patients.

Resectability and the change of treatment plan

The major advantage of diagnostic laparoscopy for patients with a gastrointestinal tumor is the prevention of unnecessary explorative laparotomies. The information provided by SL in our patients changed the initial therapeutic plan in 17 (37.8%) of the 45 patients. An unnecessary laparotomy was avoided in these patients. Other authors mention similar figures: 20.2% to 33.3% [10, 19, 39].

Laparoscopy is also an effective staging modality, providing new means of directing appropriate treatment strategies [40]. If a multimodal therapeutic strategy is considered, SL should be compulsory, at least in prospective therapeutic studies. The trial conducted by Cunningham et al [41] confirms that perioperative therapy with a regimen of ECF improves the outcome for patients with resectable gastric cancer identified before gastrectomy. The MAGIC Trial chemotherapy regimen consisted of three preoperative and three postoperative cycles of intravenous epirubicin (E) and cisplatin (C) on day 1, and a continuous intravenous infusion of fluorouracil (F) for 21 days. Neoadjuvant chemotherapy induced downstaging of the disease in 11 (61.1%) of the 18 patients with positive cytology on SL [19]. In another study, 11 patients noncurable on SL, received neoadjuvant chemotherapy. In 7 of the 11 cases, salvage surgery was done. A second SL after completion of neoadjuvant therapy was performed in four cases. Three of the four were considered curable and underwent resection. Second-look laparoscopy enables accurate assessment of the chemotherapeutic response, which can help in decisions about salvage surgery [37].

At present we do not have a program of neoadjuvant chemotherapy for gastric cancer in our hospital. Only 12 of the 45 patients had a Stage I or Stage II disease and negative cytology (CY0) on SL (plus L-US and frozen sections). If the 16 >Stage II patients with M0 on SL, who might have benefited from chemotherapy or chemoradiation, are added to the 17 patients with M1 on SL, the number of patients in whom the initial therapeutic plan might have been changed would be 33 (73.3%).

The additional cost of laparoscopy should be more than offset by the decreased morbidity and expense of hospitalization for those patients in whom an unnecessary laparotomy was avoided [33]. However, it has been questioned whether this procedure also prevents late laparotomies, that are necessary for palliative treatment during follow-up [33, 42]. The increase in expertise in laparoscopic surgery and the development of new radiologic, endoscopic and laparoscopic technologies will offer less invasive alternatives of palliation [2, 4]. In our patients we performed 4 palliative laparoscopic surgical procedures in the 17 M1 patients on SL.

Safety

Laparoscopy is a safe staging modality [40]. Port site metastases are uncommon even in advanced stages [43] and usually associated with widespread progressive disease [13].

Morbidity of SL is usually low (1-3%) and mainly represented by wound complications [44]. Staging laparoscopy in 389 patients with various neoplasms resulted in conversion to open in 5% of the cases, and complications related to laparoscopy in 4% of the patients [45]. In a retrospective study of 747 patients undergoing a diagnostic laparoscopy, severe complications were found in 11 cases (1.5%), of which 5 were converted to open surgery while one patient with metastatic gastric cancer died of a multiple organic failure following a laparoscopic tumor biopsy (0.13%) [46].

The future role of staging laparoscopy in the treatment decision and multdisciplinary therapy of gastric cancers is emerging; its major advantage of preventing unnecessary laparotomies and its good safety profile are more than encouraging for future studies. The new approaches with neoadjuvant chemotherapy, currently under investigation, will probably enhance and further define the role and the importance of staging laparoscopy in patients with gastric cancer.

Conclusion

Staging laparoscopy is a safe and effective staging modality in patients with gastric carcinoma. It avoids unnecessary laparotomies in a significant number of

patients and should be mandatory if neoadjuvant treatment is planned.

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Conflicts of interest

None to declare.

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