

ORIGINAL PAPERS

Endoscopic ultrasound *versus* multidetector computed tomography in preoperative gastric cancer staging

Marta Cimavilla-Román¹, Carlos de-la-Serna-Higuera¹, Andrea Loza-Vargas¹, César Benito-Fernández², Jesús Barrio-Andrés¹, Beatriz Madrigal-Rubiales³, Gabriel Fernández-Pérez⁴ and Manuel Pérez-Miranda¹

Departments of ¹Gastroenterology, ²General Surgery, ³Pathology and ⁴Radiology. Hospital. Universitario Río Hortega. Valladolid, Spain

ABSTRACT

Introduction: Endoscopic ultrasonography (EUS) is the gold standard technique in loco-regional staging of gastric adenocarcinoma (GAC). Nevertheless, the introduction of multidetector-row computed tomography (MDCT) allows accurate studies to be performed.

Objective: To compare the diagnostic yield of EUS and MDCT in loco-regional preoperative staging of gastric adenocarcinoma.

Material and methods: This was a retrospective and comparative study of all surgical patients with GAC and preoperative staging by EUS and 64-row MDCT. The results for each case were compared with the histological data.

Results: Seventy seven surgical patients with GAC were identified and forty two had a complete preoperative staging and were finally included in the study. With regard to overall accuracy of T staging, EUS was superior to MDCT (62% *vs* 50%). In a subanalysis of early stages (T1-T2) and advanced stages (T3-T4), accuracy and sensitivity (S) were higher for EUS than for MDCT (83.3% *vs* 64.29% and 84.4% *vs* 59.5% respectively), although this did not reach statistical significance. The overall accuracy and sensitivity of EUS for N staging was lower than that for MDCT, although neither comparison reached statistical significance (57% *vs* 64% and 29% *vs* 55%).

Conclusions: EUS diagnostic yield is similar to new MDCT with regard to T and N preoperative staging of GAC. Nevertheless, both techniques should be considered as complementary until more extensive and randomized studies can confirm these results.

Key words: Gastric cancer. Staging. Endoscopic ultrasonography. Multidetector computed tomography.

INTRODUCTION

Gastric cancer is the fourth most frequent tumor worldwide and the second cause of cancer related death (1). Surgical treatment is considered to be the only curative option. However, new treatments have been recently proposed that improve survival and decrease morbidity and mortality. Endoscopic mucosal resection provides an alternative to

surgery in early stages of the disease (T1a). In locally advanced tumors, neoadjuvant chemotherapy improves the chances of a subsequent complete tumor resection (1). An accurate preoperative staging is necessary in order provide an individualized treatment according to local and distant extension of the disease. Computed tomography (CT) is one of the diagnostic techniques used to determine tumor stage in gastric cancer and was traditionally used to evaluate the presence of distant metastasis. However, due to recent technological advances such as multidetector CT (MDCT), this also provides an accurate evaluation of loco-regional extension (2,3). In recent years, endoscopic ultrasonography (EUS) has been shown to be highly efficient in staging gastric adenocarcinoma (GAC) due to its ability to differentiate the gastric wall layers and evaluate the perigastric anatomical structures (4-8). Many studies have demonstrated the value of EUS in loco-regional staging of gastric cancer. However, some professionals question its superiority over MDCT due to limited and heterogeneous studies (9-13). The aim of this study was to compare EUS and MDCT accuracy in local staging of gastric adenocarcinoma.

MATERIAL AND METHODS

Study population

This was a retrospective and comparative study carried out from January 2012 to January 2016. All surgical patients that underwent a curative resection of GAC (total/partial gastrectomy and lymphadenectomy) with preoperative staging by MDCT and EUS were included in the study. All patients who had received neoadjuvant therapy and those with metastatic disease (M1) at diagnosis were excluded from the study. The MDCT and EUS staging results were compared with histological data of surgical specimens. Radiolo-

Received: 05-10-2016
Accepted: 07-07-2017

Correspondence: Carlos de la Serna Higuera. Department of Digestive Diseases. Hospital Universitario Río Hortega. C/ Dulzaina, 2. 47012 Valladolid, Spain
e-mail: csernah@hotmail.com

Cimavilla-Román M, De-la-Serna-Higuera C, Loza-Vargas A, Benito-Fernández C, Barrio-Andrés J, Madrigal-Rubiales B, Fernández-Pérez G, Pérez-Miranda M. Endoscopic ultrasound versus multidetector computed tomography in preoperative gastric cancer staging. *Rev Esp Enferm Dig* 2017;109(11):761-767.

DOI: 10.17235/reed.2017.4638/2016

gists and endoscopists had access to previous imaging results in some cases.

Histological study

Histological staging was performed by an expert pathologist in gastrointestinal histology. TNM classification was used according to the 7th edition (ed. 2010) of the American Joint Committee on Cancer (AJCC) (14). T1 stage was defined by the invasion of the lamina propria or submucosa, T2 tumors invade the muscularis propria, T3 tumors penetrate the subserosal connective tissue and T4 tumors invade the serosa or adjacent structures.

Endoscopic ultrasound study

The Olympus endoscopic ultrasound GF-UMQ 130 (Olympus, Hamburg) equipment was used with frequencies of 7.5 and 12 MHz. The exploration was carried out with the patient in the left lateral position and sedated using midazolam and propofol. Exploration was performed from the pylorus to the cardias after complete aspiration of the air contained in the gastric cavity; 200-300 ml of water were instilled and perpendicular images of the gastric wall were obtained in order to evaluate the normal mural gastric pattern distributed in five conventional layers. These included: 1st hyperechoic layer, interface between the water and superficial mucosa; 2nd hypoechoic layer, deep mucosa-muscularis mucosae; 3rd hyperechoic layer, submucosa; 4th hypoechoic layer, muscularis propria; and 5th hyperechoic layer, adventitia. Ecoendoscopic staging was performed according to the 7th edition AJCC criteria (14). T staging was performed as previously described. N staging was as follows: N0, absence of pathologic regional lymphatic nodes; N1, 1-2 pathologic lymph nodes; N2, 3-6 pathologic lymph nodes; and N3, seven or more pathologic lymph nodes. Malignant adenopathy was identified when at least two of the following ecoendoscopic criteria were identified: homogeneous hypoechoic pattern, oval-rounded shape, clearly limited border and size greater than 10 mm. When adenopathies were found in distant ganglion areas, endoscopic ultrasound guided fine needle aspiration (FNAB) was carried out in cases where a positive identification of malignant cells would result in a change in therapeutic management. The existence of micro-ascites or peritoneal thickening was evaluated and was considered as a sign of advanced disease and unresectability (M1).

Informed consent was obtained from all patients before the endoscopic examination. All procedures were carried out by one physician (CSH) with more than five year experience in the unit at the time of the study. Identical protocol and inclusion criteria were used. The endoscopy result was compared with that obtained from the MDCT exploration and the surgical sample and/or exploratory laparoscopy-laparotomy.

CT study

A 64-slice MDCT scanner (Siemens SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany) was used. A total of 500 ml of diluted oral contrast was administered and an automatic

injector was used to deliver 80-100 ml of intravenous contrast (Ultravist 300; Bayer Schering Pharma, Berlin, Germany) at 2 ml/sec.

The chest and abdomen were scanned in a cranio-caudal direction with a delay time of 35 and 70 seconds, respectively. Imaging settings were as follows: tube voltage, 120 kVp; tube current, 180 mAs with automatic modulation; slice thickness, 1.25 (for a detector configuration of 64 x 0.6 mm); rotation time, 0.6 sec; and pitch, 1.2. A convolution kernel (B30) and a 512 x 512 pixel matrix were used for image reconstruction.

Axial images were reconstructed with a slice thickness of 3 mm and a reconstruction increment of 1.5 mm. Sagittal and coronal images were reconstructed with a slice thickness of 1.5 mm. Images were reviewed by two radiologists with over ten year experience in gastrointestinal CT scan interpretation using a picture archiving and communication system (PACS). The review was blinded with regard to location, size, surgical findings and histological results. TNM staging using MDCT was performed according to the 7th edition of the AJCC manual as follows:

- T1 (mucosa/submucosa): the tumor exhibits mucosal layer enhancement and/or thickening as compared to the adjacent healthy mucosa, or low-attenuated layer disruption (less than 50% of thickness).
- T2 (muscularis propria): disruption may be seen in the low-attenuated layer (more than 50% of thickness) without involvement of the outer, high-attenuated layer.
- T3 (subserosa): discriminating between the gastric lesion and the outermost gastric layer is visually impossible except with the presence of a homogeneous, well-delineated border or if the perigastric adipose tissue has a slightly festooned appearance.
- T4 (serosa/adjacent structures): the outer layer border is irregular or nodular and/or perigastric fat density is increased, or there is obliteration of the adipose layer between the gastric lesion and adjacent organs, or directly infiltrated organs can be seen.

Statistical analysis

A normal distribution of quantitative variables was determined using the Kolmogorov-Smirnov test. Quantitative variables were described as mean \pm standard deviation (SD) and qualitative variables were expressed as absolute and relative (percentage) frequencies according to their category.

A diagnostic test study was carried out using data from a contingency table of study test findings against the results of the reference test. The following parameters were estimated together with their 95% CIs: sensitivity (S), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). Diagnostic precision (DP) was defined as the percentage of correctly identified patients among the total patients assessed using the study diagnostic tests. The comparison of two proportions test was used to compare percentages; p values less than 0.05 were considered as statistically significant. The degree of agreement between the study diagnostic tests and the gold standard was also assessed using the kappa statistic. All calculations were performed using the SPSS v. 15.0 software package (SPSS Inc. Chicago, IL, 1989-2006).

RESULTS

During the study period, 77 patients diagnosed with gastric adenocarcinoma received surgical treatment with a curative intent. Pre-surgical staging with thoracoabdominal MDCT and echoendoscopy was available for 48 patients. Six patients were excluded who had received neoadjuvant therapy and then underwent a surgical procedure. The final statistical analysis included 42 patients with a reference diagnostic test and surgical specimen results. Mean study population age was 70.04 (SD 12.36) years; 26 patients were male (61.9%) and 16 were female (38.1%).

With regard to the globally assessed T stage, the diagnostic precision of EUS was superior to that of MDCT (62% vs 50%) (95% CI, 47-75% and 36-64%, respectively), although statistical significance was not reached (p = 0.38) (Table 1).

The diagnostic precision of EUS was superior to that of MDCT according to a comparative sub-analysis of ear-

ly-stage patients (T1-T2) *versus* advanced-stage patients (T3-T4) (83.3% vs 64.29%) (95% CI, 70.87-95.79% and 48.60-79.97%, respectively). However, it did not reach statistical significance (p = 0.082). The kappa coefficient for the agreement between both techniques and the final histological result was also superior for EUS (0.76 vs 0.43). When the diagnostic accuracy of EUS was specifically assessed for early stages, this value was much higher for T1 (all five cases staged as such were confirmed with the surgical specimen) than for T2 (none of the eight cases were confirmed histologically). Thus, there was a clear tendency toward understaging as five of eight (62.5%) were histologically classified as T3-T4 (Table 1).

EUS sensitivity was also superior to that of MDCT (84.4% vs 59.5%) (95% CI: 70.23-98.52% and 40.80-77.95%, respectively), with a p value at the limit of statistical significance (p = 0.05). Specificity was identical in both groups: 80%, p = 1. EUS PPV vs MDCT PPV was 93.10% vs 90.48%, with an NPV of 61.54% vs 38.10% (Table 2).

Table 1. Results of EUS and MDCT in the staging of parietal invasion (stage T)

		Histopathological staging				Total
		Stage T1	Stage T2	Stage T3	Stage T4	
EUS staging	Stage T1	5	0	0	0	5
	Stage T2	3	0	4	1	8
	Stage T3	0	1	18	4	23
	Stage T4	0	1	2	3	6
	Total	8	2	24	8	42
MDCT staging	Stage T1	7	0	3	0	10
	Stage T2	0	1	9	1	11
	Estadio T3 Stage	1	1	11	5	18
	Stage T4	0	0	1	2	3
	Total	8	2	24	8	42

Table 2. Diagnostic yield of EUS and MDCT in the staging of parietal (stage T) and ganglionic invasion (stage N)

	S	SP	PPV	NPV	LR+	LR-	
EUS	T1-T2	80%	84.4%	61.5%	93%	5.1	0.24
	T3-T4	84.4%	80%	93.1%	61.5%	4.2	0.20
	T1	62.5%	100%	100%	91.9%	> 10	0.37
	T2-T3-T4	100%	62.5%	91.9%	100%	2.87	< 0.1
	N0/Nx	29%	72.7%	75%	26.7%	1.1	0.98
MDCT	T1-T2	80%	59.4	38%	90.5%	1.97	0.33
	T3-T4	59.5%	80%	90.5%	38.10	2.97	0.51
	T1	87.5%	91.2%	70%	96.9%	9.94	0.14
	T2-T3-T4	91.2%	87.5%	96.9%	70%	7.29	0.10
	N0-Nx	54.8%	63.6%	80.95%	33.33%	1.5	0.7

S: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio; LH-: Negative likelihood ratio.

Finally, T1 patients with tumor infiltration to the submucosa including the T1a sub stage (involvement restricted to the mucous membrane), which may be approached endoscopically with curative intent, were compared to patients with more advanced stages (T2-T4). No statistically significant differences were observed between EUS and MDCT with regard to diagnostic precision (92.9% vs 90.5%; $p = 1.00$) or sensitivity (100% vs 91.2%; $p = 0.56$). Endoscopic ultrasound sensitivity was inferior to that of MDCT (62.5% vs 87.5%) only in this case but did not reach statistical significance ($p = 0.24$). Finally, the PPV and NPV of EUS for the identification of advanced gastric adenocarcinoma was 70% and 96.9% (Table 2). No differences with regard to yield were found between both techniques according to histological type (only four cases were signet cell tumors), location or presence of ulceration. The latter was not consistently recorded in reports.

With regard to N stage (N0: no nodal involvement vs N+: N1-N3), diagnostic precision was lower with EUS as compared to MDCT for N0 and higher for N+, although it did not reach statistical significance in all cases (diagnostic precision for N0 was 8/11 patients [72.72%] and 9/31 [29.03%] for N+, $p = 0.19$ and $p = 0.53$) (Table 3). The sensitivity was 29% for EUS vs 55% for MDCT ($p = 0.07$). The specificity was slightly higher for EUS, although non-significant (73% vs 63%; $p = 1$) (Table 2).

DISCUSSION

Locally advanced gastric tumors have a high rate of postoperative recurrence and a poor prognosis. Thus, identifying patients who may benefit from neoadjuvant therapy is important. During the past ten years, new adjuvant and neoadjuvant chemotherapy regimens have been introduced which improved the survival of patients with tumor infiltration into the muscularis propria (T2 or higher) or with high suspicion of lymph node infiltration (1,19-22). Previously, the standard of care for gastric cancer was almost exclusively based on surgical resection, which is dependent upon distant spread (M) rather than T and N staging (22). However, the current tailored therapy strategies require accurate and reproducible tumor staging procedures

in order to define resectability and the need for adjuvant or neoadjuvant therapy.

EUS and CT represent the most commonly used diagnostic tests in order to evaluate gastric cancer extension, the former technique for loco-regional assessment and the latter to identify distant metastasis. Previous comparative studies of EUS versus CT for the loco-regional staging of gastric tumors were performed in the 1990s, and all of them found a greater diagnostic precision with echoendoscopy as compared to conventional CT with regard to T staging (16-18). During the last few years, the development of helical and multidetector scanners has greatly advanced CT technology, providing more accurate images of the gastric wall and adjacent structures. The recent meta-analysis by Seevaratnam et al. (15) showed an overall precision of 75% for T staging with CT, which rose to 80% when MDCT with four or more detectors was used. The precision was 66% for N staging. Thus, some authors challenge the superiority of EUS over MDCT in the loco-regional staging of locally advanced gastric adenocarcinoma (13). In the only study to date that compared EUS to 64-detector MDCT, almost identical results were obtained by both techniques with regard to T and N staging (overall diagnostic precision: T, 74.7% vs 76.9; N, 66% vs 62.8%) (9).

Furthermore, the impact of the changes made to the recent editions of the TNM classification remains unknown with regard to EUS and CT staging accuracy. There are significant changes in the latest (7th) edition, on which this study is based, with respect to the previous 6th edition (2002). T4 is now assigned to serosal involvement (previously it was T3) and lymph-node count for N stages was reduced (N1: 1-2 abnormal nodes, previously 1-6, and N2: 3-6 nodes, previously 7-15) (14). In addition, the "distance" criterion has been modified since the 5th edition to "number of affected nodes", as noted by Polkowski et al. (22), which may alter EUS diagnostic yield due to the peculiarities of the technique.

The numerous studies performed during the last few decades on EUS yield for the study of gastric adenocarcinoma extension are very heterogeneous. Some describe a marked tendency for overstaging of locally advanced tumors, leading to an overuse of neoadjuvant therapy in

Table 3. Results of EUS and MDCT in the staging of ganglionic invasion (N stage)

		Histopathological staging		
		Stage N0	Stage Nx	Total
EUS staging	Stage N0	8	22	30
	Stage Nx	3	9	12
	Total	11	31	42
MDCT staging	Stage N0	7	14	21
	Stage Nx	4	17	21
	Total	11	31	42

over half of patients (23). Other studies (24,25) describe a tendency toward understaging with regard to T and N. These differences (even in the most recent systematic review of 66 publications for a total of 7,747 patients) are not clearly understood (26), but may be related to a number of factors such as varying methodology, the changes in the TNM classification, the type of ultrasound probe and practitioner experience. The yield of EUS is low when discriminating between superficial tumors (T1a *vs* T1b) and assessing N stage (N0 *vs* N+) (26). Similarly, diagnostic precision, sensitivity and specificity values are highly variable and range from 50% to 100% in all the case series reported and systematically reviewed until 2016 (5,26). A sustained tendency towards an increased sensitivity may be seen in the detection of advanced T stages (T3-4), with specificity remaining very high (above 90%) for T staging (15). Therefore, a comparison of EUS *versus* other imaging modalities (CT, magnetic resonance imaging [MRI]) is challenging due to the small number of studies and the heterogeneity of head-to-head studies reported to date (9,22,28-32).

In this series, we set out to compare the yield of EUS with a conventional probe (high-frequency miniprobes do not seem to increase diagnostic yield in advanced stages) *versus* a latest-generation MDCT using the most recent edition (7th, 2010) of the AJCC TNM classification. A pathology study of the surgical specimen was used as the gold standard.

This study shows a higher overall diagnostic precision of EUS *versus* MDCT with regard to T staging, and this difference is more pronounced in a specific sub-analysis of advanced T stages (T3 and T4) as compared to earlier stages. In advanced cases, higher diagnostic precision and sensitivity values were obtained with EUS *versus* MDCT (DP: 84% *vs* 55%; S: 84% *vs* 59.5%), with identical specificity values for both tests (80%). While absolute values were always higher for EUS, no statistically significant differences were found between the groups. There was a tendency toward statistical significance ($p = 0.05$) for sensitivity but a value < 0.05 was never achieved; this is likely due to the small sample size. The consistency with histologic data was better for echoendoscopy than for MDCT, with a kappa value of 0.76 *vs* 0.43.

Eight of 42 cases (19.04%) who met early gastric cancer criteria (T1 and any N stage, according to the AJCC) and were candidates for endoscopic or surgical treatment with a curative intent were assessed in a sub-group analysis. The diagnostic yield was higher for MDCT than for EUS (CT sensitivity of 87.5% and EUS sensitivity of 62.5%) although, specificity and PPV were 100% for patients diagnosed with EUS. In general, EUS overstaged three patients with early gastric adenocarcinoma and appropriately identified all patients with advanced gastric adenocarcinoma.

These results suggest that EUS with a conventional 7.5-12 MHz probe provides very high sensitivity and overall diagnostic precision in the T staging of gastric adenocar-

cinoma. The overall diagnostic precision of EUS was 62% and 50% for CT, which is comparable to the latest generation MDCT. Most relevant is the diagnostic precision for advanced T stages (T3-T4), with a sensitivity of 84% with EUS and 59.5% for MDCT. Therefore, patients requiring neoadjuvant chemotherapy may be identified, which has a demonstrated significant increase in survival (15-21). The diagnostic precision results for EUS in T staging obtained in this study are similar to those reported by recent meta-analyses and other previous studies (Polkowski [22], 63%; Hwang [9], 61.7%). However, they are slightly lower than those reported in the Spanish study by Repiso et al. (70%) (4) and the study by Tsendsuren (68.3%) (32). Even though no statistically significant differences were found between both techniques, as demonstrated in a previous study comparing EUS and MDCT (9), this may be related in our case to a limited sample size. The impact that higher-frequency EUS probes, a prospective randomized design and an increased homogeneous sample size could have on these results is unclear. It should be noted that the differences in T staging results identified by previous studies do not seem attributable to the newer criteria established by the AJCC in the 7th edition. This is due to the fact that the modifications included only refer to the discrimination between T3 and T4 in the setting of advanced gastric cancer (serosal involvement was considered T3 in the 6th edition and T4 in the 7th edition), and these stages were not specifically addressed in this study.

In patients with early-stage gastric cancer (T1), EUS sensitivity decreases significantly *versus* MDCT (62.5% *vs* 87.5%), albeit at the expense of a specificity of 100%. This low diagnostic yield of EUS for T1 is difficult to assess due to the reduced sample size in this subgroup. However, it is similar to that reported in the literature (6-9) and does not seem to be improved by the use of high-frequency miniprobes (5,6,15). In fact, ulceration, central depression and extension greater than 20 mm are factors associated with overstaging by EUS (6). In such cases, direct endoscopic resection/dissection is advised without prior EUS staging when endoscopic semiology suggests an early stage (30) as the diagnostic precision of miniprobes is almost identical to that of conventional endoscopy in some studies (79.5% *vs* 79%) (31). The results of this study in patients with early stage gastric adenocarcinoma may be influenced by the small number of T1 patients (19.04%) which is in contrast with reported series from Southeast Asian countries where gastric cancer screening is performed (65% of T1 cases in the South Korean study by Hwang et al.) (9).

With regard to N staging, our results corroborate those from previous comparative studies using conventional CT, where a higher diagnostic precision and sensitivity were seen for CT in N+ patients regardless of the imaging criteria used to classify a lymph node as pathological (22). The diagnostic precision and sensitivity results of MDCT were superior (CT *vs* EUS sensitivity, 55% *vs* 29%), although they never reached statistical significance despite

the apparently reduced N requirement in the latest TNM classification (7th edition).

Our study has limitations derived from its retrospective nature, reduced sample size (particularly for early stage patients) and the fact that physicians analyzing the images could be aware of the results of previous tests. Furthermore, the eventual surgical treatment was not strictly influenced in all patients by the staging results provided by both tests according to the recently issued SEOM guidelines (21). However, the study strengths included the ability to fully compare conventional EUS as implemented in most institutions, latest-generation CT and the laparotomy/surgical specimen as a gold standard in all patients. This is also the only recent staging study using the latest TNM classification (7th edition, 2010) and discusses its potential impact on diagnostic yield.

To conclude, our results seem altogether to suggest that echoendoscopy still plays a major role in the loco-regional T staging of gastric cancer, with a high diagnostic yield which is comparable to that of the latest generation helical multidetector CT. In view of the technical limitations of EUS in the assessment of N stage, the irreplaceable status of CT for the study of distant spread (M) and the lack of prospective, controlled, larger studies, we consider both tests as complementary for the preoperative assessment of gastric cancer and the planning of individualized treatment. Further studies are needed for a clearer definition of the future role of endoscopic ultrasound *versus* newer MDCT scanners in this setting.

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