

## Evaluation of Siewert Classification in Gastro-Esophageal Junction Adenocarcinoma: What Is the Role of Endoscopic Ultrasonography?

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**Background:** Preoperative assessment of gastro-esophageal junction (GEJ) adenocarcinoma stage and its location according to Siewert are essential for planning the therapeutic approach. The present study was aimed at analyzing the utility of endoscopic ultrasonography (EUS) in evaluating GEJ adenocarcinoma stage and whether this modality added to EGD improves assessment of Siewert type.

**Methods:** The results of 51 patients studied by EGD plus EUS (EGD/EUS group) were compared with the results of 54 patients studied by EGD only (EGD group).

**Results:** A differentiation of pT1 tumors was attempted by measurement of the tumor length using 4 cm as a criterion. This goal was not achieved because of a high rate of advanced tumors less than 4 cm (sensitivity and specificity were 81.3% and 34.2%, respectively). Conversely EUS ability in pT1 assessment was very reliable (92%). The accuracy in defining the Siewert type was 72.5% and 64.8% for EGD/EUS and EGD groups, respectively ( $P = 0.394$ ). Some difficulties in distinguishing between type II and III tumors were observed in both groups with an extremely low specificity (44%) in classifying type II tumors by EGD group.

**Conclusions:** EUS seems to be essential in differentiating pT1 from advanced tumors. It shows an accuracy in defining the Siewert type of 72.5%, with some difficulties in distinguishing from type II and III tumors.

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**KEY WORDS:** gastro-esophageal junction adenocarcinoma; endoscopic ultrasonography; preoperative staging; Siewert classification

### INTRODUCTION

The incidence of gastro-esophageal junction (GEJ) adenocarcinoma has increased substantially in Western countries over the previous three decades [1,2], and adenocarcinoma is now reported as the most common esophageal malignancy in white males [3].

In GEJ adenocarcinoma, the preoperative assessment of the tumor location according to the Siewert classification and the estimation of the length of esophageal and gastric invasion are essential for planning the surgical approach. Furthermore, recently published studies showed promising results of neoadjuvant chemo-radiotherapy in this tumor [4,5]. A precise assessment of the tumor stage is hence essential before considering any of these aggressive multimodality treatments.

Although endoscopic ultrasonography (EUS) is firmly established in local staging of esophageal and gastric cancer [6,7], few studies investigated this modality in GEJ adenocarcinoma [8–12].

The present study was aimed at evaluating EUS compared to endoscopy (EGD) in assessment of the Siewert type and in the judgement of the invasion length both to the esophagus and stomach in GEJ adenocarcinoma.

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Moreover, the possibility of differentiating T1 from advanced tumors by measurement of the tumor length as the accuracy of EUS in T staging was studied.

## MATERIALS AND METHODS

Between January 1988 and April 2003, 139 consecutive patients with histologically confirmed adenocarcinoma of the GEJ underwent resection with curative intent at the First Department of General Surgery, University of Verona, Italy. The staging work-up included upper EGD in all the patients. Among these, 86 patients were additionally studied by EUS. Twenty-four cases out of the 86 underwent preoperative radio-chemotherapy and were excluded from the study, since no accurate evaluation is possible after multimodality treatment [13]. Analysis was hence performed on 115 patients with a median age of 68 years (range: 27–84) and a male to female ratio of 5.8 to 1. Endoscopy plus endoscopic ultrasonography were attempted in 62 cases, while preoperative judgement was limited to endoscopic examination in 53 cases. As shown in Figure 1 no analysis was possible due to nontraversable tumors in 10 out of the 115 patients (8.7%). Fifty-one patients were evaluated by endoscopy plus endoscopic ultrasonography (EGD/EUS group) and 54 by endoscopy only (EGD group).

EGD was performed first in all the cases with a Pentax EG endoscope (series 2901–2940) measuring 9.8 mm in diameter. EUS was carried out using a Machida-Toshiba front-view endoscope measuring 12 mm in diameter with

a 7.5-MHz linear probe at the distal end. The probe was covered with a water-filled balloon to ensure good transmission of the ultrasound images. GEJ was defined by the squamocolumnar junction or, in the case of a columnar lining of the esophagus, by the proximal extent of the gastric rugal folds [14]. The EUS image of the normal GEJ shows five alternating high-echo and low-echo layers. The tumor was identified as a hypoechogenic disruption of these layers, as described in a previous study [15].

The patients were divided in three types according to Siewert on the basis of the tumor center: type I, tumor of the cardia extending to the esophagus with the center lying 1–5 cm above the GEJ; type II, tumor of the cardia with the center lying 1 cm above to 2 cm below the GEJ; type III, tumor of the cardia extending to the stomach with the center lying 2–5 cm below the GEJ [16]. The extent of neoplastic invasion of the esophagus and stomach is routinely evaluated at our institution in view of the distance from the incisors on the basis of markings on the endoscope shaft. The patients were also divided into three groups according to the esophageal and gastric invasion length: below 2 cm (<2 cm); from 2 to 4 cm (2–4 cm); greater than 4 cm (>4 cm).

Depth of tumor invasion (T) and lymph node metastasis (N) were defined according to the 1997 TNM UICC classification.

A lymph node was considered metastatic when it appeared hypoechogenic, roundish, and well demarcated.

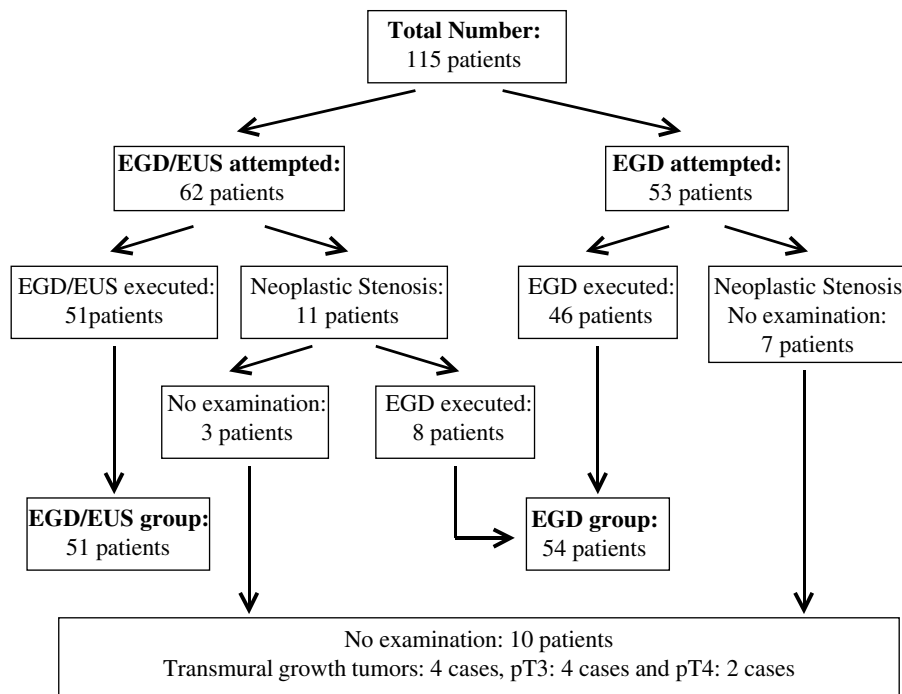


Fig. 1. The figure shows how the two groups of patients (EGD/EUS and EGD groups) were ultimately sorted out after excluding those in which the examination was not completed because of neoplastic stenosis.

Nodal stations without evidence of nodes were considered negative [17]. Since EUS is unable to detect metastases to the extra-perigastric lymph nodes because of its poor distance resolution, only perigastric and periesophageal lymph nodes were studied [18].

The preoperative EUS findings were compared with the results of the histopathological examination of the resected specimen for depth of invasion (T) and lymph node involvement (N). Assignment to one of the three Siewert types and measurement of the length of neoplastic invasion to the esophagus or stomach were accomplished immediately after resection by the surgeon himself.

To evaluate significance of differences between EGD/EUS and EGD groups, Chi-square test was used for categorical data and ANOVA test for continuous variables.

## RESULTS

The preoperatively measured average (mean  $\pm$  SD) tumor length in the 105 patients was  $4.5 \pm 2.1$  cm (median 4.2, range 0.6–10) compared to  $4.9 \pm 2.3$  cm (median 4.5, range 0.5–13) measured on the resected specimen ( $P=0.186$ ). No statistical difference was observed within any of the two groups between the preoperative assessment and the measurement on the resected specimen. In EGD/EUS group, the preoperative mean length was  $4.4 \pm 2.1$  cm (median 4, range 0.6–10) and it was  $4.9 \pm 2.5$  cm (median 4.5, range 0.5–13) on the resected specimen ( $P=0.259$ ). In EGD group, endoscopy measured an average extension of  $4.6 \pm 2.2$  cm (median 4.5, range 1–10), compared to  $4.9 \pm 2.1$  cm (median 5, range 1–9) after resection ( $P=0.470$ ).

The preoperative assessed mean length was  $2.3 \pm 1.5$  cm (median 2, range 0.6–6.5) for pT1,  $4.9 \pm 1.6$  cm (median 5, range 1–9) for pT2,  $5 \pm 2.3$  cm (median 5, range 1.5–10) for pT3, and  $5 \pm 1.3$  cm (median 4.5, range 3.5–7) for pT4 ( $P<0.001$ ). There was no possibility of differentiating pT2, pT3, and pT4 tumors on the basis of the length of the neoplasm ( $P=0.966$ ). The sensitivity in pT1 tumors assessment using 4 cm length as a criterion was 81.3% (13/16). On the other hand, pT2, pT3, and pT4 tumors showed an infiltration length minor than 4 cm in 28.1% (25/89) of the cases (specificity in pT1 assessment: 34.2%) ( $P=0.437$ ) (Fig. 2).

The results of EUS in evaluating the T stage are reported in Table I. The overall accuracy was only 52.9% (27/51) with respect to the unreliable results in assessing the pT2 class (sensitivity: 31.8%). In contrast, the results were good in diagnosing pT1 tumors (sensitivity and specificity: 75%). The sensitivity rose to 97.3% (36/37) and the overall accuracy to 86.3% (44/51) when analyzing transmural growth tumors and pT3 class together.

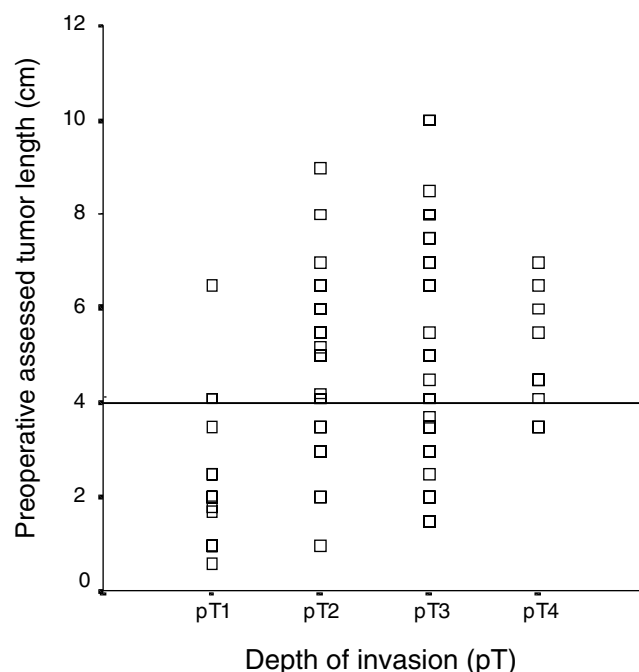


Fig. 2. Graphic representation of tumor length with the 4 cm threshold in relation to the depth of invasion (T). Each mark corresponds to one or more cases.

The overall accuracy in evaluating the N stage was 68.6% (35/51) with a sensitivity of 71.4% (10/14) for pN0 cases and 66.7% (25/37) for pN1.

Siewert type was correctly assigned in 72.5% and 64.8% of the cases in EGD/EUS and EGD groups, respectively ( $P=0.394$ ) (Table II). In both the two groups, the sensitivity was good for type I and type II tumors, while some difficulties were encountered in classifying type III (the sensitivity was 61.1% and 55.6% in EGD/EUS and EGD groups, respectively). In particular the specificity in classifying type II tumors by endoscopy alone was extremely low (70.8% vs. 44.0% in EGD/EUS and EGD groups, respectively) ( $P=0.058$ ).

The extent of invasion to the esophagus was correctly judged in 43 out of 51 cases (84.3%) in EGD/EUS group and in 38 out of 54 (70.4%) in EGD group ( $P=0.198$ ).

TABLE I. Correlation Between Endoscopic Ultrasonography (EUS) and Pathology in T Staging

Pathology	Preoperative staging			Sensitivity
	T1	T2	T3	
pT1	6	2	—	75%
pT2 <sup>a</sup>	1	7	14	31.8%
pT3	1	3	14	77.8%
pT4	—	—	3	—
Specificity	75%	58.3%	45.2%	52.9%

<sup>a</sup>In three cases tumor invasion was limited to the muscularis propria (one case was wrongly classified as T1 by EUS).

**TABLE II. Results in Preoperative Assessment of Siewert Type by Endoscopy Plus Endoscopic Ultrasonography (EGD/EUS Group) Compared to Endoscopy Alone (EUS Group)**

Specimen	Preoperative staging			Sensitivity
	Type I	Type II	Type III	
EGD/EUS group				
Type I	9	1	—	90%
Type II	1	17	5	73.9%
Type III	1	6	11	61.1%
Specificity	81.8%	70.8%	68.8%	72.5%
EGD group				
Type I	9	3	—	75%
Type II	2	11	2	73.3%
Type III	1	11	15	55.6%
Specificity	69.2%	44%	88.2%	64.8%

(Table III). In particular, no advantage adding EUS was observed in assessing “<2 cm” and “>4 cm” tumors, whereas sensitivity was somewhat increased in the evaluation of the “2–4 cm” class (80.6% vs. 50% in EGD/EUS and EGD groups, respectively) ( $P = 0.074$ ).

The extent of gastric invasion was 66.7% and 64.8% in EGD/EUS and EGD groups, respectively ( $P = 0.842$ ) (Table IV). The sensitivity diminished with the increasing length of neoplastic invasion in both groups.

## DISCUSSION

Endoscopic ultrasonography is the most reliable procedure for local staging of esophageal and gastric carcinoma [6,7]. Even though EUS has become widespread and there are several reports on its clinical application [19], little data is available on preoperative staging of GEJ adenocarcinoma, and none analyzing the results in the evaluation of tumor length, or in the classification of the Siewert type. Recent evidences suggest that preoperative chemo-radiotherapy may improve survival in

**TABLE III. Results in Preoperative Assessment of the Length of Esophageal Invasion by Endoscopy Plus Endoscopic Ultrasonography (EGD/EUS Group) Compared to Endoscopy Alone (EGD Group)**

Specimen	Preoperative staging			Sensitivity
	<2 cm	2–4 cm	>4 cm	
EGD/EUS group				
<2 cm	26	3	—	89.7%
2–4 cm	2	12	1	80.6%
>4 cm	—	2	5	71.4%
Specificity	92.9%	70.6%	83.3%	84.3%
EGD group				
<2 cm	28	5	—	84.8%
2–4 cm	6	9	3	50%
>4 cm	—	—	3	100%
Specificity	82.4%	64.3%	50%	74.1%

**TABLE IV. Results in Preoperative Assessment of the Length of Gastric Invasion by Endoscopy Plus Endoscopic Ultrasonography (EGD/EUS Group) Compared to Endoscopy Alone (EGD Group)**

Specimen	Preoperative staging			Sensitivity
	<2 cm	2–4 cm	>4 cm	
EGD/EUS group				
<2 cm	15	1	—	93.8%
2–4 cm	7	11	—	61.1%
>4 cm	4	5	8	47.1%
Specificity	57.7%	64.7%	100%	66.7%
EGD group				
<2 cm	18	1	—	94.7%
2–4 cm	4	9	5	50%
>4 cm	2	7	8	47.1%
Specificity	75%	52.9%	61.5%	64.8%

GEJ adenocarcinoma [4,5]. A correct staging of these tumors is hence essential to identify the patients that would benefit by neoadjuvant treatments.

In our previous experience on EUS [10], we reported an unreliable overall accuracy in T evaluation of 55.2%, due to a high number of errors in differentiating pT2 from pT3 tumors. In the present series, as recently reported by Bosing et al. [12], the overall accuracy remains poor (52.9%) because of the difficulty in distinguishing between tumors invading the serosa and the subserosa, but mainly because of the absence of the serosa in part of the cardia region. The actual TNM classification considers tumors as T3 if they penetrate the visceral peritoneum so even tumors with transmural growth do not always fulfill this condition. Nevertheless, differentiating between tumors with transmural growth and invasion of the perigastric fat and T3 tumors is not essential given their similar clinical behavior and prognosis [20,21]. On this basis a revision of the current staging system has been already proposed [22].

Sensitivity and specificity in evaluation of pT1 tumors was 75% and the accuracy in excluding patients not suited for multimodality treatment exceeded 92%. Because the series is based on a surgically resected cohort, no tumors preoperatively staged as T4 were described. Three patients preoperatively classified as T3 showed initial infiltration of the pancreatic capsula (one case) and diaphragm (two cases) at surgery.

An attempt of differentiating T class by measurement of the tumor length was made. Results in measurement of the tumor extension were reliable both in EGD and EGD/EUS groups. In GEJ adenocarcinoma, as opposed to what was recently reported for squamous cancer of the esophagus [23], the depth of neoplastic invasion (T) is not significantly correlated to its length. In this series, evaluation of neoplastic extension was insufficient for differentiating early (pT1) from advanced tumors since a high number of the latter class was less than 4 cm in



length (sensitivity and specificity in pT1 assessments were 81.3% and 34.2%, respectively) (Fig. 2).

Adenocarcinoma of the GEJ remains one of the most challenging tumors to treat. The evaluation of the tumor invasion, both proximally to the esophagus and distally to the stomach, and particularly the determination of the type according to Siewert are essential for planning the surgical approach. Siewert and colleagues reported that a preoperative classification based on a combination of contrast radiographs, endoscopy and computed tomography uncommonly needs to be modified in relation to the intraoperative findings [24]. On this basis they plan the surgical resection treating type I cancer by a subtotal esophagectomy with proximal gastrectomy and type II and III cancers by a total gastrectomy with transabdominal resection of the distal esophagus after widely splitting the anterior esophageal hiatus [24]. While the extent of resection of type I and type III cancers is well defined the optimal surgical procedure for true cardia cancer (type II) is still controversial. It is not defined if the resection has to be extended proximally performing an esophagectomy as in type I tumors or distally performing a total gastrectomy as in type III tumors. From this perspective the preoperative precise definition of the length of invasion of the esophagus and stomach could be of help in the decision making.

In the present experience, the overall accuracy in preoperative classification of Siewert type was approximately 70% with somewhat better results adding EUS to endoscopic examination. The sensitivity progressively diminished from type I to type III tumors in both groups mainly because of the difficulty in differentiating true cardia cancer (type II) from subcardial tumor (type III). In EGD group, specificity in determining type II tumors was very low (44%). The troublesome classification of type II and III is probably due to the imprecise results in the evaluation of gastric invasion because of the difficulty in positioning the probe on the entire circumference of the cardia region and in the gastric fundus. The invasion of the stomach is therefore frequently studied by retroflexed view endoscopy only.

On the other hand, encouraging results in evaluating the length of esophageal invasion were observed by EUS. Our present results confirm the findings reported by our previous experience [10] and by Natsugoe et al. [9] who correctly identified the extent of esophageal involvement in 94% of cases. EUS added to EGD yielded an improvement, even if not statistically significant, in the evaluation of esophageal invasion especially in "2–4 cm" tumors. The sensitivity in defining this class was 80% in EGD/EUS group and 50% in EGD group.

A limitation of the present study is the retrospective analysis of the data and the fact that the EGD cases were predominantly early in the series. EUS apparatus has

been available at our Institution since 1990 and about 65% of EUS examinations were carried out in the second half of the study. However, it is our opinion that the results have not been largely influenced since, even though the quality of EGD equipment has improved during the study period, the capability of evaluating the length of extension has not been changing significantly.

In conclusion, endoscopic ultrasonography (i) seems to be essential in differentiating pT1 from advanced tumors; (ii) seems to improve the definition of the esophageal invasion length, especially in "2–4 cm" class; (iii) shows an accuracy in defining the Siewert type of 70% with some difficulties in distinguishing from type II and III tumors.

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