Accuracy of Endoscopic Ultrasonography for Gastric Cancer Staging

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ABSTRACT: Gastric cancer remains a health problem, with treatment indications varying with the TNM stage. We aimed in this study to highlight the role of EUS in GC patients and also to calculate the accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of EUS for T and N staging in our group of patients with this disease. In this study, we included 41 GC patients, and individual values for every T stage accuracy, sensitivity, specificity, PPV, NPV, correct staging, understaging, and overstaging were calculated. EUS overall accuracy for T staging was 58.53%, with the highest sensitivity reached for the T4 stage, 95.83%. For N+ vs. N-staging, EUS accuracy was 68.29%, with a sensitivity of 75% and a specificity of 44.44%. The positive and negative predicted values for the presence or absence of nodal disease were 82.75%, respectively 33.33%. In conclusion, this study confirmed the importance of EUS for the assessment of GC T and N stage and highlighted the role of this tool in the detection of liver micrometastasis unrevealed by other imaging techniques like abdominal ultrasound or MSCT.

KEYWORDS: Gastric cancer staging, endoscopic ultrasound, TNM stage.

Introduction

Gastric cancer (GC) remains a serious health problem although a persistent decrease trend in its incidence was observed in the last 10 years [1,2].

Its heterogeneous nature still makes it unpredictable, while its prognosis is mainly related to diagnosis disease stage, genomic characteristics as well as histologic type [3-5].

Assessing the TNM stage allows harbors perhaps a major burden since its assessment is associated with a five-year survival rate but more importantly, it helps in taking the proper treatment decisions [6].

Many methods are available for the GC TNM stages such as endoscopic ultrasound (EUS), multidetector computer tomography (MDCT), magnetic resonance imaging (MRI), transabdominal ultrasound (TAUS), and positron emission tomography (PET).

However, all of them have different results in terms of tumor depth invasion, lymph nodes involvement, and the presence or absence of metastasis, which rather limits their use if taken in a solitary manner [7-10].

EUS is recommended as the method of choice for T staging due to well possibility of differentiation between gastric wall layers [11].

Even though many studies have shared their experience on EUS staging of preoperative GC, there is still room to improve the technique since it may be adopted as the first line for regional tumor involvement against other methods.

EUS accuracy rates are still heterogeneous with reports ranging from 60-90% for the T stage and 50-90% for N stage [12-14].

The therapeutic approach is directly related to the TNM stage, thus, a correct algorithm of staging is necessary.

Moreover, dividing between lower and advanced stages, not only by MDCT imaging, which is the preferred method for metastasis first evaluation, is essential to establish the patient’s prognosis [15].

The aim of our study is to assess the EUS performance in GC staging, by focusing on T and N stage, which might propose patients as candidates for surgery.

Materials and Methods

Study Design and Patients

In this study, we included patients with confirmed GC that were addressed for EUS preoperative TNM staging for a period of 24 months.

The inclusion criteria were: patients (1) with biopsy-proven diagnosis of gastric adenocarcinoma (2) regardless of T and N stage, (3) with or without neoadjuvant therapy, (4) age 18 to 90 years old, (5) with signed written...
informed consent (6) who underwent surgery with a clear histopathological result of the specimen.

Patients with (1) other histopathological types GC (gastrointestinal stromal tumors, gastric lymphoma, neuroendocrine tumors), (2) gastroesophageal junction tumors, or (3) with metastasis (M1) were excluded.

The study was approved by the ethics committee (No 09/12.01.2019) and all procedures were performed according to the Declaration of Helsinki, after signing an informed consent.

**EUS TNM Staging**

EUS was performed by an experienced endoscopist using a radial front-viewing echoendoscope (echoendoscope Olympus, GF-UCT180, tower Olympus Evis Exera II CV-180, Olympus Optical Corporation, Tokyo, Japan) coupled with ultrasound equipment (Hitachi-Aloka Prosound Alpha 7, Hitachi Aloka Medical Ltd., Tokyo, Japan) and the TNM stage was concluded according to the 8th edition of the AJCC TNM Staging System [16].

Malignant perigastric lymph nodes were noted if perigastric rounded, enlarged structures, more than 0.8 cm in diameter, with low-level echoes, homogeneous, well-circumscribed were present.

**Follow-up**

Patients with complicated tumors, such as bleeding, occlusion, were considered as emergencies and underwent surgery.

Otherwise, patients were treated according to the AJCC guidelines, according to their stage. Pathologic examination was performed with pTNM being assessed.

**Data Analysis**

Preoperative T and N stages evaluated using EUS were compared with pathology reports from the surgical specimens.

With available data, accuracy, sensitivity, specificity, PPV and NPV of EUS in GC T and N staging were calculated.

**Results**

**Patients Characteristics**

A total of 50 consecutive patients with endoscopic biopsy-proven diagnosis of gastric cancer that were referred to the Research Center of Gastroenterology and Hepatology Craiova, University of Medicine and Pharmacy of Craiova, ROMANIA for EUS local preoperative staging between November 1st 2019 to November 1st 2021, entered in this study.

After inclusions and exclusion criteria were applied, 6 patients were excluded due to they were diagnosed with other histologic type than adenocarcinoma (5 gastric lymphomas, 1 GIST).

After EUS was performed, three of the 44 remaining patients were excluded due to the presence of micrometastasis revealed by this examination (Figure 1).

**Figure 1. Graphic representation of all patients diagnosed at Research Center of Gastroenterology and Hepatology Craiova (RCGHC) with GC, between November 1st 2019 to November 1st 2021.**

GC: gastric cancer, MDCT: multidetector computer tomography, TAUS: transabdominal ultrasound, EUS: endoscopic ultrasound, COVID 19: Coronavirus disease 2019, GIST: gastrointestinal stromal tumors, RCGHC: Research Center of Gastroenterology and Hepatology Craiova.

All the 41 patients which remained included, after a mean interval of 3 weeks followed curative (34 patients) or palliative intent (7 patients) surgical treatment depending on the recommendation of the multidisciplinary team for each case. 4 patients were purposed for palliative surgical intervention due to gastrointestinal bleeding and 3 due to bowel obstruction.

The most important clinical and pathological characteristics are shown in Table 1.
Table 1. Patient’s characteristics.

| Patient’s characteristics      | Percent |
|--------------------------------|---------|
| Age, mean                      | 65.02 (range 51-86) |
| Gender, male/female            | 27/14   |
| Tumor location                 |         |
| Cardia                         | 3       |
| Body                           | 16      |
| Antrum                         | 22      |
| Histological type              |         |
| WHO classification             |         |
| tubular adenocarcinoma         | 21      |
| tubulo-papillary adenocarcinoma| 6       |
| signet ring cell carcinoma     | 6       |
| undifferentiated adenocarcinoma| 4       |
| mixed adenocarcinoma           | 4       |
| Lauren classification          |         |
| intestinal                     | 27      |
| Diffuse                        | 14      |
| Tumor differentiation          |         |
| G2                             | 12      |
| G3                             | 29      |
| T stage                        |         |
| T1                             | 0       |
| T2                             | 6       |
| T3                             | 2       |
| T4                             | 33      |
| N stage                        |         |
| N0                             | 12      |
| N1                             | 1       |
| N2                             | 15      |
| N3                             | 13      |
| Tumor size                     |         |
| <5 cm                          | 8       |
| 5-10 cm                        | 14      |
| >10 cm                         | 19      |

WHO: World Health Organization; T and N stages-assessed by EUS; 
EUS and pathological staging

The accuracy of EUS was determined by comparing the EUS T stage with the reference test, pathological T stage evaluated on surgical specimen, according to the 8th edition of AJCC TNM Staging System as shown in Table 2 [16].

Table 2. EUS assessment of T stage compared with pathological results.

| EUS stage | T1 | T2 | T3 | T4 | Total |
|-----------|----|----|----|----|-------|
| T1        | 0  | 0  | 0  | 0  | 0     |
| T2        | 6  | 1  | 0  | 0  | 2     |
| T3        | 2  | 1  | 0  | 0  | 4     |
| T4        | 33 | 9  | 23 | 33 | 41    |

EUS: endoscopic ultrasonography; pT-pathological T stage.

The value of overall accuracy for T staging with EUS in this study was 58.53%.

The highest sensitivity in EUS T staging was reached by T4 stage, 95.83%, while the specificity of EUS in this stage had the lowest value of all stages, 41.17%.

The PPV for the EUS T4 stage was 69.69%, which was the highest value.

For T2 staging EUS reached the maximum value of NPV, 94.28%. For T4 stage, EUS was able to correct estimated 23 of 24 patients (95.83%), with only 1 patient which was understaged to T3 stage.

For T1 stage all patients were overstaged (100%).

Individual values for every T stage accuracy, sensitivity, specificity, PPV, NPV, correct staging, understaging and overstaging were calculated and are exposed in Figures 2-7.

Figure 2. EUS T1-T4 staging accuracy.
Figure 3. EUS T1-T4 staging sensitivity.

Figure 4. EUS T1-T4 staging specificity.

Figure 5. EUS T1-T4 staging PPV.

Figure 6. EUS T1-T4 staging NPV.

Figure 7. EUS T1-T4 correct staging, understaging and overstaging.

For N+ vs. N-staging (Table 3), EUS accuracy was 68.29%, with a sensitivity of 75% and a specificity of 44.44%.

The positive and negative predicted values for the presence or absence of nodal disease were 82.75%, respectively 33.33%.

24 of 32 patients with nodal disease were correct staged as N+ while 8 were understaged (N-).

| EUS stage | N0 | N+ | Total |
|-----------|----|----|-------|
| N0        | 4  | 8  | 12    |
| N+        | 5  | 24 | 29    |
| Total     | 9  | 32 | 41    |

Table 3. EUS assessment of N stage compared with pathological results.

EUS: endoscopic ultrasonography; pN-pathological N stage.
Figure 8. A case of a T4b stage moderate differentiated tubulo-papillary gastric adenocarcinoma. (A) Endoscopic image of an ulcerated lesion located in the body of the stomach; (B) EUS image showing the lesion that involves all the layers of the gastric wall with no clear limits with the left hepatic lobe (T4b).

Discussion

The prognostic and treatment of patients with GC remain topics of great interest.

Histological type is a well-known prognostic factor, and according to Lauren classification, there are two types of GC, diffuse and intestinal type, with better outcome for the last one [17].

A more important factor with impact in treatment decision is the TNM stage of the disease, the reason why an accurate evaluation of the locoregional and distant extension of GC is imperative [18].

A correct TNM staging is also wanted due to the close correlation with outcomes.

For example, T1a, T1b, T2, T3, T4 are associated with 5-year survival rates of 94.4, 86.9%, 76.3%, 64.6%, and 31.1%, respectively [6].

Multiple images techniques are used to obtain a correct assessment of disease extension. For tumor invasion, EUS is considered the most suitable method to evaluate the T stage because of its high precision in differentiating all 5 layers of the gastric wall.

Treatment options vary with the extension of the disease, and for early GC which includes Tis or T1a, endoscopic resection is indicated.

Patients with locoregional disease are investigated for surgically fit, with or without the recommendation of NAC, the first group being associated with better outcomes and overall survival [19-21].

No patient was diagnosed with T1 stage and therefore endoscopic treatment was not performed for our group of patients.

Two other methods are used to evaluate patients with GC, MDCT, and MRI.

The main disadvantages of MDCT are the risk of nephropathy induced by contrast agents and the potential harm of ionizing radiations [22].

Despite the safety profile and better overall T staging accuracy than MDCT, MRI has not been mentioned in actual guidelines of GC preoperative assessment [14,23,24].

The utility of MDCT and MRI is in the evaluation of lymph nodes involvement, even those present on a variable distance of gastric wall, and the presence or absence of metastasis on patients with GC [25].

Regarding the results of our study, the accuracy of EUS for T4 stage (Figure 8), which represented more than half of the total number of patients, was comparable with a study that included 610 patients, 73.17% vs. 63.3% [26].

The specificity and sensitivity values of EUS for T4 stage were closer to those found by Redondo et al., 41.17% vs. 61% specificity and 95.83% vs. 77.3% sensitivity.

The specificity value for EUS in positive lymphoid nodes detection was 44.44%, much lower than in Fairweather et al. study (86.4%) but close to the results of Perlaza et al. (51.6%).

Similar values of sensitivity for EUS N+detection (75%) were described in two others studies Cimavilla-Roman et al. and Feng et al. 73% and 76%, respectively [26-29].
Multiple factors like inflammation, edema, fibrosis can influence the EUS diagnostic accuracy, due to the increased associated probability of over-and understaging [30,31].

Unfortunately, in our study, no patient with pT1 stage was correctly assessed by EUS and all 4 were understaged like T2 stage and the real accuracy for T1 stage can’t be truly estimated. Also a high incidence on T1 overstaging was observed in other study of 232 patients.

Contrary, from T4 stage group only one patient, was understaged like T3 stage, the rest of 95.83% were correct staged reaching higher values than Chaoqun Han found in his study (57.5%) [30].

EUS has low accuracy in differentiation between subserosa and serosa involvement, fact that was observed in our study because 9 patients with T3 were overstaged by EUS in T4a stage [32].

Our study had some limitations, mainly focusing on the low number of patients. Also we did not encounter many patients in the T1 stage, which are direct candidates for endoscopic submucosal dissection.

The utility of EUS in M stage assessment is low compared with other imaging methods and when the presence of metastasis is demonstrated, the T stage assessment by EUS has a minimal impact on treatment decision.

Even the role of EUS in M stage assessment is limited, EUS was able to highlight liver micrometastasis on 3 patients, unrevealed on MDCT or TAUS.

Conclusion

Our study confirms that EUS should be considered for locoregional disease extension of GC, and it may be considered as the first line of imaging method for TN stage.

Also, by providing an EUS view of the T and N stage, the correct treatment modality might be chosen, thus ensuring a better prognosis for the patient.

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Conflict of interests

None to declare.

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