Endoscopic Ultrasound Staging of Gastric Cancer after Neoadjuvant Chemotherapy with Flot Regimen

Germana de Nucci *, Silvia della Torre, Roberta Muscia, Giuseppe Fierro, Valeria Smiroldo, Enzo Domenico Mandelli, Franca Di Nuovo, Roberto Bollina, Gianpiero Manes

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Article

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Germana de Nucci [1], Silvia della Torre [2], Roberta Muscia [1], Giuseppe Fierro [1], Valeria Smiroldo [2], Enzo Domenico Mandelli [1], Franca di Nuovo [3], Roberto Bollina [2] and Gianpiero Manes [1]

[1] Gastroenterology and Digestive Endoscopy Unit, ASST Rhodense, Garbagnate Milanese, Milan, Italy

[2] Oncology Unit, Asst Rhodense, Rho, Milan, [3]Pathology Unit, Asst Rhodense, Garbagnate Milanese, Milan

* Correspondence: germanadenucci1@gmail.com; Tel.: +39-02994302937; Fax: +39-02994302905

ABSTRACT: Background: Gastric cancer is one of the most common malignant tumors in the gastrointestinal tract. Neoadjuvant chemotherapy may be administered as a means of "downstaging" a locally advanced tumor prior to curative resection. Perioperative chemotherapy with FLOT regimen (florouracile, leuvocorin, oxaliplatin, docetaxel) has shown to improve overall survival in patients with advanced gastric cancer (AGC). The aim of our study was to evaluate the endoscopic ultrasound (EUS) accuracy of T and N staging of AGC compared with surgical specimen after FLOT. **Methods:** We retrospectively analyzed 29 patients with AGC, who had their preoperative TNM staging with EUS and computer tomography (CT) and who underwent neoadjuvant chemotherapy with FLOT. Then patients were evaluated with a second EUS and CT to determine eventual downstaging. EUS staging was compared with post surgical pathology used as gold standard. **Results:** At eus evaluation downstaging of tumor depth (T) alone was observed in 8 patients (27,6%), of nodes involvement (N) alone in 6 patients (20,7 %), and both in 3 patients (10,3%); at CT exam the downstaging occurred only in 11 patients out of 29 (38%). The overall accuracy of preoperative T and N staging by EUS was 68.75% (95%CI 41.34-88.98) and 81.25% (95%CI 54.35-95.95) when compared to the postoperative histopathological staging. **Conclusions:** Our results showed that EUS-based AGC restaging after FLOT regimen has an adequate diagnostic accuracy on T (68.75%) and N (81.25%). In order to identify which patients could have a beneficial response from FLOT regimen, EUS appears one of the best tool to have a precise evaluation of post chemio pre-surgical patient status.

Keywords: gastric cancer; endoscopic ultrasound stadiation; neoadjuvant chemotherapy; FLOT regimen; restaging

1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors of the gastrointestinal (GI) tract and the second most common cause of cancer-related death worldwide [1]. The only potentially curative treatment for locally advanced gastric cancer (LAGC) is surgery, which is feasible in less than 50% of cases [2]. Patients with LAGC have a poor prognosis related not only to the low curative resection but also to the high recurrence rates [3-6]. In the last decade, there has been a significant change in the approach to LAGC due to the positive impact of neoadjuvant treatment and improvement in preoperative staging, which is mandatory to ensure the best individual therapeutic modality. [7]. For patients with a T3/T4 stage or with positive lymph nodes, neoadjuvant therapy (chemotherapy, radiotherapy or both) is highly advised [8-10], with the goal to downstage the tumor prior to attempt curative resection. Another rationale for neoadjuvant therapy is to spear patients who will develop distant metastases during treatment, the morbidity of a futile gastrectomy [1-12].

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In the last years, the use of a new perioperative chemotherapy scheme named FLOT (5-fluorouracil, Leucovorin, Oxaliplatin and Docetaxel) improved overall survival in patients with advanced gastric or gastroesophageal junction adenocarcinomas as compared with previous regimens, i.e ECF (epirubicin, cisplatin and 5-fluorouracil) or ECX (Epirubicin, Cisplatin and Capecitabine). A study from the German Oncological Study Group investigating perioperative FLOT regimen versus ECF/ECX, demonstrated a significantly longer overall survival for the FLOT regimen (overall survival 50 months versus 35 months, HR 0.77; P=0.012), with higher rates of pathological response (15.6% versus 5.8%), and no major concerns for toxicity. Based on these data, neoadjuvant FLOT should be regarded as standard of care, unless there is a formal contraindication for its use or the patient is not fit for triplet chemotherapy [13,14].

With the introduction of this new neoadjuvant regiment, identification of patients with a better post-therapy response is crucial to establish the most effective subsequent therapeutic approach so thar many authors have proposed different methods to evaluate tumor regression after neoadjuvant FLOT [15].

Among these, endoscopic ultrasound (EUS) is able to provide precise images of tumor extension changes and is already routinely utilized to diagnose and stage GI cancers [16]. For preoperative loco-regional staging of GC, EUS has been established as the most effective diagnostic tool over other imaging modalities such as CT [26-27] [17-19], due to its capability to precisely identify the tumoral proximal and distal extension, to assess gastric wall depth of invasion (T Stage) [20-21], and to assess lymph node involvement (N Stage). [22-23]. Overall pre-operative accuracy of EUS ranges between 78-92% for T stage and 63-78% for the N stage. T stage accuracy is superior for more advanced malignancies (T3-T4), as compared to early lesions (T1-T2 lesions) [24-27].

Despite all the above considerations, only few data exploring the accuracy of EUS restaging after neoadjuvant chemotherapy, in particular after FLOT regimen, are available in patients who subsequently underwent total or subtotal gastrectomy.

The aim of our study was to retrospectively evaluate EUS accuracy in assessing T and N staging after neoadjuvant FLOT regimen in LAGC patients who subsequently underwent curative surgery.

2. Materials and Methods

We retrospectively retrieved from a prospectively collected Oncology Unit database all patients with GC who, between November 2017 and December 2024, underwent neoadjuvant chemotherapy using a FLOT scheme and then underwent surgical resection at General Surgery of ASST Rhodense Hospital, Garbagnate Milanese (MI).

All patients were staged following a precise standardized algorithm using CT and EUS within one month before chemotherapy (Table 2). PET exam was not routinely performed in all patients but only when there were doubts about N stage or presence of distant metastases after CT/EUS evaluation. All patients underwent neoadjuvant FLOT regimen, which included docetaxel (50 mg/m^2), oxaliplatin (85 mg/m^2) and leucovorin (200 mg/m^2) with short-term fluorouracil (2600 mg/m^2 as a 24-hour infusion), all on day 1 and administered every two weeks for eight weeks before surgery and a second cycle with the same scheme after surgery.

At the end of FLOT regimen, patients had a second EUS and CT examination to re-evaluate T and N stages prior surgery. EUS was done using a therapeutic echoendoscope (EG-3870UTK, Pentax Medical, Tokyo Japan) by the same expert operator (GDN with >15 years experience) and findings were categorized according to ninth edition of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM classification system [28]. Local tumor infiltration was established by evaluation of the involvement of the five-layer structure of the gastric wall. T1 lesion were defined as lesions confined to the mucosa (T1a) or the submucosa (T1b); T2 lesion with involvement limited to the fourth layer (muscolaris propria); T3 lesion characterize by penetration through the fifth layer and invasion of the serosa; T4 lesion when adjacent organs and tissues were infiltrated by the tumor. EUS evaluation of N stage was based on characteristics and number of metastatic perigastric lymph nodes. A lymph node was deemed metastatic when it had

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round borders, hypoechoic echostructure, no visible hyperechoic and vascolarized hylum, and measured more than one cm. Stage N0 was considered when no lymph nodes were present and N1 in case of affected ones. Surgery was performed in all patients within one month from the end of chemotherapy, close to the EUS and CT examinations.

EUS TN stage was compared with histopathological TN stage of the surgical specimens, which represents the gold standard, by using the seventh edition of the UICC/AJCC classification system. The study was approved by the internal scientific ethics committee.

3. Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS software v.15.0) for Windows. Descriptive statistics included calculation of mean values and standard deviation (SD) of continuous variables, and percentages and proportions of categorical variables. Statistical analysis was performed using chi-square and Mann–Whitney U test, when appropriate. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of EUS and CT with 95% confidence interval (CI) were calculated, considering surgical histopathology as gold standard. A sub-analysis of diagnostic accuracy of EUS and CT on T stage and N stage\ was also performed.

Agreement between EUS and CT findings on FLOT protocol response was established by Cohen's kappa (k), and results were interpreted as follows: values ≤ 0 indicate no agreement and 0.01–0.20 as none to slight agreement, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as perfect agreement.

Finally, diagnostic accuracy of EUS and CT in respect to surgical specimen was compared by means of McNemar test.

4. Results

During the study period, fifty-five patients with LAGC were staged using CT and EUS. 29 (53%) of them underwent FLOT and were considered for this study. Among the remaining patients, 25 underwent upfront surgery and one refused to adhere to therapy due to the appearance of alopecia.

Demographics and clinical characteristics of the 29 patients who underwent neoadjuvant FLOT are summarized in Table 1. Fifteen patients were male (62.5%), with a median age of 65.3 ± 8.07 years. Tumor was localized in the angulus in eight patients (27.6%), in the antrum in nine (31%), in the body in ten (34,5%) and in the cardias in the remaining two patients (6,9%), respectively. At the time of diagnosis, median serum Ca19-9 and CEA were 53.6 ± 89.5 ng/ml and 21.6 ± 39.3 ng/ml, respectively.

4.1. EUS and CT Scan Clinical Staging Before Chemiotherapy

Clinical stage before neoadjuvant chemotherapy on the basis of EUS was as follows: stage IIA in five patients (17.2%); stage IIB in six (20.7%); stage IIIA in sixteen patients (55,2%) and stage IIIB in two (6.9%), respectively. CT-based staging revealed stage IB in four patients (13.8%), stage IIA in six (20,7%), stage IIB in three (10.3%), stage IIIA in fifteen patients (51,8%) and stage IIIB in the remaining one (3,4%), respectively (Table 1)

Table 1. Clinical and demographic characteristics of the study population.

FEATURES	ALL PATIENTS (n=29)
Gender (Male/Female)	15/14
Age years, mean	65.3 ± 8.07
Tumor location	
Angulus	8 (37.5%)

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Antrum	9 (37.5%)
Body	10(18.7%)
Cardias	2 (6.3%)
Tumor markers	
Ca 19.9, mean (U/ml)	53.6 ± 89.5
CEA, mean (ng/ml)	21.6 ± 39.3
Clinical stage (UICC/AJCC classification) Eus based	
stage IIA	5 (17.2 %)
stage IIB	6 (20.7%)
stage IIIA	16 (55.2%)
stage III B	2 (10.3%)
Clinical stage (UICC/AJCC classification) CT scan based	
stage IB	4 (13.8%)
stage IIA	6 (20.7%)
stage IIB	3 (10.3%)
stage IIIA	15 (51,8)
stage IIIB	1 (3.4%)

4.2. Restanging After Chemiotherapy

EUS re-staging after FLOT regimen detected stage IB in five patients (17.3%), stage IIA in seven (24,1%), stage IIB in nine (31%), stage IIIA in six (20,7%) and stage IIIB in two patients (6.9%), respectively. Overall, EUS tumor (T) downstaging was detected in eight patients (27,6%), lymph node (N) downstaging in six patients (20,7%), and both T and N downstaging in three patients (10, 3%) (Table 2), in the remaining 12 patients (41,4%) eus showed no significant changes respect of pre FLOT regimen

CT-based re-staging after neoadjuvant therapy disclosed a stage IB in six subjects (20,7%), stage IIA in eight (27,6%), stage IIB in five (17,3%) and stage IIIA in ten patients (34.4%). CT tumor (T) downstaging was identified at in nine patients (31%), lymph node (N) downstaging in four subjects (13,8%), while both T and N downstaging in two patients (6.9%), no down staging in the remaining fourteen (Table 2). EUS and CT showed only a moderate agreement for overall downstaging after neoadjuvant therapy (Cohen's Kappa 0,5).

4.3. Surgical Pathology Comparison

At surgical pathology, stage IB was found in six subjects (20,7%), stage IIA in four (13,8%), stage IIB in seven (24,1%), stage IIIA in four (13,8%), stage IIIB in five (17,2%), and stage IIIC in three subjects (10.3%) (Table 2).

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Table 2. TNM staging by EUS and CT pre-FLOT and post-FLOT.

	stage IB	stage IIA	stage IIB	stage IIIA	stage IIIB	stage IIIC
EUS pre-FLOT	0	5 (17.2%)	6 (20.7%)	16 (55.2%)	2 (6.9%)	0
CT pre-FLOT	4 (13.8 %)	6 (20.7%)	3 (10.3%)	15 (51.8 %)	1 (3.4.%)	0
EUS post-FLOT	5 (17.3%)	7 (24.1%)	9 (31%)	6 (20.7%)	2 (6.9%)	0
CT post-FLOT	6 (20.7%)	8 (27.6%)	5 (17.3%)	10 (34.4%)	0	0
Histopathological staging	6 (20.7%)	4 (13.8%)	7 (24.1%)	4 (13.8%)	5 (17.2%)	3 (10.3%)

When compared to surgical staging, overall sensitivity, specificity, PPV, NPV and accuracy of EUS for T staging were 84,6% (95% CI 54.55-98.08), 0%, 79.6% (95% CI 74.41-82.22), 0%, and 69,8% (95% CI 41.34-88.98), respectively. Overall, sensitivity, specificity, PPV, NPV, and accuracy for N staging were 90.9% (95% CI 58.72-99.77), 61% (95% CI 14.66-94.73), 83.5% (95% CI 62.71-93.7), 76% (95% CI 28.85-95.69), and 83.3% (95% CI, 54.35-95.95), respectively. CT staging compared to surgical pathology showed a sensitivity, specificity, PPV, NPV, and accuracy for T staging of 67.7% (95% CI 38.38-88.18), 0%, 91.9% (95% CI 87.49-93.47), 0%, and 65.5% (95% CI 35.43-84.8). For N staging, sensitivity, specificity, PPV, NPV, and accuracy were 77.9% (95% CI 46.19-94,96), 35.3% (95% CI 0.84-90,57), 84.3% (95%CI 68.04-92.15), 26% (95% CI 4.83-68.66), and 69.8% (95% CI 41.34-88.98), respectively (Table 3).

Table 3. Accuracy, sensitivity and specificity of preoperative T and N staging by EUS and CT.

	Accuracy	Sensitivity	Specificity	PPV	NPV
EUS T-staging	69..8% (95%CI 41.34-88.98)	84.6% (95%CI 54.55-98.08)	0%	79.6% (95%CI 74.41-82.22)	0%
EUS N-staging	83.3% (95%CI 54.35-95.95)	90.9% (95%CI 58.72-99.77)	61% (95%CI 14.66-94.73)	83.5% (95% CI 62.71-93.7)	76% (95% CI 28.85-95.69)
CT T-staging	65.5% (95%CI 35.43-84.8)	67.7% (95%CI 38.38-88.18)	0%	91.9% (95% CI 87.49-93.47)	0%
CT N-staging	68.8% (95%CI 41.34-88.98)	77.9% (95%CI 46.19-94.96)	35.3% (95%CI 0.84-90.57)	84.3% (95%CI 68.04-92.15)	26% (95% CI 4.83-68.66)

When compared to surgical specimen after FLOT regimen, a moderate agreement was found for both EUS (Cohen's Kappa 0,5) and CT (Cohen's Kappa 0,46).

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Finally, when EUS and CT diagnostic accuracies were matched up to surgical pathology, no statistically significant differences were found for T staging (p=0.4), while EUS N staging was significantly more accurate than CT (p=0.02).

5. Discussion

The aim of our study was to retrospectively evaluate accuracy of EUS in reassessing T and N staging after neoadjuvant FLOT regimen in patients with locally advanced gastric cancer who subsequently underwent attempt curative surgery. Overall, we found that EUS accuracy for T and N staging compared to surgical pathology were 68.8% and 81.3%, which were significantly better than those obtained with CT evaluation, especially for lymph node status (p =0.02).

Neoadjuvant chemotherapy, in particular the promising new FLOT regimen that replaced previous protocols, plays a fundamental role in treatment of patients with LAGC. [13] These patients usually undergo upfront neoadjuvant treatment [29], because tumor resection is often deemed not feasible at initial evaluation. More over in these patients, recent several studies have reported that administration of preoperative FLOT regimen chemotherapy reached a significant overall survival advantage comparing to upfront surgery. [15]

To select patients suitable for FLOT, appropriate staging is mandatory. At present, EUS is considered the most accurate loco-regional preoperative tool to stage gastric cancer, in particular LAGC, to correctly establish T and N status. [30] After administration of neoadjuvant chemotherapy, EUS re-staging is still under-utilized mostly because there are several well-recognized limitations of the technique responsible for under- and over-staging. Under-staging can occur due to presence of micrometastases located in the deeper layers of the gastric wall or in apparently benign lymph nodes at EUS evaluation.[31] Conversely, over-staging can also be due to the presence of ipoechogenic micro digitation that involve the deeper layers of gastric wall due to post-chemotherapy fibrosis and inflammation (especially in ulcerative type tumors). In addition, presence of large, ipoechoic reactive lymph nodes, which may mistakenly be judged as malignant by EUS morphological evaluation and that cannot be sampled because of interpose tumor that would cause false positive results [32-33]

To date, there are few available studies that have examined the re-staging accuracy of EUS on T and N after neoadjuvant chemotherapy and have determined the clinical implications of this approach in selecting patients who may benefit the most from surgery. [26-27] In particular there are no data on EUS re-staging after the newly and more effective neoadjuvant FLOT regimen, which has been reported to be promising, especially to treat lymph nodes metastases, thus limiting the spread of the disease. [34]

Based on these premises, we performed a retrospective review of all our patients who were treated with neoadjuvant FLOT regimen and who underwent EUS restaging prior to surgical resection over a 3-year period. Overall, we found that diagnostic accuracy for EUS T and N restaging were 68.8% and 81.3% compared to surgical pathology, respectively.

In our group of patients it's reasonable affirm that FLOT regimen has shown the chance to influence the N status, that is one of the most important prognostic indicator for patients' prognosis and survival and highly influences if a successive curative surgery is feasible or not. [35]. However it's important to specify that in our series the final decision about surgery was not only related to the result of restaging and several other considerations were made during our multidisciplinary meeting. [36]

In our cohort, accuracy of EUS for T and N re-staging outperformed CT evaluation similarly to the primary staging setting, with an agreement between the two imaging modalities that still remains unsatisfactory (50%). Indeed compared to CT, EUS demonstrated to be more accurate for LAGC loco-regional staging when results from both examinations were compared to the surgical specimen. If we would have considered only restaging by CT, three patients out of 16 (18%) (Table 3) would have been considered to have a worst staging compared to surgical pathology, thus precluding them from surgical resection.

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To our knowledge, this is the first study to evaluate accuracy of EUS restaging of LAGC after FLOT regimen and to compare it with that of CT. Nevertheless, the current study has some limitations: it is retrospective with all the inherent limitations of this type of studies; the number of included patients is small; no comparison between EUS and PET was done, which can be important to assess lymph node detection rate a vital information to determine patients' prognosis and survival.

In conclusion, EUS restaging of LAGC seems very promising. Prospective, multicenter studies are warranted to better establish the impact of EUS restaging in a large cohort of patients with LAG. The selection process based on re-staging can become of primary importance to spare patients with a poor response to neoadjuvant therapy from gastric surgery, which can be associated with high morbidity (50%-64%) and mortality (2%-6%) of, especially total gastrectomy [36],

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POTENTIAL COMPETING INTERESTS: none to declare.

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CONFLICT OF INTEREST: none to declare.

Abbreviations

ACG	advanced gastric cancer
CI	confidence interval
CT	computed tomography
EUS	endoscopy ultrasound
FLOT	florouracile, leuvocorin, oxaliplatin, docetaxel
NPV	negative predictive value
PPV	positive predictive value
SPSS	Statistical Package for Social Sciences
TNM	tumor, lymph nodes, metastases

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