

Preoperative EUS evaluation of the response to neoadjuvant therapy for gastric and esophagogastric junction cancer is correlated with survival: A single retrospective study of 97 patients

Solène Hoibian¹, Marc Giovannini¹, Aurélie Autret¹, Christian Pesenti¹, Erwan Bories¹, Jean-Philippe Ratone¹, Yanis Dahel¹, Slimane Dermeche¹, Hélène Meillat¹, Jérôme Guiramand¹, Fabrice Caillol¹

¹Department of Endoscopy, Institut Paoli-Calmettes, Marseille, France

ABSTRACT

Background and Objectives: The European Society for Medical Oncology suggests performing EUS staging for esophagogastric junction and gastric cancers to further assess the T and N stages. The use of EUS after neoadjuvant therapy (NT) is still under debate. We aimed to evaluate the contribution of EUS after NT to staging, therapeutic choices, and prognosis prediction. **Subjects and Methods:** In 97 patients with esophagogastric junction and gastric cancers who received NT (chemotherapy or radiochemotherapy) followed by carcinologic surgery, EUS was performed before (uT, uN) and after (yuT, yuN) NT. We compared the results of EUS staging after NT (yuT and yuN) and final histology (ypT and ypN). We analyzed the correlation between overall survival (OS), disease-free survival (DFS), and the objective and subjective responses to NT evaluated by EUS (comparison of uT and yuT and uN and yuN with OS and DFS). **Results:** EUS staging detected metastasis that went undetected by computed tomography in 16% of metastatic patients. The accuracy between EUS after NT and postoperative pathological findings was 44.4% (34.2%; 54.7%) for T stage and 49.3% (37.5%; 61.1%) for N stage. On multivariate analysis, OS had significantly correlated with the objective response to NT. In the case of a response to NT, the median OS was 64.77 months, and in the case of stable disease, the median OS was 22.9 months ($P = 0.01$). **Conclusion:** EUS after NT can be used for staging. Despite its moderate accuracy, the evaluation of the response to NT by EUS seems to be correlated with patient prognosis.

Key words: esophagogastric junction cancer, EUS, gastric cancer, neoadjuvant therapy, prognosis

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Address for correspondence

Dr. Solène Hoibian, Institut Paoli-Calmettes, 232 Boulevard Sainte Marguerite, BP 156, 13273 Marseille Cedex 9, France.

E-mail: hoibians@ipc.unicancer.fr

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INTRODUCTION

Gastric and esophagogastric junction cancers are a major health problem, with 951,000 new cases reported worldwide in 2012.^[1]

The European Society for Medical Oncology recommends neoadjuvant therapy (NT); for all tumors classified as N+ or >T1 at the initial staging, a pretherapeutic evaluation is necessary.^[2]

The European Society of Gastrointestinal Endoscopy (ESGE) suggests performing EUS staging for esophageal and gastric cancers to avoid unnecessary surgery.^[3] Several series have shown that EUS-fine-needle aspiration has a significant impact on treatment decisions, by revealing distant metastases that go undetected with other imaging techniques in 8%–15% of cases, and demonstrates high accuracy for T and N staging.^[4]

There is an ongoing debate regarding whether EUS is useful for tumor staging after NT, and EUS is still not recommended. Data in the literature show moderate accuracy for EUS in gastric cancer staging after NT.^[5] However, some authors find EUS to be a useful tool for assessing the response to NT.^[6]

The policy of our unit is to perform EUS before and after NT. This retrospective study aimed to evaluate our management strategy for esophagogastric junction and gastric adenocarcinomas, with a focus on EUS after NT.

The primary end point of this study was overall survival (OS) according to T and N evolution after NT evaluated by EUS.

The secondary end points were the accuracy of EUS in staging and disease-free survival (DFS) according to T and N evolution after NT evaluated by EUS.

SUBJECTS AND METHODS

Patients

All patients older than 18 years who benefited from surgery for gastric or esophagogastric junction adenocarcinoma after receiving NT and who were evaluated by two EUS procedures (before and after NT) were included in the study.

The exclusion criteria were as follows: metastatic patients, patients who did not undergo surgery (unable

to tolerate surgery, refusal of surgery), patients who did not undergo two EUS procedures (before and after NT), and patients who did not receive NT.

Design

We performed a retrospective single-center study. First, we found patients for our study by reviewing the list of all patients who underwent EUS of the esophagogastric tract between 2007 and 2017 according to medical codes. Then, we selected all the patients evaluated by EUS for gastric or esophagogastric junction adenocarcinoma.

Data collection

The data collected were as follows: patient characteristics, endoscopic findings, results of the initial computed tomography (CT) examination, EUS tumor-node-metastasis (TNM) stage before and after NT, type of NT, postoperative pathological findings, surgical data, postoperative therapy, presence of recurrence, location of recurrence, and death. EUS staging was performed only if the patient did not have metastatic disease according to CT examination.

The objective response to NT corresponds to the evolution of T and N stages before (uT, uN) and after (yuT, yuN) NT evaluated by EUS (upstaging, downstaging, and stable) and was categorized as follows: response (T stability or downstaging and N stability or downstaging), stable (T and N stable), or progression (T or N progression).

The subjective response to NT corresponds to the subjective evaluation of the response by the endoscopist. This was indexed as two categories: response and stable disease or disease progression.

Procedures

EUS was performed under general anesthesia in the left lateral decubitus position with a linear or radial EUS endoscope (PENTAX™, Hambourg, Germany) before and after NT. A complete examination of the mediastinal, lombo-aortic, splenic, and coeliac lymph nodes; pancreas; liver; esophagus; and stomach was performed. A biopsy was performed with a fine needle only if it induced a therapeutic change, such as a metastatic lymph node or other metastatic site, which in case of positivity would be a contraindication for surgical resection.

Tumors were staged according to the TNM classification. Concerning lymph nodes, standard EUS

predictive characteristics of lymph node metastasis described in the literature were used, including echo-poor structure, sharply demarcated borders, rounded contour, and size >10 mm.^[7]

Surgery was performed between 4 and 8 weeks after the end of NT (gastrectomy with transhiatal distal esophagectomy or total or subtotal gastrectomy). Based on the latest French surgical guidelines, we performed a D1+ lymphadenectomy, including the coeliac, left gastric, common hepatic, and splenic artery stations. Splenectomy was not routinely performed.^[8]

Siewert Type I–II adenocarcinomas were treated with transhiatal esophagectomy and two-field lymphadenectomy (mediastinal and abdominal). Siewert Type III adenocarcinomas were treated with total or subtotal gastrectomy with D1 + lymphadenectomy.

Follow-up

All patients underwent regular follow-up with CT and a clinical examination every 3 months during the first 3 years and then every 6 months during the next 2 years. Tumor relapse, tumor location, and death were recorded. Survival was defined as the time from diagnosis to the time of death.

Statistical analysis

All analyses were conducted using Statistical Analysis System version 9.4 (SAS Institute, Inc., Cary, NC, USA). All confidence intervals listed utilized a 95% threshold.

We analyzed DFS and OS by Kaplan–Meier survival curves (at 36 and 60 months) and the Cox method. The Chi-squared test was used to analyze EUS staging accuracy in relation to the clinicopathological features.

Ethical consideration

This was a retrospective study based on prospective data and was performed according to an institutional review board agreement under the authority of the CNIL, the French regulatory body responsible for enforcing data privacy. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's Human Research Committee.

Outcomes

The primary end point for this study was OS according to the objective response to NT evaluated by EUS.

The secondary end points were the accuracy between the EUS evaluation after NT (yuT, yuN) and postoperative pathological findings, OS according to the subjective response to NT evaluated by EUS, and DFS according to the objective and subjective responses to NT.

RESULTS

A total of 209 patients were examined because they underwent EUS to evaluate gastric or esophagogastric junction adenocarcinoma in our institution.

Ninety-seven patients were included in the study.

Patient exclusion

Among the 112 excluded patients, 68 had metastasis ($n = 68/112$, 60.7%). Metastasis was diagnosed in 58.8% of patients during the initial CT and EUS TNM staging, in 20.5% of patients during CT and EUS staging after NT, and in 20.5% of patients during surgery.

EUS staging detected metastasis that was undetected by CT in 11 patients, either before ($n = 8/68$) or after ($n = 3/68$) NT.

However, despite EUS and CT examinations before and after NT, 30% of the patients ($n = 21/68$), were rejected for curative treatment during the surgical exploration. Fourteen patients had metastatic disease due to peritoneal carcinosis ($n = 12/14$) and liver metastasis ($n = 2/14$). Seven patients had locally advanced nonresectable cancer.

Fourteen patients were deemed unfit to undergo surgery, and one patient died during surgery from heart failure. Four patients refused surgery, ten underwent only one EUS, and eight patients did not receive any NT (Inclusion criteria are represented in Figure 1).

Patient characteristics

The mean patient age was 60.0 years. Nearly 54.6% of the patients were older than 60 years. In total, 67% of the patients were male. Among the patients, 17.5%, 64.9%, and 16.5% were classified as American Society of Anesthesiologists (ASA) 1, ASA 2, and ASA 3, respectively (Patients' selection is represented in Figure 2).

Tumor characteristics

Regarding postoperative pathological findings, 10.3% of the tumors were ypT0, 9.3% were ypT1, 26.8% were ypT2, 42.2%

were ypT3, and 11.3% were ypT4. Micronodules of peritoneal carcinosis were found in the final histology examinations of three patients and thus were classified as metastatic. In total, 54.6% of the patients were N+ ($n = 53/97$).

Tumor characteristics are presented in Tables 1 and 2.

Neoadjuvant therapy

In total, 76.3% ($n = 74/97$) of the patients received perioperative chemotherapy, and 23.7% ($n = 23/97$) received radiochemotherapy.

Various regimens of chemotherapy were used according to the different standards over the years of the study (fluorouracil plus leucovorin-oxaliplatin, 14.4%; epirubicin-cisplatin-fluorouracil plus leucovorin, 25%; epirubicin-oxaliplatin-capecitabine, 22.6%; epirubicin-cisplatin-capecitabine, 2.0%; carboplatin-capecitabine, carboplatin-5 fluorouracil, doxorubicin-cisplatin-fluorouracil plus leucovorin, 5.1%; taxotere-cisplatin-fluorouracil plus leucovorin, 1.0%; cisplatin-fluorouracil plus leucovorin, 5.1%; carboplatin-fluorouracil plus leucovorin, 4.1%; and doxorubicin-cisplatin-fluorouracil plus leucovorin, 1.0%).

Table 1. Tumor characteristics

Location	Patients ($n=97$), n (%)
Cardia	55 (56.7)
Other part of the stomach	39 (40.2)
Lower third of the esophagus	3 (3)
Siewert Type I	23 (37.7)
Siewert Type II	20 (32.8)
Siewert Type III	18 (29.5)
Linitis	26 (26.8)
Signet cells	21 (21.6)

Table 2. Postoperative pathological findings

	Patients ($n = 97$), n (%)
T0N0	7 (7.2)
T0N1	3 (3.1)
T1N0	9 (9.3)
T2N0	16 (16.5)
T2N1	8 (8.2)
T2N2	2 (2.1)
T3N0	10 (10.3)
T3N1	14 (14.4)
T3N2	8 (8.2)
T3N3	9 (9.3)
T4N0	1 (1.0)
T4N1	2 (2.1)
T4N2	3 (3.1)
T4N3	2 (2.1)
M1	3 (3.1)

Concerning radiochemotherapy, most patients received 45 Gy along with chemotherapy (platin and fluorouracil plus leucovorin [cisplatin, fluorouracil plus leucovorin-cisplatin, and fluorouracil plus leucovorin-oxaliplatin]).

In total, 58.7% of the patients ($n = 57/97$) received adjuvant treatment: 7 patients (12.7%) received radiochemotherapy and 48 patients (87.3%) received chemotherapy.

Surgery

Subtotal gastrectomy was performed in 6.2% of the patients, total gastrectomy was performed in 44.3% of the patients, transhiatal esogastrectomy was performed in 50.5% of the patients, and total esogastrectomy with coloplasty was performed in 1.0% of the patients. Four patients did not undergo a margin-free (R0) resection (4.1%).

Accuracy between EUS and postoperative pathological findings

The accuracy between EUS after NT and postoperative pathological findings was as follows: 44.4% (34.2%; 54.7%) for T stage and 49.3% (37.5%; 61.1%) for N stage.

The accuracy of determining the T stage after chemotherapy (42.25% [30.80%–53.70%]) versus after radiochemotherapy (52.63% [30.20%–75.10%]) was not statistically significantly different ($P = 0.91$). The accuracy of determining the N stage after chemotherapy (44.00% [30.20%–57.80%]) versus after radiochemotherapy (63.15% [41.50%–84.90%]) was also not statistically significantly different ($P = 0.15$).

ypT2 and ypT4 tumors were not accurately staged by EUS (only 11.5% and 9%, respectively, had accurate T staging).

yuN was underestimated compared to ypN (52% of yuN0 vs. 45% of ypN0).

The results of EUS evaluations before and after NT are presented in Figures 3-5. Subjective response to neoadjuvant therapy are presented in Table 3.

Overall survival, disease-free survival, and EUS-evaluated response to neoadjuvant therapy

The median OS time was 93.8 months, and the 5-year survival rate was 56%. The median follow-up period was 56.9 months (41.9–69.7). The median DFS time was 29.9 months. Forty-six percent of the patients experienced recurrence. Recurrence was mostly metastatic (83.3% of patients); only 7.1% of the patients experienced local

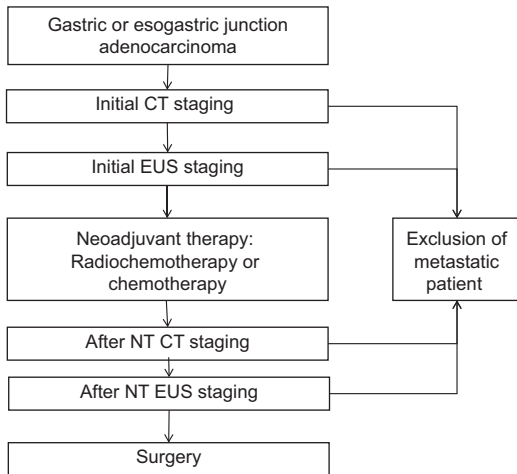


Figure 1. Study flow diagram

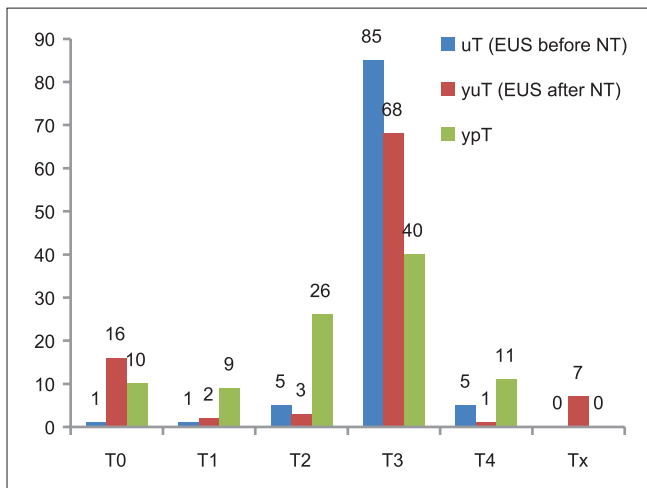


Figure 3. Results of EUS evaluations before, after neoadjuvant therapy and final histology for the T (uT, yuT, and ypT)

recurrence and 9.5% had combined local and metastatic recurrence. The most frequent metastatic site was the peritoneum, followed by the liver and lung.

Overall survival

On univariate analysis, OS had significantly correlated with ypT, ypN, ypM, margin-free resection (R0), ASA score, and the objective and subjective responses to NT. On multivariate analysis, OS had significantly correlated with the objective response to NT. In the case of a response, the median OS time was 64.77 months, and in the case of stable disease, the median OS time was 22.9 months ($P = 0.01$) (Multivariate analysis of overall survival according to the objective response to neoadjuvant therapy is represented in Figure 6)[Table 4].

Disease-free survival

On univariate analysis, DFS had significantly correlated with ypT, ypN, margin-free resection (R0), ASA score, and the subjective response to NT. On multivariate analysis, the

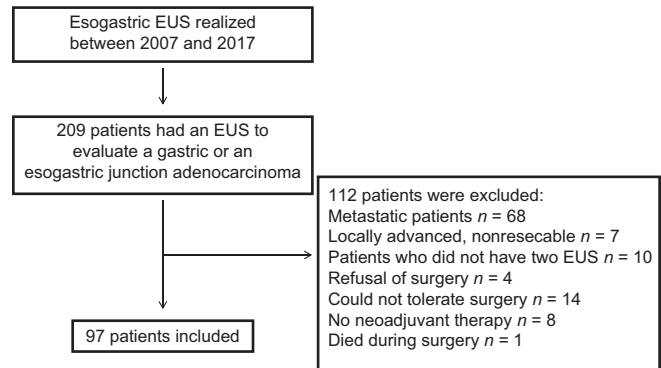


Figure 2. Patients included

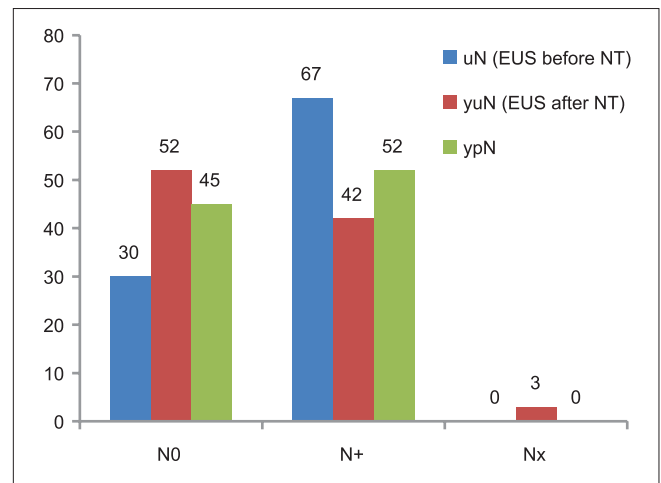


Figure 4. Results of EUS evaluations before, after neoadjuvant therapy and final histology for the N (uN, yuN, and ypN)

Table 3. Subjective response to neoadjuvant therapy

	Patients (n=67), n (%)
Response	
Complete response	3 (4.5)
Very good response	17 (25.4)
Good response	14 (20.9)
Response	11 (16.4)
Stable	21 (31.3)
Progression	1 (1.5)

correlation between DFS and the objective response to NT evaluated by EUS was close to significance ($P = 0.08$). In the case of a response, the median DFS time was 64.8 months, and in the case of stable disease, the median DFS time was 22.9 months. (Multivariate analysis of disease-free survival according to the objective response to neoadjuvant therapy is represented in Figure 7) [Table 5].

DISCUSSION

This retrospective study is one of the first and largest to our knowledge to focus on the response to NT as

Table 4. Multivariate analysis for overall survival according to the objective response to neoadjuvant therapy

Class	Number of observation	Hazard ratio (95% CI)	P
ypN			
N0	45	1	0.0001
N1, N2, N3	52	5.26 (2.27-12.2)	
ypT			
T0	10	1	0.2271
T1, T2, T3, T4	87	3.47 (0.461-026.0)	
Objective response			
Progression	9	2.49 (1.18-5.26)	0.0163
Response	44	1	
Stable	44	4.20 (1.25-14.1)	
ASA			
1	20	1	0.2466
2-3	77	0.625 (0.282-1.38)	

ASA: American Society of Anesthesiologists; CI: Confidence interval.

Table 5. Multivariate analysis for disease-free survival according to the objective response to neoadjuvant therapy

Class	Number of observation	Hazard ratio (95% CI)	P
ypN			
N0	45	1	0.0002
N1, N2, N3	52	3.63 (1.82-7.24)	
Margin-free resection			
R0	93	1	0.1427
R1	4	2.08 (0.781-5.54)	
ypT			
T0	10	1	0.4400
T1, T2, T3, T4	87	1.62 (0.478-5.46)	
Objective response			
Progression	9	1.74 (0.925-3.27)	0.0857
Response	44	1	
Stable	44	1.85 (0.592-5.78)	
ASA			
1	20	1	0.0050
2-3	77	0.375 (0.189-0.744)	

ASA: American Society of Anesthesiologists; CI: Confidence interval.

evaluated by EUS and patient prognosis. We found a correlation between the objective response to NT evaluated by EUS and patient prognosis. Indeed, the median OS had significantly improved in patients with a response to NT evaluated by EUS (multivariate analysis $P = 0.01$). Bohle *et al.* also revealed the prognostic capability of repeated EUS before and after NT in gastric cancer and found that a decrease in tumor mass was positively correlated with a good prognosis.^[6] Another study found similar results regarding the response to NT evaluated by EUS and survival but used contrast-enhanced harmonic EUS (SonoVue[®]) to characterize the response.^[9]

Several studies, including the MAGIC trial, have shown that perioperative chemotherapy significantly improves the OS of patients with gastric and esophagogastric junction carcinomas.^[10] The approach used to evaluate the

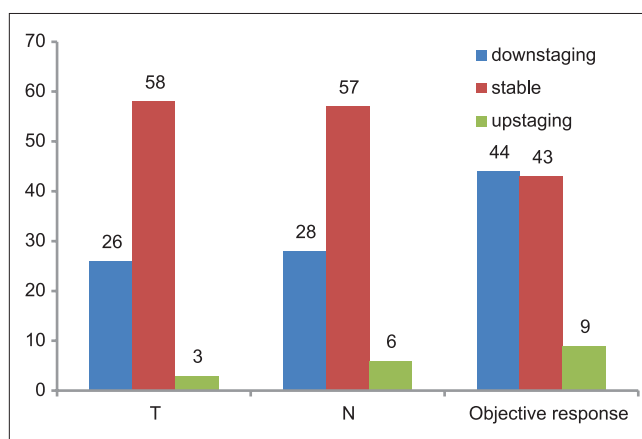


Figure 5. Evolution of EUS evaluations before, after neoadjuvant therapy for the T and the N (uT and yuT and uN and yuN)

effectiveness of neoadjuvant chemotherapy is important in clinical practice. Xu *et al.* showed that the RECIST

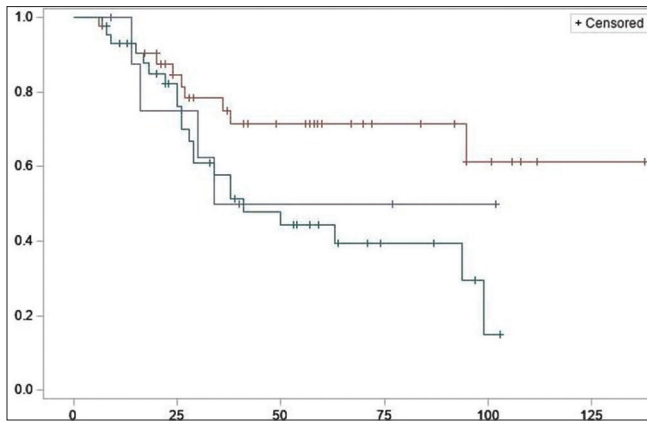


Figure 6. Multivariate analysis of overall survival according to the objective response to neoadjuvant therapy

v1.1 classification was not a prognostic factor for DFS and OS in the univariate analysis of locally advanced gastric cancer after adjuvant chemotherapy.^[11] Therefore, CT is not sufficient to evaluate tumor response. EUS could help clinicians evaluate the prognosis and tumor sensitivity to radiotherapy and chemotherapy before surgery and lead to a patient-tailored approach. Borggreve *et al.* designed the PRIDE study to develop a multimodal prediction model for the histopathological response to neoadjuvant chemoradiotherapy for esophageal cancer, including EUS evaluation.^[12]

Our results show that the accuracy of EUS after NT was 44.44% (34.2%; 54.7%) for evaluating the T stage and 49.3% (37.5%; 61.1%) for evaluating the N stage, which is not excellent. However, these results corroborate those of previous studies. Lopci *et al.* evaluated the sensitivity/specificity of CT (39%/86%), positron emission tomography (PET)-CT (30%/98%), and EUS (50%/81%) for detection of metastatic lymph nodes in Siewert I/II adenocarcinoma in mediastinal and abdominal stations. They concluded that EUS performed better than PET-CT in gastric cancer N staging and restaging.^[13] Endosonographic features predictive of malignancy are accurate (in increasing order of importance: echo-poor structure, sharply demarcated borders, rounded contour, and size >10 mm).^[14] However, a limitation of EUS evaluation of lymph nodes is the lack of systematic histology. In our study, a biopsy was performed with a fine needle only if the result of the ponction would result in a therapeutic change (to confirm a metastatic lymph node or an other metastatic site).

The accuracy of T staging ranged from 47% to 63%, and that of N staging ranged from 39% to 53%.^[15] The moderate accuracy can be explained by

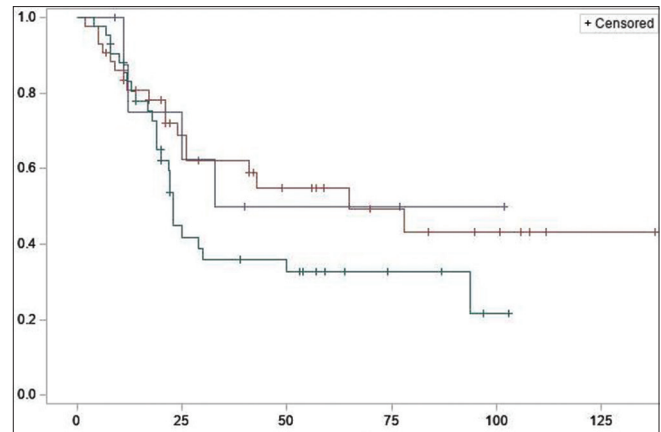


Figure 7. Multivariate analysis of disease-free survival according to the objective response to neoadjuvant therapy

posttherapeutic reshuffling caused by chemotherapy and radiochemotherapy. Tumor necrosis induces inflammation and the modification of wall layers. Our results showed no significant difference in accuracy for T and N staging after radiochemotherapy *versus* that after chemotherapy. Because yuT can be difficult to evaluate, endoscopists did not classify the T stage for 7.2% ($n = 7/97$) of the patients after NT, and the T stage was never classified during the initial staging. Indeed, it is difficult to assess the difference between the loss of differentiation of the wall layers because of complete tumor response and persistence of tumor invasion in all layers. Bohle *et al.* found that a maximal tumor thickness of <15mm after chemotherapy was significantly associated with recurrence-free follow-up and could be a good parameter, independent of the wall layer structure.^[6] Swisher *et al.* also found that after radiochemotherapy for esophageal cancer, measurements that correlated with the pathological response included the following: CT esophageal wall thickness (13.3 *vs.* 15.3 mm, $P = 0.04$), EUS mass size (0.7 *vs.* 1.7 cm, $P = 0.01$), and PET standard uptake value (3.1 *vs.* 5.8, $P = 0.01$).^[16]

Despite its moderate accuracy compared to final histology, T and N evolution after NT evaluated by EUS was able to predict the prognosis, possibly because an important parameter of the prognosis is the evolution of T and N after NT rather than the initial or post-NT EUS staging. In our unit, EUS was performed before and after NT by the same operator, which allowed us to reduce the discrepancy of EUS evaluation between two different operators and better evaluate the evolution of the disease after NT.

Only 9 patients had tumor progression during NT, 44 had tumor downstaging, and 43 were stable. Concerning

the M stage, 16% of the metastatic patients were rejected for surgery because of findings of distant lesions with EUS, confirming the ESGE recommendations to perform EUS staging to avoid unnecessary surgery.

Concerning our OS results, we reported an OS time of 93.8 months and a 5-year survival rate of 56% with various chemotherapy regimens (mostly epirubicin and cisplatin plus fluorouracil). These results are surprisingly good. Indeed, Al-Batran *et al.*, who evaluated the FLOT regimen, found that OS was higher in the FLOT group than that in the ECF/ECX group (50 months *vs.* 35 months), with 5-year survival rates of 45% and 36%, respectively.^[17] These good survival results can be partially explained by differences in the study populations (fewer ypT ≥ 3 tumors: 46.3% in our study *vs.* 62% to 56% in the FLOT trial). Concerning surgery, all of the procedures were performed by one dedicated gastric cancer surgeon; only 4.1% of the patients in our study did not undergo margin-free resection, compared to 15% to 22% of patients in the FLOT trial. Almost 59% of the patients received postoperative treatment. As described by Birkmeyer *et al.*, a high-volume hospital is associated with higher late survival rates after esophagectomy and gastrectomy.^[18] A good selection of patients, notably by repeated EUS, could contribute to this good survival result. We suggest that the use of EUS allows better selection of patients, resulting in exclusion of patients with metastasis undetected by CT with a poor prognosis or patients with nonresectable tumors (risk of R1 resection, also associated with a poor prognosis).

Our study has several limitations. It is a retrospective single-center study with a moderate number of patients. Further prospective studies could confirm these results and elaborate different therapeutic strategies based on the response to NT.

CONCLUSION

We found it useful to evaluate our patients by EUS before and after NT to determine their disease stage with good accuracy and propose the most dedicated treatment. Moreover, the correlation between the response to NT, evaluated by EUS, and survival could be helpful in therapeutic management.

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Conflicts of interest

There are no conflicts of interest.

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