Endosonographic Tumor Staging for Treatment Decision in Resectable Gastric Cancer

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Abstract

Background and Aims: Neoadjuvant preoperative chemotherapy is the standard of care in locally advanced resectable gastric cancer. Therefore, accurate locoregional staging is essential for treatment decision. EUS is believed to be the most performant diagnostic method for locoregional staging. However, it is questionable, if results from centers of excellence can be maintained in clinical routine. **Methods**: We retrospectively analyzed the data of 62 resectable gastric cancers staged by EUS during routine clinical work-up. Preoperative variables (tumor size and site, histological differentiation) were compared with the postoperative pathology. **Results:** 19 locally limited (T1-2, N0), and 43 locally advanced (T3-4, or N+ irrespective of T stage) were analyzed. The sensitivity of EUS for the detection of locally advanced disease was 93%, with a specificity of 78%. **Conclusions:** Even in daily routine practice, differentiation of locally limited and advanced disease with EUS can be performed with high sensitivity and good specificity. Therefore, EUS is an essential part of the diagnostic procedure in patients with gastric cancer.

Key words

Gastric cancer – endosonography – tumor staging – EUS.

Introduction

Due to the advent of multimodal therapy, treatment of gastric cancer has changed dramatically. Recent studies clearly show that patients with locally advanced tumors (T3-4, or node-positive cancer irrespective of T-stage) are able to profit from neoadjuvant polychemotherapy [1]. So, exact locoregional tumor staging is essential for treatment decisions.

Endoscopic ultrasound (EUS) is believed to be the most performant diagnostic tool for locoregional staging of gastric cancer [2], changing the treatment decisions in a substantial number of patients [3]. Because of its unique spatial resolution, EUS is able to discriminate the different layers of the gastric wall, i.e. mucosa, submucosa, muscularis propria, and serosa. Therefore, excellent differentiation of T-stage, and to a lesser extent, nodal staging is possible. However, the accuracy of EUS in the staging of gastric cancer differs in the literature, showing less accurate data in recent studies compared to those previously [4]. Furthermore, data whether the results from centers of excellence can be maintained in clinical routine are scarce. Therefore, the aim of our study was to analyze if EUS is sufficient to discriminate locally advanced from locally limited disease, and if in clinical routine EUS is as useful as in a study context.

Methods

At our institution, EUS is an integral part of the diagnostic procedure of every patient with gastric cancer. We retrospectively analyzed a series of 61 consecutive gastric cancer patients without distant metastasis, with all together 62 resectable gastric carcinomas. Preoperative variables (sex, age, location of tumor, histology) and the postoperative pathology (TNM-classification, 5th edition) were analyzed to determine the factors influencing the accuracy of endosonographic staging. Histological assessment was performed by the Department of Pathology at our institution according to the WHO classification into well differentiated and undifferentiated tumors (poorly differentiated, signet cell carcinoma). EUS was done by four different investigators, each with a several years' experience in EUS. We used the Olympus GIF-UM 160 radial scanner covering a range of 5 to 20 MHz. EUS was performed under conscious sedation with midazolam or propofol. The assessment of T stage

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was based on the generally accepted 5-layer sonographic structure of the gastric wall: infiltration of the first, second, and third inner layer: uT1 (Fig. 1); infiltration up to the fourth layer: uT2; infiltration of the fifth layer with irregular outer boarding: uT3 (Fig. 2); infiltration of adjacent organs such as pancreas, liver, spleen, colon: uT4. Nodal staging was grouped in two categories: N- and N+. Nodal positivity was defined as one or more locoregional lymph nodes with one or more criteria of malignancy: a diameter of > 10 mm, an echo-poor texture, and a sharp margin (Fig. 3). During EUS, in addition to primary tumor extent and nodal status, possible sites for distant metastases in the reach of EUS, such as left liver lobe, adrenal gland, peritoneum, or mediastinal lymph node, were checked as well. Only patients without metastasis at these sites were included in the study.

Prior to surgery, no neoadjuvant therapy was performed. Surgery consisted of total or partial gastrectomy, or transthoracal/transhiatal resection of the cardia and lower esophagus, depending on tumor location. In most cases, a D2-lymph node dissection was performed. Seventeen lymph nodes were analyzed histologically. The resected lymph nodes were not mapped in a one-to-one correspondence by site. Locally limited disease was defined as a T1 or T2-tumor without nodal metastases. All other tumors (T3-T4, or nodal positive disease irrespective of T stadium) were defined as locally advanced disease.

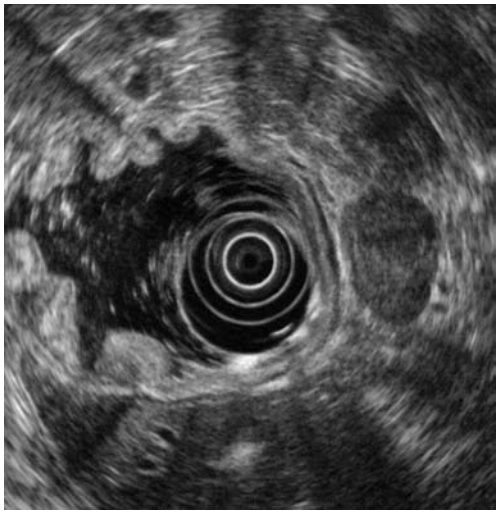

Fig 3. Gastric cancer uN+ with enlarged perigastral lymph node.

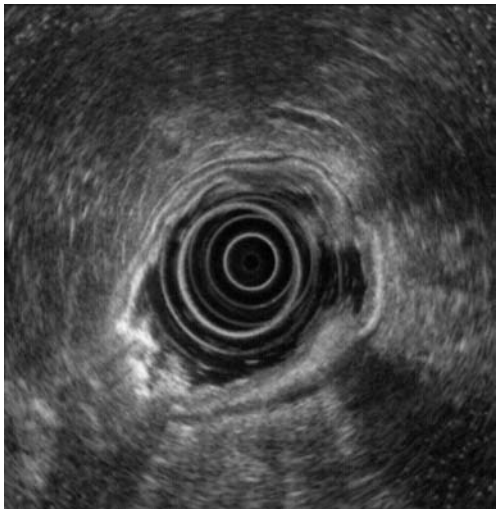

Fig 1. Gastric cancer uT1 with infiltration of the mucosa.

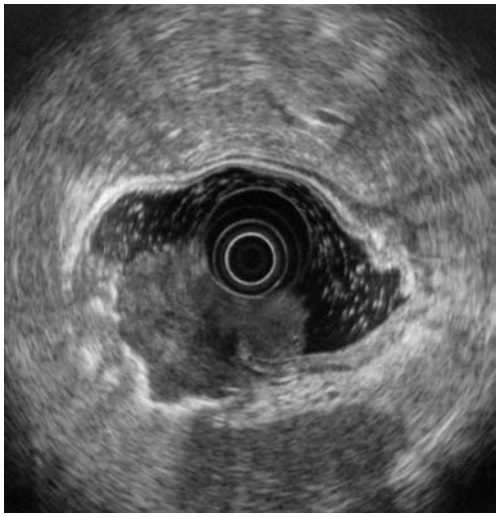

Fig 2. Gastric cancer uT3 with infiltration of the complete gastric wall and perforation of the serosa.

Results

Patients' characteristics are summarized in Table I. Tumor locations were grouped in two categories: antrum/corpus (34 tumors), and fundus/cardia (28 tumors). One patient had two distinct tumors, one in the antrum, and the other one in the corpus. By histological examination, fifteen tumors

Table I. Characteristics of the study patients

		Number
Sex (male/female)		48/13
Mean age (years)		63
Tumor location	antrum/body	34
	fundus/cardia	28
Histology	well differentiated	15
	poorly differentiated	47
T stage	pT1	15
	pT2	25
	pT3	20
	pT4	2
Nodal stage	pN0	23
	pN1	23
	pN2	12
	pN3	4
Locally limited disease (pT1-2)		19
Locally extended disease (pT3-4; or N + irrespective of T-stage)		43

were well differentiated, whereas 47 were undifferentiated, including 13 with goblet cell differentiation. According to the histopathological examination of the resected specimen, there were 15 pT1, 25 pT2, 20 pT3, and 2 pT4 carcinomas. Nodal metastasis was found in 39 patients (pN1 stage: 23, pN2 stage 12, and pN3 stage: 4 patients). Therefore, 19 tumors were classified as locally limited (pT1-2, pN0), and 43 as locally advanced cancer (pT3-4; or nodal positive disease regardless of T-stage) (Table I).

According to EUS, 4 tumors were classified as a T1-tumor, 20 as T2, 37 as T3, and 1 as T4-carcinoma. Table II shows the relationship between EUS and histopathological T-stage. All in all, according to T-stage, EUS correctly classified only 30/62 tumors. EUS overstaged 27, and understaged 5 tumors. Marked inaccuracy could be observed especially in T1 and T2 tumors. EUS often overstaged pT1-carcinoma, as having T2-disease. The same could be observed with pT2-tumors. Better discrimination could be achieved in pT3 and pT4-tumors (Table II). No difference according to tumor location or histological differentiation could be observed.

Table II. Accuracy of EUS in the preoperative assessment of T stage

		EUS staging			
		uT1	uT2	uT3	uT4
Histological staging	pT1	3	9	3	
	pT2	1	9	14	1
	pT3		2	18	
	pT4			2	

EUS correctly identified nodal metastasis in 30 of 39 patients. In 5 patients, the EUS result was false positive. Sensitivity was higher in patients with extended lymph node metastases classified as having pN2- and pN3-tumors (13/16), than in tumors staged as pN1 (17/23). Table III summarizes the relationship between histological and endosonographical nodal staging. There was a tendency for a better accuracy of nodal staging in tumors located at the fundus/cardia (24/28 correctly classified), compared to tumors of the antrum/corpus region (25/34 correctly classified). No influence of histological differentiation could be observed.

Table III. Accuracy of EUS in the preoperative assessment of N stage

		EUS staging	
		uN-	uN+
Histological staging	pN-	18	5
	pN+	9	30

In contrast to the relatively low accuracy of EUS according to the local T-staging, discrimination between locally limited and advanced disease by EUS was reasonably successful: EUS correctly identified 40 of 43 locally advanced tumors, resulting in a sensitivity of 93%. Four of 19 locally limited tumors were misclassified as locally advanced cancer, resulting in a specificity of 78%. All in all, EUS correctly classified 55 of 62 gastric carcinomas (Table IV). There was a tendency for better results in tumors of the cardia and fundus (27/28 correctly staged), than in tumors located in the antrum or body (28/34 correctly staged). No differences could be observed due to histological differentiation.

Table IV. Accuracy of EUS in the preoperative assessment of locally limited and locally advanced tumors

		EUS staging	
		locally limited tumor	locally advanced tumor
Histological staging	locally limited tumor	15	4
	locally advanced tumor	3	40

Discussion

The accuracy of EUS in the T staging of gastric cancer differs markedly in the literature, covering a range of 65 to 92% in several literature surveys and meta-analyses [2, 5, 6]. In part, this is probably due to the different study populations. For the interpretation of the results reported, it is necessary to analyze not only the EUS technology, such as the use of miniprobes instead of regular scanners, but also to look at the different patient collectives. Some studies dealt with a very selective group of patients, i.e. mainly small carcinomas: if a study population consists predominantly of patients with T1 and T2 carcinoma, with only a few T3-T4 stage neoplasms [7, 8], the accuracy in identifying a T1-tumor will be very high due to case selection bias. In contrast to this, our study, like other recent reports [9-13], covers the "normal" collective presenting in clinical routine in the western world. In these recent reports of comparable collectives, the accuracy of T-staging differed between 63% [10] and 78% [9], with other study results ranging in between [11-13]. In our study, as reported by other authors [10], the accuracy of T-staging was unsatisfactorily low especially in pT1- and pT2-tumors. Similar to other studies [9- 13], the accuracy was higher in pT3-stage, with 18/20 tumors being correctly classified.

According to previous reports [9, 14], overstaging was much more common than understaging. Overstaging of tumor infiltration depth is a well known phenomenon of EUS in gastric cancer staging, especially in smaller (pT1-pT2) tumors [9, 10, 12, 13]. Probably, this is due to misinterpretation of inflammatory reaction, peritumoral necrosis or fibrosis, or tangential imaging of the gastric wall.

As previously suggested, the accuracy in T- staging in routine clinical practice appears to be lower in more recent reports than previously reported [14]. In our study, EUS was the routine part of normal diagnostic work-up, and not of an investigational study. Therefore, circumstances such as a less accurate examination due to shortness of time, or influence of the investigator by the results of other diagnostic techniques, i.e. endoscopy, or CT-scan, can not be excluded. However,

this setting mirrors daily clinical practice. Furthermore, it cannot be ruled out that our poor result is in part due to an insufficient examinator´s expertise. However - probably due to the small numbers - no significant difference could be observed between the four investigators, despite their different personal experience. Probably, the use of modern electronic scanners will lead to better results. However, in the future, differentiation of T2 and T3-tumors will become even more difficult due to the new 7th edition of TNM classification: it will be extremely difficult to differentiate T2-tumors (infiltrating the m. propria) from T3-carcinomas (infiltrating the subserosa).

There are conflicting results in the literature according to the influence of tumor localization on the diagnostic accuracy of EUS in T staging [13, 14]. We did not observe any relationship between tumor site or histological differentiation [12] and diagnostic accuracy.

Over the last years, several new editions of the WHO TNM classification from the 4th (1987) to the 7th (2009) disclaimed new definitions for nodal disease (N1 to N3). Not surprisingly, different morfopathological classifications caused different and sometimes conflicting results according to the accuracy of EUS staging, especially a lower accuracy with the 5th edition compared to the 4th edition, which was based on the distance between primary tumor and lymph node metastasis [10]. However, for treatment decision regarding preoperative neoadjuvant chemotherapy, the exact amount of involved lymph nodes is not mandatory. So, from a practical point of view, we only differentiated node-negative from node-positive disease. The accuracy of nodal staging was significantly better than the identification of different T-stages (49/62 correctly classified). These results are comparable [9, 11] or better [10,12,13] than previously reported. With respect to N-stage, understaging was more common than overstaging.

In general, in the literature, N-staging is said to be less accurate than local T-staging [15]. It is suggested that this may be due to limited penetration of the ultrasound beam. Willis et al [9] reported that in their study understaging was more common in N2-stage (4th edition of TNM-classification 1987, i.e. lymph nodes at a distance of >3 cm apart from the primary lesion) than in the N1-stage (lymph node at a distance < 3 cm apart). However, during EUS examination, normally all areas covering the D1- and the D2-compartment can be examined. Only for the D3-compartment, accessibility is limited with EUS. Therefore, a limited penetration alone can not explain this impaired accuracy. In our view, the problem is mainly caused by a generally less impressive difference in acoustic impedance between perigastric fat tissue and lymph nodes, i.e. compared to the mediastinum in the staging of esophageal cancer, where visualization of lymph nodes even as small as 2-3 mm in diameter is much easier. Not surprisingly, interobserver agreement was reported to be higher for lymph node staging in esophageal cancer than in gastric carcinoma [16]. Probably, this led to the better results of lymph node staging in tumors of the fundus and cardia compared to a more distal location in our study.

Furthermore, the analysis of accuracy depends on the number of lymph nodes resected. There are only a few reports in the literature with detailed information about the extent of lymph node resection [9-11]. Especially in older studies, one must suspect that only a D1, or even a D0-resection was performed, impairing the reliability of EUS lymph node staging. In our study, after D2-lymphadenectomy, a sufficient number of up to 35 lymph nodes were analyzed histologically for a proper N-staging. Whereas in our study the resected lymph nodes were not mapped in a one-to-one correspondence by site, EUS generally identified less suspicious lymph nodes in the individual patient than revealed by the pathological examination of the resected specimen. Thus, EUS missed a substantial number of affected lymph nodes. This may be due to the fact that not seldom only microscopic nodal infiltration is present; furthermore, the largest lymph node must not be the one harbouring the metastasis [17]. However, the use of different parameters for metastatic lymph nodes, i.e. a smaller critical diameter, did not lead to better results [10, 16]. Not surprisingly, EUS lymph node staging was more effective in patients with extended lymph node disease: the more lymph nodes are involved, the better will be the chance for the identification of even one pathological lymph node by EUS. It is unknown if the use of modern electronic echoendoscopes would increase the diagnostic yield compared to the mechanical transducers used in our study.

In the staging of esophageal cancer, EUS-FNP of lymph node sites such celiac trunk nodes increased the diagnostic yield [18]. In the case of gastric cancer, studies are lacking for loco-regional lymph node staging with EUS-FNP. However, EUS-FNP of distant lymph nodes can result in a significant change in treatment, as analyzed by Hassan et al [19] for patients with esophago-gastric junction tumors: mediastinal, i.e. subcarinar lymph node metastasis will switch the patient to palliation. In our study, no patient presented with enlarged mediastinal lymph nodes.

EUS-elastography is a new tool, used for the differentiation of pancreatic tumors and lymph node staging. Compared to conventional B-mode, elastography increased the diagnostic accuracy, but without reaching the results of EUS-FNP as the diagnostic gold standard. Therefore, elastography is considered to be a complementary technique, and can not replace tissue confirmation [20].

Despite the low accuracy of individual T-staging, differentiation of locally limited from locally extended tumor was possible with excellent sensitivity (93%) and fair specifity (78%). Obviously, the limited accuracy of separate T- and N-staging was overcome by the integrative analysis of these two parameters. This is due to the fact that the identification of larger, pT3 and pT4 tumors, was more accurate than the differentiation of pT1 or pT2 disease. Taken together with the reasonable accuracy in identifying nodal-positive disease, a satisfactory result was achieved. In other words, according to treatment decision analysis, only 3 of 43 patients with locally advanced tumors would have been mistakenly withdrawn from neoadjuvant therapy,

whereas 4 of 19 patients with locally limited disease would have been given unnecessary preoperative chemotherapy. From a clinical point of view, in the setting of neoadjuvant chemotherapy in gastric cancer, a high sensitivity for advanced disease is more important than specificity. Clinical data clearly shows that the withholding of neoadjuvant chemotherapy in locally advanced tumors will impair the patient´s chance of cure, whereas neoadjvant chemotherapy in the group with limited cancer will not result in increased mortality [1].

Conclusion

Even in daily routine practice, differentiation of locally limited and advanced gastric cancer with EUS can be performed with high sensitivity and good specificity. Therefore, EUS is an essential part of the diagnostic procedure in patients with resectable gastric cancer.

Conflicts of interest

Nothing to declare.

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