Original Article

WIENER KLINISCHE WOCHENSCHRIFT
The Middle European Journal of Medicine
Printed in Austria

Wien Klin Wochenschr (2006) 118 [Suppl 2]: 48–51
DOI 10.1007/s00508-006-0552-y

Does endoscopic ultrasound staging already allow individual treatment regimens in gastric cancer

Stojan Potrč[1], **Marjan Skalicky**[2], and **Arpad Ivanecz**[1]

[1]Department of Abdominal and General Surgery, Maribor Teaching Hospital, Maribor, Slovenia
[2]Department of Gastroenterology and Endoscopy, Maribor Teaching Hospital, Maribor, Slovenia

Summary. *Aim:* The aim of our study was to evaluate the accuracy of preoperative TNM staging with endoscopic ultrasound (EUS) in gastric cancer patients in comparison with the pathohistological stage of the resected specimen, and to determine the possible implications of EUS for individualized treatment of gastric cancer patients at our institution.

Patients and methods: The study included 82 patients operated for resectable gastric cancer between January 1st 2001 and July 1st 2003 at the Maribor Teaching Hospital Department of Abdominal and General Surgery. The EUS stage was assessed preoperatively at the Endoscopical Unit, and the pathohistological stage in the resected specimen was determined postoperatively at the Department of Pathologic Morphology according to recommended standards.

Results: Comparison of EUS and pathohistological assessments revealed accuracy of EUS staging for loco-regional tumor infiltration (category T) in 68% of patients. The accuracy of EUS staging was 68% for T1, 69% for T2, 69% for T3 and 60% for T4. Lymph nodes (category N) were correctly staged with EUS in 57% of cases. The EUS stage was correct for lymph nodes with no metastases (N–) in 40% of cases, and for lymph nodes with metastases (N+) in 90%. There was no significant difference in accuracy of EUS staging with regard to tumor site ($P = 0.768$) or tumor size ($P = 0.766$).

Conclusions: According to our results the accuracy of EUS staging matched pathohistological staging with regard to tumor infiltration and lymph node stage in 68% and 57% of cases respectively. Underestimation of the final T2 and T3 stages as T1 stage by EUS presents a problem regarding the consistency of EUS examination at our institution, particularly with respect to individual treatment for early gastric cancer. The present uncertainty in EUS stage reliability makes it necessary to have a strategy of radical resection with D2 lymphadenectomy in patients within EUS stages T1–T3, with additional CT examinations in more advanced EUS stages in order to visualize the circumstances of tumor growth. Nevertheless, EUS provides an opportunity for the surgeon to gain more insight into the loco-regional circumstances of the gastric tumor process. For development of individual modes of treatment based on EUS staging, a more reliable assessment of EUS stage is mandatory.

Key words: Endoscopical ultrasonography, gastric cancer, staging.

Introduction

The principles of surgical treatment for gastric cancer, elaborated in the last decades in Japan and some western centers, have been stated in several reports [1–6]. Recently, a shift towards more individualized, stage-dependent treatments for gastric cancer patients has been suggested (endoscopical tumor ablation, sentinel node detection, chemo- and radiotherapy), with the intention of achieving the same, or even better, treatment efficiency with less burdensome procedures for patients with early and advanced disease [7]. With this strategy, reliable preoperative loco-regional staging of tumors is essential for proper decision making. EUS has been in use since the early 1980s but has been slow to gain acceptance in the field of gastric cancer in some western countries, including Slovenia. The reliability of this examination in gastric cancer patients is superior to that of percutaneous ultrasonography, CT and NMR [7–9]. EUS imaging of the wall-layers of gastrointestinal hollow organs can be very accurate and defines the depth of tumor invasion throughout the wall layers [8, 10–13]. At the same time it offers an insight into the close vicinity of the affected organ, the relationship of the malignant process to nearby organs and the condition of regional lymphatic nodes [9, 10]. According to data from the literature, the accuracy of EUS staging is 78% to 92% for depth of tumor growth (category T) and 63% to 78% concerning the lymph nodes (category N) [8, 11–15]. Based on our own data, we analyzed the accuracy of EUS staging in comparison with the pathohistological TNM stage of the resected tumor specimen.

Patients and methods

In this prospective study we analyzed data on EUS staging and pathohistological stage in 82 patients with gastrectomy for gastric cancer. These patients were operated on at our institution between January 1st, 2001 and July 1st, 2003.

All patients underwent EUS examination as a standard preoperative examination and in accordance with the recommended standards published in the literature [6–10]. The EUS examinations were performed using an Olympus EUM-20 one-channel pan-endoscope with a video camera and a 360 degree rotational ultrasonography probe with frequencies of 7.5 and 12 MHz. Two gastroenterologists from the Department of Gastroenterology and Endoscopy took all the EUS images. Depth of tumor infiltration throughout the gastric wall was assessed according to EUS criteria using TNM classification as recommended by the UICC [12, 19, 20], and expressed by the values EUS T1–T4. Similarly the lymph nodes were assessed according to EUS criteria and expressed as EUS N– (lymph nodes without metastasis) and EUS N+ (lymph nodes with metastasis).

Surgical treatment for these patients was total gastrectomy or distal subtotal gastric resection with lymphadenectomy D2, and optional splenectomy. Procedures were undertaken according to the principles and recommendations on gastric cancer treatment [1, 16–18]. A potentially curative operation (R0) was performed on 73 patients and a palliative (R2) resection in the remaining nine.

All resected tumor specimens were sent for pathohistological examination and assessed by a pathologist at the Department of Pathologic Morphology at the Maribor Teaching Hospital. Among other properties (histological cancer type according to WHO, type according to Lauren, histological differentiation of cancer, vascular and perineural invasion, peritumorous inflammatory infiltration) the depth of tumor invasion was assessed and expressed as pT1–pT4. All lymph nodes were examined and the state expressed as N0, N1 or N2. Macroscopic and microscopic descriptions were made according to standards and recommendations [21, 22].

In order to compare the results in our analysis we united categories pN1 and pN2 into pN+. Lymph nodes without metastases were labeled as N–.

Clinical and pathological data were prospectively stored in a computerized database. Descriptive statistical analyses were done using χ^2. We used the SPSS statistical program for all statistical calculations.

Results

Among 82 patients with gastric cancer, tumors were located in the lower third of the stomach in 27 patients, in the middle third in 31 and in the upper third in 24. We performed a total gastrectomy on 42 patients, distal on 36 and proximal subtotal gastrectomy on four. For 72 patients the resection was R0 and for the remaining 10 patients was R2.

Matching of the EUS and pathohistological stages regarding the depth of tumor infiltration and lymph node involvement is given in Tables 1 and 2. The overall accuracy of EUS staging for depth of tumor infiltration (T) was 68% (67% for T1, 68% for T2, 69% for T3, 60% for T4) and 57% for lymph nodes (40% for N–, 90% for N+). In nine patients with EUS stage T2, six patients with EUS stage T3 and in two patients with EUS stage T4, the EUS stage was overestimated with regard to depth of tumor infiltration. In one of three patients with EUS stage T1, in five patients with EUS stage T2 and three patients with EUS stage T3, the EUS stage was underestimated with regard to the depth of infiltration. In assessing lymph node involvement the EUS stage was underestimated in 32 (60%) patients and overestimated in three (10%). The accuracy of EUS staging with regard to tumor site was 62% for distal gastric tumors, 70% for middle tumors and 70% for proximal tumors (Table 3). The difference was not statistically significant (Pearson χ^2: $P = 0.768$). In the pathohistological reports, exact dimensions of the tumor were given for 70 resected specimens. Thirty tumors were smaller than 50 mm and 40 measured 50 mm or more; there was no difference in matching of the EUS and pathohistological stages (less than 50 mm: 66% vs 50 mm and more: 68%; Pearson χ^2: $P = 0.766$) (Table 4).

Table 1. Matching of EUS (EUS T) and pathohistological (pT) stages with regard to depth of tumor infiltration

	pT1	pT2	pT3	pT4	Sum	Accuracy of EUS
EUS T1	2			1	3	67%
EUS T2	9	31	3	2	45	69%
EUS T3	2	4	20	3	29	69%
EUS T4			2	3	5	60%
Sum	13	35	25	9	82	68%

Discussion

Individualized regimens have been recently introduced in the treatment of gastric cancer [7, 13, 14]. To reduce the burden of standard radical surgery for patients with early gastric cancer, less invasive procedures such as endoscopical tumor ablative methods or limited laparoscopic resection have already been introduced in many centers, achieving the same therapeutic goal as classic standard regimens [23–25]. The treatment of advanced gastric cancer is becoming multimodal in terms of preoperative radio- and/or chemotherapy to achieve down-staging of the tumor [24–26]. For such a regimen a reliable preoperative staging that matches the pathohistological stage is essential [6, 8, 9]. According to many reports from experienced centers, EUS of the stomach is currently the only method that provides reliable insight into the loco-regional stage in gastric cancer patients before the operation, reliable enough to be safely used for determining the type of individualized regimen as mentioned above [8–13]. These authors report very high accuracy of EUS staging compared with definitive pathohistological staging [8, 12–14]. For depth of infiltration, the accuracy rate of EUS in these studies was 80% to 100% for T1, 65% to

Table 2. Matching of EUS (EUS N– or +) and pathohistological (pN– or +) stages with regard to the presence or absence of metastases in lymph nodes

	pN–	PN+	Sum	Accuracy of EUS
EUS N–	21	32	53	40%
EUS N+	3	26	29	90%
Sum	24	58	82	57%

Table 3. Accuracy of the EUS stage with regard to the site of the tumor (Pearson chi-squared test: $P = 0.768$)

EUS stage	Tumor site on the stomach			Sum
	Distal third	Middle third	Proximal third	
Correct	17	22	17	56
Not correct	10	9	7	26
Sum	27	31	24	82

75% for T2, 85% to 95% for T3 and 70% to 85% for T4 [8, 24, 27]. From the same studies the accuracy of EUS for lymph nodes with metastases was about 70%. Unfortunately our results do not concur with these reports. Although the majority of the studies mentioned above report high accuracy rates of EUS staging, there are also reports from many authors with results comparable to ours. Their results, like ours, reveal possible under- or overestimation of EUS staging, particularly concerning the lymph nodes, and this suggests that the accuracy of EUS is still not sufficient for selection of patients for endoscopic resection [6, 7, 28, 29]. Other important factors seem to be the site, size and shape of the tumor. The performance of EUS and its accuracy rate appears to be lower for carcinomas at the cardia, for tumors larger than 5 cm and for ulcerous lesions [30, 32, 33]. Our analysis did not reveal any significant difference in accuracy of EUS staging regarding the site or size of the gastric tumor. Studies that show a high accuracy rate in EUS staging with regard to depth of infiltration admit the limitations of EUS in evaluating regional lymph node metastasis, despite the new generation of video-endoscopic ultrasonography [13, 14, 31]. This again can affect the introduction of endoscopical tumor ablative methods in a defined group of patients with early gastric cancer. In addition, high inter-observer variability even among experienced examiners has been reported [32]. As shown by our results at least 12.5% of patients (6 of 48) were under-staged to T1 or T2 and over 60% (32 of 52) were under-staged to N0 according to EUS investigation of the stomach. Hypothetically, less aggressive individualized treatment in these patients, if implemented, might not give the results expected with a standard regimen. As in the discussion by Willis et al. [6], which is also our opinion, the present uncertainty of EUS staging requires a strategy of radical resection with D2 lymphadenectomy in patients with EUS stages T1–T3 and additional CT examination in the more advanced EUS stages to determine the circumstances of tumor growth. Ultimately, in patients where radical resection of the tumor seems doubtful according to EUS (as in T4, N+ and presence of ascites), diagnostic laparoscopy can be performed to confirm the diagnosis. Thus EUS staging, as in our study, can only be considered as orientation of the loco-regional stage and cannot yet be used for any individualized treatment. The indication for more individualized regimens according to the EUS stage, especially for early gastric cancer, is at present reserved for highly selected patients at our institution. As stressed by many authors, high volume of patients, experienced examiners, correct selection of different EUS probes and their implementation for different degrees of tumor infiltration and shape are necessary requirements for increasing the reliability of the method [8, 33–36]. In addition, the EUS operator should be familiar with the TNM staging system [19, 28]. Once higher accuracy of EUS staging has been achieved, best provided as under study conditions, this standard must also be retained in routine clinical examinations [29, 32]. Only then, in a particular institution, can EUS staging become fundamental in planning a more individual therapeutic approach; for example, in deciding whether neo-adjuvant chemotherapy and radiation therapy are necessary or whether less invasive procedures are possible. Meanwhile, the relatively low reliability of preoperative EUS staging in our institution, as well as in others in the western world, presents a certain restraint in the introduction of individual regimens of treatment in patients with gastric cancer.

Table 4. Accuracy of the EUS stage with regard to the size of the tumor (data of exact size available for 70 patients) (Pearson chi-squared test: $P = 0.766$)

	Size of the tumor	
EUS stage	Less than 50 mm	50 mm or more
Correct	20	28
Not correct	10	12

References

1. Roder JD (1997) Gastrointestinale Tumoren. Empfehlungen zur Diagnostik, Therapie und Nachsorge. 5., vollkommen neu bearbeitete Auflage. Schriftenreihe des Tumorzentrum München, 42
2. Potrc S, Kavalar R, Hajdinjak T, Horvat M, Vidovic D, Gadzijev E (2004) What have we learned from surgical treatment of gastric adenocarcinoma? A comparison of two periods. Wien Klin Wochenschr 116 [Suppl 2]: 56–59
3. Siewert JR (1992) Magenkarzinom. In: Chirurgische Gastroenterologie, 2. Aufl. Springer, Berlin, S 675–740
4. Jaehne J, Meyer HJ, Maschek H, Geerlings H, Burns E, Pichlmayr R (1992) Lymphadenectomy in gastric carcinoma. A prospective and prognostic study. Arch Surg 127: 290–294
5. Cheung LY, Delore R (2001) Stomach. In: Townsend CM (ed) Sabiston textbook of surgery, 16th edn (etc). Saunders, Philadelphia, pp 855–865
6. Willis S, Truong S, Gribnitz S, Fass J, Schumpelick V (2000) Endoscopic ultrasonography in the preoperative staging of gastric cancer: accuracy and impact on surgical therapy. Surg Endosc 14: 951–954
7. Heyer T, Frieling T, Haussinger D (1998) How accurate is preoperative staging as a basis for treatment decisions in gastric carcinoma? Schweiz Rundsch Med Prax 87: 443–446
8. Wei-Dong Xi, Cong Zhao, Guo-Sheng Ren (2003) Endoscopic ultrasonography in preoperative staging of gastric cancer: determination of tumor invasion depth, nodal involvement and surgical resectability. World J Gastroenterol 9: 254–257

9. Zhang QL (1998) Present status and prospect of endoscopic ultrasonography. Chin J Dig Endosc 15: 195–196
10. Galetti G, Fusaroli P (2001) Endoscopic ultrasonography. Endoscopy 33: 158–166
11. Rosch T (1995) Endosonographic staging of gastric cancer: a review of literature results. Gastrointest Endosc Clin N Am 5: 549–557
12. Zuccaro G (1998) Diagnosis and staging of gastric carcinoma by endoscopic ultrasonography. Chapter13. In: Meyers AM (ed) Neoplasms of the digestive tract. Imaging, staging and management. Lippincott Raven, New York, pp 137–142
13. Wang JY, Hsieh JS, Huang YS, Huang CJ, Hou MF, Huang TJ (1998) Endoscopic ultrasonography for preoperative locoregional staging and assessment of resectability in gastric cancer. Clin Imaging 22: 355–359
14. Mancino G, Bozzetti F, Schicchi A, Schiavo M, Spinelli P, Andreola S (2000) Preoperative endoscopic ultrasonography in patients with gastric cancer. Tumori 86: 139–141
15. Yan C, Zhu ZG, Zhu Q, Yan M, Chen J, Liu BY, Yin HR, Lin YZ (2003) A preliminary study of endoscopic ultrasonography in the preoperative staging of early gastric carcinoma. Zhonghua Zhong Liu Za Zhi 25: 390–393
16. Siewert JR (1992) Magenkarzinom. In: Chirurgische Gastroenterologie, 2. Aufl. Springer, Berlin, S 675–740
17. Barash P, Cullen B, Stoelting R (1996) Preoperative evaluation. In: Fleisher L (ed) Clinical anesthesia, 3rd edn. Lippincott-Raven, Philadelphia New York, pp 444
18. Žakelj B (1995) Standardna R0 resekcija. In: Kirurgija želodca: zbornik simpozija, Ljubljana 1995. Klinični center, Kirurške klinike, Kirurška šola, Ljubljana, pp 113–115
19. Watanabe H, Jass JR, Sobin LH (1990) Histological typing of oesophageal and gastric tumors. 2nd edn. WHO International Histological Classification of Tumors. Springer, Berlin
20. Rohde H, Gebbensleben B, Bauer P, Stutzer H, Zieschang J (1989) Has there been any improvement in the staging of gastric cancer? Findings from the German Gastric Cancer TNM Study Group. Cancer 64: 2465–2481
21. Repše S (1995) Razširjene multivisceralne resekcije pri raku želodca. In: Kirurgija želodca. Zbornik simpozija, Ljubljana 1995. Klinični center, Kirurške klinike, Kirurška šola, Ljubljana, pp 129–133
22. Hruban RH, Westra WH (1996) Surgical pathology dissection: an illustrated guide. Springer, New York, NY
23. Adachi Y, Shiraishi N, Kitano S (2002) Modern treatment of early gastric cancer: review of the Japanese Experience. Dig Surg 19: 333–339
24. Javaid G, Shah OJ, Dar MA, Shah P, Wani NA, Zargar SA (2004) Role of endoscopic ultrasonography in preoperative staging of gastric carcinoma. ANZ J Surg 74: 108–111
25. Guo W, Zhang YL, Zhou DY, Zhang WD (1999) The correlation of preoperative EUS staging and p53 gene mutation in gastric cancer. Shijie Huaren Xiaohua Zazhi 7: 1094–1095
26. Ausch C, Rosen HR, Schiessel R (1996) The value of adjuvant and neoadjuvant chemotherapy in treatment of stomach carcinoma. Wien Klin Wochenschr 108: 496–504
27. Nattermann C, Dancygier H (1993) Endosonography in diagnosis and staging of malignant tumors of the stomach. A prospective comparative study between endosonography, computerized tomography and conventional ultrasonography. Z Gastroenerol 31: 719–726
28. Wang JY, Hsieh JS, Huang CJ, Hou MF, Huang TJ (1998) Endoscopic ultrasonography for preoperative staging and assessment of resectability in gastric cancer. Clin Imaging 22: 355–359
29. Bosing N, Schumacher B, Frieling T, Ohmann C, Jungblut R, Lubke H, Bohner H, Verreet P, Roher HD (2003) Endoscopic ultrasound in routine clinical practice for staging of adenocarcinoma of the stomach and distal oesophagus. Chirurg 74: 214–221
30. May A, Gunter E, Roth F, Gossner L, Stolte M, Vieth M, Ell C (2004) Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 53: 634–640
31. Tseng LJ, Mo LR, Tio TL, Fresner YT, Jao N, Lin RC, Kuo JY, Chang KK, Wang CH, Wey KC (2000) Video-endoscopic ultrasonography in staging gastric carcinoma. Hepatogastroenterology 47: 897–900
32. Meining A, Rosch T, Wolf A, Lorenz R, Allescher HD, Kauer W, Dittler HJ (2003) High interobserver variability in endosonographic staging of upper gastrointestinal cancers. Z Gastroenterol 41: 391–394
33. Heeren PA, van Westreenen HL, Geersing GJ, van Dullemen HM, Plukker JT (2004) Influence of tumor characteristics on the accuracy of endoscopic ultrasonography in staging cancer of the esophagus and esophagogastric junction. Endoscopy 36: 966–971
34. Schlick T, Heintz A, Junginger T (1999) The examiner's learning effect and its influence on the quality of endoscopic ultrasonography in carcinoma of the esophagus and gastric cardia. Surg Endosc 13: 894–898
35. Yanai H, Tada M, Karita M, Okita K (1996) Diagnostic utility of 20-megahertz linear endoscopic ultrasonography in early gastric cancer. Gastrointest Endosc 44: 29–33
36. Okamura S, Tsutsui A, Muguruma N, Ichikawa S, Sogabe M, Okita Y, Fukuda T, Hayashi S, Okahisa T, Shibata H, Ito S, Sano T (1999) The utility and limitations of an ultrasonic miniprobe in the staging of gastric cancer. J Med Invest 46: 49–53

Correspondence: Stojan Potrč, M.D., Department of Abdominal and General Surgery, Maribor Teaching Hospital, Ljubljanska 5, 2000 Maribor, Slovenia,
E-mail: stojan.potrc@guest.arnes.si