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The usefulness of endoscopic ultrasonography in differentiation between benign and malignant gastric ulcer

Endoskopska ultrasonografija u diferenciranju benignog od malignog ulkusa želuca

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Abstract

Background/Aim. Gastric ulcer may be benign or malignant. In terms of therapy and patient's prognosis early detection of malignancy is very important. The aim of this study was to assess the usefulness of endoscopic ultrasound (EUS) in differentiation between benign and malignant gastric ulcer. **Methods.** A prospective study included 20 consecutive adult patients with malignant gastric ulceration and 20 consecutive adult patients with benign gastric ulceration. All the patients underwent EUS. A total of 6 parameters were analyzed: ulcer width, ulcer depth, the thickness of the gastric wall along the edge of ulceration (T_0), the thickness of the gastric wall 2 cm from the edge of ulceration (T_2), loss of layering structure of the gastric wall, and the presence of regional lymph nodes. EUS criteria for malignancy and a point-score of malignancy were defined. The critical value of total point-score was also calculated showing the best reliability parameters. **Results.** There are 4 criteria for malignancy of gastric ulceration: $T_0 >$ 10 mm, $T_2 >$ 5 mm, EUS visualization of at least one lymph node, loss of layering structure of the gastric wall. Furthermore, $T_2 >$ 5 mm was the only EUS independent predictor of ulcer malignancy. The total point score of ≥ 4 was the cut-off point-score value which gave the best reliability parameters in the assessment of malignant ulcers: sensitivity of 70%, specificity of 95%, positive predictive value of 93.3%, negative predictive value of 76% and accuracy of 82.5%. **Conclusion.** According to the results obtained in this study, we can conclude that EUS is usefull in differentiation between benign and malignant gastric ulcer.

Key words:
endosonography; stomach ulcer; diagnosis, differential; neoplasms.

Apstrakt

Uvod/Cilj. Ulkus želuca može biti benigna ili maligna bolest. Iz aspekta lečenja i prognoze bolesnika, rano otkrivanje maligniteta veoma je važno. Cilj studije bio je da se proceni uloga endoskopskog ultrazvuka (EUS) u diferenciranju benignih od malignih ulkusa želuca. **Metod.** Prospektivnom studijom bilo je obuhvaćeno 20 konsekutivnih odraslih bolesnika sa malignim ulkusom želuca i dvadeset konsekutivnih odraslih bolesnika sa benignim ulkusom želuca. Svim bolesnicima rađena je EUS. Analizirano je šest parametara: širina ulkusa, dubina ulkusa, zadebljanje zida želuca uz ivicu ulceracije (D_0), zadebljanje zida želuca 2 cm od ivice ulceracije (D_2), gubitak slojevne strukture zida želuca i prisustvo regionalnih limfnih čvorova. Formulisani su EUS kriterijumi maligniteta i poen-skor maligniteta. Takođe je proračunata kritična vrednost ukupnog poen-skora, koji je za procenu maligniteta imao najbolje parametre pouzdanosti. **Rezultati.** Postoje četiri kriterijuma maligniteta želudačne ulceracije: $D_0 >$ 10 mm; $D_2 >$ 5 mm, EUS vizualizacija bar jednog limfnog čvora i gubitak slojevne strukture zida želuca. Jedini nezavisni prediktor maligniteta ulceracije bila je vrednost $D_2 >$ 5 mm. Za ukupni poen-skor ≥ 4 dobijeni su najbolji parametri pouzdanosti za procenu maligniteta ulkusa: senzitivnost od 70%, specifičnost od 95%, pozitivna prediktivna stopa od 93,3%, negativna prediktivna stopa od 76% i tačnost od 82,5%. **Zaključak.** Prema rezultatima ove studije može se zaključiti da je metoda EUS korisna za diferenciranje benignih od malignih ulkusa želuca.

Ključne reči:
endosonografija; želudac, ulkus; dijagnoza, diferencijalna; neoplazme.

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Introduction

Gastric ulcer has been defined as a defect in the mucosal surface greater than 5 mm in size, with depth to the submucosa [1]. It may be the consequence of a benign or a malignant disease. In terms of therapy and patient′s prognosis early detection of malignancy is very important. However, the differential diagnosis between benign and malignant ulcers can be difficult. Gastroscopy with biopsy is the most frequently used diagnostic tool. But, sometimes endoscopic appearance of the ulcer does not correlate with the histopathological diagnosis. Repeated biopsies, during the follow up period can show malignant cells even in the case of healed chronic gastric ulcer [2, 3]. Although endoscopic ultrasonography (EUS) is an useful method for gastric wall visualizing, the available data about its role in the differential diagnosis between benign and malignant gastric ulcers are scarce [4].

The aim of this study was to assess the usefulness of EUS in differentiation between benign and malignant gastric ulcer.

Methods

Study design and patient population

A prospective study included 20 consecutive adult patients with malignant gastric ulceration and 20 consecutive adult patients with benign gastric ulceration, treated in our hospital. Informed written consent to participation in the study was obtained from each patient before endosonographic examination. The ethical aspect of this study was approved by the local Ethics Committee.

Diagnosis of gastric ulcer

Gastric ulcer was initially diagnosed by gastroscopy and biopsy. We took four biopsy specimens from ulcer edges and an additional biopsy specimen from the base. Biological nature of ulceration was confirmed histopathologically.

Endosonographic examination

All the patients underwent endosonographic examination using a radial scanning echoendoscope (EU-M30, Olympus) at 7.5 MHz frequency. Examination was preceded by topical oropharyngeal anesthesia. The agitated patients were sedated by intravenously administered midazolam (3–5 mg) or diazepam (5–15 mg). During examination the patients were in the supine position on the left side. A water filled balloon around the transducer was used to provide a fluid interface between the transducer and the gastric wall.

We analyzed 6 endosonographic parameters: ulcer width, ulcer depth, the thickness of the gastric wall along the edge of ulceration (T_0), the thickness of the gastric wall 2 cm from the ulceration edge (T_2), loss of layering structure of the gastric wall, and the presence of regional lymph nodes. Loss of layering structure of the gastric wall was defined as discontinuity in the layers of the gastric wall below the mucosa.

Each of the 6 endosonographic parameters was compared between the groups with benign and malignant ulcers and those showing a statistically significant difference were considered the EUS criteria of malignancy. Independent predictors of malignancy were defined, as well.

Finally, we made a point-score of malignancy, so what we scored was the existence of EUS criteria of malignancy with two points (for independent predictors) or one point (for other EUS criteria of malignancy). The points were tallied and a total point score of malignancy was defined. The critical value of total point-score was also calculated showing the best reliability parameters: sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Statistical analysis

Data processing was performed using SPSS 11.5 for Windows software (SPSS, Inc., Chicago, IL). Average values were presented as mean value ± standard deviation, and a *p*-value of 0.05 (two-sided) was considered to be statistically significant. Two sets of parametric data were compared by the unpaired Student's *t*-test and two sets of categorical data were compared by the Mann-Whitney's *U*-test and the Pearson's (χ^2) test. Binary logistic regression analysis was performed to define EUS criteria of malignancy, and Forwald: Wald multivariate logistic regression analysis was used to define independent predictors of malignancy.

Results

Characteristics of the patients

Benign gastric ulcer was diagnosed in 11 males and 9 females (average age 65.7 ± 10.4 years). Malignat gastrisc ulcer was diagnosed in 13 males and 7 females (average age 59.5 ± 13.5 years). The lesser curvature was the most frequent ulcer site, both for benign (60%) and malignant ulcers (50%).

Ulcer width and ulcer depth

Ulcer width ranged 4.2–30 mm for benign and 3–35 mm for malignant ulceration and ulcer depth ranged 2–17 mm for benign and 2–15 mm for malignant ulcerations (Tables 1 and 2). In relation to benign ulcers, malignant ulcers were wider in average (16.3 ± 7.5 mm and 14.6 ± 7.2 mm, respectively) and deeper in average (7.4 ± 4.1 mm and 5.4 ± 3.7 mm, respectively), but the differences were not statistically significant (unpaired Student's *t*-test, $p > 0.05$) (Table 3).

T_0 ranged 4–17 mm for benign and 3–24.5 mm for malignant ulcerations (Tables 1 and 2). In average, To was significantly greater in malignant ulcer group than in benign ulcer group (13.2 ± 5.8 mm and 9.1 ± 3.2 mm; $p = 0.009$; unpaired Student's *t*-test) (Table 3). Thickness of 10 mm was defined as a cut-off value which provided maximum statistical significance in differentiation between benign and malignant ulcers. That was proved both by the Mann-Whitney *U*-test ($p = 0.001$; $Z = -3.138$) and the Pearson's (χ^2) test ($p = 0.001$; $\chi^2 = 10.101$).

Table 1

Endosonographic parameters and endosonographic criteria of malignancy in the patients with benign ulcers

Patient No	Endosonographic parameters						EUS criteria of malignancy				Point score
	U_w (mm)	U_d (mm)	T_0 (mm)	T_2 (mm)	LLS	LN presence	A	B	C	D	Σ
1	27	17	17	10	+	+	1	**2**	1	1	5
2	25	9	10	10	+	-	-	**2**	-	1	3
3	9	3	7	3	-	+	-	-	1	-	1
4	10	2	8	3	+	-	-	-	-	1	1
5	20	9.6	16.6	2.7	+	-	1	-	-	1	2
6	13	4	9	5	+	-	-	-	-	1	1
7	12.1	4.5	13.1	4.2	-	-	1	-	-	-	1
8	4.2	2	7.2	3.2	+	-	-	-	-	1	1
9	19	9	4	3	-	+	-	-	1	-	1
10	17	6.1	6	4	-	-	-	-	-	-	0
11	5.5	2.5	7.6	3.6	-	-	-	-	-	-	0
12	16.2	6.5	7.3	3.3	+	-	-	-	-	1	1
13	10	2.3	8.3	3.1	-	-	-	-	-	-	0
14	17	4	7	3	-	-	-	-	-	-	0
15	10	5	9	5	+	-	-	-	-	1	1
16	16.5	4.5	9.4	4.7	+	+	-	-	1	1	2
17	17	4	7	4	+	-	-	-	-	1	1
18	6.9	3.1	8.4	3.3	+	-	-	-	-	1	1
19	7.4	2	10	3.6	-	-	-	-	-	-	0
20	30	8	11	5	+	-	1	-	-	1	2

Uw – ulcer width; Ud – ulcer depth; T_0 – gastric wall thickness along the edge of ulceration; T_2 – gastric wall thickness 2 cm from the ulceration edge; LLS – loss of layering structure of the gastric wall; LN – lymph nodes; EUS – endosonographic ultrasound; A ⇒ T_0 > 10 mm; B ⇒ T_2 > 5 mm; C ⇒ EUS visualization of at least 1 lymph node; D ⇒ loss of layering structure of the gastric wall.

Table 2

Endosonographic parameters and endosonographic criteria of malignancy in patients with malignant ulcers

Patient No	Edosonographic parameters						EUS criteria of malignancy				Point score
	U_w (mm)	U_d (mm)	T_0 (mm)	T_2 (mm)	LLS	LN presence	A	B	C	D	Σ
1	8	2	4.1	3	-	-	-	-	-	-	0
2	10	10	3	3	+	+	-	-	1	1	2
3	8	4	18.9	10	+	+	1	2	1	1	5
4	11.4	15	14	4	+	-	1	-	-	1	2
5	19.1	8.3	9.6	5.2	+	+	-	2	1	1	4
6	26.7	13.9	22.2	7	+	+	1	2	1	1	5
7	14.4	8.3	13.8	12.3	+	+	1	2	1	1	5
8	16.7	3.6	8.4	8.8	+	+	-	2	1	1	4
9	23.2	9.2	15.3	4.1	+	+	1	-	1	1	3
10	15.7	6.5	15	5.7	+	+	1	2	1	1	5
11	16.8	12	14.9	8	+	+	1	2	1	1	5
12	10	4	15	15	+	+	1	2	1	1	5
13	20	15	18	15	+	+	1	2	1	1	5
14	14.2	6.6	8.2	3	+	-	-	-	-	1	1
15	3	2	3.5	3	-	-	-	-	-	-	0
16	22	8	16	20	+	-	1	2	-	1	4
17	22	6	24.5	10	+	+	1	2	1	1	5
18	10	2	15.8	7.8	+	-	1	2	-	1	4
19	35	5	12.5	20.3	+	+	1	2	1	1	5
20	20.6	6	12	8	+	-	1	2	-	1	4

Uw – ulcer width; Ud – ulcer depth; T_0 – gastric wall thickness along the edge of ulceration; T_2 – gastric wall thickness 2 cm from the ulceration edge; LLS – loss of layering structure of the gastric wall; LN – lymph nodes; EUS – endosonographic ultrasound; A ⇒ T_0 > 10 mm; B ⇒ T_2 > 5 mm; C ⇒ EUS visualization of at least 1 lymph node; D ⇒ loss of layering structure of the gastric wall.

Table 3

Endosonographic parameters in patients with gastric ulceration in our series

Endosonographic parameters	Benign ulceration	Malignant ulceration	*p*	Statistical parameters
Ulcer width (mm), $\bar{x} \pm SD$	14.6 ± 7.2	16.3 ± 7.5	> 0.05[a]	
Ulcer depth (mm), $\bar{x} \pm SD$	5.4 ± 3.7	7.4 ± 4.1	> 0.05[a]	
T_0 (mm), $\bar{x} \pm SD$	9.1 ± 3.2	13.2 ± 5.8	0.009[a]	t = -2.755 CI = -7.0957/-1.0843
T_2 (mm), $\bar{x} \pm SD$	4.3 ± 2.1	8.7 ± 5.4	0.002[a]	t = -3.336 CI = -6.9498/-1.7002
LLS, n	12	18	0.031[b]	Z^b =-2.163 χ^2c = 4.800 (DF = 1)
Visualisation of lymph node, n	4	13	0.004[b]	Z^b = -2.842 χ^2c = 8.286 (DF = 1)

T_0 – gastric wall thickness along the edge of ulceration; T_2 – gastric wall thickness 2 cm from the ulceration edge; LLS – loss of layering structure of the gastric wall; $\bar{x}$ – mean; SD – standard deviation; n – number of patients; [a]unpaired-samples Student's *t*-test (DF = 38). [b]Mann-Whitney *U*-test; [c]χ^2 test; CI – confidence interval; $p \leq 0.05$ considered to be statistically significant.

T_2 ranged 2.7–10 mm for benign and 3–20.3 mm for malignant ulcerations (Tables 1 and 2). In average, T_2 was significantly greater in the malignant ulcer group than in the benign ulcer group (8.7 ± 5.4 mm and 4.3 ± 2.1 mm; $p = 0.002$, unpaired Student's *t*-test) (Table 3). Thickness of 5 mm was defined as a cut-off value which provided a maximum statistical significance in differentiation between benign and malignant ulcers. That was proved both by the Mann Whitney *U*-test ($p < 0.001$; Z = -3.824) and the Pearson's (χ^2) test ($p < 0.001$; $\chi^2 = 15.000$).

Loss of layering structure of the gastric wall existed in 18 of 20 (90%) malignant and in 12 of 20 (60%) benign ulceration and the difference was statistically significant (Mann-Whitney *U*-test and Pearson's χ^2 test; $p = 0.031$) (Table 3).

Lymph nodes

Lymph nodes were found in 4 of 20 (20%) benign and in 13 of 20 (65%) malignant ulcerations, and this difference was statistically significant (Mann Whitney *U*-test and Pearson's χ^2 test ; $p = 0.004$) (Table 3). The number of endosonographically seen lymph nodes was 1–2 (1.5 ± 0.5 in average) for benign ulcer group and 1–7 (3.5 ± 2.2 in average) for the malignant ulcer group. All endosonographically seen lymph nodes were with round shape and hypoechoic features, regardless of whether it was malignant or benign ulceration. Furthermore, clear outer border existed in all lymph nodes, seen by endosonographic examination of malignant ulcerations, and in 2 out of 4 patients with benign ulcer. There was the diameter of lymph node greater than 10 mm in 84.6% (11 of 13) of malignant ulcerations and in 25% (1 of 4) of benign ulcerations.

EUS criteria for ulcer malignancy

Binary logistic analysis revealed 4 significant criteria for malignancy of gastric ulceration: A $\Rightarrow$ $T_0 > 10$ mm; B $\Rightarrow$ $T_2 > 5$ mm; C $\Rightarrow$ EUS visualization of at least one lymph node; D $\Rightarrow$ Loss of layering structure of the gastric wall (Table 4). Furtherrmore, $T_2 > 5$ mm was the only EUS independent predictor of ulcer malignancy (Forwald: Wald multivariate logistic regression analysis; $p = 0.001$; RR = 0.048; CI = 0.008/0.273).

Point-score of malignancy

Maximal total point-score of malignancy was 5 points (2 points for independent predictor and 1 point for other 3 EUS criteria for ulcer malignancy). There was a total point score of ≥ 4 in 14 malignant and in only 1 benign ulceration (Tables 1 and 2). This was the cut-off point-score value which gave the best reliability parameters in the assessment of malignant ulcers: sensitivity of 70%, specificity of 95%, positive predictive value of 93.3%, negative predictive value of 76% and accuracy of 82.5%.

Discussion

Over the last 25 years EUS has become accurate diagnostic and therapeutic procedure. It is usefull for locoregional staging of primary gastric, esophageal and rectal cancer and for the diagnosis of gastric subepithelial lesions smaller than 2 cm and small pancreatic tumors [5–10]. It is also recommended for the diagnosis of choledocholithiasis due to smaller number of complications compared to endoscopic retrograde cholongiopancreatography [11]. Therapeutic interventions such as drainage of peripancreatic fluid collections, pancreatic cyst ablation and celiac plexus neurolysis can be performed under linear endoscopic ultrasound guidance [12, 13]. Furthermore, recent data show the role of EUS in creating bilioenteric and enteroenteric anastomosis in selective situations [12].

The role of EUS in the differential diagnosis of benign and malignant ulcers has been poorly investigated. The main method for differentiating benign from malignant ulcer is still gastroscopy with biopsy, but sometimes, gastric carcinoma endoscopically may look like a benign ulcer. Moreover endoscopic biopsies do not always confirm malignancy, leading to delays in correct diagnosis. Some authors suggest "that the location and diameter of gastric ulcers may be used as a marker of risk factors for developing gastric cancer" [14]. According to our results, the difference in the width and depth of ulceration, between malignant and benign ulcers was not statistically significant. In the study by Lv et al. [15], biopsies from the ulcer bases and edges at the repeated endoscopies, have shown better results in detection of gastric cancer in comparasion with the biopsies taken from the edges of ulcers only [15]. Some studies demonstrated that magnifying endoscopy with narrow-band imaging has an advantage in comparison with conventional endoscopy for differential diagnosis of a small depressed gastric lesion [16, 17], while chromoendoscopy has not improved the differentiation of gastric ulcers with respect to their origin [18]. We found different data about the usefulness of computed tomography (CT) virtual gastrocopy. According to the results of Mochetta et al. [19] study, CT virtual gastroscopy is superior to conventional endoscopy and allows differentiation between benign and malignant gastric ulcer based on morpho-

Table 4

Endosonographic ultrasound criteria for ulcer malignancy in the patients with gastric ulceration (binary logistic analysis)

Endosonographic criteria	Benign ulceration	Malignant ulceration	*p*	Statistical parameters
$T_0 > 10$ mm	4	14	0.003	RR = 0.107 CI = 0.025/0.459
$T_2 > 5$ mm	2	14	0.001	RR = 0.048 CI = 0.008/0.273
Loss of layering structure of the gastric wall	12	18	0.04	RR = 0.167 CI = 0.030/0.924
Visualisation of lymph node	4	13	0.006	RR = 0.135 CI = 0.032/0.562

T_0 – gastric wall thickness along the edge of ulceration; T_2 – gastric wall thickness 2 cm from the ulceration edge; RR – relative risk, CI – confidence interval; $p \leq 0.05$ considered to be statistically significant.

logical features. In the study by Chen et al. [20] virtual gastroscopy and classic endoscopy "were almost equally useful" in differentiation between malignant and benign gastric ulcers.

In contrast to aforementioned diagnostic procedures, EUS allows visualization of the gastric wall, but this advantage was rarely used for differential diagnosis of gastric ulcers. Both types of ulcers may share the same basic endosonography findings: low echo mass (originated from fibrosis and granulation), symmetrical or asymmetrical convergence of the submucosal layer, thickening of the gastric wall, making diagnosis difficult [21, 22]. Zhang et al. [4] formulated the following characteristics of malignant gastric ulcer: unclear architectures, hypoechoic mass with partial or total destruction of the normal wall architecture and malignant lymph nodes.

According to our study there are 4 significant criteria of malignancy of gastric ulceration: $T_0 > 10$ mm; $T_2 > 5$ mm; EUS visualization of at least one lymph node and the loss of layering structure of the gastric wall.

In our patients gastric wall thickness was significantly higher in the malignant ulcer group than in the benign ulcer group. It is known that the thickened gastric wall in patients with benign gastric ulcer correlates well with the spread of fibrosis [21]. The majority of authors agree that in cases of ulcerative cancers the thickening of the gastric wall correlates better with the spread of fibrosis, than with cancer invasion, which leads to overestimation of the depth of invasion [22–26]. In the available literature we were unable to find any data on the significance of the wall thickness in the differential diagnosis between benign and malignant gastric ulcer. According to our results the values greater than 10 mm and 5 mm for T_0 and T_2 respectively, were defined as criteria of malignancy. Moreover, T2 greater than 5 mm was found as the only EUS independent predictor of ulcer malignancy. Interestingly, the maximum thickness of the gastric wall we found in patients with malignant lymphoma. Among 3 of the patients with malignant lymphoma, T_0 was greater than 20 mm in 2 of the patients, while T_2 was greater than 20 mm in 1 patient.

Our results show that EUS visualization of at least 1 lymphe node significantly increases the likelihood of ulcer malignancy. All endosonographically seen lymph nodes were with round shape and hypoechoic features, regardless of whether it was malignant or benign ulceration. Because of that, shape and echogenicity of lymph node are not a reliable criterion for differentiating benign from malignant ulcers. Valid statistical analysis of the differences between benign and malignant ulcers based on the diameter of a lymph node and the clarity of its outer border was impossible because of a small sample in benign ulcers. In the study of Gill et al. [27] round shape, a short axis greater than 8.3 mm, and sharp margins were predictive of the involvement of lymph node by metastasis. Similar results were published by some other authors [28, 29]. On the other side, Jamil et al. [30] poented out that echo feature of lymphe node is not a reliable sign of malignancy and they suggest fine needle aspiration under endoscopic ultrasound guidance.

Histopathological examinations of gastric wall and lymph nodes were done in 14 of the patients with malignant ulcerations, who underwent gastric surgery. Endosonographic assessment of T stage coincided with the postoperative histopathological findings in 12 of 14 (85.7%) operated patients. The T stage was underestimated in 2 of the patients. Endosonographic assessment of the N stage coincided with the postoperative histopathological findings in 9 of 14 (64.3%) operated patients. The N-stage was underestimated in 4 of the patients and overestimated in 1 patient.

Loss of layering structure of the gastric wall may exists in both types of ulcerations, due to the spread of fibrosis or cancerous tissue below the mucosa [21, 24]. According to our results, there was the loss of layering structure of the gastric wall in 90% of ulcerative carcinoma. This parameter was incuded in the criteria of malignancy in the study by Zhang et al. [4].

Combining EUS criteria of malignancy increases the reliability in defining the biological nature of gastric ulceration. Assessment of malignancy of gastric ulcers based on 4 EUS criteria and point-score, which were formulated in our study, is fast and reliable. In comparasion with the results of Zhang et al. [4], only the sensitivity of EUS for diagnosis of malignancy in our study was lower: 75% *vs* 83.8% [4]. However, further experience gained on larger series of patients will be the best way to check the reliability of these criteria and possibly to correct them.

Conclusion

Our results point to the usefulness of endosonographic ultrasound in differentiation benign from malignant gastric ulcer. It is very important, especially in case of disagreement between the endoscopic appearance of ulcerations and histological findings.

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