Greyscale and contrast enhanced ultrasonography for characterization of gastric malignant tumors

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Abstract

Aims: To evaluate the utility of grey scale ultrasonography (US) and contrast enhanced ultrasonography (CEUS) for characterization of malignant gastric tumors. **Material and methods:** The study was conducted prospectively and it included a number of 30 patients with malignant gastric tumors diagnosed through upper tract endoscopy and biopsy: 25 adenocarcinomas, 3 lymphomas, and 2 stromal tumors. All the patients were examined by US, followed immediately by CEUS, using both oral and intravenous contrast agents. CEUS assessed the dynamics of the contrast agent during the arterial phase and the venous phase. The distribution characteristics of the contrast agent inside the region of interest (ROI) were also evaluated. Twenty four patients underwent surgery. **Results:** Adenocarcinomas presented heterogeneous enhancement with variable pattern, followed by a delayed wash-out in almost all of the situations. Lymphomas presented a variable pattern, intensity and homogeneity of the enhancement, followed by delayed wash-out. Stromal tumors showed early arterial intense and homogenous enhancement followed by moderate wash-out in venous phase. **Conclusions:** Grey scale US and CEUS are useful methods in characterizing gastric tumors and contribute to a more adequate evaluation of the lesions. The dynamics of the contrast agent may be suggestive for the anatomopathological nature of the tumor. Larger studies will be necessary in order to determine the practical value of the method.

Keywords: contrast enhanced ultrasonography; gastric cancer; stomach ultrasonography; tumor characterization

Introduction

The incidence of the gastric cancer patients has been decreasing during the last decades; however, the prognosis for the patients remains poor. At the moment the gastric cancer is the 5th most frequent cancer in the world and represents the third cause of death by cancer [1].

Malignant gastric tumors are represented by adenocarcinomas 94%, lymphomas 4%, stromal (1%), and other tumors 1% [2,3].

The prognosis in gastric cancer is good in early stages, stages which are usually asymptomatic. The presence of symptoms signifies local and regional advanced disease and the effectiveness of treatment is dramatically decreasing in the cases where the disease has exceeded the organ's limits .

The gold standard for diagnosis is represented by the upper tract endoscopy. This method detects tumors directly and allows a targeted biopsy, while adding endoscopic ultrasonography (US) to the exam may reveal

parietal invasion [4-8]. In the case of ulcerative tumors, diffuse tumors, or tumors originating from deeper layers of the stomach, biopsy may be inconclusive or produces false negative results [9,10].

Abdominal US is an easily available, reproducible, patient-friendly technique, which can be performed in correlation with the clinical examination. The data provided is both anatomical and functional [11,12]. The optimization of the method by using contrast agents represents a new step in improving the performance of this method. Initially used for studying vascular and parenchymal organs pathology, contrast enhanced ultrasonography (CEUS) is constantly expanding its applicability, in the last few years being used in the pathology of all abdominal organs [13].

At the moment, there are several studies regarding the preoperative diagnosis of gastric tumors using CEUS in patients with stomach cancer [14-17]. These studies are focused on highlighting the tumoral mass and less on finding a correlation between tumor histology and the behavior of the tumoral tissue on contrast administration. The vascularization of the tumoral tissue is different from that of the normal gastric wall. Tumor angiogenesis, anarchic cellular proliferation, and the development of arterial-venous shunts create a different vascular pattern from that of the normal gastric wall, thus developing the premises for a particular behavior upon vascular contrast administration [18].

The treatment of gastric tumors depends on the histology type and it is based on the wide surgical resection of the tumor and lymphadenectomy in case of the adenocarcinoma [19,20], antibiotics, chemotherapy, and surgery in selected cases of gastric lymphoma [21], and in limited resection, without lymphadenectomy, accompanied by chemotherapy in stromal tumors (GIST) [22]. In this context, the preoperative recognition of the type of the disease is extremely important for the implementation of an optimal treatment.

The aim of our study was to establish the value of CEUS and grey-scale US in describing specific features of gastric tumors with respect to macroscopic appearance and histology, and thereby optimize the diagnosis of gastric cancer.

Material and methods

Subjects

The present study was conducted prospectively between 2012 and 2014, on 30 patients with gastric tumors, in 'Prof. Dr. Octavian Fodor' Gastroenterology and Hepatology Institute, Cluj-Napoca. The study was approved be local ethic committee and informed and written consent was obtained from all the patients. The inclusion criteria were: patients over 18 years old, diagnosis of a primary gastric tumor established through upper tract endoscopy and biopsy, tumor visible at transabdominal US exam. Patients with tumors originating in other structures and invading the stomach as well as cases with tumors not visible by transabdominal US exam were excluded.

Ultrasonography

The US examinations were executed by the same, highly experienced, examiner using a General Electric GE9 ultrasound machine with a multifrequency convex transducer (2-5MHz). All patients consumed 100 ml oral contrast (plain water) and were examined after 30 seconds. All patients underwent standard US and CEUS examinations.

The transducer was placed in the epigastric region in two perpendicular views and several intermediate views. The vertical and horizontal parts of the stomach were examined successively. For this purpose the patients were asked to sit in a semi-sitting position. An overall visualization of the stomach and identification of the anatomic parts (cardia, vertical region, horizontal region, and pylorus) were performed. The gastric tumor was identified, localized, and characterized.

The US staging of the tumor was realized according to Bormann's classification [23]. Tumor penetration was noted as u1 = limited to the mucosa, u2 = mucosa and submucosa, u3 = reaching the serosa, but confined to it, and u4 = invasion of surrounding structures. Macroscopic form was noted as I (polypoid), II (ulcerative form with distinct, elevated borders), III (ulcerative with infiltrated base) and IV (diffuse thickening). Identification of round lymph nodes was noted n1, and lack of visualization n0. Visualization of liver metastases were noted m1, while the absence of metastases with m0. After visualizing the lesion, using the SonoLiver software, a region of interest (ROI) was drawn. This includes border ROI (including tumor and surrounding tissue), lesion ROI (perimeter of the lesion) and reference ROI (normal US scanning area located in the border ROI at 5cm of lesion ROI). The blood vessels inside the ROI were evaluated by using color flow map (CFM). For this purpose the machine was set for low velocities and the image acquisition was performed with the patient in apnea. The presence of vessels was noted with 1 and their absence with 0.

The CEUS examination immediately followed the conventional one. The contrast agent (CA) that was used was Sonovue (Bracco, Italy), in quantity of 1.6 cm^3 diluted in 10 ml saline solution. A mechanical index of 0.09-0.11 was used and a single focus was positioned under

ROI. By using the "dual mode image" a combination of the fundamental and harmonic echoes was realized. The CEUS examination time was 5 minutes and the behavior of the lesion ROI was evaluated during the arterial phase (first 30 seconds from de administration of the CA) and the venous phase (the interval between 31 and 45 seconds from de administration).

The following US parameters were evaluated: 1) tumor enhancement with CA: present or absent; 2) the enhancement pattern of the CA during the arterial phase compared with the reference ROI: early enhancement (the tumor enhanced before the reference ROI), late enhancement (the tumor enhancement after the reference ROI), or identical enhancement of the tumor and reference ROI. The enhancement was characterized as homogeneous or inhomogeneous; 3) the intensity of the CA enhancement was evaluated as identical, increased, or decreased compared with reference ROI; 4) the washout pattern characterized as accelerated (when the CA left the tumor before it left the reference ROI), delayed (when the CA persisted in the tumor longer than the in reference ROI), or identical with that of the reference ROI. The washout phase was divided into early (the 31-45 seconds interval from the CA administration) and late washout (the 46-120 seconds interval from the CA administration). After 120 seconds from the CA administration a US evaluation of the liver was performed to highlight possible metastases.

At the end of the US examination an ultrasound staging of the tumor was performed.

Surgical procedures

Following investigations, 24 patients underwent surgery. Total or subtotal gastrectomy with eso-jejunal Roux-en-Y anastomosis or gastroduodenal anastomosis with D2 lymphadenectomy was performed. In 6 patients surgery was contraindicated.

Anatomopathology

The anatomopathologist was blinded from all preoperatory examinations. Tissue processing specimens were formalin fixed, paraffin-embedded, and hematoxylin-eosin stained. In some cases, immunohistochemical staining methods were used to ascertain the diagnose. Maximum tumor diameter, macroscopic appearance, depth invasion, histological type, degree of differentiation, and lymph node involvement were noted. The Borrmann classification of gastric cancer [23] was used to describe the macroscopic features. Adenocarcinomas were divided according to Japanese classification of gastric cancer [24]. The staging of the disease was performed according to the American Joint Committee on Cancer (AJCC) 2010 [25].

Statistical analysis

For statistical analysis we used IMB SPSS 20 statistics software. In order to determine the correlations between different variables involved in our study, we used the 2-tailed Student test. A p-value<0.05 was considered as statistically significant.

Results

The study was performed on 30 patients (20 male, mean age 62.5 years old). The endoscopic biopsy diagnosed 25 cases of adenocarcinoma, 3 cases of lymphoma and 2 cases of gastrointestinal stromal tumors (GIST).

There was a correlation between the enhancement pattern of CA during arterial phase and Bormann tumor type (p=0.021). Polypoid forms tend to upload CA faster, followed by ulcerative-infiltrative, ulcerative, and infiltrative forms. There was an inverse correlation between arterial uptake and tumor differentiation (p=0.021). For well-differentiated tumors, arterial uptake was slower than for poorly differentiated or undifferentiated tumors.

Table I. Contrast agent dynamic for adenocarcinomas, lymphomas and stromal tumors

CA dynamics		Types of tumors		
		Adenocarcinomas (n=25)	Lymphomas (n=3)	Stromal tumors (n=2)
Enhancement pattern	Early	13	2	2
	Identical	0	0	0
	Delay	12	1	0
Enhancement intensity	Intense	4	3	2
	Identical	0	0	0
	Weak	11	0	0
Enhancement homogeneity	Homogenous	4	0	2
	Heterogeneous	21	3	0
Washout pattern	Early	2	0	0
	Identical	2	0	0
	Delay	21	3	2

CA = contrast agent; n = number of cases

No correlation could be found between uptake in arterial phase and depth of invasion.

We found an inverse correlation between the maximum intensity of the capture and the degree of tumor differentiation (p=0.024) (well or average differentiated tumors tend to record higher values of capture intensity compared to poorly differentiated or undifferentiated tumors) and a direct correlation between the homogeneity of the enhancement and the tumor type (p=0.034). GIST captures homogeneously, all lymphomas captured heterogeneously, and adenocarcinomas captured predominantly heterogeneous. No correlation between the homogeneity of CA capture and depth invasion and the degree of tumor differentiation was found. Also, there was no correlation between the mean transit time and the Bormann type, histological type, degree of tumor differentiation, and depth invasion. In Table I are detailed CA dynamic for adenocarcinomas, lymphomas, and GIST.

In the adenocarcinomas, the tumor behavior at CEUS examination was inhomogeneous as an expression of the differences in vascularization of these tumors (fig1). The CEUS profile of lymphomas is characterized by a variable uptake pattern, intense and heterogeneous enhancement and a delayed washout (fig 2). The profile of the studied GIST is represented by early, intense, homogeneous enhancement followed by a slow washout of the CA (fig 3).

As a result of the investigations, 24 patients underwent surgery. Out of these 24 patients, 19 were adenocarcinomas, 3 were lymphomas and 2 patients were with GIST. Grey scale US revealed liver metastases in 5 cases that were confirmed intraoperatively. In 1 patient, the surgeon found liver metastases that had not been detected by
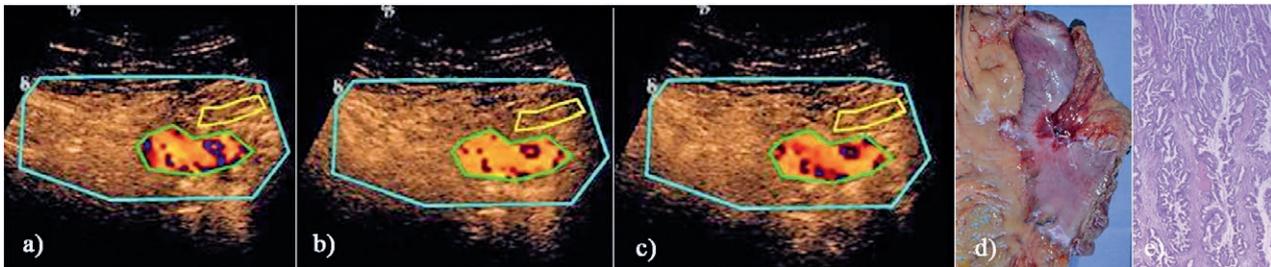

Fig 1. CEUS examination of gastric adenocarcinoma with perfusion maps showing CA uptake (a), heterogeneous enhancement (b), and delayed washout (c); d) surgery specimen of subtotal gastrectomy; e) histopathology aspect, HE 100X.

Fig 2. CEUS examination of gastric lymphoma with perfusion maps of gastric lymphoma showing intense CA uptake (a), heterogeneous enhancement (b), and delayed washout (c); d) surgery specimen of total gastrectomy; e) histopathology aspect, HE 100X.
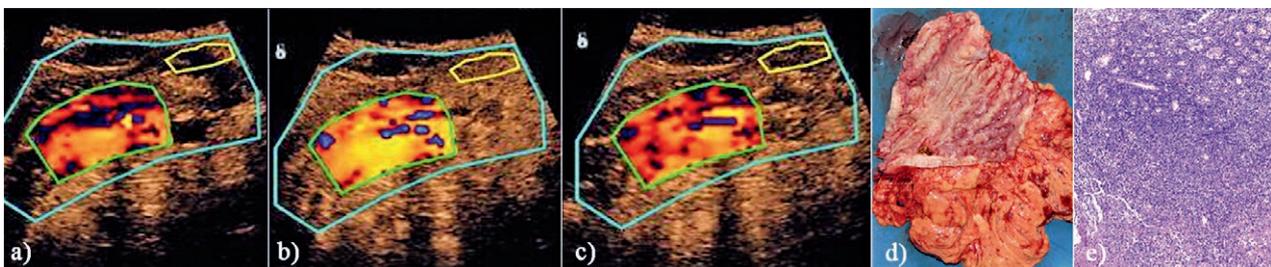

Fig 3. CEUS examination of gastric stromal tumor showing intense CA uptake, homogenous enhancement (a), and delayed washout (b); c) surgery specimen; d) histopathology aspect, HE 100X.

Table II. Correlation between grey scale ultrasonography and pathology in tumor characterization with US accuracy

Parameters		Grey-scale US	Pathology	US accuracy
Macroscopic form* (Bormann)	I	9	9	100%
	II	0	0	100%
	III	7	11	63.6%
	IV	8	4	50%
Tumor size (cm)	< 2	2	2	87.5%
	2<4	3	3	
	4<6	6	7	
	6<8	3	2	
	8<10	5	3	
	>10	5	7	
Depth invasion	u1/T1	1	2	58.3%
	u2/T2	5	1	
	u3/T3	13	10	
	u4/T4	5	11	
Lymph nodes	n0	8	6	91.6%
	n1	16	18	
Liver metastases	m0	19	18	95.5%
	m1	5	6	
Stage	1	1	1	87.5%
	2	6	3	
	3	11	12	
	4	6	8	

*I polypoid, II ulcerative form with distinct, elevated borders, III ulcerative with infiltrated base, IV diffuse thickening

US. The grey scale US and anatomopathology findings in the surgical patients are listed in Table II.

Discussions

Literature studies demonstrate a high utility of ultrasonography in the diagnosis of symptomatic gastric cancer [26]. The development of the CEUS created the premises for characterizing the tissue microcirculation [27]. Being highly sensitive in detecting pathological alterations of the microcirculation [28-30], it allows not only to identify the tumoral tissue compared to normal gastric wall but also to differentiate between adenocarcinoma, lymphoma, and GIST. Gastric adenocarcinomas are both macroscopically and microscopically heterogeneous tumors, and this characteristic explains the variable pattern of CEUS which consists of accelerated or delayed enhancement, predominantly heterogeneous, followed by a delayed CA washout. These features are consistent with the feeding vessels and distorted nourishing vasculature of gastric carcinoma described by Shi et al [31]. We could not find published data about the CEUS profile of gastric lymphomas, but in our cases the tumor was characterized by a variable uptake pattern, intense

and heterogeneous enhancement, and a delayed washout. Concerning GIST, we found an early, intense, homogeneous enhancement followed by a slow washout of the CA, the same as Shi et al [31] and Stock et al [32] .

US and CEUS allowed us a good appraisal of Borrmann macroscopic types, tumor size, lymph node involvement, and a fair measurement of depth invasion, consistent with the results obtained by Fang Wei et al [33]. A step forward may have been the use of CEUS in following the response to neoadjuvant chemotherapy before surgical resection in patients with locally-advanced gastric cancer [34].

The main weakness of the study is the number of patients enrolled in the study, which gives the study limited accuracy, especially in the case of GIST and lymphomas. Although blinded to the endoscopic and histopathologic results, the ultrasonographer was aware of the presence of a gastric tumor. No intra- or interobserver variability was investigated. No case of linitis plastica was present in our study. Six of our patients were not eligible for surgery and in these cases no correlations could be made between the US appearance and the macroscopic tumor characteristics and the anatomopathological staging.

Conclusions

US combined with CEUS is a promising imaging technique for the macroscopic characterization of gastric tumors and for giving a hint on the histological type in cases where biopsy is inconclusive or negative and thus influence therapy. We proved the value of CEUS by combining qualitative and semiquantitative evaluations in the assessment of the various histopathological tumor types.

US and CEUS does not substitute upper tract endoscopy, but it brings additional data about tumor macroscopic type, size, penetration, and lymph node involvement. Further studies are necessary in order to define the accuracy and indications of the method.

Conflict of interests: none

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