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The role of i.v. and oral contrast enhanced ultrasonography in the characterization of gastric tumors. A preliminary study.

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Abstract

Objective: To identify the diagnosis benefits of harmonics optimized i.v. contrast enhanced ultrasonography (CEUS) in the detection and characterization of several gastric neoplasms. **Material and method:** The study group included 10 patients with gastric neoplasms, either epithelial or stromal. The examination included grey scale ultrasonography combined with hydrosonography and harmonics ultrasonography with i.v. contrast media, centered on the tumor, using the surrounding normal gastric wall as witness. All cases were examined by endoscopy, followed by a pathology report and eight of the patients underwent surgery. CEUS followed the dynamics of the contrast media during the arterial (up to 30 seconds since administration) and venous (30 to 60 seconds since administration) phases. The characteristics of contrast uptake in the region of interest were also studied. **Results:** In gastric tumors an non-homogeneous uptake was registered during the arterial phase followed by contrast wash-out during the venous phase. In stromal tumors (GIST) there was an accelerated and uniform uptake in the arterial phase, while the wash-out was delayed. CEUS was able to show the masses in all cases. The aspect of the lesions on the grey scale images – infiltration of polyp – consolidated the diagnosis. **Conclusions:** The analysis of the cases included in the study proved that CEUS represents a promising method in the characterization of infiltrative and proliferative gastric tumors. The information must be combined with those obtained from the 2D harmonics ultrasound exam. Extended studies, on a higher number of cases, are necessary in order to demonstrate the practical use of the method.

Keywords: contrast enhanced ultrasonography, hydrosonography, gastric tumors

Introduction

Even though gastric tumors have a high frequency their detection is often delayed in practice in order for a curative treatment to be attempted. Gastric cancer is on the fourth place among all cancers with an annual detection rate of about 930 000 [1]. The high mortality rate demonstrates the limited efficiency of the therapeutic means once the disease is settled [2]. The patient's complaints are often uncharacteristic and that is why the diagnosis is not based on the clinical exam, but rather on paraclinical investigations.

Upper digestive tract endoscopy is the gold standard in the diagnosis of gastric tumors (detection, characterization, biopsy under visual control). Unfortunately, this investigation it is not accepted by all patients, as it is rather invasive and traumatizing. There is an obvious tendency in modern medicine to identify widely accessible, well-tolerated, non invasive, precise diagnosis procedures. Imaging investigations fall under the category of diagnosis techniques with screening potential [3].

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Trans-abdominal ultrasonography (US) can meet these criteria as it is widely available and frequently performed in close relation with the clinical exam. The data obtained by US are anatomic, like appearance of the organ walls (thickness, structure), stomach components, its anatomic relationship with other organs, but also functional data [5]. There are many studies found in literature regarding the ultrasonographic exploration of the stomach. Most of them are centered on the usefulness of the method in preoperative staging of a tumor using CEUS [6-8]. There are less studies focused on tumor characterization using i.v. CEUS. It is accepted that the dynamics of the contrast media within gastric tumors can be a characteristic of the circulatory bed in a manner similar to the one found in other neoplastic processes, like hepatic, pancreatic or splenic tumors [9-11].

According to all of the above, our study is focused on evaluating the diagnostic and characterization benefits of CEUS in gastric tumors.

Material and method

During April and July 2012, 10 patients (6 males and 4 females) with neoplasm diagnostic were examined by ultrasound in the Ultrasonography Lab. The study was performed with the agreement of the Ethics Committee of the institute and with the informed and written consent of the patients. All patients were first examined by conventional grey scale US and afterwards using the CEUS technique. The selection criteria of the patients were: a certain diagnosis of gastric tumor established by upper digestive tract endoscopy and confirmed with a pathology exam; gastric mass visible using grey scale US. Patients with an inconclusive grey scale examination were not included in the study.

Conventional US was performed using a General Electric GE 7 machine, with a multifrequency convex transducer (2-5 MHz). The examination was performed after the endoscopic exam, which was considered the gold standard for tumor detection. All the investigations were performed by the same, well-experienced, examiner and consisted of a grey scale and color Doppler (CFM) exploration, immediately followed by the CEUS. In every case the epigastric approach, in two perpendicular views, was used, as well as intermediary views. All the patients were administered oral contrast media. The vertical segment of the stomach and the antrum were examined separately. Therefore the patients were placed in a semi-seated position and were given to drink 75-100 cmc of plain water. The ultrasound US examination was initiated at about 30 seconds after the water ingestion.

The following elements were noted during the examination: stomach overall visualization with a distinct identification of each segment (esocardial junction, vertical segment, and antrum); identification of the gastric mass, defining its macroscopic features (infiltrative, proliferative, polypoid, or ulcerated), ultrasonographic local staging (establishing the degree of tumor penetration, where "ut4" = tumor invasion in surrounding organs; "ut3" = tumor invasion in all the layers of the gastric wall, without going past the serosa; "ut2" = involvement of the mucosa and submucosa, with no direct contact with the serosa; "ut1" = strict involvement of the mucosa); identification of the peritumoral lymph nodes ("u n1" = one round, hypoechoic lymph node close to the mass; "u n2" = at least 2 lymph nodes, with the above characteristics, at distance from one another); detection of liver metastasis (when present a "u m1" stage was established) [12]. The CFM exam was used to detecting the presence of vessels within the region of interest (ROI). For this exploration the settings of the machine were changed for low velocities and image acquisition was performed during apnea. The quantification of the information was based only on the presence/absence of the vessels.

CEUS was performed immediately after the conventional US. The exam consisted of an i.v. administration of 1.6 cmc of contrast media (Sonovue, Bracco, Italy), followed by a bolus injection of 10 ml of saline solution. The exploration was executed with a mechanical index of 0.09 – 0.10, with the focus placed under the ROI, with a dual mode image which combined fundamental echoes image with harmonics echoes image. The exam was continuous starting from the moment of the i.v. administration until up to 5 minutes after that moment. The behavior of the ROI was evaluated as well as of the mass during the arterial phase (first 30 seconds after injection) and during the venous phase (more than 30 seconds since contrast administration). The next were followed: a. the uptake model during the arterial phase reported to the surrounding normal gastric wall (witness role) was defined as early uptake (before witness tissue uptake), delayed uptake (after the witness tissue uptake), homogeneous (uniform) or non-homogeneous (non-uniform); b. the wash-out model reported to the witness area and the wash-out speed (early wash-out, the first seconds of the venous phase; delayed wash-out, over 45 – 50 seconds). At 120 seconds from injection the CEUS of the stomach was completed with a liver examination in order to detect possible metastases.

Results

The histology exam revealed adenocarcinoma of various degrees of differentiation in 7 cases, gastric lymphoma in 1 case and stromal tumors (GIST) in 2 cases.

Grey scale US showed an infiltrative mass in 7 cases (1 with stenosis and 1 with ulceration), 2 cases with a polypoid tumor and 1 proliferative tumor with large base implantation.

CEUS showed specific alterations in all the cases. Therefore, in each case there was an arterial uptake and a venous wash-out, both events occurring at different times compared with the witness gastric wall, thus demonstrating a pathological circulation (fig 1). All the cases with a polypoid aspect of the mass proved to be stromal tumors (GIST) that presented intense, homogeneous uptake, but the moment contrast media entered ROI was early in one situation and delayed in the other (fig 2-4). Liver metastases were identified in two cases both on grey scale US and CEUS. A detailed description of the grey scale US aspect and the CEUS aspect is found in the following table I. The aspect of the surgery specimens was compared with the ultrasound findings (fig 5). An analysis of the variation of the vascular signal intensity (TIC) revealed a delay between blood entering ROI and entering the witness gastric wall (fig 6).

Table I. Conventional and contrast enhanced ultrasonographic aspects found in the study group cases.

No.	Patient	2D Ultrasonography	CEUS	Diagnosis before surgery	Postoperative diagnosis
1.	T. S. m, 55 y	Infiltrative mass (postoperative margins, anterior wall). Peritumoral lymph nodes. u t2 n1 m0	Early, homogeneous, intense arterial uptake. Early, intense venous wash-out,	Recurrent, infiltrative, gastric adenocarcinoma	Gastric adenocarcinoma. Tumor recurrence on the postoperative margins. Metastatic lymph nodes. p t2 n1 m0
2.	O. V. m, 65 y	Infiltrative mass (antrum, larger curvature). u t3 n0 m1	Early, intense, non-homogeneous arterial uptake. Early, moderate venous wash-out.	Infiltrative gastric adenocarcinoma (antrum). Liver metastases.	Partially differentiated gastric adenocarcinoma. p t3 n2 m1
3.	M. A. f, 76	Infiltrative mass (antrum) u t2 n0 m0	Delayed, moderate, non-homogeneous arterial uptake. Delayed, moderate venous wash-out.	Gastric adenocarcinoma (antrum)	Gastric adenocarcinoma. p t3 n2 m0
4.	O. I., m, 58	Polypoid mass (gastric body). u t3 n0 m0	Early, homogeneous, intense arterial uptake. Venous wash-out absent.	GIST (antrum).	GIST. p t3 n0 m0
5.	G. V, m, 79	Polypoid mass (gastric body). u t3 n0 m0	Delayed, homogeneous, intense arterial uptake. Slow, moderate venous wash-out.	Leiomyoma.	GIST. pT3 n0 mx
6.	S. A., f, 48	Infiltration + ulceration (antrum, larger curvature) u t3 n0 m0	Early, intense, homogeneous arterial uptake. Delayed, non-homogeneous, moderate wash-out.	Ulcerated antrum adenocarcinoma	Posterior wall gastric adenocarcinoma. p t4 n3b M0
7.	S. A. f, 82	Proliferation + ulceration (antrum) u t2 n0 m0	Delayed, homogeneous, intense arterial uptake. Early venous wash-out.	Gastric adenocarcinoma (polypoid, antrum)	Antrum adenocarcinoma. p t1 n0 m0
8.	M. I., m, 66	Infiltration (gastric body, anterior wall). Ascites. u t3 n1 m1	Weak, delayed, non-homogeneous arterial uptake. Delayed, non-homogeneous venous wash-out.	Gastric adenocarcinoma (infiltrative, antrum and larger curvature). Liver and peritoneal metastases.	Gastric adenocarcinoma p t4 n2 m1
9.	F.F., f, 78	Infiltration + ulceration (antrum) u t3 n2 m1	Early, non-homogeneous, intense arterial uptake. Delayed, non-homogeneous venous wash-out.	Gastric lymphoma	- surgery was not performed due to the poor state of the patient.
10.	C.V, b, 27	Infiltration + stenosis (antrum) u t3 n1 m0	Early, homogeneous, intense arterial uptake. Delayed, homogeneous wash-out.	Gastric adenocarcinoma	- surgery was not performed

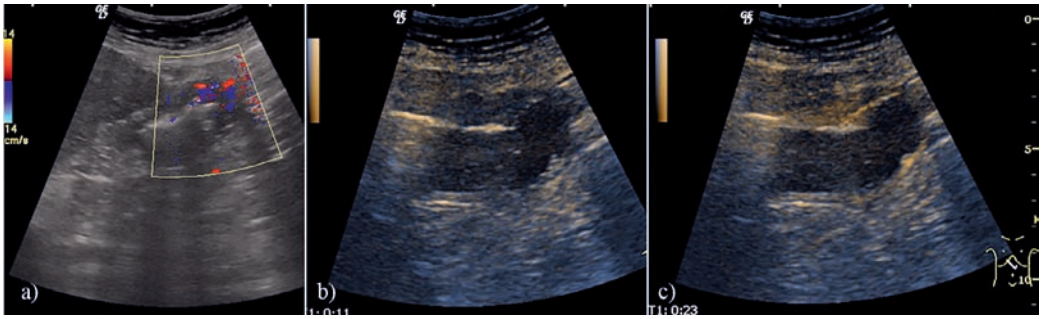


Fig 1. Neoplasm (adenocarcinoma) of the anterior face and larger curvature of the stomach. a) Pathological thickening of the gastric wall as well as increase of the vascular signal (CFM) may be noticed. b) CEUS examination with water contrast. At 11 seconds after i.v. contrast administration there is no signal in the region of interest. c) CEUS examination with water contrast during the arterial phase. Compared with b) the presence of harmonic echoes may be observed, as well a clear demarcation of the region of interest reported to the witness posterior gastric wall.

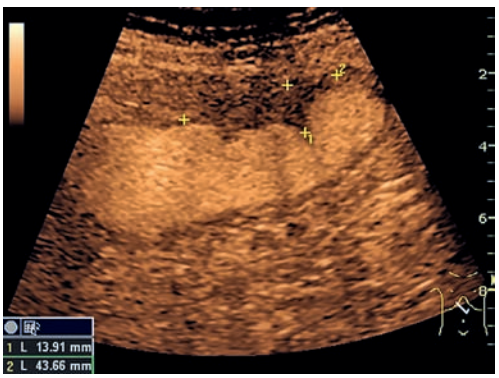


Fig 2. Examination with water oral contrast (plain water + Sonovue) combined with CEUS during the delayed phase. The gastric mass is very well delineated and the wash-out pattern is suggestive for the neoplastic character.

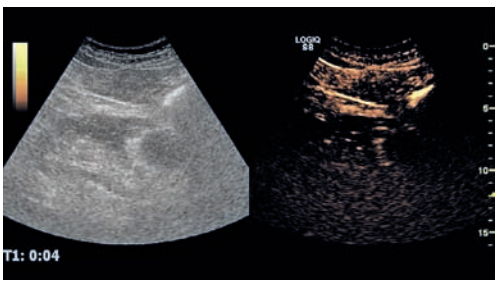


Fig 3. Dual mode examination (conventional exam on the left, CEUS arterial phase on the right). The conventional exploration demonstrates a proliferative, polypoid aspect of the tumor within the stomach cavity (left) (stromal tumor – GIST).

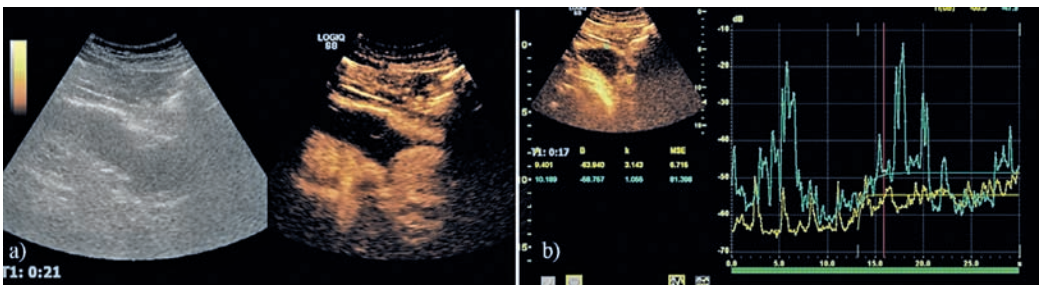


Fig 4. a) Dual mode examination. CEUS shows intense, homogeneous uptake during the arterial phase (21 seconds from administration); b) Contrast curves analysis shows the concomitant onset of tumor and gastric wall uptake, with a decreased intensity within the tumor.

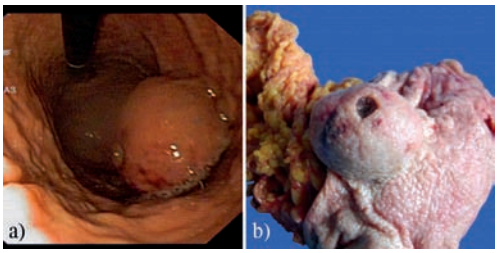


Fig 5. Macroscopic aspect of the polypoid gastric tumor (GIST) from fig 5: a) endoscopic aspect; b) surgery specimen

Discussions

The US exploration of the stomach has an important practical value. This value comes from the non-invasive and rather "friendly" character of this method and its large availability. Last, but not least, US is an investigation with clinical characters, often considered as part of the clinical exam of a patient. Most certainly, trans-abdominal US has limitations in visualizing various parts of the stomach, like the larger curvature and the sub-diaphragmatic segment, which are both usually obscured by the presence of air. In these situations the examination is considered inconclusive and therefore endoscopy is performed for tumor detection and endosonography for tumor staging [6]. Even in these circumstances there are authors that underline on the utility of trans-abdominal ultrasound in establishing the diagnosis in patients with specific complaints [13].

When symptoms like incoercible vomiting, severe weight loss, or ascites are present, trans-abdominal US is highly indicated, all the more since the exam is possible and an eventual mass is most probably large. An US exam of the stomach is depending on the acquisition of a clear image that allows for a complete visualization of the organ. In normal conditions the examination of the stomach is not always accurate enough. There are several possible adjustments that optimize the ultrasound image, for example administration of oral contrast. The oral contrast may consist of water alone or it may be combined with contrast agents [14]. In this second category is the use of gas bubbles diluted in water (2 – 3 drops of Sonovue diluted in 50 – 100 cmc water). There are studies that demonstrate the superior value of this procedure in the clear delineation of the mass as well as in identifying luminal stenosis [14].

The evaluation of the digestive tract vascularization represents a rather new area of study and is meant to detect microcirculation in inflammatory and tumoral lesions using the Doppler technique [15]. This feature allows for the identification of vessels within the tumor or within the pathologic digestive wall only at velocities that are higher than 2 cm/sec. This velocity limit makes color or spectral Doppler US inadequate for an accurate characterization of a pathological circulatory bed. Even more than that, the normal motility of the stomach produces color or velocity artifacts that diminish that utility of the procedure, unlike similar applications in the pathology of the colon where motility is reduced [16].

In the last years harmonic i.v. contrast ultrasonography (CEUS) has gained increased popularity [17,18]. Its main applications are in the characterization and detection of liver masses, in the identification of ischemic or infarcted areas, in the visualization of extravascular blood leaks (in stenting procedures or in aneurysm surgery) as well as in the evaluation of various oncologic treatments efficiency [19,20]. CEUS also proved to be useful in the diagnosis, quantification and detecting prognosis indicators in digestive tract inflammatory diseases like hemorrhagic colitis and Crohn's disease [15].

CEUS is based on the identification of the harmonic echoes resulted from the exposure of the gas microbubbles within the i.v. contrast agent to an ultrasound beam

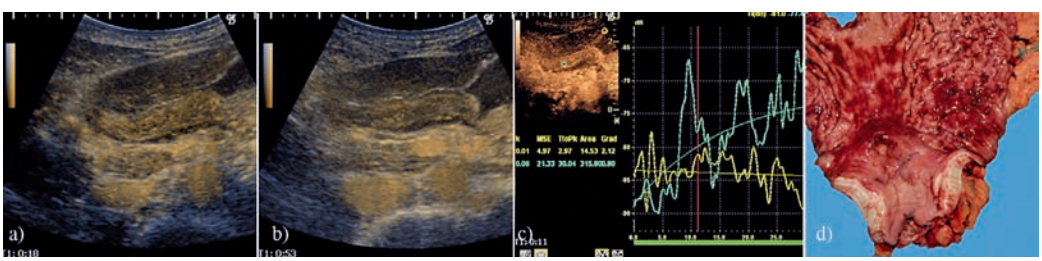


Fig 6. Stenosing, infiltrative neoplasm of the antrum (adenocarcinoma). a) CEUS arterial phase (18 seconds); b) CEUS venous phase (53 seconds); c) analysis of the time intensity curves (TIC) shows the delay between the entrance of the blood in the tumor circulatory bed (green) compared with witness circulatory bed (yellow); d) surgery specimen

with a variable mechanical index, usually around 0.09 – 0.10. The method is highly specific for the presence of blood, even when it is stagnating. The generated echoes are separate from the basic echoes which makes the examination fall into the category of high resolution functional imaging. The qualities of CEUS are multiple. Among these we can list: a. lack of significant side-effects (high dilution of the contrast agent); b. excellent temporal resolution, superior to other sectional examinations, because of it's continuous, dynamic character; c. angiospecificity and high sensitivity in the presence of a vascular pathology. The data obtained by CEUS are both qualitative and quantitative. The qualitative component allows for the appreciation of the spatial architecture of the circulatory bed, for echos intensity (in direct correlation with the capillary bed volume), the dynamics of contrast transition through the region of interest reported to the arterial phase (first 30 seconds from i.v. injection) and the venous phase (between 30 and 60 seconds). The model of uptake within the circulatory bed, complete or partial, homogeneous or non homogeneous, represent information that define the degree of blood fill in the region of interest. The quantitative component allows for a graphic evaluation of the contrast transition through the region of interest. The data is a function of the echoes intensity represented in time. The resulted curve permits an appreciation of the flow tendency for a period of time of up to 30 seconds as well as a characterization of the circulatory debit at given time. The experience gained in the last 10 years, according to literature, demonstrated on a high number of cases, that in the vast majority of malignancies there is a typical CEUS behavior represented by an arterial uptake of the contrast media followed by a rather quick wash-out. This behavior is correlated with the presence of arteriovenous shunts and a well-represented circulatory bed. In our casuistry this suggestive behavior was identified in all cases. The uptake was intense and non-homogeneous in infiltrative malignant tumors, while the two case of GIST presented an intense, homogeneous uptake during the arterial phase and no wash-out. Even if the number of cases is low, the differences of behavior between the two types of tumors encourages for further studies. Even more, in every case the arterial phase of the examination allowed for a better demarcation of the mass from the normal gastric wall. This observation makes us believe that the method might contribute to a better tumor staging by a more precise delimitation of the neoplastic circulatory bed.

The present study has its strengths and weaknesses. One of the strengths is represented by the originality of the idea – i.v. contrast examination of gastric tumors in combination with hydrosonography and demonstration of the added value of CEUS by a qualitative and quantitative analysis of the information. There are few studies published in literature regarding this application. The weakness of the study is represented by the low number of cases. It is obvious that valid conclusions require a much larger group of patients with neoplastic pathology of various stages, confirmed by surgery and pathology. But even under these circumstances our observations encourage us to believe that i.v. contrast ultrasonography may have diagnosis benefits in tumor characterization. The utility of the procedure may be considered in the evaluation of chemotherapy efficiency in inoperable patients. Last, but not least, the CEUS of the liver in the delayed phase (over 2 minutes) may detect liver metastases with a performance comparable with that of computed tomography [18].

Conclusions

Trans-abdominal ultrasonography allows for the detection and characterization of gastric tumors. Adding oral contrast to the investigation raises the accuracy of the conventional image, while CEUS permits identification of various parameters that correlate with the nature of the tumor. CEUS examination allows for a better definition of the tumor by identifying the neoplastic circulatory bed. A continuation of this study with an increased number of cases is mandatory in order to draw valid conclusions.

Conflict of interest: none

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