Contrast enhanced and Doppler ultrasonography in the characterization of the microcirculation. Expectancies and performances

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Abstract

Normal and pathological vascularization can be examined using imaging methods. The use of contrast agents (CA), tracers or markers within the bloodstream, has gained more and more applications in the last years. The dynamics of the CA passing through a region of interest is directly correlated with the morphological and functional characteristics of the bloodstream in that particular area. Doppler ultrasonography provides information only regarding the flow within large vessels, the method having limited spatial resolution and sensitivity in the assessment of the capillary flow. Contrast-enhanced ultrasonography (CEUS) enables the detection of very slow blood flow or stagnating blood in vessels measuring as little as 40 microns. This feature is extremely valuable in the characterization of a circulatory bed and for the evaluation of the tumoral angiogenesis process. CEUS may be used both for diagnosis and for the assessment of treatment efficiency. Further on various aspects regarding this method, its advantages and limitations and arguments for its systematic use in oncology, will be presented in this review.

Keywords: angiogenesis; ultrasound; contrast; functional imaging.

Modern oncology is undergoing numerous challenges, beginning with early tumor and recurrence detection and ending with the necessity to quickly and thoroughly evaluate the efficiency of the treatment. The clinical exam of the patient, which lacks sensitivity, is often accompanied by delayed conclusions and therefore must be correlated with functional, biochemical (tumoral markers) investigations, and imaging techniques. There are many imaging techniques available: computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET – CT), ultrasonography (US) [1-3].

Classically, a "convincing" sign for a "favorable response to therapy", identified by either of the imaging techniques mentioned above, is represented by a reduction in size of the primary tumor and/or the metastases, demonstrated through repeated evaluations, performed at well-established time intervals [4]. The use of morphometric criteria (size, volume, number, and structure) for the evaluation of therapeutic efficiency is possible by all imaging procedures and it is known as the RECIST criteria (Response Evaluation Criteria in Solid Tumor) [4].

Classic chemotherapy drugs aim the destruction of the tumor cells which explains the use of the RECIST criteria. But tumor reduction does not always represent a proof of tumor annihilation. It is well known that isles of malignant cells may continue to exist in a latent state for many years and, in special conditions, these can multiply and become a tumor recurrence. The size criteria has a degree of relativity. When there is hemorrhage or inflammation within the tumor, an increase of the tumoral volume is observed that does not represent in fact a real evolution of the condition.

In the last years, several of the imaging procedures have known technological developments focused on functional application, tumoral biology and the angiogenesis processes. Functional imaging characterizes tumors by their metabolic intensity, which is actually based on the dynamics of their neovascularity. The identification and characterization of the capillary bed through various imaging techniques may represent diagnosis criteria in oncology. Dynamic CT, MRI and especially PET-CT studies have recognized performances, but present the disadvantage of being expensive and require radiation exposure [5,6].

Even though it is not a standard procedure, as it is non reproducible and operator dependent, US may replace, in certain situations and using specific applications, the more expensive, radiating techniques.

US presents both advantages and disadvantages. Among its advantages it is the capacity to characterize tumors. Masses are visualized separately due to their distinct acoustic impedance. The criteria used for their description are delineation (demarcation), echostructure (in direct relationship with their components), echogenicity (in relationship with the fluid or solid nature of the tumor), compliance (elasticity – which is evaluated with newly introduced techniques of color coded elastography). Other advantages of the method are its simplicity, the low cost efficiency ratio and the easy handling. The facile access to US makes this method available whenever it is necessary, with no restrictions related to space, time of the exploration, invasiveness or excessive costs. Ultrasonography combined with the usage of i.v. contrast agents (contrast-enhanced ultrasonography- CEUS) allows the description of the vascular pattern of masses, being used successfully in experimental studies regarding the efficiency of the newly developed antiangiogenic therapies [7].

US has a limited value in situations when the tumor is deeper located, has an infiltrative pattern, or when there are gas-containing or bone structures between the region of interest and the transducer. US is operator dependent and it is not recommend for the evaluation of tumor dynamics under treatment.

This paper aims to present the potential that US has in the characterization of the capillary bed in various situations, the relationship vascularity – neoplasia – inflammatory process as well as the place and role that US may have at this moment in oncology.

Morphofunctional features of microcirculation. Angiogenesis.

Normal circulatory bed. Normal organ vascularity may be systemized in a simple manner in feeding vessels (arteries) and evacuation vessels (veins). Between these there is an intermediate circulatory bed (capillaries) characterized by small caliber lumens consisting of single layer of endothelial cells. The essential nutritive exchanges that guarantee a normal life of the cells, from their genesis to their apoptosis, is realized by the capillary system. Capillary vessels have extremely thin walls that allow the passage of nutrients and oxygen by diffusion. Capillaries, organized as a network or circulatory bed, provide a huge access surface for the blood to the parenchymas, and thus guarantees a sufficient supply of nutrients and oxygen even to the last cell of the body. The distribution pattern of the capillaries is well-organized, having specific features depending on each organ. For example the capillary system of the liver has a sinusoidal pattern. Another example is represented by the renal parenchyma which consists of cortical and medullar structures with a different pattern of the capillary bed. The spatial distribution of the capillaries, correlated with a certain degree of specialization of the cells that comprise the parenchyma, represent the premise for the complex functions specific to each organ, liver, spleen, kidney, thyroid, etc.

Pathological circulatory bed. The onset of a pathological process must have vascular determinism and consequences. Therefore, an *inflammatory process* is characterized by the dilatation of the capillary bed and by a conservation of the number of vessels. In *acute inflammation* there are hemodynamic changes characterized by an increase of the blood velocity and debit, accompanied by a significant growth of the capillary bed volume. This process is self-limited, if the etiopathogenetic factor disappears, leading to a "deflation" of the capillary bed which turns back to normal. In *chronic inflammation*, which is characterized by the persistence of the causing factor, new blood vessels are developed, a process called angiogenesis; the density and distribution of these vessels is controlled by inflammation mediators [8]. A *chronic ischemic process* is initially characterized by a reduction of the capillary debit and caliber in an area that is more or less well-defined depending on whether or not the arterial feeding network is terminal or not. The process is accompanied by collateral arterial vessels development. A *necrotic parenchyma* does not contain a capillary bed any longer, but rather a more or less liquefied tissue, partially or completely replaced by fibrotic elements that represent the scar component of the region. A *benign tumor* has well-defined feeding vessels, with a spatial distribution that is relatively organized towards the cells. The vessels have the tendency to multiply which implicitly suggests a "quiet" parenchyma characterized by a normal cellular cycle and an organized spatial distribution of the consisting elements.

Tumor angiogenensis represents a process of vascular development and multiplication which aims to provide the necessary supply of oxygen and nutrients towards malignant masses [9]. Below 2 mm, the conglomerate of malignant cells feeds through diffusion. Above 2 mm, tumoral cells produce angiogenic mediators that stimulate the development of new vessels, using normal circulation neighboring the tumor as a starting point. New vessels have an accelerated multiplication rate and a chaotic development and thus realize a rich spatial structure, with a "tree-like" appearance, which penetrate into the tumoral mass and provide a large diffusion surface, in direct contact with the neoplastic cells [9,10]. A *malignant tumor* therefore has numerous feeding vessels that originate from normal vascular structures; these have no precapillary sphincter and thus provide an increased blood flow into the neoplastic territory. The spatial distribution of the new tumoral vessels is anarchic, very different from the organized pattern of the normal vascularity, and the vascular density is inhomogeneous [11].

The angiogenesis process has become a central topic in oncology once molecules that mediate this process, like the vascular endothelial growth factor (VEGF), as well as several inhibitors with therapeutic potential, were identified [12].

An imaging description of the tumoral vessels, which are structurally and functionally different from normal vessels, presents a diagnosis value and allows the assessment of the neoangiogenetic therapy efficiency [13,14].

Doppler Ultrasonography (DUS). DUS detects blood flow at velocities as low as 2 cm/s, grants the color coding of the flow ("color flow map" technique – CFM) and the measurement of the flow velocities and of the debits in vessels wider than 100 microns, being also useful in exploring angiogenesis [15].

Within the limits of the spatial and temporal resolution of the present equipments, DUS allows the characterization of the capillary bed. Therefore, the *normal circulatory bed* consists of thin-walled vessels which radiate from the organ hilum towards the capsule. This pattern is more obvious in large organs like the liver or spleen. Organs like the kidney, the thyroid gland or the testicle have a different appearance of their normal vascularity, which is also characteristic and easy to identify and describe. *The inflammatory capillary bed* is not as simple to demonstrate with DUS due to the reduced sensitivity of the method to low velocity flows.

In tumoral pathology, DUS can identify flow patterns specific to benign (focal nodular hyperplasia) and malignant tumors, the "basket" vascular pattern being characteristic to hepatocarcinoma (HCC). Studies performed on various types of tumors (for example skin melanoma)

have demonstrated that DUS can accurately identify the neoangiogenesis process and may establish prognosis criteria for the recurrence potential of aggressive tumors [16,17].

DUS has limitations, among which is its inability to identify the slow blood flow characteristic to capillary microcirculation. The "power mode" application might overcome this limitation, but it is excessively sensitive and nondiscriminatory with other types of movement like tissue vibration or organ movement neighboring tumors. All Doppler procedures have the disadvantage of variability from one examination to another, both inter and intraobserver. Even more, acquiring a Doppler signal from a single target vessel is difficult when a tumor has numerous feeding pedicles with a sinuous spatial trajectory. Spectral ultrasonography is concerned with the insonation angle that must be lower than 60° from the axis of the vessel. There is a significant number of parameters that must be identical upon each examination: the wall filter, color gain, scan frequency, for a good reproducibility of the method [18].

The advantages of DUS must also be regarded. The method is widely available as the vast majority of commercial equipments are supplied with the Doppler mode. In general, tumoral and inflammatory vessels have higher flow velocities, which make them more "visible" upon the CFM interrogation. The DUS allows an evaluation of larger anatomical areas which are crossed by multiple vessels. There are ways to quantify the acquired information and this makes the method reproducible. For the spectral application these parameters are: the flow velocity at a given moment, the relative blood volume, and the relative blood debit [19]. For the color coded application an additional parameter is represented by the number of pixels in a well-established region of interest. Once these data are introduced in a data base this enables the evaluation of the chemotherapy efficiency in different types of tumors [20]. A video recording of the images, an electronic marking of tumor delineation and the percentage calculation of the number of color pixels reported to the total number of pixels found in the region of interest (called "vascularity index") represents a similar technique with that of digital assessment of microvascular density by immunohistochemy [21]. The color coded Doppler techniques allow the formulation of mathematical models that illustrate the features of intratumoral blood flow [22].

Harmonic and i.v. contrast ultrasonograph. Harmonic ultrasonography, which has developed in the last decade, uses wide band transducers that have the ability to produce multiple frequency ultrasound fascicles. The echoes reception is similar to that of the classical probes,

but it can be selective, focused either on all echoes either only on the harmonic ones. The harmonic echoes are whole multiples or fractions of the fundamental echoes. They may be produced by the tissues (THI technique) or by the contrast agents [23]. The combination of harmonic US with CEUS represents an important progress for US.

Contrast agents (CA) are extemporaneous prepared fluids, made of gas microbubbles, enveloped in a rigid or elastic membrane. Their main effect on the US image is represented by and important increase of the signal to noise ratio, with values that can reach at 20 – 25 dB. There two types of contrast agents:

– I[st] generation contrast agents (ex. Levovist, Schering, Germany) have a limited circulatory stability. They are used in association with the "destructive" examination technique that is based on the breaking of the microbubbles within the large vessels, the microcirculation or the reticuloendothelial system by a high acoustic power US beam. This method has a proved value in detecting liver metastases [24,25], but it is limited by the reduced circulatory stability of the CA which shortens the exploration and has limited accuracy as far as the microcirculation is concerned.

– IInd generation contrast agents (Sonovue, Bracco, Italia; Luminity, Lantheus; Optison, GE Healthcare, USA; Sonazoid®; Daiichi- Sankyo, Tokyo, Japan) have longer circulatory stability, up to several minutes. These are the molecules used in the present (table I).

The microbubbles have very small sizes, 2-8 microns, which generate harmonic echoes when passing through a low mechanical index (0.09 – 0.11) ultrasound field. The large range of microbubbles dimensions makes them detectable with 3.5 to 7 MHz transducers which enables the visualization of both superficial and deep anatomical structures of the human body.

The use of CA allows the assessment of the capillary microcirculation, where the vessels have very small diameters, as little as 40 microns. The spatial resolution of CEUS is 0.2 – 2 mm [26]. At the level of the capillary bed the flow velocities are very slow, even presenting moments of stagnation. Even in such situations the visualization of the blood stream is possible with the aid of CEUS. The contrast agents used in ultrasonography have an angiospecific nature as they do not pass into the interstitial tissue, thus representing a vascular marker useful for microcirculation evaluation in normal and pathological conditions [27].

The CEUS exam consists of a CA injection into a cubital vein succeeded by a continuous observation of the ultrasonographic image beginning when the first echoes appear in the region of interest and ending when these are completely disappeared. It   is recommended to use a double screen, consisting of two "real time" images, a grey scale one and a harmonic one. The mechanical index is set at a value between 0.09 and 0.11. A single focus will be used and it will be placed under the region of interest. The CEUS exam focuses on a single lesion which will be continuously examined for several minutes. Each time additional information are required a new contrast injection is needed. In a similar way, another injection is necessary when a different lesion, from a different topographic site, must be examined.

A CEUS examination, performed over a period of 60 – 90 seconds, allows the characterization of the transition dynamics of the CA into an area, starting with the entrance of the CA into the capillary bed ("wash in") and ending with the complete exit of the CA ("wash out"). The transition pattern of the CA through the region of interest may be analyzed based on several parameters. Therefore, the transition dynamics of the CA through the region of interest is divided into "phases" which are directly connected with the initial, arterial, moment and the final, venous, moment. The arterial phase is illustrated by an abrupt increase of echogenicity (fig 1a,b).

The arterial phase is followed by an intermediate phase, corresponding to the enhancement of the capillary bed, which is one of the major objectives of the exploration [28] (fig 1c). In the end there is a CA "wash-out" from the region of interest that is actually the final phase (fig 1d).

Table I. IInd generation contrast agents used in harmonic ultrasonography. Characterization and importance for clinical practice.

| Characteristic	Consequences
Size of microbubbles: 2-8 microns	Pass through the pulmonary capillary barrier They present repeated recirculations between pulmonary and systemic circulation
Elastic outer membrane	Non-linear vibration. It generates harmonic echoes in the case of an exposure to an ultrasound field with low acoustic power (0.009 – 0.11)
Gas content	Increased acoustic impedance with up to 25 dB. Blood stream visibility.
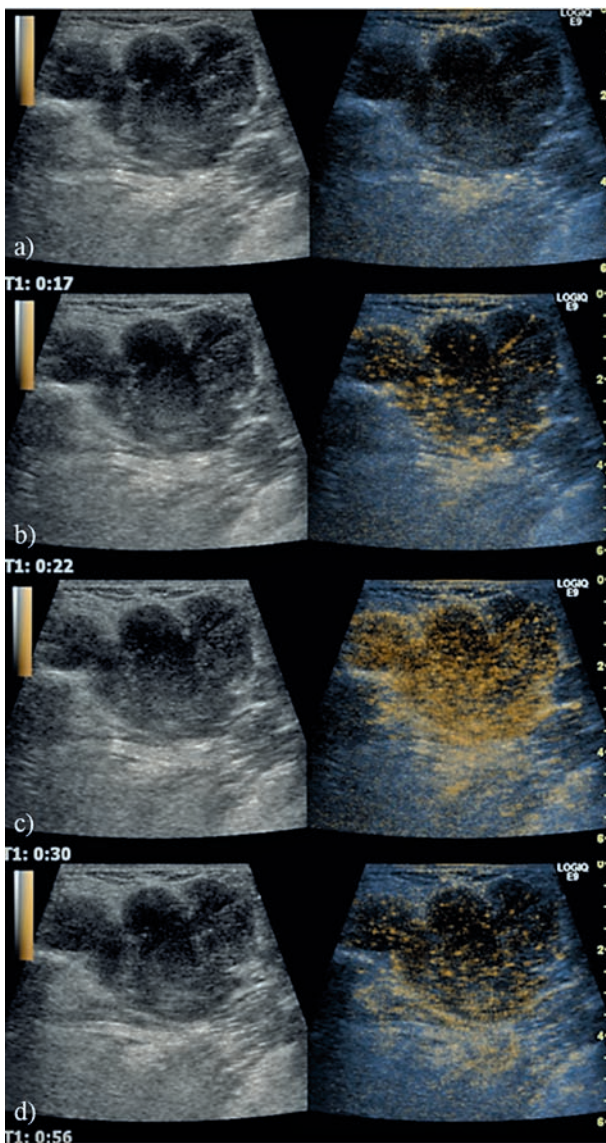
Fig 1. Lymph node, CEUS examination. a) Dual mode image showing the 2D ultrasound aspect on the left and the harmonic image with a low mechanical index on the right; b) arterial phase (22 seconds). The onset of the CA entrance within the region of interest is visualized; c) arterial phase (30 seconds). The up-take of the circulatory bed with CA is complete; d) delayed, venous phase. The echoes are significantly reduced within the region of interest. This aspect corresponds to a delayed venous phase when the circulatory bed is washed out.

Table II. Normal circulatory bed, CEUS aspect.

Homogeneous, progressive arterial up-take.
"Tree-like", uniform spatial distribution.
Persistent aspect depending on the parenchyma.
Uniform, delayed wash-out.

The phases that were mentioned are characteristic to the vast majority of the organs (table II).

The liver presents certain characteristics due to its double vascularity: arterial (originating from the abdominal aorta through the celiac trunk) and venous through the portal system. Because of this, there is an additional phase of vascular input (usually between 30 and 120 seconds from the moment of CA injection) immediately following the arterial phase (which is usually between 10-30 seconds after the moment of CA injection into the cubital vein). The amplitude of the capillary bed is correlated with a plateau of the echogenicity that lasts longer or shorter depending on the organ. In the case of the liver and spleen this plateau lasts longer and is conditioned by the blood accumulation at the level of the sinusoids (in the case of the liver) as well as the reticulo-endothelial system (both spleen and liver). The kidney also has blood flow particularities determined by its individual histological structure.

An analysis of the capillary bed transition with the purpose of characterizing it can be done in a qualitative or quantitative manner. For the qualitative analysis the following items are observed:

a) appearance of the arterial phase (conditioned by the heart activity as well as the distance between the vein where the CA is administered and the examined organ);

b) celerity and length of the arterial phase (conditioned by the compliance of the capillary bed)

c) spatial distribution of the CA within the region of interest and the course of penetration in the ROI (in relation with the number of arterial feeding vessels as well as their spatial distribution) (fig 2-5);

d) the up-take pattern (homogeneous or inhomogeneous, in relation with the permeability of the capillary bed) (fig 6);

e) the moment and the speed of CA wash-out (in relation with the presence of arterial-venous communications that may define the malignant nature of the region of interest) (fig 7).

The primary digital data extracted from the US machine ("raw data"; obtained before the DICOM compression of the information) or the final data, extracted from the hard disk of the equipment and displayed on the screen, are use for the quantitative analysis. This is based on the graphic representation of the variation in time of the CA "marked" blood stream echogenicity. This representation is called the "time-intensity curve" (TIC). The TIC analysis has a maximum accuracy when the region of interest is completely static. In practice, there are very few situations when the lesion respects this condition, in most cases there is some movement induced by the patient's breathing (especially in abdominal organs). There are soft-
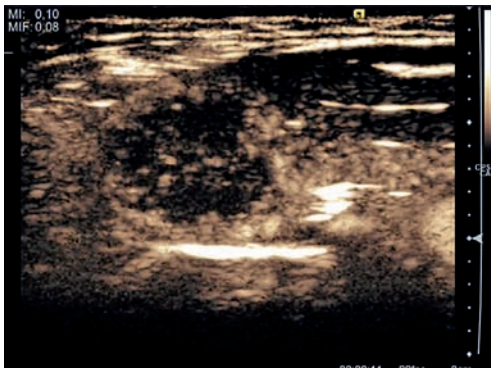
Fig 2. Tumoral lymph node. Inhomogeneous up-take in the region of interest, with areas of lack of signal which correspond to areas of necrosis.
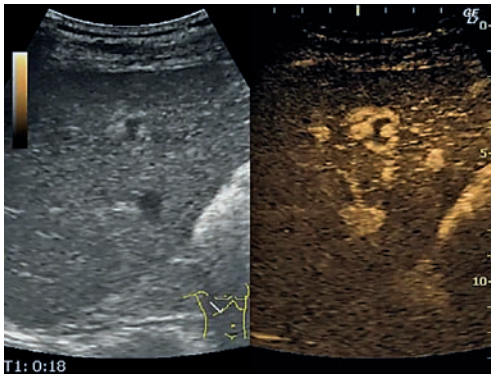

Fig 3. Liver hemangioma. The CA up-take is progressive, from periphery towards the centre of the lesion.
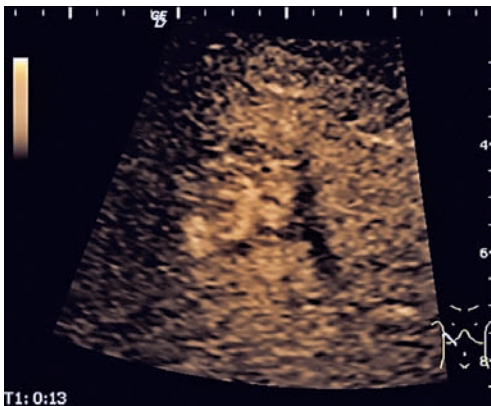

Fig 4. Focal nodular hyperplasia of the liver. A "spoke-wheel" pattern of the CA distribution is noted.

Fig 5. Hepatocellular carcinoma. The spatial distribution of the vessels within the tumor has a "tree-like", chaotic, disorganized pattern. Multiple feeding pedicles are also observed.
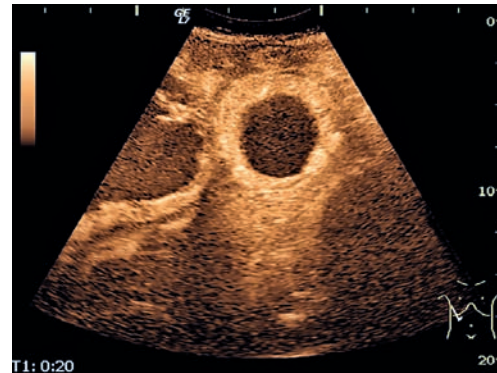

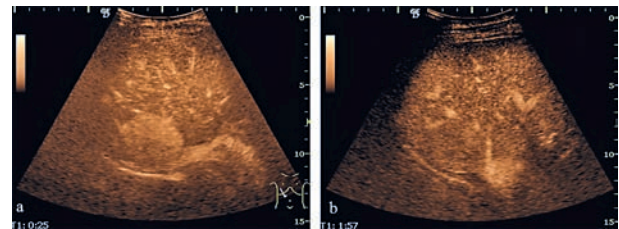**Fig 6.** Liver metastasis with central necrosis.

Fig 7. Hepatocellular carcinoma. A complete and accelerated up-take is registered during the arterial phase (a) and a CA wash-out during the delayed portal venous phase (b).

wares that produce a "mediation" of the echoes variability in time and tumor movement [29]. The TIC analysis must also consider the way the CA was administered. Therefore, when there was a "bolus" injection the changes observed on the screen are continuously registered, starting with the moment of CA injection for a period of 5 minutes or until the CA disappears from the blood flow. When the CA is administered through an IV infusion, a uniform enhancement of the capillary bed with microbubbles is observed. The quantification begins the moment the echoes appear, which is considered the "zero" moment of the CA entering the capillary bed. This second procedure is more accurate in defining the circulatory features and allows repeating the measurements centered on the same or on different regions of interest. It has the disadvantage that it is more time consuming and more sophisticated as it requires the use of special pumps as infusers [30].

TIC interpretation may have a global or a detailed nature. The global analysis shows in a more objective manner than the eye of the examiner the CA's way of transition through the ROI.

The detailed analysis consists of an evaluation of the mathematical parameters connected with the echoes vectorial representation at a certain moment. There are several mathematical models, all of them having the CA's echogenicity in the blood stream as their source of information. These information and the mathematical models are statistically analyzed and they represent a useful data regarding the capillary bed (the maximum intensity of the signal from the contrast curve, called "peak intensity", and the area under the curve – AUC) or the circulatory debit in that area (the period of time from moment 0 to maximum intensity – "time to peak" – TTP; the enhancement time of the circulatory bed – "wash in time" – WIT – representing the time from the 5% moment to 95 % enhancement; the "wash-out" time of the circulatory bed – WOT – representing the time between the systolic peak to the complete CA exit from the ROI); the mean transition time of the region of interest – MTT) [31].

The way the CA passes through the circulatory bed and the spatial distribution of the vessels in the region of interest are organized in "models" that are directly connected with their nature. In the case of malignant tumors there is an early and abrupt entrance of the CA in the circulatory bed followed by an exit of the CA from the region of interest at the end of the arterial phase or at the beginning of the venous phase (fig 8).

This process is explained by the existence of arteriovenous communications. The "wash-out" process from the circulatory bed can be a measure of the degree of cellular differentiation and implicitly of tumor aggressive [32]. In highly differentiated tumors the "wash-out"
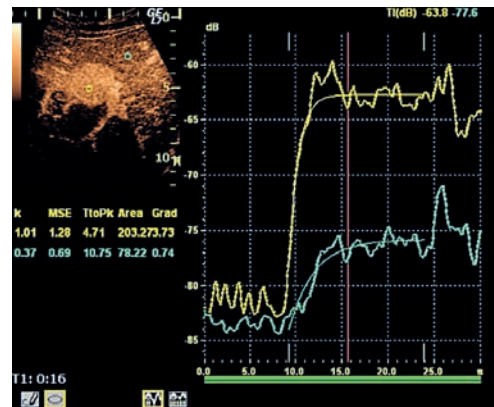

Fig 8. Hepatocellular carcinoma. The examination of the TIC shows a quick enhancement of the tumor during the arterial phase (yellow) compared with the normal liver parenchyma (green).
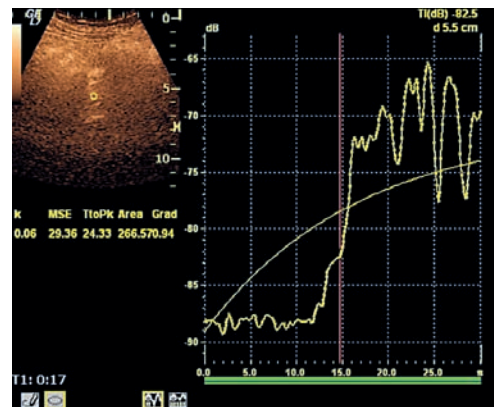

Fig 9. Colon polyp. The examination of the TIC confirms the suspicion of a vascular tumor based on the accelerated arterial up-take.

may be delayed or even absent. The use of the CEUS parameters in evaluating neoangiogenesis was validated by experimental studies and in clinical practice in hepatocarcinoma, ovarian and breast tumors [33-35]. The quantification of the blood perfusion using the contrast curves allows an assessment of the antiangiogenetic therapy validity; in the present the effect of the antiangiogenetic molecules is done indirectly through morphometric measurements that reflect tumoral growth inhibition. In that regard, the first experimental studies were performed by comparing CEUS curves with immunohistochemichal studies which evaluate vascular density using high-resolution microscopy. The conclusion was that the response to antiangiogenetic therapy can be evaluated using the CEUS curves parameters [7,36]. Clinical studies under development propose the following protocol: a CEUS examination before treatment, followed
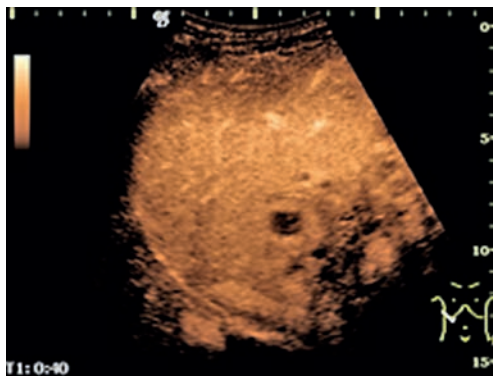
Fig 10. Liver abscess. An exaggerated echogenicity of the liver parenchyma that surrounds the collection is noted, suggesting parenchyma congestion.
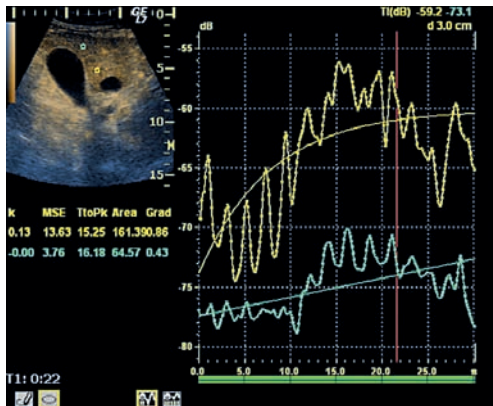

Fig 11. Liver abscess. The analysis of the TIC shows an important enhancement of the liver parenchyma that surrounds the lesion, suggesting congestion.

by subsequent exams at 7 days, 14 days and 2 months after treatment onset. Using the CEUS quantification of tumor perfusion variations under antiangiogenetic treatment, the potential response to therapy can be assessed earlier [37]. In *benign tumors*, the CA up-take is moderate during the arterial phase, while the wash-out is moderate or absent (fig 9).

In *ischemic conditions* the arterial enhancement is moderate, in discrepancy with the behavior of the neighboring parenchyma when this has normal vascularity. The wash-out is also moderate, depending on the enhancement as well as on the magnitude of the collateral circulation. In *necrosis* there is no enhancement during the arterial phase and therefore there is no wash-out in the venous phase. In *inflammatory processes* there is a diffuse enhancement of the circulatory bed without a clear delineation from the normal parenchyma (fig 10, fig 11).

During the venous phase there is moderate, slow wash-out (table III).

CEUS applications. The method is considered valid in numerous conditions. The first in this category is the characterization of the liver tumors [38], where CEUS has increased diagnosis accuracy when compared with CT and MRI [39]. When the method is combined with the quantification procedure it is also useful in the evaluation of liver tumors undergoing chemotherapy [37]. In last years the range of applications has increased greatly [40]. Solid and cystic focal pancreatic lesions can thus be differentiated based on the circulatory pattern [41-43] (fig 12).

Table III. Pathological circulatory bed. CEUS up-take models in conditions with vascular expression.

| Pathology	Arterial phase	Venous phase	Spatial characteristics of the circulatory bed	Observations
Malignant tumors	Increased up-take	Increased wash-out	Disorganized, with areas of unequal irrigation. The up-take is realized through several vascular pedicles.	CA wash-out may be variable depending on the tumor differentiation degree.
Benign tumors	Moderate or increased up take	Slow or absent wash-out	Organized. The up-take is realized through a single feeding pedicle. Intratumoral vessels have a "tree-like" appearance. There is clear delineation or a capsule around the circulatory bed.	
Inflammation	Increased up take	Slow or absent wash-out	Organized. Diffuse up-take. There is no vascular pedicle and no capsule around the circulatory bed.	
Ischemia	Slow or absent up-take	Slow or absent wash-out	Inhomogeneous	
Necrosis	No up take	No wash-out	Irregular delineation through vascularized tissue.	
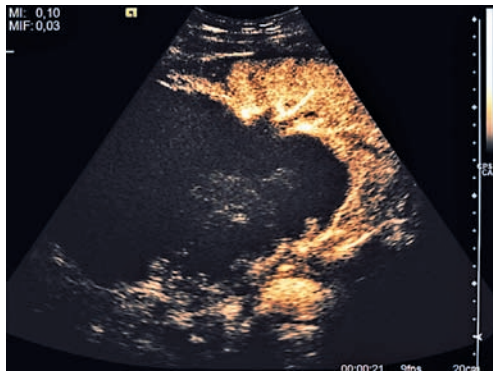
Fig 12. Pancreatic pseudocyst. A clear delineation is observed between the necrotic tissues and the normally vascularized surrounding tissue.

Table IV. Limitations of the CEUS exploration

1. Dependent a good-quality 2D ultrasonographic image
2. Deep located lesions
3. Centered on a single lesion
4. Equipment and operator-dependent
5. Increases the cost of the US exploration.

The effect of chemotherapy on pancreatic adenocarcinoma may be assessed with a higher accuracy using this technique [44]. In traumatic and tumoral pathology of the spleen CEUS also shows increased performances [45]. There is a clinically useful application in the area of renal ischemia, a situation when contrast-enhanced CT is contraindicated [46]. The method is also useful in abdominal trauma [47], in detecting blood leaks in ruptured aneurysms [48], in identifying vascular complications after liver transplantation [49], in revealing the necrotic tissue in acute necrotic pancreatitis [50]. There are also encouraging results in the evaluation of the parietal inflammatory process accompanying bowel inflammatory diseases [51] as well as in rheumatic conditions [52].

CEUS limitations. One of the most significant limits of CEUS is represented by the unifocal nature of the examination, a continuous exploration, centered on a single lesion, being absolutely necessary in order to obtain maximum information. More than that, the equipment used for CEUS must be dedicated to non linear harmonic examinations. Other aspects that must be considered are the relatively high cost of the contrast agent and the operator-dependent character of the procedure [31] (table IV).

Conclusions

The ultrasound examination of the blood vessels is based on the Doppler and CA harmonic techniques. CEUS is therefore the recommended procedure to characterize a capillary bed. The method is based on the identification of the harmonic echoes generated by the gas microbubbles that were exposed to low acoustic power ultrasounds. The acquired information is accurate and allows for the appreciation of the CA transition dynamics through the region of interest. The features CA passage through a ROI permits the definition of the health or altered status of that particular area. The method has both qualitative and quantitative attributes. The performances of contrast-enhanced ultrasonography will be optimized in the future once the matrix 3D transducers will be introduced. The technique allows the assessment of oncologic treatment efficiency using contrast curves which are a way to objectify the procedure. Extensions of this method are expected in the future in the field of targeted chemotherapy. All these data represent arguments for its systematic use in oncology, in various applications, with performances similar to those of CT or MRI.

Conflict of interest: none

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