Thieme

The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Short Version)

Die EFSUMB-Leitlinien und Empfehlungen für den klinischen Einsatz des kontrastverstärkten Ultraschalls (CEUS) bei nicht-hepatischen Anwendungen: Update 2017 (Kurzversion)

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ABSTRACT

The updated version of the EFSUMB guidelines on the application of non-hepatic contrast-enhanced ultrasound (CEUS) deals with the use of microbubble ultrasound contrast outside the liver in the many established and emerging applications.

ZUSAMMENFASSUNG

Die aktualisierte Version der EFSUMB-Leitlinien für die Anwendung von nicht-hepatischem kontrastverstärktem Ultraschall (CEUS) befasst sich mit der Verwendung von Mikrobläschen Ultraschall-Kontrastmitteln außerhalb der Leber in zahlreichen etablierten und neu entstehenden Einsatzbereichen.

Introduction and general considerations

Previous contrast-enhanced ultrasound (CEUS) documents from the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) encompassing hepatic and non-hepatic applications have been published with a statement on CEUS use in pediatric applications. The present document reflects the current applications in non-hepatic CEUS and updates the previous EFSUMB guidelines published in 2012. The EFSUMB guidelines on CEUS are intended to inform clinical practice rather than to report on research projects. Thus, they are a digest of current findings, formulated by a group of experts and are primarily based on surveys of the published peer-reviewed literature (so that abstracts and conference proceedings are excluded). Levels of evidence (LoE) and grade of recommendation (GoR) are formulated and presented to the reader to enable comprehensive understanding of the current clinical status of each CEUS application and based on the criteria used as in previous EFSUMB guidelines; levels of evidence and grades of recommendations are assigned according to the Oxford Centre for Evidence-based Medicine criteria (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). A consensus opinion was established by vote as follows: strong consensus (> 95 %), broad consensus (75 – 95 %), with approval, disapproval or abstaining from each participant. It is important to consider that nearly all applications contained in the current guidelines are "off-label" and are likely to remain so for some time. This does not present an impediment to the use of ultrasound contrast agents (UCAs) when applied outside licensing, a topic detailed in an accompanying article to previous guidelines. Indeed the EFSUMB guidelines provide the evidence to incorporate UCAs into clinical practice despite being "off-label", influencing regulatory authorities to sanction use as recently demonstrated by the Food and Drug Administration of the United States of America approval of UCAs in pediatric practice.

In general, CEUS is most useful where an abnormality can be displayed on B-mode ultrasound (US), and the better the quality of the B-mode imaging, the better the quality of the CEUS images. Importantly, CEUS is always used as an extension of conventional US (B-mode and color Doppler). Contrast studies should always be interpreted in the context of the overall clinical picture, other imaging and laboratory tests.

Overall, UCAs are mainly used as vascular agents following intravenous injection and they highlight the macro- and microvascular systems. However, they can also be instilled into body cavities, both normal and pathological. Instillation into the urinary bladder for vesicoureteral reflux is a classic example. Other examples include instillation into drainage catheters to define their position, the extent of the cavity and its continuity. Intradermal injection is used as a form of lymphangiography, with the UCA being spontaneously taken up into the lymphatics as an extension of their normal particle trapping activity. It is used to highlight sentinel lymph nodes, chiefly in breast cancer.

Investigator training

One of the central strategies of EFSUMB is to ensure high-quality US education and sustain excellent professional standards in CEUS training and practice. Previously, EFSUMB defined three levels of training requirements in a minimal training standards document, with specific reference to CEUS in Appendix 14. EFSUMB recommends that CEUS should be performed by operators that have achieved competence Level 1, as it has been recognized that the diagnostic performance of CEUS is dependent on the observer's level of experience. Accordingly, appropriate training and education is strongly advised for every investigator who performs CEUS examinations. Furthermore, investigators should ensure that their US scanning machine is optimized for CEUS acquisition and the post-processing of data. The operator must gain sufficient knowledge of indications and contraindications of CEUS and training in

ultrasound contrast agent administration and perform CEUS within the medico-legal framework of each individual country.

RECOMMENDATION 1

The operator must gain sufficient knowledge and training in CEUS, ultrasound contrast agent administration and contraindications, and perform the examination within the medico-legal framework of each individual country (LoE 5, GoR C). Strong consensus (20/0/0, 100 %)

Terminology

Equipment

Ultrasound equipment based on contrast-specific ultrasound modes is needed for CEUS examinations, based on the separation between non-linear response induced by microbubble UCA oscillations and linear US signal reflected by tissues. In order to decrease the non-linear harmonic US signals generated by the tissues themselves, a low acoustic pressure is generally used, based on a low mechanical index (MI). Generally, a low MI examination is typically considered below 0.3 in order to minimize microbubble disruption, but also reduce tissue harmonics and artifacts. Nevertheless, most of the US systems are able to perform CEUS examinations with lower values of the MI, even 0.08 or 0.05, and MI values vary with the different US manufacturers.

Terminology

Ultrasound contrast agents are used for enhancement of the US signal from flowing blood as they are limited to the blood vessels (blood pool UCA). They were initially developed to enhance the Doppler US signals, based on higher MI techniques as opposed to the currently widely applied low MI specific modes. During high MI Doppler modes, injection of a UCA as a bolus produces "blooming", due to flash or movement artifacts, which are not visible using specific harmonic imaging modes. The CEUS acronym has been introduced by EFSUMB and is generally accepted as the official term describing contrast enhanced ultrasonography techniques. Low MI techniques are preferred to the high MI techniques based on Doppler or power Doppler modes. Most of the ultrasound systems have a dual split-screen display setting, with the low MI CEUS image shown alongside a conventional B-mode image. In the CEUS window, only a few signals from intensely reflective structures (e. g. calcifications or interfaces that produce large differences in acoustic impedance) should be seen, dependent on the settings of the MI and gain. Modes with a single screen display can also be used, where the CEUS image is displayed as a color overlay on the conventional B-mode image.

Each examined lesion should be described in terms of enhancement, taking into account the temporal behavior, degree of enhancement as compared with the surrounding tissues (non-enhanced, hypo-enhanced, iso-enhanced or hyper-enhanced), as well as the contrast distribution (homogeneity or heterogeneity).

Two phases are described for most organs that have a single arterial blood supply (except the liver and lungs):

a) the arterial phase starts from around 10 – 20 seconds until around 35 – 40 seconds after contrast injection, showing a progressive degree of enhancement;
b) the venous phase starts from around 30 to 45 seconds after contrast injection, showing a plateau and then a progressive decrease.

Safety

UCAs are administered safely in various applications with minimal risk to patients. They are not excreted through the kidneys, and can be safely administered to patients with renal insufficiency with no risk of contrast-related nephropathy or nephrogenic systemic fibrosis. There is no need for blood tests prior to UCA injection, and there is no evidence of any effect on thyroid function, as UCAs do not contain iodine. UCAs have a very low rate of anaphylactoid reactions (1:7000 patients, 0.014 %), significantly lower than the rate with iodinated state-of-the–art CT agents (35 – 95:100 000 patients, 0.035 – 0.095 %), comparable to the rate of severe anaphylactoid reactions associated with gadolinium-based contrast agents at 0.001 – 0.01 %. Serious anaphylactoid reactions to UCAs are observed in approximately 1:10 000 exposures.

Data from 75 completed studies (pooled data from 6307 patients) in North America, Europe, and Asia showed that the most frequent adverse events were headache (2.1 %), nausea (0.9 %), chest pain (0.8 %) and chest discomfort (0.5 %). All other adverse events occurred at a frequency of < 0.5 %. Most adverse events were mild and resolved spontaneously within a short time without sequelae. In most cases allergy-like events and hypotension occurred within a few minutes following the injection of the UCA. The overall reported rate of fatalities attributed to one UCA, SonoVue™ (Bracco, Milan), is low (14/2447 083 exposed patients; 0.0006 %) and compares favorably with the risk for fatal events reported for iodinated contrast agents (approximately 0.001 %). In all reported fatalities after use of a UCA, in both cardiac and non-cardiac cases, an underlying patient medical circumstance played a major role in the fatal outcome. The intravesical administration of UCAs has been evaluated in a total of 7082 children described in 15 studies and in a European survey of 4131 children with 0.8 % reported adverse events, mostly related to bladder catheterization.

Contrast-enhanced ultrasound is also used off-label in the pediatric population, and in renal assessment, and in numerous other documented areas. The Food and Drug Administration (FDA) in the United States of America (USA) recently approved the use of Lumason™ (marketed as SonoVue™ Bracco, Milan, outside the USA) for pediatric liver imaging, which is an important development for pediatric imaging. A significant reduction of ionizing radiation exposure can be achieved in many areas by using CEUS in pediatric patients.

RECOMMENDATION 2

Intravenous CEUS use is safe and effective in both adult and pediatric populations (LoE 2a, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 3

Intracavitary use of ultrasound contrast agents is safe (LoE 1b, GoR B). Strong consensus (20/0/0, 100 %)

Genitourinary

Bladder

Background

Noninvasive diagnostic imaging may play a role in urinary bladder tumors, but cannot replace cystoscopy and pathologic staging. The depth of wall invasion, the histological grade and the extension outside the bladder are main factors determining prognosis and therapeutic approach.

Study procedure

Optimal bladder filling (approximately 2/3 of the total bladder volume) is critical. Insufficient filling prevents lesion detection, while excessive distension results in bladder wall thinning and reduced conspicuity of the wall layer, making it difficult to differentiate a superficial from an infiltrating lesion. The layers of the bladder wall can be differentiated after UCA administration; the mucosa, and particularly the submucosal layer, exhibit early and intense enhancement that persists for 1 – 2 minutes, whereas the muscular layer has lesser and delayed enhancement.

Image interpretation

Characterization of mural lesions

CEUS improves the differential diagnosis of intraluminal lesions, allowing the detection of tumors, which are vascularized and enhance, in contrast to non-enhancing hematomas. In 35 patients with cystoscopy and biopsy as the reference standard, CEUS correctly assessed tumor presence or absence in 88 % of cases.

Bladder tumor staging

CEUS is superior to conventional B-mode US for identifying infiltration of the muscle layer, but magnetic resonance (MR) and computed tomography (CT) imaging are essential for the local staging of bladder tumors. The ability to predict tumor grading based on the pattern of CEUS enhancement remains under evaluation.

Limitations

In patients with anatomical circumstances leading to poor urinary bladder visualization, CEUS cannot always provide the desired information. Similar to MR and CT imaging of bladder tumor detection, an important limitation of CEUS is the difficulty in identifying both small (< 1 cm) lesions and large flat, plaque-like tumors. Tumor position can affect the quality of CEUS depiction and the accuracy of staging. Tumors in the anterior portion of the bladder dome are sometimes difficult to visualize. Columnar hypertrophy of the bladder wall and prostatic hypertrophy can hide or mimic urothelial polypoid projections. Benign tumors and focal cystitis are other uncommon conditions that present with focal bladder wall enhancement and can mimic a malignant lesion. CEUS is unable to provide a panoramic bladder view, as in the case of CT and MR imaging.

RECOMMENDATION 4

The most useful application of CEUS is the differential diagnosis of bladder cancer from hematoma in patients with hematuria when the diagnosis is equivocal on conventional B-mode and Doppler US (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

Kidney

Background

Ultrasound is the preferred imaging modality in patients with known or suspected renal disease for assessing renal size, detecting focal lesions and obstruction of the collecting system and for identifying vascular disorders but it cannot definitively distinguish between benign and malignant lesions. Doppler US helps to characterize renal blood flow, with limitations of attenuation, low sensitivity for very slow blood flow, and angle dependency.

Study procedure

The kidneys enhance rapidly and intensely after UCA administration, with potential to assess both the macro- and the microvasculature, the former immediately after UCA arrival. The arterial pedicle and main branches enhance first, followed rapidly by the segmental, interlobar, arcuate and interlobular arteries and then complete cortical enhancement. Medullary enhancement follows, with the outer medulla enhancing first, followed by gradual fill-in of the pyramids. As UCAs are not excreted by the kidneys, there is no UCA in the renal collecting system. With CEUS only two enhancement phases occur: a cortical phase, 15 – 30 s after UCA administration with cortical enhancement seen, and a parenchymal phase, where both cortex enhancement and medulla enhancement occur 25s – 4mins after UCA administration. There is normally excellent depiction of renal perfusion throughout the kidney, superior to Doppler US. Contrast enhancement is reported to be less intense and fades earlier in patients with chronic renal disease.

Renal Ischemia

Excellent diagnostic performance of CEUS in the detection of renal parenchymal ischemia, similar to that of CT imaging and superior to color Doppler US has been reported. Infarcts appear as wedge-shaped non-enhancing areas within an otherwise enhanced kidney. The excellent spatial resolution of CEUS allows clear differentiation between renal infarction and cortical necrosis, which appears as non-enhancing cortical areas with preserved hilar vascularity. Differentiation between hypo-perfused and non-perfused areas is clear following UCA administration; only infarcted areas completely lack contrast enhancement.

Renal Focal Lesions

Differential diagnosis between solid renal masses and pseudotumors

CEUS is used to differentiate between renal tumors and mimicking anatomical variations not characterized with B-mode and conventional Doppler US. Pseudotumors have the same enhancing characteristics as the surrounding parenchyma in all phases, while the enhancement in renal tumors in the majority of cases differs from the surrounding parenchyma, with a difference in the degree or distribution of enhancement in at least one vascular phase. Renal tumors, however, do not show specific perfusion patterns. Virtually iso-enhancing tumors in all vascular phases are encountered in up to 5 % of solid renal lesions. A normal perfusion pattern on CEUS is a major criterion for the differential diagnosis between an iso-enhancing renal lesion and a pseudotumor. A pseudotumor demonstrates the vascular architecture of normal renal parenchyma, displayed during the early arterial phase, with branching from the hilum to the periphery without disruption of vessels or aberrant vessels.

Characterization of complex cystic renal masses

CEUS is appropriate in the Bosniak classification of renal cysts and is suggested to be superior to CT imaging for detecting additional septa, thickening of the wall or septa, and solid components. CEUS allows the characterization of renal cystic lesions as benign or malignant with at least the same accuracy as CT imaging, but CT remains the reference method for staging patients with malignant cystic lesions. CEUS is well suited for the follow-up of non-surgical complex cystic lesions and has potential to replace CT. The absence of ionizing radiation is advantageous. The presence of lesion calcification hampers CEUS evaluation of complex cysts masses.

Characterization of indeterminate renal masses

In clinical practice, most abdominal CT imaging studies are not performed with a specific renal protocol to characterize renal lesions, frequently indeterminate renal lesions are identified. Follow-up US assessment should be comprehensive, including CEUS, to obviate an unnecessary correctly protocoled repeat CT study. B-mode US can determine the presence of a simple benign cyst. CEUS is more sensitive than CT for detecting blood flow in hypovascularized lesions and can be used to distinguish between complex cysts and solid lesions, particularly those which remain unresolved after CT imaging, B-mode and color Doppler US.

Renal infections

The diagnosis of acute uncomplicated pyelonephritis is based on clinical examination and laboratory findings. Conventional B-mode US is used to exclude urinary obstruction and renal calculi. Additional investigations should be considered if the patient remains febrile following 72 hours of treatment. In these patients, with complicated pyelonephritis, CEUS is effective in identifying inflammatory involvement, characterized by round or wedge-shaped hypovascular parenchymal areas, most conspicuous during the parenchymal late phase. An abscess is manifested as a non-enhancing area, with or without rim or septal enhancement, solitary or within areas of pyelonephritis. CEUS can be used to monitor the resolution of abscesses, which can be prolonged, even with clinical improvement.

Evaluation of solid renal lesions

A number of studies have attempted to evaluate the differentiation of renal tumors, particularly angiomyolipoma and renal cell carcinoma, by means of different features of time-intensity curves after UCA administration. The majority of angiomyolipomas are reliably differentiated with CT or MR imaging and although results are promising with CEUS, overlap with both qualitative and quantitative analyses with different tumors is evident. In expert hands, CEUS may help identify renal vein invasion by cancer, as the arterial vascularization of the thrombus may differentiate bland thrombus (non-enhancing) from tumor invasion (enhancing thrombus).

RECOMMENDATION 5

CEUS can be used to diagnose ischemic renal disorders, such as infarction (LoE 1b, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 6

CEUS can differentiate between renal tumors and anatomical variants mimicking a renal tumor (“pseudotumors”) when conventional US is equivocal (LoE 1b, GoR A). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 7

CEUS can be used to characterize complex cysts according to the Bosniak criteria (LoE 1b, GoR A). Broad Consensus (15/2/3, 88 %)

RECOMMENDATION 8

CEUS can be used to characterize indeterminate renal lesions (LoE 1b, GoR A). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 9

CEUS can be used for the identification of renal abscesses in complicated acute pyelonephritis (LoE 1b, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 10

CEUS can be used for the follow-up of non-surgical renal lesions (LoE 4, GoR C). Strong consensus (20/0/0, 100 %)

Vesicoureteral Reflux (VUR)

Background

Conventional voiding cystourethrography remains the gold standard for the detection of VUR, notwithstanding ionizing radiation concerns, despite contrast-enhanced voiding urosonography (ceVUS) being the superior option. Many early comparative studies between ceVUS and cystourethrography were obtained with Levovist™ (Schering AG, Berlin), now no longer available UCA. SonoVue™ (Bracco SpA, Milan), recently licensed for this purpose, performs comparatively well, and has a favorable safety profile in children with high diagnostic performance for the detection of reflux and for assessment of the urethra.

Study procedure

The basic steps of ceVUS are:

a) B-mode US evaluation of the kidneys and bladder
b) Intravesical administration of UCA diluted in normal sterile saline
c) Repeated imaging of the bladder and kidneys with CEUS during and after bladder filling and while voiding
d) During voiding urethrosonography (transpubic and/or transperineal) may be added.

UCA can be administered via a transurethral bladder catheter or via suprapubic puncture (0.1 – 0.5 mL SonoVue™ in 500 mL 0.9 % saline), by slow instillation during CEUS monitoring, until adequate enhancement of the bladder content is achieved; dose adjustment with excessive shadowing or insufficient signal. A full bladder is necessary for suprapubic puncture.

Diagnosis of vesicoureteral reflux

Reflux is diagnosed when the UCA appears in one or both ureters and/or the pelvicalyceal system. Vesicoureteral reflux is graded I–V depending on severity, analogous to the international reflux grading system of voiding cystourethrography. US imaging is continued during and after voiding with the child supine, prone, sitting, or standing, always imaging the kidneys and bladder alternately as the position allows.

Contrast-enhanced voiding urosonography has a higher rate of vesicoureteral reflux detection compared to voiding cystourethrography, as ceVUS is more sensitive to the detection of small amounts of refluxed UCA. Moreover ceVUS imaging is continuous, while fluoroscopy is intermittent with cystourethrography, allowing better detection of intermittent reflux on CEUS. Notably, reflux episodes missed on voiding cystourethrography but detected with ceVUS tend to be higher grade, and of greater clinical concern. The ability to detect clinically important reflux and the lack of ionizing radiation, support the use of ceVUS for initial diagnostic and follow-up evaluation of VUR in boys and girls, as well as screening of high-risk patients. A limitation of ceVUS is the inability to image the entire urinary tract simultaneously. Furthermore ceVUS is not recommended as the primary imaging modality for reflux, if the bladder or one of the kidneys is not depicted on US, for specific urethral and/or bladder functional and anatomical evaluation and when imaging is required for detailed anatomical assessment, e. g. in the evaluation of recto-urethral fistulas in neonates with anorectal malformation. The urethra may also be evaluated effectively both in girls and in boys. Although evidence is limited, the technique is promising.

Contrast-enhanced voiding urosonography has been used for vesicoureteral reflux in renal transplant recipients with recurrent urinary tract infections, both in adults and children. In 23 adult renal transplant recipients, ceVUS was compared with radionuclide cystography, in 37 adult patients ceVUS was compared with conventional voiding cystourethrography and in 27 patients (8 children or adolescents, 19 adults) cycling ceVUS (i. e., obtained by filling the bladder and having the patient void around the urinary bladder catheter two times) was compared with ceVUS in the first cycle. Results indicated that ceVUS was highly effective in detecting vesicoureteral reflux in adult renal transplant recipients. Compared to techniques involving exposure to ionizing radiation, the sensitivity and specificity ranged between 75 % – 93 % and 71 % – 95 %, respectively. Compared with the first cycle, cyclic ceVUS did not improve detection sensitivity for vesicoureteral reflux, but revealed higher grades of reflux.

RECOMMENDATION 11

Contrast-enhanced voiding urosonography should be the initial examination for suspected vesicoureteral reflux in girls (LoE 1a, GoR A) and in boys (LoE 2b, GoR B). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 12

Contrast-enhanced voiding urosonography should be used in the follow-up of vesicoureteral reflux in girls and boys after conservative or surgical treatment. (LoE 1a, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 13

Contrast-enhanced voiding urosonography should be used to screen high-risk patients for reflux (e. g., siblings, transplanted kidney) (LoE 1a, GoR A). Strong Consensus (19/0/1, 100 %)

Scrotum

Background

Despite US being the imaging modality of choice for examination of the scrotum, findings may be equivocal and misinterpretation can result in an unnecessary orchiectomy. A challenge is the unequivocal differentiation between hypovascular and avascular lesions, presuming that an avascular lesion implies benign disease, which may be impossible on color Doppler US. CEUS provides a practical solution by increasing the confidence of the interpretation of lesion vascularity and of scrotal and cord vessels, allowing for appropriate clinical management.

Study procedure

A B-mode and color Doppler US examination of the lesion with linear high-frequency transducers should be performed to relate to the subsequent CEUS findings. A higher UCA concentration is required to examine the scrotal contents; typically 4.8 mL of SonoVue™ (Bracco SpA, Milan). The arterial phase in CEUS is the most important aspect of the examination. The testis and epididymis enhance rapidly but the arrival time varies between individuals. The arteries enhance first, followed within seconds by complete parenchymal enhancement. The scrotal wall tends to enhance to a lesser degree than the contents. There is no accumulation of UCA in the parenchyma of the testis and the enhancement declines over a variable period of time such that there is minimal residual enhancement by three minutes.

Patterns of disease

Torsion of the spermatic cord

The sensitivity of color Doppler US with current equipment for the identification and diagnosis of spermatic cord testicular torsion is adequate, even in the small volume testes of children. In a small series of men with spermatic cord torsion, CEUS confirmed the absence of vascularization, but failed to add any clinically significant information to unenhanced color Doppler US. There is no data to recommend the use of CEUS in spermatic cord torsion, although the absence of global vascularity can be clearly depicted.

Segmental Infarction

The appearance of acute segmental testicular infarction on conventional B-mode and color Doppler US is variable. Often the benign nature of the lesion is established by its wedge shape with markedly diminished or absent color Doppler flow. The main concern is the differentiation of a segmental infarction with a rounded configuration from a poorly vascularized tumor. CEUS improves the characterization of segmental infarction by demonstrating one or more ischemic parenchymal lobules separated by normal testicular vessels. Subacute segmental infarction characteristically exhibits a perilesional rim of enhancement, which diminishes over time and is eventually lost with changes in lesion shape and shrinkage.

Trauma

Conventional B-mode and color Doppler assessment of the testis in trauma is well established, but underestimates the extent of injury. Besides integrity or interruption of the tunica albuginea, the most important information for the surgeon is the extent of viable testicular tissue, an evaluation which is often difficult with conventional Doppler US because the injured testis is often hypovascular even in viable regions, as a consequence of testicular edema compromising vascular flow. CEUS allows delineation between the non-enhancing devascularized tissue and the enhancing viable parenchyma, enabling organ-sparing treatment. Moreover, CEUS offers a clear delineation of fracture lines and intratesticular hematomas.

Inflammation

Epididymo-orchitis is a clinical diagnosis and is usually easily confirmed on color Doppler US. Abscess formation is relatively common in cases of severe epididymo-orchitis, whereas venous infarction is exceedingly rare, thought to be a consequence of local swelling occluding the venous drainage of portions of the testis or of the entire testis. CEUS may be used in selected cases of severe epididymo-orchitis. It allows unequivocal assessment of the presence or absence of vascular supply within focal testicular lesions. However, since both infarction and intratesticular abscess lack internal vessels, absolute differentiation remains difficult. CEUS may be able to determine the development of an abscess at an earlier stage, or the complete extent of a large abscess, and allow for prompt treatment.

Tumors and complex cysts

The current understanding is that testicular tumors with a diameter of less than 1.5 cm may not show flow on color Doppler US and thus may be misinterpreted as a benign lesion, the purported hallmark of malignancy being an increase in vascularity. Simple testicular cysts are usually benign, but any wall irregularity or echogenic debris may be suggestive of a (rare) cystic testicular tumor. CEUS is able to confirm the absence of vascularity in benign complex cysts and epidermoid cysts. It is thought that virtually all testicular tumors display vascularization on CEUS, with the exception of any cystic component and regions of necrosis. Very rare exceptions may be represented by extensively necrotic lesions, and by the so-called “burned out” testicular tumor.

Evaluation of solid testicular lesions

Several investigators have discussed the possibility of differentiating testicular tumors with CEUS, particularly between a malignant seminoma and a benign Leydig cell tumor. Using time-intensity curves, evaluating the wash-in and washout curves may help distinguish malignant from benign tumors, with a prolonged washout observed in Leydig cell tumors, and reported rapid wash-in

and raised enhancement for Leydig cell tumors in comparison seminoma. Although these results are promising, both qualitative and quantitative CEUS analyses overlap between different histological types. Quantification of CEUS of testicular tumors remains a research tool. There is limited use of CEUS in intrascrotal extratesticular focal lesions, with no evidence regarding the usefulness for the differentiation of solid lesions.

Spontaneous intratesticular hematoma

Testicular hematoma can rarely present with acute scrotal pain in a patient with no history of trauma. US demonstrates an intratesticular mass suggesting malignancy, but the lack of enhancement is a good marker for the absence of vascularity and for a benign lesion, leading to a presumptive diagnosis and conservative management.

RECOMMENDATION 14

CEUS can distinguish vascularized from non-vascularized focal testicular lesions, helping to exclude malignancy (LoE 1a, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 15

CEUS can discriminate non-viable regions in testicular trauma (LoE 2b, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 16

Testicular CEUS can identify segmental infarction (LoE 2b, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 17

CEUS can identify abscess formation and infarction in severe epididymo-orchitis (LoE 2b, GoR B). Strong Consensus (18/0/2, 100 %)

Prostate Cancer

Background

Conventional B-mode and Doppler transrectal US imaging have a limited role in the detection of prostate cancer because of poor sensitivity and specificity (approximately 50 – 60 %) and B-mode US is only used to guide prostate biopsies. There is a correlation between angiogenesis, as represented by microvascular density, and the presence of prostate cancer, its stage and survival. Therefore, attempts have been made with contrast-enhanced color Doppler US to improve the detection and diagnosis of prostate cancer, with a reported increase in the detection rate of targeted biopsies of nearly 50 % compared to systematic biopsies. Low MI transrectal CEUS became available during the last decade when contrast-specific modalities were also implemented on endocavitary transducers, with further studies forthcoming.

Study procedure

Diagnostic CEUS is performed using transrectal US and typically a bolus of 2.4 mL of SonoVue™ (Bracco SpA, Milan) is administered to image particularly the inflow of UCA in a single plane. The most useful characteristics for an area suspicious for prostate cancer are a rapid inflow and/or an increased maximal enhancement compared to the surrounding tissue. Multiple UCA injections (typically four) are needed to image several planes. CEUS has been used for follow-up of ablative treatments, with either a bolus injection or an infusion of UCA used to visualize perfusion defects resulting from the ablative therapy.

Image interpretation and limitations

Preliminary CEUS results appear to confirm the findings of contrast-enhanced Doppler US, with the lack of specificity of enhancing areas and of any other pattern suggesting cancer. The evidence for the use of CEUS in the prostate remains limited and the role of CEUS in prostate cancer should still be considered a research subject. New improvements and new techniques are becoming available with the potential to increase the role of CEUS in prostate cancer detection and diagnosis. 4 D contrast-enhanced transrectal US imaging has now been introduced and objective quantification techniques are being developed. The first use of targeted UCA in humans was reported for prostate cancer; these VEGF-R2 targeted microbubbles were tested in a phase 0 trial in 24 patients (https://www.clinicaltrials.gov/ct2/show/NCT01253213?term=BR55&rank=2?). The combination of CEUS and other US modalities such as elastography, in multi-parametric US could pave the way to a future clinically significant role for CEUS in prostate cancer detection and diagnosis.

RECOMMENDATION 18

Although CEUS for the improvement of the prostate cancer detection rate is an active research field, it currently cannot be recommended for clinical use (LoE 5, GoR C). Strong Consensus (16/0/4, 100 %)

Transplanted Kidney

All of the applications of CEUS in native kidneys also apply to renal transplants. B-mode and Doppler US are the modalities of choice for imaging transplanted kidneys but are limited in the assessment of microcirculation and the characterization of focal masses, inflammatory changes and complex cysts. CEUS can image the microcirculation which is essential for assessing acute and chronic graft dysfunction, and is sensitive in the diagnosis of infarction, seen as a defect in all phases. The defect on CEUS is smaller than on Doppler US, a manifestation of the imaging of smaller vessels on CEUS. Cortical infarction and ischemia (absent flow compared

to hypoperfusion respectively) can be reliably differentiated on CEUS, a feature not possible by conventional Doppler US. Different quantitative functional data have been assessed on time-intensity curves, all related to impaired parenchymal perfusion (e. g. longer time to peak, lower wash-in slopes, longer mean-transit time) and associated with a worse prognosis of graft function and survival. Although these preliminary results are promising, further studies are needed to assess whether the detection of hemodynamic changes in renal grafts affects the management of patients with poorly functioning transplants. Consequently the quantification of CEUS is still considered a research field in transplant assessment.

RECOMMENDATION 19

CEUS can be used to identify renal transplant ischemia and vascular complications (LoE 3b, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 20

CEUS can be used to characterize complex cysts in renal transplant according to the Bosniak criteria (LoE 2b, GoR B). Strong Consensus (18/0/2, 100 %)

RECOMMENDATION 21

CEUS can be used to characterize indeterminate transplant renal lesions (LoE 2b, GoR B). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 22

CEUS can help evaluate patients with acute pyelonephritis (LoE 3a, GoR B). Strong Consensus (18/0/2, 100 %)

Adrenal Glands

Conventional US is able to detect adrenal gland tumors, usually readily on the right side, but characterization is more difficult. Size, irregular contours, inhomogeneity, loss of normal adrenal gland anatomy, and infiltration into adjacent organs, or the diaphragm, and vessels are criteria for malignancy. Malignant adrenal tumors may infiltrate and occlude the adrenal vein; the vascularity of a tumor thrombus may be demonstrated on CEUS. No CEUS criteria can reliably differentiate between benign and malignant adrenal gland tumors, with conflicting reports. Dynamic CEUS using time-intensity curve analysis has been deployed in the investigation of adrenal gland tumors without clear differentiation. CEUS may demonstrate characteristic hypervascularity of some adrenal gland tumors, e. g., pheochromocytoma, which typically also have necrotic regions with no contrast enhancement.

RECOMMENDATION 23

There is no evidence that CEUS can readily differentiate benign from malignant adrenal gland tumors (LoE 2b, GoR B). Strong consensus (20/0/0, 100 %)

Obstetrics and Gynecology

Obstetrics

The use of UCA in obstetrics is not indicated as there has been limited research related to the uncertainty of a possible underlying harmful effect. No recent human or animal studies have been performed. It is unknown whether the UCA passes through the placenta, though this seems unlikely as previously suggested. CEUS to assess a pregnant mother should be balanced against the risk of other imaging modalities.

Gynecology

Uterus

Both endometrial and cervical tumors have been assessed with CEUS. Perfusion differences between endometrial polyps and cancer have been documented, and CEUS during uterine artery embolization to treat leiomyomas might be useful. Currently there is some benefit to the CEUS diagnosis of endometrial carcinoma. No prospective trials have confirmed the value of CEUS for assessing uterine tumors and there is no proven clinical indication for CEUS use in the examination of the endometrium or the myometrium.

Adnexa

Differentiation of benign from malignant adnexal masses was attempted by visual assessment of UCA distribution and by quantification of enhanced Doppler signals, but despite some difference in average values for some variables, no feature with sufficient clinical potential was obtained. By using CEUS, it was demonstrated that adnexal masses without internal enhancement are invariably benign, but the presence of enhancement is not a specific sign of malignancy. CEUS does not greatly improve the accuracy of color Doppler US for the diagnosis of malignancy in adnexal masses. A multicenter study on the diagnosis of malignancy in adnexal masses, including quantitative CEUS features, confirmed that CEUS was not superior to conventional color Doppler US. Although CEUS findings differed between benign and malignant ovarian masses, there was substantial overlap between benign and borderline tumors, although CEUS was able to differentiate invasive malignancies from other tumors.

RECOMMENDATION 24

There are no recommended gynecological clinical indications for the use of CEUS, despite the finding that the absence of any enhancement in adnexal masses corresponds to benign lesions (LoE 2b, GoR A). Strong consensus (19/1/0, 95 %)

Pancreas

Background

CEUS is not indicated for the detection of focal solid or cystic pancreatic lesions, but CEUS improves the characterization of lesions seen on US.

Study Procedure

CEUS is superior to Doppler US techniques for the visualization of intrapancreatic vessels. Enhancement begins immediately after aortic enhancement, with an arterial phase (10 to 30 s), a venous phase (30 to approximately 120 s). With a pancreatic mass, the CEUS examination also aims to characterize and confirm peripancreatic vascular associations. The late venous phase begins about 120 seconds after the contrast injection and lasts for about 4 minutes. A late phase liver evaluation may identify possible metastatic lesions.

Pancreatic Masses

The enhancement pattern of focal pancreatic lesions is compared with the adjacent pancreatic tissue. The field of view should include both. This is mandatory with an isovascular mass but not essential with a hypovascular (hypoenhanced with few internal microbubbles) or hypervascular (hyperenhanced) mass. CEUS provides clear distinction between vascularized solid lesions and cysts and provides information lesions indeterminate on CT, and may aid targeting areas following a first negative biopsy.

Adenocarcinoma

Ductal adenocarcinoma, the most common primary malignancy, is typically hypo-enhancing in all phases, because of the desmoplastic reaction with low vascular density that is present in 90 % of cases. Lesion size, margins and the relationship with peripancreatic vessels are better visualized with CEUS. However, for assessing resectability, B-mode and color Doppler US are also adequate. CEUS is essential for lesion characterization and accurate liver staging. CEUS can help with US-guided pancreatic biopsy. Changes in pancreatic tumor vascularization during chemotherapy have been documented with CEUS.

Neuroendocrine tumors

Neuroendocrine tumors typically present as hyper-enhancing lesions in the arterial phase of CEUS examinations, owing to their abundant arterialization, often not seen on color Doppler US. Necrotic avascular areas result in inhomogeneous enhancement in larger tumors. Based on the ENETs Consensus Guidelines, CEUS is reported as an imaging method for the diagnosis of neuroendocrine neoplasms.

Mucin-producing cystic tumors

CEUS improves the differentiation between pseudocysts and cystic tumors of the pancreas by accurately demonstrating vascularization of lesion septa or nodularity. Mucinous cystadenoma is potentially malignant (may transform into cystadenocarcinoma), and it is usually depicted as an unilocular round cystic lesion, with particulate content, irregular thick walls, internal septa and parietal nodules which enhance on CEUS. Intraductal papillary mucinous neoplasms (IPMN) are divided into main duct and side branch duct types. CEUS is helpful for differentiating between perfused (nodules) and non-perfused (mucin plugs) areas. CEUS can be employed in the follow-up of borderline cystic lesions of the pancreas, if well visualized on US, in order to reduce the use of MR imaging.

Serous cystadenoma

Serous cystadenoma is a benign cystic lesion, typically with a lobulated microcystic appearance with thin and centrally oriented septa, which are vascularized on CEUS. When the cysts are minute, microcystic serous cystadenomas may mimic a solid lesion, both on conventional US and CEUS, being hyperenhanced on CEUS. Definitive differential diagnosis with respect to IPMN side branch duct types is not possible on CEUS. Exclusion of the presence of communication between the cystic lesion and the main pancreatic duct is required.

Pseudocysts

Pseudocysts typically contain non-vascularized debris, typically found in the early stages. Pseudocysts do not enhance at any phase with CEUS, even when heterogeneous on B-mode US. The reported sensitivity and specificity of CEUS in characterizing pseudocysts is up to 100 %.

Pancreatitis

With acute pancreatitis, CEUS may delineate necrotic areas, which do not enhance. If the pancreatic region is clearly visible on US, CEUS can be used in the follow-up of acute pancreatitis following CT staging, to reduce further CT examinations. Good accuracy of CEUS for detecting necrotic lesions in acute pancreatitis (97.4 %) has been reported. Significant correlation between CEUS and CT was found for the pancreatitis CT severity index, extent of necrosis and Balthazar grade, and as a predictor of severity in an episode of acute pancreatitis. CEUS can be used as a follow-up imaging method in patients with initial CT staging at admission. Focal mass-forming pancreatitis and autoimmune pancreatitis have been reported to have similar enhancement to that of the normal pancreatic parenchyma and may be useful in to differentiate pancreatic cancer.

Pancreatic Transplant

As with renal allografts, US is the modality of choice for imaging pancreatic transplants. CEUS can add extra value and diagnostic confidence when assessing graft perfusion and vascular complications such as arterial and venous thrombosis, particularly in complicated situations. CEUS can image the microcirculation to allow evaluation of viability and may provide prognostic information. Early quantitative functional data shows promise in the diagnosis and management of rejection and represents a research field in transplant assessment.

RECOMMENDATION 25
In solid pancreatic lesions detected on ultrasound, CEUS can be used to reliably characterize ductal adenocarcinoma (LoE 1a, GoR A). Broad consensus (18/0/2, 90 %)

RECOMMENDATION 26
CEUS can be used to distinguish between pancreatic ductal adenocarcinoma and neuroendocrine tumors (LoE 1a, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 27
CEUS can be used to differentiate between cystic neoplasms and pseudocysts (LoE 1a, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 28
CEUS can be used to differentiate vascular (solid) from avascular (e. g. liquid or necrotic) components of a pancreatic lesion (LoE 1b, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 29
CEUS can be used to define the dimensions and margins of a pancreatic lesion and its vascular relationships (LoE 2b, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 30
CEUS can be used to diagnose and follow-up acute necrotizing pancreatitis (LoE 1b, GoR A). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 31
CEUS can be used in the follow-up of indeterminate cystic pancreatic lesions (LoE 1b, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 32
CEUS may improve the accuracy of percutaneous ultrasound-guided pancreatic procedures (LoE 2a, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 33
CEUS can be used to assess pancreatic graft ischemia and other vascular disorders (LoE 3b, GoR C). Strong consensus (20/0/0, 100 %)

The Gastrointestinal Tract

Background

Ultrasound imaging of the gastrointestinal (GI) tract using ≥ 7.5 MHz transducers usually reveals 5 wall layers and can identify a thickened bowel wall and focal lesions. The imaging of the bowel wall with CEUS requires a higher UCA dose, typically 4.8 mL of SonoVue™, a consequence of fewer microbubbles of the appropriate size to resonate at higher frequencies. The time of arrival of the UCA in the intestinal capillaries is usually 10 – 20 sec after injection, predominantly in the submucosal layer, with maximum concentration (peak intensity) reached after 30 – 40 sec. The arterial phase (0 – 30 s) is followed by a venous phase that lasts from 30 – 120 s.

Study procedure

The bowel should be examined in B-mode and Doppler US modes to detect the distribution of the relevant pathology, allowing the area of interest to be targeted for CEUS examination. A difference in perfusion between healthy and diseased bowel can be recognized by CEUS. CEUS examination allows arterial and venous phases to be examined for two minutes and the possibility for a late phase liver examination for metastasis, if relevant.

Inflammatory Bowel Disease (IBD)

CEUS enables quantification of bowel wall vascularity in patients with Crohn's disease and is used to evaluate adult and pediatric IBD patients. CEUS correlates well with MR imaging of intestinal wall enhancement.

Disease activity

CEUS can add to B-mode and Doppler US in the evaluation of disease activity in IBD. CEUS performs more reliably than power Doppler in estimating disease activity in Crohn's. Enhancement in different wall layers can be evaluated and quantified in Crohn's disease and correlates to a clinical activity index (CDAI) with good sensitivity and specificity. In ulcerative colitis, CEUS parameters correlate well with histological markers of inflammation. Quantitative measurements of bowel enhancement obtained by

CEUS also correlate with a severity grade determined at endoscopy. Furthermore, histological markers of inflammation correlate well with CEUS perfusion. Moreover, US evaluation of the changes of bowel wall enhancement during anti-inflammatory therapy may be useful for the clinical monitoring of Crohn's disease activity. CEUS can also be used to assess postoperative recurrence of Crohn's disease. Two meta-analyses concluded that CEUS in the assessment of IBD activity is accurate and a highly sensitive and specific method.

Distinguishing between fibrous and inflammatory strictures

In patients with a stricture of the bowel and resultant bowel obstruction, it is important to determine if there is active inflammation at the site of stricture or if this segment is fibrotic. Preliminary studies indicate that the use of UCA appears to be effective in the recognition of predominantly cicatricial stenosis in patients with Crohn's disease, although data is conflicting. Using CEUS, the active inflammatory components will enhance, whereas the fibrotic stricture will not. Absolute values for blood volume, flow and mean transit time of the bowel confirm that it is possible to distinguish between fibrous and inflammatory strictures in Crohn's disease.

Abscesses

Distinguishing abscesses from inflammatory infiltrates is an important clinical task in the management of Crohn's disease. If areas of a significant size close to an affected bowel loop are completely devoid of UCA signals, this lesion represents an avascular abscess rather than inflammatory infiltrates.

Fistulas

By injecting a UCA mixed with saline into one of the orifices of a fistula, it is possible to improve visualization of fistula routes in Crohn's disease, defining endocavitary and intraluminary locations. Fistulas from blood vessels to intestines can also be detected using conventional intravenous CEUS.

Intestinal Tumors

US is not the imaging modality of choice for detecting intestinal polyps or tumors. Tumor vascularity can be evaluated by CEUS and contrast enhancement of rectal cancer has been shown to correlate with histological vessel density. Neuroendocrine tumors and gastrointestinal stromal tumors (GIST) of the stomach and small bowel are highly vascularized and CEUS can be applied for perfusion analysis and planning of US-guided biopsies to avoid punctures of necrotic tumor parts. Furthermore, the hypervascular (95 %) metastasis from neuroendocrine tumors to lymph nodes and the liver can be detected and characterized by CEUS.

Transplanted bowel

CEUS allows the detection of hypoperfusion of a bowel transplant graft. As in other bowel diseases, CEUS can be used to evaluate the bowel wall perfusion as well as the patency of visceral vessels with the advantage of bedside examination. CEUS can also diagnose other organ complications after bowel transplantation, e. g. pancreatitis, when other imaging techniques cannot be performed. CEUS also allows diagnosis and monitoring of treatment response of intestinal acute graft versus host disease (I-aGVHD) after allografting. The detection of transmural penetration of the UCA into the bowel lumen indicates I-aGVHD.

Limitations

It is difficult to visualize all bowel segments using transabdominal US. Intestinal peristalsis and luminal air will impair image quality and reduce the repeatability of the quantitative measurement of bowel enhancement patterns. Improved detection of intestinal inflammation may be enabled with targeted specific ligands attached to the UCA. However, more studies are needed to establish the exact role of CEUS in the imaging of gastrointestinal pathology, and when performing multicenter studies, it is mandatory to standardize acquisition and software for quantification.

RECOMMENDATION 34

CEUS can be used to evaluate the vascularity of the gastrointestinal wall (LoE 1a, GoR A) and gastrointestinal tumors (LoE 4, GoR B). Broad Consensus (12/4/2, 75 %)

RECOMMENDATION 35

CEUS can be used to estimate disease activity in inflammatory bowel disease (LoE 1a, GoR A) and to discern between fibrous and inflammatory strictures in Crohn's disease (LoE 2b, GoR B). Strong consensus (19/1/0, 95 %)

RECOMMENDATION 36

CEUS can be used to monitor the effect of treatment in Crohn's disease (LoE 4, GoR B). Broad Consensus (17/1/2, 94 %)

RECOMMENDATION 37

CEUS can be used to detect abscesses (LoE 4, GoR C) and to confirm and track the route of fistulae (LoE 4, GoR C). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 38

CEUS can contribute to the evaluation of perfusion and vascular complications after intestinal transplantation (LoE 4, GoR C). Strong Consensus (18/0/2, 100 %)

Spleen

Background

Splenic abnormalities are uncommon and frequently difficult to detect and characterize with conventional US. The spleen is ideally suited for CEUS due to its superficial location, homogeneous parenchyma, high vascularity, small size and long-lasting enhancement profile. CEUS is a well-established technique for increasing diagnostic confidence and accuracy in splenic US.

Study procedure

Although UCAs remain entirely intravascular, they are sequestrated by the spleen, resulting in persistent late phase enhancement. Enhancement is inhomogeneous in the arterial phase ("zebra striped" pattern, similar to contrast-enhanced CT and MR imaging) but becomes homogeneous within 60 seconds and usually persists for longer than 5 minutes. The arterial (10 – 35 s) and late parenchymal phases (3 – 5 min) are most valuable diagnostically. Scanning should be continuous during the arterial phase but then intermittent to avoid UCA destruction. Enhancement of focal lesions is compared to adjacent (enhanced) splenic parenchyma. Deeper lesions can be obscured if a large volume of UCA is administered. 1.2 – 2.4 mL of SonoVue™ is usually the optimal dose.

Indications and image interpretation

Abnormal splenic size

CEUS is not helpful in identifying the etiology of diffuse splenomegaly. Reduced or absent enhancement in a small spleen may indicate functional hypo/asplenia.

Lesion identification

Where the splenic parenchyma is inhomogeneous on B-mode US, the addition of CEUS will frequently demonstrate focal lesions.

Ectopic splenic tissue

Ectopic splenic tissue will enhance with the same pattern as the normal spleen. Late parenchymal enhancement will differentiate splenunculi and splenosis from pathological masses.

Splenic infarction

Infarction may be difficult to detect on conventional US, particularly when isoechoic in the acute stage. CEUS improves detection and characterization by demonstrating avascular, usually wedge-shaped, lesions. Enhancement will be absent in patients with total splenic infarction. CEUS can identify asymptomatic splenic infarction in patients with pancreatitis and infective endocarditis.

Characterization of focal splenic lesions (FSL)

Cystic lesions

CEUS can be used in selected cases to show that complex cysts are avascular and therefore likely to be benign. Rim or septal enhancement may be a feature of splenic abscess formation.

Solid lesions

B-mode and color Doppler US have low accuracy for the diagnosis of solid lesions. Small echogenic lesions are usually, but not always, benign, while echo-poor lesions are more likely to be malignant. Correlation with the clinical history and laboratory tests is essential. Benign vascular tumors (BVT: hemangioma and hamartoma) are the most common benign lesions and secondary tumors (lymphoma and metastases) are the most common malignant lesions. No enhancement (in any phase) or persistent late phase enhancement is characteristic of benign lesions. Late phase washout is a feature of malignant lesions, but less pronounced washout is also seen in many benign lesions. Arterial phase hyper-/isoenhancement is an independent predictor of a BVT, more commonly seen in hemangiomas with an atypical appearance on conventional US. Nodular peripheral enhancement with progressive centripetal filling is unusual in splenic hemangiomas. Intralesional vessels, heterogeneous enhancement, necrotic regions and a dotted enhancement pattern favor a diagnosis of malignancy.

Triage of patients with FSL

Lesions showing low-level arterial enhancement and progressive late-phase contrast washout usually require further imaging or biopsy, particularly in high-risk groups. FSL with benign enhancement characteristics will usually be suitable for interval imaging.

RECOMMENDATION 39

CEUS may be used to improve the detection of focal splenic abnormalities (LoE 2b, GoR B). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 40

CEUS can be used to characterize suspected accessory spleens or splenosis (LoE 2b, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 41

CEUS can be used to diagnose splenic infarction (LoE 2b, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 42

CEUS can identify benign focal splenic lesions by showing persistent enhancement in the late phase (LoE 2b, GoR B). Strong Consensus (18/0/2, 100%)

Peripheral Vascular System and Aorta

Background

The extracerebral vascular systems with indications for CEUS include the cervical carotid artery and the abdominal aorta, with less emphasis on peripheral arterial disease. Conventional US techniques are limited with respect to the demonstration of slow flow, especially in small vessels such as the vasa vasorum or collaterals and flow in critical stenosis, and the addition of a UCA may be useful.

Study Procedures

CEUS of the carotid and peripheral arteries is carried out with linear transducers (5 – 10 MHz) and the abdominal aorta is visualized with convex transducers (2.5 – 9 MHz). For diagnostic views of the vessels, 1.0 to 2.4 mL of SonoVue™ is intravenously administered as a bolus injection, followed by 10 mL of 0.9 % normal saline solution.

Carotid Artery

Stenosis

Color and spectral Doppler US is the established imaging modality for suspected carotid artery disease. CEUS improves the sensitivity of Doppler US and can distinguish occlusion from tight subocclusive stenosis, comparable to contrast-enhanced CT angiography. CEUS improves the delineation of the endovascular border, characterizing the geometry of pre-stenotic, intra-stenotic and post-stenotic segments without the aliasing and blooming artifacts or angle dependence issues of Doppler US. CEUS does not provide flow information.

Follow-up after carotid stenting

CEUS is a reliable method for evaluating re-stenosis after internal carotid artery stenting. CEUS has fewer intrastenotic flow artifacts compared to Doppler US, resulting in improved visualization and depiction of the complete length and morphology of the stenosis.

Dissection

CEUS has been used to identify carotid dissection. MR imaging remains the reference standard in the diagnosis of cervical vessel dissections. When it is contraindicated, the diagnostic accuracy of US examinations can be improved by the use of CEUS.

Complications after vascular intervention

Post-surgical fistula track visualization can be difficult using Doppler US but is improved with CEUS without artifacts. Additionally, CEUS may help to image flow in false aneurysms with greater precision than Doppler US.

Plaque characterization

The accepted predictor of stroke risk is the degree of carotid stenosis, with contributing imaging features recognized. Plaque ulceration, which is a reliable marker of plaque vulnerability, can be clearly imaged using CEUS, which has superior sensitivity and diagnostic accuracy for the assessment of ulceration compared with conventional Doppler US. Plaque neovascularization demonstrated by CEUS correlates well with histological findings, depicts inflammation as a marker of plaque vulnerability, and may be used to predict cerebral ischemic events and stratify risk for coronary artery disease. The role of CEUS in routine clinical practice remains to be confirmed, particularly as objective assessment with quantification tools remains to be standardized.

Large vessel vasculitides

CEUS can also be used for the evaluation of large-vessel vasculitides, particularly to assess vascularization within the vessel wall. It improves the visualization of the lumen border, and allows dynamic assessment of carotid wall vascularization, which is a potential marker of disease activity.

Vertebral artery

A hypoplastic vertebral artery is more frequently a risk factor for vertebrobasilar ischemia. A narrowed restricted artery (in the paired arteries) is more prone to closure, especially when other risk factors are present. Under difficult examining conditions, detection of low blood flow velocities in cases of hypoplasia can be difficult using conventional Doppler US. CEUS may differentiate between a hypoplastic vertebral artery and an occlusion at the origin.

Abdominal aortic

CEUS can overcome some limitations of conventional US by improving the delineation of the aortic lumen and the detection of the main branching arteries. CEUS also improves the diagnosis of aortic rupture by detecting contrast extravasation.

Aortic dissections

A dissection of the abdominal aorta is usually an extension of a thoracic aortic dissection. In most cases, the true and false lumen can be discriminated with CEUS, because both early (true lumen) and late (false lumen) contrast enhancement can be detected, provided the false lumen is not thrombosed.

Inflammatory Abdominal Aortic Aneurysm

Inflammatory aneurysm of the abdominal aorta is a variant of atherosclerotic aneurysm that is characterized by inflammatory and/or fibrotic changes in the peri-aortic region of the retroperitoneum. CEUS of the inflammatory aneurysm improves differentiation between covered rupture and inflammatory aortic aneurysm.

Endovascular Aortic Graft Endoleak

An endoleak, classified into subtypes depending on the site of the leak, represents blood flow outside the stent graft lumen but within the aneurysm sac and conventionally detected by CT angiography, although CT angiography is limited in the detection of some endoleak subtypes. CEUS is able to identify and characterize an endoleak more accurately than CT angiography, with analysis of velocity and flow direction. CEUS is particularly useful

in the management of "endotension" often finding an occult endoleak, not seen on CT angiography. CEUS enhancement quantification by time-intensity curves provides additional accuracy. CEUS for the follow-up of patients with endoleak is possible.

Peripheral Vascular Disease

CEUS has been used to improve the diagnostic capabilities of peripheral vascular US but has not demonstrated superiority. Doppler US is the imaging modality of choice for the detection of complications after puncture of the femoral artery, with CEUS potentially improving diagnosis. The detection and localization of small lower leg arteries in patient with PVD requiring peripheral bypass graft surgery is improved with CEUS.

Limitations

Limitations of CEUS exploration of the carotid artery and abdominal aorta relate to any conditions that prevent adequate US penetration and also limit conventional B-mode US exploration. Of particular regard are extensive wall calcification and subcutaneous emphysema after intervention or limited examination windows.

RECOMMENDATION 43

CEUS can help differentiate between total carotid and/or vertebral artery occlusion and residual flow in a tight stenosis (LoE 3, GoR B). Strong consensus (17/0/0, 100 %)

RECOMMENDATION 44

CEUS can be useful for the evaluation of carotid plaque neovascularization which suggests plaque instability (LoE 1b, GoR B). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 45

CEUS can aid the identification of dissection of the extracranial carotid and vertebral arteries, as well as the abdominal aorta and its major branches (LoE 3, GoR C). Strong Consensus (17/0/3, 100 %)

RECOMMENDATION 46

CEUS may be an additional tool in the characterization of suspected inflammatory large vessel and abdominal aortic disease (LoE 5, GoR C). Strong Consensus (17/0/2, 100 %)

RECOMMENDATION 47

CEUS should be used in the follow-up of endovascular aortic repair (EVAR) for the detection and classification of endoleaks (LoE 1a, GoR A,). Strong consensus (20/0/0, 100 %)

Cerebral Vessels

Background

The major indication for CEUS in the examination of cerebral arteries is a poor signal with spectral Doppler US, preventing assessment of flow characteristics. Contrast-enhanced transcranial color-coded duplex sonography (CE-TCCS) is best for simultaneously depicting B-mode brain anatomy as well as vessel detection and flow spectral Doppler tracing.

Study procedures

Transducers for CE-TCCS are identical to that for TCCS (sector 1.5 – 5.0 MHz). There are two applications using UCAs: main vessel, i. e. vascular imaging, and "perfusion imaging". For vascular imaging, UCAs are utilized to enhance Doppler signals in trans-temporal or trans-nuchal transverse axial planes and coronal trans-temporal planes. Technical artifacts may cause inaccuracies: 1) bolus injection results in a blooming artifact preventing accurate Doppler spectral measurements. 2) UCA injection leads to an artificial increase (1 – 36 %) in maximum blood flow velocity, affecting stratification of a stenosis. In perfusion imaging, either low or high MI CEUS is performed with trans-temporal insonation in the axial plane, but other insonation planes may also be used.

Main intracerebral vessel imaging: interpretation and evaluation

Vascular imaging

Most importantly, CE-TCCS is used to differentiate vessel occlusion in poor insonation conditions, and to detect very slow blood flow velocities and low flow volumes (small vessels, vessel pseudo-occlusion). The Doppler spectrum adds hemodynamic information to the anatomical information provided by color Doppler US.

Examination of the anterior circulation

A poor temporal bone window (45 % in the elderly) can usually be overcome with CE-TCCS; over 85 % of the basal arteries of the circle of Willis can be depicted satisfactorily after UCA administration. CEUS infusion can be used in patients with poor acoustic windows for transcranial Doppler monitoring to test cerebral autoregulation as well as language lateralization for surgical planning.

Examination of the posterior circulation

CE-TCCS through the foramen magnum can increase the depth at which the intracranial vertebral arteries, the basilar artery, and the cerebellar artery segments can be identified and thus improve diagnostic confidence.

Internal carotid artery stenosis

Characterization of flow in the circle of Willis in patients with internal carotid artery stenosis and poor bone windows is important for estimating the risk of ipsilateral border zone infarction. Patients without collateral flow are particularly vulnerable to cross-clamping during carotid endarterectomy. The use of UCAs in these patients can provide valuable information for patient management.

Stroke patients

In acute stroke, the basal cerebral arteries can only be detected in 55 – 80 % of cases with unenhanced TCCS. Reliable diagnoses can be obtained in > 85 % with CE-TCCS with correlative findings on angiography in over 95 % of cases.

Perfusion imaging

CEUS is performed with transtemporal insonation in the axial plane in perfusion imaging, although other insonation planes may be used. After administration of a UCA, the perfusion deficit can be detected according to the affected vascular territory in stroke patients, and in patients with space-occupying intracranial lesions. CEUS perfusion imaging has been shown to improve prognostic assessment in the acute phase of cerebral ischemia and to provide comparable results to CT and MR imaging. After bolus injection, time-intensity curves can be generated to extract features that describe the perfusion characteristics quantitatively in standardized regions of interest.

Sono-thrombolysis

The combination of systemic thrombolysis and repeated administration of a UCA over an hour in patients with middle cerebral artery occlusion accelerates recanalization but also increases hemorrhage into the infarct. While of great interest as a method to enhance therapy, the hemorrhagic risk with repeated CEUS studies forced the two major sono-thrombolysis trials NOR-SASS and CLOTBUSTER to be terminated.

Limitations

Despite UCA administration, only the proximal basilar artery can be evaluated. The distal portion can be depicted transtemporally, rendering the middle portion as a diagnostic gap for CE-TCCS. The quality of transtemporal unenhanced imaging is strongly predictive of the potential diagnostic benefit from the administration of a UCA. In patients without visible intracranial structures and vessels on conventional B-mode and Doppler US, there is little benefit from the addition of a UCA. The clinical value of the quantification of enhancement is limited by both physical and technical factors, with reliable identification of the absence of enhancement rather than the exact degree of blood supply impairment.

RECOMMENDATION 48

Contrast-enhanced transcranial Doppler/color duplex sonography (TCD/TCCS) improves the diagnostic capabilities of the examination (LoE 1b, GoR A). Strong Consensus (18/0/2, 100 %)

Endoscopic

Contrast-Enhanced Endoscopic US (CE-EUS)

Background

Contrast-enhanced endoscopic ultrasound (CE-EUS) combines the advantage of high-resolution US of the gastrointestinal wall, pancreas and other organs adjacent to the upper gastrointestinal tract with the ability to delineate micro- and macrovasculature. Two different techniques are available: with contrast-enhanced Doppler EUS (CED-EUS), the intensity of Doppler signals (Color Doppler, Power Doppler) is enhanced by the UCA, imaged at a high MI, used to visualize slow, low-volume blood flow (e. g. tumor vessels). Disadvantages of this technique include artifacts caused by tissue motion and microbubble destruction. Contrast-enhanced harmonic EUS (CEH-EUS) uses low MI techniques to visualize flow in small vessels and is established as an evidence-based technique complementary to B-mode EUS and possibly EUS-elastography to differentiate solid appearing structures, to characterize mass lesions, to improve staging of gastrointestinal and pancreatobiliary cancer and for real-time guidance of diagnostic and therapeutic EUS interventions.

Study procedures

Contrast-enhanced high mechanical index EUS

In CED-EUS the color Doppler region of interest box should include the whole tumor where possible. CE endoscopic Doppler US scanning takes an extra 3 – 4 min.

Contrast-enhanced low mechanical index EUS

“Peak-hold” techniques may be used to improve visualization with low MI techniques. With the high-frequency transducers used in EUS, a larger dose of UCA is used (e. g. 4.8 mL SonoVue™).

Applications in pancreatic lesions

Differential diagnosis of solid pancreatic lesions

CE-EUS can be used to differentiate between solid pancreatic lesions, mainly the hypoenhancing pancreatic ductal adenocarcinoma (PDAC) and iso- or hyper-enhancing solid pancreatic lesions (e. g. neuroendocrine tumors, pancreatic metastases, mass-forming focal pancreatitis, and serous microcystic cystadenoma). Meta-analyses showed a pooled sensitivity of 94 % and a specificity of 89 % for the differential diagnosis of PDAC from non-PDAC independent of the CE-EUS technique used.

PDAC is characterized by hypoenhancement, irregular vascularization and a lack of venous vessels. Mass-forming focal pancreatitis exhibits netlike regular vascularization. Hypovascularity was shown to have a high diagnostic value for the detection of solid pancreatic masses ≤ 20 mm, and for the differentiation of PDAC from inflammatory and non-PDAC neoplastic masses. For small pancreatic tumors ≤ 20 mm, CED-EUS is significantly more accurate than CE-CT.

CEH-EUS is the more widely used technique for the differentiation of PDAC from other solid pancreatic lesions. With this technique, microvasculature and perfusion comparative qualitative or quantitative (time intensity curves, TIC) analysis may be performed. In general, heterogeneous hypoenhancement is typical for PDAC, whereas almost all solid non-PDAC lesions exhibit iso- or hyperenhancement. Hyperenhancement with slow washout is a typical pattern of pancreatic neuroendocrine tumors (P-NET), while filling defects are highly predictive of malignancy. In pseudo-tumoral chronic pancreatitis, isoenhancement and hyperenhancement are the most common patterns. Both focal and diffuse autoimmune pancreatitis demonstrate hyper-enhancement with CEH-EUS. Prospective studies indicate that the diagnostic accuracy of CEH-EUS and EUS-FNA is comparable. An accurate differential diagnosis of small solid pancreatic lesions is important. A retrospective multicenter study showed a high accuracy (86 %) of CEH-EUS for the differentiation of small solid pancreatic lesions ≤ 15 mm. Concomitant use of both EUS-FNA and CEH-EUS increases the diagnostic yield and accuracy of EUS-FNA. In patients with hypoenhancing solid pancreatic lesions and negative EUS-FNA, continuing suspicion of PDAC demands repeat tissue sampling.

Staging in pancreatic ductal adenocarcinoma

CEH-EUS may increase the accuracy of preoperative tumor staging and resectability evaluation of pancreatico-biliary malignancies.

Characterization of cystic pancreatic lesions

Contrast enhancement of the wall, septations, nodules or solid parts of cystic pancreatic lesions in CE-EUS reliably separates neoplastic pancreatic cysts from pseudocysts and non-neoplastic cysts. However, differentiation between serous cystadenoma and mucinous neoplastic cysts is not improved by CE-EUS. CE-EUS is significantly more reliable for the differentiation of mural nodules from intracystic mucus or debris than contrast-enhanced CT and B-mode EUS. Further characterization of mural nodules by CE-EUS (morphological type, height, degree of enhancement) has been shown to be useful for risk stratification.

Applications in non-pancreatic lesions

Gallbladder lesions

CEH-EUS improves the diagnosis of malignant gallbladder polyps and wall thickening over B-mode EUS. In gallbladder malignancy (protruding lesions as well as circumferential wall thickening), a heterogeneous enhancement pattern, the presence of perfusion defects and an irregular vessel pattern were found to be typical features with CEH-EUS. Homogeneous or absent enhancement occurs with benign lesions.

Characterization of lymph nodes

Heterogeneous lymph node enhancement with focal filling defects is present in lymph nodes with metastatic infiltration, whereas the majority of benign lymph nodes demonstrate homogeneous enhancement. However, due to similar homogeneous enhancement patterns of both benign lymph nodes and malignant lymphoma, the sensitivity was not improved over B-mode US. CEH-EUS had a similar accuracy as EUS-FNA for diagnosing lymph node metastasis of pancreatobiliary cancer.

Gastrointestinal wall lesions

Assessment of the vascularization of gastric cancer is feasible using CE-EUS. The intensity of enhancement is correlated with pathological criteria of neo-angiogenesis (microvascular density; vascular endothelial growth factor, VGEF). CEH-EUS allows the assessment of treatment-induced changes of tumor vascularity in gastric cancer. Differentiation between potentially malignant GIST and benign sub-epithelial tumors of the upper gastrointestinal tract can be improved by CE-EUS. Significantly stronger enhancement was observed in GIST than in leiomyoma and lipoma. The detection of irregular intratumoral vessels in the arterial phase and a heterogeneous enhancement pattern are highly predictive for intermediate or high-risk GIST.

Visceral vascular diseases

CE-EUS may be used to diagnose splanchnic arterial and venous occlusive disease. Moreover, CE-EUS improves the visualization of flow in esophageal varices, paraesophageal veins and perforating veins.

RECOMMENDATION 49

Both low and high mechanical index (MI) contrast-enhanced (CE)-EUS techniques can help the characterization of solid pancreatic lesions (LoE 2a; GoR B), especially low MI CE-EUS for small (≤ 20 mm) lesions (LoE 1b; GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 50

CE-EUS can be used to distinguish between pancreatic ductal adenocarcinoma and neuroendocrine tumors (LoE 1b, GoR A). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 51

CE-EUS can be used to guide and target EUS-FNA of pancreatic lesions (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 52

CE-EUS allows accurate differentiation of cystic pancreatic neoplasms from pancreatic pseudocysts (LoE 2b, GoR B). Strong consensus (20/0/0, 100 %)

Abdominal Trauma

Background

CT imaging remains the standard technique for evaluating hemodynamically stable patients with high-energy multi-trauma, allowing rapid triage and reducing morbidity and mortality. CT has inherent disadvantages, which restrict its adequacy in some clinical scenarios: the patient needs to be stable and cooperative (sedation may be required, particularly in pediatric patients), it utilizes iodinated contrast media and carries the risks associated with radiation exposure. The latter is an important limiting factor, especially when a low-risk mechanism of injury and the patient's condition would not necessarily warrant a CT examination, even though an imaging investigation is required. Focused Assessment with Sonography for Trauma (FAST) has been widely used in the diagnostic pathway of the trauma patient, with a sensitivity that ranges from 63 % to 99 % for the detection of free fluid, but has poor sensitivity in the diagnosis of parenchymal injuries. UCAs have significantly improved the diagnostic performance of B-mode US in the depiction of solid organ injuries, with performance close to that of CT: CEUS can achieve a sensitivity and specificity of 99 %, avoiding overutilization of CT.

Study procedure

Commencing from the side of clinical concern, the examination should begin with the kidneys, their enhancement being the most fleeting, followed by the adrenals, liver, pancreas and lastly the spleen. The kidneys are studied during the arterial phase, while the liver, spleen, pancreas and adrenals are studied in the venous phases. Most commonly, the CEUS examination utilizes two separate doses of intravenous UCA: one dose is used to evaluate the right kidney, right adrenal, liver and pancreas and the second dose is aimed at the left kidney, left adrenal and spleen. In follow-up CEUS examinations, the known injured organ is targeted.

Image interpretation of abdominal injuries

On CEUS, lacerations and hematomas will show a complete lack of enhancement and will be clearly demarcated against the normal parenchyma, whereas areas of contusion may demonstrate faint enhancement. CEUS may also readily depict areas of hyperemia, infarct and active bleeding: any UCA pooling in the abdominal cavity will indicate the presence of ongoing hemorrhage, management becomes interventional. Crucial complications such as devascularized parenchyma, pseudoaneurysm formation and acute cortical necrosis of the kidney can also be promptly diagnosed on CEUS. CEUS can also allow further evaluation of abdominal injuries where CT findings are uncertain due to artifacts or where CT is discouraged e. g.in renal impairment and in children. CEUS can confidently exclude major abdominal visceral injuries and therefore, patients sustaining minor, low-energy trauma can be discharged following a normal CEUS examination without the need to perform a CT examination.

Limitations

CEUS cannot diagnose traumatic lesions of the pelvicalyceal system, UCAs being purely intravascular and not excreted through the renal collecting system. The limitations with respect to bowel injury and a hemodynamically unstable patient would warrant a CT examination rather than a CEUS examination.

RECOMMENDATION 53

CEUS can be used in hemodynamically stable patients with isolated blunt moderate-energy abdominal trauma to evaluate solid organ injury as an alternative to CT, particularly in children (LoE 1b, GoR A). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 54

CEUS can be used to further evaluate uncertain CT findings related to abdominal trauma (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

RECOMMENDATION 55

CEUS can be used in the follow-up of conservatively managed abdominal trauma to reduce the number of CT examinations, particularly in children (LoE 1b, GoR B). Strong consensus (20/0/0, 100 %)

Superficial Structures

Thyroid

Background

An increasing thyroid malignancy incidence (≤ 8 per 100 000 in Europe) would benefit from a noninvasive diagnostic method that allows reliable differentiation between malignant and benign thyroid nodules, superior to the current B-mode US features. CEUS is able to focus on the analysis of macro- and microvascularization patterns.

Study procedure

Thyroid nodule assessment

Qualitative parameters

Qualitative parameters characterize nodule vascularization compared to the surrounding tissue, defined as intensity, homogeneity, UCA uptake and washout rate. Hypoenhancement is the most precise predictor of malignancy on CEUS with high sensitivity, specificity and accuracy of 82 %, 85 % and 84 % respectively. A heterogeneous contrast enhancement pattern has a sensitivity, specificity and accuracy of 88.2 %, 92.5 % and 90.4 %, respectively. A ring enhancement pattern of a solid thyroid nodule is likely a benign feature with a sensitivity, specificity and accuracy of 83.0 %, 94.1 % and 88.5 %, respectively.

Quantitative parameters

Time-intensity curves (TIC) for quantitative analysis are generated by placing the region of interest (ROI) in the nodule occupying the largest possible nodule area and comparing it to the surrounding tissues. The following parameters are evaluated: area of ROI, wash-in slope, time to peak, peak intensity, area under the curve, mean transit time and washout. Time-intensity curve patterns of washout may appear as poly-phasic or mono-phasic related to the heterogeneity of the nodule and histology, with a sensitivity, specificity and accuracy of 76.9 %, 84.8 % and 82.6 %, respectively.

Size

Nodule size affects CEUS examination and interpretation. A nodule < 10 mm shows absent vascularization (incomplete neovascularization), while larger nodules > 10 mm appear hypervascular.

Image interpretation

The diagnostic value of CEUS has been analyzed in a meta-analysis showing high pooled accuracy of CEUS in the differentiation between benign and malignant nodules. There is insufficient evidence regarding the application of CEUS in the assessment of thyroiditis.

Limitations

CEUS is a promising noninvasive method for the differential diagnosis of benign and malignant thyroid nodules. However, overlapping data between CEUS qualitative and quantitative evaluation parameters and criteria of benign and malignant nodules indicate a limitation in the interpretation of tumor microvascularity. No single indicator is sufficiently sensitive or specific. Therefore, the results should be interpreted in conjunction with the clinical data, conventional US and other imaging examination findings to improve diagnostic accuracy in the assessment of thyroid nodules.

RECOMMENDATION 56

CEUS for the characterization of thyroid nodules is an active research field but at present cannot be recommended for clinical use (LoE 2b, GoR C). Strong Consensus (19/0/1, 100 %)

Lymph Nodes

Background

The US discrimination between benign and malignant superficial lymphadenopathy is dependent on shape, anatomical appearance and vascular pattern with a wide range of sensitivities and specificities. UCAs have been shown to increase the accuracy of the analysis of the vascular pattern using the conventional color Doppler mode.

Study procedure

Normal linear high-frequency transducers enabled for CEUS examination with higher doses of UCA administered, normally 4.8 mL of SonoVue™, as in other superficial structures, are used.

Image interpretation

Malignant neo-vascularization, demonstrated when vessels penetrate the capsule of the node away from the hilum, is a characteristic feature of a metastatic lymph node. A benign reactive lymph node has preserved morphology and vascular anatomy, with a single vascular pedicle at the hilum, containing both arteries and veins, regularly branching towards the periphery of the lymph node. Display of the vascular anatomy can be facilitated by the addition of UCA during color Doppler US. Using low MI CEUS techniques further improves characterization with a sensitivity and specificity of 93 % and 88 %, respectively.

US studies of lymph node vascularization have limitations, with most studies undertaken in specialized units and in patients with known head and neck cancer, melanoma or breast cancer. Vessel distribution analysis is usually satisfactory if the whole lymph node is involved but is less informative when focal lymph node involvement or necrosis renders a CEUS examination (as well as other imaging modalities) inconclusive. Lymph nodes with lymphoma infiltration are unique as the vascular pattern resembles that of non-malignant nodes, with a reported “speckled” pattern and a different configuration on time-intensity curves that may help to improve diagnosis.

RECOMMENDATION 57

CEUS for the characterization of superficial lymphadenopathy is an active research field but at present cannot be recommended for clinical use (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

Salivary Glands

Background

The B-mode US, Doppler US, elastography and CEUS appearance of parotid gland lesions has been analyzed to discriminate benign from malignant lesions. CEUS investigations were initially performed with high MI US using color Doppler and later with low MI techniques. The role of CEUS assessment of parotid gland lesions is limited by a paucity of studies, and relies on expert opinion.

Study procedure

Normal linear high-frequency transducers enabled for CEUS examination with higher doses of UCA administered, normally 4.8 mL of SonoVue™, as in other superficial structures, are used but fractionated doses have also been used.

Image interpretation

Qualitative approach

Malignant lesions demonstrate chaotic vessel formation on color Doppler US with increased enhancement with CEUS or with prominent organized vessel formation combined with slight enhancement on CEUS. Monomorphic adenomas showed vascularization patterns of all other entities. Pleomorphic adenomas with minor vessel identification on color Doppler US result in poor perfusion on CEUS. All Warthin's tumors show prominent internal vessel visualization on color Doppler US and increased enhancement with CEUS. According to the morphologic and distribution features of microvascularity, CEUS imaging of the lesions can be classified into three types: diffuse homogeneous enhancement (type 1), heterogeneous enhancement (type 2) and no enhancement/iso-enhancement (type 3). Types 1 and 3 are suggestive of benign tumors; Type 2 can indicate the presence of a malignant lesion.

Quantitative approach

Parotid gland lesions can be divided into different benign and malignant lesions by using specific time-intensity curve parameters from CEUS measurements. Malignant lesions appear highly vascularized, while benign lesions enhance less. The area under curve (AUC) and mean transit time (MTT) show significantly higher values for malignant lesions. The intratumoral time to peak in pleomorphic adenoma appears markedly longer than in cystadenolymphoma.

RECOMMENDATION 58

CEUS for the characterization of salivary gland lesions cannot be recommended for clinical use (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

Breast

Background

CEUS in the differential diagnosis of breast masses was an early application, with encouraging initial results, but this early promise has not been fulfilled, despite numerous studies using modern methods including temporal accumulation methods (microvascular imaging). Studies relating CEUS, MR imaging and biological factors and studies to obtain a precise qualitative and quantitative vascular map of the tumor, which appears to correlate well with prognostic factors or use CEUS to identify BI-RADS category 3 or 4 small breast lesions have all been conducted, without specific patterns of CEUS enhancement of malignant lesions. A single study documented characteristic CEUS enhancement patterns which could be helpful for identifying papillary lesions and for predicting a potentially malignant papilloma. CEUS has been used to estimate tumor size in invasive ductal cancer, which in turn predicted regional lymph node metastasis. Notwithstanding, no specific pattern indicating malignancy has been identified and, although an important research topic, cannot be recommended for routine clinical use.

RECOMMENDATION 59

CEUS for the characterization of breast lesions is an active research field but at present cannot be recommended for clinical use (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

Sentinel lymph nodes

CEUS can be used for detecting axillary sentinel lymph nodes in cancer patients. SonoVue™ 1 mL (or 2 mL Sonazoid™) as the UCA is injected intradermally into the locally anesthetized periareolar skin towards the upper outer quadrant of the involved breast. The UCA is taken up by the subdermal lymphatics and the enhanced lymphatics can be traced to the sentinel node(s). Initial experience indicates that the method is non-toxic and performs as well as the blue dye or radioisotope methods. It enables core biopsy of the sentinel node and, if positive on histology, is a reliable indicator of nodal involvement, directing patient counselling.

RECOMMENDATION 60

CEUS with intradermal injection of contrast agent to identify the sentinel lymph node is an active research field but at present cannot be recommended for clinical use (LoE 2b, GoR C). Strong consensus (20/0/0, 100 %)

Inflammatory joint diseases

Background

Color or power Doppler US can detect the vascularity in the synovial proliferation associated with inflammatory activity. However, these US techniques have limited sensitivity and could benefit from the addition of a UCA.

Study procedure

Reports on the use of UCAs in inflammatory joint disease detect enhancement by conventional color or power Doppler US (CE Doppler). A full dose of 4.8 mL (SonoVue™) is used with standard transducers and equipment when investigating joints with CEUS.

Image interpretation

Arthritis and synovitis

Microscopic examination of synovial biopsies shows angiogenesis from the earliest stages of inflammatory disease. Proliferation of hypervascularized pannus can be detected before joint destruction. It correlates with disease activity and appears to be crucial to its invasive and destructive behavior. The development of novel biological therapies (e. g. tumor necrosis factor-alpha inhibitors), which target the microvasculature, needs more sensitive vascular imaging to assess response to treatment. The addition of UCAs to Doppler US significantly improves the detection of vascularity in active rheumatoid arthritis and psoriatic arthritis. There is also evidence that CE power Doppler US helps to differentiate active from inactive disease in subclinical juvenile rheumatoid arthritis of the knee. CE Doppler correlates with the findings of CEMR imaging, indicating the degree of inflammation in patients with synovitis. CE Doppler is also more useful in the diagnosis of sacroiliitis than conventional Doppler.

Differentiation between synovial pannus and fluid

Early detection of vascularized synovia is a primary goal of the assessment of inflammation. CE Doppler US improves the differentiation between active synovitis and other articular thickenings, such as fibrotic pannus and articular fluid.

Bursae and tendon

Contrast administration can highlight peripheral enhancement on Doppler US, corresponding to the vascularized synovial lining of an inflamed bursa, and can better differentiate between fluid, fibrous and hypervascular synovial thickening in comparison to non-enhanced Doppler US.

Therapeutic follow-up

Successful treatment results in a decrease in synovial thickening and necrosis of the pannus with reduction of vascularity and Doppler US signals. The distinction between fibrous pannus and active synovial proliferation is important during follow-up, because the volume of the synovium itself is not clinically significant, as it may contain varying amounts of fibrous tissue. Fibrotic pannus shows no vascularity on conventional power Doppler US and lacks enhancement on CEUS.

RECOMMENDATION 61

CEUS for the further assessment of the degree of vascularization and for treatment monitoring in joints is an active research field but at present cannot be recommended for clinical use (LoE 2b, GoR C). Strong Consensus (18/0/2, 100 %)

Gallbladder diseases

Background

B-mode and color Doppler US are the first-line imaging modalities for the diagnosis of gallbladder disease. The use of CEUS improves the diagnostic accuracy of US in selected cases. CEUS is not indicated if conventional US provides a clear diagnosis.

Study Procedure

For evaluation of the gallbladder wall, 1.2 – 2.4 mL of SonoVue™ is used, unless a high frequency transducer is used when the dose is increased to 4.8 mL, with the arterial phase (< 30 s) differentiated from the venous phase (> 31 s). CEUS study of the gallbladder wall evaluates perfusion, contrast kinetics, branching intramural vessels and gallbladder wall integrity; with a late liver sweep for malignant metastasis.

Cholecystitis

Acute cholecystitis is normally associated with cholelithiasis, acalculous cholecystitis accounts for the minority of cases, but is associated with a higher incidence of gangrene and perforation. In acute cholecystitis, the inflammatory process may involve the adjacent liver tissue (“reactive hepatitis”) causing hepatic arterial hyperenhancement on CEUS. Gangrenous cholecystitis, transmural necrosis of the gallbladder wall, causes a discontinuous or irregular gallbladder on CEUS. CEUS should be considered in patients at risk for complicated acute cholecystitis. Superficial or infiltrating gallbladder carcinoma may mimic chronic cholecystitis, presenting with diffuse wall thickening, with stones or sludge obscuring a malignant tumor. CEUS may help to detect a silent carcinoma.

Tumors of the gallbladder wall

Polypoid lesions

Polypoid gallbladder lesions are commonly seen on US (2.6 % – 12.1 % of cholecystectomy specimens). In primary sclerosing cholangitis and gastrointestinal polyposis syndromes, 60 % of gallbladder polyps are malignant. Malignancy in gallbladder polyps between 6 – 10 mm is extremely rare, while polyps > 10 mm are regarded as preinvasive adenomas and papillary neoplasms. Adenomas have a wider vascular stalk, thought to be significant, that is best seen on CEUS. It remains unclear if CEUS can contribute to the differentiation between polyps, adenomas and noninvasive

gallbladder carcinoma. Polyps > 10 mm which show an iso- and inhomogeneous enhancement pattern may be a criterion to differentiate adenomas from cholesterol polyps.

Adenomyomatosis

Adenomyomatosis is a hyperplastic process of the gallbladder wall affecting the complete gallbladder wall or parts of it, with the fundus representing the most frequent site. No intrinsic malignant potential has been described, but has been reported at 6.6 % in Asia. On CEUS, the thickened wall demonstrates isoenhancement with a small non-enhancement rim surrounding the gallbladder.

Adenocarcinoma of the wall

Adenocarcinoma is the most common malignancy of the gallbladder arising in the majority of cases from underlying chronic cholecystitis. Nonspecific clinical signs result in a late diagnosis with a 5-year survival rate of 5 %. Differentiation between benign and malignant gallbladder tumors cannot be made by hyperenhancement during the arterial phase as gallbladder cancers (85 %) and benign gallbladder diseases (70 %) both show hyperenhancement. The CEUS features of washout within 35 s after UCA administration, the destruction of gallbladder wall integrity and infiltration of the adjacent liver tissue are highly suggestive features of malignancy and highly suggestive of gallbladder cancer. CEUS can be used to differentiate between GB tumors and biliary sludge. Gallbladder wall destruction beneath a solid lesion and the infiltration of adjacent liver tissue are highly suggestive features of malignancy.

Gallbladder metastasis

Metastatic lesions of the gallbladder wall are rare with melanoma accounting for > 50 %. On B-mode and CEUS, exophytic mural tumor nodules extend into the lumen of the gallbladder, with CEUS indicating a flow away from the wall.

RECOMMENDATION 62

CEUS can be used in acute cholecystitis to better detect local complications (LoE 2b, GoR B). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 63

CEUS may differentiate chronic cholecystitis from gallbladder carcinoma (LoE 2b, GoR B). Strong Consensus (19/0/1, 100 %)

RECOMMENDATION 64

CEUS is able to differentiate between a perfused gallbladder lesion and motionless biliary sludge (LoE 4, GoR C). Strong consensus (20/0/0, 100 %)

Neurosurgery

Background

Intraoperative CEUS (iCEUS) allows for excellent evaluation with distinct enhancement phases and good delineation between lesions/vessels and healthy structures. These iCEUS features, together with high temporal and spatial resolution, make iCEUS invaluable in neurosurgery for vascular and oncological applications.

Study procedure

Ultrasound equipment

A contrast-enabled multi-frequency linear array transducer (3 – 11 MHz), most using frequently the UCA SonoVue™, is deployed.

Examination technique

Patient positioning and craniotomy must be designed to allow direct contact of the transducer with the brain surface or the cavity filled with saline, to allow transducer manipulation. A preliminary CEUS examination is performed through the dura-mater after bone flap removal, preceded by a B-mode US examination, allowing identification of anatomical landmarks and lesion position/relationships. A standard evaluation to identify principal arteries, capillary and veins in the region of interest, evaluating the timing distribution and degree of UCA enhancement, is required.

Intraoperative applications

Intraoperative evaluation of cerebral and spinal neoplastic lesions

Neoplastic lesion identification

Standard B-mode US is able to visualize and delineate most neoplastic lesions, both intra- and extra-axial. In intrinsic tumors with ill-defined borders or in the presence of brain edema, B-mode US is insufficient to evaluate tumor morphology and borders. iCEUS highlights the tumor parenchyma and the tumor-brain interface accurately, relying on the abnormal density of capillaries between the pathological tissue and the surrounding parenchyma.

Tumor characterization

The degree of contrast enhancement and distribution is related to the density of capillaries in the region of interest. iCEUS allows real-time characterization of different histological types and grades dependent on timing, distribution and degree of contrast enhancement.

Tumor vascularization and surgical strategy

The direct visualization of parental and surrounding vessels allows determination of vessel location in the surgical field and optimizes the surgical strategy, allowing for early tumor devascularization before removal, thus reducing intraoperative bleeding.

Tumor resection control

Safe repeated iCEUS examinations during surgery allow visualization of residual tumor within the surgical cavity, overcoming B-mode US limitations. iCEUS also allows assessment of complete tumor removal, showing no remaining enhancing areas and an absence of abnormal venous drainage.

Intraoperative angio-sonography for cerebral and spinal vascular lesions

Vascular malformations are identified with Doppler US. iCEUS allows interpretation of the vascular tree prior to surgical exposure. iCEUS is able to determine the location of a vessel and follow its entire course and may be used with many different vascular abnormalities. iCEUS can also verify exclusion of the lesion from the circulation at the end of the procedure, and can also asses flow direction, vessel patency after aneurysm clipping, and brain perfusion in the distal territories.

Intraoperative contrast-enhanced ultrasound in traumatic brain surgery

iCEUS during surgery for trauma allows distinction between normal and injured brain tissue, more clearly than B-mode and color Doppler US. This improves the accuracy of the classification of traumatic brain injury, effectively removing hematoma and/or infarcted brain while preserving healthy tissue.

Limitations

Operator training is paramount and the craniotomy has to be large enough to allow free transducer movement. Transducer pressure on neural structures must not damage vessels or the parenchyma. Static retractors must be temporarily removed during iCEUS evaluation. The use of hemostatic materials must be limited to prevent artifact formation and restriction of the field of view.

RECOMMENDATION 65

Intraoperative CEUS is indicated in neuro-oncological procedures for tumor identification, assessment of boundaries, perfusion pattern and evaluation of residual tumor (LoE 4, GoR C). Strong consensus (19/0/0, 100 %)

RECOMMENDATION 66

Intraoperative CEUS is indicated in angiosonography for neurovascular procedures (LoE 4, GoR C). Strong consensus (19/0/0, 100 %)

RECOMMENDATION 67

Intraoperative CEUS is indicated in traumatic brain surgery to demonstrate tissue viability (LoE 4, GoR C). Strong Consensus (18/0/1, 100 %)

Interventional CEUS

Background

CEUS has obvious potential during US-guided interventional procedures. Any CEUS guided intervention can be performed in a similar manner to the routine US-guided version of the procedure. It may be necessary to use two UCA injections, one to plan the procedure and a second to perform it. Alternatively, infusion may be used throughout the procedure. Besides the established use of CEUS in relation to percutaneous ablation and the potential benefit from intracavity CEUS, potential indications relate to accurate delineation of tissue vascularization.

Avoiding biopsy of necrotic tissue

By directing the biopsy needle towards contrast enhanced areas within the target lesion, sampling from necrotic parts of the tumor can be avoided, resulting in an up to 15 % increase in diagnostic accuracy reported in large tumors and liver metastases and in lung, neck and musculoskeletal tumors.

Biopsy of poorly visualized or “invisible” lesions

When a biopsy is required based on findings from CT, MR or PET-CT imaging and the lesion is not clearly visualized or not visualized with B-mode US, CEUS may be helpful in two different ways: the target lesion suspected from previous imaging may become conspicuous on CEUS or additional lesions that are more accessible for biopsy may be visualized and biopsied.

Further benefits from CEUS in interventional US

CEUS may be used to:

a) Diagnose and monitor all stages of bleeding related to interventional procedures and guide percutaneous local application of hemostatic drugs.
b) Improve breast cancer staging by identifying and guiding biopsy of the sentinel node after intradermal CEUS if axillary B-mode US is normal.
c) Improve visualization of poorly depicted fluid collections.
d) Avoid biopsy of lesions if CEUS study unequivocally shows benign lesion, e. g. hepatic hemangioma.

RECOMMENDATION 68

CEUS can be helpful in avoiding necrotic tissue or identifying perfused tissue in the biopsy of tumors (LoE 2b, GoR C). Strong consensus (19/0/0, 100 %)

RECOMMENDATION 69

CEUS can be helpful in identifying biopsy targets inconspicuous on US (LoE 2b, GoR C). Strong Consensus (17/0/2, 100 %)

Interstitial Ablation Therapy

Background

Interstitial ablation treatments are nonsurgical options for the management of confined tumors in the liver, kidney, prostate and uterus. CT and MR imaging represent the standard imaging modalities to assess therapeutic efficacy, but with evidence of the useful role of CEUS in the detection, guidance and confirmation of treatment success.

Kidney

Thermal ablation is an accepted treatment option for unresectable renal cell carcinoma (RCC). The American Urological Association guidelines recommend ablation in patients with T1a disease (< 4 cm) with high surgical risk, or in case of solitary kidney. Until recently, both preprocedural diagnostic workup and postprocedural follow-up of patients referred for RCC ablation have included CT and/or MR imaging, whereas conventional B-mode US is frequently used for guidance during the ablation procedure. CEUS is an important tool in the management of these patients and plays a decisive role in all stages of percutaneous ablation therapies.

Study procedure

Pretreatment evaluation

Diffuse heterogeneous enhancement in the arterial phase, washout in the late phase and perilesional rim-like enhancement are typical features of renal malignancies. Identification of a pseudocapsule predicts improved ablation efficacy, and inclusion of CEUS in the preprocedural imaging workup is useful to compare preablation and post-ablation tumor viability.

Intraprocedural evaluation

Intraprocedural ablation evaluation is important but CEUS can be affected by gas artifacts of the ablation technique that can mask evaluation of tumor necrosis. Normally a 10- to 15-minute postablation period should be allowed before assessing the outcome. CEUS has demonstrated high sensitivity, specificity and accuracy for the early detection of residual un-ablated tumor, comparable to CT and MR imaging.

Follow-up

Surveillance is recommended in patients who have undergone ablation due to a high local recurrence rate for tumors > 3 cm, with suggested imaging surveillance every 6 months as CEUS can detect early recurrence not visible on B-mode US. For the evaluation of residual or recurrent RCC, the sensitivity and specificity of CEUS are 82.2 – 100 % and 96.6 – 100 %, respectively. The concordance of CEUS with CT or MR imaging is between 80 % and 100 %.

Prostate

Interstitial ablation through high-intensity focused ultrasound (HIFU) can be applied in localized prostate cancer in patients at high surgical risk or for local recurrence after radiotherapy. There is good concordance between MR and CEUS imaging, with CEUS being able to clearly and correctly identify the devascularized area of necrosis and the residual viable tissue, permitting immediate repeat treatment.

Uterus

CEUS in the intraprocedural evaluation of treatment response of benign uterine fibroids to US-guided HIFU demonstrated that CEUS correlated well with MR imaging. Four studies for the evaluation of the therapeutic efficacy of uterine fibroids compared the performance of CEUS to MR or unenhanced US with CEUS performing well compared to MR and better than B-mode US.

RECOMMENDATION 70

CEUS may be used in the management of patients treated with ablation therapies including renal cell carcinoma (LoE 1b, GoR B), uterine fibroids (GOR C) and prostate cancer (GOR C). Strong consensus (18/1/0, 95 %)

Miscellaneous

Intracavitary uses

Background

Extravascular or intracavitary administration of UCAs may be used as a problem-solving tool, recognized in a number of reports as an adjunct to US-guided interventional techniques, with practical advice detailing the available concepts and techniques.

Study procedure

No standard UCA dosage has been established for intracavitary applications. The range reported is 0.1 mL – 1 mL SonoVue™ (or a few drops) diluted in ≥ 10 mL 0.9 % normal saline. A higher UCA dose may be needed for high-frequency US transducers.

Injection into physiological cavities

Imaging of tubal patency

Originally performed using agitated saline infused into the uterine cavity, hystero-salpingo-sonography has a 12 % false-negative patency rate. Contrast-enhanced hystero-salpingo-contrast sonography (CE-HyCoSy) with SonoVue™ provides better specificity, but is low for the diagnosis of an occlusion. CE-HyCoSy should only be performed if conventional hystero-salpingo-contrast sonography does not show patency.

Detection of peritoneal-pleural communication

The detection of direct connections between the abdominal and pleural cavities, hepatic hydrothorax, can be established in cirrhotic patients by injecting a UCA into the peritoneal cavity, early (< 2 days) after thoracentesis and demonstrating UCA passage into the pleural cavity.

CEUS-guided percutaneous transhepatic cholangiography

CEUS-guided percutaneous cholangiography is able to delineate the biliary tree via an indwelling T-tube in place of the conventional fluoroscopic techniques, with the advantage of 3 D techniques. This technique allows for deployment at the point of care. UCA for endoscopic retrograde cholangiography (CEUS-ERC) has been reported.

Intracavitary CEUS for guiding percutaneous nephrostomy

Intracavitary CEUS can guide percutaneous nephrostomy and assess complications and is able to confirm the needle or catheter position, evaluate the site of obstruction and assess catheter-related complications. Patients with contraindications to iodinated contrast agents are suitable for this technique or at the point of care.

Salivary glands

CEUS injected into the main duct of a salivary gland may be a diagnostic method to categorize obstructive diseases of the salivary glands. The salivary gland is cannulated with appropriate dilatators and the plastic tube of a peripheral vein catheter is inserted.

Injection into non-physiological cavities

CEUS for the imaging of fistula

CEUS detection and classification of fistulas, irrespective of the underlying disease, is effective. The following conditions have been reported: rectovaginal fistulas via a transvaginal approach, vesico-intestinal fistulas via a transabdominal approach and anal fistulas via the transrectal approach.

CEUS for the imaging of abscesses

Image-guided treatment of abscesses includes drainage with a needle or catheter, plus lavage. Direct injection of a UCA through the needle or catheter has been reported to facilitate confirmation of correct needle or catheter position and allows evaluation of any communication between cavities in complex abscesses.

RECOMMENDATION 71

Intracavitary CEUS allows identification of needle or catheter position, delineation of any cavity or duct, improved tracking of a fistula, optionally supplemented by intravenous CEUS (LoE 3, GoR C). Strong consensus (19/0/0, 100 %)

Free Tissue Transplants

Background

Free flap reconstruction of complex defects after trauma, tumor resection, burns, or poor wound healing is able to restore the integrity of the defect and provide return of function. Despite technical refinement, flap loss due to vascular compromise occurs and is a serious complication. Early identification of vascular compromise and prompt revision permits early flap salvage, with CEUS being an ideal technique for the early detection of reduced vascularization. CEUS is the only imaging method for the evaluation of dynamic changes of microvascularization during surgery and postoperative follow-up

Study procedure

High-frequency transducers (≥6 MHz) are used to evaluate the microcirculation of the cutaneous, subcutaneous, and deeper layers of free flaps most frequently using 1.2 – 2.4 mL SonoVue™. Postoperative TIC analysis allows calculation of peak and time to peak of enhancement and regional blood volume.

Image Interpretation

Preoperative planning

The blood vessels in the transplanted free flap are small (1 – 2 mm). The surgeon needs to know the integrity of the flow, precise number, course and position of these blood vessels in order to estimate the proportion with a good blood supply. Evaluation to determine time to peak (TTP), relative blood flow (rBF) and relative blood volume (rBV) as well as the evaluation of the critical microvascularization in the different layers of the free flaps is undertaken.

Intraoperative imaging

CEUS enables the identification of perforator vessels intraoperatively, detecting abnormalities, to allow a more accurate decision as to whether the entire flap is perfused and if the estimated flap size is correct.

Postoperative monitoring

The feeding vessels or, if there is a connection to a bypass, the anastomosis, as well as the free flap vessels is examined identifying thrombosis, embolism, twisting, kinking, or compression to confirm successful surgical salvage.

Critical microvascularization

A significant difference between normally vascularized and compromised flaps can be observed most usefully with TTP and RBF. For CEUS and CE-MRI, the mean signal increase of the TIC was significantly higher in ROIs of normally perfused flaps compared to compromised flaps. With CEUS, the exact size of the necrotic regions, hematoma or seroma can be evaluated by analyzing avascular areas.

Limitations

A limitation for the evaluation of flap perfusion is the time allowed after a bolus injection of the UCA. Continuous infusion may improve this, but this has not been evaluated.

RECOMMENDATION 72

CEUS may be used for the pre-, peri-, and postoperative evaluation of vascularization in free flap transplantation (LoE 2, GoR B). Strong consensus (19/0/0, 100 %)

Lung

Background

US of parenchymal lung lesions targets only those lesions abutting the pleura, and in this context, an accurate diagnosis is possible. CEUS in the evaluation of lung lesions is less well investigated. The lung parenchyma has a dual arterial system, the pulmonary arteries and the bronchial arteries. The ratio between blood supply from pulmonary arteries and bronchial arteries varies depending on the etiology of the underlying disease.

Study Procedure

The administered dose varies (SonoVue™ 2.4, rarely 4.8 mL) followed by a bolus of normal saline, with the enhancement continuously observed for at least 30 seconds. A time to enhancement of < 10 seconds is indicative of a predominant supply from pulmonary arteries.

Clinical applications

CEUS might be a valuable tool to differentiate benign from malignant lesions and in the assessment of pulmonary embolic consolidation. Studies are limited, with few patients to allow for determination of the diagnostic value of CEUS in the evaluation of lung lesions.

Pneumonia

Pneumonia is mainly supplied by the pulmonary artery, resulting in early (< 10 seconds) homogenous enhancement. CEUS has also been reported to be a valuable tool for detecting and guiding drainage of abscess formation within pneumonia.

Pulmonary embolism

Embolic consolidations in patients with pulmonary embolism are reported to show absent or non-homogenous enhancement on CEUS, a consequence of variable degrees of bronchial arterial supply. This feature could be helpful for distinguishing pulmonary infarction from pneumonia or compression atelectasis.

Atelectasis

Compression atelectasis is mainly supplied by the pulmonary artery and demonstrates early, marked enhancement on CEUS, whereas obstructive atelectasis presents with a delayed enhancement pattern. Responsive vasoconstriction in obstructive atelectasis is considered responsible for the differences in enhancement pattern, but this is debatable.

Lung cancer

The enhancement pattern of lung cancer is variable, but there are suggestions that delayed (> 7.5 seconds) enhancement in neoplastic lesions might be a useful characterization of malignant pulmonary lesions. CEUS may be used to avoid areas of necrosis in US-guided biopsies to increase diagnostic accuracy.

RECOMMENDATION 73

CEUS may be used to delineate lung abscesses (LoE 3b, GoR C) and to guide US biopsy of non-necrotic areas of visualized lung lesions (LoE 3b, GoR C). Strong Consensus (16/0/3, 100 %)

Tumor Response Assessment

Background

The advent of novel therapies targeting tumor angiogenesis and vascularity has highlighted the need for accurate and reproducible quantitative techniques to assess early changes in tumor vascularity. However, as these therapies are predominantly cytostatic, current response assessment, which is based on interval evaluation of the tumor size using the Response Evaluation Criteria In Solid Tumors (RECIST), is inadequate as it reflects only late changes and is unable to identify non-responders at an early time-point.

Study procedure

Dynamic contrast-enhanced US (DCE-US) can be performed using two different approaches with different results:

Bolus injection of a UCA with TIC analysis

Single plane imaging is usually performed at 10 – 20 frames per second for the duration of the enhancement. The average intensity within a region of interest (ROI) can be displayed as a function of time, i. e., a TIC which describes the wash-in and washout of the UCA in the ROI. In addition, a second ROI can be placed in a reference tissue for comparison purposes. The majority of clinical studies to date are based on this method.

Intravenous infusion of a UCA with disruption-replenishment analysis

The UCA is administered over 5 to 20 minutes. UCA is first imaged without being disrupted at a low MI, then the MI is increased for a few frames, causing microbubble disruption. Immediately after that, the MI is returned to the non-disrupting level to observe the replenishment of the microbubbles into the ROI. Various models describe the echo-signal dynamics during the UCA-replenishment phase, which can be used for flow analysis. Initially, monitoring for tumor response with UCAs relied on qualitative analyses, but new methodologies have been developed to produce more robust and semi-quantitative indices. Analyses of the TIC, including wash-in

and washout times, can be performed with curve fitting to determine functional indices. The main indices include: peak intensity (PI); area under the curve (AUC); area under the wash-in (AUWI); area under the washout (AUWO; all corresponding to blood volume); time to peak intensity (TPI); slope of the wash-in (SWI; both corresponding to blood flow); and mean transit time (MTT). No permeability information can be obtained because of the pure blood pool nature of microbubbles.

Clinical application

Early clinical trials employed qualitative analysis in the assessment of the response of different tumors such as gastrointestinal stromal tumor (GIST) or renal cell carcinoma. More recently, there have been studies using semi-quantitative techniques with UCA bolus injection in renal cell carcinoma, hepatocellular carcinoma (HCC) and GIST. Studies showed that two indices representing blood volume correlated with the RECIST response; one study on renal cell carcinoma demonstrated a correlation of such indices with Progression Free Survival and Overall Survival. The results could not be reproduced in a study tested the disruption-replenishment technique versus Progression Free Survival assessed by the RECIST method.

A multicenter study of various types of tumors treated with anti-angiogenic therapies, such as metastatic renal cell carcinoma, GIST, colon cancer, melanoma, breast cancer and HCC, with approximately half of the tumors being located outside the liver, is currently being conducted in 539 patients with more than 2000 DCE-US scans. A quality score was proposed in a standardized acquisition, with AUC being the best parameter. A decrease of 40 % at one month was significantly correlated with Freedom From Progression (FFP) and also with Overall Survival which is the best endpoint for the validation of a biomarker. There is now emerging evidence that DCE-US may be used with appropriate tools to differentiate between responders and non-responders at an earlier stage than conventional methods and this potentially allows tailoring of the treatment regimen, particularly changing treatment for non-responders. DCE-US has been endorsed by the European Medical Oncology Society to assess response under biological therapy for GIST.

RECOMMENDATION 74

Dynamic CEUS can be utilized to assess response to biologic therapy in metastatic GIST and in other tumors (LoE 1b, GoR A). Strong Consensus (15/0/4, 100 %)

Conflict of Interest

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Fabio Piscaglia: Speaker honoraria Bracco, Bayer; Advisory Board Member, Bayer; Research support, Esaote
Maija Radzina: Speaker honoaria, Bayer, Covidien; Congress participation support, Bayer
Adrian Saftiou: Speaker honoraria, Pentax Medical Singapore Ltd; Consulting/Advisory board, Mediglobe Corporation Gmbh; Congress participation support, Hitachi Medical Systems UK
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Representatives of these companies were in attendance at this meeting, to assist with technical product information but did not take part in writing of this manuscript or the recommendations.