Contrast-enhanced ultrasound for monitoring nonsurgical treatments of uterine fibroids– A systematic review

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Abstract

Nonsurgical treatment options for uterine fibroids are uterine artery embolization (UAE), high intensity focused ultrasound ablation (HIFUA), and percutaneous microwave ablation (PMWA). Magnetic resonance imaging (MRI) is the reference standard imaging method before and after these procedures. Contrast-enhanced ultrasound (CEUS) has been studied as an alternative to MRI for evaluating the fibroids' characteristics and responses to nonsurgical treatments. English literatures investigating the application of CEUS as an adjunct to monitor UAE, HIFUA or PMWA in uterine fibroid treatments in human were searched in PubMed, Ovid Medline, and Scopus databases from January 2000 through June 7th, 2020. Two independent reviewers analyzed 128 publications, out of which 17 were included. Based on this systematic review, CEUS provides detailed data about fibroid volume and vascularization prior, during, and post UAE, and it helps determine the endpoint of the procedure. HIFUA with Intraprocedural CEUS has faster volume shrinkage over a shorter time period with less needed energy and provides early detection of residual tissue after HIFUA. CEUS and contrast-enhanced MRI (CE-MRI) have sufficient agreement to be used interchangeably in the clinic to evaluate the therapeutic effect of PMWA and HIFUA of fibroids.

Keywords

Uterine fibroid; contrast-enhanced ultrasound; uterine artery embolization; percutaneous microwave ablation; High-intensity focused ultrasound ablation

Introduction:

Fibroids are the most common benign tumors of the uterus in women over the age of 40 years. They are monoclonal tumors arising from a single smooth muscle cell of the

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myometrium (Holdsworth-Carson et al. 2014). Uterine fibroids may exhibit symptoms like excessive bleeding and anemia, pelvic pain, bowel and bladder dysfunction, pregnancy losses and infertility depending on their size, number and location (Brolmann & Huirne. 2008). Hysterectomy is the most common surgical procedure in fibroids with abnormal uterine bleeding or bulk-related symptoms (Borah et al. 2016), but there are alternative nonsurgical treatment options such as uterine artery embolization (UAE), high intensity focused ultrasound ablation (HIFUA), and percutaneous microwave ablation (PMWA) (Sohn et al. 2018). UAE is a technique performed to induce volume reduction in uterine fibroids by obstructing bilateral uterine arteries via micro catheter under fluoroscopy (Keung et al. 2018), while HIFUA is a therapeutic modality that induces thermal necrosis of biological tissues by focusing high-energy ultrasound waves at one specific target (Kim 2017). PMWA is also a thermal ablation technique in which the electromagnetic energy is delivered to the target tissue by a needle like antenna, then microwave radiation induces coagulative necrosis in the tissue surrounding the antenna (Carrafiello et al. 2008)

Currently, MRI without and with contrast is the reference standard for evaluating uterine fibroids prior to any of these treatments (Williams et al. 2011), and interventional radiologist are turning to post-procedural MRI as a follow-up post treatment to determine treatment efficacy (Chrisman et al. 2009). However, MRI is quite expensive, time consuming, and not always available in all medical centers. Moreover, insurance coverage for post-procedure MRIs is becoming a rarity, which is a concern for many patients. Thus, a more available, time-saving, and cost-effective imaging modality is highly needed for assisting those non-surgical treatments.

CEUS, which is a relatively new technique in this field, has been studied as an alternative to MRI because of its lower cost, real-time analysis, and fewer side effects. CEUS uses ultrasound contrast agents (UCAs) which are gas-filled microbubbles with diameters less than 8 μm, and a lipid, protein, or a polymer shell (Lyshchik 2019). UCAs strongly scatter the incident pulse due to marked difference in acoustic impedance at the blood gas interface (Chong et al. 2018). They also undergo volumetric oscillation due to high compressibility of the gas inside the microbubbles, and enhance the backscattered ultrasound signals much more than the surrounding tissues. Contrast specific imaging modes such as harmonic imaging can distinguish the backscattered echoes of the UCAs from received echoes of the tissue (Stride et al. 2003). Since microbubble are the same size as red blood cells, they do not extravasate into the interstitial space and are limited to the intravascular space, which makes them perfect for imaging the micro and macro vasculature. The signal intensity is proportional to the amount of microbubbles in the analyzed tissue and is related to the perfusion in the region of interest (Dietrich et al. 2012). Currently, there are three UCAs approved by the FDA. Definity (Lantheus Medical Imaging, N Billerica, MA) and Optison (GE Healthcare, Princeton, NJ) are approved for echocardiography only, but can be used off-label elsewhere. Lumason (Bracco SpA, Milan, Italy) - known as Sonovue in the rest of the world-has been approved for cardiac and non-cardiac use in the United States in 2016 (Chong et al. 2018).

The vascular enhancement pattern of uterine fibroid with CEUS has been reported in a few studies (Zhang et al. 2010; Stoelinga et al. 2018). There are two characteristic phases -early

and late-in the enhancement process of fibroids. The early phase begins after UCA injection, when the enhancement is first observed in the fibroids until it reaches its maximum level (Zhang et al. 2010). During the late phase, the enhancement returns to the baseline level (i.e., wash out).-The fibroids enhance earlier than surrounding myometrium and display faster washout than the myometrium in around 95% of the cases, leaving a black-hole impression (hypo-enhancement) facilitating the determination of the location, size, and number of the tumors, since the contour of the tumors become clearly visible (Zhang et al. 2010;Stoelinga et al. 2018). CEUS provides additional details in terms of fibroids' pseudo-capsule, central necrosis, and intra-lesion vascularity pattern (quantified based on time–intensity curves), compared to grey-scale ultrasound, sonoelastography, and color/power ultrasound (Stoelinga et al. 2018) (figure 1).

Our systematic review aimed to evaluate the application and safety of CEUS as an adjunct to monitoring UAE, HIFUA, and PMWA for fibroid treatment. All included studies had been approved by an ethics committee or institutional review board.

Material and Methods:

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (Moher et al. 2009) (Figure 2). The current study is a systematic review of previously published studies institutional review board approval and patient consent were not necessary.

Search strategy and study selection

English literature investigations of the safety and application of CEUS as an adjunct to monitor UAE, HIFUA or PMWA in uterine fibroid treatments in human were searched for in PubMed, Ovid Medline, and Scopus databases from January 2000 through June 7th, 2020. The search strategy was (Contrast enhanced ultrasound OR contrast-enhanced ultrasound OR contrast enhanced ultrasonography OR contrast-enhanced ultrasonography OR contrast-enhanced sonography OR contrast enhanced sonography OR CEUS) AND (uterine fibroid OR uterine myoma OR uterine myoma OR uterine fibroid OR uterine leiomyoma) AND (Uterine artery embolization OR UAE OR Percutaneous microwave ablation OR HIFU OR High intensity focused ultrasound). The detailed search strategy is shown in Supplementary Table 1.

The initial search and assessment of the eligibility of the studies were independently reviewed by two authors (M.T., P.M.) and disagreements were resolved by a third reader (F. F.). Studies were eligible for inclusion if they had addressed the feasibility, efficiency and/or safety of the peri-procedural CEUS in nonsurgical uterine fibroid treatment. Only human studies with full text in English were assessed for inclusion. Studies without detailed method and result section were excluded. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches.

Results

One hundred twenty-eight potential studies were identified and retrieved for evaluation. After removing the duplicates and exclusion of studies based on the title and abstract, 28 remained for full text review. After two authors independently reviewed the articles, nine did not directly discuss the safety or application of CEUS in nonsurgical treatments of uterine fibroids and further two were excluded, due to inadequate data in method section or results. When consensus was reached by the authors, 17 publications met the inclusion criteria. Among the selected 17 papers, 6 studies focused on the usage of CEUS in UAE, 9 studies were discussing the applications of CEUS in HIFUA, and 2 studies focused on the usage of CEUS in PMWA. (Tables 1–3)

CEUS in UAE treatment of fibroids

In 2004, Marret et al reported a completely perfused uterus with enlarged areas, due to the fibroids observed in the pre-UAE CEUS exam and persistent perfusion in the myometrium but not in the fibroids on the post-UAE CEUS exam (CEUS was performed before UAE, after left UAE, and after bilateral UAE) (Marret et al. 2004). Thus, the authors concluded that CEUS could be used for monitoring UAE, at the end of embolization, and 24 hours later. They added that CEUS could check for myometrial perfusion to avoid over-embolization and confirm that redistribution of the embolic material has not occurred. An example from our practice of this pre- and post UAE CEUS enhancement pattern is shown in Figure 3.

Typically, the angiographic endpoint of the UAE procedure is occlusion of the fibroids' vessels, while a sluggish forward flow is maintained in the main uterine arteries (Pelage et al. 2005). Dorenberg and colleagues evaluated the feasibility of using CEUS during UAE to correctly define the endpoint of embolization (complete devascularization of all fibroids) (Dorenberg et al. 2007). CEUS was performed reaching the angiographic endpoint, while the angiographic catheters in both uterine arteries were still in place, and the procedure was continued until CEUS showed complete lack of enhancement of the fibroids, or continuing the procedure was no longer technically possible. When compared with post-procedural MRI studies, the CEUS findings matched with the post-procedural CE-MRI in terms of the degree of devascularization after UAE, supporting CEUS as a feasible technique during UAE (Dorenberg et al. 2007). Between the years 2006 to 2009, this group of researchers also performed 30 UAE studies with CEUS and found that CEUS changed the endpoint of embolization in 17% of patients, and 97% of patients showed complete infarction of all fibroids on follow-up MRI after 3 months (Dorenberg et al. 2012).

Similarly, Sconfienza et al carried out a study during which CEUS prior to, immediately after, 1 and 6 months after UAE, and dynamic MR prior to and 3 months after UAE were performed. In each examination, the size and perfusion of the fibroids, the devascularized area, and areas of persistent perfusion after treatment were evaluated. In all cases, CEUS findings were similar to those of the CE-MRI examination, indicating that CEUS could provide good visualization of fibroid size and vascularity prior to and after UAE. Moreover, they also found performing CEUS while the catheter was still in the uterine artery provided the opportunity to directly evaluate the interruption of the fibroid's blood supply instead of

indirect angiographic evaluation of devascularization, which also decreased the radiation exposure time and amount of embolic material needed during UAE (Sconfienza et al, 2008).

Subsequently, CEUS was applied to understand the characteristics of fibroid microvascularization before and after UAE, how fibroids can be embolized without embolization of the myometrium, the radiologic predictive factors for successful embolization and to evaluate the concordance with CE-MRI (Marret et al, 2014). Compared to conventional pre-embolization Doppler ultrasound that only showed rim vascularity in 50% of uterine fibroids, pre-embolization CEUS and CE-MRI provided detailed data for fibroids' vascularization location and quantification with total enhancement rates of 82.5% and 80%, respectively. There was also a perfect concordance between the pre-embolization perfusion observed with CE-MRI and CEUS. However, in the post-embolization period, Marret et al. found that enhancement in CEUS on post-operative day 1 after UAE could be evidence of probable clinical failure in the intermediate term, while CEUS results at 6 months after UAE did not correlate with clinical failure nor agreed with the MRI results. With CEUS, myometrium was totally perfused in 70% and 100% of patients in one day and six months post-embolization, respectively. No quantitative vascular indicators predicting the clinical results were found (Marret 2014).

Recently, the discordance between CEUS and MRI was presented in a case where a 39-year-old woman with an enlarged uterus underwent UAE with the use of intraoperative CEUS to evaluate the uterine fibroids' vascularity and determine the endpoint of embolization peri-operatively. While CEUS findings immediately after UAE were interpreted as 'complete devascularization' of the fibroids, the 6 months follow-up MRI findings showed a remaining smaller fibroid with enhancement at the inferolateral of the posterior aspect of the uterus (Pesapane et al. 2020). The authors explained that the misinterpretation of CEUS findings as complete devascularization in cases with multiple fibroids in a same ultrasound plan may be related to 'satisfaction of search' of the operators following recognizing the bulk of devascularized fibroids and caution should be made to alleviate this risk. No adverse reaction has been reported in the studies reviewed above.

CEUS in HIFUA treatment of fibroids

Typically, with CE-MRI after HIFUA, the unenhanced part of the treated area represents the non-perfused volume (NPV) and the fractional ablation (NPV/uterine fibroid volume before HIFUA) is the most important factor for the long-term clinical outcomes of HIFUA; completely ablated lesions do not enhance, which reflects the disappearance of the blood supply and subsequent necrosis, while any residual tumor is observed as a focal enhancing area within the ablated areas, and diffused enhancement indicates failed treatment (Funaki et al. 2007; Stewart et al. 2007). In 2007 Zhou and colleagues conducted the first study comparing CEUS with MRI within 1 week after HIFUA in patients with uterine fibroids. This study demonstrated the same results with CEUS and CE-MRI in terms of typical coagulative necrosis and vascular damage, which were further confirmed by pathology. The authors concluded that CEUS is useful to evaluate the early therapeutic effect of HIFUA and has 100% negative predictive value for evaluating the residual unablated tumor, suggesting that immediate MRI follow-up after HIFUA is not necessary. CEUS may also help in

targeting the residual tumor foci during the additional ablation procedure in fibroids requiring repeat HIFUA (Zhou et al. 2007).

UCAs has been demonstrated to collapse when exposed to higher acoustic pressures (typically > 500 kPa), causing local mechanical injury to the ablated tissue and also enhancing the heating effect of high intensity focused ultrasound (HIFU) (Kajiyama et al. 2010). In 2012, in order to compare the therapeutic response to HIFUA in fibroid treatment, Peng et al. conducted a retrospective study of 162 HIFUAs performed 10 minutes after SonoVue injection and HIFUA in 129 patients without SonoVue injection. They found the median sonication time for ablating 1 cm^3 of fibroid volume was significantly shorter in the group with SonoVue (16 seconds) than without it (26 seconds; p = 0.005), and the median fractional ablation immediately after HIFU treatment was 86.0% in the group using SonoVue, and 83.0% in the group without SonoVue (p = 0.025). When fibroids were categorized based on their size, the sonication time to achieve the greyscale changes was significantly different between two groups in fibroids between 4-8 cm in diameter (p < 0.001), but the rate of massive grey scale changes, fractional ablation, and non-perfused volume were not significantly different between the two groups when fibroids were >4 cm in diameter. Therefore, Peng and colleagues concluded that microbubbles are safe to use and enhance the effect of HIFUA in uterine fibroid treatment (Peng et al. 2012).

More prospective studies were conducted to investigate the effect of SonoVue in HIFUA treatment. In 2014, Jiang et al. conducted a randomized trial with 40 patients in the SonoVue group and 40 patients in the control group (Jiang et al. 2014). SonoVue was injected 5 minutes before starting HIFUA in the active group and immediately after the ablation in both groups. A post-HIFUA CE-MRI was performed 1 day after treatment to evaluate the fractional ablation. Results showed the rate of greyscale changes was significantly greater and had an early occurrence in the group receiving SonoVue before HIFUA than in the control group (p < 0.003), and significantly less acoustic energy was needed for ablating 1 mm^3 of fibroid volume in the SonoVue group than in the control group (p = 0.029). Thus, Jiang et al. concluded that SonoVue may assist in achieving greater fractional ablation, long term symptomatic relief, and less additional post-ablation fibroid treatments (Jiang et al. 2014).

In 2015, Orsi et al. conducted the first blinded randomized study comparing ultrasound guided HIFUA and a control group without intraprocedural CEUS (Orsi et al. 2015). This study found that intraprocedural CEUS has faster volume shrinkage over a shorter time period with less needed energy, confirming the results of Jiang and colleagues' study. Also, they found intraprocedural CEUS could provide early detection of residual tissue after ablation, which reduced the need for additional treatments. The same results were achieved when Isern and colleagues retrospectively analyzed data of 390 uterine fibroids, among which 155 were treated with SonoVue and 235 were treated without SonoVue during HIFUA (Isern et al. 2015). Their results also showed the total ablation time to achieve the same NPV and the average acoustic energy used for ablating 1 mm^3 was significantly less in the SonoVue group (p=0.001), and the NPV by post-HIFU MRI was significantly higher in the SonoVue group (p = 0.031), while fibroids' vascularity and size made no significant difference to the results (Isern et al. 2015)

In 2018, Chen et al also conducted a controlled randomized trial on 120 patients with a single uterine fibroid treated with HIFUA. Subjects were randomly divided into 4 groups with SonoVue used in Groups A and B and saline used in Groups C and D as controls. Results showed that NPV ratio was significantly higher in the SonoVue group than that in the saline group ($p = 0.006$), and starting HIFUA earlier after SonoVue injection (6 minutes in groups A &C vs. 10 minutes in groups B&D) was safe and could significantly shorten the treatment time ($p = 0.013$) and sonication time ($p = 0.04$) (Chen et al. 2018).

To further study the correlation between CEUS and CE-MRI, Peng et al (2015) conducted a study where 68 patients underwent CE-MRI before and 1 day after HIFUA for uterine fibroid treatment and CEUS pretreatment, intraprocedural, and immediate post HIFUA. Results showed CEUS and CE-MRI correlated well in terms of size and volume of the fibroids, and NPV ($r > 0.94$), and CEUS was reliable for assessing the treatment response (Peng et al. 2015).

CEUS to predict treatment response before HIFUA

HIFUA exerts its therapeutic effects by thermal ablation of the tissue causing greyscale changes visualized on conventional ultrasound (figure 4) (Zhang et al. 2017). Since blood perfusion in the target tissue is an important factor influencing the energy distribution of the thermal ablation, an accurate, repeatable, and feasible assessment of blood perfusion in uterine fibroid before HIFUA is essential for predicting the therapeutic outcomes (Kim 2017). Achieving a fractional ablation higher than 70% indicates safer and more effective HIFUA for uterine fibroid treatment (Wei et al. 2018). In 2019, Wang and co-workers tried to quantitatively assess the perfusion characteristics of uterine fibroids using CEUS before HIFUA and determined its ability to predict the outcomes of HIFUA in patients with uterine fibroids (Wang et al. 2019). Using an automatic contrast quantification software built into the HIFU equipment, time intensity parameters from recorded video clips of CEUS were measured. Post treatment volume and NPV were also measured from CE-MRI, considering the fractional ablation 70% as a favorable therapeutic outcome. Results revealed that patients in the group with a fractional ablation of 70 % had a longer mean arrival time, peak time, and enhancement time alongside with lower mean enhancement intensity and enhancement rate when compared to those with a fractional ablation of <70% ($p < 0.05$). Wang and colleagues concluded that the enhancement rate by CEUS had the highest area under the curve in the ROC curve analysis, followed by the time to peak and enhancement intensity, suggesting the enhancement rate (or estimated perfusion) as the best indicator of diagnostic efficacy, and of the perfusion characteristics of uterine fibroids which may be a valuable indicator for predicting the ablation efficacy of HIFUA.

Safety Concerns of the use of CEUS during HIFUA

There were also concerns about the safety of using CEUS during HIFUA of uterine fibroids. Cheng et al. published a retrospective study in 2015 showing that the intra-operative HIFU-related adverse effects, such as leg pain, sacrum/buttock pain, groin pain, pain in the treated region, and discomfort on skin were more frequent among patients who were injected with Sonovue ($n = 844$) than those who were not ($n = 819$) ($p < 0.05$), while the post-procedural HIFU-related complications showed no significant difference between these two groups

except for higher rate of pain in the lower abdominal wall in the Sonovue group (p < 0.05). Additionally, among the group exposed to SonoVue, two patients experienced acute renal failure with elevated creatinine levels, one at day 2 and one at day 5 post-procedure. One patient had history of hypertension, and the other had a 6-year history of using nonsteroidal anti-inflammatory drugs (NSAIDS). Both of them underwent continuous renal replacement therapy and recovered after two weeks. It should be mentioned that the routine bowel preparation before HIFU could make some patients dehydrated. Therefore, Cheng et al. concluded that using SonoVue to assess HIFU treatment efficacy is safe, but may increase the occurrence of some common yet tolerable HIFU-related side effects. They also recommended renal function monitoring in patients with a history of hypertension or taking NSAIDS (Cheng et al. 2015).

CEUS in PMWA treatment of fibroids

In 2012, Wang et al. conducted a study to evaluate the imaging manifestations and relationships between conventional ultrasound and CEUS in PMWA treatment of fibroids. During PMWA, microbubbles in boiling tissue caused enhancing hyperechoic signals on grayscale ultrasound started from the microwave emission point until covered the entire fibroid. Upon stopping the emission, the hyperechoic microbubbles in the target tissue gradually vanished, but echoes in ablated areas were still significantly higher than the adjacent myometrium. Results showed hyperechoic area in grayscale was significantly larger than non-enhancement area by CEUS, when compared immediately after PMWA (p<0.01). CEUS non-enhanced area immediately after ablation was also slightly smaller than CEUS non-enhanced area 12–24 hours after ablation; albeit not a significant difference. Wang and colleagues thus, concluded that conventional ultrasound can depict the thermal field range immediately after microwave ablation although the boundaries are not as clear as on CEUS images, and CEUS displays ablated area as a clear enhancement void with distinct boundaries 12-24 hours after the ablation. CEUS enhanced area immediately after PMWA may be influenced by remnant microbubbles in the thermal field and result in underestimating the ablation range for inexperienced operators (Wang et al. 2012).

Lei et al. (2014) compared ablation volumes obtained from CEUS and CE-MRI using the intraclass correlation coefficient (ICC) and Bland-Altman analysis. All patients (N = 18) underwent preoperative ultrasound guided uterine biopsy, PMWA, postoperative ultrasound guided uterine biopsy, CEUS 7 days after ablation, and CE-MRI within 3 days after CEUS. ICC, Bland-Altman analysis and Bradley-Blackwood test results showed an excellent agreement between ablated volumes obtained from CEUS and CE-MRI, so that CEUS and CEMRI could be used interchangeably in the clinic to evaluate the therapeutic effect and follow up in PMWA of fibroids (Lei et al. 2014).

Conclusion:

According to the reviewed studies, CEUS provides detailed and clinically useful data about fibroid volume and vascularization prior to UAE, helps with determining the endpoint of embolization during the procedure, and can be used as a convenient follow-up imaging technique post UAE to evaluate the efficacy of the procedure. CEUS can minimize the

radiation exposure time for patients whenever used as an alternative for angiography during the procedure.

HIFUA of uterine fibroids with intraprocedural CEUS imaging by SonoVue has shown faster volume reduction in a shorter term with less required energy. Data obtained from CEUS and CE-MRI before and after HIFUA showed good correlation, presenting CEUS as a cost-effective alternative for pre and post treatment imaging method of choice, especially when MRI is contraindicated or is not available or covered by insurance. The enhancement rate (as a measure of perfusion) obtained by CEUS before HIFUA may be an indicator for predicting the efficacy of HIFUA, where CEUS after HIFUA of uterine fibroid, might help with predicting clinical therapeutic response. Of note, using SonoVue to assess HIFU treatment efficacy may increase the occurrence of some common yet tolerable HIFU-related side effects in exposed patients or impair renal function in those with pre-existing hypertension or long history of NSAIDS usage. Thus, adequate hydration and appropriate pain control should be practiced during the procedure.

Based on available data, CEUS and CE-MRI have also shown sufficient agreement to be used interchangeably in the clinic to evaluate the therapeutic effect of PMWA of fibroids. Twelve to 24 hours after PMWA, CEUS displays a sharp and distinct boundary of ablated area with no blood supply and can confirm either successful ablation or residual unablated tissue.

Compared to MRI, CEUS is an inexpensive and better accessible imaging technique. However, comparing it with conventional sonography, adding an IV contrast agent is quite a difference from patient and logistic perspective and not all sonographers and physicians are familiar with this technique. There are also some intrinsic limitation same as conventional sonography. For example, the scanning field is small and only one uterine fibroid or several uterine fibroids on the same plane can be observed with a single injection of contrast agent.

With the growing trend toward non-surgical uterine fibroid treatments and necessity of an available cost-effective follow-up imaging method, there is need for future research in this field to recognize the valid advantages and possible pitfalls of CEUS as an adjunct to UAE, HIFUA, and PMWA. Characterizing fibroids based on quantitative CEUS findings and evaluating the corresponding therapeutic results might also be a promising topic for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

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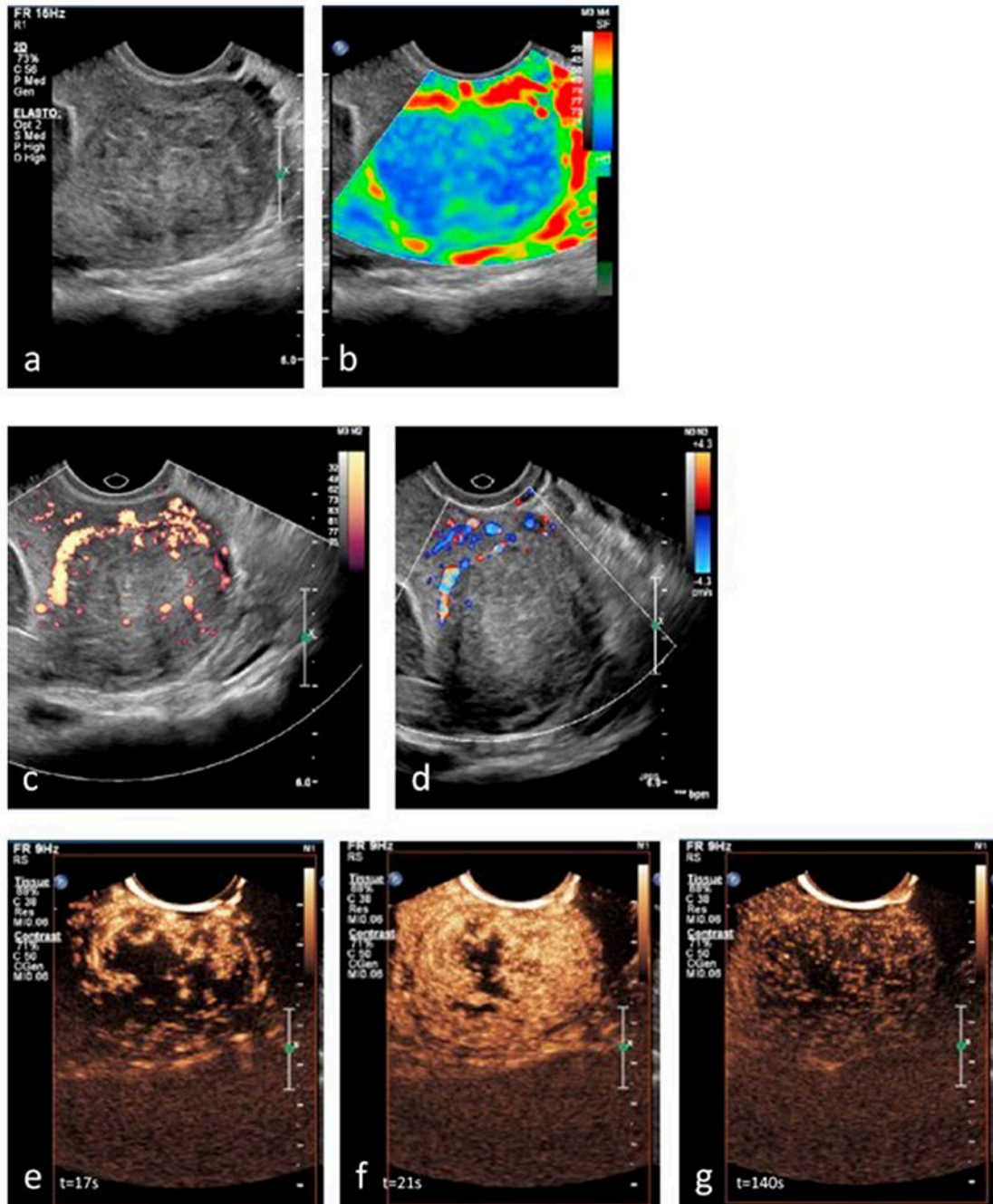
Figure 1.
Adopted from (Stoelinga et al, 2018) with permission. All sonographic examinations were performed using a transvaginal probe from the same patient (a) Grey-scale ultrasound image revealing a well-delineated subserosal fibroid (4.2 cm) (b) Sonoelastography image revealing the fibroid's center in *blue* (stiff tissue) with a pseudo-capsule in *red* (soft tissue). Small *green* areas indicating softer tissue are present in the fibroid's center (c) Power Doppler image revealing the peripheral vascular network (pseudo-capsule) and a few larger vessels in the fibroid's center (d) Color Doppler imaging revealing the proximal part of the

pseudo-capsule (e)CEUS image obtained 17 s after contrast injection ($t = 17$ s), revealing peripheral enhancement with vessels from the exterior to interior of the fibroid during wash-in of contrast (f) CEUS image at $t = 21$ s revealing heterogeneous enhancement of the entire fibroid with hypo-echogenic, avascular areas in the fibroid's center (g) CEUS image at $t = 140$ s revealing gradual wash-out of contrast from the fibroid.
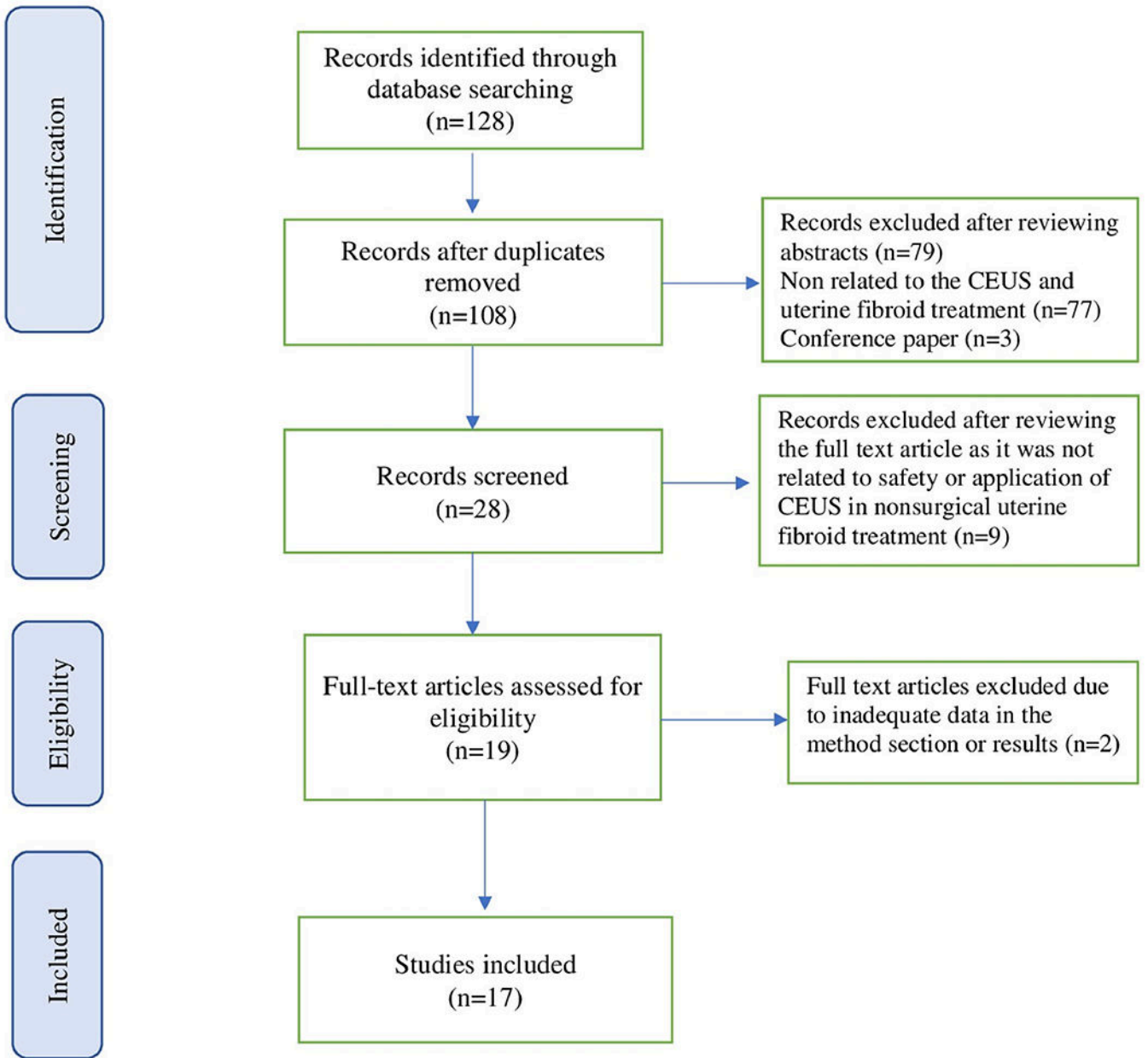
Figure 2.
The PRISMA diagram of literature retrieved.
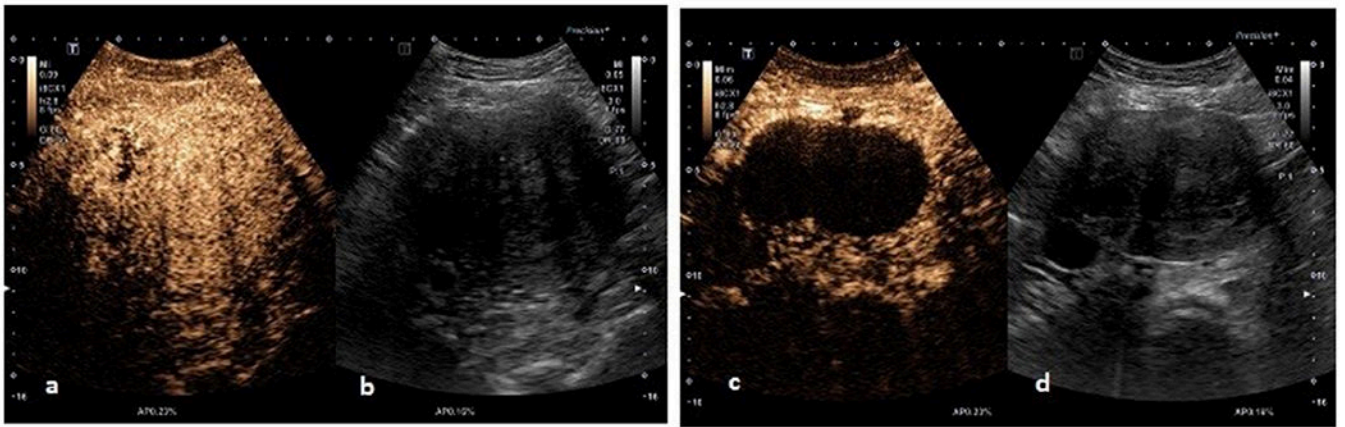
Figure 3.
(a, b). CEUS image and grey-scale ultrasound image of an intramural fibroid before UAE
revealing vascularity inside the fibroid, (c, d) CEUS image and grey-scale ultrasound image
of an intramural fibroid three months after UAE revealing loss of vascularity inside the
fibroid.
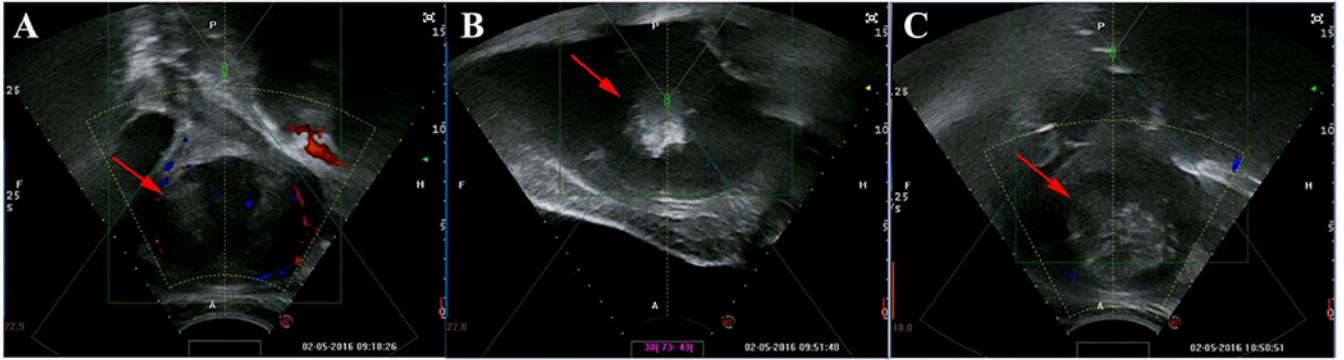
Figure 4.
Adopted from (Zhang et al, 2017) with permission. Large greyscale changes during treatment of a 26-year-old patient with a 7.5-cm fibroid. (A) Ultrasound image with Doppler obtained prior to HIFUA showing a hypoechoic fibroid with surrounding small blood vessel (red arrow). (B) Large grey-scale change arising within targeted area during treatment (red arrow). (C) Ultrasound image with Doppler obtained at the end of HIFUA showing a complete large greyscale change inside fibroid (red arrow) with disappearance of surrounding blood supply

Table 1.

Application of CEUS in UAE for uterine fibroid treatment

Author Year Country	Objective of the study	Study design	Mean age of patients (years)	Number of patients	Number of fibroids	Uterine fibroids' mean diameter or volume by ultrasound (pre-UAE)	Equipment used for CEUS - Probe used for CEUS	Ultrasound contrast agent dose, brand, and the protocol of use	Adverse reaction to UCA	Main results of the study
Marret et al. 2004 France	Evaluate the feasibility of using perioperative CEUS to assess the efficacy of UAE	Case report	50	1	3	35 mm (range: 25-64)	Esatune* ultrasound scanner - Convex probe	1 ml of SonoVue† was injected before UAE, after left UAE and after bilateral UAE	None	CEUS can be used to monitor UAE perioperative and immediately post-operative to prevent ischemic complications
Dorenberg et al. 2007 Norway	Evaluate the feasibility of using CEUS during UAE to define the correct end-point of the procedure	Prospective	38.7	10	NR	NR	Sequoia 512 scanner**-4C1 curved-array probe	2.4 ml SonoVue†† (IV bolus) followed by a flush of 5 ml saline solution was injected before and immediately after UAE	NR	CEUS during UAE may adjust the end-point of procedure and decrease the risk of clinical failure, the need for reinterventions, and the radiation dose
Sconfienza et al. 2008 Italy	Analyze the potential value of pre-and posttreatment CEUS to assess UAE outcomes	Prospective	NR	12	21	52 mm (range: 35-90 mm)	Philips iU22 scanner***-Transabdominal probe	4.8 ml SonoVue†† (IV bolus) followed by a flush of 5 ml saline solution Immediately before and immediately after UAE		CEUS is effective for assessing the completeness of vascular occlusion following UAE and it is comparable with clinical and MRI results
Dorenberg et al. 2012 Norway	Determine feasibility of the use of CEUS during UAE	Retrospective	41	30	NR	120 cm³ (range: 66-238 cm³)	Sequoia 512 scanner**-Transabdominal probe	2.4 ml SonoVue†† (IV bolus) followed by a flush of 10 mL saline solution was injected at the angiographie endpoint of UAE	NR	CEUS was technically successful during the UAE in all patients and adjusted the end-point of procedure in 5 cases
Marret et al. 2014 France	Investigate the fibroids vascularization distribution patterns using CEUS before and after UAE, with the evaluation of radiologic predictive	Prospective	44 ± 6	40a	NR	311 cm³ (range: 167-613 cm³)	Technos MPX scanner*-Transabdominal and transvaginal probes	2.4 ml SonoVue†† (IV bolus) followed by a flush of 5 ml saline solution was injected one day before, one day after, and	NR	Partial or total enhancement on CEUS after UAE can be evidence of probable clinical failure in the intermediate term, however no quantitative vascular

Author Year Country	Objective of the study	Study design	Mean age of patients (years)	Number of patients	Number of fibroids	Uterine fibroids' mean diameter or volume by ultrasound (pre-UAE)	Equipment used for CEUS - Probe used for CEUS	Ultrasound contrast agent dose, brand, and the protocol of use	Adverse reaction to UCA	Main results of the study
	factors for successful embolization							6-12 months later		indicator predicting the clinical results was found
Pesapane et al. 2020 Italy	Using CEUS perioperatively to assess the target uterine fibroid's vascularity and determine the embolization endpoint	Case report and literature review	39	1	Multiple fibroids	9.5cm by MRI	ACUSON 3000§§	2.4 ml SonoVue†† (IV bolus) followed by a flush of 10 mL saline solution was injected Pre UAE, during arterial phase, and immediately at the angiographie endpoint of UAE	NR	CEUS is feasible and practical to assess the vascularity of uterine fibroids during UAE Caution should be taken to avoid misinterpretation of complete devscularization in cases of multiple fibroids (some fibroids may obscure other vascularized fibroids on CEUS)

CEUS: contrast enhanced ultrasound; UAE: uterine artery embolization; UCA: ultrasound contrast agent; IV: intravenous; MRI: magnetic resonance imaging; NR: not reported

†(Bracco International BV, Amsterdam, The Netherlands),

††(SonoVue, Bracco, Milano, Italy)

*(Esaote, Genova, Italy) and dedicated software (CnTI, Esaote)

**(Siemens, Erlangen, Germany) and dedicated software (Cadence)

***(Koninklijke Philips Electronics, Eindhoven, The Netherlands)

§(Philips, Bothell, WA, USA)

§§(Siemens, Erlangen, Germany)

Table 2.

Application of CEUS in HIFUA for uterine fibroid treatment

Author Year Country	Objective of the study	Study design	Number of patients-fibroids	Uterine fibroids' mean diameter or volume by ultrasound	Mean age of patients (years)	UCA dose, brand, and the protocol of use	Adverse reaction to UCA	Equipment used for CEUS	Results of the study
Zhou et al. 2007 China	Evaluate the utility of CEUS in assessing the therapeutic response to HIFUA	Prospective	64 - 64	53 ± 12 mm (range: 32-89 mm)	39.1 ± 5.6	2.4 ml of SonoVue* (IV bolus) was injected, followed by a flush of 5.0 mL saline	None	Toshiba Aplio 80**	CEUS showed 100% NPV for finding any residual unablated tumor in the HIFU ablated zone CEUS can help to target the residual tumor during the additional ablation procedure
Peng et al. 2012 China	Evaluate the clinical value of the contrast agent SonoVue* in the treatment of uterine fibroids with therapeutic HIFUA	Retrospective	**Group of patients treated by HIFUA with SonoVue***			2.0 ml of SonoVue* (IV bolus) was injected 10 minutes before HIFUA 1.5 ml of SonoVue* (IV bolus) during or/and immediately after HIFUA	There were no significant differences in adverse effects between the two groups	My-Lab 70† ultrasoun d imaging machine	CEUS can be used to assess the extent of ablation during HIFUA Non-perfused volume/fibroid volume was 86.0% in the group with SonoVue* and 83.0% in the group without SonoVue* The sonication time for ablating 1 cm³ of fibroid volume was significantly shorter in the group with SonoVue than without it
			162-162	56 mm (range: 29–120 mm)	36.9 ± 6.0				
			Group of patients treated by HIFUA without SonoVue*						
			129-129	46 mm (range:21–128 mm)	40.0 ± 5.8				
Jiang et al. 2014 China	Evaluate the role of the ultrasound contrast agent SonoVue* in enhancing the effects of HIFUA	Prospective	**Group of patients treated by HIFUA with SonoVue***			2.0 ml of SonoVue* (IV bolus) was injected 5 minutes before HIFUA in SonoVue* group 1.5 ml of SonoVue* (IV bolus) was injected immediately after HIFUA to assess the therapeutic response in both	There were no significant differences in adverse effects between the two groups	My-Lab 70† ultrasoun d imaging machine	SonoVue* is able to safely decrease the sonication time and acoustic energy required in HIFUA for uterine fibroids treatment
			40-40	47 ± 17 mm (range:21–88 mm)	39.2 ± 5.4				
			Group of patients treated by HIFUA without SonoVue*						
			40-40	51 ± 23 mm (range:20–99 mm)	40.5 ± 5.7				

Author Year Country	Objective of the study	Study design	Number of patients-fibroids	Uterine fibroids' mean diameter or volume by ultrasound	Mean age of patients (years)	UCA dose, brand, and the protocol of use	Adverse reaction to UCA	Equipment used for CEUS	Results of the study
						SonoVue* and control groups			
Orsi et al. 2015 Italy	Evaluate safety and effective ness of CEUS on HIFUA of uterine fibroids	Prospective (blind randomized)	Group of patients treated by HIFUA with SonoVue*			2.4 of SonoVue* (IV bolus) was injected before, during and after HIFUA	There were no significant differences in adverse effects between the two groups	My-Lab 70[†] ultrasound imaging machine	CEUS was safe and effective in enhancing ultrasound guidance during HIFUA for uterine fibroids treatment CEUS reduced the treatment time and treatment repetitions (for incomplete fibroid ablation) CEUS during HIFUA increased the volume reduction at 1 and 3 months, but not at 6 months, between the two groups at MRI
			17-20	419 cm³ (range: 47.3–1865.0 cm³)	43.1				
			Group of patients treated by HIFUA without SonoVue*						
			16-17	189.5 cm³ (range: 34.6–709.5 cm³)	42				
Peng et al. 2015 China	Investigate CEUS to evaluate treatment response of uterine fibroids to HIFUA	Prospective	68-68	75.2 cm³ (range: 34.2–127.3 cm³)	39.3 ± 6.6	2.0 ml of SonoVue (IV bolus) was injected 8 minutes before HIFUA 1.5 ml of SonoVue (IV bolus) was injected during and/or immediately after HIFUA to assess the therapeutic response	None	My-Lab 70[†] ultrasound imaging machine	CEUS clearly showed the size of fibroids and the non-perfused areas of the fibroid during or immediately after HIFUA
Cheng et al. 2015 China	Evaluate adverse effects of HIFUA for fibroids in a comparison between procedures with and without the use of UCA	Retrospective	Group of patients treated by HIFUA with SonoVue*			2.0 ml of SonoVue* (IV bolus) was injected 5 minutes before procedure and 1.5 ml of SonoVue* (IV bolus) was injected immediately	Intraprocedural sacrum/butto ck pain, groin pain, leg pain, pain in the treated region, and discomfort on the skin, and post procedural lower abdominal pain are significantly higher in the	My-Lab 70[†] ultrasound imaging machine	SonoVue may increase the incidence rates of some common intraprocedural HIFUA-related adverse effects, however it can be safely used to assess HIFUA
			844-NR	57.2 cm³	NR				
			Group of patients treated by HIFUA without SonoVue*						
			819-NR	57.4 cm³	NR				

Author Year Country	Objective of the study	Study design	Number of patients-fibroids	Uterine fibroids' mean diameter or volume by ultrasound	Mean age of patients (years)	UCA dose, brand, and the protocol of use	Adverse reaction to UCA	Equipment used for CEUS	Results of the study
						after HIFUA to assess the therapeutic response in the group of patients treated by HIFUA with SonoVue	group of patients treated by HIFUA with SonoVue Two acute renal failures also occurred in the group of patients treated by HIFUA with SonoVue		treatment efficacy
Isern et al. 2015 Spain	Assessment of the therapeutic effect of SonoVue on HIFUA fo different subtypes of uterine fibroids	Retrospective	**Group of patients treated by HIFUA with SonoVue***			2.0 ml of SonoVue* (IV bolus) was injected 2 minutes before procedure	No serious adverse reaction to UCA was reported and no significant difference between two groups in terms of reported adverse events	My-Lab 70[†] ultrasound imaging machine	Therapeutic SonoVue significantly decreases the time and energy needed for HIFUA of the same fibroid volume in all types of fibroid.
			124-155	87cm^3 (range: 2-982)	41±6 (range: 25-53)				
			Group of patients treated by HIFUA without SonoVue*						
			196-235	127 cm^3 (range: 2-736)	40±6 (range: 26-54)				
Chen et al. 2018 China	Investigate UCA effects on HIFUA for uterine treatment, with dosage comparison	Prospective (randomized controlled trial)	**Group of patients treated by HIFUA with SonoVue* (6 minutes before HIFUA)**			1.5 ml of SonoVue* (IV bolus) was injected, followed by a flush of 5 ml saline solution 6 minutes before HIFUA	Radiation pain, sacrococcygeal/ buttock pain, groin pain discomfort on the on the skin, and lower abdominal pain were transient There were no significant difference in the rate of adverse effects among the four groups (p > 0.05	My-Lab 70[†] ultrasound imaging machine	SonoVue enhanced the effect of HIFUA for uterine fibroids treatment, shortened HIFU treatment time and sonication time, with an increase in the rate of grey-scale changes and non-perfused volume ratio HIFUA was safe and more effective as it was started earlier after SonoVue injection
			30-30	79.6 ± 81.8 cm^3	40.3 ± 6.7				
			Group of patients treated by HIFUA with SonoVue* (10 minutes before HIFUA)			1.5 ml of SonoVue* was injected (IV bolus), followed by a flush of 5 ml saline solution 10 minutes before HIFUA			
			30-30	58.7 ± 41.8 cm^3	40.1 ± 4.7				
			Group of patients treated by HIFUA with saline 6 minutes before HIFUA (without SonoVue*)			1.5 ml of saline (IV bolus) was injected 6 minutes before HIFUA			
			30-30	66.3 ± 49.9 cm^3	40.3 ± 5.9				
			Group of patients treated by HIFUA with saline 10 minutes before HIFUA (without SonoVue*)			1.5 ml of saline (IV bolus) was injected 10 minutes before HIFUA			
			30-30	81.5 ± 98.3 cm^3	42.1 ± 4.8				

Author Year Country	Objective of the study	Study design	Number of patients-fibroids	Uterine fibroids' mean diameter or volume by ultrasound	Mean age of patients (years)	UCA dose, brand, and the protocol of use	Adverse reaction to UCA	Equipment used for CEUS	Results of the study
Wang et al. 2019 China	Assess quantitative perfusion parameters from CEUS for the clinical outcome of HIFUA in uterine fibroid treatment	Retrospective	263-263	81.2 ± 38.7 cm^3	38.2 ± 5.6	2.0 ml SonoVue[*] (IV bolus) was injected, followed by a flush of 5 ml saline solution immediately before HIFUA	None	NR	CEUS derived quantitative parameters such as higher time parameters and lower intensity parameters are linked to a better treatment outcome

CEUS: contrast enhanced ultrasound; CEMRI: contras enhanced magnetic resonance imaging; HIFUA: high intensity focused ultrasound ablation; HIFU: high-intensity focused ultrasound; NPV: negative predictive value; UCA: Ultrasound contrast agent; IV: intravenous

[*] (SonoVue, Bracco, Milan, Italy)

[**] (Toshiba, Tokyo, Japan)

[†] (Esaote; Genoa, Italy

Table 3.

Application of CEUS in PMWA for uterine fibroid treatment

Author Year Country	Objective of the study	Study design	Number of patients-fibroids	Uterine fibroids' mean diameter by ultrasound	Mean age of patients (years)	UCA dose, brand, and the protocol of use	Adverse reaction to UCA	Equipment used for CEUS	Results of the study
Wang et al. 2012 China	Evaluate image changes and the relationship between conventional ultrasonography and CEUS in the perioperative period of PMWA for efficacy assessment	NR	29-31	NR	40±5.25	2.4 ml of SonoVue* (IV bolus) was injected, followed by a flush of 5.0 mL saline	NR	Siemens sequoia 512 ultrasound system (the probe frequency was 2.5–4.5 MHz)	Non-enhanced CEUS areas immediately after PMW, correlated with hyperechoic area on grayscale ultrasound, representing the ablated area CEUS displays sharp and distinct boundaries of ablated area 12-24 hours after ablation and can be used for efficacy assessment
Lei et al. 2014 China	CEUS and CEMRI comparison after PMWA for uterine fibroid treatment	Retrospective	18-20	5.56 ± 1.26 cm	39.83 ± 5.83	2.4 ml of SonoVue* (IV bolus) was injected, followed by a flush of 5.0 ml saline	NR	Siemens Sequoia 512 ultrasound system (the probe frequency was 2.5–4.5 MHz)	CEUS and CEMRI agreed sufficiently to be used interchangeably in evaluating the ablated volumes of uterine fibroids treated with PMWA

CEUS: contrast enhanced ultrasound; PMWA: percutaneous microwave ablation

*(Bracco, Milan, Italy)

**(Acuson, Mountain View, CA, USA)