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Département des services de chirurgie et d'anesthésiologie

Service d'Urologie

The utility of intraoperative contrast-enhanced ultrasound in detecting residual disease after focal HIFU for localized prostate cancer

THESE

préparée sous la direction du Docteur Massimo Valerio

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Frédéric BACCHETTA

Médecin diplômé de la Confédération Suisse
Originaire de Lausanne (VD)

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The utility of intraoperative contrast-enhanced ultrasound in detecting residual disease after focal HIFU for localized prostate cancer

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Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé

Contexte et objectifs : L'ultrason focalisé à haute intensité (HIFU) est un traitement émergent pour certains hommes atteints du cancer de la prostate localisé. L'une des limites de l'HIFU est l'absence d'un outil fiable pour mesurer l'effet du traitement en peropératoire. L'ultrason avec injection de contraste (CEUS) s'est révélé être une modalité prometteuse pour évaluer l'étendue et les limites de l'ablation des tissus. L'objectif de cette étude était d'évaluer la valeur du CEUS immédiatement après l'HIFU focal.

Matériels et méthodes : Analyse rétrospective d'un registre tenu de manière prospective, comprenant des patients consécutifs bénéficiant un HIFU focal (Focal One). Les candidats à l'HIFU focal étaient des hommes naïfs de traitement ayant ≥10 ans d'espérance de vie, l'antigène spécifique de la prostate (PSA) ≤ 20 ng/ml, un stade TNM ≤ T2c N0 M0 avec une lésion visible à l'IRM multiparamétrique (IRMmp) concordant avec un cancer de la prostate histologiquement prouvé. L'évaluation par CEUS a été effectuée immédiatement à la fin de la procédure. Sur la base de l'évaluation du résultat du CEUS par le chirurgien, un nouvel HIFU a été effectué, suivi d'une seconde évaluation CEUS. Pour tester notre hypothèse, la capacité du CEUS d'exclure un cancer cliniquement significatif a été comparée aux résultats de l'IRMmp précoce. La concordance entre les deux tests a été mesurée à l'aide du kappa de Cohen. Le meilleur modèle incluant des prédicteurs pertinents a été calculé avec le CEUS ou avec l'IRMmp afin de déterminer leur valeur ajoutée respective.

Résultats : Sur 66 hommes ayant bénéficié d'un HIFU, 32 répondaient aux critères d'éligibilité. Un traitement bifocal a été effectué chez un homme, ce qui a porté à 33 le nombre de lésions traitées. Une seconde ablation basée sur le CEUS a été réalisée en peropératoire sur 13 lésions (39 %). Le taux de biopsie positive pour un cancer cliniquement significatif dans les zones traitées était de 30 % (10/33). La valeur prédictive négative du CEUS et de l'IRMmp précoce était de 71 % (intervalle de confiance de 95 % : 59 %-82 %). La concordance entre le CEUS et l'IRMmp était significative avec une concordance de 72,7 % (P = 0,001). Le modèle incluant le CEUS a montré le meilleur résultat avec une aire sous la courbe de 0,881.

Conclusion : Le CEUS a une valeur ajoutée plus élevée que l'IRMmp précoce pour exclure un cancer cliniquement significatif après un HIFU focal. L'utilisation du CEUS en peropératoire afin d'améliorer l'efficacité de l'HIFU focal devrait être évaluée.

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UROLOGIC ONCOLOGY

Clinical-Prostate cancer

The utility of intraoperative contrast-enhanced ultrasound in detecting residual disease after focal HIFU for localized prostate cancer

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Abstract

Background and objectives: Focal high intensity focused ultrasound (HIFU) is an emerging treatment for selected men with localized prostate cancer. A limitation of HIFU is the absence of a reliable tool to measure treatment effect intraoperatively. Contrast-enhanced ultrasound (CEUS) has been shown to be a promising modality for assessing the extent and boundaries of tissue ablation. The aim of this study was to assess the value of CEUS immediately after focal HIFU.

Materials and methods: Retrospective analysis of a prospectively maintained registry including consecutive men undergoing focal HIFU (Focal One). Candidates for focal HIFU were treatment naive men with ≥10 years life expectancy, prostate-specific antigen (PSA) ≤ 20 ng/ml, TNM primary tumor, regional lymph nodes, distant metastasis stage ≤ T2c N0 M0 with a multiparametric MRI (mpMRI) visible lesion concordant with histologically proven prostate cancer. CEUS evaluation was performed immediately at the end of the procedure. Based on the surgeon's estimation of CEUS imaging, re-HIFU was performed, followed by another CEUS evaluation. To test our hypothesis, the results of the CEUS were compared to the results of early mpMRI to rule out clinically significant cancer. The concordance between the 2 tests was measured using the Cohen's kappa. The best model including relevant predictors was calculated with CEUS or with mpMRI to determine their respective added value.

Results: Of 66 men who underwent HIFU, 32 met eligibility criteria. Bifocal treatment was performed in 1 man, increasing the number of treated lesions to 33. Further ablation based on CEUS was delivered intraoperatively to 13 lesions (39%). The positive biopsy rate for clinically significant cancer in the treated zones was 30% (10/33). The negative predictive value of CEUS and early mpMRI was 71% (95% confidence interval: 59%−82%). Concordance between CEUS and mpMRI was significant with a 72.7% agreement ($P = 0.001$). The model with CEUS showed the best accuracy with an area under the curve of 0.881.

Conclusion: CEUS has a higher added value compared to early mpMRI in ruling out clinically significant cancer after focal HIFU. It should be evaluated whether the use of CEUS intraoperatively enhances the efficacy of focal HIFU.

Keywords: Prostate cancer; Focal therapy; HIFU; Contrast-enhanced ultrasound

1. Introduction

Focal therapy is an emerging treatment for men with localized prostate cancer (CaP). Among the different sources of energy available to deliver focal therapy, high intensity focused ultrasound (HIFU) is one of the most evaluated in prospective clinical trials. Consistent evidence shows that focal HIFU is safe, has a low toxicity profile and encouraging oncological outcome in the medium term [1,2]. Comparative effectiveness research against standard

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of care is ongoing [3]. While many deem this technology attractive, some limitations in patient selection and treatment delivery have restricted its dissemination.

A key limitation of focal HIFU is the absence of a reliable tool to measure treatment effect during the delivery of energy. The ablation effect is due to small confluent points of focal intensity heating the target area up to 90˚C inducing tissue destruction by thermal coagulative necrosis and/or acoustic cavitation. This translates into hyperechoic changes visible on standard ultrasound, the so-called "Uchida" effect [4]. These treatment-related modifications are inhomogeneous, tissue-dependent and are therefore considered unreliable; as a consequence, gray-scale ultrasound is not employed to modify the treatment delivery according to these changes. This issue is a key one as the absence of real-time monitoring during treatment might lead to incomplete ablation which is currently observed in up to 1 out of 10 men treated with focal HIFU who need additional treatment in the target area in the first year after therapy [5,6].

Late multiparametric MRI (mpMRI) at 6 to 12 months after focal HIFU has been shown to be accurate to determine complete ablation; in contrast, early MRI relying on contrast-enhanced sequences is less accurate and its utility has been recently questioned [7]. Also, it is not possible to employ mpMRI during treatment delivery, as transrectal HIFU devices are not MR-compatible. If a reliable imaging tool was available at the time of treatment, the retreatment rate might be considerably lower.

Contrast-enhanced ultrasound (CEUS) is a promising modality for assessing the extent and boundaries of tissue ablation after HIFU [8–12]. In the unique prospective study comparing early CEUS after whole-gland HIFU (0–3 days) with mpMRI findings, it has been shown that the correlation between these 2 imaging modalities is consistent [8]. While some surgeons are using CEUS at the end of focal HIFU in order to determine whether the targeted ablation is complete, the diagnostic performance of intraoperative CEUS has not been tested in this setting. The aim of this study was to assess the diagnostic value of CEUS immediately after focal HIFU, and to determine whether it could replace early MRI.

2. Materials and methods

2.1. Design

This is a retrospective analysis of a prospectively maintained registry including consecutive men undergoing focal HIFU in 2 centers (Centre Hospitalier Universitaire Vaudois and Clinique Générale Beaulieu, Switzerland). The registry is running since September 2014, and is independently maintained by local staff. Consecutive men scheduled for focal HIFU are offered to participate in this registry including standardized follow-up and patient-reported outcome measures. For this study, we selected treatment-naive men undergoing focal HIFU since its adoption up to July 2016. Each patient gave written informed consent to use his clinical data for research and quality control purpose.

2.2. Population

The diagnostic pathway is standardized. Men with suspected localized CaP undergo first a multiparametric 3T MRI with a pelvic and an endorectal coil including T1-, T2-weighted, dynamic contrast enhancement and diffusion-weighted imaging, following international standards [13]. MpMRI are reported by 2 dedicated uroradiologists, according to PIRADS version 2 [14]. Transperineal template mapping biopsy, or transrectal saturation biopsy with software-based MR-TRUS elastic fusion targeted biopsy are proposed to men who might be eligible, and are interested in focal therapy. Candidates for focal therapy are considered men with $\geq$ 10 years life expectancy, prostate-specific antigen (PSA) $\leq$ 20 ng/ml, radiological stage $\leq$T2c N0 M0, MR visible lesion concordant with histologically proven CaP, and absence of significant disease elsewhere in the gland. For the purpose of this study, the significance threshold has been set at Gleason score $\geq$3 + 4 and/or maximum cancer core length $\geq$4 mm.

2.3. Interventions

Focal HIFU was performed using the Focal One device (EDAP TMS SA). Preoperatively, T2-weighted and apparent diffusion coefficient axial sequences were uploaded in the device. Prostate and lesion contouring was performed in T2-weighted images employing the embedded software provided by the manufacturer. Intraoperatively, the patient was positioned in a right lateral position, a Foley catheter was placed and a third-generation Cephalosporin was administered. TRUS images were automatically acquired by an axial scan of the gland. After contouring, MR-TRUS elastic fusion was performed and the ablation area was determined according to mpMRI and biopsy results with a 5 to 10 mm margin. At least 5 minutes after HIFU and always till the disappearance of the hyperechoic changes related to tissue changes (Uchida changes), 2.4 ml ultrasound contrast agent (SonoVue, Bracco, Italy) was administered intravenously, and CEUS evaluation was performed in the axial plane once the contrast was visible in the prostate. According to the interpretation of CEUS images by the surgeon, additional energy was delivered to complete the ablation in the area deemed undertreated. At the end of the second procedure, another CEUS evaluation was carried out, but no additional HIFU was delivered (Figs. 1–2).

2.4. Follow-up

Follow-up included catheter withdrawal and early contrast-enhanced MRI 5 to 10 days after treatment to confirm the extent of ablation and the absence of surrounding organ

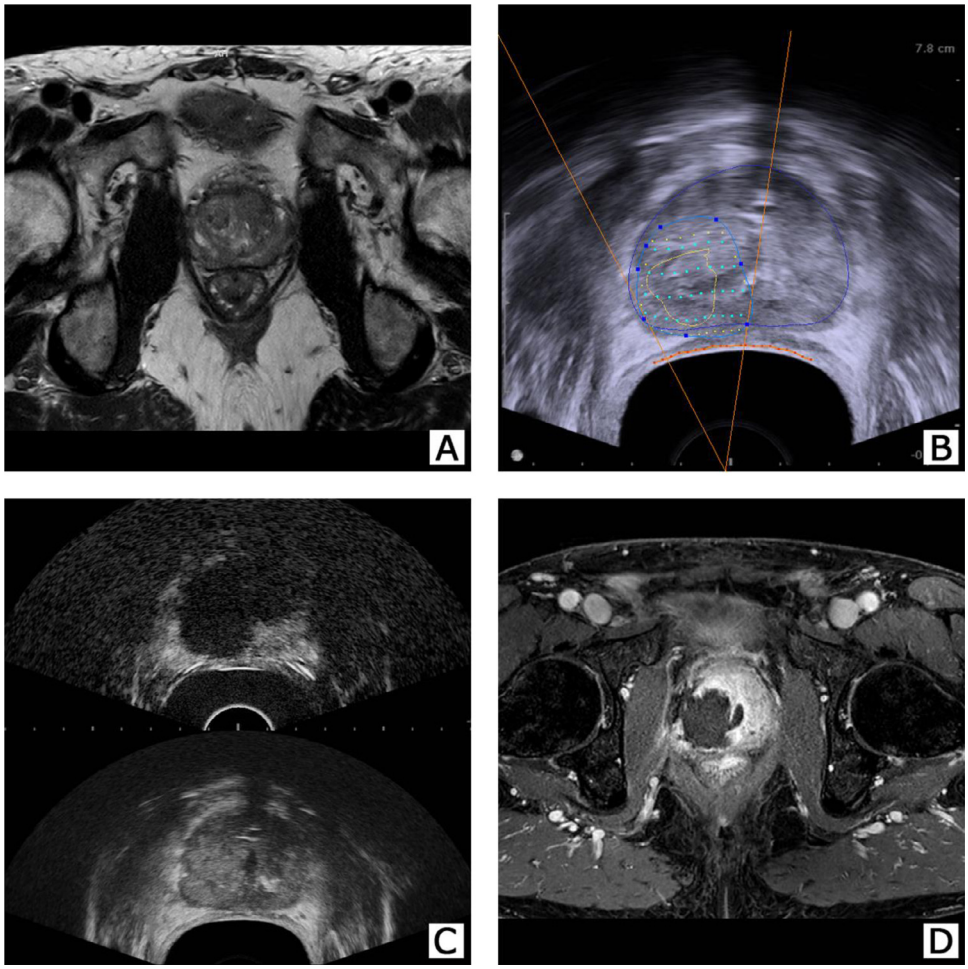

Fig. 1. Clinical case: right middle posterior Gleason 7 = 3 + 4 lesion. Pretreatment mpMRI shows a PIRADS 4 lesion (A). Intraoperative gray-scale US showing the planned treatment area (dotted line; B). Post-treatment CEUS with a score of S0 (C). Early mpMRI with dynamic contrast enhancement, score of 0 (D). No clinically significant cancer at control biopsy.

injury. Afterward, men were followed every 3 months with PSA assessment; mpMRI was performed at 6 to 12 months after treatment. Control biopsies were discussed according to the presence of insignificant lesions under surveillance, the results of late mpMRI and biochemical response. CEUS and early mpMRI results were not considered triggers for control biopsy.

2.5. Imaging interpretation

Preoperative mpMRI were interpreted using the PIRADS v2 system, visible lesions were assigned individually a score of 3 to 5. The CEUS images were directly extracted from the Focal One device; its score was retrospectively determined by an experienced radiologist (MM) following the scoring system proposed by Rouvière et al. [15]: S0: no enhancement in the mpMRI visible lesion; S1: mild enhancement in the MRI visible lesion; S2: marked enhancement in the MRI visible lesion. The early post-HIFU mpMRI contrast-enhanced sequences were also given a score 0 to 2 following a similar system suggested by Dickinson et al. [16]: 0: lowest suspicion of residual cancer; 1: margin of the vacuolization zone close to the treated lesion; 2: enhancement in the lesion location. The PIRADS v2 score cannot be assigned based on early mpMRI after focal HIFU. Late mpMRI was interpreted using the PIRADS v2 classification, with likelihood or presence of significant disease assigned for every treated lesion. In the case of bifocal ablations, each treated zone was analyzed separately. For the purpose of this analysis, imaging interpretation was dichotomized: positive early MRI and CEUS were considered when the score was $\geq$1; positive late mpMRI was considered when the score was $\geq$3. Control biopsies were performed through a targeted cognitive approach, and were combined with systematic biopsy, when this was judged clinically indicated.

2.6. Statistical analysis

To determine the ability of CEUS to rule out clinically significant residual disease in the treated area, we determined its diagnostic accuracy against early mpMRI,

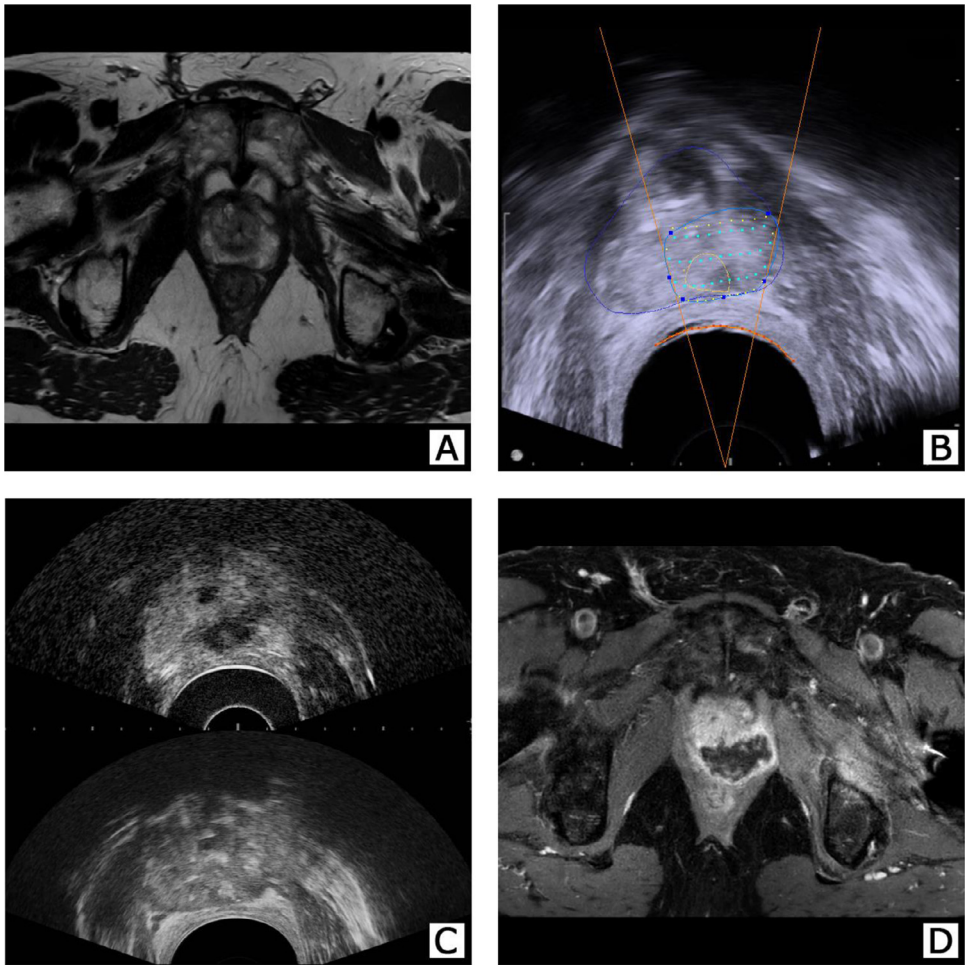

Fig. 2. Clinical case: left apical posterolateral Gleason 7 = 4 + 3 lesion. Pretreatment mpMRI shows a PIRADS 4 lesion (A). Intraoperative gray-scale US showing the planned treatment area (dotted line; B). Post-treatment CEUS with a score of S1 (C). Early mpMRI with dynamic contrast enhancement score of 1 (D). Control biopsy positive for clinically significant cancer.

considering control biopsy as the reference test. Afterward, the concordance between the CEUS and early mpMRI was measured using the Cohen's kappa coefficient. A model including PSA at 6 months, PSA density and late mpMRI for predicting the absence of clinically significant cancer at control biopsy was analyzed using the area under the receiver operator characteristic curve (AUROC). These variables were included in the base model in light of recent evidence highlighting their importance. The results of CEUS or early mpMRI were added to the model in order to determine their respective added value.

3. Results

A total of 66 men underwent focal HIFU within the study timeframe. Of these, 34 had to be excluded (16 did not have postoperative biopsies, 10 had insufficient data, 3 had previous radiation therapy, 2 men did not give consent to use their clinical data, 2 had clinically significant cancer left untreated, and 1 had an nonvisible lesion on MRI). Baseline characteristics are described in Table 1.

Of the 32 patients included, one of them (3%) had a bifocal treatment; therefore, the overall number of treated zones was 33. All statistical analyses were performed at a zonal

Table 1
Baseline characteristics.

Variable	Value
Age at intervention (yr), median (IQR)	69.0 (63–73)
Baseline PSA (ng/ml), median (IQR)	7.2 (5.3–8.4)
Prostate volume (ml), median (IQR)	45 (30–58)
Lesion on mpMRI, total	33
Volume (ml), median (IQR)	0.52 (0.33–1.2)
PIRADS 3	5 (15%)
PIRADS 4	16 (48%)
PIRADS 5	12 (36%)
Total number of cores, median (IQR)	13.5 (12–21)
Number of positive cores, median (IQR)	3 (2–5)
Maximum cancer core length (mm), median (IQR)	5 (3–7)
Pretreatment Gleason score	
3 + 3	14 (42%)
3 + 4	13 (39%)
4 + 3	5 (15%)
4 + 4	1 (3%)

Table 2
HIFU characteristics.

Type of HIFU treatment	
Focal	24 (75%)
Bifocal	1 (3%)
Hemiablation	6 (19%)
Hockey-stick ablation	1 (3%)
Treatment strategy	
Ablation of all known cancer	29 (91%)
Index ablation with surveillance of clinically insignificant lesion	3 (9%)
Impact of CEUS	
Further treatment	13 (39%)
No further treatment	20 (61%)
Treated volume estimation (ml), median (IQR)	
First treatment	9.7 (7.8−13.1)
Retreatment	5.5 (3.2−6.8)
Overall treatment	11.2 (9.4−16.3)

level. The median estimated treated volume was 9.7 ml (interquartile range (IQR): 7.8−13.1) for the first treatment; when further treatment was delivered, 5.5 ml (IQR: 3.2−6.8) additional prostatic tissue was ablated for a median overall volume treated per session at 11.2 ml (IQR: 9.4−16.3; Table 2). Further treatment after CEUS was performed in 13 lesions (39%). Based on CEUS interpretation, 21 lesions (64%) were scored S0, 11 (33%) were scored S1 and 1 (3%) was scored S2.

Control biopsies were carried out at a median of 13.8 months (IQR: 12.5−14.6) after focal therapy. Significant and insignificant cancer within the treated area was found in 10 (30%) and 8 (24%), respectively.

In terms of detection of residual significant cancer, CEUS provided a sensitivity of 40% (95% confidence interval [CI]: 12%−74%), a specificity of 65% (95% CI: 43%−84%), a positive predictive value of 33% (95% CI: 16%−56%), and a negative predictive value of 71% (95% CI: 59%−82%; Table 3). When analyzing the concordance between CEUS and early mpMRI to predict absence of clinically significant cancer at control biopsy, the Cohen's kappa coefficient was found to be 0.45 ($P = 0.001$), which is equivalent to a 72.7% agreement rate.

Table 3
Diagnostic accuracy of CEUS, early mpMRI, and late mpMRI scores against control biopsies.

CEUS scores (95% confidence interval)	
Sensitivity	40% (12%−74%)
Specificity	65% (43%−84%)
PPV	33% (16%−56%)
NPV	71% (59%−82%)
Early mpMRI scores (95% confidence interval)	
Sensitivity	40% (12%−74%)
Specificity	65% (43%−84%)
PPV	33% (16%−56%)
NPV	71% (59%−82%)
Late mpMRI scores (95% confidence interval)	
Sensitivity	40% (12%−74%)
Specificity	91% (72%−99%)
PPV	67% (30%−90%)
NPV	78% (58%−89%)
AUROC using different models	
PSA at 6 months, PSA density, late mpMRI	0.801
PSA at 6 months, PSA density, late mpMRI, early mpMRI	0.835
PSA at 6 months, PSA density, late mpMRI, CEUS	0.881

The model for predicting absence of clinically significant cancer at control biopsy using PSA at 6 months, PSA density and late mpMRI showed an AUROC of 0.801. When adding the results of early mpMRI to the model, the AUROC was 0.835; whereas when the results of CEUS were added to the model, the AUROC increased to 0.881.

4. Discussion

This study shows that CEUS and early mpMRI after focal HIFU have comparable diagnostic accuracy. The 2 tests are concordant in most cases; however, CEUS has an independent diagnostic value in addition to known predictors to rule out the presence of residual significant cancer after focal HIFU.

Prior to discuss our results, we feel it is important to acknowledge the limitations of this study. First, the small sample size makes it difficult to achieve definitive conclusion; this study should be regarded as the first attempt to explore the utility of intraoperative CEUS after focal HIFU. Of note, Sonovue injection is not an approved intervention for CaP evaluation in Switzerland. Second, CEUS and early mpMRI were interpreted using a 3-point Likert-type score, which have not been validated. Further research is needed in order to validate the interpretation of these tests, and explore their clinical utility; this can be performed only when more experience and reliable data will be acquired. Third, the results might be biased in favor of CEUS as this was performed intra-operatively, and based on its results, further treatment was delivered in around one third of the study population. While this might have had a positive impact on the performance of CEUS, this reflects clinical practice and we were not able to test hypothesis in a more reliable manner within a registry setting. Fourth, from the initial number of patients, we had to exclude a certain number of patients, mainly because they did not have a control biopsy. This produces a selection bias in the study population and an incorporation bias in estimating the best AUROC as PSA and mpMRI were both criteria to prompt control biopsy and part of the basic model. As this was performed as a part of a registry, we were not able to impose a control biopsy to every patient. The utility of control biopsy was discussed with every patient, and those who were more at risk of having residual disease underwent histological sampling.

Although virtually all sources of energy used to deliver focal therapy lack intraoperative control of tissue ablation, the utility of CEUS has been only partially explored. Indeed, except for cryotherapy that uses thermocouples to monitor treatment effect, the other thermal and nonthermal

sources of energy lack of standardized intraoperative control to measure tissue ablation. Rouvière et al. [8] investigated CEUS in the context of HIFU whole-gland ablation. They developed the subjective 3-point Likert-type score that we used in this study in order to determine the likelihood of residual disease after HIFU. They found that CEUS clearly depicts tissue necrosis immediately after treatment, with 78% of S0 zones showing absence of viable tissue, and 79% and 92% of S1 and S2 zones containing nonablated tissue, respectively. In another study performed by Van den Bos et al. [17], CEUS was investigated for treatment monitoring after irreversible electroporation by correlating the estimated ablation area on CEUS with the results of definitive pathology. This study showed a good correlation between the 2 tests with a Pearson index of $r = 80$ ($n = 9$).

In over 1 patient out of 3, based on the CEUS appearance of the treated area, the surgeon decided to deliver further treatment, emphasizing the impact of CEUS in real practice. Compared to mpMRI, CEUS has the advantage that it can be used intra-operatively, which translates in the possibility to immediately consolidate or even extend the margin ablation as needed. CEUS has also attractive characteristics, which might enhance its adoption. It has a low toxicity profile, it is not expensive, and can be widely used in contrast to magnetic resonance technologies which are limited in some patients suffering from claustrophobia or harboring metal implants. Whether the use of intraoperative CEUS actually decreases the retreatment rate is yet to be determined. Exploring this question in a more valid manner would require a randomization process in which the use of CEUS is permitted in 1 arm and not in another. Although CEUS and early mpMRI had equivalent diagnostic performance in detecting residual disease at control biopsy, CEUS clearly had an independent value as compared to known predictors. Indeed, mpMRI at 6 to 12 months after focal HIFU has clearly better accuracy than early mpMRI in light of the absence and resolution of postoperative artifacts. Many have actually proposed to discontinue the systematic use of early mpMRI as its results have little impact on the overall management in light of its low accuracy. In other words, as late mpMRI is systematically performed prior to control biopsy, and early MRI drives no change in the follow-up, its value is questioned. Our study suggests that CEUS is an additional source of information and might help in completing the ablation with margin as well as to determine the likelihood of residual disease. This study is hypothesis-generating; further studies are needed to better predict the effectiveness of focal treatment with HIFU.

From an oncological perspective, our results are in the high range of series exploring clinically significant residual cancer after focal HIFU. This is likely to be linked to a verification bias since the utility of control biopsy was discussed on a patient-basis, and men who were very unlikely to harbor residual disease did not undergo biopsy. This obviously skewed the results toward a high rate (30%) of significant residual disease than in other series in which biopsies were performed "per protocol" [18]. Also, it is important to note that there is no consensus on the definition of clinically significant cancer [19], and other authors might use less restrictive definitions than the one used in the present study.

5. Conclusion

CEUS and early mpMRI have similar diagnostic accuracy in detecting clinically significant disease after focal HIFU. The 2 tests are concordant in the majority of patients. CEUS has an independent added value compared to early mpMRI in ruling out clinically significant CaP in addition to known predictors of recurrence. Further research is needed to determine whether it enhances the overall efficacy of focal therapy.

Conflicts of interest

None to declare.

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