# Multiparametric ultrasound for prostate cancer detection and localization: Correlation of B-mode, shearwave elastography and contrast-enhanced ultrasound with radical prostatectomy specimens

# Multiparametric Ultrasound for Prostate Cancer Detection and Localization: Correlation of B-mode, Shear Wave Elastography and Contrast Enhanced Ultrasound with Radical Prostatectomy Specimens

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**Abbreviations and Acronyms**

3D = 3-dimensional
CEUS = contrast enhanced US
csPCa = clinically significant PCa
CUDI = contrast US dispersion imaging
DRE = digital rectal examination
GS = Gleason score
mpMRI = multiparametric MRI
mpUS = multiparametric US
MRI = magnetic resonance imaging
NPV = negative predictive value
PCa = prostate cancer
PI-RADS = Prostate Imaging Reporting and Data System
PSA = prostate specific antigen
PZ = peripheral zone
ROI = region of interest
RP = radical prostatectomy
SWE = shear wave elastography
TZ = transition zone
UCA = US contrast agent
US = ultrasound
v2 = version 2

**Purpose:** Similar to multiparametric magnetic resonance imaging, multiparametric ultrasound represents a promising approach to prostate cancer imaging. We determined the diagnostic performance of B-mode, shear wave elastography and contrast enhanced ultrasound with quantification software as well as the combination, multiparametric ultrasound, for clinically significant prostate cancer localization using radical prostatectomy histopathology as the reference standard.

**Materials and Methods:** From May 2017 to July 2017, 50 men with biopsy proven prostate cancer underwent multiparametric ultrasound before radical prostatectomy at 1 center. Three readers independently evaluated 12 anatomical regions of interest for the likelihood of clinically significant prostate cancer on a 5-point Likert scale for all separate ultrasound modalities and multiparametric ultrasound. A logistic linear mixed model was used to estimate diagnostic performance for the localization of clinically significant prostate cancer (any tumor with Gleason score 3 + 4 = 7 or greater, tumor volume 0.5 ml or greater, extraprostatic extension or stage pN1) using a Likert score of 3 or greater and 4 or greater as the threshold. To detect the index lesion the readers selected the 2 most suspicious regions of interest.

**Results:** A total of 48 men were included in the final analysis. The region of interest specific sensitivity of multiparametric ultrasound (Likert 3 or greater) for clinically significant prostate cancer was 74% (95% CI 67–80) compared to 55% (95% CI 47–63), 55% (95% CI 47–63) and 59% (95% CI 51–67) for B-mode, shear wave elastography and contrast enhanced ultrasound, respectively. Multiparametric ultrasound sensitivity was significantly

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higher for Likert thresholds and all different clinically significant prostate cancer definitions (all $p < 0.05$). Multiparametric ultrasound improved the detection of index lesion prostate cancer.

**Conclusions:** Multiparametric ultrasound of the prostate, consisting of B-mode, shear wave elastography and contrast enhanced ultrasound with parametric maps, improved localization and index lesion detection of clinically significant prostate cancer compared to single ultrasound modalities, yielding good sensitivity.

**Key Words:** prostatic neoplasms, diagnostic imaging, ultrasonography, elasticity imaging techniques, contrast media

THE diagnosis of PCa is evolving toward an imaging driven approach. Increasingly mpMRI is used as a tool for targeted biopsy. Recently 3 prospective multicenter trials in biopsy naïve men demonstrated that, compared to systematic biopsy, mpMRI targeted biopsy decreased the number of biopsy procedures and reduced the detection of insignificant PCa while maintaining csPCa detection.[1–3] However, complete substitution of systematic biopsy by mpMRI targeted biopsy is currently not recommended as the mpMRI pathway still misses some men with csPCa.[4,5] Resources such as radiologic and urological expertise, MRI gantry time and reimbursement costs also represent logistic and financial challenges.[6]

US is widely available and portable, purchasing the machine is less expensive and US is more familiar to the urologist. However, US is mainly used for biopsy guidance. US is gaining increasing interest since new US modalities such as CEUS with quantification analyses, elastography and micro-US have shown encouraging results for PCa and csPCa localization.[7–10] During CEUS an intravenously administered suspension of gas filled microbubbles (ie UCAs) is used to visualize microvascular flow patterns. Quantification by CUDI has been developed to assess UCA bolus kinetics and, therefore, the alterations caused by PCa angiogenesis in the prostate microvasculature.[11] In addition, PCa typically shows increased stiffness because of higher cellular density and collagen depositions.[12] In contrast to real-time elastography, SWE allows for the quantitative estimation of tissue elasticity without the need for manually exerted transducer pressure.[10]

Similar to mpMRI, the exploration of different US modalities in multiparametric fashion to combine relevant information from complementary PCa phenomena could be essential to improve US based imaging of csPCa. However, to date mpUS has hardly been investigated.[13] In this clinical study we evaluated the diagnostic performance of B-mode, SWE and CEUS using parametric maps and combination mpUS to detect and localize csPCa. RP histopathology served as the reference standard.

## MATERIALS AND METHODS

### Trial Design

This prospective, single center, institutional review board approved study included 50 men with biopsy proven PCa scheduled for RP at the Prostate Cancer Center, Martini-Klinik Hamburg, Hamburg, Germany. The study protocol is prospectively registered on ClinicalTrials.gov (NCT03091231) and it was published previously.[14] The study also received Institutional Review Board approval (IRB No. PV5439).

### Study Population

Participants were eligible for study if they had biopsy proven PCa with serum PSA 20 ng/ml or less and a DRE that did not suggest extracapsular disease. Men with contraindications to CEUS or who underwent previous PCa therapy were excluded from study. To maintain SWE image quality an upper prostate volume threshold of 80 ml was adopted. All men provided written informed consent.

### Ultrasound Imaging

***Protocol.*** From May 2017 to July 2017, 50 men underwent US on an Aixplorer® clinical US scanner with a Super Endocavity™ SE12-3 end fire endorectal coil. Supplementary figure 1 (https://www.jurology.com) shows the flow chart. The prostate was examined in 3 planes (base, mid and apex) using 3 scanning modalities (B-mode, SWE and CEUS) sequentially (figs. 1 and 2). For CEUS a 2.4 ml bolus of SonoVue® per plane was used. CEUS recordings were quantified by CUDI directly after acquisition.[15,16] Study procedures were written in detail in the study protocol.[14]

***Evaluation.*** Images from individual modalities or a combination (ie mpUS) were evaluated by 3 readers in random order (supplementary fig. 2, https://www.jurology.com). Readers received 2 days of training and were blinded to clinical and pathological data. SWE and CEUS were evaluated in conjunction with B-mode as the 2 modalities should be interpreted while considering B-mode findings.[17,18]

To study csPCa localization the readers used a 5-point Likert scale to score left and right quadrants in the PZ and the TZ in each plane for a total of 12 anatomical ROIs per patient. The presence of csPCa was scored as 1—highly unlikely, 2—unlikely, 3—equivocal, 4—likely or 5—highly likely in that specific ROI (supplementary fig. 3, https://www.jurology.com). The Likert score of mpUS was left to reader discretion. In addition, readers were asked to select the most suspicious ROI (ROI 1) and the second most suspicious ROI (ROI 2) to examine the use of mpUS

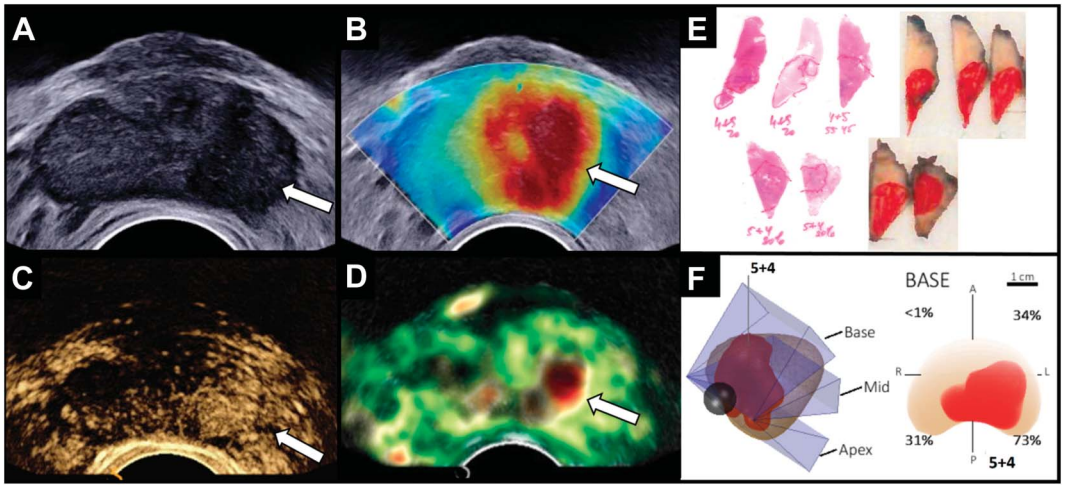


**Figure 1.** Base prostate plane mpUS in 67-year-old man with PSA 18.4 ng/ml. *A*, B-mode reveals suspicious hypoechoic lesion (arrow) in prostate left side. *B*, SWE shows highly suspicious stiffness (arrow) in left prostate. *C*, suspicious early enhancement (arrow) in left prostate on contrast enhanced US. *D*, suspicious red focus (arrow) on CUDI parametric map in left prostate. *E*, histopathology demonstrates clinically significant Gleason score 5 + 4 = 9 PCa in prostate left base. Reduced from ×2. *F*, histopathological correlation of US with histopathology shows 3 positive ROIs at prostate base plane, including left and right PZ, and left TZ.

to potentially target index lesion PCa. Supplementary table 1 (https://www.jurology.com) shows the US experience.

### Radical Prostatectomy and Histopathology

RP was performed with an intraoperative neurovascular frozen section examination. These frozen sections were processed separately from the resected specimen. Histopathological analysis was performed according to institutional standards with complete embedding of the prostate in 4 mm thick axial step-section slices. A uropathologist determined the location, stage and percent of Gleason Grade 3, 4 and 5 patterns in the RP and the frozen section(s) in accordance with the ISUP (International Society of Urological Pathology) recommendations.[19] The index lesion was defined as the lesion with the highest GS or, in case of multiple lesions with the same GS, the lesion with the largest volume.

### Histopathological Correlation of Imaging

As written in detail in our protocol, we used an automated histopathological correlation method in line with our previous published work to match RP histopathology to US.[14,20] To this end a 3D histopathological model of the excised prostate was reconstructed by interpolating the tumor delineations on the pathology slices in 3 dimensions. Apical, mid and basal cross-sections of this 3D histopathological model were projected on the actual US image.

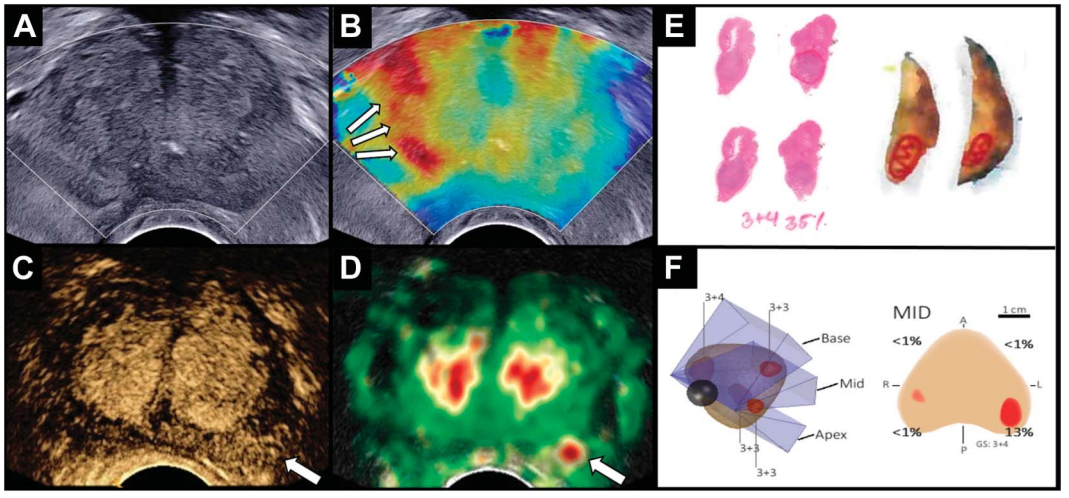


**Figure 2.** Mid prostate plane mpUS in 69-year-old man with PSA 8.2 ng/ml. *A*, heterogeneous signal intensity on B-mode. *B*, SWE shows asymmetrical diffuse increased stiffness (arrows) in right TZ. *C*, suspicious early enhancement (arrow) in prostate left PZ on CEUS. Note round, well circumscribed, symmetrical early enhancement in each TZ, which is benign morphology. *D*, suspicious red focus (arrow) on CUDI parametric map. *E*, histopathology reveals unilateral Gleason score 3 + 4 = 7 csPCa in left PZ. Reduced from ×2. *F*, histopathological correlation of US with histopathology demonstrates 1 positive ROI in prostate left PZ mid plane.

### Statistics

Baseline characteristics are reported descriptively. We used a logistic linear mixed model including US modality as the fixed effect and cross random effects for patients and ROI levels to estimate the diagnostic performance (sensitivity, specificity, NPV and positive predictive value) of each US modality for csPCa localization at the Likert 3 or greater and 4 or greater thresholds.[21] The primary definition of csPCa was any GS 3 + 4 = 7 or greater PCa, a tumor volume of 0.5 ml or greater, extraprostatic extension or positive lymph node status.[22] We also analyzed more stringent definitions of csPCa, including GS 3 + 4 = 7 or greater with a tumor volume of 0.5 ml or greater and GS 4 + 3 = 7 or greater. The index lesion was determined at the patient level as a positive result if the selected ROI contained the index lesion PCa.

Interobserver agreement was evaluated by the Krippendorff $\alpha$ for nominal outcomes with the bootstrapped 95% CI ranging from 0—no agreement to 1—excellent agreement. Two-sided statistical tests were performed with $p < 0.05$ considered statistically significant. We used SPSS® for Windows®, version 25.0 and R, version 3.5.1 (https://www.r-project.org/foundation/).

## RESULTS

### Baseline Characteristics

Two men did not undergo RP. Thus, 48 men (96%) with a total of 576 ROIs were available for final analysis. Median age was 65 years (IQR 58–70) and median PSA was 7.7 ng/ml (IQR 5.4–10.2) (see table). Of the men 36 (75%) had overall GS 3 + 4 = 7 (Grade Group 2) PCa at RP and 11 (23%) had GS 4 + 3 = 7 or greater (Grade Group 3 or greater) PCa. Supplementary table 2 (https://www.jurology.com) shows ROI specific pathology findings. Median US scan time was 27 minutes (IQR 25–28). There were no adverse events or procedure failures during or after US imaging.

*Clinical characteristics*

| | | |
|---|---|---|
| No. pts | 48 | |
| Median age (IQR) | 65 | (58–70) |
| No. PCa family history (%): | | |
| Yes | 8 | (17) |
| No | 40 | (83) |
| Median ng/ml preop PSA (IQR) | 7.7 | (5.4–10.2) |
| No. DRE finding (%): | | |
| Normal | 32 | (67) |
| Abnormal | 16 | (33) |
| No. prostate clinical T-stage (%): | | |
| T1c | 32 | (67) |
| T2a-b | 15 | (31) |
| T2c | 1 | (2) |
| Median ml prostate vol (IQR) | 40 | (34–49) |
| No. B-mode finding (%): | | |
| Normal | 26 | (55) |
| Abnormal | 21 | (45) |
| Median ng/ml/ml PSA density (IQR) | 0.18 | (0.14–0.24) |
| No. biopsy Grade Group/Gleason score (%): | | |
| 1/3 + 3 = 6 | 8 | (17) |
| 2/3 + 4 = 7 | 22 | (46) |
| 3/4 + 3 = 7 | 8 | (17) |
| 4/8 | 7 | (15) |
| 5/9-10 | 3 | (6) |
| No. pathological T-stage (%): | | |
| T2a-b | 2 | (4) |
| T2c | 31 | (65) |
| T3a | 12 | (25) |
| T3b | 3 | (6) |
| No. RP overall Grade Group/Gleason Score (%): | | |
| 1/3 + 3 = 6 | 1 | (2) |
| 2/3 + 4 = 7 | 36 | (75) |
| 3/4 + 3 = 7 | 10 | (21) |
| 5/5 + 4 = 9 | 1 | (2) |
| No. RP index lesion Grade Group/Gleason score (%): | | |
| 1/3 + 3 = 6 | 1 | (2) |
| 2/3 + 4 = 7 | 30 | (63) |
| 3/4 + 3 = 7 | 6 | (13) |
| 4/8 | 6 | (13) |
| 5/9-10 | 5 | (10) |
| No. extended pelvic lymph node dissection (%): | | |
| Nx | 1 | (2) |
| N0 | 42 | (88) |
| N1 | 5 | (10) |

### Prostate Cancer Localization

***Overall.*** Supplementary table 3 (https://www.jurology.com) shows the ROI specific diagnostic performance of B-mode, SWE, CEUS and mpUS. Using a Likert 3 or greater threshold to define primary csPCa, mpUS achieved 74% sensitivity (95% CI 67–80) and 59% specificity (95% CI 53–65). The ROI specific sensitivity of mpUS was significantly higher for all csPCa definitions at the Likert 3 or greater and the Likert 4 or greater threshold in comparison to B-mode, SWE and CEUS (all $p < 0.05$). For the primary definition ROI specificity for mpUS did not significantly differ among B-mode, SWE and CEUS while it was significantly lower for some stringent csPCa definitions ($p < 0.05$). The NPV of mpUS for csPCa varied from 70% using the primary definition to 93% using the most stringent definition.

***Peripheral and Transition Zones.*** Supplementary tables 4 and 5 (https://www.jurology.com) list ROI specific sensitivity and specificity of B-mode, SWE, CEUS and mpUS for csPCa localization in the PZ and the TZ. ROI specific sensitivity of mpUS was higher for the PZ than the TZ at 80% vs 67% for a primary definition of Likert 3 or greater.

### Index Lesion Detection

Supplementary figure 4 (https://www.jurology.com) shows that index lesion detection by B-mode, SWE, CEUS and mpUS increased with a higher index lesion GS. If ROI 1 and ROI 2 were accurately targeted, this would have resulted in an 88% index lesion detection rate for mpUS compared to 70%, 72% and 73% for SWE, B-mode and CEUS, respectively ($p < 0.05$).

### Interobserver Agreement

Among the readers the Krippendorff $\alpha$ coefficient of the reliability of a Likert score of 3 or greater was

0.23 (95% CI 0.18–0.28) for B-mode, 0.36 (0.31–0.42) for SWE, 0.32 (0.26–0.37) for CEUS and 0.33 (0.28–0.38) for mpUS. For a Likert score of 4 or greater the reliability of findings was 0.20 (0.14–0.26) for B-mode, 0.36 (0.27–0.44) for SWE, 0.48 (0.41–0.54) for CEUS and 0.46 (0.39–0.52) for mpUS.

## DISCUSSION

Recent years have shown that a standardized multiparametric approach to MRI improved the diagnostic performance compared with T2-weighted imaging only.[23–26] Although it has scarcely been investigated, this rationale could also apply to US.[13] Preliminary studies of mpUS showed promising results but were limited by study design, evaluation of only mpUS of target lesions and the use of real-time elastography, which is notorious for operator dependence.[27,28] To our knowledge we report the first study to prospectively evaluate the diagnostic performance of B-mode, SWE and CEUS alone and in combination (ie mpUS) to localize csPCa and detect its index lesion.

As demonstrated, mpUS on a clinical scanner is safe and feasible, and can be performed in less than 30 minutes with good imaging quality. All single US modalities demonstrated limited overall sensitivity and specificity for csPCa localization. In contrast, mpUS had significantly improved sensitivity for all csPCa definitions at the 2 Likert thresholds with appreciable 74% to 85% sensitivity when considering a Likert score of 3 or greater to be suspicious. This resulted in a NPV of mpUS for csPCa of 70% to 93% depending on the csPCa definition. In addition, mpUS significantly improved the detection of GS 3 + 4 = 7 or greater index lesion PCa compared to the single US modalities.

Interestingly it seemed difficult to identify PZ tumors on SWE while TZ tumors were frequently missed on CEUS/CUDI and B-mode. In the recent literature large overlapping SWE stiffness values of insignificant PCa and csPCa were noted in the PZ.[12] In addition, the TZ is often composed of intermixed amounts of glandular and stromal tissue, demonstrating heterogeneous signal intensity on B-mode, while benign prostatic hyperplasia nodules in the TZ limit PCa visualization on CEUS. In light of this, combining these US modalities into mpUS using quantification software, which is inherent to SWE and added to CEUS with CUDI, seems essential to accurately image PCa on US.

Despite these positive findings, the specificity of mpUS at a Likert score of 3 or greater significantly decreased in the more stringent models while improved specificity at a Likert score of 4 or greater was achieved at the expense of sensitivity. A possible explanation of the low mpUS specificity could be that 2 readers had limited clinical experience, especially with SWE. As a result there may have been a possible tendency to consider dubious regions as equivocal (Likert score 3) so that csPCa would not be missed. Specificity must be further improved and promising results have been reported with machine learning based analysis of radiomics. Future work will focus on the development of a machine learning framework for mpUS classification, allowing for the integration of a range of US (radiomic) features to aid the clinician in the characterization of csPCa on US.[29]

The diagnostic performance of mpUS in our study has many similarities with that in previously published studies of mpMRI. When using RP as the reference standard, mpMRI studies have demonstrated 59% to 80% sensitivity for csPCa.[23–25] Like mpUS, mpMRI also showed increasing sensitivity for larger and more aggressive tumors while a recent Cochrane meta-analysis revealed a low pooled specificity for mpMRI of only 0.37 (95% CI 0.29–0.46) for Gleason score 3 + 4 = 7 or greater PCa.[5,30]

Like the PI-RADS for prostate MRI, continuous refinements in imaging interpretation and score assignment also seem necessary to further improve the diagnostic performance of mpUS and the moderate interobserver agreement in our current study. However, mpUS currently lacks the standardization and consistency which PI-RADS provides for mpMRI. Because US studies of PCa are known for excessive variation in acquisition, interpretation and reporting, the usefulness of US remains a subject of debate despite some promising results. Our study using a consistent and standardized mpUS approach could be seen as an important first step for multicenter standardization, evaluation and implementation of mpUS in the clinical setting.

Besides the small sample size, there were some other limitations to our study. 1) Studies of RP histopathology provide an accurate ground truth reference but spectrum bias is to be expected since subjects must have PCa and elect surgery. Therefore, we excluded men with PSA greater than 20 ng/ml and/or DRE suggestive of extracapsular disease to make our results more generalizable to the population referred for imaging targeted biopsy. 2) Awareness that study participants had biopsy proven PCa may have biased image interpretation by the readers. 3) The prostate was evaluated in 2-dimensional US with the risk of missing tumors outside the predefined imaging planes. Although a 3D US approach can overcome these limitations and reduce the number of UCA injections, to our knowledge no clinical scanner currently has the ability to perform 3D mpUS.

We chose a 12 ROI based template per prostate for our localization analyses. Although errors in the registration procedure of US and RP histopathology caused by gland deformation, fixation related shrinkage, and a mismatch in US imaging and pathology plane orientation were largely mitigated by the dedicated 3D registration framework, the separate histopathological examination of intraoperative frozen sections posed an additional challenge.[20] The current PI-RADS v2 sector map includes 36 prostate ROIs but it seems unlikely that the sensitivity of mpUS vs mpMRI would be overestimated. After all, the majority of mpMRI studies also used 12 ROIs or the PI-RADS v2 sector map, applying additional analytical methods to minimize potential errors in the radiologic-pathological correlation in which PCa was often classified as correctly identified in the chosen ROI or any region in the immediate vicinity.[23–26] Recognizing the important evolving role of mpMRI in PCa diagnosis, we retrospectively evaluated all available mpMRIs to enable a comparison of mpUS with mpMRI in this study. Unfortunately most of the 29 available MRIs were performed elsewhere and did not meet PI-RADS v2 quality requirements.

Our study with a standardized US imaging approach shows promise. However, further investigations in the biopsy setting are needed as the clinical usefulness of mpUS depends not only on lesion scoring but also on targeting accuracy. Only then will we be able to definitively determine whether mpUS may complement the mpMRI targeted biopsy procedure or even rival mpMRI as a diagnostic imaging tool.

## CONCLUSIONS

Prostate mpUS, consisting of B-mode, SWE and CEUS/CUDI, significantly improved the sensitivity of csPCa localization and demonstrated high ability to detect the index lesion compared with individual US modalities. Similar to mpMRI, the combination of complementary US modalities into mpUS could bring accurate US imaging of csPCa within reach.

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## EDITORIAL COMMENT

The authors evaluated the diagnostic performance of B-mode, SWE and CEUS with quantification software and the combination mpUS to detect csPCa. They concluded that prostate mpUS improved localization and index lesion detection of csPCa compared with the single US modalities.

This study is interesting because these results are close to the diagnostic performance of prostate mpMRI. In the mpMRI era transrectal US and related technologies seem to have limited value and they have been neglected for PCa diagnosis. On the contrary, this study provides insight into the diagnosis of PCa. This report may motivate people to study US methods of diagnosing cancer. Moreover, as already discussed by the authors (reference 14 in article), this study provides information on the question of whether mpUS could potentially serve as a triage test to exclude significant PCa. It may also invite us to consider mpUS before performing mpMRI in some patients.

However, I have some concern about how these good results could be translated to clinical practice. The authors report their experience with CEUS but this modality cannot be used routinely. I would rather consider only the association of B-mode and SWE (a sort of biparametric US), which might provide good results. Since mpMRI has already become the first line examination in all settings, the lack of any comparison of these findings with mpMRI significantly limits the power of this study.

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## REPLY BY AUTHORS

We appreciate this opportunity to address the concerns in the comment on our article evaluating the diagnostic performance of mpUS for histopathologically confirmed csPCa.

This study incorporated a consistent and standardized mpUS approach with clearly defined interpretation criteria for each ultrasound modality, including B-mode, SWE and CEUS. With a median scan time of 28 minutes on a clinical US scanner we believe that our mpUS approach is routinely feasible. Currently biparametric US seems too ambitious as reported inferior results of SWE have already included B-mode. Although we recognize that high quality US is experience dependent and CEUS currently requires multiple acquisitions, 3D (contrast enhanced) US and automated analysis of US images might ease the use of mpUS in the future.[1]

Indeed, mpMRI has achieved worldwide acceptance in academic and community settings. As a result US is unadvisedly neglected while it remains inextricably linked to prostate biopsy due to its simplicity, practicality and cost-effectiveness. Especially now the recent literature has undeniably shown comparable csPCa detection rates for cognitive, MRI-transrectal US fusion and direct in-bore MRI biopsy, respectively.[2] Furthermore, there is still an unmet need to identify men who will benefit from mpMRI and biopsy while reducing the number of unnecessary MRIs, biopsies and diagnoses of low risk PCa. In this light up-front state-of-the-art mpUS can be envisaged.

Future studies should be encouraged to investigate whether mpUS may complement the mpMRI pathway or even rival mpMRI as a diagnostic imaging tool.

## REFERENCES

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