Parker P, Twiddy M, Rigby A, Whybrow P, Simms M. Evaluating the Role of Ultrasound in Prostate Cancer trial – phase 1: Early experience of micro-ultrasound in the United Kingdom. Ultrasound. (Journal Volume Number and Issue Number) pp. xx-xx. Copyright © 2024 by The British Medical Ultrasound Society. DOI: https://doi.org/10.1177/1742271X231226302.

Evaluating the Role of Ultrasound in Prostate cancer (ERUP) trial – Phase 1 early experience of micro-ultrasound in the UK

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Abstract

Purpose: To evaluate if the use of micro-ultrasound (microUS) can detect significant prostate (csPCa) pathology when compared to histology obtained during a transperineal prostate biopsy.

Methods: Patients suspected of having prostate cancer, who had a prebiopsy MRI and could tolerate a transrectal examination were prospectively recruited. All patients had a microUS scan prior to their biopsy. The findings of MRI, microUS, and histology were risk stratified in accordance with local pathways. Comparison of assigned risk scores were made using histology as the reference standard.

Results: Data from 101 patients were evaluated. Histology showed that csPCa was detected in 48.5% (n = 49/101) of patients. Moderate inter-rater agreement was found in both MRI and MicroUS with K of 0.31 in both modalities. High risk findings were identified in 81% (n = 82/101) patients at MRI and in 66% (n = 67/101) patients at microUS. Sensitivity and specificity of MRI was found to be 87% and 34.6% and for microUS 73.3% and 53.8% respectively.

Conclusion: A limitation of this study was that the biopsy was not performed with microUS which may have resulted in unidentified cancers and lowered the apparent accuracy of the technique. However, we conclude that whilst microUS was diagnostic, MRI demonstrated higher sensitivity in our local population and remains the pre-biopsy imaging modality of choice. However, the higher specificity of microUS identified does indicate that it may be of value when MRI is contraindicated. The role of microUS, within an active surveillance pathway for prostate cancer, warrants further investigation.

Keywords: Sonographer · MicroUS · Diagnosis · Prostate biopsy · Active Surveillance

Main Article

Background

The detection of prostate cancer (PCa) is increasing in the UK as well as world-wide [1] This increase is led, in part, by prostate serum antigen [PSA] selective screening in the USA [2] and the efforts to increase awareness of prostate cancer by The Movember Foundation [3] and Prostate Cancer UK [4] charities. Despite the fact that 1 in 8 men will develop some form of prostate cancer within their lifetime, and that around 47,000 men in the UK will be diagnosed with prostate cancer per year [3, 4, 5], the cancer specific mortality rate remains low at ≤ 1.5% [6].

Diagnosis, detection and surveillance

The diagnosis of prostate cancer is histological following a biopsy procedure. This procedure usually involves a transrectal ultrasound (TRUS) examination that guides where appropriate biopsies of the prostate are taken. To aid detection of clinically significant cancer, reduce the detection of disease which is considered to be low risk, and attempt to reduce post-biopsy complication rates, the use of multiparametric magnetic resonance imaging (mpMRI) is recommended [7, 8, 9] which can then be further employed to guide the site of biopsy. However, a recent review by the National Institute for Health and Care Excellence (NICE) [10] has identified that there is insufficient evidence to recommend routine adoption of MRI fusion biopsy systems to diagnose prostate cancers and, as such, high quality ultrasound imaging is required to identify the targets of most concern. An editorial review by Kasivisvanathan et al [11] describes the use of mpMRI and mpMRI targeted biopsies in the prediction of long term outcomes for men on an AS pathway. Regular access to high quality mpMRI in terms of capacity, imaging protocols, and reporting standards is required for this to be a valuable asset to an AS programme [12]. However, as Glass & Dall'Era [13] recognise, there are persistent and on-going multiple barriers to the widespread use of mpMRI for AS, again including quality, cost, and capacity. In addition, for some men, mpMRI is contraindicated or they are unable to tolerate the enclosed examination. For these, and for those where mpMRI capacity is unavailable, the only current monitoring process is repeat PSA blood tests and repeat invasive prostate biopsy. It is therefore timely to review the options that modern, alternative imaging modalities present to this cohort of patients.

Ultrasound Technology:

Standard B-Mode ultrasound imaging can assess the appearance of the prostate as a whole and identify regions of interest (ROI) within the gland although poor spatial resolution of early endorectal transducers precluded this modality as having a useful role in PCa diagnosis [14].

Technological advances within the last five years have potentially changed that and there is now evidence that ultrasound may, indeed, have a useful role in the identification of prostate cancer [12, 15, 16]. MicroUS is a relatively new technique in the field of transrectal imaging [17] and is bespoke to a particular manufacturer (Exact Imaging™ Markham, Canada). The system utilises transducer emitting a scanning frequency of 29MHz to increase both axial and lateral spatial resolution of the prostate. The construction of the microUS system provides a 4-fold higher crystal density along the transducer (512 vs 128 crystals) and a consequent increase in penetration up to 6cm [18]. A resolution to 70 microns [18] is achieved with the consequent significant increase in spatial resolution which enables detection of the prostatic anatomy in exquisite detail. Despite the increased crystal density, the microUS probe has only a marginally wider diameter than a standard endorectal transducer (18mm compared to 15mm) but has a tapered head and is well tolerated by patients.

There are promising results from published studies [12, 17, 19 - 21] that support the use of microUS in PCa. The 2019 meta-analysis published by Zhang et al [22] demonstrated that micro-US has a high sensitivity (91%) but poor specificity (49%) potentially due to the learning curve of a new technique not commonly employed in the diagnosis of PCa at that time. MicroUS has been identified by Fusco et al [23] as having benefits for patients with suspected prostate cancer in whom MRI is contraindicated and the 30% improvement in spatial resolution identified by Dariane et al [24] may improve lesion detection. However, microUS, as a diagnostic imaging technology, remains in its infancy with no clear recommendations for use here in the UK [23].

The installation of a microUS machine into the ultrasound department of a large teaching hospital in the UK has facilitated research to continue to further evaluate the diagnostic capacity of this technology within the UK health economy. Locally, a service evaluation of mpMRI capacity identified a gap in service for men being monitored for the progression of PCa was identified and it was hypothesised that microUS may provide the imaging services for this cohort of patients. As such, the aim of this study is to evaluate its role in the active surveillance of PCa and to employ this technology within the research design of the wider **E**valuating the **R**ole of **U**ltrasound in **P**rostate cancer (ERUP) trial. This is a multiphase trial with the purpose of this phase 1 study to evaluate the performance of microUS compared to standard ultrasound fusion guided transperineal biopsy of the prostate. We ask the question, can microUS ultrasound identify significant prostate pathology?

Ethical Approval

The ERUP trial was approved by the Oxford Research Ethics Committee [reference 21/SC/0326] on 23 November 2021 and the protocol registered with www.clinicaltrails.gov [NCT05326282] [25]. University ethics and NHS Trust approvals were obtained.

Materials and Methods

Patient cohort and study design

All men suspected of having PCa, who had a prostate MRI were prospectively approached and sent a patient information sheet outlining the purpose of the study and their potential involvement recruited. Men unable to tolerate a transrectal examination were excluded. All patients signed a written informed consent before enrolment. All men recruited required diagnostic ultrasound guided transperineal prostate biopsy under local anaesthesia (LATP Bx) either due to focal anomalies identified at MRI or due to increased risk of PCa due to positive close family history (father, brother) and/or due to a prostate specific antigen density (PSAD) of ≥ 0.15. The microUS imaging for this study was performed immediately prior to the planned biopsy procedure.

MicroUS, biopsy and MRI

All patients had their prostates imaged using the 29 MHz ExactVu™ microUS system with a side-fire endorectal probe. A standard protocol required images to be recorded in a longitudinal plane as real-time transverse imaging is not possible using this transducer. All MicroUS and the LATP Bx were performed by one of five sonographers experienced in ultrasound guided prostate biopsy procedures and observed by a second of the five sonographers. Both practitioners were blinded to the previous MRI results. A worksheet was completed in consensus with both sonographers indicating site and maximum score of microUS findings. All prostates were classified according to Prostate Risk Identification Using Micro-Ultrasound [PRI-MUS] score [17]. Following the ultrasound examination the sonographers were unblinded to the MRI. All patients then progressed to LATP Bx performed using a 7 MHz biplanar transducer of an Aplio i700 machine (Canon Medical Systems, Crawley, UK) as per the standard patient care pathway. Where required, a MRI fusion guided targeted biopsy was performed using the same system. Where no lesion had been identified at MRI, but the patient had risk factors for PCa (positive family history and or PSAD >0.15), an 18 core systematic LATP Bx was performed.

Histology outcomes were risk stratified to align with the clinical management pathway utilised in the standard care of these patients. Given the complexities of correlating Gleason scores, MR and ultrasound appearances, and the reporting systems of PIRADS V2 [26] and PRI-MUS [17], a pragmatic

approach of a 3 point risk stratification, approved by clinical colleagues, was employed for the data analysis of this study [Table 1].

Table 1: Locally agreed risk stratification tool for MRI and MicroUS assessment

Risk	Low	Low	Equivocal	High	High
Risk Score	**1**	**1**	**2**	**3**	**3**
Histology	Benign/ no cancer detected	Low grade PIN; ASAP	High grade PIN; Gleason 3+3 /3+4 & cancer core length < 6mm	Gleason 3+3 / 3+4 with cancer core length ≥ 6mm	Gleason ≥ 4+3
microUS PRI-MUS	1; low risk anterior gland	2; low risk anterior gland	3	4, High risk anterior gland	5; High risk anterior gland
MRI PIRADS V2	1	2	3	4	5

Comparison of MRI and histology, and microUS and histology, were made and agreement rates calculated using the risk stratification with histology as the reference standard. Images 1 and 2 demonstrate typical features of high risk imaging findings at microUS and MRI respectively; images 3 and 4 demonstrate low risk features of both imaging modalities.

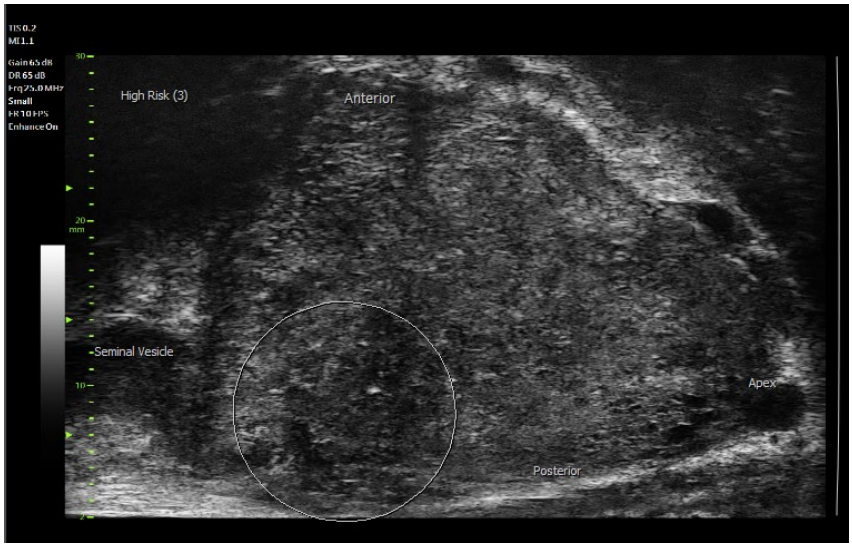


Image 1: MicroUS Image of high risk prostate – region of interest marked. LS Section.

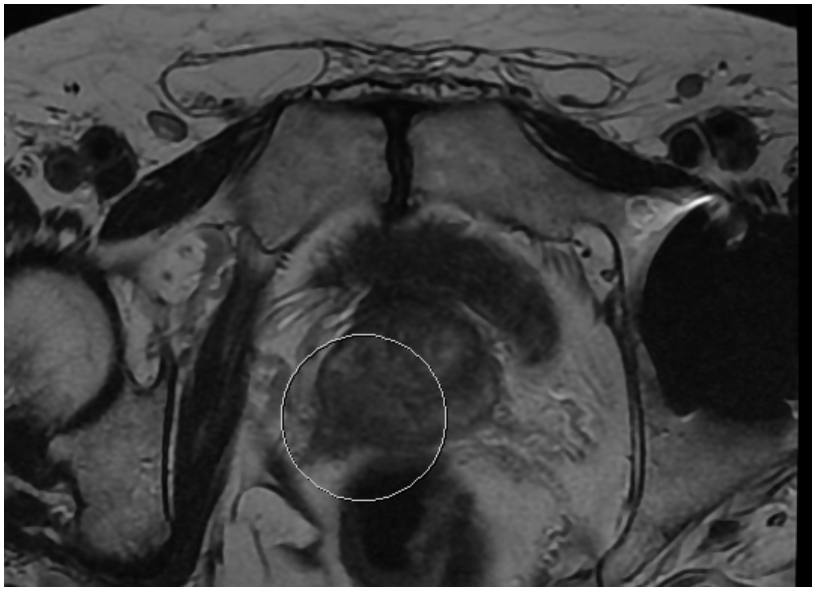


Image 2: T2 MRI of high risk prostate – region of interest marked. Axial plane

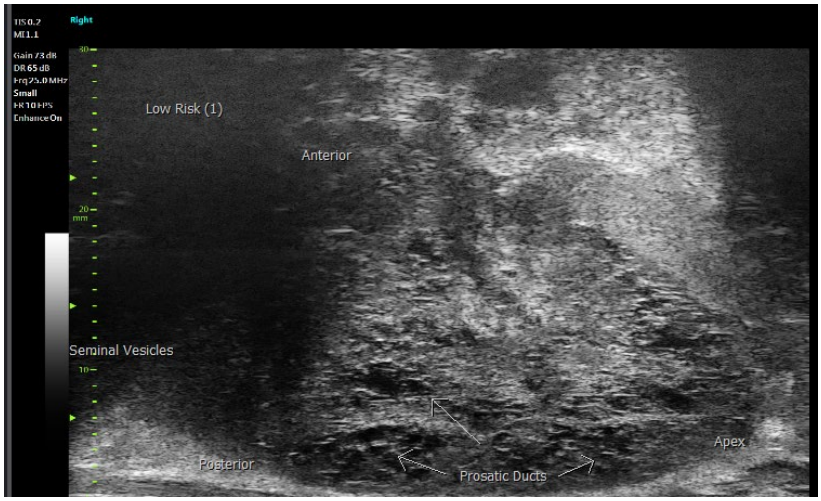


Image 3: MicroUS image of low risk prostate demonstrating ductal patches throughout. LS section

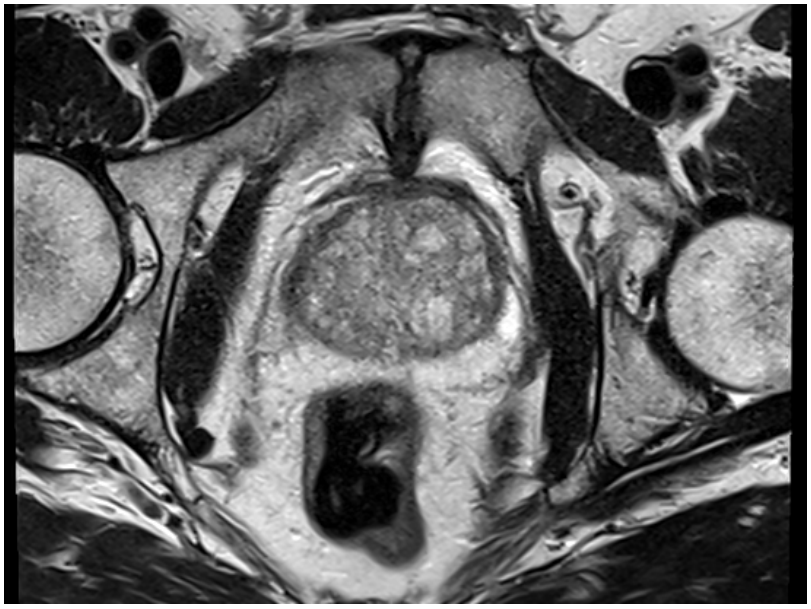


Image 4: T2 MRI of low risk prostate demonstrating normal peripheral and transition zones. Axial plane

Statistical analysis

To understand the degree of agreement between the microUS classification and histology, a kappa (K) statistical test [27] was performed. Percentage agreement rates and inter-reviewer reliability (IRR) were calculated and relative strength of agreement determined in accordance with the methods of Landis and Koch [27]. To take into account the inherent descriptive characteristics that were employed when classifying microUS, a weighted kappa test was also applied. Results were further analysed to understand if there was a difference in agreement between microUS and histology depending upon the given risk stratification score. 3 x 3 contingency tables were created. For the purposes of calculating the sensitivity and specificity, equivocal imaging scores were deemed to be in agreement with high and equivocal risk histology scores as this cohort either have low grade malignancy or high grade, pre-cancerous benign disease and requires follow on management, even if this is unlikely to be radical treatment [table 2]. All analyses were performed using STATA®17.0 (StataCorp, College Station, Texas).

Table 2: 3 x 3 table criteria for determining sensitivity and specificity of imaging reviews

Imaging risk category	**Histology risk category**		
	High	Equivocal	Low
High	**TP**	**TP**	**FP**
Equivocal	**TP**	**TP**	**FP**
Low	**FN**	**FN**	**TN**

Key:
TP = True positive
TN = True negative
FP = False positive
FN = False negative

Results

Recruitment for participation in this study commenced in March 2022 and was completed in October 2022. In total, 107 patients were identified who met the eligibility criteria. All were invited to participate in the ERUP study; 2 declined, 3 patients were unable to tolerate the micro-US examination and 1 had incomplete imaging datasets recorded and was therefore excluded. Of the 101 participants, ages ranged from 47 – 84 years of age (median 67) and their PSA ranged from 0.82 – 50 (median 6.4). Prostate volume was calculated from the pre biopsy MRI and ranged from 16 – 167 mL (average 50 mL). The PSAD was calculated in all cases and ranged from 0.04 – 0.93 (median 0.14).

A PI-RADS v2 score [26] was assigned to each MRI report. PI-RADS v2 takes into account the size of the abnormality although the size of abnormality was infrequently provided on the reports and has been excluded as a criteria for analysis from this review. Contrast is not given as part of the prostate MRI protocol in our institution. Given these limitations of local MRI, the highest PI-RADS v2 score was assigned into high, equivocal or low risk (table 3) using the local risk stratification tool.

Table 3: PI-RADS V2 & PRI-MUS scores demonstrating assigned risk stratification

PI-RADS / PRI-MUS Score	**MRI Frequency (N = number of patients in group)**	**MicroUS Frequency (N = number of patients in group)**	**Assigned Risk stratification**
1	4	5	Low
2	15	29	Low
3	21	17	Equivocal
4	41	31	High
5	20	13	High
High Risk (anterior zone)		6	High
Total	**101**	**101**	

MicroUS

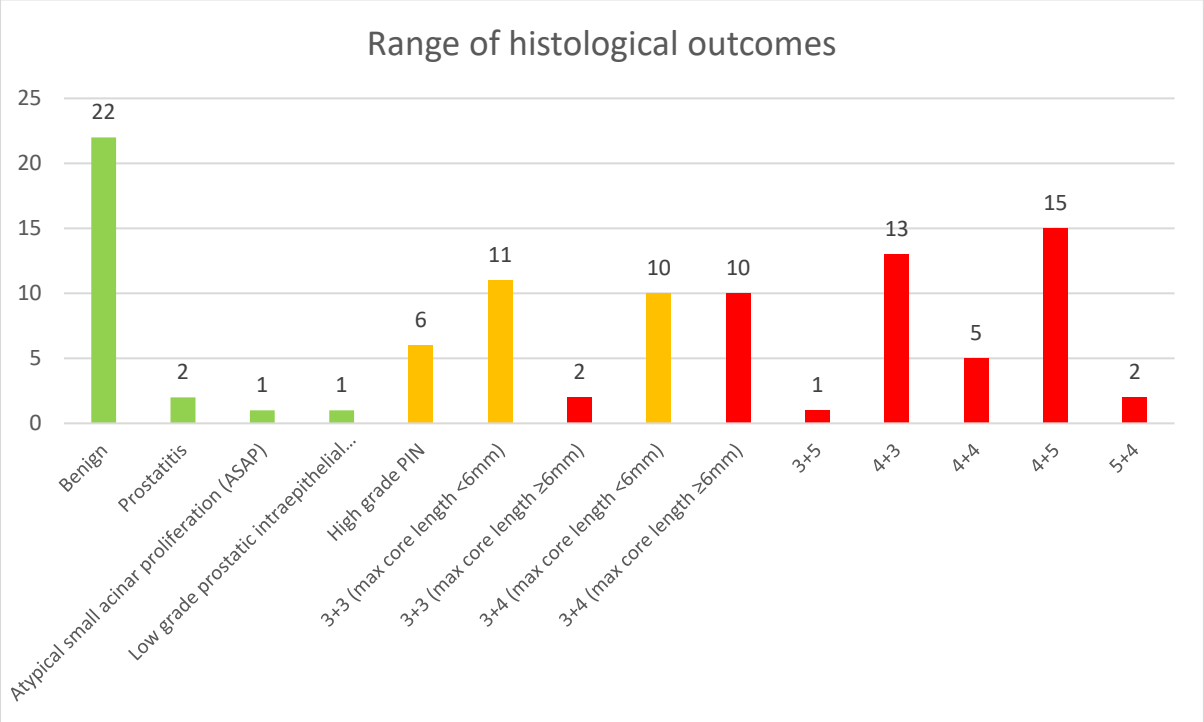
A PRI-MUS score was assigned to each of the microUS examinations following consensus decision by the two sonographers. Abnormalities identified in the anterior zone only were categorised into high risk appearances. There were 6 patients with high risk abnormalities only identified in the anterior

zone, 54 with abnormalities in the peripheral zone only, 34 with low risk PRI-MUS scores throughout the gland, and 7 with unspecified sites but documented as equivocal risk. Each PRIMUS score was assigned a risk stratification (table 3).

76 men had focal target(s) of abnormality identified on MRI and proceeded to fusion guided LATP Bx; the remaining 25 patients underwent an 18 core systematic biopsy. All biopsy were undertaken using the Canon Aplio i700 machine as per the standard care pathway within our institution.

Histological outcomes

Histology outcomes ranged from benign findings with no disease present through to high grade clinically significant prostate cancer (csPCa) with Gleason score of 5 + 4. The range of histological outcomes is presented in figure 1. csPCa, defined as Gleason score 3+3 and Gleason 3+4 with core lengths of over 6mm respectively, and above was detected in 48.5% of this cohort. Using the local risk stratification, there were 49 high risk outcomes requiring radical treatment, 26 with equivocal outcomes requiring follow up, and 26 with low risk of disease. csPCa was detected in 62% (n = 48/78) of targeted LATP Bx procedures and in 4% (n = 1/25) of those with no apparent target on pre biopsy imaging.



MicroUS Agreement

A comparison of the assigned risk stratification of microUS, and of MRI, with the histological outcomes was made. Of these 101 cases, there was agreement between the microUS and histology

in 57 cases. Percentage agreement and kappa analysis of microUS with histology demonstrated IRR of 56.4% and Κ of 0.31 respectively. To account for the learning curve of sonographers undertaking this new examination, inter-reviewer agreement rates were calculated to assess if there was any difference in performance as experience was gained. A similar and not statically different percentage agreement and IRR was demonstrated with the first 50 patients when compared to the second 51 patients with IRR of 58% and Κ of 0.34 compared to IRR of 54.9% and Κ of 0.26 respectively. A weighted kappa test was performed so that disagreements between the differing risk stratification categories could be taken into account. With this weighting, performance was improved and IRR of 71.8% and Κ of 0.39 demonstrated.

MRI agreement

When comparing MRI with histology, the IRR was found to be similar to that of the microUS agreement. Percentage agreement and kappa analysis of MRI with histology does not demonstrate significant differences of performance compared to microUS with an IRR of 58.4% and Κ of 0.31 calculated for MRI, although when using a weighted kappa test, microUS agreement was marginally better.

Further analysis was undertaken to determine the sensitivity and specificity of microUS compared to MRI when the risk stratification had been taken into account. The sensitivity and specificity of the baseline microUS was calculated at 73.3% and 53.8% respectively. A comparative assessment was made with the MRI risk stratification scores and sensitivity of 87% and specificity of 34.6% were found in this cohort. Whilst MRI reports a higher proportion of true high risk disease than compared to the baseline microUS (n = 44/49 compared to microUS n= 37/49) it is shown to under report low risk disease and has a lower true negative rate than was demonstrated with microUS (n = 9/26 compared to microUS n=14/26). Whilst the specificity is less than that of microUS, the sensitivity of MRI to high risk disease is higher than that of microUS. As such, in our cohort, MRI remains the reference standard pre-biopsy imaging test of choice.

Discussion

This study has been undertaken as part of a wider proof of concept trial designed to determine if there is any signal of efficacy in this new technology in the active surveillance of prostate cancer. As Tranquillo et al [28] discuss, a proof of concept study allows testing of study designs, new technologies or theories before either a wider study is performed or the new technology is more widely utilised. The study protocol for the broader ERUP trial was designed so that data could be collated to plan the future scope of microUS within the local active surveillance population. Data

presented here represents phase 1 of the trial and was designed to evaluate the use of microUS in the identification of prostate disease. MicroUS was available within the clinical department and was taken advantage of for the ERUP study. MicroUS, as previously discussed, is a novel and emerging technology. A recent systematic review by Sountoulides et al [19] concluded that comparable detection rates of PCa were obtained using microUS guided biopsy compared to MRI guided biopsy but that further trials are warranted. The ERUP study is a multi-phase research project and was not designed to solely test the diagnostic accuracy of this new technology but to evaluate if there are any features that can be identified by reviewers that correlate with disease at histology. The aim of this first phase of the ERUP trial was to understand if there are features within a microUS imaging protocol that could be exploited to identify pathology within the prostate which may indicate disease and subsequently be used as a tool to assess progression. This first phase is an image interpretation study which has contributed to the assessment of accuracy of microUS.

MicroUS performance

Using the locally agreed three point risk stratification, sensitivity and specificity of microUS was found to be 73.3% and 53.8% respectively. Data published within a recent review of microUS by Basso Dias and Ghai [21] reports a study by Lugehzzani et al [29] which found a sensitivity of 89.7% and a specificity of 26.0% for microUS in detecting PCa. Another study by Klotz [20] identified that microUS had a sensitivity of 94% and a specificity of 22%. The sensitivity demonstrated in this ERUP phase 1 study is lower than both of these previous studies but specificity is improved. Analysis of the results also took into account any change due to increased experience or additional training but there was no improvement over time; indeed, agreement was marginally better for the initial 50 participants than the latter recruits ($\kappa = 0.34$ compared to κ of 0.26) but remained moderate. It is noted, however, that when a weighted kappa test was employed, which takes into account the differences in scoring between the three criteria, the IRR improved to $\kappa = 0.39$ and future studies investigating where best microUS agrees with histology are indicated. It is acknowledged that data for this research was collected early in the implementation of this new technology into clinical practice and none of the practitioners had established experience using or interpreting images with such increased spatial resolution. A third phase of the ERUP study has been undertaken to explore the normalisation of this new imaging parameter into routine practice. Results are currently being analysed with the aim of increasing our understanding of why our specificity and sensitivity results differ from previous published data.

MRI performance

MRI is integral within the prostate cancer pathway. Indeed, the ERUP study is not aiming to replace MRI; its aim is to identify if it can supplement MRI in patients under active surveillance or those in whom MRI is contraindicated. If microUS is to be used, its performance will need to be comparable with the imaging reference standard of MRI. It is well documented that there is variability in the current use of MRI [30] although a study published by Greer et al [31] reports excellent agreement between radiologists regardless of level of experience, in part due to the advent of the PIRADS V2 guidance [26]. Using the three point risk stratification, local MRI was found to have sensitivity of 87% and a specificity of 34.6%. These results are comparable with the findings by Klotz [20] who also compared mpMRI with the identification of csPCa. He found a sensitivity of 90% and a specificity of 22% for MRI undertaken in a similar cohort of patients who underwent microUS and biopsy.

Limitations

There are limitations of phase 1 of the ERUP study, not least the overall lack of experience in microUS before data collection commenced. Delays directly contributable to the COVID-19 pandemic resulted in insufficient time for pre-trial scanning to be undertaken and, therefore, experience was not optimally gained prior to the recruitment of participants. Recruitment could not be delayed due to time constraints of the research project being undertaken. The majority of experience was gained during the data collection period of the study and repeating the study, once additional experience is gained may demonstrate improved agreement rates between microUS, histology and mpMRI. Unfortunately, to date, there are only two systems installed in the UK and there has been no availability for cross site learning or interaction which has hindered our ability to gain knowledge from other users.

The second limitation relates to the methods employed for tissue collection for histological analysis. This entire cohort had an LATP Bx performed but these were undertaken using a standard frequency ultrasound probe and machine. Targeted biopsies were only performed on MRI identified lesions, not on those areas of abnormality identified at the microUS examination. As such, focal abnormalities that may have only been identified on microUS have not been sampled and may add to the reduced sensitivity and specificity identified in this study. Indeed, the labelling of "False Positive" microUS samples may skew the data because they could conceivably have been positive if sampled under microUS guidance. Had microUS been used to guide biopsy, and areas of high risk been sampled, this may have raised both the specificity and sensitivity of microUS by increasing true positives. This approach to our study may also explain the difference between the values presented in this work and those in other studies of the technology.

Studies by both Sountoulides et al [19] and Dariane et al [24] have identified that microUS guided biopsy compared favourably with standard ultrasound guided biopsy for the detection of csPCa. Indeed, Sountoulides et al [19] identify that microUS guided biopsy may detect fewer non-significant cancers than the more traditional MRI targeted procedures. Greater experience with this technology is required to improve confidence in the LATP Bx technique using microUS within our local practice.

In addition, whilst not all men had a focal abnormality identified at MRI, all were effectively screened by MRI prior to biopsy and were at high risk of PCa. As such, we are unable to conclude from this work what the results would have been if microUS had been used in place of MRI for pre-biopsy screening. A further limitation is the utilisation of our three-point risk stratification system to analyse agreement between imaging modalities and histology. This system aligns well with patient management; low risk patients commonly discharged, equivocal findings being offered active surveillance as first line treatment, and high-risk patients, regardless of the grading of their significant prostate cancer being offered radical treatment. This method only enables a crude analysis of findings but is advocated as a method to support diagnostic and management pathways [32]. However, further analysis of these data to better understand agreement rates between sites, PRI-MUS scores, PI-RADS V2 scores, and histology is needed and will be interrogated as the ERUP trail continues into phase 2.

Conclusion

The results of phase 1 have indicated that the inter-reviewer agreement of microUS is moderate when imaging is performed in real time and there are two practitioners observing and providing a consensus agreement of results. There are limitations of this study, notwithstanding the limited experience of the sonographers at the time the data was collected. The sensitivity of microUS in this study is lower than in previous published studies but with a better specificity. We conclude that microUS did not perform as well as MRI currently in our local patient population. This is likely due to the limitations of this image interpretation study but a contributory factor is that microUS was not utilised to directly guide the biopsy procedure. Future research will address this as the specificity of microUS in this study does suggest that it may continue to have a role when no significant disease is present as part of an active surveillance pathway.

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Word count: 3780