Prostatic Diseases and Male Voiding Dysfunction

Comparison in Detection Rate of Clinically Significant Prostate Cancer Between Microultrasound-guided Prostate Biopsy (ExactVu) and Multiparametric Resonance Imaging-guided Prostate Biopsy (Koelis System)

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OBJECTIVES To compare the detection rate of clinically significant prostate cancer (csPC) and prostate cancer (PC) and to find out the diagnostic concordance between microultrasound (mUS), a high-resolution imaging system that can identify suspicious prostate lesions and biopsy them in real time, and multiparametric magnetic resonance imaging (mpMRI)-guided prostate fusion biopsies.

METHODS A prospective, multicenter, single-blind, single cohort study was conducted involving 80 patients with clinically suspected PC who underwent concomitant mpMRI-guided fusion prostate biopsy (Koelis System) and mUS-guided biopsy (ExactVu System)

RESULTS The detection rate of csPC was slightly higher for image-guided fusion biopsy (21.25% vs 18.75%), but this difference was not statistically significant ($P = .453$). There was also no significant difference in overall PC diagnosis (50% vs 51.25%, $P = .897$). The degree of agreement between the 2 diagnostic techniques for the detection of csPC as assessed by Cohen's Kappa concordance index was satisfactory $\hat{\kappa} = 0.676$. The degree of International Society of Urological Pathology of targeted biopsies obtained from concordant lesions was also represented by satisfactory concordance with a Kappa index of $\hat{\kappa} = 0.696$.

CONCLUSION mUS-guided biopsy is presented as an effective diagnostic method for the diagnosis of csPC compared to image-guided fusion biopsy. No differences are found in the detection rates of csPC and PC between the 2 strategies and satisfactory concordance is found in terms of histopathological findings. UROLOGY xx: xxx–xxx, xxxx.

Prostate cancer (PC) is a major public health problem in the male population. With an estimated 1.4 million new cases and 375,000 deaths worldwide, it is the second most common cancer in this population group and ranked fifth among cancer deaths in 2020.[1]

After the introduction of prostate-specific antigen (PSA) for clinical use between 1980 and 1990, there have been variations in the detection rates of patients with PC, with a higher number of cases in the first years since its introduction, leading to overdiagnosis and overtreatment. Since 2000, the use of PSA was reduced, but subsequently, a greater number of patients with advanced disease were detected at the time of diagnosis, with an increase in mortality that was most patent between 2008 and 2012.[2]

Since then, several diagnostic blood and urine tests have been developed in order to know the individual risk

Funding Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Submitted: May 26, 2023, accepted (with revisions): September 12, 2023

of developing clinically significant prostate cancer (csPC), as defined by the International Society of Urological Pathology grade (ISUP ≥2).[3] Classic transrectal ultrasound-guided random sampling of the prostate as a method of diagnostic confirmation of PC has high detection rates of non-significant PC,[4] as well as the possibility of missing clinically significant disease in up to 30% of patients.[5]

Multiparametric magnetic resonance imaging (mpMRI) of the prostate assesses the anatomy of the gland and its functional component, combining T2-weighted images and functional sequences to detect suspicious lesions of PC.[6] The Prostate Imaging-Reporting and Data System (PI-RADS) classification, which aims to standardize imaging evaluation of the prostate, has undergone several changes since its inception to address inconsistencies and limitations.[7] Several studies, including PRECISION,[8] PROMIS,[9] and MRI-FIRST,[10] demonstrated that mpMRI-guided biopsies are superior in increasing the detection of csPC and reducing the rate of non-significant cancer. Furthermore, by performing a prior mpMRI, the need for biopsy is reduced by 28%-38%,[9-11] and transperineal fusion biopsy has a superior safety profile compared to conventional biopsy.[11]

The latest recommendation of the European Association of Urology Guidelines in case of clinical suspicion of PC is to perform mpMRI prior to the first biopsy. In case of a positive mpMRI result (defined as a PI-RADS ≥3), a combined systematic and targeted biopsy should be performed, with a strong level of evidence.[6]

However, mpMRI is an expensive test not widely available and, although inter-observer differences are increasingly refined, its interpretation can be complex and subject to variability. Furthermore, its use is limited in patients with claustrophobia, pacemakers, gadolinium allergy, and severe renal failure.[12,13] In addition, fusion biopsy with mpMRI, although superior to conventional biopsy, may miss 15% of patients with csPC.[14,15] Therefore, in order to overcome some of these limitations, other well-known imaging techniques, such as ultrasonography, have been optimized. These implementations include the use of Doppler, transrectal ultrasound contrasted with air bubbles and shear-wave elastography. Although these techniques have shown improvements, their use still remains limited.[16-19]

One of the most recent advances is the development of high-resolution microultrasound (mUS). The ExactVu system (Exact Imaging, Markham, Canada) is a mUS device that operates at 29 MHz and provides higher spatial resolution compared to conventional systems that usually work between 8 and 12 MHz, improving resolution by 300%.[20] mUS is proposed as a more affordable test with a shorter learning curve, performed in real-time, and offers fewer restrictions on its performance without sacrificing the detection rate, which is intended to be comparable with mpMRI.[21]

The main objective of this study is to compare the detection rate of csPC between image fusion-guided biopsy (Koelis Trinity system, Meylan, France) and mUS-guided biopsy (ExactVu system). The secondary objectives are to compare the overall PC detection rate and to know the diagnostic concordance of csPC between the 2 systems.

MATERIAL AND METHODS

A prospective, multicenter, single-blinded study was conducted involving patients with clinically suspected PC in the period from May 2021 to June 2022, who underwent both mpMRI fusion-guided transperineal biopsy (Koelis) and mUS-guided biopsy (ExactVu) of suspicious lesions, plus standard random biopsy. All patients agreed to participate in the study and signed the informed consent. The study obtained the institutional review board approval. Inclusion criteria were clinical suspicion of prostate cancer (PSA ≥4 ng/mL and/or abnormal digital rectal examination) and the presence of at least one PI-RADS ≥3 lesion on mpMRCI. Patients with a previous diagnosis of PC or with a contraindication for prostate biopsy were excluded from the study.

This study has been reviewed and approved by the local ethics committee with approval code 21.03.1791-GHM

Multiparametric Prostate Resonance

mpMRI images were performed on a 3T resonator without endorectal coil and were evaluated and classified by a group of experienced radiologists, following the PI-RADS V2.1 protocol.[7]

Prostatic Biopsy

All patients initially underwent transrectal mUS (ExactVu) performed by a trained urologist who was unaware of the mpMRI result. Ultrasonography was performed according to the protocol of Ghai et al[20] and suspicious lesions were identified and classified according to their location, Prostate Risk Identification Using Micro-Ultrasound (PRI-MUS) grade, and contact with the prostatic capsule. Then, a targeted prostate biopsy was performed in real-time with a transperineally guided transducer, obtaining 3-5 cores from each lesion PRI-MUS ≥3. Subsequently, another urologist specialized in mpMRI fusion biopsy obtained at least 3 cores from the PI-RADS ≥3 lesions on mpMRI, also with transperineal guidance. Once targeted sampling is completed, 10-15 random biopsies were performed.

Histopathology. Biopsy cores were sent individually to anatomic pathology. The pathological outcome was analyzed with Gleason score and ISUP 2014.[22] The presence of csPC was defined as the presence of at least one cylinder diagnosed with Gleason ≥7 or ISUP ≥2.

Statistical Analysis

Statistical analysis was performed with SPSS software (v.2 8.0; IBM, Armonk, NY). Descriptive analysis was performed including measures of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables. Student's *t* test and chi-square test were used to compare means and frequencies, respectively. McNemar's test was used to compare the dichotomous results of the proportions obtained between both diagnostic methods and

Table 1. Basal, clinical, and biopsy characteristics.

Parameters	
Age, mean (SD)	69.1 (9.02)
PSA, ng/mL, mean (SD)	7.66 (6.29)
Prostate volume, cm^3, mean (SD)	61.34 (31.7)
Distribution of PI-RADS lesions in mpMRI, n (%)	
PI-RADS 3	33 (31.73)
PI-RADS 4	56 (53.85)
PI-RADS 5	15 (14.42)
Number of cores obtained in image fusion biopsy, mean (SD)	4.70 (2.48)
Total positive cores obtained in image fusion biopsy, mean (SD)	3.36 (2.39)
Distribution of PRI-MUS lesions in mUS, n (%)	
PRI-MUS 3	17 (14.41)
PRI-MUS 4	80 (67.8)
PRI-MUS 5	21 (17.79)
Number of total cores obtained in biopsy by mUS, mean (SD)	3.16 (0.89)
Total positive cores obtained in mUS biopsy, mean (SD)	2.75 (0.78)

mpMRI, multi-parametric magnetic resonance imaging; mUS, microultrasound; PI-RADS, Prostate Imaging-Reporting and Data System; PRI-MUS, Prostate Risk Identification Using Micro-Ultrasound; PSA, prostate-specific antigen; SD, standard deviation.

the concordance of these results was evaluated with Cohen's kappa index. Statistical significance was established at < 0.05. Sample size was calculated to be 54 patients, with a confidence level of 95% and statistical power of 80%.

RESULTS

The demographic and clinical characteristics of the patients are summarized in Table 1. Eighty patients were included in the study. The mean age was 69.1 years (standard deviation (SD) ± 9.02) and only 2.5% had a family history of prostate cancer. The mean PSA was 7.66 ng/mL (SD ± 6.29) and digital rectal examination was abnormal in 18.75% of the patients.

A total of 104 lesions were observed by mpMRI and 118 lesions by mUS. PIRADS and PRI-MUS characteristics of the lesions and the information about the cores obtained in the biopsy are also included in Table 1.

In targeted biopsies obtained by mpMRI fusion, 41/80 (51.25%) patients with PC were detected, in 17/80 (21.25%) corresponding to a csPC. Combining mpMRI fusion-targeted biopsy and random biopsies, a PC detection rate of 44/80 (55%) and csPC of 19/80 (23.75%) were observed. Under this modality, there was a change of diagnosis (cancer undetected by the other approaches) in 4 patients all of whom were ISUP 1, 2. In the analysis by target lesions, of the 104 lesions located by mpMRI, 45/104 (43.27%) were positive, in 19/104 (18.27%) being csPC. The detection rate of csCP increased significantly from 9.1%, 16.07%, and 46.67% in patients with PI-RADS 3, 4, and 5 lesions, respectively.

Random biopsies detected PC in 29/80 (36.25%) patients, with 6/80 (20.67%) csPC. Three patients with PC who were not detected by mUS or fusion biopsies were identified on random biopsy, all ISUP 1. In 3 cases, there was an improvement of ISUP grade compared to directed biopsies (ISUP 2-4, ISUP 1-2, ISUP 2-3).

By mUS-directed biopsy, 40/80 (50%) patients were detected PC of any grade, and csPC was detected in 15/80 (18.75%) of the cases. The mUS-directed biopsy changed the diagnosis in 3 patients diagnosed with cancer (2 ISUP-1 and 1 ISUP-3), 2 of which were also negative during the random biopsy. In the evaluation by target lesions, PC was detected in 47/118 (39.83%) and csPC in 15/118 (12.71%). The PRI-MUS grades found in csCP cases were 0%, 12.5%, and 23.8% in PRI-MUS 3, 4, and 5, respectively.

Figure 1 shows data on histopathological features obtained by mUS, image fusion, and random biopsies.

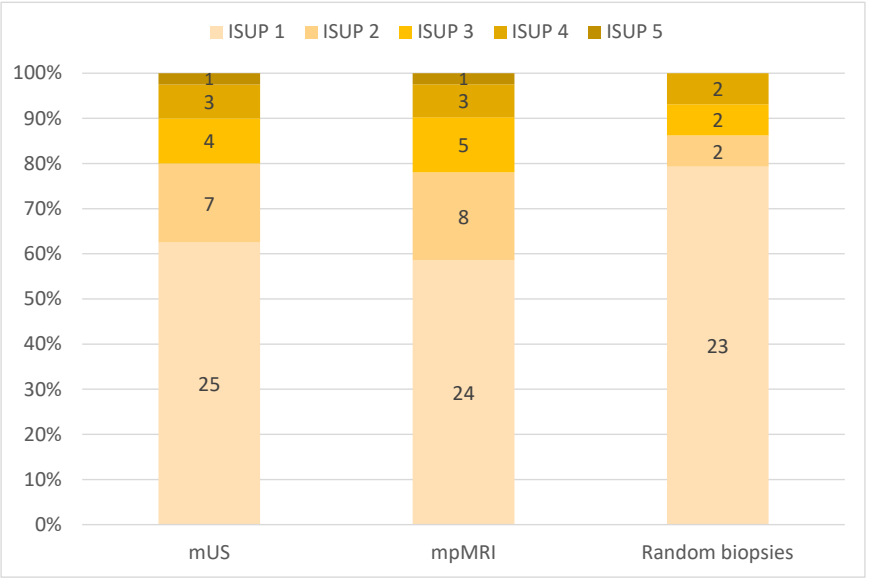

Figure 1. Pathological anatomy of patients with prostate cancer detected by different techniques. ISUP, International Society of Urological Pathology; mpMRI, multi-parametric magnetic resonance imaging; mUS, microultrasounds.

The detection rate of csPC was then slightly higher for image-guided fusion biopsy (21.25% vs 18.75%); however, this difference was not statistically significant ($P = .453$). There was also no significant difference in overall PC diagnosis (50% vs 51.25, $P = .897$).

The degree of agreement between both diagnostic techniques for the detection of csPC assessed by Cohen's kappa index was $\hat{\kappa} = 0.676$ and for PC global $\hat{\kappa} = 0.791$, which according to Landis and Koch[23] would be satisfactory in both cases.

Although overall in the total number of suspicious lesions described, mUS was concordant with mpMRI only in 48.2% ($\hat{\kappa} = 0.594$, showing moderate concordance), if only the main lesion (lesion 1 described) is taken into account, we find a concordance of 83.75% (concordance of $\hat{\kappa} = 0.795$, showing satisfactory concordance). The degree of ISUP of targeted biopsies obtained from concordant lesions was also represented by satisfactory concordance with a Kappa index of $\hat{\kappa} = 0.696$.

Multivariate logistic regression models were adjusted to test predictors of PC and csPC such as age, PSA, rectal examination, PRI-MUS, and PI-RADS, without obtaining statistically significant results in any of the scenarios.

Sensitivity, specificity, positive and negative predictive values (PPV and NPV) data for both diagnostic tests could not be determined as only patients with positive mpMRI were included, and all patients had, in addition, at least one positive lesion by mUS (PRI-MUS ≥3).

DISCUSSION

In recent years, technological advances have brought a major change in the diagnosis of prostate cancer. mpMRI of the prostate is a useful tool for detecting csPC and reducing the need for biopsy, but there are still in its interpretation, access, and subsequent application in the male population at risk of prostate cancer.[9-11]

Since the introduction of mUS, its utility in PC diagnosis has been evaluated in multiple studies. In 2016, a protocol for the evaluation of images obtained in real-time by transrectal mUS of the prostate and a system for characterizing the imaging findings were presented with the aim of interpreting and identifying the risk of cancer with this technology.[20] Similar to PI-RADS, the PRI-MUS system gives a value from 1-5 based on ultrasound findings highly correlated with significant disease (PRI-MUS 4 and 5), those of intermediate probability (PRI-MUS 3), and those with benign characteristics (PRI-MUS 1 and 2). In the same study, a mean accuracy of 0.60 ± 0.02 was obtained, similar to that reported in studies using the PI-RADS protocol.[20]

mUS has demonstrated a sensitivity and specificity of 68% and 73%, respectively,[16] with a higher accuracy for the detection of high-grade PC compared to conventional biopsy (84% vs 60%).[24] Its accuracy seems to be better if the peripheral zone, where the highest percentage of prostate cancers develop, whereas the sensitivity for the transition zone is around 45%.[16]

A multicenter study published by Klotz et al[4] compared a cohort of 1040 patients with suspected PC with the aim of comparing the sensitivity, specificity, PPV, and NPV of targeted biopsy by mpMRI fusion and directed biopsy by mUS for the detection of csPC. The results showed that the sensitivity of mUS was superior to mpMRI fusion (94% vs 90%, $P = .03$) without obtaining major changes in specificity (22% vs 23%), positioning mUS as an alternative in the initial evaluation of patients at risk of PC.

Other studies evaluating the performance of mUS for the detection of csPC in smaller populations have shown sensitivity, specificity, PPV, and NPV values ranging between 91% and 96%, 17% and 49%, 33% and 43%, and 82% and 92%, respectively.[25-26] These slightly lower specificity values have been attributed by some authors to the learning curve.[25]

In our study, we found that the detection rate of csPC was slightly higher in the case of mpMRI fusion targeted biopsy (21.25% vs 18.75%). However, these data showed no statistical significance ($P = .453$). Results obtained comparing the detection rates of csPC and total PC between both methods are also supported by a satisfactory agreement obtained by Cohen's kappa index. Despite this high level of concordance in terms of histopathological findings, we found that only 48.2% of the lesion in both imaging techniques coincided anatomically (moderate concordance). This may be explained, rather than to real differences, to the subjective variability of lesion location between the 2 urologists involved. Furthermore, if only the primary lesion is taken into account, we found a concordance of 83.75% ($\hat{\kappa} = 0.795$, satisfactory concordance). The degree of ISUP of targeted biopsies obtained from concordant lesions was also represented by satisfactory concordance with a Kappa index of $\hat{\kappa} = 0.696$. We further note that the detection rates for csPC increased from 0%, 12.5%, and 23.8% in patients with PRI-MUS 3, 4, and 5 lesions, although these were lower than the detection rates of 9.1%, 16.07%, and 46.67% for PI-RADS 3, 4, and 5, respectively.

Our results contrast with those previously published in a population of 269 patients.[27] In that study, csPC detection rate for mUS-guided biopsy was 38% vs 23% for mpMRI-guided fusion prostate biopsy ($P = .02$). This difference was not appreciated when random biopsies were added to the targeted biopsies, where there was also superiority for mUS, but without statistical significance ($P = .24$). In terms of overall PC detection rates, no difference was found between the 2 methods, 68% vs 64% ($P = .624$), respectively.

In another study of 120 patients, a diagnostic rate for PC of 55% vs 60% ($P = .58$) and csPC of 46.7% vs 38.3% ($P = .356$) was obtained for mUS directed biopsy and cognitive fusion biopsy with mpMRI, results concordant with those presented in this paper.[28]

An extensive comparative analysis between the results of both techniques was performed in a systematic review and meta-analysis published in 2021, including 1125 patients from 13 different studies, where a pool detection ratio of 1.05 (95% CI 0.93-1.19) was found[21] for those

cases with an ISUP PC ≥2. In this same review, the status of the urologist at the time of performing the targeted biopsy (blind or not) does not seem to affect the detection rate, which also did not occur when a cognitive or image fusion approach was used.[29]

Our study adds information to the results recently observed about the usefulness of mUS in the diagnosis of PC, and more specifically of csPC. These results propose this novel diagnostic technique as an alternative that shows advantages over the gold standard technique (it is a fast, convenient, cost-effective method that allows real-time biopsies in a single procedure and without mpMRI). This is the first publication of this study cohort and is intended to be updated.

A limitation of the study is a potential risk of selection bias, as only patients who had a positive mpMRI (PI-RADS ≥3) were included, which impeded the estimation of sensitivity, specificity, PPV, and NPV with this diagnostic method. On the other hand, although the urologist who performed the mUS did not know the mpMRI results before performing the biopsy, he did know that the inclusion criterion was to have a PI-RADS result ≥3, which is also a bias of this study. Finally, the sample size, although larger than the minimum necessary estimated before starting the study (56 patients), could also have been a limitation, which is represented by not being able to obtain independent variables for csPC in the logistic regression.

In conclusion, mUS appears to be an equally relevant diagnostic method for the diagnosis of clinically significant and overall prostate cancer compared to the current standard, mpMRI fusion-guided targeted biopsy.

Ethical approval: This study has been reviewed and approved by the ethics committee and adheres to the principles outlined in the Declaration of Helsinki (approval code 21.03.1791-GHM). Informed consent was obtained from all participants prior to their inclusion in the study.Registry and the Registration No. of the study/trial (Registration number in a public trials registry: N/A.Animal studies: N/A.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgment. To everyone who has made this work possible and has actively collaborated obtaining data.

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EDITORIAL COMMENT

Over the last century, a great deal of progress has been made in the diagnosis of prostate cancer. From the days of finger-guided biopsies to the use of transrectal ultrasound to localize the prostate for biopsy. However, it was not until relatively recently that imaging was able to identify lesions suspicious for prostate cancer and help guide biopsies. First came multiparametric MRI, which was truly a revolution in the diagnosis of prostate cancer. Using this information at the time of biopsy required fusing the MRI images to the ultrasound which comes with several technical challenges, and introduces complexity and error if the registration is not optimal. Microultrasound tries to overcome some of these challenges by offering real-time visualization and direct targeting of suspicious lesions.

Since its introduction, several studies have attempted to compare the accuracy of microultrasound to MRI at the time of biopsy.[1] They are often limited by a lack of blinding of the MRI results, thus artificially inflating the sensitivity of microultrasound for the detection of clinically significant prostate cancer. Further, as highlighted in the above study by Rojo et al, the concordance between MRI and microultrasound on a per lesion basis is poor. There is no doubt that microultrasound increases the imaging resolution of the prostate, the challenge becomes recognizing patterns that are suspicious for prostate cancer. There remains a great deal of subjectivity in the interpretation of lesions on microultrasound, and it appears that it does not necessarily visualize the same lesions seen on MRI. Therefore, it is unclear if this technology can be used to replace MRI, or should be used to complement it. The ongoing randomized trial comparing these 2 technologies should help answer most of these questions, and further refine the ideal diagnostic pathway in this disease.[2]

Nevertheless, the fact that studies continue to support the need for systematic biopsies (ref), and that clinically significant prostate cancer is only found in less than half of even the highest suspicion lesions, suggests that further improvements in prostate imaging are needed. Hopefully in the near future we will be able to accurately identify most significant prostate cancers and eliminate some of the guessing that plagues us in this field.

Declaration of Competing Interest

None.

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https://doi.org/10.1016/j.urology.2023.09.050
UROLOGY xx: xxxx, xxxx.

AUTHORS REPLY

We appreciate the thoughtful insights provided in the Editorial Comment regarding our article, "Comparison in Detection Rate of Clinically Significant Prostate Cancer Between Microultrasound-uided Prostate Biopsy (ExactVu) and Multiparametric Resonance Imaging-guided Prostate Biopsy (Koelis System)." Your comments underscore the dynamic landscape of prostate cancer

diagnosis and the evolving role of advanced imaging modalities.

We concur with the historical perspective you've outlined, highlighting the transformative journey in prostate cancer diagnosis. Indeed, from finger-guided biopsies to transrectal ultrasound-guided localization, each era has brought valuable contributions to patient care. The emergence of multiparametric magnetic resonance imaging (MRI) as a diagnostic tool has indeed been a milestone, revolutionizing our ability to identify suspicious prostate lesions.

Your observations regarding the challenges associated with fusing MRI and ultrasound images resonate with our study's focus on microultrasound (mUS). We acknowledge the importance of optimal registration in utilizing both modalities effectively. The real-time visualization and direct targeting capabilities of mUS aim to address some of these challenges, providing a promising alternative for clinicians.

We appreciate the reference to ongoing studies comparing the accuracy of mUS to MRI, and we acknowledge that blinding MRI results is an essential aspect of unbiased assessment. The concordance between MRI and mUS on a per-lesion basis, as highlighted by the study you mentioned, emphasizes the need for continued research in this field. We agree that recognizing suspicious patterns on mUS can be subjective, and our study contributes to the evolving understanding of this technology's capabilities.

Your comment regarding whether mUS should replace or complement MRI is a pivotal question. Our study aims to contribute to this discussion by providing valuable data on the diagnostic performance of mUS. We eagerly await the results of ongoing randomized trials that will further illuminate the ideal diagnostic pathway.

Lastly, we concur with your assessment of the need for further improvements in prostate imaging. As you aptly noted, the quest for accurately identifying significant prostate cancers remains a paramount goal. We share your optimism that advancements in imaging technologies will help mitigate uncertainties in prostate cancer diagnosis.

Declaration of Competing Interest

The authors have no conflicts of interest or disclosures related to this article.

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https://doi.org/10.1016/j.urology.2023.09.051