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Research Article

The feasibility of distance to the tumor of biopsy cores to estimate the extracapsular extension

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ABSTRACT

Background: To investigate the predictive capability of a new parameter, the distance between the fibromuscular capsule and the tumor as measured using a prostate biopsy core (referred to as "distance to the tumor" [DTT]), for the presence of extracapsular extension (ECE).

Materials and methods: We analyzed specimens obtained from 246 patients diagnosed with prostate cancer. All patients underwent prebiopsy, prostate magnetic resonance imaging (MRI), and subsequent prostatectomy. DTT measurements were obtained for each prostate biopsy core, and the minimum (min) DTT was extracted. We assessed the relationship between min DTT, MRI-estimated ECE, and pathological ECE, considering factors such as the PI-RADS score and tumor location.

Results: In this study of 246 patients, the mean age was 65.8 years, and the mean prostate-specific antigen (PSA) level was 18.9 ng/ml. Patients with suspicious lesions in the peripheral zone and pathological ECE displayed higher rates of positive digital rectal examination (DRE), elevated PSA levels, and shorter DTT values in the biopsy cores. DTT demonstrated an accurate estimation of the presence of ECE, similar to MRI findings. Min DTT exhibited higher accuracy for peripheral zone masses, with a cutoff value of 1.0 mm for min DTT predicting ECE (AUC: 0.84, sensitivity: 72.23%, specificity: 77.78%, $P < 0.01$). Of the 246 patients, 66 had no ECE on MRI; however, 18 of these patients displayed pathological ECE, with 14 having DTT values <1.0 mm.

Conclusions: Min DTT, positive DRE results, and a higher Gleason grade were significantly associated with ECE. DTT measurements of <1 mm can provide a more accurate prediction of ECE in the peripheral zone of the prostate than MRI-based assessments.

1. Introduction

In the case of localized prostate cancer, nerve-sparing (NS) prostatectomy offers the advantage of improving postoperative quality of life while reducing the risk of complications such as potency and incontinence.[1,2] Nonetheless, the NS approach carries the potential risk of a positive surgical margin, underscoring the importance of its careful application. Furthermore, in active surveillance (AS), the precise staging of localized prostate cancer using prostate biopsy is essential to determine the suitability of AS for low-grade cases.[3–5] However, in nearly half of patients with clinically low-risk prostate cancer, the surgical pathology findings differ after prostatectomy.[6,7] Even in cases with intermediate-risk profiles based on a single positive biopsy core, there is a notable discordance of 37% and 58% in grading after prostatectomy.[8] As a result, it becomes imperative to emphasize the importance of identifying the extracapsular extension (ECE) prior to making the initial treatment decision. This is particularly relevant for patients undergoing prostate radiotherapy or brachytherapy to avoid damaging periprostatic tissue and ensure optimal radiation dose delivery. Relying solely on preoperative imaging may not suffice to determine the most appropriate treatment or achieve a favorable prognosis.[9] Primary radiation therapy is also vital for distinguishing capsular invasion in tumor cases, particularly when prostatectomy is not performed, making the determination of precise capsular extension challenging. Studies related to magnetic resonance imaging (MRI) have demonstrated the utility of preoperative ECE identification.[10] Some researchers have previously proposed new parameters such as the distance to the tumor (DTT), to assess the presence of ECE based on

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prostate biopsy cores.[11,12] However, there are limitations in understanding the sole function of DTT in this context. Therefore, our study aims to reassess the practicality of DTT in identifying pathological ECE in comparison with MRI results.

2. Material and methods

We conducted an analysis of specimens obtained from 246 patients diagnosed with prostate cancer who underwent prostatectomy between May 2016 and May 2021. To assess the extent of disease and guide biopsy, all patients underwent prebiopsy prostate MRI and fusion transrectal prostate biopsy, focusing on suspicious MRI-based lesions. Each proximal tip of the biopsy cores was marked with ink for polarity identification.

For our study, we specifically measured the DTT, defined as the length between the peripheral end (PE) marked with tissue ink (Davidson Marking System 8 oz blue marking dye; Bradley Products, Bloomington, MN, USA) and the tumor on each biopsy core. From each patient, we extracted one core with minimal (min) DTT, and we subsequently evaluated its correlation with ECE in the prostatectomy specimens. We also evaluated the diagnostic accuracy of min DTT and MRI for estimating ECE. A total of 978 out of the 1,117 cores, comprising 861 randomly harvested prostate cores and 256 MRI/US fusion-targeted cores, were analyzed. However, 139 cores (12.4%) were excluded due to fragmented biopsy cores.

2.1. Biopsy protocol

A spring-driven 18-gauge needle-core biopsy gun (Max Core Biopsy; BARD, Covington, GA, USA) was used to perform systematic core and three-core targeted MRI/US fusion biopsies under the guidance of ultrasound imaging. All biopsies were conducted by a urologist (KKP) with >15 years of experience in prostate biopsies and 8 years of expertise in MRI/US fusion biopsy. Patients were positioned in the left lateral decubitus posture, and intrarectal lidocaine jelly, along with 5 mL of 2% lidocaine, was administered as a local anesthetic. Prophylactic oral ciprofloxacin (500 mg) was administered once daily, 30 min before and 2 days after the biopsy. MRI/US fusion-targeted biopsies were performed based on the PI-RADS (version 2) information provided by the base pair MRI. In cases where suspicious lesions had a PI-RADS score of 3, three-core targeted biopsies were performed, followed by 10–12 core systemic biopsies. The distal ends of the biopsy cores were marked ex vivo with ink to distinguish laterality. Tissue was harvested using a spring-loaded 16-gauge disposable biopsy needle with a 22-mm penetration depth (Max-Core™ Disposable Core Biopsy Instrument, Bard).

2.2. Magnetic resonance imaging protocol

We utilized a 3T MRI system (Intera Achieva; Philips Medical Systems, Best, Netherlands) equipped with a pelvic phased-array coil for conducting MRI scans prior to prostate biopsy. Our imaging protocol consisted of T2-weighted turbo spin-echo and diffusion-weighted (DW) imaging. T2-weighted turbo spin-echo images were acquired in three orthogonal planes. For DW imaging, we employed a single-shot echo-planar imaging technique with b-values of 0 and 500 s/mm. The apparent diffusion coefficient DW maps were automatically generated on a pixel-by-pixel basis.

2.3. Image analysis

Two highly experienced radiologists, Jung Sub Lee (JSL) (with 11 years of experience) and Bong Soo Kim (BSK) (with 18 years of experience), were tasked with reviewing all the images. Both radiologists had accumulated 7 years of experience in PI-RADS (version 2) scoring. They conducted a consensus review of the biparametric MRI images obtained from all patients to identify regions containing the target lesion and assign a PI-RADS score to each lesion. In situations where more than one suspicious lesion was present, they recommended targeting both lesions using an MRI/US fusion biopsy.

2.4. Magnetic resonance image-ultrasound fusion protocol

We conducted an MRI/US fusion-guided biopsy with the aid of electromagnetic (EM) tracking to target suspicious lesions identified on the MRI. An EM field generator (Northern Digital Inc., Waterloo, ON, Canada) was positioned above the pelvis, enabling real-time tracking of a custom biopsy probe equipped with a passive EM tracking sensor (Traxtal Inc., A Philips Healthcare Company, Toronto, ON, Canada). Subsequently, MRI T2 axial and/or DW images were imported into a Philips/PercuNav system (Royal Philips Electronics, Amsterdam, the Netherlands). Manual alignment was performed between the apex of the prostate on T2-weighted axial MR and a transrectal US image, with further matching of the verumontanum and bladder neck on both images. The embedded fusion software (PercuNav) enabled the identification of the target lesion in areas suspected based on the MRI report, all in real-time on transrectal ultrasound axial images.

2.5. Pathology

We performed biopsies following the minimum consensus requirements outlined by the Pathology Committee of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[13] In brief, each biopsy core was placed in a cassette, and the cores were flatly embedded. Multiple sections of each biopsy core were cut at various levels to ensure that small adenocarcinoma foci were not overlooked.

We meticulously recorded both the number and locations of positive cores, along with the Gleason scores of each positive core. Additionally, we measured DTT using biopsy specimens (Fig. 1). In the case of prostatectomy specimens, we assessed tumor location, burden, the presence of capsular penetration, surgical margin status, and Gleason scores. Fragmented cores were excluded from our analysis as they did not provide accurate information for measuring the distance between the prostate capsule and the tumor.

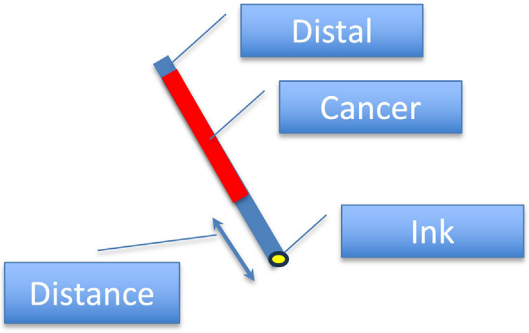

Fig. 1. Distance to the tumor.

2.6. Statistical analysis

We conducted a comparative analysis of patient characteristics between the conventional and base-pair MRI-based screening groups. The Student's t-test was utilized, and the analysis was carried out using Prism 5.1 D (GraphPad Software Inc., San Diego, CA, USA). All tests were two-tailed, and a significance level of $P < 0.05$ was deemed significant.

3. Results

The average patient age was 65.8 years, and their mean prostate-specific antigen (PSA) level was 18.9 ng/ml. After prostatectomy, 70 (28.5%) patients had positive resection margins, with 165 (67.0%) and 81 (32.8%) having reported pathologic stages of T2 and T3, respectively. None of the patients had T4 disease.

We analyzed a total of 246 patients using the PI-RADS score and the location of the suspicious lesions. We categorized and compared the presence of PI-RADS lesions >3 and/or pathological ECE (Tables 1 and 2). Patients with ECE and suspicious lesions in the peripheral zone of the prostate had a higher rate of positive digital rectal examination (DRE) (15.6%, $P < 0.01$), elevated baseline PSA levels (21.1%, $P < 0.03$), and a shorter DTT on biopsy cores (0.35 mm, $P < 0.01$) compared with those without ECE. The MRI-based estimation of ECE was also significantly more prevalent in patients with ECE (44.5% vs. 5.4%, $P < 0.01$). Patients with suspicious lesions in the transitional zone also displayed a significant difference in the MRI-estimated ECE rate (33.3% vs. 7.1%, $P < 0.01$), but other factors did not demonstrate significance (Table 2).

In the analysis involving participants with Prostate Imaging—Reporting and Data System (PIRADS) scores >3, receiver operating characteristics curve (ROC) analysis revealed that DTT had an area under curve (AUC) of 0.70 (95% CI, 0.57—0.83). This performance was comparable with MRI alone for estimated ECE (AUC 0.69; 95% CI, 0.54—0.83) in our cohort. However, as depicted in Fig. 2, when the analysis was limited to peripheral zone prostatic masses, the AUC increased to 0.84 (95% CI, 0.73—0.95).

Participants with PI-RADS scores >3 demonstrated an ROC AUC of 0.84 for the ability of DTT to predict ECE, with the best cutoff value being 1.0 mm (AUC: 0.84, sensitivity: 72.23%, specificity: 77.78%, $P < 0.01$).

In univariate logistic regression analysis, significant predictors for ECE included DTT <1 mm (odds ratio [OR]: 2.90, $P < 0.01$), positive DRE (OR: 2.72, $P = 0.03$), and the sum of biopsy Gleason scores (OR: 1.77, $P = 0.04$). In multivariable models, other variables no longer remained significant, and the most robust predictor was DTT <1 mm (Table 3).

Out of 246 patients, 66 (26.8.3%) did not display prostatic capsule invasion in their prostate MRI. However, 18 (27.3%) of them had a pathological capsule invasion in their prostatectomy specimens. Among the 18 patients with upstaging, 14 had DTT measurements <1.0 mm.

Table 1
Baseline patient characteristics with less than Prostate Imaging—Reporting and Data System 3 on prebiopsy magnetic resonance imaging.

PIRADS	<3	
Location of suspicious tumor based on pre biopsy MRI	n/a	
Surgical pathology	ECE	no ECE
Number of patients	0	30
DRE positive rate (%)	0	0
Baseline PSA, mean (ng/ml)	n/a	6.2 ± 2.7
Age, mean (years)	n/a	66.3 ± 4.7
Biopsy ISUP grade, median (IQR)	n/a	1 (1—3)
Cancer core percentage, mean (%)	n/a	25 ± 25.1
Distance to tumor (mm)	n/a	2.7 ± 1.6
Pre operative MR estimated ECE (%)	0	0

DRE, digital rectal examination; ECE, extracapsular extension; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; n/a, non applicable; PIRADS, Prostate Imaging—Reporting and Data System; PSA, prostate-specific antigen. *statistical significance defined for $P < 0.05$.

4. Discussion

Accurate determination of ECE is crucial for effectively treating and predicting the prognosis of patients with prostate cancer. Traditional methods such as clinical staging, serum PSA levels, and Gleason scores have limitations in precisely assessing the extent of prostate cancer invasion into adjacent tissues.[6,9] Although preoperative imaging such as MRI, offers high-resolution anatomical details and aids in ECE detection, it has its own limitations, particularly in detecting subtle ECE or invasion that may only become apparent through postoperative pathological examinations.[14]

Biopsy specimens provide an alternative method for detecting capsular invasion by measuring the distance between the tumor and the inked distal tip. This method offers the potential for more precise staging and can assist clinicians in determining appropriate treatment strategies, particularly for patients who have not undergone prostatectomy.

Our study demonstrates the practicality of using DTT to identify ECE through transrectal prostate biopsy cores. For patients with suspicious lesions (PI-RADS > 3), we found that the shorter the minimum distance among the DTT measurements from all biopsy cores, the higher the likelihood of postoperative ECE. Moreover, a DTT of <1 mm appears to have superior diagnostic value for predicting postoperative ECE compared with relying solely on MRI-based estimations. These findings have significant clinical implications, offering a more precise method for determining postoperative ECE.

Ponholzer et al[11] reported that marking the PE of biopsy cores and the positivity of PE could increase the risk of positive surgical margins in prostatectomy specimens. Their study involved 445 patients, of whom 174 (39.1%) had positive PE, and ultimately, 132 (29.7%) had reports of positive resectional margins. In the multivariate analysis, PE positivity proved to be a better predictor than biopsy Gleason score, PSA level, and the percentage of positive cores. Although this study examined PE and its practicality, it did not analyze the results separately based on tumor location. Consequently, depending on tumor location, a transrectally harvested biopsy core may not provide a clear explanation for the presence of ECE after prostatectomy.

Singla et al[12] also reported the practicality of inked PE and quantified DTT from transrectally harvested biopsy cores. They demonstrated that a positive core located ≤1 mm from the capsule could predict side-specific capsular invasion in prostatectomy specimens. However, the AUC for proximity was slightly lower (0.572). This discrepancy in results could be attributed to the inclusion of low-quality biopsy cores such as fragmented cores, which were not separately analyzed based on transitional and peripheral zones. Conversely, our study showed that the transitional zone had a slightly lower AUC (0.698) than the prostate peripheral zone (AUC = 0.840).

Park et al introduced an MRI-based scoring system to estimate the risks of positive resection margins and ECE, which included various factors such as tumor-capsule contact length, tumor burden, location, PI-RADS score, apical depth, and prostate volume. This system demonstrated good prediction for positive surgical margins (AUC: 0.80; 95% confidence interval: 0.76—0.83). Notably, radiological tumor contact length strongly correlated with the

Table 2
Baseline analysis stratified by location of suspicious tumor and pathologic extracapsular extension in patients with more than Prostate Imaging–Reporting and Data System 3.

PIRADS	≥3					
Location of suspicious tumor based on pre biopsy MRI	PZ			TZ		
Surgical pathology	ECE	no ECE	*P*	ECE	no ECE	*P*
Number of patients	54	111		9	42	
DRE positive rate (%)	15.6	1.2	<0.01*	7.2	1.5	0.06
Baseline PSA, mean (ng/ml)	21.1 ± 17.7	7.7 ± 5.9	0.03*	13.9 ± 10.3	9.0 ± 6.3	0.54
Age, mean (years)	71.3 ± 6.3	67.4 ± 6.7	0.92	71.0 ± 8.6	65.9 ± 5.6	0.91
Biopsy ISUP grade, median (IQR)	3 (1–5)	2 (1–3)	0.07	1 (1–3)	2 (1–5)	0.09
Cancer core percentage, mean (%)	66.1 ± 45.1	47.4 ± 26.1		47.5 ± 13.4	53.9 ± 31.8	0.89
Distance to tumor (mm)	0.35 ± 0.5	2.46 ± 2.91	<0.01*	1.66 ± 2.8	2.64 ± 3.0	0.78
Pre operative MR estimated ECE (%)	44.5 ± 51.6	5.4 ± 22.9	<0.01*	33.3 ± 57.3	7.1 ± 26.3	<0.01*

DRE, digital rectal examination; ECE, extracapsular extension; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; PIRADS, Prostate Imaging–Reporting and Data System; PSA, prostate-specific antigen; PZ, peripheral zone of the prostate; TZ, transitional zone of the prostate. *statistical significance defined for $P < 0.05$.

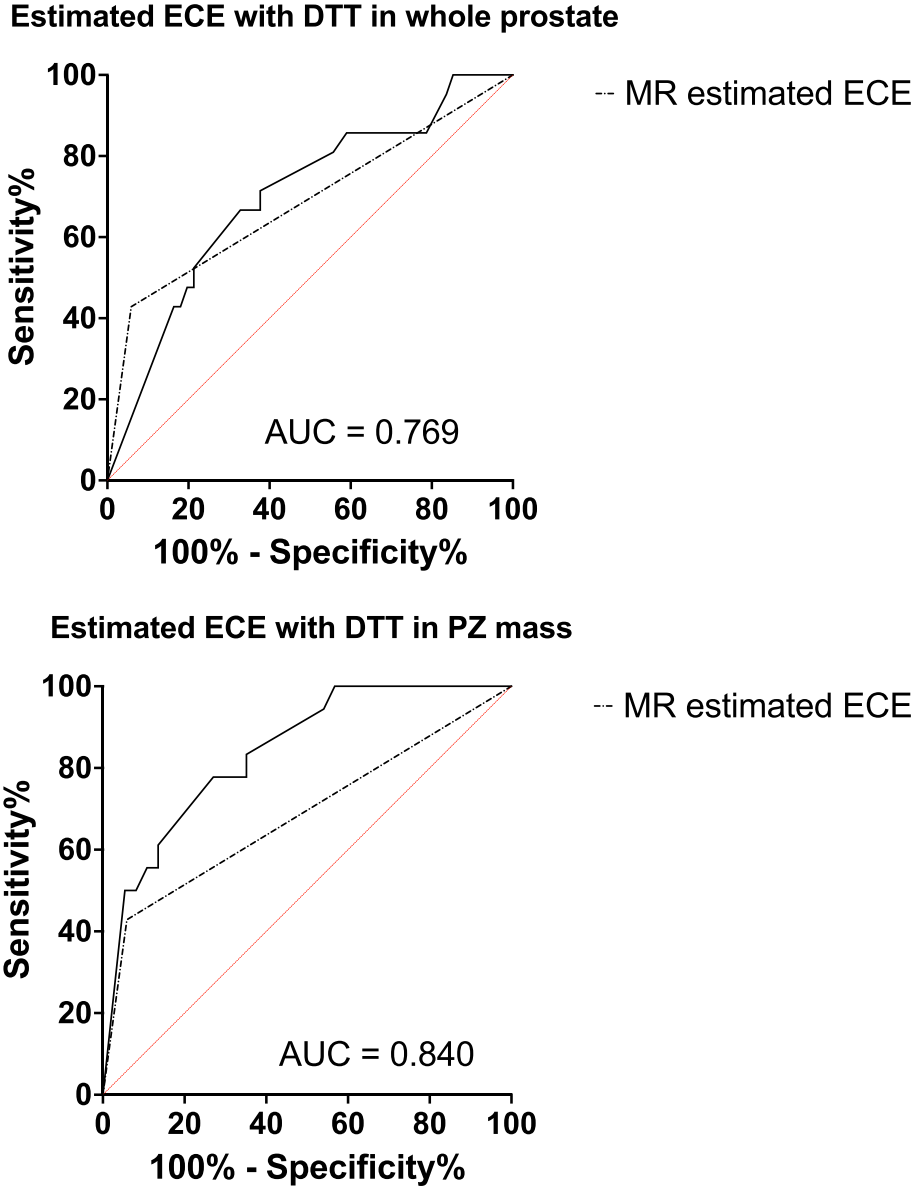

Fig. 2. Receiver operating characteristic (ROC) curves for prediction of extracapsular extension (ECE). MR estimated ECE: AUC 0.69 (95% CI 0.54–0.83). AUC, area under curve; DTT, distance to tumor; ECE, extracapsular extension; MR, magnetic resonance image; PZ, peripheral zone of the prostate.

Table 3
Univariate and multivariate logistic regression analysis for predictors of extracapsular extension in whole patients.

	Variable	OR (CI)*	P value
Univariate analysis	Sum of biopsy Gleason	1.77 (1.30–2.41)	0.04**
	Prebiopsy PSA level	1.03 (0.95–1.12)	0.53
	Positive DRE	2.72 (1.90–4.99)	0.03**
	Age	1.03 (0.99–1.08)	0.19
	Cancer core percentage	1.59 (1.29–1.95)	0.78
	Distance to tumor <1 mm	2.90 (1.79–10.71)	<0.01**
Multivariate analysis	Sum of biopsy Gleason	1.26 (1.10–2.21)	0.84
	Positive DRE	2.17 (1.69–3.35)	0.23
	Distance to tumor <1 mm	3.80 (1.19–8.91)	<0.01**

*OR, odds ratio; CI, confidence interval (95%). **statistical significance defined for $P < 0.05$. ECE, extracapsular extension; PSA, prostate-specific antigen; DRE, digital rectal exam.

pathological tumor contact length (correlation coefficient, 0.839).[10] However, our study suggests that microscopically measured tumor capsule length may offer a simpler and more applicable approach with less interpretation variation for estimating the true status of ECE than relying solely on MRI-based estimation.

The condition of biopsy cores holds significant importance when analyzing their additional characteristics. When calculating the distance to a tumor, it is crucial to ensure that the core remains intact without fragmentation, elongation, or loss of the core end during pathological processing. Montironi et al[15] have also reported difficulties in interpreting cores that are lost, conglomerated, or fragmented. Notably, the analysis of the prostate biopsy core condition was not included in the aforementioned studies on the distance to the tumor. Unfortunately, in our study, approximately 12.4% of cores had to be excluded because of fragmentation.

To effectively identify capsule invasion using biopsy cores, we believe that the appropriate criteria for core status should be defined. Additionally, one should consider the possibility of losing the end part that makes contact with the capsule during the preparation of pathological slides. In ERSPC, Kwast et al[13] reported variations in the length of biopsy cores across different centers, and the number of adequate needle biopsies for each case also varied. Many biopsies are fragmented, which hinders adequate evaluation.

There are limitations to our study. It was performed using a single-institution cohort with a small sample size and excluded fragmented cores, which might have provided valuable information regarding ECE. These factors may have restricted our ability to achieve statistical significance in the multivariable analysis. Second, when performing a biopsy, the needle usually needs to be pushed against the rectal wall and into the prostate before the core is shot and retrieved. Since the degree of the initial point of the core cannot be uniformly measured, the DTT can only be considered a subjective parameter. Therefore, we decided to exclude the inappropriate cores according to a similar prior study[13] because, in the preliminary study, we had identified the problem. We performed a transrectal biopsy without pushing the rectal wall and just contacting the wall. Despite our every effort to acquire the appropriate core, the length of the core could be measured subjectively. To overcome the subjectivity. We chose the shortest one for each biopsy core. If we gave the exact value to the DTT of each targeted and random biopsy to evaluate the detectability of extracapsular extension, the results could be inconsistent. To maintain consistency, it is important to identify the shortest one based on the DTT of multiple cores. We believed that we could overcome subjectivity through this multiple sampling. And the last. When we perform the prostate biopsy and uniformly acceptably harvested cores (even if the distal end was an uncontained capsule), the distance to the distal end is most important. We believed the shortest length meant invasion of extracapsular extension rather than the mean or median value. The median or mean value of DTT was also not significant based on the unpublished results.

Our technique offers several advantages, including minimal additional cost and time, safety, ease of learning, and applicability to all prostate biopsies. It provides spatial information during biopsy interpretation and can complement other clinical factors in decision-making. However, the decision to adopt this technique should take into account multiple factors, and further validation in a larger patient cohort is necessary.

5. Conclusion

Our study suggests that the distance between the tumor and the inked end, as measured by DTT, exhibits a stronger association with ECE than with a positive DRE, PSA level, or tumor grade. Therefore, DTT could serve as a valuable tool for determining the clinical stage and predicting the risk of ECE in patients with prostate cancer. Integrating DTT measurements into routine prostate biopsy procedures may enhance the accuracy of prostate cancer staging and aid in selecting appropriate treatment strategies.

Ethics statement

For human study.

The present study protocol was reviewed and approved by the institutional review board of Jeju University Hospital (Reg. No. 2021-02-004). Informed consent was submitted by all subjects when they were enrolled.

Author contribution

Conceptualization: Kyung Kgi Park, Kyung Kgi Park. Data curation: Kyung Kgi Park, Chang Lim Hyun. Formal analysis: Kyung Kgi Park. Funding acquisition: Kyung Kgi Park. Investigation: Kyung Kgi Park. Methodology: Kyung Kgi Park. Project administration: Kyung Kgi Park. Resources: Kyung Kgi Park. Software: Kyung Kgi Park. Supervision: Kyung Kgi Park. Validation: Chang Lim Hyun. Visualization: Kyung Kgi Park. Writing – original draft: Kyung Kgi Park. Writing – review & editing: Kyung Kgi Park.

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Conflicts of interest

The authors have nothing to disclose.

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