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Is Systematic Biopsy Mandatory in Addition to Targeted Biopsy in Patients with a PI-RADS 5 Lesion Identified on Magnetic Resonance Imaging?

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Abstract

Objective: Most of the lesions classified as prostate imaging-reporting and data system (PI-RADS) 5 represent clinically significant prostate cancers; the utility of systematic biopsy (SB) in addition to magnetic resonance imaging-targeted biopsy (MRI-TB) is unclear. We evaluated clinically significant prostate cancer detection via SB, TB alone, and combined SB and TB in men with a PI-RADS 5 lesion. The aim of this study was to determine whether SB can be avoided in the case of PI-RADS 5.

Materials and Methods: Patients undergoing MRI-TB+SB with a PI-RADS 5 lesion were retrospectively reviewed in a prospectively collected database. Pathology obtained from the MRI-TB was then compared with that of the SB. All patients underwent multiparametric MRI followed by transrectal/transperineal TB of PI-RADS 5 lesion and 12-core SB. The prostate cancer and clinically significant prostate cancer (grade group ≥ 2) detection on SB, MRI-TB and MRI-TB+SB were determined for all men. A subgroup analysis of the combined group was also performed to identify performances of TB alone, SB alone, and combination of TB+SB for the prediction of final pathology at radical prostatectomy. Statistical significance was set at $p < 0.05$.

Results: We identified PI-RADS 5 lesions in 315 patients. 199/315 men, were found to have prostate cancer. Of these, 163 cases were clinically significant. The detection rate of prostate cancer for MRI-TB+SB, MRI-TB and SB was 63%, 59% and 49%, respectively, and the detection rate for clinically significant prostate cancer was 51%, 48% and 37%, respectively. SB detected an additional 6.5% of any grade prostate cancer and 6.7% clinically significant prostate cancer over TB. A total of 89 patients had prostate specific antigen density > 0.15 ng/mL. All patients with prostate-specific antigen density (PSAD) > 0.28 had cancer of any grade. The clinically significant prostate cancer detection rate improved with increased PSAD for SB. Among 102 patients, 8 had upgraded pathology from MRI-TB+SB. MRI-TB and SB pathology of the PI-RADS 5 lesion separately predicted final pathology with 81% and 69% concordance, respectively. The the downgrade was lowest in both methods, but the upgrade was higher in SB.

Conclusion: In the presence of a PI-RADS 5 lesion, SB offers minimal additional but not negligible clinical value. The safety of omitting SB awaits further research.

Keywords: Concordance, PI-RADS 5, prostate cancer, systematic biopsy, targeted biopsy

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Introduction

Prostate cancer (PCa) is the second most common malignancy among men worldwide (1). Prior research has shown that multiparametric magnetic resonance imaging (MRI) targeted biopsy (TB) identifies clinically significant PCas more accurately than conventional systematic biopsy (SB) in men with suspected localized PCa (2-5). MRI-TB has resulted in greater detection of clinically significant PCa with less detection of clinically insignificant cancer than SB alone (6,7). Nevertheless, systematic 12-core biopsy is often performed in addition to TB as the combination results in increased detection of clinically significant PCa (3,8). Additionally, such practice allows for tissue sampling of the gland beyond suspicious lesions, as 10-24% of clinically significant PCas are not visualized on MRI (9). Prostate imaging-reporting and data system (PI-RADS) 5 lesions represent clinically significant PCa [Gleason grade group (GG) 2 or greater] between 75% and 95% of the time (10). Given the high prevalence of such clinically significant cancer in these lesions, the utility of concurrent SB is uncertain. In a recent study evaluating the role of SB in patients on active surveillance, the added value from performing SB in patients with PI-RADS 5 lesions was minimal (11). In this context, we aimed to investigate the utility of SB in addition to TB in all patients with PI-RADS 5 lesions to determine whether some patients can be spared from additional and unnecessary biopsies.

Materials and Methods

We retrospectively reviewed completely anonymized data provided by nation-wide tertiary centers in the PCa Database of the Turkish Urooncology Association. MRI-targeted prostate biopsy in conjunction with 12 core systematic biopsies for PI-RADS 5 lesions at our database were included in the study. All patients gave consent for the study.

All multiparametric MRI (mpMRI) for targeted biopsies was reviewed by designated institutional radiologists. In patients with a PI-RADS-lesion 5 [according to PI-RADS-v2 classification (10)], MRI-targeted ultrasound fusion biopsy using different software-based platforms, according to participant center's property (MIMS Symphony Dx® [MIM Software], bk3000® [BKMedical], UroNav® [InVivo Corp, Philips]), was conducted. MRI image fusion targeted biopsies were taken from each target, obtaining at least 2 core samples from each target lesion. In addition to targeted biopsies, the systematic biopsies were also performed using a 12-core approach.

Analysis was performed by reporting frequencies and percentages, in an effort to determine the number of cancers missed from omission of the SB. If patients had more than one PI-RADS 5 lesion, the lesions were analyzed together in such a way that analysis was performed per patient rather than per lesion.

The detection rates of PCa and clinically significant PCa (GG ≥ 2) on SB, TB, and SB+TB were determined for all men.

Statistical Analysis

Study data were collected and managed using research electronic data capture (REDCap) electronic data capture tools

hosted at Turkish Urooncology Association (12-14). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (12,13).

The t-test, Mann-Whitney U test, and chi-square test were used to analyze the relationships among categorical and continuous variables between two biopsy methods and three biopsy schemes within the combined biopsy method. Statistical Package for the Social Sciences (SPSS) version 22.0 was used for all statistical analyses. P-values less than 0.05 were considered statistically significant.

Results

Data from 315 patients who underwent MRI-TB+SB and who had PI-RADS 5 lesions were evaluated. Patient demographics of the study cohort stratified by biopsy approach are depicted in Table 1. Median number of TB cores sampled per region of interest was 5.1. Mean age, prostate-specific antigen (PSA) and prostate volume were 65.7 years, 10.7 ng/mL, and 54 mL respectively.

Table 1. Descriptive characteristics and pathologic results of patients

		PI-RADS 5 (n=315)
Age		65.7 $\pm$ 7.5
BMI (n=267)		27.7 $\pm$ 5.4
PSA		10.7 $\pm$ 8.1
PSAD (n=89)		0.28 $\pm$ 0.28
DRE	Benign	254 (87.9%)
	Malign	35 (12.1%)
Prostate volume (n=89)		54.1 $\pm$ 28.7
PNI		41 (13.3%)
Transrectal		232
Transperineal		93
mpMRI number of lesion (ROI)		2.7 $\pm$ 2.2
Biopsy core per lesion		5.1 $\pm$ 4.7
PCa		
• Combine MRI-TB+SB		199 (63.2%)
• MR-TB		186 (59.7%)
• SB		157 (49.8%)
sPCa		
• Combine MRI-TB+SB		163 (51.7%)
• MR-TB		152 (48.3%)
• SB		119 (37.8%)
RP		(n=102)
• Upgrade		25 (24.5%)
• Concordance		59 (57.8%)
• Downgrade		18 (17.6%)

BMI: Body mass index, PNI: Perineural invasion, ROI: Region of interest, sPCA: Significant prostate cancer, PI-RADS: Prostate imaging-reporting and data system, SB: Systematic biopsy, TB: Targeted biopsy, MRI: Magnetic resonance imaging, PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, DRE: Digital rectal exam

PCa was detected in 199 patients with combined MR targeted + SB (63%), in 186 patients with Targeted only, and in 157 patients with SB, respectively. SB alone missed 42 patients, and TB missed only 13 cases of any grade cancer. There was a significant difference in the missed cancer ratio between TB and SB (10.2% vs. 24.4%) in any grade of cancer, and significant cancer detection by SB alone was significantly lower than by TB alone. Most of the patients having cancer with PI-RADS 5 lesions biopsied were found to be significant cancer (81.9%). SB alone missed 44 patients and TB missed only 11 patients with significant PCa. SB added 11/163 (6.7%) of significant PCa detection.

We analyzed which clinical factors impact the risk of clinically significant PCa (csPCa) detection by MRI TB-SB. The multivariate regression model proved that the following clinical parameters were significantly increasing the probability of PCa detection: Age and abnormal DRE (Table 2). In our cohort, all patients with abnormal digital rectal exam (DRE), except one, were found to have PCa. The detection of PCa in the cohort with high PSA density (PSAD) was higher compared to other cohorts. However we are unable to test whether PSAD was a significant predictor of cancer detection in each biopsy technique due to small sample size of patients having PSAD values registered which were only 25% of the entire cohort.

One hundred-two patients who underwent radical prostatectomy were evaluated for concordance. TB showed significantly higher concordance over SB at RP (Table 3). Twenty-eight patients were found to have significant PCa on radical prostatectomy, which that went undetected or undergraded with SB biopsy. The number of downgrades was lowest in both methods, but the number of upgrades was highest in SB.

Discussion

The main goal of our study was to investigate whether omitting SB in PI-RADS 5 lesions could impact the csPCa detection rate. Our results confirmed that in PI-RADS 5, TB has a significantly higher csPCa detection rate compared to SB, with 48% vs. 37%, respectively. We also confirmed that omitting SB may contribute to a slight reduction in the csPCa detection rate by 6.7%. Our

results are consistent with data from recent studies. Ahdoot et al. (3) found that TB-only biopsy misses 5.8% of csPCa. In a Cochrane meta-analysis, the added value of SB in csPCa detection in a biopsy-naïve setting was 4.3% (14). The results from our study and recent studies in the literature indicate that concomitant SB has a marginal impact on csPCa detection in PI-RADS 5 patients.

There are several arguments that advise against SB omission. We should consider the limited sensitivity of mpMRI in detecting all csPCa foci, as approximately 30% of csPCa are invisible on mpMRI (15). Moreover, PCa is characterized by multifocal growth, which is present in about 20% of the cases (16). In the study by Checcucci et al. (17), PCa was detected via concomitant SB, contralaterally to index lesions in 36% of csPCa cases detected via TB. It has also been proven (18) that a higher PI-RADS score increases the likelihood of csPCa presence outside the index lesion. In PI-RADS 5 patients, csPCa presence outside the index lesion can be seen in up to 60% of cases (19).

In addition to the PI-RADS score, other potential predictors of csPCa detection via SB are under investigation, such as PSA, PSAD, biopsy setting, DRE status, lesion location, and prostate volume. However, no risk-adapted strategy or nomogram has clearly been proposed to avoid concomitant SB yet. In our work, we also confirmed that PSAD is another significant predictor that increases the detection rate of csPCa in PI-RADS 5 patients. We determined that a PSAD level of 0.28 ng/mL² is important for detecting PCa. The results of our analysis are consistent with the available literature, which indicates that PSAD and PI-RADS scores are complementary in the detection of PCa. Recent publications based on a comparison of histopathology reports from a biopsy and radical prostatectomy indicate that high PSAD values are also associated with higher tumor volume and a higher probability of underestimating the Gleason score (20).

In our cohort, 102 patients who underwent radical prostatectomy were evaluated for concordance. MRI-TB was superior in predicting the result of final histopathological analysis for PI-RADS 5 compared to systematic biopsies. TB showed significantly higher concordance than SB at RP. Twenty-eight patients were found to have significant PCa on radical prostatectomy whom went undetected or undergraded with SB only. Downgrade was lowest in both methods but upgrade was

Table 2. Multivariable logistic regression analyses predicting factors effecting biopsy results

	PI-RADS 5 MRI- TB+SB		
	Benign (n=129)	PCa (n=186)	p
Age	63.9±7.1	66.9±7.6	<0.001
BMI	27.1±4.2	27.9±5.7	1
DRE positive	1 (0.07%)	34 (18.3%)	<0.001
PSA	9.4±6.8	11.6±8.8	0.03
PV	54.1±1	54.1±28.7	0.570
mpMRI number of lesion	1.6±1.2	1.7±1.6	0.760
Number of cores per lesion	5.4±4.9	4.9±4.5	0.351

DRE: Digital rectal exam, BMI: Body mass index, PV: Prostate volume PCa: Prostate cancer, PI-RADS: Prostate imaging-reporting and data system, SB: Systematic biopsy, TB: Targeted biopsy, MRI: Magnetic resonance imaging

Table 3. Concordance at radical prostatectomy

	RP insPCa (n=10)	RP sPCa (n=92)
Combine MRI-TB+SB		
• insPCa	6 (60%)	8 (8.7%)
• sPCa	4 (40%)	84 (91.3%)
MRI-TB		
• benign	3 (30%)	7 (7.6%)
• insPCa	5 (50%)	10 (10.9%)
• sPCa	2 (20%)	75 (81.5%)
SB		
• benign	0 (0%)	14 (15.2%)
• insPCa	6 (60%)	14 (15.2%)
• sPCa	4 (40%)	64 (69.6%)

RP: Radical prostatectomy, insPCa: Insignificant prostate cancer, sPCa: Significant prostate cancer, SB: Systematic biopsy, TB: Targeted biopsy, MRI: Magnetic resonance imaging

higher in SB. Upgrading may be due to inadequate sampling by SB, where small foci of Gleason 4-5 are undetected at biopsy but documented at radical prostatectomy (21). MRI targeted biopsies are more prone to downgrading and systematic biopsies are more frequently upgraded. Downgrading may occur for several reasons, including over-sampling of the very small (less than 5%) foci of Gleason pattern 4 or 5 cancer (22). There is a risk of oversampling with an increased number of targets registered by a radiologist and an increased number of biopsy cores taken at the discretion of the biopsy performer. If SB is omitted, our results showed that 7 patients with clinically significant PCa at radical prostatectomy would be missed initially. Several recent studies indicate that SB may reduce the likelihood of Gleason score underestimation (22). Moreover, taking cores from areas surrounding a suspicious lesion can reduce sampling error and may provide a better estimation of the Gleason score (23). Similarly, several technical issues of TB are also under investigation. For example, the number of targeted cores taken per lesion may impact csPCa detection and Gleason score estimation (24). In particular, obtaining three to four cores (current standard) from high-volume lesions, such as PI-RADS 5, may not be sufficient to adequately estimate the Gleason score (25). Moreover, mpMRI alone has a limited ability to predict local stage and extra-prostatic extension (26). As a result, a TB-only approach may impact clinical decisions, such as qualification for local treatment or planning the extension of surgical intervention. For example, the presence of a PCa outside the index lesion can preclude focal treatment. The local stage of PCa also provides implications regarding neurovascular bundle sparing during radical prostatectomy. It is also worth noting that the percentage of PCa involvement in the systemic cores is an important prognostic factor, indicating the risk of biochemical progression or pelvic lymph node involvement (27). Therefore, the omission of SB may have a negative impact on adequate PCa local staging and prognostic risk group determination.

Study Limitations

The major limitations of our study are its retrospective nature and analysis. Our study was multi-center and retrospective. The study population was heterogeneous, as it included both transperineal and transrectal biopsies. The analysis did not include epidemiological factors such as body mass index or comorbidities. The mpMRI images were obtained from external radiological centers, and they were described by radiologists with different levels of experience; therefore, there may have been certain discrepancies in the assessment of the PI-RADS scores. Another limitation is that TB data were obtained from 5 different centers performed by 7 different urologists using different MRI and MRI-US fusion devices. Failure of mpMRI fusion biopsy due to incorrect mpMRI image registration and mismatch of image planes, inaccurate sampling, and intralesion Gleason score heterogeneity, may have impacted our results. Another important limitation is that there was no centralized pathological examination; instead, multicentric pathological examinations were conducted by uropathologists at their respective centers. However, our data reflect the real-life nationwide picture. The comparisons of biopsy methods were performed per patient rather than per lesion. The mean number of cores were 5 in our study which may reflect overdiagnosis in TB group.

Conclusion

The results of our study indicate that in PI-RADS 5 lesions, the probability of detecting csPCa in SB is significantly lower than in TB. Omitting SB is also associated with risk of missing csPCa in 6.7% of cases. In patients with PI-RADS 5 lesions, SB in addition to TB adds minimal but not negligible clinical value. Sparing these patients from SB may be considered to reduce patient morbidity. However, the omission of SB may impact local staging by failing to detect multifocal csPCa and thus may affect therapeutic decisions. Further prospective studies are needed to set strict recommendations.

Ethics

Ethics Committee Approval: Ethics committee approval is not required for the study however several ethics committee approval have been registered earlier for our Turkish Urooncology Cancer Database.

Informed Consent: All patients gave consent for the study.

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Surgical and Medical Practices: G.A., S.S., L.T., S.B., C.Y.B., E.S., İ.A., Concept: G.A., S.Ç., Design: G.A., S.Ç., Data Collection or Processing: S. Çet., S.S., S.Ç., L.T., S.E., S.B., İ.A., C.Y.B., S.Y., Analysis or Interpretation: B.Ş., L.T., G.A., S.Ç., S.S., Literature Search: S.Çet., Writing: G.A.

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Association of Pathological Tumor-to-kidney Volume Ratio with Adverse Pathological Features After Radical Nephrectomy: An Exploratory Retrospective Cohort Study

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Abstract

Objective: To evaluate the association of the pathology-derived tumor-to-kidney volume ratio (T/K ratio) with adverse pathological features and assess whether it provides prognostic information for cancer-specific survival (CSS) beyond maximum tumor diameter in renal cell carcinoma (RCC) patients undergoing radical nephrectomy.

Materials and Methods: We retrospectively reviewed the records of 151 patients who underwent radical nephrectomy for non-metastatic RCC between 2005 and 2018. Tumor and kidney volumes were calculated from three orthogonal dimensions measured pathologically using the ellipsoid formula. An exploratory data-derived T/K ratio cut-off of 0.45 was used for group comparisons. Associations were evaluated using group comparisons, Spearman correlation, Kaplan-Meier analysis, and a parsimonious Cox model (T/K ratio and maximum tumor diameter), with CSS as the primary endpoint.

Results: The high T/K ratio group (n=28) had a greater tumor diameter than the low-ratio group (8.5 vs. 5.0 cm; $p<0.001$) and higher frequencies of renal vein involvement, microvascular invasion, tumor necrosis, collecting system invasion, and positive surgical margins (all $p<0.05$). The T/K ratio correlated strongly with tumor volume ($p=0.789$) and maximum diameter ($p=0.747$), but not with kidney volume ($p=0.089$). Median follow-up was 73 months [95% confidence interval (CI), 62-86]. Five-year CSS was 66.9% (95% CI, 42.2-82.9%) in the high-ratio group and 94.7% (95% CI, 87.6-97.8%) in the low-ratio group ($p<0.001$). In the parsimonious model, the T/K ratio was not independently associated with cancer-specific mortality after adjustment for diameter [hazard ratio (HR) per 0.10 increase, 1.14; 95% CI, 0.90-1.44; $p=0.262$], whereas diameter remained significant (HR per 1 cm, 1.21; 95% CI, 1.03-1.41; $p=0.022$).

Conclusion: A high T/K ratio was associated with adverse pathological findings and inferior unadjusted survival, but showed no independent association with cancer-specific mortality after adjustment for maximum tumor diameter. The ratio should be considered an exploratory morphometric index.

Keywords: Carcinoma, renal cell, nephrectomy, tumor burden, organ size, survival analysis

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2-3% of adult malignancies and 80-90% of malignant renal tumors (1-4). Tumor size remains central to the classification of localized RCC. In the eighth edition of the American Joint Committee on Cancer system, kidney-confined tumors are separated into T1 and T2 size categories according to maximum diameter (5). This approach does not describe the proportional tumor burden within the affected kidney.

Volumetric measurements may characterize tumor burden more comprehensively than a single linear diameter. Maximum diameter may not accurately represent true tumor volume,

particularly for larger or irregular tumors (6). Kidney volume has also been associated with tumor diameter and adverse histological findings (7). Three-dimensional tumor volume has shown prognostic associations with cancer-specific survival (CSS), overall survival (OS), recurrence, and metastasis in RCC cohorts (8-10). Kabay et al. (9) further reported that the ratio of tumor volume to kidney volume increased across RCC size categories.

Normalizing tumor volume to kidney volume is a practical morphometric approach, but it remains uncertain whether the resulting tumor-to-kidney volume ratio (T/K ratio) provides information beyond conventional tumor size. We therefore investigated the association of the pathology-derived T/K

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ratio with adverse pathological features and CSS—considered the primary survival endpoint given its direct relevance to RCC-specific outcomes—in patients undergoing radical nephrectomy. We also assessed its correlation with maximum tumor diameter and absolute tumor volume, examined whether it remained associated with CSS after adjustment for maximum tumor diameter, and described OS as a secondary, unadjusted outcome.

Materials and Methods

Study Design and Patients

This retrospective cohort study was conducted at a single tertiary referral center. The study was approved by the Local Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (decision no: 2018/08, date: 11.04.2018) and conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent was waived because of the retrospective design of the study. Medical records of 232 patients who underwent open or laparoscopic radical nephrectomy for a renal tumor between January 2005 and August 2018 were reviewed. Patients were excluded because of age <18 years (n=4), previous renal surgery (n=6), a known non-RCC malignancy (n=14), previous chemotherapy, radiotherapy, or immunotherapy (n=11), metastatic disease at diagnosis (n=5), chronic hepatitis or cirrhosis (n=4), benign or non-RCC histology (n=22), pathological stage pT3b or higher (n=2), or incomplete records (n=13). The final cohort comprised 151 patients.

Clinical and Pathological Assessment

Demographic characteristics, surgical approach, and pathological findings were recorded. All specimens were re-evaluated by a single experienced pathologist. The histological subtype was classified according to the 2016 World Health Organization classification. The WHO/ISUP nucleolar grade was applied to clear cell and papillary RCC; chromophobe RCC was not graded and was therefore considered not applicable in grade-related analyses. Renal vein involvement, sarcomatoid differentiation, microvascular invasion, renal capsule invasion, tumor necrosis, collecting system invasion, perirenal fat invasion, and surgical margin status were recorded separately.

Diameter-based Tumor Categorization

For descriptive morphometric analyses, tumors were categorized according to maximum tumor diameter, using the original unrounded measurements, as ≤ 4 cm, >4-7 cm, >7-10 cm, and >10 cm; dimensions displayed in the tables were rounded for reporting. Renal vein involvement, collecting system invasion, and perirenal fat invasion were analyzed as separate adverse pathological findings and were not incorporated into this diameter-based categorization.

Volume Calculation and T/K Ratio

Kidney volume was defined as the total ellipsoid volume of the nephrectomy specimen, including the tumor mass, rather than the tumor-free parenchymal volume. Tumor and kidney

dimensions were abstracted from the contemporaneous gross pathology reports and reviewed for consistency by a single pathologist. Perinephric and hilar fat were excluded from measurements of kidney dimensions. Three orthogonal dimensions (length, width, and height) of the tumor and the kidney were used to calculate their volumes using the ellipsoid formula: $V = \pi/6 \times \text{length} \times \text{width} \times \text{height}$. Interobserver and intraobserver reproducibility of the gross measurements was not formally assessed. A kidney was operationally defined as atrophic when pathological volume was $<130 \text{ cm}^3$ and/or the longest axis was $<9 \text{ cm}$ (11,12). The T/K ratio was calculated by dividing tumor volume by kidney volume.

Follow-up and Statistical Analysis

Patients were followed every 3-6 months during the first two years and annually thereafter. Vital status and cause of death were obtained from medical records and, when necessary, from telephone interviews with patients or relatives. CSS and OS were calculated from surgery to death from RCC and to death from any cause, respectively, or to the last known follow-up; CSS was considered the primary survival endpoint, and OS was examined descriptively. Median follow-up was estimated by the reverse Kaplan-Meier method. The T/K ratio cut-off of 0.45 was an exploratory data-derived threshold, selected in the original analysis using conventional receiver operating characteristic (ROC) methods with cancer-specific death status as the binary outcome. Because this approach did not account for censoring and the cut-off was derived and evaluated in the same cohort, it was used only for descriptive, hypothesis-generating comparisons and did not represent a validated clinical threshold. Analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA), and MedCalc Statistical Software Version 16 demo (MedCalc Software Ltd., Ostend, Belgium). Continuous variables are presented as median (range) and compared using the Mann-Whitney U test. Categorical variables were compared using Pearson's chi-square test, Yates-corrected chi-square test, or Fisher's exact test, as appropriate. Associations among continuous morphometric variables were assessed using Spearman rank correlation. Survival was estimated with Kaplan-Meier analysis and compared by the log-rank test. Given the limited number of cancer-specific deaths, a parsimonious Cox proportional hazards model was prespecified to examine whether the continuous T/K ratio provided information beyond maximum tumor diameter in predicting CSS. The T/K ratio was scaled per 0.10-unit increase, and tumor diameter was scaled per 1-cm increase. The proportional hazards assumption was assessed using Schoenfeld residuals. Analyses were complete-case; the WHO/ISUP grade was not applicable to chromophobe RCC. No adjustment was made for multiple comparisons, and all analyses were considered exploratory. A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 151 patients were included: 107 men (70.9%) and 44 women (29.1%); the median age was 62 years (range, 34-89). Radical nephrectomy was performed through an open

approach in 144 patients (95.4%) and laparoscopically in 7 patients (4.6%). The median maximum tumor diameter was 5.5 cm (1.8-18.0); the median tumor volume was 45.04 cm³ (1.24-1647.36); the median kidney volume was 293.02 cm³ (13-2808); and the median T/K ratio was 0.18 (<0.01-0.91). The diameter categories were ≤4 cm in 41 patients (27.2%), >4-7 cm in 71 (47.0%), >7-10 cm in 21 (13.9%), and >10 cm in 18 (11.9%). Twenty-one patients (13.9%) had an atrophic kidney. Histological subtype was clear cell in 123 patients (81.5%), papillary in 13 (8.6%), and chromophobe in 15 (9.9%). WHO/ISUP grade was evaluable in 136 clear cell or papillary tumors (Table 1).

Exploratory T/K Ratio Groups

In the original exploratory analysis, ROC analysis, using cancer-specific death as the binary outcome, yielded an area under the curve (AUC) of 0.698 [95% confidence interval (CI), 0.612-0.744; p=0.005] for the T/K ratio; the Youden index identified 0.45 as the value that maximized the sum of sensitivity (50.0%) and specificity (86.6%) in this cohort. This value should not be interpreted as a clinically validated optimal threshold. As noted in the Methods, this approach did not account for censoring, and the cut-off was derived and evaluated in the same cohort; therefore, it was used only as an exploratory, data-derived cut-off for descriptive and hypothesis-generating comparisons.

Table 1. Demographic, clinical, and pathological characteristics and comparison of the exploratory T/K ratio groups

Variable	All (n=151)	Low T/K (n=123)	High T/K (n=28)	p-value
Age, years, median (range)	62 (34-89)	62 (34-89)	62 (40-82)	0.538
Sex, male, n (%)	107 (70.9)	82 (66.7)	25 (89.3)	0.032
Body weight, kg, median (range)	78 (45-118)	79 (49-118)	75.5 (45-115)	0.850
Tumor volume, cm ³ , median (range)	45.04 (1.24-1647.36)	37.44 (1.24-946.40)	207.02 (6.86-1647.36)	<0.001
Kidney volume, cm ³ , median (range)	293.02 (13.00-2808.00)	283.92 (23.40-2808.00)	360.62 (13.00-2242.24)	0.276
Maximum tumor diameter, cm, median (range)	5.5 (1.8-18.0)	5.0 (1.8-14.0)	8.5 (2.5-18.0)	<0.001
T/K ratio, median (range)	0.18 (<0.01-0.91)	0.14 (<0.01-0.44)	0.54 (0.45-0.91)	<0.001
Diameter category, n (%)				<0.001
≤4 cm	41 (27.2)	40 (32.5)	1 (3.6)	
>4-7 cm	71 (47.0)	65 (52.8)	6 (21.4)	
>7-10 cm	21 (13.9)	10 (8.1)	11 (39.3)	
>10 cm	18 (11.9)	8 (6.5)	10 (35.7)	
Atrophic kidney, n (%)	21 (13.9)	19 (15.4)	2 (7.1)	0.368
Histological subtype, n (%)				0.399
Clear cell	123 (81.5)	100 (81.3)	23 (82.1)	
Papillary	13 (8.6)	12 (9.8)	1 (3.6)	
Chromophobe	15 (9.9)	11 (8.9)	4 (14.3)	
WHO/ISUP grade, n (%)				0.061
Grade 1	14/136 (10.3)	13/112 (11.6)	1/24 (4.2)	
Grade 2	83/136 (61.0)	67/112 (59.8)	16/24 (66.7)	
Grade 3	31/136 (22.8)	28/112 (25.0)	3/24 (12.5)	
Grade 4	8/136 (5.9)	4/112 (3.6)	4/24 (16.7)	
Renal vein involvement, n (%)	10 (6.6)	5 (4.1)	5 (17.9)	0.020
Sarcomatoid differentiation, n (%)	5 (3.3)	3 (2.4)	2 (7.1)	0.231
Microvascular invasion, n (%)	15 (9.9)	7 (5.7)	8 (28.6)	0.001
Renal capsule invasion, n (%)	42 (27.8)	31 (25.2)	11 (39.3)	0.162
Tumor necrosis, n (%)	26 (17.2)	16 (13.0)	10 (35.7)	0.010
Collecting system invasion, n (%)	13 (8.6)	6 (4.9)	7 (25.0)	0.003
Perirenal fat invasion, n (%)	14 (9.3)	10 (8.1)	4 (14.3)	0.295
Positive surgical margin, n (%)	4 (2.6)	1 (0.8)	3 (10.7)	0.020

WHO/ISUP grade was applicable to clear cell and papillary RCC and was not assigned to chromophobe RCC; grade was evaluable in 136 patients overall, 112 in the low-ratio group, and 24 in the high-ratio group. The T/K ratio cut-off (0.45) used to define the low and high groups was an exploratory, data-derived threshold (see Methods) and has not been externally validated
Data are median (range) or n (%), T/K: Tumor-to-kidney volume ratio, RCC: renal cell carcinoma

Using this cut-off, 123 patients (81.5%) were classified as having a low T/K ratio, and 28 (18.5%) were classified as having a high ratio. Median maximum tumor diameter was significantly greater in the high-ratio group than in the low-ratio group (8.5 vs. 5.0 cm; $p < 0.001$), as was median tumor volume (207.02 vs. 37.44 cm³; $p < 0.001$). Kidney volume did not differ significantly between groups ($p = 0.276$). The high-ratio group had a higher proportion of men (89.3% vs. 66.7%; $p = 0.032$). The high-ratio group had larger diameter categories ($p < 0.001$) and higher frequencies of renal vein involvement (17.9% vs. 4.1%; $p = 0.020$), microvascular invasion (28.6% vs. 5.7%; $p = 0.001$), tumor necrosis (35.7% vs. 13.0%; $p = 0.010$), collecting system invasion (25.0% vs. 4.9%; $p = 0.003$), and positive surgical margins (10.7% vs. 0.8%; $p = 0.020$) (Table 1). As a continuous variable, the median T/K ratio increased across the ≤ 4 cm, >4 -7 cm, >7 -10 cm, and >10 cm diameter categories (0.06, 0.18, 0.45, and 0.47, respectively; $p < 0.001$).

Correlation Analysis

The T/K ratio was strongly correlated with tumor volume (Spearman $\rho = 0.789$; $p < 0.001$) and maximum tumor diameter ($\rho = 0.747$; $p < 0.001$), but not with kidney volume ($\rho = 0.089$; $p = 0.280$). Tumor volume was strongly correlated with maximum diameter ($\rho = 0.968$; $p < 0.001$). Full correlations among morphometric variables are presented in Supplementary Table 1.

Survival Outcomes

The median follow-up calculated using the reverse Kaplan-Meier method was 73 months (95% CI, 62-86). Thirty-nine patients (25.8%) died, including 20 (13.2%) from RCC. Five-year CSS was 94.7% (95% CI, 87.6%-97.8%) in the low-ratio group and 66.9% (95% CI, 42.2%-82.9%) in the high-ratio group (log-rank $p < 0.001$; Figure 1). OS also differed significantly between the low- and high-ratio groups (log-rank $p = 0.008$). Because OS was examined descriptively only, consistent with CSS being the primary endpoint, group-specific OS estimates are not reported in further detail. In univariate Cox analysis, the exploratory high-ratio group was associated with cancer-specific mortality [hazard ratio (HR), 6.05; 95% CI, 2.51-14.56; $p < 0.001$]. In the parsimonious model containing the two continuous morphometric variables, the T/K ratio was not independently associated with cancer-specific mortality after adjustment for maximum tumor diameter (HR per 0.10-unit increase, 1.14; 95% CI, 0.90-1.44; $p = 0.262$), whereas maximum tumor diameter remained significant (HR per 1-cm increase, 1.21; 95% CI, 1.03-1.41; $p = 0.022$) (Table 2). The proportional hazards assumption was not violated.

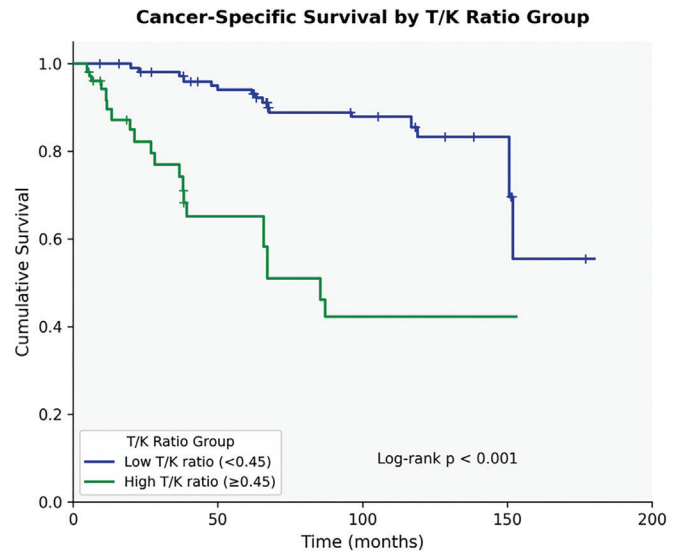


Figure 1. Kaplan-Meier cancer-specific survival curves according to the exploratory T/K ratio cut-off of 0.45. Vertical marks indicate censored observations

T/K: Tumor-to-kidney volume ratio

Discussion

This exploratory study assessed a pathology-derived T/K volume ratio in patients undergoing radical nephrectomy for non-metastatic RCC. A high ratio was associated with larger tumors, higher tumor- diameter categories, several adverse pathological findings, and inferior unadjusted CSS and OS. However, the T/K ratio was strongly correlated with maximum tumor diameter and absolute tumor volume, not correlated with kidney volume, and not independently associated with cancer-specific mortality after adjustment for maximum diameter. These findings indicate that, in this cohort, the ratio predominantly reflects tumor burden and that there was no independent association with cancer-specific mortality after accounting for maximum diameter.

Prior studies support the prognostic relevance of RCC volumetry. Jorns et al. (8) reported a stronger association of three-dimensional tumor volume than diameter with CSS in pT1 clear cell RCC, and Chen et al. (10) found tumor volume to predict CSS, OS, metastasis, and local recurrence in localized clear cell RCC. Kabay et al. (9) showed that the T/K ratio increased across RCC stages. We observed a similar gradient across diameter categories. Nevertheless, tumor volume and diameter were almost collinear in our cohort ($\rho = 0.968$), and the T/K ratio itself correlated strongly with both measures. Secil et al. (13) similarly

Table 2. Cox proportional hazards analysis for cancer-specific survival

Variable	Univariate HR (95% CI)	p-value	Parsimonious adjusted HR (95% CI)	p-value
T/K ratio, per 0.10-unit increase	1.36 (1.15-1.61)	<0.001	1.14 (0.90-1.44)	0.262
Maximum tumor diameter, per 1-cm increase	1.28 (1.13-1.44)	<0.001	1.21 (1.03-1.41)	0.022
High T/K ratio group (≥ 0.45)	6.05 (2.51-14.56)	<0.001	-	-
The high T/K ratio group (≥ 0.45) reflects the same exploratory, data-derived cut-off described in the Methods				
CI: Confidence interval, HR: Hazard ratio, T/K: Tumor-to-kidney volume ratio				

found that tumor volume stratified survival in unadjusted analyses but did not remain independently prognostic after multivariable adjustment.

The high-ratio group also exhibited higher frequencies of renal vein involvement, microvascular invasion, collecting-system invasion, tumor necrosis, and positive surgical margins. These findings are clinically relevant because venous and microvascular invasion, collecting system invasion, necrosis, and margin status have been associated with adverse RCC outcomes (14-18). However, these associations should not be interpreted as evidence of a distinct biological mechanism. Because tumor volume forms the numerator of the ratio, larger and more locally extensive tumors are expected to yield higher T/K values. The significant sex imbalance between the ratio groups and the lack of normalization of pathological kidney measurements to body size or sex may also contribute to residual confounding.

The survival separation produced by the exploratory data-derived cut-off of 0.45 was substantial, but the threshold was derived and tested in the same cohort and did not account for censoring when originally selected; it should therefore continue to be regarded as descriptive and hypothesis-generating rather than a validated clinical threshold. The limited model was deliberately restricted to the T/K ratio and maximum diameter because only 20 cancer-specific deaths occurred; more extensive regression would produce unstable estimates in this sample (19). In this model, maximum diameter remained significant while the T/K ratio was not independently associated with cancer-specific mortality after adjustment for maximum diameter. Thus, the present data do not provide evidence of incremental prognostic value over conventional tumor size in this cohort, and the ratio should not currently be used to determine treatment or surveillance.

Study Limitations

Several limitations should be acknowledged. The study was retrospective and single-center, spanning 2005-2018, during which surgical practice, pathological reporting, and follow-up may have changed. The cohort included only patients selected for radical nephrectomy and, therefore, did not represent all localized renal masses, particularly patients treated with partial nephrectomy or active surveillance. The number of cancer-specific deaths was limited, and the exploratory data-derived cut-off lacked internal resampling and external validation. OS was examined only descriptively, given the decision to restrict the adjusted model to CSS in order to limit overfitting risk; conclusions regarding OS are therefore limited to unadjusted comparisons. The diameter categories used for descriptive analysis do not represent complete pathological TNM stages, as invasion-related findings were recorded and analyzed separately. Tumor and kidney dimensions were abstracted from gross pathology reports, using an ellipsoid approximation rather than from manual segmentation or from cross-sectional imaging-based volumetry; irregular shapes may be misrepresented, and interobserver and intraobserver reproducibility were not assessed. Preoperative imaging-based volumetry was not included; therefore, the preoperative applicability of the index cannot be inferred. Cause of death was occasionally determined

through interviews with relatives, which may introduce misclassification. Finally, multiple exploratory comparisons were performed without multiplicity adjustment.

Conclusion

The pathology-derived T/K ratio was associated with larger tumors, adverse pathological findings, and poorer unadjusted survival. However, in this cohort, no independent association with cancer-specific mortality was detected after adjustment for maximum tumor diameter. The T/K ratio should therefore be regarded as an exploratory morphometric index rather than a validated prognostic tool.

Ethics

Ethics Committee Approval: The study was approved by the Local Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (decision no: 2018/08, date: 11.04.2018).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.D.D., R.G., Ö.Ç., B.A., N.A.M., Concept: E.D.D., N.A.M., Design: E.D.D., Data Collection or Processing: E.D.D., Ö.Ç., Analysis or Interpretation: E.D.D., R.G., Literature Search: E.D.D., Writing: E.D.D., Ö.Ç., N.A.M.

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Guideline Concordance for Salvage Therapy in Recurrent Prostate Cancer: A Structured Comparison of EAU, AUA, and NCCN Recommendations

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Abstract

Objective: To compare European Association of Urology (EAU), American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (AUA/ASTRO/SUO), and National Comprehensive Cancer Network (NCCN) recommendations for salvage treatment of recurrent prostate cancer using a harmonized item-level framework.

Materials and Methods: This document-based study compared the EAU Prostate Cancer Guideline limited update March 2026, AUA/ASTRO/SUO Salvage Therapy Guideline 2024, and NCCN Prostate Cancer Version 5.2026. Ten domains were decomposed into 35 items. Two authors independently coded recommendation characteristics and operational actionability. Concordance was classified as complete, partial, or discordant; evidence-gap and evidence-limited statuses were recorded separately. Clinical concordance was assessed separately from operational actionability. Pairwise exact-code agreement, linearly weighted Cohen's kappa, and Gwet's AC2 were calculated using actionability codes.

Results: At the unweighted item level, complete agreement occurred in 12 of 35 items (34.3%), and partial agreement occurred in 23 of 35 (65.7%); no directly opposing clinical direction was identified. One domain contained only complete-agreement items, three contained only partial-agreement items, and six contained both types of items. Nine partial-agreement items (39.1%) carried evidence-status qualifiers: two evidence-gap zones and seven evidence-limited zones. Pairwise exact-code agreement ranged from 68.6% to 74.3; weighted Cohen's kappa ranged from 0.364 to 0.496; Gwet's AC2 ranged from 0.733 to 0.780; overall AC2 was 0.755. These coefficients reflect operational actionability, not clinical concordance. The strongest consensus concerned histological confirmation and metastatic exclusion before curative-intent local salvage after radiotherapy; early, risk-adapted salvage radiotherapy at low prostate-specific antigen (PSA) after prostatectomy; and avoiding withholding prostate-bed radiotherapy because of negative prostate-specific membrane antigen positron emission tomography.

Conclusion: The guidelines showed broad directional alignment without clinical opposition, although most concordance was partial. Differences remained in PSA thresholds, imaging timing, selection between adjuvant and early-salvage approaches, pelvic nodal irradiation, indication for and duration of androgen deprivation therapy, oligometastatic therapy, and definitions of recurrence after focal or ablative treatment. The recommendations should not be considered interchangeable.

Keywords: Prostatic neoplasms, salvage therapy, practice guidelines as topic, neoplasm recurrence, local, positron emission tomography computed tomography

Introduction

Recurrent prostate cancer following radical prostatectomy (RP), radiotherapy (RT), or focal/ablative therapy includes: persistent prostate-specific antigen (PSA) elevation, delayed biochemical recurrence (BCR), isolated local recurrence, pelvic nodal relapse, and oligometastatic disease. Differing natural history, curability,

morbidity, and systemic therapy needs prompt non-identical European Association of Urology (EAU), American Urological Association (AUA), and National Comprehensive Cancer Network (NCCN) salvage pathways (1-3).

After RP, decisions involve early salvage RT (SRT), molecular imaging, androgen deprivation therapy (ADT), and pelvic nodal treatment. After RT or focal/ablative therapy, recurrence must be

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confirmed, metastasis must be excluded, and salvage therapy must be selected. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) localizes recurrence earlier, but treatment implications remain incompletely standardized (1,2,4,5).

Salvage was selected as a clinically complex and operationally less standardized area. Clinicians must integrate PSA kinetics, PSMA PET findings, prior therapy, pathological risk, life expectancy, toxicity, and patient preference, while guidelines frame decisions differently or rely on evolving evidence. The resulting uncertainty regarding imaging, SRT initiation and intensification, and the management of post-RT or focal/ablative recurrence warrants an item-level comparison of harmonized, preference-sensitive, and evidence-limited guidance.

Structured comparisons identify guideline convergence and divergence (6,7). Concordance studies use predefined clinical domains, ordinal categories, and quantitative agreement metrics; evidence-alignment reviews similarly distinguish full, partial, and non-alignment (8,9). We compared EAU, AUA, and NCCN salvage recommendations for recurrent prostate cancer, focusing on clinical concordance and guideline-specific operational actionability.

Materials and Methods

This study is a document-based comparative analysis of publicly available clinical practice guidelines. No human participants, patient data, medical records, biological samples, or identifiable information were involved.

Therefore, according to institutional and international research ethics principles, ethics committee approval and informed consent were not required for this study.

The study was conducted using publicly accessible guideline documents only and did not involve any intervention or interaction with human subjects.

Study Design

This document-based cross-sectional comparison generated item-level data through structured extraction, independent coding, clinical adjudication, and quantitative analysis. The unit of analysis was a predefined recommendation or algorithm item, not a patient. Unlike reviews or meta-analyses, it applied an explicit, reproducible coding framework and conducted agreement analyses on primary guideline documents.

The primary outcome was item-level concordance among EAU, AUA, and NCCN recommendations. Secondary outcomes included explicit PSA thresholds, imaging triggers, eligible populations, intensification criteria, recommendation qualifications, and evidence-gap qualifiers.

Guideline Eligibility and Source Selection

The *a priori* corpus comprised three professional full-text guidelines: the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guideline, Limited Update March 2026; AUA Salvage Therapy for Prostate Cancer Guideline (2024); and NCCN Prostate Cancer, Version 5.2026 (1-3). All were accessed and archived, unchanged, on May 15, 2026, and were used throughout

extraction, coding, and consensus. The NCCN extraction used only the archived Version 5.2026, despite subsequent updates. These were the latest full-text versions relevant to salvage when the corpus was fixed. Patient materials, pocket/non-professional summaries, non-prostate guidelines, and superseded versions were excluded. External studies informed only the Discussion section, not item definition, coding, or adjudication.

Parent Domains, Item-level Extraction, and Concordance Coding

The framework was developed in two stages. First, ten parent domains captured salvage decisions: BCR and PSA-persistence definitions; PSMA PET timing and thresholds; negative PSMA PET before SRT; adjuvant versus early SRT after RP; SRT target volume; ADT indication and duration with SRT; high-risk BCR features; local recurrence after primary RT; pelvic nodal and oligometastatic recurrence; and recurrence after focal or ablative therapy, including follow-up and counseling.

Second, calibration mapping divided these domains into 35 recommendation- or algorithm-related items. Operational definitions, source locators, extraction variables, and coding rules were finalized before independent extraction and remained unchanged. Supplementary Table S1 provides the extraction and adjudication codebook. The 35 items served as primary analytical units; ten parent domains supported a stratified interpretation. Because the domains contained unequal numbers of items (range: 1-6), summaries present item-level distributions rather than domain scores.

For each item, two investigators independently recorded the relevant section, statement, printed page, or algorithm-page locator and summarized each recommendation. Prespecified fields included direction, PSA threshold, imaging modality, population, treatment, strength or evidence category, and qualifications. Differing grading systems precluded numerical pooling of recommendation strength. Supplementary Table S1 presents source locators, recommendations, actionability codes, concordance categories, evidence-status qualifiers, and adjudication rationales.

Assessing 35 items across three guidelines generated 105 guideline-item units. Prior to consensus, explicitness was rated as follows: 0, not addressed or outside scope; 1, discussed without an actionable recommendation, supported by insufficient evidence, or investigational; 2, conditionally, weakly, optionally, or selectively recommended; and 3, explicitly directed, standard, preferred, recommended, or by using “should” or “offer.” This analysis assessed reviewer reproducibility and identified units requiring source re-evaluation.

Discrepant units were reassessed against primary passages and resolved by consensus. Final three-level guideline-specific actionability codes and clinical concordance categories were assigned using prespecified definitions. No disagreement remained unresolved; thus, third-party adjudication was unnecessary.

Consistent with previous methods (8,9), concordance was classified as complete agreement, partial agreement, or disagreement. Complete agreement required an identical direction, without differences that would change the decision.

Partial agreement indicated a shared direction alongside meaningful differences in thresholds, timing, eligibility, treatment intensity or duration, terminology, evidence grading, and explicitness. Disagreement required that directions be directly opposing in comparable contexts. Operational differences, therefore, remained in partial agreement when the direction aligned.

Evidence status was not a fourth category. Evidence-gap zones were unresolved states lacking a validated, shared definition or a standardized follow-up endpoint; evidence-limited zones had aligned or overlapping directions but lacked sufficient comparative or outcome evidence to establish a preferred modality, a selection rule, or an integration strategy. These qualifiers could accompany partial agreement because they describe evidence, rather than inter-guideline similarity. Due to guideline-corpus limitations, they did not constitute independent systematic evidence grading.

Final concordance was clinically adjudicated rather than mechanically derived from actionability. Actionability measured explicitness and operationalization; concordance measured similarity. Identical profiles could remain partially concordant when thresholds, eligibility, triggers, or consequences differed; conversely, differing profiles could remain clinically concordant when they shared direction, even if it was less explicit or conditional.

Statistical Analysis

Pre-consensus reproducibility across 105 independently rated guideline-item units was summarized using exact agreement, agreement within one category, and the number and magnitude of discrepancies. These extraction and coding metrics differed from inter-guideline analyses of final consensus codes.

Final clinical concordance (one adjudicated outcome per item) was summarized as frequencies and percentages for the 35 items and presented separately from actionability. Each guideline item was assigned an ordinal actionability code: 0= absent/not standardized; 1= qualified, implicit, or less standardized; and 2= explicit/actionable. Pairwise exact-code agreement and linearly weighted Cohen's kappa were used to compare EAU with AUA and NCCN, and AUA with NCCN, retaining prespecified categories (0-2) even if unobserved. Given kappa's marginal-distribution sensitivity, linearly weighted Gwet's AC2 was a sensitivity analysis (10). Linearly weighted Fleiss' kappa was used secondarily to summarize three profiles, but it did not represent conventional inter-rater reliability because guidelines are documents, not human raters. Kappa and AC2 measured operational actionability and explicitness, but not clinical concordance, guideline validity or superiority, or patient outcomes.

No deterministic crosswalk linked actionability to concordance. Evidence-status qualifiers were tabulated separately and excluded from concordance coding and weighted kappa/AC2 analyses. Equal codes did not establish complete agreement, nor did unequal codes indicate disagreement. Each item contributed one observation. Clinical-importance weighting was omitted because no validated framework or prospectively elicited stakeholder weights existed, and post-hoc weighting would add

subjectivity. Percentages represented unweighted descriptive frequencies rather than clinical-importance composites. To limit unequal counts of domain items, item numbers and complete and partial distributions were summarized within each domain; no pooled or weighted domain score was calculated.

Results

Guideline Corpus and Extracted Recommendation Items

The corpus comprised the EAU Prostate Cancer Guideline Limited Update March 2026, AUA Salvage Therapy for Prostate Cancer Guideline (2024), and NCCN Prostate Cancer, Version 5.2026 (1-3). Table 1 summarizes versions, sources, access dates, archived files, structures, and salvage scope. Thirty-five items, grouped into ten parent domains, covered the following: biochemical definitions; molecular imaging; post-RP SRT timing/field; ADT selection/duration; high-risk BCR features; post-RT local salvage; pelvic nodal/oligometastatic recurrence; and recurrence after focal/ablative therapy. Supplementary Table S1 provides the extraction and adjudication codebook, source locators, and rationales.

The frameworks differed structurally. AUA was the most salvage-specific and explicit regarding negative PSMA PET, ADT selection, post-RT/focal-therapy recurrence, regional recurrence, and oligometastasis. The EAU specified criteria for PSA persistence, BCR risk groups, PSMA PET thresholds, and SRT/ADT evidence. Algorithm-oriented NCCN termed initial BCR treatment "secondary therapy" and embedded details in pathway footnotes and principles.

Pre-consensus Reviewer Agreement and Consensus Resolution

Before consensus, investigators assigned identical ratings to 77/105 guideline-item units (73.3%) and assigned ratings within one category to 103/105 guideline-item units (98.1%). Exact agreement was 20/35 (57.1%) for EAU, 29/35 (82.9%) for AUA, and 28/35 (80.0%) for NCCN. Among the 28 discrepancies, 26 differed by one category, and two differed by two categories. Both of the two-category discrepancies concerned item 3—confirming a rising ultrasensitive PSA trend and acting before conventional BCR—and neither constituted an extreme 0-versus-3 disagreement. All items were re-examined against the primary passages and resolved by consensus of two investigators before final matrix construction. Because 35 items generated three guideline-specific ratings, consensus is reported at the 105-unit level.

Overall Item-level Concordance

Across guidelines, 12/35 items (34.3%) showed complete agreement and 23/35 items (65.7%) showed partial agreement; none met the prespecified directly-opposing-direction criterion (0/35). This finding, which is classification-dependent, neither implies identical recommendations nor excludes meaningful differences.

Complete agreement was most evident for histological confirmation and metastatic exclusion before curative-intent local salvage after RT; early risk-adapted SRT at low PSA after

Table 1. Characteristics and salvage-relevant scope of the included guideline frameworks

Guideline framework	Developer and structure	Salvage-relevant scope extracted	Recommendation format	Source
EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guideline (Limited update March 2026)	European multidisciplinary guideline covering diagnosis, staging, treatment, recurrence, systemic therapy, follow-up, and quality of life.	Persistent PSA after RP; PSA-only recurrence; BCR imaging; post-RP SRT; ADT with SRT; post-RT local salvage; nodal and oligometastatic recurrence; focal/ablative therapy limitations.	Strength-rated recommendations plus narrative evidence summaries and management algorithms.	Official guideline webpage: https://uroweb.org/guidelines/prostate-cancer ; accessed May 15, 2026.
AUA/ASTRO/SUO Salvage Therapy for Prostate Cancer Guideline (Approved February 2024)	Salvage-specific multidisciplinary guideline focused on recurrence after primary curative-intent treatment.	BCR after RP; timing of SRT; ultrasensitive PSA; PSMA PET; negative PET; ADT with SRT; pelvic nodal recurrence; post-RT and focal-therapy local salvage; oligorecurrence.	Numbered guideline statements with recommendation strength, evidence level, clinical principles, and expert opinion.	Official guideline webpage: https://www.auanet.org/guidelines-and-quality/guidelines/salvage-therapy-for-prostate-cancer ; accessed May 15, 2026.
NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer (Version 5.2026, January 23, 2026)	Algorithm-based oncology guideline with pathway pages, principles sections, footnotes, evidence/consensus categories, and preference categories.	PROS-9/10 PSA persistence or recurrence; BCR2 workup and treatment; principles of imaging; focal/subtotal/ablative therapy; radiation therapy; local secondary therapy post-radiation; metastasis-directed therapy.	Pathway algorithms and principles sections; recommendations are category 2A unless otherwise specified.	Official guideline webpage: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459 ; accessed May 15, 2026. The archived full-text version 5.2026, published on January 23, 2026, was utilized.

AUA: American Urological Association, ASTRO: American Society for Radiation Oncology, SUO: Society of Urologic Oncology, PSA: Prostate-specific antigen, PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography, ADT: Androgen deprivation therapy, BCR: Biochemical recurrence, EAU: European Association of Urology, NCCN: National Comprehensive Cancer Network, RP: Radical prostatectomy, RT: Radiotherapy, SRT: Salvage radiotherapy

prostatectomy; general PSMA PET endorsement in BCR; for not withholding indicated prostate-bed SRT after a negative PSMA PET. Items with partial agreement differed with respect to BCR thresholds, PSMA PET timing, adjuvant versus early SRT, pelvic nodal irradiation, ADT indication and duration, high-risk BCR definitions, oligometastatic therapy, and post-focal or ablative recurrence definitions, potentially affecting treatment selection, timing, or intensity. Among ten domains, each containing one to six items, only negative-PSMA-PET-before-SRT exhibited complete agreement throughout; ADT-with-SRT, focal/ablative-recurrence, and pelvic-nodal/oligometastatic-recurrence exhibited uniformly partial agreement. The remaining six contained both; none contained disagreement. Table 2 presents descriptive compositions rather than adjudicated domain-level categories.

Actionability and concordance were distinct. Of 20 items with identical codes, 10 showed complete agreement and 10 showed partial agreement; of 15 items with non-identical profiles, 2 showed complete agreement and 13 showed partial agreement. General PSMA PET endorsement in BCR showed complete agreement, despite a 2/1/2 profile, because the direction was shared, although AUA was more conditional. Conversely, adverse pathological features had a 2/2/2 profile but remained partially concordant because their combinations, thresholds, and intensification rules differed.

Of the 23 items with partial agreement, 14 (60.9%) reflected operational differences in thresholds, timing, eligibility, treatment intensity, duration, or explicitness. Nine (39.1%) had evidence-status qualifiers: two evidence-gap zones involving the absence of validated biochemical/follow-up standards (items 6 and 33) and seven evidence-limited zones involving nodal-directed treatment, salvage reirradiation/ablation, post-

focal/ablative management, pelvic nodal recurrence, and oligometastatic therapy (items 18, 29-32, 34, and 35). Qualifiers did not alter classification; incomplete concordance sometimes reflected limited evidence or standardization, not only by wording or operationalization. Figure 1 distinguishes 12 high-consensus anchors from 23 partial-agreement items, namely 14 operationally heterogeneous decisions, two evidence-gap zones, and seven evidence-limited zones.

Pairwise exact actionability agreement was 26/35 (74.3%) for EAU versus AUA, 25/35 (71.4%) for EAU versus NCCN, and 24/35 (68.6%) for AUA versus NCCN; the linearly weighted Cohen's kappa values were 0.496, 0.435, and 0.364, respectively. None of the 105 final codes was 0; all differences involved adjacent categories 1 and 2, making weighted and unweighted estimates identical. Pairwise linearly-weighted Gwet's AC2 sensitivity estimates were 0.780, 0.755, and 0.733; the overall three-guideline AC2 was 0.755. All guidelines shared codes in 20 of 35 items (57.1%); the secondary linearly weighted Fleiss' kappa was 0.429. These measure operational explicitness rather than adjudicated concordance (Table 3).

Table 4 separately summarizes the operationally heterogeneous domains of BCR definitions, PSA persistence, and PSMA PET use. Frameworks aligned on recognizing rising PSA after RP, applying the Phoenix definition after RT, supporting PSMA PET in BCR, and not withholding indicated prostate-bed SRT after negative PSMA PET; however, PSA thresholds, imaging timing, and post-focal/ablative biochemical endpoints remained less standardized.

Discussion

This item-level comparison found broad directional alignment but substantial operational heterogeneity: 12/35 items showed

Table 2. Parent-domain distribution and clinical synthesis of item-level concordance

Parent domain	Domain no	n	Complete	Partial	Domain-level clinical synthesis
BCR and PSA persistence definitions	1-6	6	2	4	Shared recognition of clinically relevant PSA recurrence, but differences in post-RP BCR thresholds, ultrasensitive PSA confirmation, pre-Phoenix evaluation, and biochemical definitions after focal or ablative therapy.
PSMA PET timing and thresholds	7-10	4	2	2	Broad endorsement of PSMA PET, with heterogeneity in PSA-based timing and its positioning relative to conventional imaging.
Negative PSMA PET before SRT	11	1	1	0	All frameworks support the principle that a negative PSMA PET result should not preclude otherwise indicated prostate-bed SRT, although explicitness differs.
Adjuvant RT versus early SRT after RP	12-14	3	1	2	Early risk-adapted SRT at low PSA is aligned; operational PSA thresholds and selection of patients for adjuvant RT remain different.
SRT target volume	15-18	4	1	3	The prostate bed is the shared foundational field, while elective nodal coverage, PET-positive node incorporation, and nodal-directed strategies vary.
ADT indication and duration with SRT	19-21	3	0	3	All frameworks use risk-adapted intensification, but ADT indications, selection criteria, and duration are not operationally harmonized.
High-risk BCR features	22-25	4	2	2	PSA doubling time and persistent PSA are consistently adverse; formal high-risk definitions and combinations of pathological features differ.
Local recurrence after primary RT	26-30	5	3	2	Biopsy confirmation, exclusion of metastatic disease, and salvage RP are strongly aligned; reirradiation and ablative options differ in framing and evidence thresholds.
Recurrence after focal or ablative therapy	31-33	3	0	3	Guidance differs in biopsy requirements and whole-gland salvage pathways, while biochemical endpoints and follow-up remain evidence-limited.
Pelvic nodal and oligometastatic recurrence	34-35	2	0	2	Nodal treatment strategies and the role of metastasis-directed therapy, including integration with systemic treatment, remain incompletely standardized.
Overall	1-35	35	12	23	Unweighted descriptive frequencies across the prespecified items; no item met the directly opposing clinical-direction criterion.

Complete and partial counts refer to the final item-level concordance categories. The overall 12/35 and 23/35 values are unweighted descriptive frequencies and should not be interpreted as a composite score of clinical importance. No clinical-importance weights were assigned because no validated weighting scheme was available. Domain-stratified results are shown to prevent domains containing more nested items from dominating clinical interpretation. Evidence status was evaluated separately from concordance. Among the 23 partial-agreement items, two were designated as evidence-gap zones because validated definitions or follow-up standards were absent, and seven were designated as evidence-limited zones because comparative or outcome evidence was insufficient. These qualifiers do not constitute additional concordance categories.

ADT: Androgen deprivation therapy, BCR: Biochemical recurrence, PET: Positron emission tomography, PSA: Prostate-specific antigen, PSMA: Prostate-specific membrane antigen, RP: Radical prostatectomy, RT: Radiotherapy, SRT: Salvage radiotherapy

complete agreement and 23/35 showed partial agreement, with no directly opposing direction. This definition-bound result does not exclude meaningful differences in thresholds, timing, eligibility, intensity, or duration. Equal weighting resulted in domains with more items contributing more to aggregate percentages, which represent unweighted concordance frequencies rather than clinically important decision proportions; domain summaries add context. Post-hoc weighting was avoided because no validated or prospectively elicited scheme existed. Actionability and concordance were distinct: explicit recommendations do not necessarily share thresholds, populations, or consequences; less-explicit wording may reduce actionability without changing direction. Of the 23 partial-agreement items, 14 reflected operational heterogeneity and nine reflected evidence constraints: the absence of validated biochemical/follow-up endpoints after focal or ablative therapy and limited evidence for nodal-directed treatment, salvage reirradiation/ablation, pelvic nodal management, and oligometastatic therapy. These require validated definitions and comparative outcomes rather than merely harmonized wording. After RP, the clearest shared principle was early risk-adapted intervention. All frameworks support SRT at low PSA (1-3), but

the comparison cannot be reduced to an adjuvant versus salvage dichotomy. EAU and NCCN retain adjuvant RT for selected patients with multiple adverse or very-high-risk features under-represented in modern trials; routine use is not favored for most men with undetectable PSA (1,3). The prospectively planned ARTISTIC meta-analysis of RADICALS-RT, RAVES, and GETUG-AFU 17 included 2,153 men and found no event-free survival benefit from adjuvant versus early salvage RT (HR 0.95, 95% CI 0.75-1.21; $p=0.70$); 5-year rates were 89% versus 88% (11). This supports surveillance with prompt SRT for most patients, while preserving individualized adjuvant treatments for selected very-high-risk pathologies.

PSMA PET demonstrates a technological consensus but uncertainty in management. Although improving localization (4,5), frameworks differ in timing, PSA thresholds, and treatment modification. A negative scan neither excludes microscopic prostate bed disease nor does it justify delaying indicated early SRT. AUA statement 12 advises against withholding prostate-bed SRT because PET/CT is negative (2). In a retrospective multicenter cohort of 300 patients receiving SRT despite negative PSMA PET, 3-year BCR-free, metastasis-free, and overall survival were 73.9%, 87.8%, and 99.1%; BCR-free survival was higher at pre-

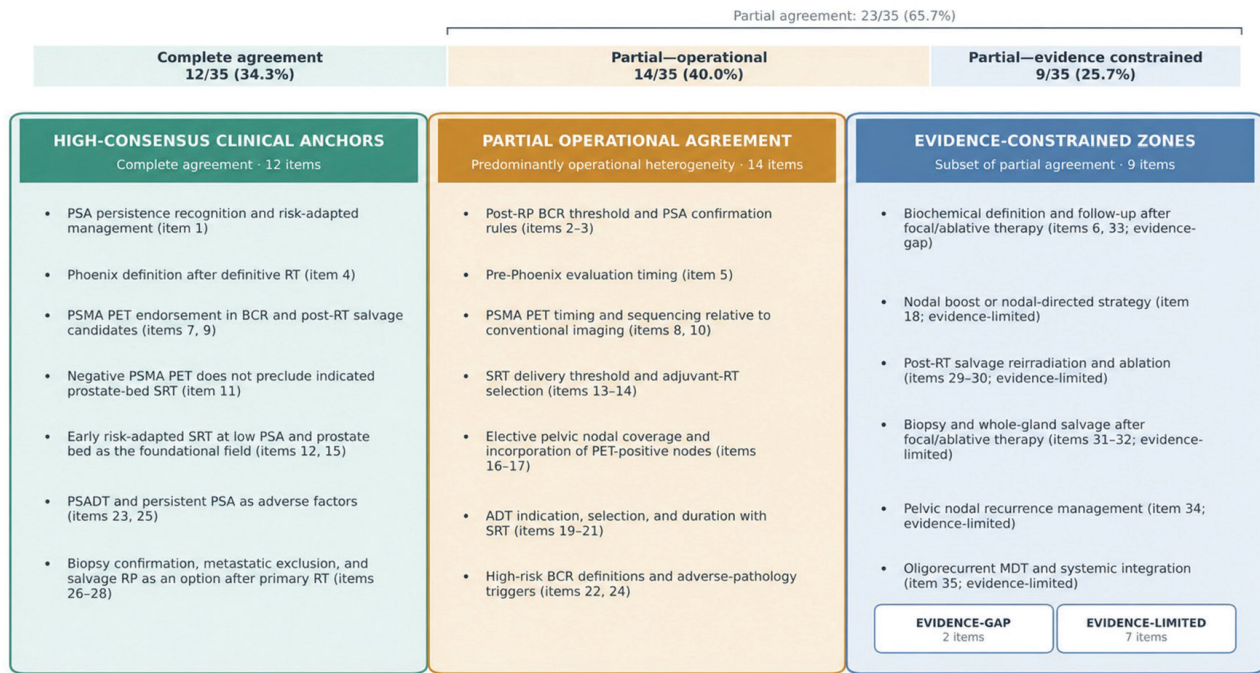


Figure 1. Practical synthesis of inter-guideline clinical concordance, operational heterogeneity, and evidence-constrained decision zones across the 35-item framework. The 35 items were first classified as complete agreement (12/35, 34.3%) or partial agreement (23/35, 65.7%); no item met the directly opposing clinical-direction criterion. The partial-agreement items were then displayed descriptively as 14 predominantly operationally heterogeneous decisions (60.9% of partial-agreement items) and nine evidence-constrained decisions (39.1%), comprising two evidence-gap zones and seven evidence-limited zones. Evidence status is an orthogonal qualifier: the nine evidence-constrained items remain within the 23 partial-agreement items and do not constitute a fourth concordance category. Counts represent unweighted item frequencies and should not be interpreted as clinical-importance-weighted estimates.

ADT: Androgen deprivation therapy, BCR: Biochemical recurrence, MDT: Metastasis-directed therapy, PET: Positron emission tomography, PSA: Prostate-specific antigen, PSADT: PSA doubling time, PSMA: Prostate-specific membrane antigen, RP: Radical prostatectomy, RT: Radiotherapy, SRT: Salvage radiotherapy.

Table 3. Agreement in guideline-specific ordinal actionability coding

Comparison	Exact-code agreement	Linearly weighted kappa	Linearly weighted Gwet's AC2	Analytical scope
EAU-AUA	26/35 (74.3%)	Cohen's $\kappa=0.496$	0.780	Pairwise operational actionability
EAU-NCCN	25/35 (71.4%)	Cohen's $\kappa=0.435$	0.755	Pairwise operational actionability
AUA-NCCN	24/35 (68.6%)	Cohen's $\kappa=0.364$	0.733	Pairwise operational actionability
Overall three-guideline summary	20/35 (57.1%)*	Fleiss' $\kappa=0.429^\dagger$	0.755	Descriptive three-profile summary

Actionability codes: 0= absent or not standardized; 1= qualified, implicit, or less standardized; and 2= explicit and actionable. All weighting analyses retained the complete prespecified 0/1/2 category set and used linear weights. No final guideline-item code was 0; therefore, all observed differences involved the adjacent categories 1 and 2, and weighted and unweighted kappa estimates were numerically identical. Gwet's AC2 was used as a sensitivity analysis because kappa may be affected by skewed marginal category distributions. These coefficients assess operational actionability and explicitness, not the final clinically adjudicated concordance category.

*: Overall exact agreement indicates that all three guidelines received the same actionability code for the item.

†: Fleiss' kappa is reported only as a secondary descriptive summary of three document-derived guideline profiles. EAU, AUA, and NCCN are not independent human raters; therefore, this coefficient should not be interpreted as conventional inter-rater reliability.

EAU: European Association of Urology, AUA: American Urological Association, NCCN: National Comprehensive Cancer Network,

PET PSA ≤ 0.5 versus >0.5 ng/mL (77.5% vs. 48.3%) (12). These findings support early SRT despite negative imaging, but lack randomized validation.

ADT and pelvic nodal RT are risk-adapted intensification strategies rather than routine additions. SPPORT, RTOG 9601, and GETUG-AFU 16 support selected intensification, but populations, PSA ranges, fields, and ADT durations differ (13–15). In SPPORT, 5-year freedom from progression was 70.9%

with prostate-bed RT, 81.3% with added short-term ADT, and 87.4% with prostate-bed and pelvic nodal RT plus short-term ADT (13). Escalation should not be generalized to every low-PSA patient. In a hypothesis-generating secondary RTOG 9601 analysis, 2 years of high-dose bicalutamide at PSA ≤ 0.6 ng/mL did not improve overall survival (HR 1.16, 95% CI 0.79–1.70) and increased other-cause mortality (subdistribution HR 1.94, 95% CI 1.17–3.20) (16). Thus, ADT and pelvic nodal RT may be suitable for adverse biology, higher PSA, a short PSA-doubling

Table 4. Focused domain-level synthesis of biochemical recurrence definitions, PSA persistence, and PSMA PET recommendations across EAU, AUA, and NCCN guidelines

Domain/item	EAU	AUA	NCCN	Harmonized interpretation
Post-RP PSA status and BCR threshold	PSA should become undetectable; PSA >0.4 ng/mL and rising best predicts metastasis; persistent PSA is separately discussed.	BCR defined as PSA ≥ 0.2 ng/mL on two determinations; rising ultrasensitive PSA should be confirmed before treatment if classical BCR is not met.	Includes PSA that never becomes undetectable, later becomes detectable and rises, or increases to >0.1 ng/mL.	All recognize rising PSA after RP as clinically relevant, but operational BCR thresholds differ.
Post-RT BCR definition	Phoenix definition is used, with selected earlier evaluation for salvage candidates.	Phoenix definition used for BCR after RT.	Phoenix definition used, while algorithms allow evaluation of PSA recurrence or positive DRE in appropriate candidates.	Complete agreement for Phoenix as reporting standard; partial agreement for evaluation before Phoenix failure.
PSA endpoints after HIFU, cryotherapy, or focal therapy	No validated PSA threshold against progression or survival.	Biopsy is recommended when salvage local therapy is considered after RT or ablative therapy, but PSA endpoint standardization is limited.	No universal post-focal follow-up protocol; recurrence workup is risk-based and biopsy-directed.	Evidence-gap qualifier: management pathways exist, but biochemical definitions remain insufficiently standardized.
PSMA PET in BCR	Recommended after RP when PSA >0.2 ng/mL if results will affect treatment; recommended after RT in candidates for curative salvage.	Next-generation molecular PET should be performed when SRT is considered; PSMA PET may replace or follow conventional imaging.	PSMA PET/CT or PET/MRI is accepted as an alternative to conventional imaging and is incorporated in BCR pathways.	Complete agreement for use of PSMA PET; partial agreement for timing, thresholds, and consequences.
Negative PSMA PET before SRT	Early SRT remains appropriate in PET-negative cases.	Do not withhold salvage prostate-bed RT solely because PET/CT is negative.	Imaging positivity is not required for secondary treatment in appropriate PSA persistence/recurrence pathways.	Negative PSMA PET does not exclude microscopic prostate-bed disease and should not automatically delay SRT.

This table provides a focused domain-level synthesis of the biochemical recurrence, PSA persistence, and PSMA PET items included in the 35-item concordance matrix provided in Supplementary Table S1. It complements the parent-domain summary in Table 2 and the guideline-specific ordinal agreement statistics in Table 3. AUA: American Urological Association, BCR: Biochemical recurrence, CT: Computed tomography, DRE: Digital rectal examination, EAU: European Association of Urology, HIFU: High-intensity focused ultrasound, MRI: Magnetic resonance imaging, NCCN: National Comprehensive Cancer Network, PET: Positron emission tomography, PSA: Prostate-specific antigen, PSMA: Prostate-specific membrane antigen, RP: Radical prostatectomy, RT: Radiotherapy, SRT: Salvage radiotherapy

time, nodal risk, persistent PSA, or imaging-positive nodes, while avoiding overtreatment of low-risk local recurrence.

The largest gaps lie outside the classic post-RP SRT. Local salvage after RT can be curative but is technically demanding and sensitive to toxicity. The MASTER meta-analysis of 150 studies found adjusted 5-year recurrence-free survival of approximately 50-60% across salvage prostatectomy, cryotherapy, HIFU, SBRT, and brachytherapy, without significant differences between evaluated modalities and salvage prostatectomy (17). Radiotherapeutic salvage was associated with lower rates of severe genitourinary toxicity than salvage prostatectomy, but heterogeneity and the predominantly retrospective nature of the evidence precluded a universally preferred approach.

Metastasis-directed therapy for oligometastatic disease may delay progression or the need for systemic treatment, but a survival benefit is unproven. In randomized phase II STOMP, median ADT-free survival was 21 months with metastasis-directed therapy versus 13 with surveillance (HR 0.60, 80% CI 0.40-0.90) (18). ORIOLE reported 6-month progression in 19% receiving stereotactic ablative RT versus 61% under observation ($p=0.005$) (19). These trials support short-term control and treatment deferral but establish neither overall survival benefit nor a uniform definition of oligorecurrence.

Recurrence after focal or ablative therapy lacks standardized biochemical definitions despite AUA and NCCN pathways (2,3). Magnetic resonance imaging, biopsy mapping, staging

imaging, multidisciplinary review, and individualized counseling remain central. Stronger consensus was accompanied by mature randomized evidence or explicit safety principles; partial agreement clustered around selection-dependent decisions, heterogeneous evidence, and uncertain long-term benefits. Figure 1 distinguishes among high-consensus anchors, partial operational agreements that require verification of framework-specific thresholds and details, and evidence-constrained decisions that require individualized, multidisciplinary interpretation. The evidence-constrained zone is nested within partial agreement, not a separate category.

Study Limitations

This document-based analysis has limitations. Different grading systems precluded the pooling of recommendation strength. Update schedules varied, and recommendations may evolve as evidence regarding PSMA PET, metastasis-directed therapy, systemic intensification, and focal therapy accrues. NCCN's algorithmic structure affected the granularity. We assessed neither patient outcomes nor which framework yielded superior survival, toxicity, or quality of life. Chance-corrected coefficients use guideline-specific ordinal actionability codes rather than adjudicated concordance categories and reflect only operational explicitness and standardization. Divergence between kappa and Gwet's AC2 indicates sensitivity to the marginal distributions in this small matrix. Because guidelines are document profiles rather than independent human raters, overall Fleiss' kappa has

limited conventional interpretability. These coefficients establish neither clinical validity, guideline superiority, nor expected patient benefit. Prospective registration and independent external verification would strengthen reproducibility.

Two authors resolved discrepant units against primary guideline documents without independent third-party adjudication; residual subjectivity remains possible. Disagreement, defined, narrowly required directly opposing directions, making its absence definition-dependent. Consequential operational differences may persist despite partial agreement, and alternative classification or weighting could yield different distributions.

Each item represented one observation despite differences in clinical importance, frequency of use, and consequences for outcomes. Unequal numbers of items cause granular domains to contribute disproportionately to aggregate percentages. Domain-stratified summaries limit overinterpretation, but are not validated as clinical-importance weights. Future comparisons could use prospectively defined clinician-, patient-, or Delphi-derived weights. Evidence-gap and evidence-limited qualifiers reflected guideline wording and evidentiary framing, not a separate systematic review or independent GRADE assessment; they indicate corpus uncertainty, not definitive judgments on all evidence. Distinguishing operational heterogeneity from evidence-limited zones required clinical judgment, although Supplementary Table S1 documents the item-level rationales.

Conclusion

Under the prespecified framework, none of the 35 recommendation or algorithm items directly opposed the clinical direction. This definition-dependent finding neither implies that guidelines are interchangeable nor excludes meaningful differences, since most agreed only partially. Alignment was strongest for histological confirmation and metastatic exclusion before local salvage after RT, for early risk-adapted SRT at low PSA after RP, and for avoiding withholding indicated prostate-bed SRT because of negative PSMA PET. Operational heterogeneity remained in BCR thresholds, PSMA PET timing, pelvic nodal irradiation, ADT selection/duration, oligometastatic therapy, and recurrence definitions after focal or ablative treatment. Thus, guidelines were broadly aligned, although several decisions remained preference-sensitive, operationally heterogeneous, or evidence-limited. Nine of the 23 partial-agreement items were evidence-constrained, reflecting shared uncertainty, insufficient standardization, and differences in wording and operations.

Item-level percentages are unweighted descriptive frequencies within the prespecified framework, rather than clinical-importance-weighted estimates or parent-domain rankings.

Ethics

Ethics Committee Approval: This study is a document-based comparative analysis of publicly available clinical practice guidelines. No human participants, patient data, medical records, biological samples, or identifiable information were involved. Therefore, according to institutional and international research ethics principles, ethics committee approval and informed consent were not required for this study.

Informed Consent: The study was conducted using publicly accessible guideline documents only and did not involve any intervention or interaction with human subjects.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.K., F.B., Concept: F.B., Design: Y.K., F.B., Data Collection or Processing: Y.K., F.B., Analysis or Interpretation: Y.K., Literature Search: F.B., Writing: Y.K.

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Supplementary Table S1 Link: <https://d2v96fxpocvxx.cloudfront.net/bda9171a-fae8-4995-8276-2138323f1e16/content-images/763454a7-af35-4896-a70f-ab9a65821fc9.pdf>

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Beyond Clinical Staging: The Combined Value of mpMRI Lesion Size and Cancer-positive Biopsy Core Rate in Predicting $\geq$ pT3 Disease

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Abstract

Objective: To investigate preoperative clinical, biopsy-related, and multiparametric magnetic resonance imaging (mpMRI)-derived factors associated with pathological stage $\geq$ pT3 after radical prostatectomy and to evaluate the discriminatory performance of significant predictors individually and in combination.

Materials and Methods: Data prospectively collected from 102 patients who underwent pre-biopsy mpMRI, transrectal ultrasound-guided prostate biopsy, and subsequent radical prostatectomy were analyzed retrospectively. Patients with radiologically detected lymph node involvement or distant metastasis were excluded. Patients were classified as having $<$ pT3 or $\geq$ pT3 disease according to final pathological findings, and preoperative clinical, biopsy-related, and mpMRI-derived parameters were compared between the two groups. Multivariable binary logistic regression was performed to identify independent predictors of $\geq$ pT3 disease. Receiver operating characteristic (ROC) curve analyses were used to evaluate the discriminatory performance of the identified predictors and derive cohort-specific thresholds.

Results: Pathological stage $\geq$ pT3 was identified in 49 patients (48.0%). Patients with $\geq$ pT3 disease had a higher cancer-positive biopsy core rate (52.28 $\pm$ 28.21% vs. 32.57 $\pm$ 17.76%; $p<0.001$) and larger MRI index lesions (median, 20.0 vs. 12.0 mm; $p<0.001$). Both variables remained independently associated with $\geq$ pT3 disease [odds ratio (OR) per 1% increase: 1.033, 95% confidence interval (CI): 1.009-1.057; $p=0.010$; OR per 1-mm increase: 1.274, 95% CI: 1.074-1.511; $p=0.005$]. The area under the curve (AUC) was 0.795 for lesion diameter, 0.703 for cancer-positive core rate, and 0.843 for the combined model. After bootstrap internal validation of the two-variable model, the optimism-corrected AUC was 0.835. ROC-derived thresholds were 17 mm and 38%, respectively. The prevalence of $\geq$ pT3 disease increased from 21.6% with neither risk factor to 47.6% with one and 91.3% with both factors (p for trend <0.001).

Conclusion: MRI index lesion diameter and the cancer-positive biopsy core rate were associated with pathological stage $\geq$ pT3. Their combined assessment may contribute to preoperative risk stratification, although external validation is required.

Keywords: Biopsy, multiparametric magnetic resonance imaging, prostate cancer, stage, tumor volume

Introduction

Prostate cancer is one of the most frequently diagnosed malignancies among men worldwide and represents a major cause of cancer-related morbidity and mortality (1). The initial diagnostic assessment is traditionally based on serum prostate-specific antigen (PSA) measurement and digital rectal examination, followed by histopathological confirmation

through prostate biopsy. In recent years, multiparametric magnetic resonance imaging (mpMRI) has become an integral component of the diagnostic pathway, improving lesion localization, guiding targeted biopsy, and contributing to risk stratification and local staging (2).

Radical prostatectomy remains one of the principal curative treatment options for patients with clinically localized prostate cancer (3). In appropriately selected patients with high-risk or

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locally advanced disease, surgery may also be performed as part of a multimodal treatment strategy that includes radiotherapy and/or systemic therapy (4). More recently, the potential role of radical prostatectomy has also been investigated in carefully selected patients with oligometastatic disease as a component of intensified multimodal management, although patient selection and the oncological benefit of this approach remain under evaluation (5).

Accurate preoperative identification of non-organ-confined disease is essential for patient counselling, surgical planning, decisions regarding nerve-sparing procedures and pelvic lymph-node dissection, and anticipation of additional postoperative treatment (4). Nevertheless, patients considered to have clinically localized disease before surgery may be found to have extraprostatic extension, seminal vesicle invasion, or pathological stage $\geq$ pT3 following radical prostatectomy. Although rectal examination, clinical stage, biopsy grade, PSA-based parameters, and mpMRI findings provide valuable staging information, no single preoperative assessment method can reliably identify all patients with occult $\geq$ pT3 disease (6).

The present study aimed to identify preoperative clinical, biopsy, and mpMRI-derived factors associated with pathological stage $\geq$ pT3 following radical prostatectomy, with particular emphasis on MRI index lesion diameter and the cancer-positive biopsy core rate. We also evaluated the discriminatory performance of these parameters individually and in combination for predicting $\geq$ pT3 disease.

Materials and Methods

Following approval by the University of Health Sciences Türkiye, Izmir City Hospital, Ethics Committee (decision no: 2024/234, date: 04.12.2024), data that had been prospectively collected from a cohort of patients who underwent preoperative imaging followed by radical prostatectomy were retrospectively reviewed. The analysis was designed to investigate the associations of clinical and mpMRI-derived parameters with final pathological T stage. A total of 102 patients were included. Eligible patients had prostate volume measured by transrectal ultrasound, underwent mpMRI before transrectal ultrasound-guided prostate biopsy, had PI-RADS scores and MRI-derived data available on lesion number and index lesion diameter, were diagnosed with prostate cancer on biopsy, and subsequently underwent radical prostatectomy. Patients with radiologically detected lymph node involvement or distant metastasis on preoperative imaging were excluded.

Patients were categorized into two groups according to the final pathological T stage reported after radical prostatectomy: those with organ-confined disease ($<$ pT3) and those with locally advanced disease ($\geq$ pT3). Demographic, clinical, biopsy-related, and mpMRI-derived characteristics were compared between the groups. The evaluated variables included age, preoperative serum PSA level, clinical T stage, biopsy ISUP grade group, cancer-positive biopsy core rate, PI-RADS category, number of MRI-detected lesions, MRI index lesion diameter, and lesion density. The cancer-positive biopsy core rate was calculated by dividing the number of cancer-positive biopsy cores by the total

number of biopsy cores obtained. Lesion density was calculated as the MRI index lesion diameter (mm) divided by the prostate volume measured by transrectal ultrasonography (mL).

Statistical Analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms. Normally distributed continuous variables were presented as mean $\pm$ standard deviation and compared using the independent-samples Student's t-test. Non-normally distributed variables were presented as medians and interquartile ranges (IQR) and were compared using the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages and compared using the chi-square test or the Fisher-Freeman-Halton exact test, as appropriate.

A multivariable binary logistic regression analysis was performed to identify independent preoperative predictors of pathological stage $\geq$ pT3. Clinical T stage, ISUP grade group on biopsy, rate of cancer-positive biopsy cores, PI-RADS category, and MRI index lesion diameter were entered into the regression model. Results were reported as odds ratios (ORs) with 95% confidence intervals (CI). Because MRI index lesion diameter had already been incorporated into the multivariable model, lesion density was not included to avoid redundancy and potential multicollinearity.

Receiver operating characteristic (ROC) curve analyses were performed to evaluate the discriminatory ability of MRI index lesion diameter and the cancer-positive biopsy core rate for predicting pathological stage $\geq$ pT3. The area under the curve and the corresponding 95% CIs were calculated. The optimal threshold for the diameter of the MRI index lesion was determined using the maximum Youden index, whereas the threshold for the cancer-positive biopsy core rate was selected as the ROC coordinate that minimizes the absolute difference between sensitivity and specificity.

A separate binary logistic regression model with two predictors, MRI index lesion diameter and cancer-positive biopsy core rate was constructed for prediction, and its predicted probabilities were used for ROC analysis. Predicted probabilities derived from the logistic regression model incorporating both parameters were subsequently used to assess the discriminatory performance of the combined model. Internal validation of the two-variable model incorporating MRI index lesion diameter and the cancer-positive biopsy core rate was performed using bootstrap resampling. For each bootstrap sample, the model was refitted and its discriminatory performance was evaluated both in the bootstrap sample and in the original cohort. Optimism was calculated as the difference between these two AUC estimates, and the mean optimism across bootstrap samples was subtracted from the apparent AUC to obtain the optimism-corrected AUC.

For clinical risk stratification, two tumor-burden risk factors were defined: MRI index lesion diameter ≥ 17 mm and cancer-positive biopsy core rate $\geq 38\%$. Patients were classified as having zero, one, or two risk factors, and the prevalence of $\geq$ pT3 disease was compared across these categories. The association between increasing risk-factor count and $\geq$ pT3 disease was evaluated

using the chi-square test and a test for linear trend. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 102 patients were included in the study. Age and preoperative PSA data were available for 100 patients. The mean age was 66.6 ± 5.6 years, and the median preoperative PSA level was 9.39 ng/mL (IQR: 6.40 - 15.32). The median number of lesions detected on MRI was 1.5 (IQR: 1 - 2); the median index lesion diameter was 13 mm (IQR: 10 - 20); and the median cancer-positive biopsy core rate was 37.98% (IQR: 23.08 - 53.85). Biopsy ISUP grade groups 1, 2, 3, 4, and 5 were identified in 41 (40.2%), 31 (30.4%), 13 (12.7%), 12 (11.8%), and 5 (4.9%) patients, respectively. On pathological examination of radical prostatectomy specimens, ISUP grade groups 1, 2, 3, 4, and 5 were observed in 20 (19.6%), 54 (52.9%), 17 (16.7%), 4 (3.9%), and 7 (6.9%) patients, respectively. The clinical stages were cT1c in 57 (55.9%), cT2a in 13 (12.7%), cT2b in 23 (22.5%), and cT2c in 9 (8.8%) patients. Final pathological staging after radical prostatectomy revealed pT2a in 16 patients (15.7%), pT2b in 1 patient (1.0%), pT2c in 36 patients (35.3%), pT3a in 26 patients (25.5%), and pT3b in 23 patients (22.6%). Final pathological examination demonstrated $< pT3$ disease in 53 patients (52.0%) and $\geq pT3$ disease in 49 patients (48.0%).

Patients were stratified according to final pathological stage as $< pT3$ ($n=53$) and $\geq pT3$ ($n=49$). Age and preoperative PSA levels were comparable between the groups (67.19 ± 4.63 vs.

65.97 ± 6.48 years, $p=0.282$; and 8.60 (IQR: 5.60 - 14.90) vs. 9.74 (IQR: 6.72 - 17.52) ng/mL, $p=0.180$, respectively). Clinical stage distribution differed significantly between the groups ($p<0.001$); cT1c disease was more frequent in the $< pT3$ group, whereas cT2b and cT2c disease were more common among patients with $\geq pT3$ pathology. Biopsy ISUP grade group distribution was also significantly different ($p=0.022$), with higher-grade disease occurring more frequently in the $\geq pT3$ group. The cancer-positive biopsy core rate was significantly higher in patients with $\geq pT3$ disease than in those with $< pT3$ disease ($52.28 \pm 28.21\%$ vs. $32.57 \pm 17.76\%$, $p<0.001$). Similarly, PI-RADS category distribution differed significantly between the groups ($p<0.001$), with PI-RADS 5 lesions being more prevalent in the $\geq pT3$ group. Although the number of MRI-detected lesions was similar between the groups [median 1.00 (IQR: 1.00 - 2.00) vs. 2.00 (IQR: 1.00 - 2.00), ($p=0.459$), both index lesion diameter and lesion density were significantly higher in patients with $\geq pT3$ disease [20.00 (IQR: 12.50 - 29.00) vs. 12.00 (IQR: 9.00 - 13.75) mm, $p<0.001$; and 0.44 (IQR: 0.28 - 0.68) vs. 0.22 (IQR: 0.13 - 0.22), $p<0.001$, respectively]. These findings are summarized in Table 1.

In the multivariable binary logistic regression analysis, the percentage of tumor involvement in biopsy specimens and index lesion diameter on MRI were independently associated with pathological stage $\geq pT3$. Each 1-percentage-point increase in biopsy tumor involvement was associated with a 3.3% increase in the odds of $\geq pT3$ disease (OR: 1.033 , 95% CI: 1.009 - 1.057 ; $p=0.010$). Similarly, each 1-mm increase in index lesion diameter on MRI was associated with a 27.4% increase

Table 1. Comparison of demographic, clinical, biopsy, and magnetic resonance imaging characteristics between patients with pathological stage $< pT3$ and $\geq pT3$ disease

		$< pT3$ (n=53)	$\geq pT3$ (n=49)	p-value
Age, years		67.19 ± 4.63	65.97 ± 6.48	0.282 ^A
Preoperative PSA, ng/mL median (IQR)		8.60 (5.60-14.90)	9.74 (6.72-17.52)	0.180 ^C
Clinical T stage	T1C	41 (77.40%)	16 (32.70%)	<0.001 ^B
	T2A	5 (9.40%)	8 (16.30%)	
	T2B	5 (9.40%)	18 (36.70%)	
	T2C	2 (3.80%)	7 (14.30%)	
Biopsy ISUP grade group	ISUP 1	27 (50.90%)	14 (28.60%)	0.022 ^B
	ISUP 2	17 (32.10%)	14 (28.60%)	
	ISUP 3	5 (9.40%)	8 (16.30%)	
	ISUP 4	4 (7.50%)	8 (16.30%)	
	ISUP 5	0 (0.00%)	5 (10.20%)	
Cancer-positive biopsy core rate, %		32.57 ± 17.76	52.28 ± 28.21	<0.001 ^A
PI-RADS category	2	0 (0.00%)	1 (2.04%)	<0.001 ^A
	3	8 (15.10%)	5 (10.20%)	
	4	36 (67.90%)	16 (32.65%)	
	5	9 (17.00%)	27 (55.11%)	
Number of MRI-detected lesions median (IQR)		2.00 (1.00-2.00)	1.00 (1.00-2.00)	0.459 ^C
MRI index lesion diameter, mm median (IQR)		12.00 (9.00-13.75)	20.00 (12.50-29.00)	<0.001 ^C
Lesion density, mm/mL median (IQR)		0.22 (0.13-0.22)	0.44 (0.28-0.68)	<0.001 ^C

IQR: Interquartile range, MRI: Magnetic resonance imaging, PSA: Prostate-specific antigen, ^C: Mann-Whitney U test, ^A: Student's t-test, ^C: Chi-square test, ^B: Fisher-Freeman-Halton exact test

in the odds of $\geq$ pT3 disease (OR: 1.274, 95% CI: 1.074-1.511; $p=0.005$). Clinical stage, biopsy ISUP grade group, and PI-RADS category were not independently associated with $\geq$ pT3 disease in the multivariable model (all $p>0.05$). Lesion density was not included in the multivariable analysis to avoid redundancy and potential multicollinearity, as MRI index lesion diameter had already been incorporated into the model. However, the markedly large standard errors observed for some ISUP grade groups and PI-RADS categories indicated sparse data and possible quasi-complete separation; therefore, the estimates for these categorical variables should be interpreted cautiously.

ROC curve analysis demonstrated that index lesion diameter on MRI had good discriminatory ability for predicting pathological stage $\geq$ pT3, with an area under the curve of 0.795 (95% CI: 0.703-0.886; $p<0.001$) (Figure 1). Based on the maximum Youden index, the optimal cut-off value was 16.5 mm, corresponding to a sensitivity of 65.3% and a specificity of 86.5%. Accordingly, an index lesion diameter of ≥ 17 mm on MRI may be considered a clinically practical threshold for identifying patients at increased risk of $\geq$ pT3 disease.

ROC curve analysis demonstrated that the proportion of cancer-positive biopsy cores had an acceptable discriminatory ability for predicting pathological stage $\geq$ pT3, with an area under the curve of 0.703 (95% CI: 0.601-0.804; $p<0.001$) (Figure 2). The ROC coordinate at which the absolute difference between sensitivity and specificity was minimized corresponded to a cut-off of 38%. At this threshold, sensitivity was 65.3% and specificity was 64.2%. Accordingly, patients with cancer involvement in $\geq 38\%$ of the sampled biopsy cores were considered to have an increased risk of pathological stage $\geq$ pT3.

A combined predictive model incorporating MRI index lesion diameter and the cancer-positive biopsy core rate demonstrated good discriminatory performance for predicting pathological

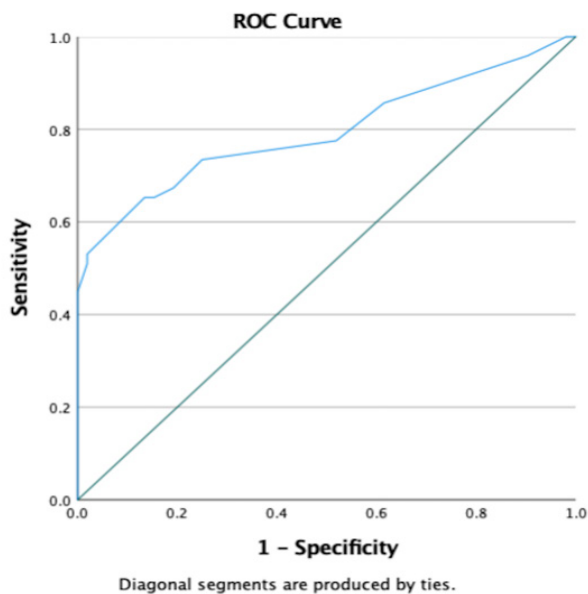


Figure 1. ROC curve of MRI index lesion diameter for predicting pathological stage $\geq$ pT3

ROC: Receiver operating characteristic, MRI: Magnetic resonance imaging

stage $\geq$ pT3, with an area under the curve of 0.843 (95% CI: 0.763-0.922; $p<0.001$) (Figure 3). The discriminatory performance of the combined model was numerically higher than that of MRI index lesion diameter alone (AUC: 0.795) and that of the cancer-positive biopsy core rate alone (AUC: 0.703), suggesting that these two tumor-burden parameters may provide complementary predictive information. Internal validation of the two-variable model using 1,000 bootstrap resamples yielded a mean optimism of 0.007, resulting in an optimism-corrected AUC of 0.835. These findings indicate that the discriminatory performance of the combined model was largely preserved after correction for optimism.

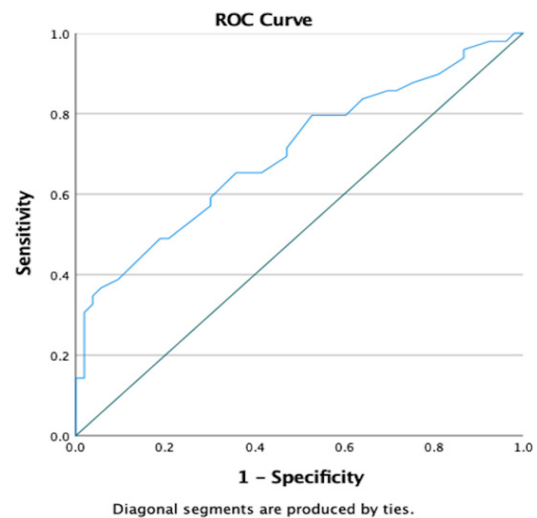


Figure 2. ROC curve of the cancer-positive biopsy core rate for predicting pathological stage $\geq$ pT3

ROC: Receiver operating characteristic

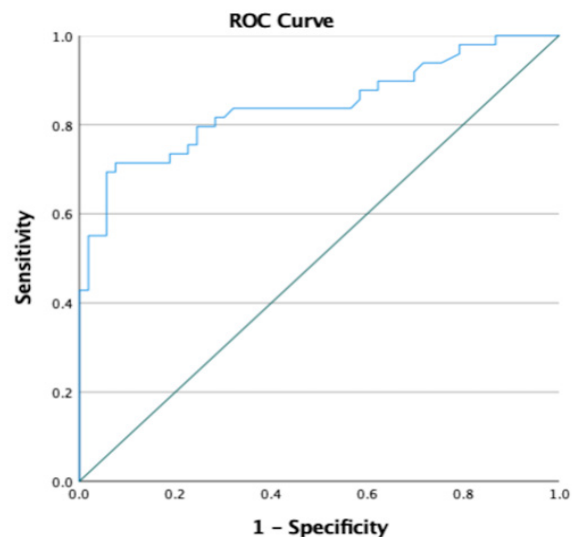


Figure 3. ROC curve of the combined model incorporating MRI index lesion diameter and the cancer-positive biopsy core rate for predicting pathological stage $\geq$ pT3

ROC: Receiver operating characteristic, MRI: Magnetic resonance imaging

When patients were stratified according to the number of tumor-burden risk factors—MRI index lesion diameter ≥ 17 mm and cancer-positive biopsy core rate $\geq 38\%$ —the prevalence of pathological stage $\geq$ pT3 increased progressively from 21.6% (8/37) among patients with no risk factors to 47.6% (20/42) among those with one risk factor and 91.3% (21/23) among those with both risk factors. The association between the number of risk factors and $\geq$ pT3 disease was statistically significant with a significant linear trend across the three risk categories ($p < 0.001$) (Table 2).

Discussion

The principal finding of the present study was that MRI index lesion diameter and the cancer-positive biopsy core rate were independently associated with pathological stage $\geq$ pT3 after radical prostatectomy. Each 1-mm increase in index lesion diameter was associated with a 27.4% increase in the odds of $\geq$ pT3 disease, whereas each 1-percentage-point increase in the cancer-positive biopsy core rate was associated with a 3.3% increase in the odds. More importantly, the model incorporating both parameters provided better discrimination than either parameter alone, reaching an AUC of 0.843. The prevalence of $\geq$ pT3 disease also increased progressively from 21.6% in patients with neither risk factor to 47.6% in those with one risk factor and 91.3% in those with both risk factors. These findings suggest that radiological and biopsy-based measures of tumor burden may provide complementary information for preoperative identification of non-organ-confined disease.

Previous studies have shown that integrating clinicopathological parameters with mpMRI findings improves the detection and risk stratification of clinically significant prostate cancer compared with either approach alone (7). Nevertheless, accurate identification of extraprostatic disease before surgery remains challenging. In the present study, clinical T stage, biopsy ISUP grade group, and PI-RADS category differed significantly between patients with $<$ pT3 and $\geq$ pT3 disease. In particular, cT2b–cT2c disease, higher biopsy grade groups, and PI-RADS 5 lesions were more frequent among patients with $\geq$ pT3 pathology. However, these categorical variables did not retain statistical significance in the multivariable model. This finding should not be interpreted as indicating that clinical stage, grade group, or PI-RADS category is clinically unimportant. Rather, their predictive information may partially overlap with the quantitative tumor-burden parameters included in the model. For example, lesion size contributes to PI-RADS categorization, and higher-volume tumors are more likely to be associated with extensive biopsy involvement. Moreover, the small number of patients in certain ISUP and PI-RADS categories resulted in large standard errors and possible quasi-complete separation, thereby limiting the reliability of their adjusted estimates.

Previous evidence indicates that models integrating MRI with clinicopathological variables generally provide better staging performance than the use of individual variables alone, although their accuracy remains imperfect (8).

MRI index lesion diameter was the strongest individual discriminator in our analysis, with an AUC of 0.795. The ≥ 17 -mm threshold demonstrated relatively high specificity of 86.5%, although its sensitivity was moderate at 65.3%. This pattern suggests that a lesion diameter above this threshold may identify a subgroup with a high probability of locally advanced pathology, whereas a lesion below this threshold cannot reliably exclude microscopic extraprostatic extension. Previous studies have similarly reported associations between MRI-derived tumor size or volume and adverse pathological features (9,10). Sugano et al. (11) showed that MRI-derived index tumor volume independently predicted extraprostatic extension, lymph-node invasion, and seminal vesicle invasion. Danacioglu et al. (12) also found that lesions larger than 10 mm were independently associated with extraprostatic extension and positive surgical margins. Our findings are further supported by Baboudjian et al. (13), who reported that a maximum lesion diameter of ≥ 15 mm on mpMRI was associated with a significantly higher rate of pathological upstaging to $\geq$ pT3a compared with lesions < 15 mm (46.5% vs. 35.0%; $p = 0.006$). In their multivariable analysis, a lesion diameter of ≥ 15 mm was also independently associated with adverse pathology, defined as a composite of $\geq$ pT3a disease, lymph node involvement, and/or ISUP grade group ≥ 3 (OR: 1.65, 95% CI: 1.14–2.39; $p = 0.01$). These findings are consistent with our observation that increasing MRI index lesion diameter is associated with a greater likelihood of pathological stage $\geq$ pT3. However, because pathological T stage was not evaluated as an isolated outcome in their adjusted model, direct comparison of the independent predictive estimates should be made cautiously (13). A meta-analysis evaluating quantitative mpMRI parameters reported pooled sensitivity and specificity values of 62% and 75%, respectively, for tumor size in predicting extraprostatic extension and emphasized that optimal thresholds varied considerably among studies (10). The 17-mm threshold observed in our cohort should therefore be considered a cohort-specific risk threshold rather than a universally applicable anatomical boundary.

The cancer-positive biopsy core rate was also independently associated with $\geq$ pT3 disease, although its individual discriminatory performance was more modest than that of MRI index lesion diameter. This variable provides an easily obtainable estimate of the extent of cancer detected across the sampled prostate rather than the percentage of tumor involvement within an individual core. Previous studies have consistently demonstrated that the proportion of cancer-positive cores is associated with pathological stage, tumor volume, seminal vesicle invasion, lymph-node involvement, and other adverse

Table 2. Distribution of pathological stage $\geq$ pT3 according to the number of tumor-burden risk factors

Number of risk factors	$<$ pT3, n	$\geq$ pT3, n	Prevalence of $\geq$ pT3, %	p-value
0	29	8	21.6%	< 0.001
1	22	20	47.6%	
2	2	21	91.3%	

pathological outcomes. Winkler et al. (14) reported that the percentage of positive biopsy cores improved the prediction of pathological stage, while Valette et al. (15) demonstrated a progressive increase in extraprostatic disease with each 10% increase in the positive-core category. These observations are consistent with our finding that the cancer-positive biopsy core rate remained independently associated with $\geq$ pT3 disease after adjustment for imaging and clinical variables.

A threshold of 38% for the cancer-positive biopsy core rate yielded a sensitivity of 65.3% and a specificity of 64.2%. This value was selected as a clinically balanced threshold rather than as the threshold producing the absolute maximum Youden index, and therefore should not be interpreted as a definitive biological cut-off. Previous studies have proposed varying thresholds for biopsy core positivity. A core positivity rate of 76% was reported to predict extraprostatic extension with a sensitivity of 65% and a specificity of 87.1%, while a dominant-side positive core rate of $\geq 55\%$ was found to provide useful discrimination for non-organ-confined disease (16,17). In a multicenter study of 698 patients with biopsy ISUP grade group 2 disease, Baboudjian et al. (13) found that a positive-core rate of $\geq 25\%$ was associated with pathological upstaging in univariable analysis, with $\geq$ pT3a disease occurring in 41.4% versus 30.5% among patients with lower cancer-positive biopsy core rates ($p=0.006$). However, the cancer-positive biopsy core rate was not independently associated with the composite endpoint of adverse pathology after multivariable adjustment (OR: 1.08, 95% CI: 0.76-1.52; $p=0.7$) (13). These variations likely reflect differences in patient selection, biopsy protocols, pathological endpoints, and methods used for threshold determination. In this context, the 38% threshold identified in our cohort provides a sensitivity-specificity-balanced estimate specifically for $\geq$ pT3 disease and may be particularly useful when combined with MRI index lesion diameter. Nevertheless, the positive-core rate may be affected by the total number of cores obtained, the distribution between systematic and targeted sampling, the lesion location, and the biopsy technique. Its routine availability, simple calculation, and absence of additional cost support its potential role in preoperative risk assessment, although external validation of the proposed threshold is required.

The most clinically relevant aspect of this study was the improvement observed when MRI index lesion diameter and the rate of cancer-positive biopsy cores were combined. The AUC of the combined model was numerically higher than the AUCs of MRI index lesion diameter alone and the cancer-positive biopsy core rate alone. Similarly, Ahmed et al. (18) reported that a model combining mpMRI-derived index lesion size and capsular contact length with biopsy-based tumor-burden parameters provided good discrimination for side-specific extracapsular extension, with an internally validated AUC of 0.83. This supports the concept that these variables represent related but non-identical dimensions of tumor burden: MRI lesion diameter reflects the radiologically visible dominant tumor focus, whereas the rate of cancer-positive biopsy cores reflects the distribution and extent of cancer captured histologically across biopsy specimens. The marked stepwise increase in $\geq$ pT3 prevalence according to the number of risk factors further supports their complementary value. The discrimination of the combined model also compares

favorably with the pooled AUC of approximately 0.80 reported for validated MRI-inclusive models predicting extraprostatic extension. However, a formal paired comparison of the ROC curves was not performed. Therefore, the statistical superiority of the combined model over either individual parameter cannot be claimed. Importantly, the proposed thresholds of 17 mm for MRI index lesion diameter and 38% for the cancer-positive biopsy core rate were derived from the present cohort and should therefore be considered cohort-specific, rather than universally applicable, cut-off values. Before these thresholds can be incorporated into routine clinical decision-making, their reproducibility and clinical utility should be confirmed in larger, independent, preferably multicenter cohorts.

The performance of our combined model should also be considered in the context of established preoperative nomograms. Traditional tools such as the Partin tables and the Memorial Sloan Kettering Cancer Center nomogram, as well as more recent MRI-inclusive models, integrate multiple clinicopathological variables to estimate the probability of extraprostatic disease. For contextual reference, a recent meta-analysis reported AUCs ranging from approximately 0.72 to 0.80 for validated traditional and MRI-inclusive models predicting extraprostatic extension (8). Similarly, Martini et al. (19) developed an mpMRI-based side-specific nomogram incorporating PSA, biopsy grade, core involvement, and MRI findings and reported an internally validated AUC of 0.82 for extracapsular extension. In the present study, bootstrap internal validation of the two-variable model yielded an optimism-corrected AUC of 0.835, indicating that its discriminatory performance was largely preserved. Nevertheless, this value should not be interpreted as evidence of equivalent or superior performance compared with established nomograms because the respective models differ in patient populations, predictors, pathological endpoints, and validation strategies, and were not evaluated within the same cohort. Accordingly, MRI index lesion diameter and the cancer-positive biopsy core rate should be regarded as potentially complementary parameters rather than replacements for established prediction tools. Direct head-to-head comparison and assessment of their incremental predictive value within validated nomograms will require larger independent cohorts and appropriate external validation.

Another notable finding was that lesion density was significantly higher in patients with $\geq$ pT3 disease. In the present study, lesion density was calculated as the MRI index lesion diameter divided by prostate volume measured by transrectal ultrasonography, thereby expressing lesion size relative to overall gland size. This approach may better reflect the proportional radiological tumor burden than absolute lesion diameter alone. Emerging studies have similarly evaluated lesion-size-to-prostate-volume parameters and reported associations with clinically significant prostate cancer detection (20). Nevertheless, lesion density has not been uniformly defined in the literature, as some studies use lesion length relative to prostate volume, whereas others use lesion volume divided by prostate volume (20,21). Because the lesion-density variable in our study shared its numerator with the index lesion diameter, it was not included in the multivariable model to avoid redundancy and potential multicollinearity. Its association with $\geq$ pT3 disease should therefore be considered exploratory and requires validation in studies specifically

designed to compare absolute and prostate-adjusted lesion measurements.

From a clinical perspective, improved recognition of occult $\geq$ pT3 disease may contribute to more realistic preoperative counselling and surgical planning. Patients with both an MRI index lesion diameter ≥ 17 mm and a cancer-positive core rate $\geq 38\%$ had a particularly high prevalence of $\geq$ pT3 pathology. Awareness of this risk may influence discussions concerning the likelihood of non-organ-confined disease, the feasibility and extent of nerve-sparing, resection margins, lymph-node assessment, and the possible need for postoperative multimodal management. Nevertheless, the proposed parameters should complement rather than replace established clinical nomograms, direct MRI signs of extraprostatic extension, pathological grade, PSA-based measures, or multidisciplinary assessment. Current guidelines support radical prostatectomy in selected cN0 patients with locally advanced disease as part of a multimodal strategy, further emphasizing the importance of accurately characterizing local disease extent before surgery (22).

Study Limitations

This study has several limitations. Its single-center design and relatively small sample size may limit generalizability, while sparse data in some clinical-stage, PI-RADS, and ISUP grade-group categories may have resulted in unstable regression estimates. The proposed cut-off values and combined model were developed and evaluated in the same cohort without external validation, and should therefore be considered cohort-specific. The proposed model was not directly compared with established clinical or MRI-inclusive nomograms within the same cohort. Interobserver variability in mpMRI interpretation and lesion measurement was not assessed. In addition, lesion density, which was calculated using MRI-derived lesion diameter and TRUS-measured prostate volume, was excluded from multivariable analysis because of its close relationship with lesion diameter. The cancer-positive biopsy core rate may also be influenced by biopsy technique and the number of systematic and targeted cores obtained. Only patients undergoing radical prostatectomy were included, and long-term oncological outcomes were not evaluated. Larger multicenter studies are needed to validate these findings.

Conclusion

MRI index lesion diameter and the cancer-positive biopsy core rate were associated with pathological stage $\geq$ pT3 after radical prostatectomy. The combined evaluation of these parameters showed a numerically higher discriminatory performance than either parameter alone, while the prevalence of $\geq$ pT3 disease increased with the number of risk factors present. These findings suggest that radiological and biopsy-derived parameters may contribute to preoperative risk assessment; however, validation in larger multicenter cohorts is needed.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, İzmir City Hospital Ethics Committee (decision no: 2024/234, date: 04.12.2024).

Informed Consent: Data that had been prospectively collected from a cohort of patients who underwent preoperative imaging followed by radical prostatectomy were retrospectively reviewed.

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Footnotes

Authorship Contributions

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Cardiac Metastasis of Medullary Phenotype Unclassified Renal Cell Carcinoma: A Case Report

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Abstract

Renal medullary carcinoma is an uncommon and aggressive variant of renal cell carcinoma (RCC), accounting for less than 0.5% of all RCC cases. It predominantly affects young individuals with sickle cell hemoglobinopathies. However, as seen in this case, unclassified medullary phenotypic RCC without hemoglobinopathy can also occur. This case report discusses a patient diagnosed with unclassified RCC of the medullary phenotype, exhibiting metastases to the left ventricle and liver. Diagnosis was confirmed through percutaneous biopsy, revealing loss of SMARCB1 expression along with positive vimentin and OCT3/4 staining. Treatment included chemotherapy with carboplatin and paclitaxel, followed by second-line therapy with cabozantinib. Left ventricular metastasis and cardiac lesions are rare but poor prognostic features of RCC. This case, one of the few documented in the literature, underscores the importance of a multidisciplinary approach to diagnosis and treatment.

Keywords: Medullary carcinoma, cardiac metastasis, medullary phenotype unclassified renal cell carcinoma, case report

Introduction

Renal cell carcinoma (RCC) represents the most common type of primary kidney cancer, accounting for approximately 80-85% of all renal neoplasms. The incidence is 4-7 per 100,000 individuals. Approximately 25-30% of people exhibit metastatic illness upon diagnosis, with the majority of instances being incidentally identified (1).

Renal medullary carcinoma (RMC) is an extremely rare and severe variant, comprising less than 0.5% of RCCs. It predominantly impacts young people with sickle cell hemoglobinopathies (2). Tumors that resemble RMC but arise in the absence of hemoglobinopathy have historically been classified as unclassified RCC with a medullary phenotype (3). Metastases from these tumors predominantly affect the lungs, liver, and lymph nodes, although cardiac metastases are exceptionally rare, with only a limited number of cases documented (4). This case report describes a patient diagnosed with unclassified RCC of the medullary phenotype, with metastases to the liver and left ventricle.

Case Report

A 26-year-old male presented to the emergency department with a 17-kg weight loss over the past several months, accompanied by fever, night sweats, tachycardia, nausea, and vomiting in the preceding month. His medical history included cleft lip repair and schizoaffective disorder. The physical examination showed no costovertebral angle tenderness or palpable abdominal mass. In contrast to the majority of RMC cases linked to sickle cell trait (5), our patient revealed no hemoglobinopathy. Transthoracic echocardiography identified a pericardial effusion and a solid-cystic mass measuring 7×3.5×8.5 cm on the left ventricular wall. Cardiac magnetic resonance imaging revealed a malignant lesion consistent with metastasis (Figure 1). Contrast-enhanced abdominal computed tomography (CT) revealed a heterogeneous tumor in the left kidney measuring 7.8×6.2×6.2 cm (Figure 2), as well as metastatic lesions in the liver (Figure 3) and retroperitoneal lymphadenopathy. The percutaneous tru-cut biopsy of the renal tumor confirmed a diagnosis of undifferentiated RCC with a medullary phenotype.

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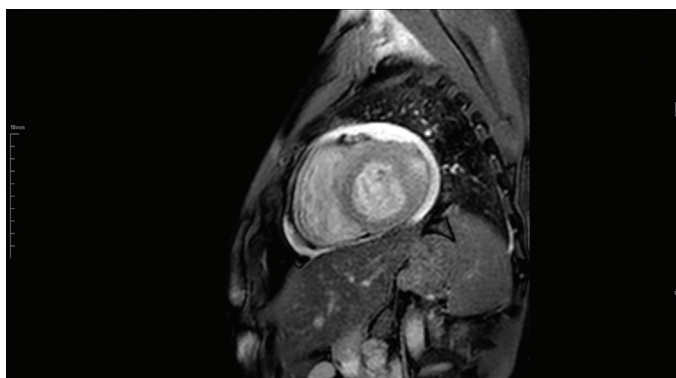


Figure 1. Metastatic lesion in the left ventricular wall on T1-weighted image in cardiac contrast-enhanced magnetic resonance imaging



Figure 2. Contrast-enhanced abdominal computed tomography showing the left renal tumor

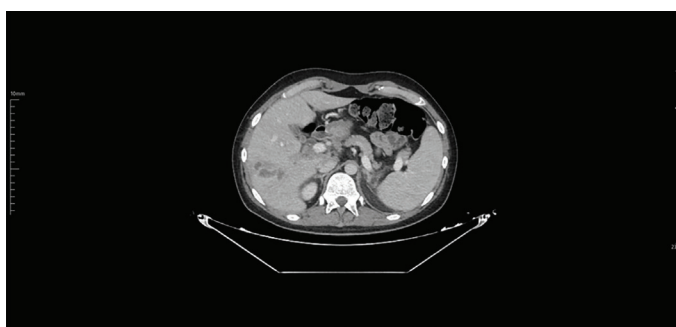


Figure 3. Contrast-enhanced abdominal computed tomography showing metastatic liver lesions

Histopathological analysis demonstrated nuclear SMARCB1 (INI1) expression and positive immunostaining for vimentin and OCT3/4. Karyotype analysis was advised for the patient. Molecular analysis indicated the absence of an *SMARCB1* gene mutation. Tissue-based karyotype analysis could not be conducted due to technical limitations. For advanced staging, the patient underwent fluorodeoxyglucose (FDG) PET imaging, which revealed that the primary renal mass had metastasized to the liver, abdominal lymph nodes, and heart. According to the IMDC risk assessment, the patient would benefit from cytoreductive nephrectomy to reduce tumor burden before systemic therapy; however, the patient declined the procedure. Following a medical oncology consultation,

chemotherapy with carboplatin and paclitaxel was commenced. The patient underwent four cycles of carboplatin-paclitaxel treatment. After completion of chemotherapy, an 18F-FDG PET/CT restaging scan was performed, revealing extensive progressive disease with a mixed metabolic response. Subsequently, cabozantinib monotherapy was commenced as a second-line treatment. While undergoing cabozantinib treatment, the patient presented with a necrotic lesion on the right foot, necessitating a tru-cut biopsy. Histopathological assessment indicated metastatic disease. The immunohistochemical examination of the biopsy samples revealed PD-L1 expression, resulting in cessation of the current treatment. The patient then commenced third-line therapy with nivolumab. A restaging imaging evaluation was scheduled following the third cycle. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Discussion

RMC is an uncommon but highly malignant tumor. The majority of patients present at an advanced stage with extensive metastatic disease. This case is remarkable because of the absence of an underlying hemoglobinopathy, despite most cases being linked to sickle cell hemoglobinopathy. RMC has been observed more commonly in males, predominantly originates from the right kidney (2). The presence of left renal involvement alongside a cardiac metastasis in the left ventricle is a rare, although clinically important, observation reported in the literature.

The diagnosis of RMC is strongly associated with loss of nuclear SMARCB1 (INI1) expression (6). This feature is also characteristic of SMARCB1/INI1-deficient medullary-like renal cell carcinoma, historically referred to as unclassified RCC with a medullary phenotype (3,6). The absence of SMARCB1 expression, coupled with positivity for OCT3/4 and vimentin, supported medullary differentiation in this patient. The literature indicates a very poor prognosis for RMC, particularly in patients presenting with metastatic disease (7).

Cardiac metastases originating from RCC are extremely uncommon, with left ventricular involvement regarded as extraordinary. RCC may invade the right atrium by direct extension through the inferior vena cava. The occurrence of left ventricular metastases, as observed in this case, may indicate hematogenous or lymphatic spread and is typically associated with poor prognosis (5).

Cahill et al. (5) reviewed RCC with cardiac metastases and highlighted the diagnostic and therapeutic challenges associated with this uncommon presentation. Cardiac metastases may present significant challenges to clinicians in both diagnostic and therapeutic settings.

Cardiac metastases are primarily documented at autopsy, whereas intraventricular involvement in living individuals is exceptionally uncommon. Despite advances in imaging techniques that improve identification of atypical metastatic locations, the literature remains sparse regarding cases of renal medullary cancer with both left-heart involvement and synchronous multiorgan metastases (5).

Davis et al. (4) provided the seminal description linking RMC with sickle cell nephropathy. Subsequent studies have confirmed the strong association between RMC and sickle cell trait while also characterizing its distinctive molecular and immunohistochemical profile (2,6).

Platinum-based chemotherapy remains an important systemic treatment approach for RMC, particularly in metastatic disease (2,7). However, as demonstrated in the current case, clinical responses may be limited. Targeted therapies such as cabozantinib have been used in individual patients, although evidence remains limited for this rare tumor (2).

The role of nephrectomy in RCC remains controversial and needs to be considered in the context of performance status, disease burden, and response to systemic therapy. In the present case, the patient refused surgery, and despite systemic treatment, the development of cardiac and peripheral metastases was noted.

Unclassified RCC with a medullary phenotype constitutes an uncommon and aggressive tumor characterized by significant metastatic potential. Rare metastatic sites, such as cardiac involvement, emphasize the systemic nature and poor prognosis of this condition, underscoring the need for a multidisciplinary approach to diagnosis and treatment. In contrast to the few occurrences documented in the literature, the present case is notable for its involvement of the left heart and for the lack of an underlying hemoglobinopathy. Documenting and molecularly characterizing these cases will be essential for improving understanding and therapeutic approaches to this complex disease.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

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