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Can Invasion of the Vas Deferens be Considered a Prognostic Marker in pT3b Prostate Cancer?

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Abstract

Objective: To assess the impact of vas deferens invasion (VDI) on prognosis, as well as clinical and pathological outcomes in patients with pT3b prostate cancer.

Materials and Methods: Patients reported as pT3b between 2010 and 2020 were included in the study. Patients were divided into two groups: Group 1 (VDI-) and Group 2 (VDI+). Biochemical recurrence-free survival (BCRFS) was compared using the Kaplan-Meier method with the log-rank test. Univariate and multivariate regression models were used to investigate the relationship between VDI and the risk of BCR.

Results: The study included 199 patients with seminal vesicle invasion (SVI) on radical prostatectomy (RP) pathology. VDI was detected in 95 patients (47.7%). No differences was found between the two groups with respect to clinical and perioperative factors, including age, preoperative prostate-specific antigen (PSA), prostate volume, PSA density, biopsy International Society of Urological Pathology (ISUP) grade, clinical N stage, preoperative European Association of Urology risk group, surgery type (open or robotic), nerve-sparing approach, surgical margin status, number of resected lymph nodes (LN), and pathological LN positivity rates. The VDI+ group exhibited higher rates of extraprostatic extension and bilateral SVI, and a more advanced ISUP grade in RP pathology ($p<0.05$). The number of patients who received adjuvant hormone therapy was higher in the VDI+ group. Sixth-week PSA values were higher in the VDI+ group ($p<0.05$). No significant difference in BCRFS was observed (log-rank test; $p=0.127$). In multivariate logistic regression analysis, pN+ and RP ISUP grade were found to be significant predictors of BCR ($p<0.05$).

Conclusion: Although the current study found that patients with VDI had lower BCRFS, the difference was not statistically significant. This condition may result from disparities in adjuvant treatments and other clinicopathological variables. Since the effect of VDI on prognosis in pT3b patients is not known, the results should be interpreted with caution. Patients with T3b prostate cancer may exhibit heterogeneous survival rates. Therefore, the indication of VDI in the pathology report appears to be an important consideration that can guide patient management.

Keywords: Biochemical recurrence, prostate cancer, seminal vesicle, survival, vas deferens

Introduction

Pathologic T stage, pathologic N stage, surgical margin positivity, and Gleason grade in radical prostatectomy (RP) specimens are significant predictors of biochemical recurrence (BCR) following RP (1,2). The presence of seminal vesicle invasion [(SVI); pT3b] is also a significant prognostic factor, and the prognosis differs significantly from that of extraprostatic invasion (pT3a). Even though it is an organ adjacent to the prostate, SVI can also be considered an independent organ invasion. The likelihood of

recurrence and lymph node (LN) invasion is higher in cases with SVI (3). The prognostic significance of seminal vesicle invasion is well established; however, the prognostic implications of vas deferens invasion (VDI), an adjacent structure to the prostate and seminal vesicles, remain unclear. The scarcity of research in this field is likely due to the fact that vas deferens sampling is not routinely recommended (4) and VDI by prostate cancer is a relatively uncommon event (5). Nevertheless, VDI is extremely rare in pT2 and pT3a stages, with most cases occurring in patients with pT3b or pT4 disease (6). The primary pathway

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of SVI is extraprostatic extension (EPE) of prostate carcinoma into the soft tissue adjacent to the ipsilateral seminal vesicle (7). This indicates that invasion of the vas deferens, which is located adjacent to the seminal vesicle, may occur via EPE. However, the histological structures of the seminal vesicle and the vas deferens are quite different; the vas deferens is firmer and more durable, suggesting that invasion of the vas deferens may be more difficult. Therefore, we suspect that tumors infiltrating the vas deferens may exhibit more aggressive features. In this study, we investigated whether VDI affects biochemical recurrence-free survival (BCRFS) in pT3b patients.

Materials and Methods

Patient Population

This study was approved by the Ankara University Human Research Ethics Committee (decision no: İ03-264-24, date: 22.04.2024). After institutional review board approval, the medical records of the patients who had undergone RP at a tertiary referral academic center between 2010 and 2020 and who were reported as pT3b were retrospectively reviewed. Of 1376 patients who had RP, 307 classified as pT3b were assessed for inclusion in the study. Patients with at least twelve core biopsies were included in the study. Patients who received neoadjuvant treatments or had inadequate follow-up data were excluded. Additionally, patients whose VDI status was unreported or inconsistently assessed were excluded from the study. A total of 199 patients with pT3b prostate cancer were included in the study. Patients were categorized into two groups based on the presence or absence of invasion of the VDI. Preoperative staging was performed according to the 8th edition of the tumor-node-metastasis classification. The grade category was assigned according to the 2014 International Society of Urological Pathology (ISUP) grading system. Patients in both groups were classified according to European Association of Urology (EAU) risk groups (low, intermediate, high, and locally advanced) based on their clinical characteristics.

Postoperative prostate-specific antigen (PSA) monitoring begins 6-8 weeks after RP and is performed every three months for the ensuing two years, then every six months. BCR is defined as two consecutive increases in PSA, with the last PSA being ≥ 0.2 ng/mL following RP.

Pathological Analysis

Two expert uropathologists (S.K. and D.E.) at our institute performed the pathological analysis of RP specimens. The RP grossing protocol in our pathology laboratory is as follows: specimens are fixed in 10% neutral buffered formalin overnight and labeled with two colors of ink for anatomical orientation. After fixation, the specimen is weighed and the dimensions of the prostate, seminal vesicles, and bilateral vas deferens are recorded. The apex and base are coned, following the ISUP consensus recommendations. Serial 4 mm sagittal sections, from apex to base, are oriented according to their anatomical positions (right, left, anterior, and posterior) and embedded as whole mounts. As with the prostate, the bilateral seminal vesicles and vas deferens are excised and submitted in their entirety. The surgical margins of the bilateral vas deferens are also submitted separately.

Microscopic evaluation includes sketching the entire specimen and tumor to fully document tumor localization and extent. The reporting of RP specimens is performed in accordance with the College of American Pathologists protocols (version: 4.2.0.0, June 2021). The histological type of the carcinoma, modified Gleason score, ISUP prognostic grade group, tumor volume, EPE, lymphovascular invasion, perineural invasion, seminal vesicle involvement, vas deferens involvement, margin status, and pathological stage are included in the final pathology report.

Statistical Analysis

The Mann-Whitney U test was applied to compare clinicopathological characteristics between groups for continuous variables, and the chi-square test was applied to compare categorical variables between groups. The Kaplan-Meier method and the log-rank test were used to estimate and compare BCRFS between groups. Additionally, univariate and multivariate Cox proportional hazards models were used to evaluate associations between variables and the risk of BCR. The multivariate model was constructed by incorporating significant variables from the univariate analysis. Statistical significance was assigned to comparisons with p-values of less than 0.05.

Results

A total of 199 patients reported as pT3b were included in the study. VDI was detected in 95 patients (47.7%) (Table 1). Preoperative patient characteristics are presented in Table 1. We were unable to demonstrate a statistically significant difference between groups in clinicopathological features such as age, American Society of Anesthesiology scores, preoperative PSA, prostate volumes, biopsy ISUP grades, and preoperative EAU risk groups ($p > 0.05$; Table 1). The time from biopsy to RP was longer in the VDI- group than in the VDI+ group (Table 1, 60 vs. 50 days, $p = 0.043$).

Perioperative and postoperative patient characteristics are outlined in Table 2. The median follow-up time of the patients in the VDI- and VDI+ groups was 65 months [interquartile range (IQR), 45-107 months] and 61 months (IQR, 39-86 months), respectively (Table 2, $p = 0.076$). The VDI+ group exhibited a greater degree of EPE and bilateral seminal vesicle invasion. In the RP specimens, EPE was identified in all but one patient in the VDI+ group, compared with 94 patients (90.4%) in the VDI- group. (Table 2, $p = 0.008$). While 43% of patients in the VDI- group had bilateral seminal vesicle invasion, 82% of patients in the VDI+ group did (Table 2, $p < 0.001$). The VDI+ group had a higher number of ISUP grade 5 patients, resulting in a significant difference in RP ISUP grades between the two groups (Table 2, $p = 0.001$). Although surgical margin positivity and pathologic LN positivity were higher in the VDI+ group, these differences did not reach statistical significance. The median PSA values at postoperative week 6 were significantly higher in the VDI+ group (Table 2; 0.04 vs. 0.14; $p < 0.001$). Although 61% of patients in the VDI- group received adjuvant RT, only 47% of patients in the VDI+ group did (Table 2, $p = 0.051$). Conversely, more patients in the VDI- group received than in the VDI+ group (Table 2, 44% vs. 77%, $p < 0.001$). BCR was detected

Parameters	Vas deferens invasion (-) n=104 (52.3%)	Vas deferens invasion (+) n=95 (47.7%)	p-value
Age, year, mean ± SD	71.51±7.55	69.71±6.8	0.08
Preoperative PSA, median (IQR)	10.7 (7.6-26.6)	15 (7.1-23.7)	0.368
Prostate MRI volume, median (IQR)	43 (32-58)	45 (37-60)	0.329
PSA density	0.28 (0.15-0.54)	0.31 (0.16-0.67)	0.622
ASA score ASA 1 ASA 2 ASA 3	43 (41.1%) 59 (56.7%) 3 (2.2%)	49 (51.1%) 44 (46.6%) 2 (2.3%)	0.397
Biopsy ISUP grade group 1 2 3 4 5	16 (15.4%) 29 (27.9%) 23 (22.1%) 21 (20.2%) 15 (14.4%)	15 (15.8%) 16 (16.8%) 29 (30.5%) 13 (13.7%) 22 (23.2%)	0.121
Preoperative EAU risk group Low Intermediate High Locally advanced	9 (8.5%) 37 (35.3%) 44 (41.9%) 15 (14.3%)	8 (8.4%) 25 (26.3%) 48 (50.5%) 14 (14.7%)	0.612
Time from biopsy to RP day, median (IQR)	60 (42-90)	50 (39-65)	0.043
Student's t-test, Mann-Whitney U test, chi-square SD: Standard deviation, PSA: Prostate-specific antigen, IQR: Interquartile range, ISUP: International Society of Urological Pathology, RP: Radical prostatectomy, EAU: European Association of Urology, ASA: American Society of Anesthesiologists, MRI: Magnetic resonance imaging			

in 34 patients (32.7%) in the VDI- group and in 38 patients (40%) in the VDI+ group (Table 2, p=0.284).

The 5-year BCRFS rates were 67% [confidence interval (CI): 58-76] and 60% (CI: 50-70) for the VDI- and VDI+ groups, respectively. Kaplan-Meier curves demonstrated no statistically significant difference in BCRFS between the 2 groups (log-rank p=0.127; Figure 1).

Cox regression models were applied to analyze the association between VDI and the risk of BCR. VDI was not associated with BCR on uni- and multivariate analysis (Table 3, p=0.3 and 0.8, respectively). Bilateral seminal vesicle invasion (p=0.006) in RP pathology, ISUP grade group 3 in biopsy (p=0.033), ISUP grade group 2 (p=0.004) and ISUP group 3 (p=0.002) in RP specimen, and pathologic LN positivity (p=0.001) were all significantly associated with BCR on univariate analysis (Table 3). On multivariate regression analysis, pathological ISUP grade groups 2 [hazard ratio (HR): 13, 95% CI: 2.3-71.4; p=0.04] and 3 (HR: 7.2, 95% CI: 1.5-33.3; p=0.012) on RP pathology, and pathological LN positivity (HR: 2.5, 95% CI: 1.3-4.5; p=0.004) were found to be significant predictors of BCR (Table 3).

Discussion

This study examines the prognostic significance of invasion of the vas deferens in patients with pT3b prostate cancer. BCR-free survival was lower in patients with VDI; however, the difference was not statistically significant. Cox regression analysis of BCR-related factors revealed that VDI was not associated with BCR. Pathological ISUP grade group in the RP specimen and pathological LN positivity were significant predictors of BCR.

Sampling of the vas deferens is not a mandatory step in the routine pathologic examination of RP specimens. Additionally, at the ISUP consensus conference reviewing the pathologic evaluation of RP specimens, it was noted that although almost half of the pathologists examined for and reported VDI, the consensus was that routine sampling of the vas deferens was not mandatory (4). An important reason for sampling the vas deferens is to evaluate the surgical margin. The rationale is that pathologists performing vas deferens sampling consider this area to be also the surgical margin of the specimen. However, the current study was planned not only because the vas deferens is the surgical margin but also because it is a distinct organ whose invasion may have prognostic significance. We support routine VD sampling in all cases because it serves both as a surgical margin and, it is believed, has prognostic significance. Because existing literature on this topic is inadequate, it is not possible to make a definitive recommendation about whether to perform VD sampling based solely on the results of this study.

Although a positive surgical margin is significant for prognosis, it is possibly not the most critical factor. Accordingly, pathologic T stage, pathologic N stage, and Gleason grade seem to be more significant prognostic factors. Würnschimmel et al. (1) presented their 20-year study of oncological outcomes in patients with localized prostate cancer at Martini-Klinik. As expected, the lowest BCRFS, metastasis-free survival, and cancer-specific survival were observed in the very high-risk group according to the National Comprehensive Cancer Network risk classification. Additionally, a survival analysis was conducted by integrating pathologic T stage and surgical margin status. The lowest BCRFS was observed in patients exhibiting seminal

Parameters	Vas deferens invasion (-) n=104 (52.3%)	Vas deferens invasion (+) n=95 (47.7%)	p-value
Follow up time, month, median (IQR)	65 (45-107)	61 (39-86)	0.076
Surgical procedure Open Robotic	59 (56.7%) 45 (43.3%)	55 (57.9%) 40 (42.1%)	0.629
Nerve sparing surgery No Yes	82 (78.6%) 22 (21.4%)	63 (66.3%) 32 (33.7%)	0.074
Extraprostatic extension No Yes	10 (9.6%) 94 (90.4%)	1 (1.1%) 94 (98.9%)	0.008
Seminal vesicle invasion Unilateral Bilateral	59 (57.3%) 45 (43.2%)	17 (17.9%) 78 (82.1%)	<0.001
ISUP grade at final pathology 1 2 3 4 5	7 (6.7%) 18 (17.3%) 26 (25%) 17 (16.4%) 36 (34.6%)	- 14 (14.7%) 28 (29.5%) 4 (4.2%) 49 (51.6%)	0.001
Positive surgical margin, n (%) Yes No	43 (41.3%) 61 (58.7%)	45 (47.4%) 50 (52.6%)	0.393
Pathological lymph node status pN0 pN+	67 (64.4%) 37 (35.6%)	50 (52.6%) 45 (47.4%)	0.156
Number of removed LNs, median (IQR)	13 (9-20)	14 (12-20)	0.086
Number of positive LNs, median (IQR)	1 (0-2)	2 (0-4)	0.202
Postoperative 6th week PSA, median (IQR)	0.04 (0.01-0.17)	0.14 (0.02-0.87)	<0.001
Adjuvant radiotherapy Yes No	64 (61.5%) 49 (38.5%)	45 (47.4%) 50 (52.6%)	0.051
Adjuvant hormonotherapy Yes No	46 (44.2%) 58 (55.8%)	73 (76.8%) 22 (23.2%)	<0.001
BCR Yes No	34 (32.7%) 70 (67.3%)	38 (40%) 57 (60%)	0.284
Student's t-test, Mann-Whitney U tests, chi-square tests PSA: Prostate-specific antigen, IQR: Interquartile range, BCR: Biochemical recurrence, LN: Lymph node, ISUP: International Society of Urological Pathology, RP: Radical prostatectomy, EAU: European Association of Urology, ASA: American Society of Anesthesiologists			

vesicle invasion (pT3b) and positive surgical margins (R1), and higher grade group correlated with poorer survival rates (1). It has also been shown that having 3 or more LNs decreases survival. In the multivariable Cox regression analysis examining the associations of these factors with BCR, Gleason grade group 4-5 (HR: 1.6), pT3a (HR: 2.5), pT3b (HR: 4.5), R1 (HR: 1.3), and pN1 (HR: 1.7) tumors were identified as significant risk factors for increased BCR (1). We can infer that seminal vesicle invasion is the most hazardous scenario identified in this study. While Würnschimmel et al.'s (1) study included a more pathologically diverse patient population, our study focused exclusively on patients with pathologic SVI, which was the patient group with the largest HR in that study. Despite the differences in samples, the findings of our study generally align with existing literature. We found that bilateral SVI was associated with BCR in univariate analysis; however, it was not statistically significant

in multivariate analysis. We can conclude that bilateral SVI does not pose an additional disadvantage with respect to BCR. In contrast to our study, the current literature indicates that bilateral SVI is associated with BCR (8,9). The study by Suh et al. (8) showed that bilateral SVI correlated with BCR, yielding a p-value of 0.049. However, the relatively low (HR: 1.197) in this study suggests that the associated risk remains minimal (8). Likewise, the study by Lee et al. (9) which involved 93 patients, identified a significant association between bilateral SVI and BCR in multivariate analysis, with a p-value of 0.047. Nonetheless, this study's small patient sample and limited p-value hinder drawing definitive conclusions about the effects of bilateral SVI on prognosis.

Another critical aspect of our study is that the pathological ISUP grade was significantly associated with BCR in multivariate

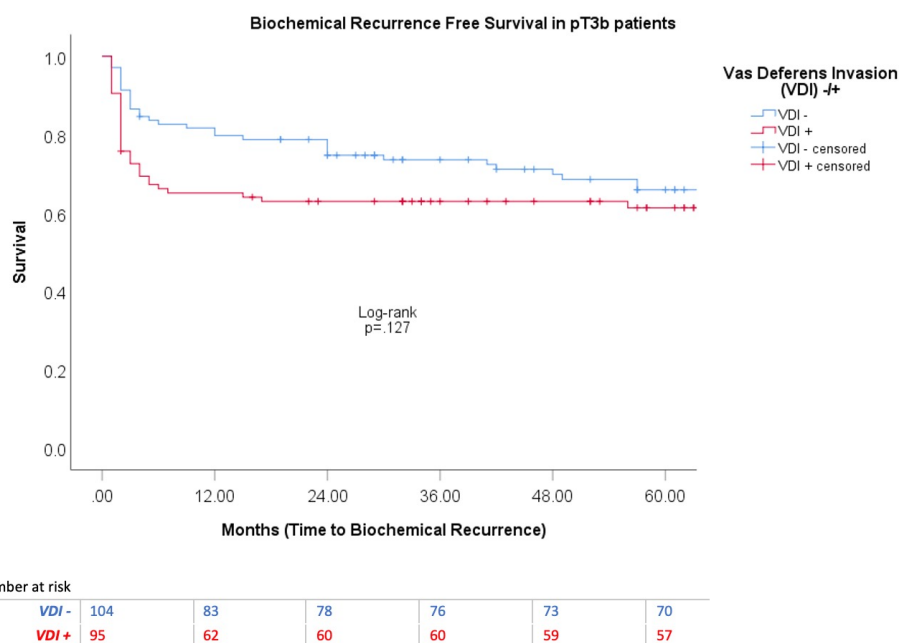


Figure 1: Biochemical recurrence free-survival Kaplan-Meier curve

	Biochemical recurrence (BCR)			
	Univariate analysis	Multivariate analysis		
	p-value*	HR	95% CI	p-value**
Age	0.2	0.982	0.947-1.018	0.4
Preoperative PSA	0.7	0.983	0.965-1.001	0.06
Biopsy ISUP grade groups				
ISUP grade 1	Reference	Reference		
ISUP grade 2	0.1	2.481	0.920-6.666	0.07
ISUP grade 3	0.033*	1.063	0.411-2.405	0.9
ISUP grade 4	0.6	1.754	0.642-4.784	0.3
ISUP grade 5	0.8	2.512	0.909-6.944	0.08
Bilateral seminal vesicle invasion	0.006*	1.757	0.962-3.245	0.063
Vas deferens invasion	0.3	1.093	0.621-1.924	0.8
ISUP grade at final pathology				
ISUP grade 1	Reference	Reference		
ISUP grade 2	0.1	12.987	2.320-71.428	0.04**
ISUP grade 3	0.004*	7.194	1.555-33.333	0.012**
ISUP grade 4	0.002*	3.875	0.645-15.151	0.2
ISUP grade 5	0.8	3.875	0.865-17.241	0.08
Positive surgical margin	0.1	1.146	0.665-1.975	0.6
Pathological lymph node positivity	0.001*	2.471	1.343-4.546	0.004**
Surgical procedure (open/robotic)	0.7	1.131	0.654-1.955	0.6

*: Univariate logistic regression analysis, **: Multivariate logistic regression analysis, HR: Hazard ratio, CI: Confidence interval, ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen

analysis, corroborating existing literature. Numerous studies have shown that higher ISUP grade groups are significantly associated with an increased risk of BCR (1,10). The absence of an association between pathologic ISUP grades 4 and 5 and BCR in our study may be attributable to other coexisting risk

factors in patients with these grades, including pathologic LN involvement, bilateral seminal vesicle invasion, and positive surgical margins. Given that the risk of BCR is already significantly elevated in patients with these characteristics, ISUP grades 4 and 5 may not further augment the risk of BCR. Multivariate analysis

of our study also demonstrated that pathologic LN positivity is one of the main risk factors for BCR. Pathologic LN positivity is a well-established risk factor for BCR in the literature (1,11). Although the effects of these factors on oncologic outcomes are well known, the impact of VDI by prostate cancer on oncologic outcomes remains unclear. Current knowledge reveals a scarcity of studies examining the impact of VDI on survival outcomes. Jang et al. (12) investigated the impact of VDI on oncological outcomes in patients with pT3b prostate cancer. The authors found that almost a quarter of the 350 pT3b prostate cancer patients had VDI; this group had worse 5-year BCRFS than the group without VDI (12). Additionally, VDI emerged as a significant predictor of BCR in the multivariate Cox analysis, with a HR of 1.39 ($p=0.039$) (12). In contrast, we observed that VDI did not affect BCRFS in our study, which was methodologically similar to this study. This difference between the two studies may be attributed to two reasons. The relatively low number of patients, a limitation of our study, may have contributed to this difference. To us, another significant factor is the exclusion of patients who received adjuvant treatment in the study by Jang et al. (12) In the current study, patients who underwent adjuvant treatment were included and examined. As is well known, adjuvant therapies are recommended by guidelines for locally advanced disease (2). The higher incidence of adjuvant HT among patients in the VDI+ group may account for the observed lower BCR within that cohort.

In a study, Saar et al. (6) examined the prevalence and extent of surgical-margin involvement of the vas deferens in 2701 consecutive RP specimens from two institutions. Of the 41 patients with positive VD surgical margins, the majority were classified as pT3b, one was pT3a, and six were pT4. The authors stated that although VD surgical margin positivity is rare, this region may sometimes be the only site of positive surgical margins. Consequently, they highlighted the significance of VD sampling. The distal segment of the vas deferens and the surgical margin are frequently investigated by pathological examination. Gözen et al. (5) investigated preperitoneal and distal VD samples in high-risk prostate cancer patients. A total of 332 individuals were sampled from the VD region between the internal inguinal ring and the obturator fossa. Among 130 pT3b patients, 18 patients (14%) exhibited distal VDI, and 1 patient presented with preperitoneal VDI. Conversely, among 104 pT3a patients, patient 1 demonstrated distal VDI and 1 patient showed preperitoneal VDI. In pT3b patients, distal VDI did not correlate with an increased risk of positive surgical margins or nodal disease. However, 2 patients with preperitoneal VDI exhibited bilateral distal VDI and features of highly aggressive disease. Of the 2 patients with preperitoneal VDI, 1 had seminal vesicle invasion, while the other did not. This also serves as a clear example that VDI can occur independently of SVI. Another study by Nguyen et al. (13) reported that local recurrences following RP were observed at the vas deferens resection site in 22% of cases. Although the study is limited by lack of specification of VDI in RP material, histological evidence at the recurrence site indicates that the majority of local recurrences arise at the anastomotic site. Therefore, the 22% rate of vas deferens involvement is noteworthy. Notably, one-third of patients with recurrence at the site of VD resection were

classified as pT2, nearly half as pT3, and almost half had the primary tumor located at the apex. The presence of recurrences in this region strongly suggests that VDI in RP specimens may have prognostic significance.

The pathology community defines invasion of the seminal vesicle as involvement of muscular tissue within the seminal vesicle wall (4,14). Ohori et al. (14) identified three distinct mechanisms for seminal vesicle invasion. type-1 involves direct internal spread along the ejaculatory duct complex into the seminal vesicles. Tumor migration does not occur within the lumen of the ejaculatory duct; instead, it invades the surrounding tissue. type-2 involvement extends beyond the prostate, penetrating the capsule and infiltrating the muscular layer of the seminal vesicle. Involvement may occur directly across the tissue plane between the base of the prostate and the seminal vesicles. The presence of isolated foci of cancer in the seminal vesicle, without direct continuity to the primary tumor, characterizes type-3 involvement. In 2007, Billis et al. (7) showed that the primary pathway of SVI is the EPE of prostate carcinoma into the soft tissue adjacent to the ipsilateral seminal vesicle, leading to infiltration of the seminal vesicle wall. The prevalence of invasion via EPE suggests that the vas deferens, located adjacent to the seminal vesicle, is also susceptible to this route. However, the histological structures of the seminal vesicle and the vas deferens are distinct. The consistency of the VD is considerably different and markedly harder than that of the adjacent structures and periprostatic tissues (15). Based on these findings, we can interpret that the muscular layer of the VD serves as a more resistant barrier to tumor invasion, similar to arterial walls. The biochemical behavior and clinical presentation of a tumor invading the VD are expected to be more aggressive. In this context, higher postoperative PSA levels, EPE rates, bilateral SVI rates, and ISUP grades at the final pathology in the VDI+ group in the current study indicate a potentially more aggressive disease course for this group of patients. However, the classification of tumors with VD invasion remains unclear due to a lack of comprehensive literature on the subject. Should these tumors be interpreted as EPE only, or as involvement of adjacent organs other than the seminal vesicle? Given the disparity in prognosis between the two groups, it is essential to clarify this issue.

The present study has some limitations, including its retrospective design and small sample size, because it was conducted at a single center and focused on a specific patient population. Although VD was fully sampled in all cases, the omission of the VD length measurement could be considered an additional limitation.

Conclusion

Patients with pT3b prostate cancer may have different survival rates depending on VD invasion status. This study revealed a difference in BCRFS between the groups with and without VDI, although it was not statistically significant. However, the results should be interpreted with caution, keeping in mind that this may be due to differences in adjuvant treatments and other clinical and pathologic parameters between the two groups. Since VDI may have prognostic significance, we recommend routine sampling of VD during RP. In order to draw more

definitive conclusions on this issue, prospective, multicenter studies with larger patient populations are needed.

Ethics

Ethics Committee Approval: This study was approved by the Ankara University Human Research Ethics Committee (decision no: 103-264-24, date: 22.04.2024).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Ç.G., K.T., S.B., E.S., Concept: Ç.A., E.S., Design: M.A.İ., Data Collection or Processing: M.C.K., A.F.Ö., E.D.S., S.K., D.E., Analysis or Interpretation: E.E., Literature Search: M.C.K., A.F.Ö., Writing: M.C.K.

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Prognostic Impact of Pre-operative Computed Tomography Quantification of Body Composition in Bladder Cancer Patients Undergoing Radical Cystectomy

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Abstract

Objective: To investigate the association between preoperative computed tomography (CT)-based abdominal muscle-fat composition and length of hospital stay, post-operative complications and cancer-specific survival in patients with bladder cancer undergoing radical cystectomy.

Materials and Methods: Preoperative CT scans of 128 patients undergoing radical cystectomy for bladder cancer between 2013-2018 were reviewed. Densitometric quantification of total, visceral (VFA), subcutaneous (SFA) and inter-muscular fat-area (IMFA), mean muscle density (between -29HU and 150HU)

(MD150) and muscle area (between -29HU and 150HU) (MA150) measurements were performed retrospectively on an axial CT image at the level of L3 vertebra. The length of hospital stays and Clavien-Dindo score was noted. In the survival analysis, 12- and 30-months were taken as the threshold values. The primary outcome measure was cancer-specific survival.

Results: A total of 96 patients (92 men and 4 women, mean age 66 years, age range 49-86 years) were included. Patients with length of hospital stay more than 10 days had significantly higher VFA/SFA ratio ($p=0.03$) and higher IMFA ($p=0.01$). In the cohort, 74% of patients had low Clavien-Dindo scores (≤ 2) with significantly higher MA150 ($p=0.02$), MD150 ($p<0.01$) and lower IMFA ($p=0.01$) compared to group with high scores. In the survival analysis, MA150 and MD150 values were significantly higher ($p=0.01$ and $p<0.01$, respectively) in survivors more than 12 months. Only MD 150 value was significantly higher in survivors more than 30 months ($p<0.01$).

Conclusion: Preoperative CT-based body composition parameters, particularly MD150 and MA150, can be used as non-invasive prognostic markers in patients undergoing radical cystectomy. These muscle-related parameters are strongly correlated with fewer surgical complications and longer cancer-specific survival, suggesting a promising role in preoperative risk stratification and patient support.

Keywords: Bladder cancer, computed tomography, cystectomy, survival

Introduction

Bladder cancer is the ninth most frequently diagnosed cancer, with approximately 83,190 estimated new cases and 16,840 estimated deaths for 2024 (1). Southern Europe has higher incidence rate both for men and women than any other region worldwide, where Spain is the most prevalent region (2). In men, the burden and rates are considerably higher than in women, with ranking it as the sixth most prevalent cancer (2).

Radical cystectomy still stands as the reference standard treatment for high-risk bladder cancer cases. Yet the development of surgical technology and less invasive procedures such as robot-assisted techniques, potential postoperative morbidity may be inevitable, especially for elderly patients or in cases of advanced disease (3). Therefore, the identification of novel risk factors specific to individuals for complications may lead to better treatment decisions and perioperative care.

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In the last decade, studies focusing on the impact of body composition on the postoperative outcomes of oncology patients have increased significantly (4,5). Sarcopenia, sarcopenic obesity and visceral obesity, which are the different measures of body composition, have been defined as adverse prognostic factors in cancer patients (6). The excess accumulation of visceral fat in the abdominal cavity is known as visceral obesity. Sarcopenia is defined as progressive and generalised skeletal muscle disorder that occurs as a result of low muscle mass and impaired muscle strength and quality (7). The combination of sarcopenia and obesity is defined as sarcopenic obesity.

Several studies have investigated the role of body composition parameters on the outcomes of urinary bladder cancer patients with particularly the negative impact of excess visceral fat and loss of skeletal muscle mass (8-10). Those studies mostly used computed tomography (CT) due to high accuracy and reproducibility. It is possible to define lean body mass, subcutaneous (SFA) fat and visceral fat with CT, which are reported to be prognostic parameters over that of body mass index (BMI) (6). As the outcome, studies mainly focused on complications after the surgery or the overall survival (11). However, few data exist regarding the association of those parameters on a complete mortality and morbidity assessment including hospital stay, adverse perioperative events and oncologic outcomes.

Our aim in this study was to investigate the association between preoperative CT-based abdominal skeletal muscle-fat composition and length of hospital stay, post-operative complications and cancer-specific survival in patients with bladder cancer undergoing radical cystectomy.

Materials and Methods

Patient Population and Study Setting

This retrospective single-centre study was Institutional Review Board of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital approved, with the need for informed consent for data analysis waived (decision number 2020/8-6, date: 08.07.2020). One hundred and twenty-eight patients undergoing radical cystectomy for bladder cancer in our institution between the years 2013 and 2018 were reviewed. The inclusion criteria were 1) adult patients with radical cystectomy for bladder cancer in our urology department 2) presence of preoperative abdominopelvic CT scan for staging purposes. The study flow with exclusion criteria is summarised in Figure 1.

CT Protocol

Routine thorax and abdominopelvic contrast-enhanced CT scans for staging were performed prior to surgery as a standard of care. For the analysis of muscle and fat distribution, only abdominopelvic CT scans were evaluated. CT examinations were performed by a 128-detector (SOMATOM Definition AS, Siemens Healthineers) or 64-detector (Aquilion, Toshiba Medical Systems) CT scanner. A total of 80-100 mL of contrast media with high iodine concentration (350-370 mg/mL) was injected with a flow rate of 3-4 mL/s, followed by a 40-60 mL saline influx. All the CT scans were held in the portal venous

phase. The scanning parameters were as follows; 120 kV, 225 mA, section thickness 0.5 mm, and reconstruction interval 0.5 mm.

CT Image Analysis

For the analysis of muscle-fat distribution, abdominopelvic CT images were sent to a commercially available software (Aquarius Workstation, TeraRecon, San Mateo, California, USA). By using fat analysis module, densitometric quantification of total, visceral (VFA), SFA and inter-muscular fat-area (IMFA), mean muscle density and skeletal muscle area measurements were performed retrospectively on a single axial CT image at the level of third lumbar vertebra. Automatic measurement was done for fat area measurements using reference lower and upper thresholds of Hounsfield unit (HU) given in the literature (Supplementary Table 1) (6,12,13). The border of each segmentation was checked, and manual correction was done whenever necessary. For the measurement of skeletal muscle area (between -29HU and 150HU) (MA150), muscle density (between -29HU and 150HU) (MD150) and IMFA, manual segmentation was done to encircle paravertebral and abdominal wall muscles, where 150 HU was taken as the upper threshold for those muscle-related measurements. VFA/SFA and VFA/MA150 were calculated. An example of measurement of fat distribution is given in Supplementary Figure 1.

Assessment of Postoperative Period, Follow-up, and Survival

All patients underwent radical cystectomy and urinary diversion or neobladder procedures. After the surgery, the length of total hospital stay, and intensive care unit (ICU) stay (in days) were noted from hospital records.

Surgical complications were stratified using Clavien-Dindo classification which was originally described in 2004 (14). This classification system is a five-scale system to grade adverse events (i.e., complications) which occur after surgical procedures and widely used in many surgical specialities (Supplementary Table 2). In the study, the grading system was dichotomised as low (Clavien-Dindo 0,1,2) and high (Clavien-Dindo 3,4,5) grades for the analysis of complications where invasive procedures are needed for the high grades.

Patients were followed up after the surgery. In the 96-patient group, six patients died from causes other than bladder cancer. They were excluded from the survival analysis to investigate the relationship between CT-based body composition parameters and cancer-specific survival. Of the 90 patients with associated disease, 47 (52.2%) died. The 43 patients still alive had a minimum follow-up of 33 months (average 56 months, maximum 96 months). For short-term survival analysis, 12 months was chosen as the threshold. For long-term survival analysis, the minimum follow-up period among patients who are still alive (i.e., 33 months in our cohort) was considered to ensure that all living patients were included, and 30 months was taken as the threshold.

Statistical Analysis

All the data were statistically analysed using IBM SPSS version 25.0. Continuous variables are summarized as the mean \pm

standard deviation, and categorical variables are summarized as the frequency and percentage. For discontinuous variables, Pearson chi-square test and Fisher's exact test was used. According to the distribution of the data, Mann-Whitney U test or Student's t-test was used where appropriate, for comparison of groups. Receiver operating characteristics (ROC) curve was used for diagnostic power evaluation. For the parameters that were statistically significant, Kaplan-Meier curves were created to determine the difference in cancer-specific survival between the groups. A value of $p < 0.05$ was considered to indicate statistical significance.

Results

Clinicopathologic Characteristics

A total of 96 patients with a mean age of 66.6 ± 8.6 years (range 49-86 years) were included in the final cohort. There were 92 (95.8%) men and 4 (4.2%) women. None of the patients included in the study received neoadjuvant chemotherapy before radical cystectomy. All the patients had the pathological confirmation of urothelial bladder cancer, without variant pathology, after radical cystectomy and most of the study group (87.5%) had high grade of cancer. Forty-seven percent of the

patients had stage 3 disease with invasion beyond the muscularis propria to the perivesical soft tissue. Detailed demographics of patients, follow-up data, and histopathological results are given in Table 1.

After the surgery, mean hospital stay of the patients were 14.3 ± 13.6 days (range 0-121). Forty (41.6%) patients were followed in ICU unit (mean 8.3 ± 19.3 days). Among all group, 10 (10.4%) patients died in the first 30 days of postoperative period (8 patients in the ICU).

Relation of Body Composition Parameters and Hospital Stay

For the analysis of length of hospital stay, "10 days" was determined as cut-off value for binary assessment of the duration (i.e., less than 10 days and more than 10 days). In the whole cohort, 8 patients died in the first 10 days. Therefore, those patients were excluded from the hospital stay analysis to avoid false positivity and not to include them in the good prognostic group with short hospital stay.

In the study, patients with length of hospital stay less than 10 days had higher muscle-related parameters, however those were not statistically significant (MA150 and MD150, $p = 0.35$ and $p = 0.27$, respectively). All the other parameters were higher

	Number (n)	Percentage (%)
Sex		
Male	92	95.8
Female	4	4.2
Mean age (year) \pm SD (range, years)	66.6 ± 8.6 (49-86)	
Mean hospital stay (days) \pm SD (range, days)	14.3 ± 13.6 days (0-121)	
ICU stay (days) \pm SD (range, days) (n=40, 41.6%)	8.3 ± 19.3 days (0-121)	
Clavien-Dindo score		
Low (0,1,2)	71	74
High (3,4,5)	25	26
Mean follow-up (months) (range, months)	14 (0-90)	
Exitus in the first 30 days of the postoperative period	10	10.4
Total exitus	53	55.2
Histologic grade of urothelial bladder cancer		
High	84	87.5
Low	12	12.5
Tumor stage		
Ta	5	5
Tis	2	2
T1	18	19
T2	27	28
T3a	28	29
T3b	17	18
Lymphovascular invasion		
Absent	54	56
Present	42	44

Ta: Non-invasive papillary urothelial carcinoma, Tis: Urothelial carcinoma *in situ*, SD : Standard deviation, ICU: Intensive care unit

in the group with more than 10 days of hospital stay, with a statistically significant VFA/SFA ratio ($p=0.03$) and IMFA ($p=0.01$) (Table 2).

Relation of Body Composition Parameters and Postoperative Complications

In the whole cohort, 71 (74%) patients had low Clavien-Dindo score, while 25 (26%) had high Clavien-Dindo score (Score 0,1,2,3,4,5 are 34,18,19,13,2,10 patients, respectively).

Patients with low Clavien-Dindo scores (≤ 2) had significantly higher MA150 ($p=0.02$), MD150 ($p<0.01$) and lower IMFA

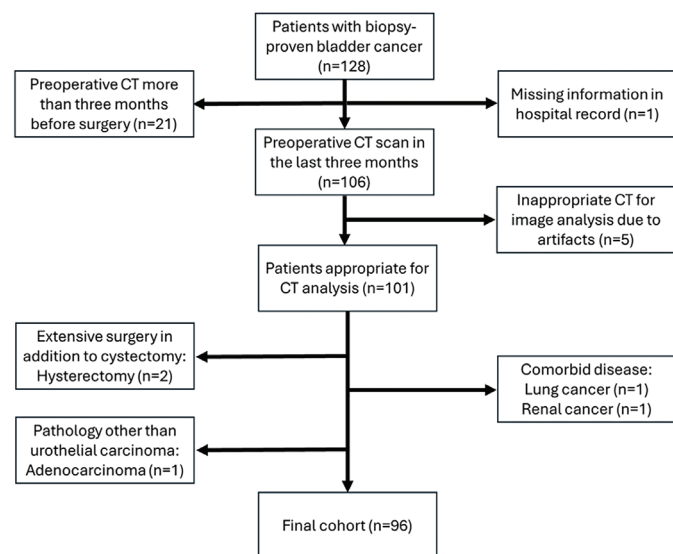


Figure 1. REMARK diagram illustrating the patient flow in the study
CT: Computed tomography

($p=0.01$) (Table 3). Although this group had higher SFA and lower VFA, VFA/SFA, VFA/MA150 values when compared to group with high Clavien-Dindo score, they were not statistically significant. When ROC analysis was performed for muscle-related parameters, area under the curve values were 0.653 for MA150 and 0.680 for MD150 (Figure 2).

Relation of Body Composition Parameters and Cancer-specific Survival

In total, 53 (55.2%) patients died in the follow-up. After exclusion of 6 patients who were deceased due to causes other than bladder cancer (traffic accident, $n=1$; myocardial infarction, $n=2$; cardiac insufficiency, $n=1$; renal insufficiency, $n=1$; intracranial hemorrhage, $n=1$), remaining 90 patients were included in the survival analysis. Mean follow-up was 14 months for this group (range 0-90 months). Twenty-nine (32.2%) patients died in the first 12 months and 11 (12.2%) patients died between 12-30 months.

In the survival analysis with the 12-months cut-off, MA150 and MD150 values were significantly higher ($p=0.01$ and $p<0.01$, respectively) in the patients with survival more than 12 months (Table 4). Although VFA, IMFA, VFA/SFA and VFA/MA150 were higher in the patients with survival less than 12 months, they were not statistically significant.

In the survival analysis with 30-months cut-off, only MD150 value was significantly higher ($p<0.01$) in the patients with survival more than 30 months (Table 5). Box-plots according to survival period and accompanying ROC curves are given in Figure 3.

For Kaplan-Meier survival analysis; median values of MA150 and MD150 were taken as thresholds (135 cm^2 and 28.6 HU, respectively). Both parameters have difference in cancer-specific survival curves with longer survival in patients with higher muscle area and muscle density. The difference was more evident for the parameter MD150 (Figure 4).

Table 2. Comparison of CT-based body composition parameters according to the length of hospital stay

	Length of hospital stay (days)	Number of patients*	Mean value	SD	p-value
VFA (cm^2)	<10	37	171.6	124.3	0.37
	>10	51	193.1	97.6	
SFA (cm^2)	<10	37	132	62.8	0.68
	>10	51	138.5	77.54	
IMFA (cm^2)	<10	37	9.04	5.53	0.01
	>10	51	11.27	10.58	
MA150 (cm^2)	<10	37	141.5	32.36	0.35
	>10	51	135.3	29.92	
MD150 (HU)	<10	37	30.34	7.56	0.27
	>10	51	28.5	7.71	
VFA/SFA	<10	37	1.26	0.62	0.03
	>10	51	1.49	1.53	
VFA/MA150	<10	37	1.18	0.74	0.09
	>10	51	1.43	0.72	

*: Eight patients who died in the first 10 days after the surgery were excluded and the analysis was done on 88 patients, IMFA: Inter-muscular fat-area, MA150: Muscle area (between -29HU and 150HU), MD150: Muscle density (between -29HU and 150HU), SFA: Subcutaneous fat area, TFA: Total fat area, VFA: Visceral fat area, SD: Standard deviation, CT: Computed tomography

Table 3. Comparison of CT-based body composition parameters according to Clavien-Dindo score					
	Clavien-Dindo score*	Number of patients	Mean value	SD	p-value
VFA (cm ²)	Low	71	183.8	112.4	0.90
	High	25	186.9	97.6	
SFA (cm ²)	Low	71	137.5	69.3	0.54
	High	25	127.6	72.2	
IMFA (cm ²)	Low	71	10.2	9.64	0.01
	High	25	13.6	8.83	
MA150 (cm ²)	Low	71	140.5	31.3	0.02
	High	25	124.6	26.84	
MD150 (HU)	Low	71	29.8	7.62	<0.01
	High	25	24.9	7.95	
VFA/SFA	Low	71	1.37	0.60	0.25
	High	25	1.46	1.20	
VFA/MA150	Low	71	1.29	0.73	0.31
	High	25	1.58	0.94	

*: Low refers to Clavien-Dindo score 0,1,2 and high refers to Clavien-Dindo score 3,4,5, IMFA: Inter-muscular fat-area, MA150: Muscle area (between -29HU and 150HU), MD150: muscle density (between -29HU and 150HU), SFA: Subcutaneous fat area, TFA: Total fat area, VFA: Visceral fat area, SD: Standard deviation, CT: Computed tomography

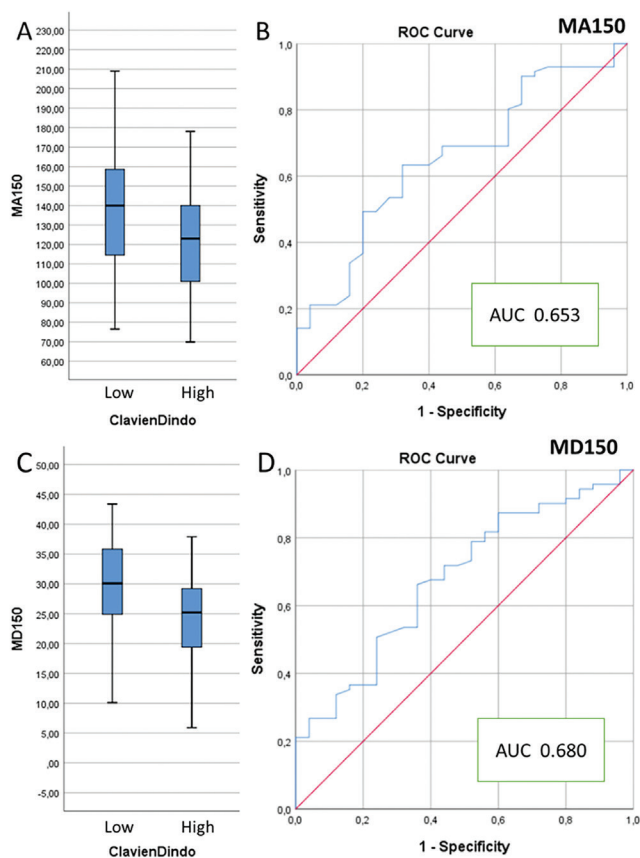


Figure 2. Box-plots of “low” and “high” Clavien-Dindo scores for MA150 (A) and MD150 (C) and accompanying ROC analysis curves (B, D, respectively) for discrimination of two groups. AUC is 0.653 for MA150 and 0.680 for MD150 MA150: Muscle area (between -29HU and 150HU), MD150: Muscle density (between -29HU and 150HU), AUC: Area under the curve, ROC: Receiver operating characteristics

Discussion

In this study, we aimed to evaluate prognostic impact of preoperative CT-based body composition parameters (i.e., visceral/subcutaneous fat area, skeletal muscle area and density) in patients with bladder cancer and assess the relationship between those parameters and postoperative comorbidities and survival. We found that abdominal muscle area, muscle density and IMFA is significantly related to Clavien-Dindo scoring system. Only muscle density was significantly related to the long-term survival (i.e., 30 months) of the patients after the surgery. However, no significant association of VFA or SFA was found with complications or survival. Only VFA/SFA ratio and IMFA were associated with long-term (i.e., >10 days) hospital stay.

BMI and sarcopenia affect a wide range of cancer and non-cancerous patients (4,6). There are many studies that show both measures have prognostic value in different patient groups (12,15,16). Although BMI and muscle area/density measurements are used in determination of sarcopenia, there are no well-established threshold values for skeletal muscle area or muscle density in the European Working Group on Sarcopenia in Older People guidelines (7,17). The measurement techniques in different modalities and the level of measurements also vary between studies (18). In several studies, at the level of L3 vertebrae, measured psoas muscle area or total skeletal muscle area is divided into BMI to calculate normalized muscle area. For instance, Smith et al. (8) measured total psoas area using threshold of -30HU and +110 HU, divided the area to BMI and calculated cut-off values of 653 cm²/m² and 523 cm²/m², in men and women, respectively. Psutka et al. (15) measured total muscle area at the level of L3 using threshold of -29 HU and +150 HU, divide into BMI, found skeletal muscle index (SMI) and determined cut-off values of 55 cm²/m² in men and 39 cm²/m² in women for SMI.

	Survival (mo)	Number of patients*	Mean value	SD	p-value
VFA (cm ²)	>12	61	178.2	110.9	0.65
	<12	29	189.5	110.4	
SFA (cm ²)	>12	61	138.7	77.2	0.35
	<12	29	123.8	55.3	
IMFA (cm ²)	>12	61	10.5	10.2	0.08
	<12	29	12.3	8.3	
MA150 (cm ²)	>12	61	141.5	31.4	0.01
	<12	29	124	26.6	
MD150 (HU)	>12	61	30.3	7.87	<0.01
	<12	29	24.1	7.04	
VFA/SFA	>12	61	1.33	0.58	0.50
	<12	29	1.43	0.60	
VFA/MA150	>12	61	1.25	0.71	0.46
	<12	29	1.44	0.84	

*: Six patients, who died due to causes other than bladder cancer, were excluded and the analysis regarding cancer-specific survival was done on 90 patients, IMFA: Inter-muscular fat-area, MA150: Muscle area (between -29HU and 150HU), MD150: Muscle density (between -29HU and 150HU), SFA: Subcutaneous fat area, TFA: Total fat area, VFA: Visceral fat area, SD: Standard deviation, CT: Computed tomography

	Survival (mo)	Number of patients*	Mean value	SD	p-value
VFA (cm ²)	>30	50	166.2	90.4	0.13
	<30	40	201.4	129.5	
SFA (cm ²)	>30	50	138.6	81.5	0.48
	<30	40	128.1	55.5	
IMFA (cm ²)	>30	50	10.4	10.8	0.80
	<30	40	12	8	
MA150 (cm ²)	>30	50	139	30.6	0.28
	<30	40	131.9	33.2	
MD150 (HU)	>30	50	30.7	7.43	<0.01
	<30	40	25.3	8.04	
VFA/SFA	>30	50	1.28	0.53	0.21
	<30	40	1.47	0.64	
VFA/MA150	>30	50	1.19	0.60	0.34
	<30	40	1.46	0.89	

*: Six patients, who died due to causes other than bladder cancer, were excluded and the analysis regarding cancer-specific survival was done on 90 patients IMFA: Inter-muscular fat-area, MA150: Muscle area (between -29HU and 150HU), MD150: Muscle density (between -29HU and 150HU), SFA: Subcutaneous fat area, TFA: Total fat area, VFA: Visceral fat area, SD: Standard deviation, CT: Computed tomography

Skeletal muscle density (SMD), which was abbreviated as MD150 in this study, is a new measurement parameter which is frequently encountered in recent studies (4,11,19). It is reported to represent the myosteatosis, in which lower density of skeletal muscle shows a higher adipose tissue content of muscle (11). However, proposed thresholds to define low SMD still vary between studies. As an example, in the study of Zhuang et al. (20), sex-specific cut-off values for low SMD were <38.5 HU for males and <28.6 HU for women. Nonetheless, those thresholds were set as <35.5 HU for males and <32.5 HU for women in the study of Xiao et al. (21). In our study, instead of using muscle density as a representative of myosteatosis, we directly measured IMFA, using a densitometric limit of -190 to -30 HU,

to show only adipose tissue within muscle compartments, which was also used in a previous study (22). IMFA was found to be significantly correlated with low Clavien-Dindo scores (i.e., ≤2) and longer hospital stay (i.e., >10 days) in our study. On the other hand, although MD150 was also associated with Clavien-Dindo score, we could not find significant relation of muscle density with the hospital stay. Therefore, we believe that IMFA may better demonstrate myosteatosis than muscle density measurements. To the best of our knowledge, IMFA has not been studied as a prognostic factor in bladder cancer patients undergoing radical cystectomy, therefore we cannot make a comparison with the literature.

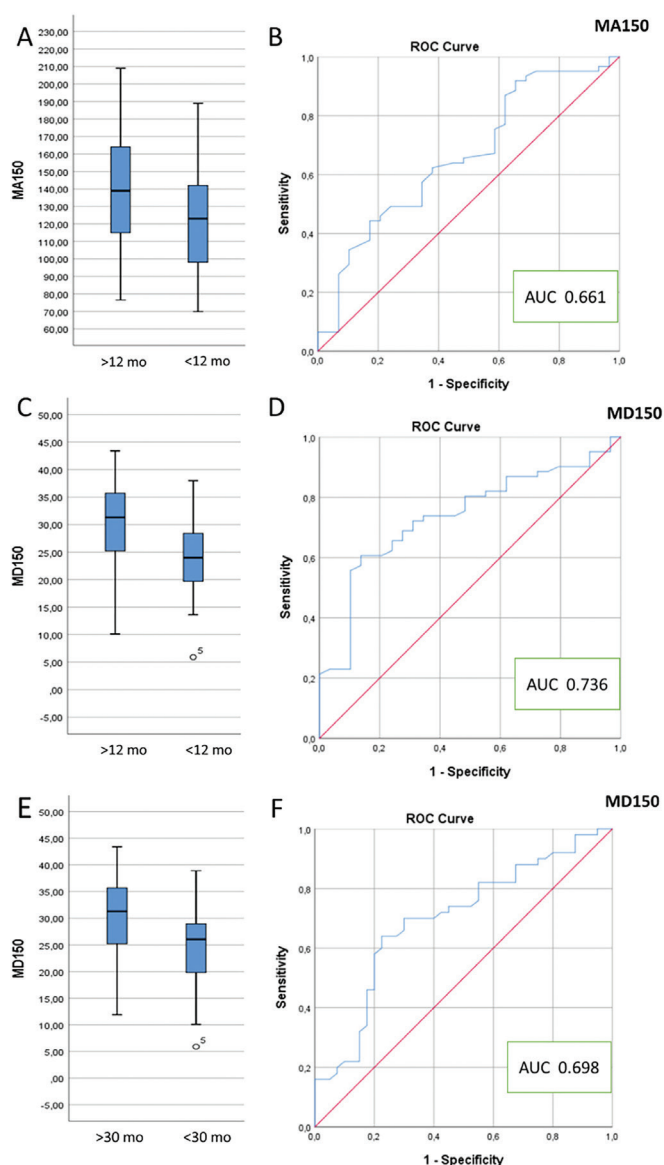


Figure 3. Box-plots of survival according to given thresholds for MA150 (12-months, (A) and MD150 (12-months, (C); 30-months, (E) and accompanying ROC analysis curves (B, D, F, respectively) for discrimination of two groups. Area under the curve is 0.661 for MA150 (12-months) and 0.736 and 0.698 for MD150 (12-months and 30-months, respectively)

MA150: Muscle area (between -29HU and 150HU), MD150: Muscle density (between -29HU and 150HU), AUC: Area under the curve, ROC: Receiver operating characteristics

Bladder cancer patients represent a population with high-risk of comorbidities, considering not only their advanced age, but also major underlying health conditions, poor performance status and tobacco use. At present, there are several existing studies on sarcopenia and body composition on bladder cancer. According to those studies, sarcopenia was found to be a strong indicator of reduced overall and cancer-specific

survival (23,24). Moreover, psoas muscle area was shown to be associated with major complications and psoas muscle index was shown to be an independent risk factor for survival after cystectomy (8,11). Similarly, our findings suggested that skeletal MA150 was significantly associated with major postoperative complications and 12-months survival after radical cystectomy. However, although trends regarding high SFA in the group with good prognosis and low VFA or VFA/SFA in the group with bad prognosis was found, there was no confirmed statistical significance in our study. Those results were also consistent with the study of Engelmann et al. (11). Moreover, myosteatosis, measured as psoas muscle or abdominal SMD was shown to predict poor cancer-specific survival in bladder cancer patients (25,26). Comparably, muscle density (i.e., MD150) was associated with both 12- and 30-months survival as well as postoperative complications after cystectomy, according to our results. Nevertheless, the prognostic roles of muscle density and IMFA, regarding myosteatosis and declined muscle quality, are warranted to be studied and validated in larger future studies to integrate them into the routine clinical practice as novel parameters in those bladder cancer patients.

Overall, preoperative assessment of sarcopenia in bladder cancer patients is essential to have an insight into the possible disease course and guide perioperative management. Early nutritional support with regulation of protein intake and prehabilitation programs, including resistance exercise, may have a significant role in improving muscle quality, hence reducing postoperative complications in sarcopenic patients. According to the European Society for Clinical Nutrition and Metabolism guidelines, in surgical patients with cancer, body composition should be assessed preoperatively, and when CT software is available, it should be used as a gold standard (27). Therefore, incorporation of CT-based body composition parameters into the routine preoperative assessment and radiology reports is of paramount importance to help stratify patients at risk and allow timely referral to nutritionists and physiotherapists in this vulnerable patient group.

Study Limitations

Our study has several limitations. First, it was a single-center retrospective study. Second, we were not able to investigate sex-specific differences due to very few numbers of female patients in our study cohort. Third, patients with muscle-invasive and muscle non-invasive bladder cancer were not further analysed. Fourth, follow-up information to assess progression-free survival was not accessible in all patients due to retrospective nature of the study and missing hospital records. Fifth, the patients' comorbidity status and scores were not available in our dataset due to insufficient data in the digital hospital records, which limited our ability to assess the impact of our results on overall survival fully. Lastly, BMI, SMI, and sarcopenia were not directly evaluated in our study due to missing patient information, particularly the weight or the height.

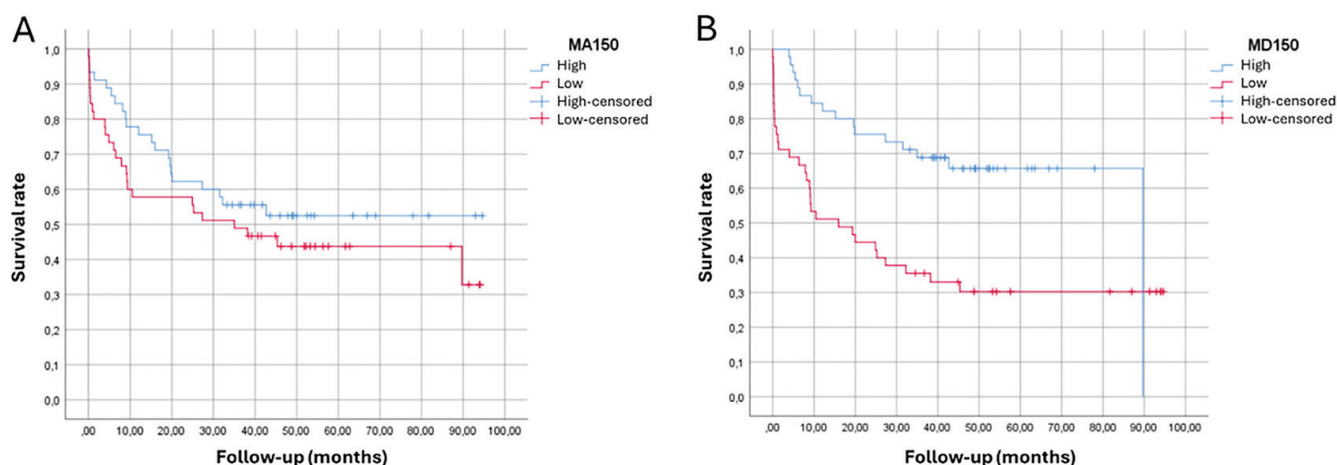


Figure 4. Kaplan Meier curves of MA150 (A) and MD150 (B) on long-term cancer-specific survival in patients with high and low values. High MA150 or MD150 were defined by the higher half

MA150: Muscle area (between -29HU and 150HU), MD150: Muscle density (between -29HU and 150HU)

Conclusion

Non-invasive and semiautomatic quantification of CT-based body composition parameters in the pre-operative CT scans may predict prognosis and improve risk stratification in bladder cancer patients undergoing radical cystectomy. This is particularly important not only in treatment planning and in decision-making regarding fitness and nutritional support for surgery, but also in counseling patients regarding expected outcomes after cystectomy.

Ethics

Ethics Committee Approval: This retrospective single-centre study was Institutional Review Board of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital approved (decision number 2020/8-6, date: 08.07.2020).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: B.Ç.T., H.Ş., Design: B.Ç.T., E.K., H.Ş., Data Collection or Processing: B.Ç.T., E.K., Analysis or Interpretation: B.Ç.T., H.Ş., Literature Search: B.Ç.T., Writing: B.Ç.T., H.Ş.

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Supplementary Links: <https://d2v96fxpocvxx.cloudfront.net/c2f7718d-0796-4c18-a6d4-3c339e748b23/content-images/e00d1451-720d-4fac-a433-4b7975ebd66c.pdf>

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The Significance of Ga-68 PSMA PET SUV_{max} Value in Distinguishing Multimetastatic from Oligometastatic and High-risk from Intermediate Risk Prostate Cancer

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Abstract

Objective: This study aims to identify the maximum standardized uptake value (SUV_{max}) value that predicts the presence of oligometastatic and high-risk prostate cancer and forecasts disease behavior.

Materials and Methods: In this retrospective analysis, patients who underwent 12-quadrant transrectal prostate biopsy in our clinic were evaluated in the study. D'Amico risk scoring was performed. Data of non-metastasis, oligometastatic and multimetastatic patients were recorded using imaging methods. Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) SUV_{max} values, prostate-specific antigen (PSA) and pathology parameters were recorded. PSA and SUV_{max} values were compared between oligometastatic/multimetastatic and D'Amico risk groups. By performing receiver operating characteristic analyses, SUV_{max} values in predicting oligometastatic and high-risk disease were tried to be predicted.

Results: According to the D'Amico risk scoring, there was no significant difference in SUV_{max} values between the low-risk group and the intermediate-risk group (p=0.18). However, a significant difference was observed between the intermediate-risk group and the high-risk group (p=0.006). According to the D'Amico risk classification, the best SUV_{max} cut-off value that distinguishes medium risk from high risk was 7.95, and the sensitivity for this value was found to be 73% and the specificity was 86%. The cut-off SUV_{max} value in distinguishing between oligometastatic and multimetastasis was found to be 12.65, and its sensitivity was 77% and specificity was 68%. The area under the curve was found to be 0.735.

Conclusion: PSMA-PET should be considered as a factor guiding treatment in prostate cancer. The SUV_{max} value of 7.95 in the distinction of high-risk prostate cancer and the SUV_{max} value of 12.65 in the distinction of multimetastatic prostate cancer are safe parameters that can be used in daily practice. It will achieve more successful results with more standardized studies conducted on larger populations and will be used in a more standardized way in planning treatment.

Keywords: Prostatic neoplasms, metastasis, SUV_{max}, Ga-68 PSMA PET/CT

Introduction

Prostate cancer ranks as the most frequently diagnosed cancer in men (21%) (1). While the 5-year survival rate for prostate cancer is around 100% in localized disease, it drops to 31% in metastatic disease (2). Although the treatment varies depending on the risk group and degree of the disease, follow-up, surgical treatment, hormonal therapy, radiotherapy and their combinations are decided according to the spread of the disease

and its aggressiveness. Perhaps the most accurate approach for prostate cancer, which is discussed today at what stage treatment is required, is to determine the risk of the severity of the disease. By performing a digital rectal examination, tests such as prostate specific antigen, imaging such as magnetic resonance, bone scintigraphy, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and using the Gleason scoring system, the potential of the disease is interpreted and treatment is planned at the beginning.

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The purpose of clinical staging in prostate cancer is to determine the burden of the disease and to treat the patient with the most appropriate treatment plan by estimating the prognosis through pre-treatment clinical parameters. The procedures to be chosen for staging are determined according to risk classification. The D'Amico risk classification is the most frequently utilized system for grouping prostate cancer risk (3).

Oligometastatic disease can be defined as an intermediate stage between local advanced disease and widespread metastasis. Especially with the development of diagnostic and staging methods such as functional imaging, oligometastatic disease is diagnosed more frequently than before. Our knowledge of oligometastatic disease has matured over the past two decades (4). Clinical studies play a crucial role in closely observing patients, enabling the detection of even the smallest masses through advanced imaging techniques, and uncovering treatments that extend the survival of individuals affected by the disease (5). Due to the lack of consensus on the definition of oligometastatic prostate cancer, the criteria frequently referenced are based on the CHAARTED and LATITUDE trials (6). Prostate cancer with a limited number of metastases, typically fewer than five lesions, is defined as oligometastatic. This form of the disease involves lesions contained within the axial versus the appendicular skeleton (7). This definition of oligometastasis has also been included in the European Urology Guidelines (8,9).

Surgical procedures or stereotactic radiotherapy may serve as appropriate alternatives for a limited number of metastatic lesions categorized as oligometastatic (10). Several studies have reported that radical treatment approaches—such as radical prostatectomy or radiotherapy—when applied in addition to hormone therapy, improve overall survival in patients with oligometastatic prostate cancer. In metastatic prostate cancer, it is essential to determine the tumor burden in order to achieve satisfactory treatment outcomes (11). Therefore, it is important to distinguish oligometastatic disease from multimetastatic disease in the initial staging. Prostate cancer cells display high levels of Type II transmembrane glycoprotein antigen (PSMA) on their surface. As the tumor grade increases, Ga-68 PSMA uptake and maximum standardized uptake value (SUV_{max}) increase (12). In this way, malignant lesions can be distinguished from benign lesions, and metastases of prostate cancer and even recurrences after treatment can be detected.

In this study, we aim to determine the relationship between SUV_{max} value of prostate cancer primary lesion in Ga-68 PSMA scan and the D'Amico risk score, ISUP grade, lymph node involvement, oligometastasis and neurovascular invasion.

Materials and Methods

The data of patients who underwent 12-quadrant transrectal ultrasound-guided prostate biopsy for the purpose of investigating prostate cancer were evaluated retrospectively. ISUP grade scores of the patients were recorded using Gleason parameters according to the conditions implemented by the International Society of Urological Pathology in 2014 (13). D'Amico risk groups were evaluated according to prostate biopsy material. Categorized as mentioned in the European Urology Guidelines (9).

Prostate-specific antigen (PSA) (total) values of the patients measured before treatment were recorded. It was ensured that no more than 45 days elapsed between the PSMA PET and PSA measurement period. Ga-68 PSMA PET/CT results of the patients were evaluated. Metastases were recorded. Neurovascular invasion and lymph node metastasis parameters were recorded according to prostate biopsy and PSMA PET data. Metastases were defined based on PSMA PET/CT findings. In this study, metastatic lesions were evaluated radiologically without histopathological confirmation and were defined as nuclear medicine imaging foci showing PSMA uptake consistent with metastasis.

In our study, we adopted the definition of oligometastasis consistent with previous studies and those accepted in the European Urology Guidelines (7,8). Oligometastasis was defined as the presence of five or fewer metastatic lesions.

The study was initiated by obtaining approval numbered 2023-11/06, dated: 16.11.2023, from the Scientific Research Ethics Committee of Sivas Cumhuriyet University. All evaluations in our study were made in accordance with the ethical rules of the 1964 Declaration of Helsinki. Since our study was retrospective, consent was not obtained from the included patients.

Patients who had previously undergone transurethral prostate resection, radical prostatectomy, pelvic radiotherapy, or hormone therapy were excluded from the study.

Ga-68 PSMA PET Imaging Technique and SUV_{max} Measurement

Patients were administered of 2 MBq/kg of Ga-68 PSMA 45 to 60 minutes prior to imaging. All patients underwent imaging (GE Medical Systems, LLC, 3000 N. WI., U.S.A.). Firstly, CT imaging was performed. PET imaging was performed in three dimensions, including cranium and feet, for approximately 3 minutes in each bed position. CT and PET images were matched and fused. Subsequently, visual and semi-quantitative analyses were performed by a single nuclear medicine specialist (ZH). The highest measured SUV_{max} value in the prostate was recorded. The regions of bone, lymph nodes, and visceral organs exhibiting PSMA expression were recorded as a result of the whole-body scan.

Statistical Analysis

SPSS 20.0 software was used for statistical analysis (IBM Inc., Chicago, IL, USA). Descriptive statistics were utilized to assess numerical variables. The normality of the PSA and SUV_{max} values was evaluated (Kolmogorov-Smirnov test), which indicated that both variables were non-parametric. Consequently, comparisons were made using the Mann-Whitney U test and the Kruskal-Wallis test. Significant results of the post-hoc analysis are indicated in the tables with superscript letters, and the Dunn post-hoc test was applied for pairwise comparisons following the Kruskal-Wallis test. Receiver operating characteristic (ROC) analysis was used to determine the SUV_{max} value that best predicts multimetastatic and high-risk prostate cancer, and the area under the curve (AUC) values were presented with their 95% confidence intervals (CI). All tests were two-sided, with 95% CIs and p-values reported (p<0.05).

Results

The data of 81 patients between 2018 and 2024 were retrospectively examined, but 5 patients were not included in the study because all data could not be accessed, 2 patients transurethral surgery was performed. A total of 74 patients were included in the study, with a median age of 69.40 years (range: 52-84 years). When divided into categories, patients under the age of 65 constituted 35% of the patients and patients over the age of 65 constituted 65%. Thirty-eight of 74 patients (51%) were locally and locally advanced (non-metastatic), 36 (49%) were metastatic. Twenty-nine of them (38%) were oligometastatic and 7 were multi-metastatic (9%). Of the 74 patients, 35 (47%) had lymph node metastasis, 29 (39%) had bone metastasis, and 7 (9%) had visceral metastasis. Of the 35 patients with lymph node metastases, 12 had only pelvic lymph nodes, 23 had pelvic and extra-pelvic lymph node metastases. Of patients, 12 (16%), 13 (18%), 12 (16%), 23 (31%), and 14 (19%) were reported as ISUP grade groups 1, 2, 3, 4, and 5 respectively. According to D'Amico risk classification, there were 4 patients with low risk (5%), 11 patients with medium risk (15%), and 24 patients with high risk (32%). According to the biopsy material results the number of patients with positive neurovascular invasion was 39 (53%) (Table 1).

Prostatic primary tumor SUV_{max} and PSA values were significantly different between the metastatic and non-metastatic groups. The p-values were 0.025 and 0.007 respectively. When the groups were evaluated as no metastasis, oligometastasis and multiple metastasis, PSA and SUV_{max} values showed significant differences between the groups. P-values were 0.00 and 0.01, respectively. According to D'Amico risk grouping, PSA and SUV_{max} values were found to be different between intermediate risk and high risk groups. P-values were found to be 0.003 and 0.006, respectively. PSA and SUV_{max} values were not significantly different between groups with and without visceral metastasis (Table 2). When the lymph node metastasis groups were evaluated as no lymph node, pelvic and extrapelvic metastasis,

here was a significant difference between the groups in terms of PSA and SUV_{max} values. The p-values were 0.035 and 0.010, respectively.

According to the D'Amico risk scoring, there was no significant difference in SUV_{max} values between the low-risk group and the intermediate-risk group (p=0.18). However, a significant difference was observed between the intermediate-risk group and the high-risk group (p=0.006). Box plot graph is shown in Figure 1.

According to the D'Amico risk classification, the best SUV_{max} cut-off value that distinguishes low and medium risk from high risk was 7.95, and the sensitivity for this value was found to be 73% and the specificity was 86%. When the ROC curve was evaluated, the AUC was found to be 0.829 (95% CI: 0.72-0.94). The ROC curve is shown in Figure 2.

The cut-off SUV_{max} value in distinguishing between oligometastatic and multimetastasis was found to be 12.65, and its sensitivity was 77% and specificity was 68%. The AUC was found to be 0.735 (95% CI: 0.61-0.86). The ROC curve is shown in Figure 3.

Discussion

One of the things that is as important as the stage of the cancer in choosing treatment for prostate cancer is the tumor burden and behavior of the cancer (14,15). In our study, the prostatic SUV_{max} value of metastatic prostate cancer and the PSA and SUV_{max} values of non-metastatic prostatic cancer were found to be statistically different. Likewise, in the D'Amico risk grouping, which determines the risk of the disease, a significant difference was found between the intermediate and the high-risk group. There were also differences between oligometastatic and multimetastatic groups, which is important in treatment management. These differences give us valuable information at the initial evaluation stage of the disease. Especially in the D'Amico risk grouping, while there is no difference between the

Table 1. The statistical results of the groups, PSA and SUV_{max} values

		n (%)	PSA	p-value	SUV _{max}	p-value
			Mean ± standard error		Mean ± standard error	
ISUP grade	1	12 (16%)	23.56±6.26	0.270	6.03±0.76	0.046*
	2	13 (18%)	115.44 ±87.92		8.95±2.85	
	3	12 (16%)	374.46±269.57		17.07±3.36	
	4	23 (31%)	240.64±151.83		15.97±2.99	
	5	14 (19%)	688.23±367.58		15.55±2.60	
D'Amico	Intermediate risk	11 (15%)	5.36±1.54	0.003*	5.05±0.85	0.006*
	High-risk	24 (32%)	24.53±5.11		13.66±2.76	
Neurovascular invasion	None	35 (47%)	385.22±141.01	0.173	11.84 ± 1.52	0.046*
	Exist	39 (53%)	204.21±133.48		14.47±2.51	
Lymph node	None	39 (53%)	118.25±84.32	0.035*	11.34±1.64	0.010*
	Pelvic	12 (16%)	496.96±192.8		11.23± 4.18	
	Extrapelvic	23 (31%)	472.94±118.34		17.45±2.44	

*: Statistically significant (p<0.05), ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen; SUV_{max}: Maximum standardized uptake value

		n (%)	PSA		SUV _{max}	
			Mean ± standard error	p-value	Mean ± standard error	p-value
Metastasis	None	38 (51%)	25.33±3.66	0.007*	10.28±1.81	0.025*
	Exist	36 (49%)	569.02± 189.37		16.33±1.90	
Bone metastasis	None	45 (61%)	35.49±5.46	0.009*	12.08±1.85	0.042*
	Exist	29 (39%)	684.48±230.61		14.73±1.91	
Visceral Metastasis	None	67 (91%)	287.40±105.90	0.744	13.05±1.45	0.089
	Exist	7 (9%)	313.04±159.91		14.74±3.38	
Metastasis	None-metastasis	38 (51%)	25.33±3.66	0.00*	10.28±1.81	0.01*
	Oligo	29 (39%)	125.00±23.63		11.29±1.71	
	Multiple	7 (10%)	865.27±96.81		19.94±3.88	

*: Statistically significant (p<0.05), PSA: Prostate-specific antigen, SUV_{max}: Maximum standardized uptake value

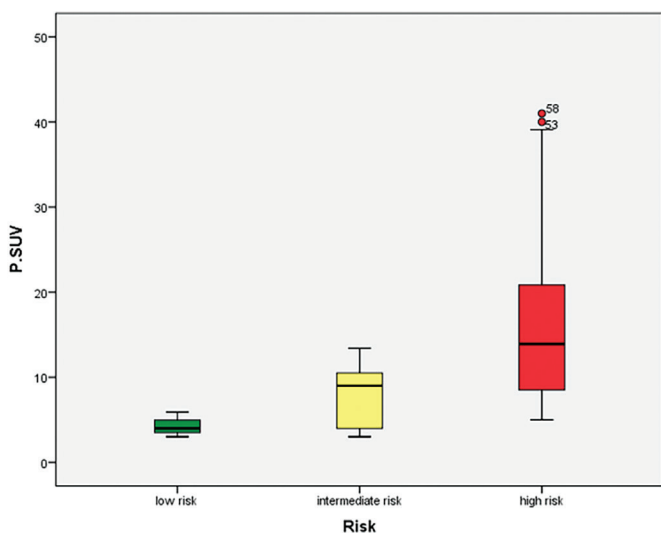
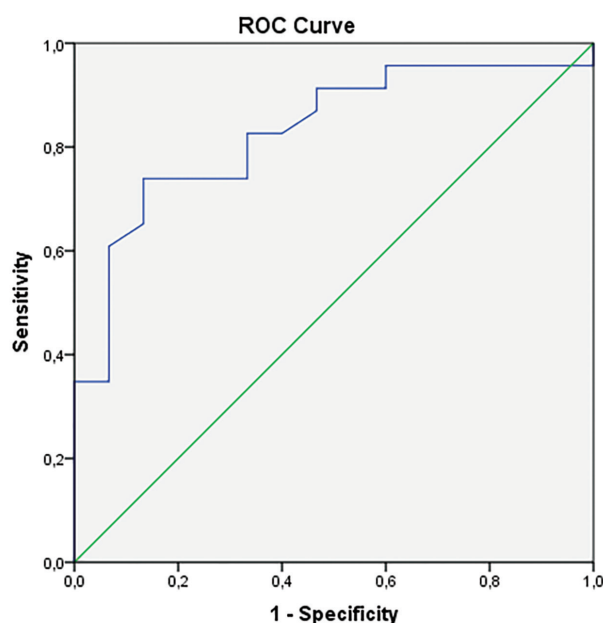


Figure 1. Box plot of SUV_{max} values by D'Amico risk groups
X-axis: Risk groups, Y-axis: Primary tumor, SUV_{max}: Medians and outliers are shown

low and medium risk groups, the fact that there is a significant difference in the high risk group shows that it provides valuable information in predicting the risk. The difference in SUV_{max} values in the ISUP rating system shows that the SUV_{max} value can be used in scientific studies in this direction in the future. For example, an upgrade rate of 38-72% is observed after radical prostatectomy (16,17). Various nomograms have been produced using Gleason score and clinical stages to predict this upgrade (18). SUV_{max} value can also be used as a predictor in this regard and this issue should be investigated with new studies.

We see that PSMA PET is of increasing importance in determining metastasis and lymph node involvement before surgery. In the study conducted by Meijer et al. (19), it was observed that adding PSMA PET data to nomograms increased the success of predicting lymph node involvement. However, in a study



Diagonal segments are produced by ties.

Figure 2. ROC curve for SUV_{max} distinguishing low-intermediate vs. high D'Amico risk

X-axis: 1-Specificity, Y-axis: Sensitivity, ROC: Receiver operating characteristic
conducted by Klingenberg et al. (20), a result was obtained that did not fully support other studies. Although the SUV_{max} value increased with increasing ISUP value in the cohort consisting only of the high-risk patient population, the fact that even the lowest SUV_{max} values coincided with high ISUP values was found to be a reason that questions its applicability.

Due to the widespread use of PET/CT, many scientific articles have been written so far on the diagnosis and treatment processes of prostate cancer. In Pepe et al.'s (21) manuscript, they found the best cut-off value of SUV_{max} value that can be

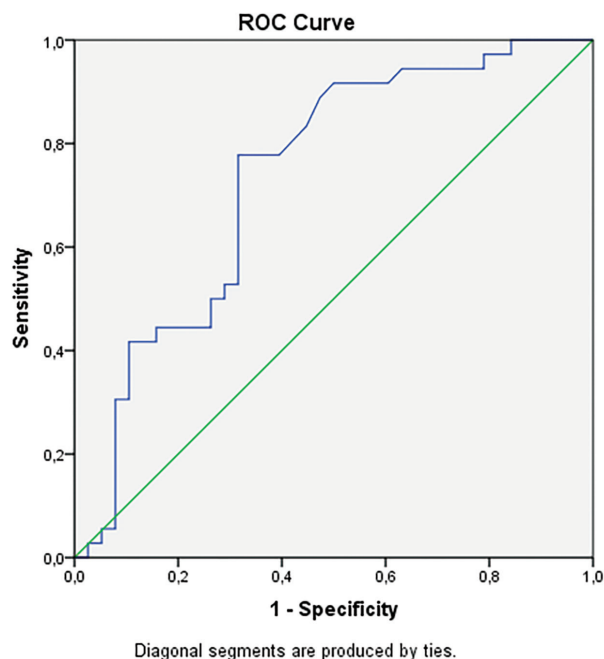


Figure 3. ROC curve for SUV_{max} distinguishing oligometastatic vs. multimetastatic disease

X-axis: 1-Specificity, Y-axis: Sensitivity, ROC: Receiver operating characteristic

used in the diagnosis of prostate cancer to be 8.0. For this value, the presence of ISUP grade group 1 was found with 87.7% accuracy, the presence of grade group 2 was found with 89.3% accuracy, and the presence of Grade group 3 and above was found with 100% accuracy (21). In the article of Demirci et al. (22), written on the same subject, they found a significant difference between SUV_{max} values and risk groups, and the cut-off value in detecting high-risk disease was found to be 9.1, and 78% sensitivity and 81% specificity were determined for this value. These differences in cut-off values across studies may be attributed to variations in patient selection criteria, imaging intervals between biopsy and PET/CT, and methods used for determining the optimal threshold. In a study conducted by Yi et al. (23) with 147 patients, the cut-off SUV_{max} value of the intermediate and high risk prostate cancer group was found to be 10.12. In our case series of 74 patients, we found this value to be 7.95.

There are many articles aimed at detecting oligometastatic prostate cancer, which guides prostate cancer treatment and has become increasingly important over the last 20 years. In the study conducted by Erdođan et al. (24), they found a cut-off SUV_{max} value of 7.96 in the distinction between oligometastatic and metastatic prostate cancers. For this value, 68% sensitivity and 86% specificity were determined (24). In our study, this value was 12.65, and the reason for this difference may be due to the absence of a visceral metastatic patient group in Erdođan et al.'s (24) study or may be related to the excess of extreme values in our study. There are many other studies on this subject, and although most of them have similar aims and results, the numbers and statistics do not completely match each other. The reasons for these are that no studies have been conducted on large and standardized sample groups and the times between

prostate biopsy and PSMA PET/CT are different in the studies. Due to different clinics, there are many factors affecting the results such as scintigraphy evaluation and interpretation standardizations and pathologist differences. Based on all these evaluations, it is concluded that standardized and organized randomized controlled studies with larger samples are needed.

Study Limitations

A limitation of our diagnostic approach is the lack of histopathological confirmation of metastatic lesions. Since metastases were identified solely based on nuclear imaging findings, differences in sensitivity and specificity compared with surgically or pathologically confirmed diagnoses should be considered. This limitation may have influenced the detection rates and SUV_{max} threshold values in our study. The other limitation of our study can be stated as being retrospective and the study sample consisting of a low number of patients.

Conclusion

As a result, not only the pathological diagnosis but also the risk and severity are important in prostate cancer. PSMA-PET should be considered as a factor guiding treatment in prostate cancer. The SUV_{max} value of 7.95 (sensitivity 73%, specificity 86%) in the distinction of high-risk prostate cancer and the SUV_{max} value of 12.65 (sensitivity 77%, specificity 68%) in the distinction of multimetastatic prostate cancer are safe parameters that can be used in daily practice. It will achieve more successful results with more standardized studies conducted on larger populations and will be used in a more standardized way in planning treatment.

Ethics

Ethics Committee Approval: The study was initiated by obtaining approval numbered 2023-11/06, dated: 16.11.2023, from the Scientific Research Ethics Committee of Sivas Cumhuriyet University.

Informed Consent: Since our study was retrospective, consent was not obtained from the included patients.

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ö., A.A., H.S., E.K., Concept: İ.E.E., A.A., H.S., Design: A.Ö., Data Collection or Processing: A.Ö., A.A., Analysis or Interpretation: İ.E.E., A.Ö., Literature Search: İ.E.E., Z.H., E.K., Writing: İ.E.E., A.Ö.

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Incidental Prostate Cancer After HoLEP: Evaluation of Predictive Factors

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Abstract

Objective: To evaluate the predictive value of demographic, preoperative, and postoperative clinical parameters for detecting incidental prostate cancer (iPCa) in patients undergoing holmium laser enucleation of the prostate (HoLEP).

Materials and Methods: Clinical records of male patients who underwent HoLEP for BPH between 01.01.2023 and 01.01.2024 were retrospectively reviewed. Demographic, preoperative, and postoperative data, including total prostate-specific antigen (PSA), free PSA, and PSA density (PSAd), were analysed. The role of these measurements and data in predicting the likelihood of iPCa in patients whose pathology results revealed iPCa were evaluated.

Results: A total of 112 patients underwent HoLEP, including 96 with BPH (85.7%) (group 1) and 16 with iPCa (Group 2) (14.3%). Median age was 66.5 years. Demographic data and PSA levels were comparable between groups. PSAd was significantly higher in Group 2 (0.06 vs. 0.04 ng/mL/cc, p=0.008), and PSAd ≥ 0.15 was more frequent in Group 2 (25% vs. 5.2%, p=0.023). Pathology revealed 68.7% Gleason grade group 1, all under active surveillance, and 31.3% grade group 2-5, treated with radiotherapy \pm hormonal therapy. Multivariate analysis identified PSAd as the only independent predictor of iPCa (odds ratio: 9.09, 95% confidence interval: 1.12-73.8, p=0.01). Receiver operating characteristic analysis showed moderate diagnostic performance for PSAd (AUC: 0.71), with a 0.08 ng/mL/cc threshold yielding 75% sensitivity and 69.7% specificity.

Conclusion: iPCa after HoLEP is relatively common but mostly low-grade, with favourable oncological outcomes. Preoperative PSAd was identified as a significant predictor of iPCa. These findings may aid in preoperative patient counselling and risk-stratified management. Active surveillance appears safe and effective for low-grade iPCa.

Keywords: Incidental prostate cancer, HoLEP, PSA density, BPH

Introduction

Benign prostatic hyperplasia (BPH) is a common urological condition in aging men and accounts for the majority of urology outpatient visits (1,2). By causing benign enlargement of the prostate, BPH leads to voiding symptoms and storage symptoms (3). If left untreated, it may lead to irreversible alterations in the detrusor muscle, resulting in bladder dysfunction, chronic urinary retention, and eventually upper urinary tract damage and kidney failure (4).

According to the European Association of Urology (EAU) guidelines, the first-line treatment for BPH consists of lifestyle modifications. Pharmacological treatments are recommended as second-line therapies depending on patient symptoms.

When these treatments are insufficient, surgical treatment options may be considered (5,6). Among the surgical options for BPH, holmium laser enucleation of the prostate (HoLEP) surgery has become one of the most preferred methods due to advancements in laser technology and its favourable outcomes (7).

During the preoperative evaluation of patients undergoing BPH surgery, in addition to functional assessment, routine screening for prostate cancer is performed via digital rectal examination and measurement of serum prostate-specific antigen (PSA) (6).

However, even when prostate cancer screening is performed in accordance with EAU guidelines and patients without suspicious findings proceed to BPH surgery, incidental prostate cancer (iPCa) may still be detected in postoperative surgical specimens.

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Several studies in the literature have aimed to identify predictive factors for iPCa following BPH surgery (8-10). It is important to make sure patients are aware that this diagnosis could be discovered after undergoing surgery for BPH.

In this study, we aimed to evaluate, based on our institutional experience, the effectiveness of demographic characteristics and preoperative and postoperative clinical parameters in predicting the likelihood of detecting iPCa in patients who underwent HoLEP surgery at our clinic.

Materials and Methods

Clinical records between 01.01.2023 and 01.01.2024 were reviewed for the study. The demographic parameters, preoperative and postoperative data, and pathology results of patients who underwent HoLEP surgery for BPH in our clinic were retrospectively evaluated. Evaluation and treatments for these patients were applied based on the EAU guidelines (6). Ethical approval for the study was obtained from the Local Ethics Committee of Marmara University Faculty of Medicine (protocol no: 09.2025-25.0940, date: 21.11.2025).

Male patients over 40 years of age who underwent surgery for BPH in our hospital during this period were included in the study. Data from patients with at least one year of follow-up were recorded. Patients with incomplete or irregular data, previous BPH surgery, a history of prostate cancer, or abnormal rectal examination findings were excluded from the study. Prostate biopsy or multiparametric magnetic resonance imaging (MRI) was performed selectively in patients with clinical suspicion of malignancy (e.g., elevated PSA, abnormal rectal examination). Patients without a prior diagnosis of prostate cancer underwent HoLEP for benign prostatic enlargement, and iPCa was defined as cancer detected in the surgical specimen.

HoLEP procedures were performed using a 60-watt holmium: YAG laser (Quanta Cyber Ho model) with a 550 μ m laser fiber. Laser settings were constant in all patients, being 2 Joules x 30 Hertz in Virtual Basket pulse modulation mode. All surgical procedures were performed by an experienced surgeon who had performed at least 100 HoLEP procedures. All surgeries were carried out using the en bloc technique.

Demographic data, preoperative and postoperative medical histories, physical examination findings, total PSA, free PSA, and PSA density (PSAd) records of male patients over 40 years of age who underwent surgery for BPH were retrospectively analysed statistically. PSAd was calculated as the ratio of serum PSA level (ng/mL) to prostate volume (cc), with prostate volume measured by preoperative imaging. Prostate volume was expressed in cubic centimeters (cc), which is equivalent to milliliters. The role of these measurements and data in predicting the likelihood of iPCa in patients whose pathology results revealed iPCa were evaluated.

Patients without iPCa were considered group 1, while those with iPCa were considered group 2. The demographic, preoperative, and postoperative data of these groups were compared based on the obtained results. Parameters that showed statistically significant differences in the group with iPCa were analysed in more detail, and their effects were discussed. Parameters with significant differences between groups were analysed as

continuous variables in regression models to maintain statistical power and prevent potential information loss associated with arbitrary categorization. In addition, pathology data and treatments applied as a result of the diagnosis in patients with iPCa were reported.

The primary outcome of this study was the incidence of iPCa detected in patients undergoing HoLEP for BPH. Secondary outcomes included the assessment of demographic and clinical parameters (age, PSA, PSAd, prostate volume, comorbidities) as potential predictors of iPCa, the distribution of Gleason grade groups among patients with iPCa, and the subsequent management strategies and short-term postoperative outcomes.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS 25.0. Due to non-normal data distribution (Kolmogorov-Smirnov test), non-parametric tests were applied. Numerical data were presented as median interquartile range, and categorical data as counts/percentages. The chi-square test was used to analyse categorical data, while the Mann-Whitney U test was used to compare groups. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive value of relevant parameters. Multivariate regression analysis was conducted to determine independent predictors. A p-value <0.05 was considered statistically significant.

Results

A total of 112 patients who underwent HoLEP were included in the analysis, of whom 96 (85.7%) had BPH and 16 (14.3%) were incidentally diagnosed with prostate cancer. The median age of the patients included in the study was 66.5 (62-72) years. The median prostate volume was 80 cc (62.75-120), the total PSA was 3.58 ng/mL (1.94-6.71), and the PSAd was 0.048 (0.024-0.091). The demographic and clinical characteristics of the groups are presented in Table 1. There were no significant differences between groups in terms of age, body mass index (BMI), hypertension, dyslipidaemia, or diabetes mellitus. Median prostate volume tended to be lower in Group 2, but the difference did not reach statistical significance. Preoperative total PSA, free PSA, and f/t PSA ratio were comparable between groups. However, PSAd was significantly higher in group 2 (0.06 vs. 0.04 ng/mL/cc, $p=0.008$). When categorized, PSAd ≥ 0.15 ng/mL/cc was more frequent in Group 2 (25% vs. 5.2%), demonstrating statistical significance ($p=0.023$). Postoperative PSA and the pre/postoperative PSA ratio showed no significant differences between the groups.

Pathological evaluation of the incidental cancer cohort revealed that 11 patients (68.7%) had Gleason grade group 1 disease, all managed with active surveillance. Five patients (31.3%) had Gleason grade group 2-5 disease; 60% of these were stage T1a and 40% T1b. Four patients received radiotherapy combined with hormonal therapy and one underwent radiotherapy alone (Table 2).

In multivariate logistic regression analysis (Table 3), PSAd emerged as the only significant independent predictor of iPCa [odds ratio: 9.09, 95% confidence interval (CI): 1.12-73.8, $p=0.01$]. The odds ratio for PSAd reflects the change in the risk of iPCa per 0.01 unit increase in PSAd.

ROC curve analysis demonstrated that PSAd had a moderate diagnostic performance for detecting iPCa, with an AUC of 0.71 (95% CI: 0.583-0.837). As illustrated in Figure 1, PSAd showed a reasonable discrimination ability, with an optimal cut-off value of 0.08 ng/mL/cc providing a sensitivity of 75% and a specificity of 69.7%.

Discussion

In this study of 112 patients undergoing HoLEP, 14.3% were incidentally diagnosed with prostate cancer, while the majority had BPH. The groups were comparable in terms of age, BMI, and comorbidities, and there were no significant differences in preoperative total PSA, free PSA, or f/t PSA ratio. Notably, PSAd was significantly higher in patients with iPCa, with a greater proportion exhibiting PSAd ≥ 0.15 ng/mL/cc. Most incidental cancers were Gleason grade group 1 and managed with active surveillance, whereas a minority had higher-grade disease requiring radiotherapy, with or without hormonal therapy. Multivariate analysis identified PSAd as the only independent predictor of iPCa. ROC analysis further supported its diagnostic value, showing a moderate performance (AUC: 0.71) with a threshold of 0.08 ng/mL/cc yielding 75% sensitivity and 69.7% specificity. As this study focused on iPCa, only patients without a known diagnosis of prostate cancer prior to surgery were included. However, the lack of a standardized preoperative biopsy or imaging protocol may have resulted in undiagnosed prostate cancer in some patients, which should be considered when interpreting the results.

A review of the literature shows that there are publications investigating predictive factors for iPCa in patients undergoing

HoLEP, similar to our study. In a retrospective study by Sid Ahmed and Nkwam (11), iPCa was detected in 259 HoLEP patients at a rate of 14.3%. This rate is very similar to the iPCa incidence observed in our study. In Sid Ahmed and Nkwam's (11) study, most cancers were low-grade (Gleason 6), and only a very small proportion (1.5%) were high-grade (Gleason ≥ 8). Unlike our study, when evaluating patients with iPCa, only age was significantly higher, while PSA, PSAd, and prostate volume did not differ significantly from patients with benign histology. Most incidental cancers were suitable for conservative management.

In a large cohort of 913 patients undergoing HoLEP, Sakai et al. (12) found that 20% had iPCa. Higher PSAd, preoperative biopsy status, and ongoing 5-alpha reductase inhibitor therapy were associated with iPCa detection, but the authors noted that these factors alone are not sufficient to reliably identify high-risk patients in advance. Their results highlight the importance of a standardized, risk-adapted preoperative approach, including imaging and selective biopsy, to improve detection of clinically significant prostate cancer before non-oncologic surgery.

In a study by Elkoushy et al. (13) including 1,242 HoLEP patients, the rate of iPCa was reported as 5.6%. Considering that reported iPCa rates in the literature range from 5% to 20%, the 14.3% rate observed in our study appears generally consistent with previous findings. Elkoushy et al. (13) identified patient age and PSAd as preoperative factors associated with iPCa, while prostate volume was similar between groups; these findings are in line with our results. In their study, a PSAd cut-off of 0.092 yielded a sensitivity of 0.83 and specificity of 0.67. In our ROC analysis, a PSAd cut-off of 0.08 showed a sensitivity of 0.75 and specificity of 0.69. This comparison supports the value

	Group 1 (n=96)	Group 2 (n=16)	p-value
Age (years) median (IQR)	66.5 (62-72)	68.5 (62.25-74.75)	0.407
BMI (kg/m ²) median (IQR)	27.5 (25.18-30.8)	28.08 (26.68-29.91)	0.886
Hypertension, n (%)	35 (36.5)	4 (25)	0.373
Dyslipidaemia, n (%)	23 (24)	4 (25)	0.573
Diabetes mellitus, n (%)	28 (29.2)	4 (25)	0.496
Prostate volume (cc) median (IQR)	85 (65-122)	67 (57-90)	0.107
Total PSA (ng/mL) median (IQR)	3.53 (1.97-6.71)	4.28 (1.67-9.69)	0.812
Total PSA Group (ng/mL), n (%)			
0-4	56 (58.9)	8 (50)	0.506
4-10	26 (27.4)	4 (25)	
10-20	13 (13.7)	4 (25)	
Free PSA (ng/mL) median (IQR)	0.56 (0.33-0.72)	0.96 (0.39-1.72)	0.429
f/t PSA ratio median (IQR)	0.19 (0.14-0.33)	0.22 (0.16-0.3)	0.843
PSAd (ng/mL/cc)	0.04 (0.02-0.09)	0.06 (0.04-0.14)	0.008
PSAd group, n (%)			
<0.15	91 (94.8)	12 (75)	0.023
≥ 0.15	5 (5.2)	4 (25)	
Post-operative PSA (ng/mL) median (IQR)	0.37 (0.23-0.52)	1.31 (0.7-2.44)	0.178
Pre/post operative PSA ratio median (IQR)	6.53 (3.01-13.39)	3.03 (2.04-27.48)	0.744

BMI: Body mass index, PSA: Prostate-specific antigen, PSAd: PSA density, f/t PSA: Free-to-total PSA ratio, IQR: Interquartile range

of PSA_d as a predictive parameter for iPCa and indicates that, despite slight variations between cohorts, it remains a clinically meaningful indicator. The authors also emphasize that PSA_d can be particularly useful in predicting iPCa risk in older patients

	Gleason grade 1 (n=11)	Gleason grade 2-5 (n=5)
Stage n (%)		
T1a	11 (100)	3 (60)
T1b	0	2 (40)
Treatment n (%)		
Active surveillance	11 (100)	0
Radiotherapy	0	1 (20)
Radiotherapy + hormonal therapy	0	4 (80)
Hormonal therapy	0	0
Surgery	0	0

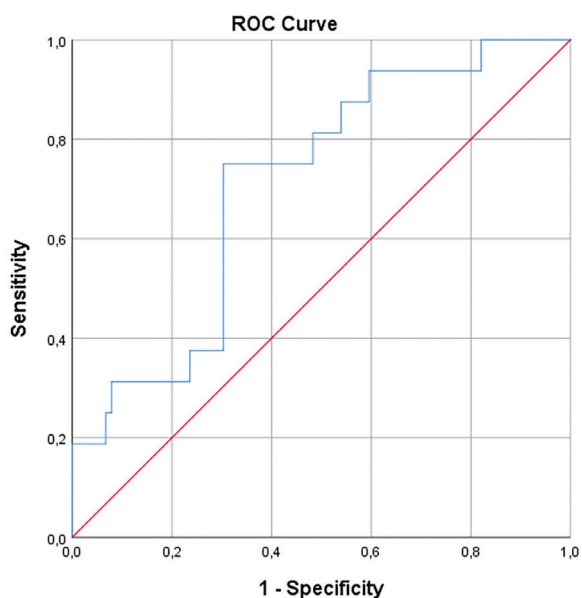
	OR	95% CI	p-value
PSA _d (0.01 ng/mL increase)	9.09	1.12-73.8	0.01
Age (per 1 year increase)	0.97	0.96-1.10	0.33
Prostate volume (per 1 cc increase)	0.99	0.95-1.05	0.12
Total PSA (per 1 ng/mL increase)	0.97	0.95-1.12	0.42

OR: Odds ratio, CI: Confidence interval, PSA: Prostate specific antigen, PSA_d: PSA density

and that active surveillance after HoLEP is a safe and effective management strategy for low-grade cancers.

In their retrospective study of 777 HoLEP patients, Shvero et al. (14) reported an iPCa rate of 7.1%. Among these patients, 61.8% had low-grade (GG1) iPCa, and clinically significant cancer was rare. This rate is similar to the pathology results in our study, where the proportion of GG1 patients was 68.7%. Unlike our study, smaller preoperative prostate volume was identified as a predictive factor for iPCa, with a 13% reduction in risk for every 10 mL increase in prostate volume. In addition, older age and smaller prostate volume were found to be risk factors for higher-grade (GG2 and above) iPCa. The observed differences in these findings may be attributable to cohort size and patient demographic characteristics.

A review of the literature shows that there are also systematic reviews on this topic. In the review by Cheng et al. (15), the incidence, predictive factors, and oncological outcomes of iPCa in men undergoing endoscopic prostate enucleation were investigated. Sixty-one studies were included in the qualitative synthesis, and 55 studies were included in the meta-analysis. The pooled incidence of iPCa was 8% (95% CI: 7.3-8.8). The results showed that increasing age, higher preoperative PSA and PSA_d, smaller prostate volume, higher postoperative PSA velocity, and lower enucleated prostate weight were significantly associated with iPCa. In BPH patients, the mean preoperative and postoperative PSA levels were 5.58±1.48 ng/dL and 1.06±0.27 ng/mL, respectively, while in iPCa patients these values were 7.72±2.90 ng/mL and 2.77±1.66 ng/mL. The mean PSA reduction was 82±1.8% for BPH patients and 68.2±12.1% for iPCa patients. According to pathology results, the majority of iPCa cases (68.7%) were managed with active surveillance.



Risk factor	AUC (CI %)	Threshold value	p-value	Sensitivity (%)	Specificity (%)
Incidental prostate cancer	0.71 (0.583-0.837)	0.08	0.04	75	69.7

PSA: Prostate specific antigen, CI: Confidence interval, ROC: Receiver operating characteristic

Figure 1. ROC analysis for PSA-density

The study suggests that the incidence of iPCa after enucleation of the prostate is approximately 8%, and in BPH patients a postoperative PSA <2.0 ng/mL and a PSA reduction >70% can be expected.

In the review by Yilmaz et al. (16), which included only studies of patients with iPCa after HoLEP (19 studies in total), the rate of iPCa after HoLEP was found to range from 5.64% to 23.3%. In this review, functional and oncological outcomes were generally reported as favourable, and a wide range of treatment options was suggested to be available.

The results of our study indicate that iPCa after HoLEP is not uncommon, although it is mostly low-grade, and oncological outcomes are generally favourable. Preoperative PSA_d was found to be important in predicting the risk of iPCa. The identification of a PSA_d cut-off value of 0.08 ng/mL/cc provides clinically relevant information for the preoperative assessment of patients undergoing HoLEP. Given that these patients often present with significantly enlarged prostate volumes, total PSA alone may be insufficient to accurately reflect cancer risk. In this setting, PSA_d offers a more refined risk stratification by accounting for prostate volume. Patients with PSA_d values above this threshold may warrant further diagnostic evaluation, including multiparametric MRI or targeted biopsy, to exclude clinically significant prostate cancer prior to surgery. On the other hand, patients with low PSA_d may be managed more conservatively, potentially avoiding unnecessary invasive procedures. In light of these findings, incorporating PSA_d into routine clinical practice may enhance patient counselling, optimize preoperative decision-making, and contribute to a more individualized approach in the management of benign prostatic obstruction.

Study Limitations

This study has several limitations, including its retrospective single-center design and relatively small sample size. These factors may have influenced the detection rate of iPCa and limit the generalizability of the findings. Second, preoperative prostate biopsy and multiparametric MRI were not routinely performed in all patients, as these modalities are generally reserved for individuals with clinical suspicion of prostate cancer. Therefore, some patients may have had undiagnosed malignancy prior to surgery, which was subsequently detected incidentally. Although this approach reflects real-world clinical practice, it may have influenced the incidence and detection of iPCa in our cohort. Additionally, long-term oncological follow-up was available for only a limited number of patients during the study period; therefore, more extensive data are needed regarding the long-term prognosis of iPCa and the management of rare high-grade cases. Future studies with larger, multicentre cohorts are needed to provide more robust evidence regarding the long-term prognosis of iPCa and the management of rare high-grade cases.

Conclusion

In summary, iPCa after HoLEP is not uncommon, although it is mostly low-grade, and oncological outcomes are generally favourable. Our study demonstrates that preoperative PSA_d is an important parameters in predicting the risk of iPCa. These findings may help surgeons and clinicians to inform patients

preoperatively and to develop risk-stratified approaches. In particular, since the likelihood of iPCa may be higher in patients with elevated PSA_d values, appropriate preoperative evaluation and patient counselling are crucial. In low-grade iPCa cases, active surveillance after HoLEP can be considered a safe and effective management strategy.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Local Ethics Committee of Marmara University Faculty of Medicine (protocol no: 09.2025-25.0940, date: 21.11.2025).

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Spontaneous Bladder Rupture After Radiotherapy

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Abstract

Radiotherapy, applied to the lower abdomen and pelvis may result in urological complications due to damage to surrounding healthy tissues. A seventy-year-old male patient who underwent radical prostatectomy and who received 35 fractions of radiotherapy (2 Gy per fraction, total of 70 Gy) to the prostate bed using an intensity-modulated radiotherapy technique for biochemical recurrence presented to our clinic with haematuria. Cystoscopy revealed perforation in the left lateral wall of the bladder.

Keywords: Humans, urinary bladder, radiotherapy, rupture, spontaneous

Introduction

Spontaneous bladder rupture was first described by Altman and Horsburgh in 1966 in a case report. Such cases are very rare (<1%) and those caused by radiotherapy are even rarer. The possible causes of spontaneous bladder rupture include bladder and pelvic organ tumours, radiotherapy applied in pelvic organ tumours, neurogenic bladder, excessive alcohol consumption, presence of bladder in the hernia sac, chronic cystitis. In a recent review of 351 patients with spontaneous bladder rupture, it was initially misdiagnosed in 64% of cases and had an overall mortality rate of 15%, highlighting the importance of early diagnosis and appropriate management. Here, a case with spontaneous bladder rupture after radiotherapy is presented and the recent literature is discussed (1,2).

Case Report

A seventy-year-old man who underwent radical prostatectomy five years ago and who received 35 fractions of radiotherapy (total of 70 Gy) six months ago for biochemical recurrence presented to our clinic with haematuria. Physical examination revealed no pathological findings and no obvious abnormality. The patient had coronary artery disease and hypertension. Family history revealed that his aunt had breast cancer. He wasn't a smoker. Urodynamic evaluation was not performed, as the patient had no lower urinary tract symptoms.

On admission, creatinine was 0.8 mg/dL, white blood cell count was $6 \times 10^3/\mu\text{L}$, prostate specific antigen was $<0.008 \mu\text{g/L}$, total testosterone was 11 ng/dL, chemical analysis of complete urinalysis showed $>200 \text{ RBC}/\mu\text{L}$. Ultrasonography revealed that bladder contours were slightly trabeculated and a catheter balloon was observed in the lumen. Seven x 3 cm cystic area was observed on the left anterolateral side of the bladder. The patient underwent cystoscopy and a perforation area was observed in the left lateral wall. Intraoperative cystogram was then performed and extravasation extending to the retroperitoneum was observed (Figure 1). In our case, the bladder perforation was a small defect (1 cm in diameter) and was localized extraperitoneally without any connection to the peritoneal cavity. Adequate urinary drainage was achieved with 18 Fr foley catheter. Urine culture obtained at the time of admission was sterile. Intravenous antibiotics from the cephalosporin group were administered prophylactically during the initial hospitalization period. Antibiotic therapy was continued for the duration of the indwelling urinary catheter to reduce the risk of infection, particularly given the presence of urine leakage into the extraperitoneal space. Then, the patient was followed up for 15 days. After 15 days, no extravasation was observed in the control cystogram. Upon discharge, the patient was prescribed an oral antibiotic from the penicillin group.

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

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Figure 1. Cystogram showing extraperitoneal bladder rupture

Discussion

Spontaneous bladder perforation after radiotherapy is a very rare condition. According to available data, the incidence is reported to be 1:126.000. It has been reported that the incidence of side effects after curative radiotherapy is approximately 10% and 3% of these side effects are urological problems (haematuria, fistula development, cystitis and fibrosis). Spontaneous bladder rupture has been reported even 30 years after radiotherapy treatment. It is thought to be caused by radiation damage affecting division delay and interphase pause leading to cellular death and further bladder damage (3-5).

In addition to radiotherapy, other potential risk factors for spontaneous bladder rupture were considered, including infravesical obstruction and bladder-specific conditions such as tuberculosis, schistosomiasis, candidiasis, eosinophilic cystitis, and emphysematous cystitis. Structural abnormalities like bladder diverticulum and ischemic necrosis caused by atherosclerotic plaque emboli have also been reported. Bladder carcinoma is another well-recognized risk factor. Long-term cyclophosphamide therapy and early intravesical administration of mitomycin C may contribute to bladder wall damage and rupture. Neurological disorders such as paraplegia with cystitis, multiple sclerosis, and tabes dorsalis can also predispose patients to rupture. In addition, acute alcohol intoxication and the use of clean intermittent catheterization are considered possible contributing factors (4). However, the patient had no

neurological disorders, diabetes, voiding dysfunction, urethral stricture, urinary retention, history of infections, or alcohol use. Therefore, radiotherapy remained the only identifiable risk factor in this case.

Bladder perforations occur extraperitoneally in 60%, intraperitoneally in 30% and both extraperitoneally and intraperitoneally in the remaining 10%. Intraperitoneal bladder ruptures usually occur in the dome of the bladder, while extraperitoneal leaks are mostly located in the lateral walls. Intraperitoneal rupture of the bladder usually presents with sudden onset of abdominal pain, rebound, defence, distension, peritonitis findings such as high fever and decreased urine output. Changes in urea and creatinine values are due to reabsorption of both substances through the peritoneum. This condition is difficult to differentiate from other causes such as acute renal failure. Bladder rupture must be included in the differential diagnosis because of the physical examination findings seen in acute abdomen syndrome. Delay in diagnosis may lead to a mortality rate of up to 25% if it lasts for more than 24 hours (1,6). On the other hand, extraperitoneal ruptures usually present with fewer abdominal symptoms because urine does not leak into the peritoneal cavity and changes in serum electrolyte levels and elevated blood urea nitrogen (BUN) and creatinine levels are not usually the case. In extraperitoneal ruptures, contrast extravasation around the perivesical area is clearly visible. Here, also, accurate diagnosis, appropriate treatment and early intervention are essential to prevent complications (7,8).

In the literature, cystography and computed tomography are prominent in the diagnosis of bladder rupture. In cystography, extravasation of radiopaque substance given into the bladder is diagnostic (3).

There are no specific guidelines on the treatment of spontaneous bladder rupture. The European Association of Urology (EAU) recommends that intraperitoneal bladder rupture should always be surgically repaired because of its potentially life-threatening potential. For example, in the cases of Ketata et al. (4), the rupture was intraperitoneal and repair was started with laparotomy. However, conservative treatment may be considered in extraperitoneal bladder rupture. In the literature, it has been reported that both intraperitoneal and extraperitoneal bladder ruptures have been successfully treated conservatively under certain conditions without serious infection, bleeding or major injuries. In the cases of Basiri and Radfar (9), despite the presence of intraperitoneal rupture, complete recovery was achieved with conservative management (urethral catheterization and antibiotic therapy). In the case reported by Welp et al. (10), an extraperitoneal rupture that developed during treatment in a patient receiving chemoradiotherapy for cervical cancer was managed conservatively and the patient did not require surgery. The main elements of the conservative approach are adequate urinary drainage and appropriate antibiotic treatment. An indwelling catheter or puncture drainage catheter may be used for urine drainage. Additionally, laparoscopic surgical intervention may be performed in cases of intraperitoneal rupture without severe infection or other organ damage (2,8).

Conservative treatment is a safe and effective option for carefully selected patients with extraperitoneal bladder rupture. However, several potential complications should be taken into account. These include delayed or insufficient healing, which may lead to persistent urine leakage, perivesical abscess, or fistula formation. Extended catheterization may also increase the risk of infection, such as urinary tract infections or, in rare cases, urosepsis. For this reason, patients managed conservatively require close clinical and radiological monitoring. If complications arise, surgical intervention should be considered promptly (11).

Conclusion

Bladder rupture, which is a rare complication of radiotherapy, should be kept in mind in a patient who has a history of radiotherapy and presents with haematuria or abdominal pain.

Ethics

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

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