

High-risk transition zone prostate cancers confer a heightened risk for positive surgical margins after radical prostatectomy

Xin Chen

First Affiliated Hospital of Soochow University

Haodong Xu

First Affiliated Hospital of Soochow University

Jun Zhang

First Affiliated Hospital of Soochow University

Zhenyu Hang

First Affiliated Hospital of Soochow University

Tianyi Xia

Nantong University

Chen Li

Wuxi No.2 People's Hospital

Zhenfan Wang

Suzhou Ninth People's Hospital

Yuxin Lin

First Affiliated Hospital of Soochow University

Yuhua Huang

First Affiliated Hospital of Soochow University

Jianquan Hou

The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital)

Xuedong Wei

wxd0422@163.com

First Affiliated Hospital of Soochow University

Research Article

Keywords: Prostate cancer, Pathological staging, Positive surgical margins, Transition zone, Nerve-sparing surgery

Posted Date: August 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10598602/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Despite the elevated risk of positive surgical margins (PSM) in certain transition zone (TZ) prostate cancers after laparoscopic radical prostatectomy (LRP), the underlying causes remain unclear. This study seeks to identify key determinants to inform personalized surgical strategies.

Methods

This retrospective study included 451 patients from three high-volume centers who underwent LRP after preoperative multiparametric magnetic resonance imaging between 2022 and 2023.

Results

TZ tumors exhibited elevated PSM rates compared to peripheral zone (PZ) tumors in both pT2 and pT3. In the pT3 cohort, clinical under-staging was more frequent among patients with PSM in TZ tumors (69% vs. 28% in PZ, $P < 0.01$). Despite comparable PSM rates between under-staged and correctly-staged TZ tumors, the under-staged PSM cases exhibited more favorable clinical characteristics. For pT2 TZ tumors, the elevated PSM rate was predominantly apex (36% vs. 21% in PZ, $p = 0.03$) and strongly associated with nerve-sparing surgery (NS). NS was performed more frequently (59% vs. 19% in PZ) and constituted the majority (86% vs. 29% in PZ) of TZ PSM cases. Furthermore, these PSM apex TZ tumors exhibited more adverse clinical features. Accordingly, a model to predict PSM risk in apex TZ tumors was established.

Conclusions

For pT3 TZ tumors, clinical under-staging is a critical factor leading to PSM. In pT2 disease, PSM prevention is paramount when operating on apex TZ tumors with adverse features, necessitating more stringent selection criteria for NS in these cases.

Background

Prostate cancer (PCa), currently the second most common cancer among men worldwide, places a significant burden on public health resources [1]. Radical prostatectomy (RP) is the significant treatment option for patients with PCa [2, 3]. However, the relatively high incidence of postoperative positive surgical margins (PSM) (about 10%-40%) remains a key factor affecting patient prognosis [4–6].

Despite advances in multiparametric magnetic resonance imaging (Mp-MRI) diagnostic techniques, the application of preoperative neoadjuvant therapy, and intraoperative assessment of resection margins to

precisely identify tumor locations and reduce the risk of PSM following RP, the occurrence of PSM remains unavoidable in clinical practice [7–9]. In parallel, numerous retrospective studies have identified multiple risk factors for PSM, including several patient clinical characteristics, Mp-MRI features and surgeon-related factors [10–12].

The location or region of the tumor is increasingly recognized as significantly associated with the incidence of PSM [10, 13]. Lesions located in the prostatic apex or transition zone (TZ) often result in higher postoperative PSM rates [11, 14]. Lesions in the TZ region are often neglected by researchers due to their lower malignancy and proximity to internal anatomical structures. Although our previous reports identified TZ lesions as an independent risk factor for PSM, the reasons for the high PSM incidence in the TZ remain undefined [15]. As is well-established, tumor stage significantly influences the incidence of PSM. Patients with pT3 stage tumors demonstrate a substantially higher PSM rate compared to those with pT2 disease [16]. This discrepancy suggests that tumor stage may help explain why certain high-risk TZ patients develop PSM. This multicenter retrospective study aims to investigate the determinants of PSM in high-risk TZ patients, thereby informing clinical decision-making.

Methods

Patients

A total of 451 patients from three high-volume centers who underwent laparoscopic radical prostatectomy (LRP) after preoperative Mp-MRI between 2022 and 2023 was retrospectively enrolled.

Inclusion criteria: (1) Diagnosis of PCa on primary biopsy; (2) All LRP were performed by qualified attending surgeons who had completed specialized training.

Exclusion criteria: (1) MRI lesions show diffuse or unclear; (2) PI-RADS score < 4 (indicating low likelihood of malignancy) [17]; (3) Neoadjuvant endocrine therapy before radical prostate resection (potential changes in clinical characteristics); (4) Prostate-specific antigen (PSA) > 100 ng/mL (with potential inaccuracies); (5) Intraoperative margin assessment (impact on spontaneous PSM occurrence).

Mp-MRI and clinical features

All patients were imaged on the 3.0T MRI scanner with a standard spine array coil and an 18-channel body array coil. The acquisition of the imaging sequence was performed as previously reported [18]. Evaluate all MRI parameters according to the PI-RADS guidelines V2.1 [19]. Transperineal 12-cores system biopsy (8 cores in the peripheral zone, 4 cores in the TZ) and X-cores targeted biopsy (2–5 cores in MRI lesions) was performed using transrectal ultrasound and MRI fusion software [20]. Pathological evaluation of obtained specimens based on the guidelines of the Society of Urogenital Pathology and the ISUP Prostate Cancer Guidelines [21]. All cases are analyzed by two experienced radiologists or

pathologists and reviewed collectively. In the event of disagreement, additional specialists will be consulted.

Statistical analyses

All statistical analyses were performed using GraphPad Prism (version 8.0.2) and R (version 4.4.0). Independent samples t-tests were applied to the continuous variables that followed a normal distribution, while nonparametric tests were used for non-normal distributions. Categorical variables were compared using chi-square tests or Fisher's exact tests as appropriate. For multiple t-tests, p-values are adjusted using the Bonferroni correction. Using logistic regression analysis to screen for significant variables related to PSM. Regression coefficients were calculated and standardized into scores for constructing a risk score chart to visualize individual patient risk probabilities. The predictive performance of the risk score chart and the model's fit to the observed outcomes were further evaluated using ROC curves, calibration curves, decision curve analysis (DCA), and clinical impact curves. Statistical significance was set at $p < 0.05$. The study was conducted in accordance with the STROBE reporting guidelines [22].

Results

Descriptive analysis of patients

The clinical characteristics of all patients are presented in Table 1.

Table 1
Characteristics of the study patients

Variable	PSM cohort		NSM cohort	
Study patients, n (%)	158	(35.03)	293	(64.97)
Median age, yr (IQR)	71	(65, 76)	69	(65, 74)
Median initial tPSA, ng/ml (IQR)	16.73	(10.07, 24.95)	10.8	(6.80, 18.39)
Median f/tPSA, ng/ml (IQR)	0.11	(0.07, 0.14)	0.12	(0.18, 0.16)
Clinical T stage, n (%)				
≤cT2	104	(65.82)	224	(76.45)
≥cT3a	54	(34.18)	69	(23.55)
Median number of positive cores, n (IQR)	4	(2, 7)	3	(1, 5)
Biopsy ISUP grade, n (%)				
1	17	(10.76)	64	(21.84)
> 1	141	(89.24)	229	(78.16)
Mp-MRI report characteristics				
PI-RADS score, n (%)				
4	57	(36.08)	177	(60.41)
5	101	(63.92)	116	(39.59)
Lesions Location, n (%)				
PZ	63	(39.87)	164	(56.87)
TZ	88	(55.70)	103	(37.91)
PZ + TZ	7	(4.43)	26	(5.21)
ECE detected by MRI, n (%)	54	(34.18)	62	(21.16)
SVI detected by MRI, n (%)	13	(8.23)	11	(3.75)
Median largest diameter of lesion, mm (IQR)	17	(11, 21)	13	(10, 16)
Median lesion volume, ml (IQR)	1.08	(0.41, 2.48)	0.60	(0.26, 1.18)
Median prostate volume, ml (IQR)	33.07	(21.91, 42.25)	33.26	(25.04, 45.25)
Median TZ volume, ml (IQR)	14.64	(8.75, 20.77)	13.98	(8.74, 23.73)
Median lesion volume/ prostate volume, % (IQR)	3.05	(1.32, 8.43)	1.74	(0.70, 4.21)
Median TZ volume/ prostate volume, % (IQR)	43.79	(35.50, 55.85)	43.87	(34.33, 55.27)

Variable	PSM cohort		NSM cohort	
Median PSA density, ng/ml ² (IQR)	0.55	(0.27, 0.88)	0.29	(0.18, 0.63)
Postoperative pathologic characteristics				
Pathologic T stage, n (%)				
pT2	73	(46.20)	222	(75.77)
≥pT3a	85	(53.80)	71	(24.23)
Pathologic ISUP grade, n (%)				
1	2	(1.27)	22	(7.51)
> 1	156	(98.73)	271	(92.49)
ECE, n (%)	81	(51.27)	66	(22.53)
SVI, n (%)	36	(22.78)	26	(8.87)

PSM, Positive Surgical Margins; NSM, Negative Surgical Margins; IQR, interquartile; PI-RADS, Prostate Imaging Reporting and Data System; PSA, Prostate-specific antigen; ISUP, International Society of Urological Pathology; TZ or PZ patients, patients' index lesions of MRI in the TZ or PZ; PZ + TZ patients, patients' multiple lesions of MRI mapping lesions in the PZ and TZ; RP, Radical Prostatectomy; ECE, Extracapsular Extension; SVI, Seminal Vesicle Invasion.

TZ remains a consistent high-risk factor for PSM in both pT2 and pT3 patients

The patients with PSM in various T stage are presented in Fig. 1a. PSM rates were significantly higher in pT3 than in pT2 (54%, n = 156 vs. 25%, n = 295, $p < 0.01$) (Fig. 1b). TZ tumors exhibited elevated PSM rates compared to peripheral zone (PZ) tumors (46%, n = 191 vs. 27%, n = 227, $p < 0.01$) (Fig. 1c). This trend was consistent across the pT3 (73%, n = 61 vs. 42%, n = 86, $p < 0.01$) and pT2 cohorts (33%, n = 130 vs. 19%, n = 141, $p < 0.01$) (Fig. 1d-e).

Clinical under-staging significantly associated with PSM in pT3 patients

The distribution of PSM and NSM among patients with different stages (pT3 and cT3) and lesion locations (TZ and PZ) is shown in Fig. 2a. Clinical under-staging (pT3+&cT3-) was more frequent among patients with PSM in TZ tumors than in PZ tumors (69%, n = 45 vs. 28%, n = 36, $p < 0.01$) (Fig. 2b). Moreover, the overall rate of pT3 under-staging was also significantly higher in TZ tumors (69%, n = 61 vs. 30%, n = 86, $p < 0.01$) (Fig. 2c).

Despite comparable PSM rates between clinical under-staged and correctly-staged (pT3+&cT3+) TZ tumors (74%, n = 42 vs. 74%, n = 19, p = 0.99) (Fig. S1a), the clinical under-staged PSM cases exhibited more favorable clinical characteristics (largest dimension of lesion, lesion volume and lesion volume/prostate volume) (Fig. 2d-f and Fig. S1). A similar trend was observed among the total patient population and PZ patients (Fig. S2 and Fig. S3).

Additionally, pT3 TZ patients with PSM had significantly greater values in the following parameters compared to NSM patients: dimension of lesion, lesion volume, lesion volume/prostate volume, and PSA (p < 0.05) (Fig. S4).

In pT2 patients, certain apex TZ tumors present a higher risk of PSM

The distribution of PSM and NSM among patients with different lesion zones (TZ and PZ) and lesion locations (Apex, Mid and Base) is shown in Fig. 3a. In pT2 disease, TZ tumors with PSM had worse clinical characteristics (PSA, PSA density, largest dimension of lesion, lesion volume/prostate volume, ISUP grade (biopsy), number of positive cores and f/t PSA) than TZ tumors with NSM. However, this phenomenon was not observed in PZ tumors (Fig. 3b-i and Fig. S5).

Further analysis of PSM occurrence in TZ and PZ tumors across different locations among pT2 patients revealed that the higher PSM rate in pT2 TZ compared to PZ tumors was primarily driven by a disproportionate risk at the apex location (36%, n = 77 vs. 21%, n = 84, p = 0.03). The high PSM rate in apex pT2 TZ tumors was primarily attributable to nerve-sparing surgery (NS), which was performed in 59% of TZ cases (31% in PSM cases and 28% in NSM cases; n = 77), compared to 19% of PZ cases (6% in PSM cases and 13% in NSM cases; n = 84). Correspondingly, NS constituted the majority of PSM cases in TZ group (86%, n = 28 vs. 29%, n = 18 in PZ) (Fig. 3j).

Furthermore, apex pT2 TZ tumors with PSM exhibited more adverse clinical features than apex pT2 TZ tumors with NSM: PSA, PSA density, largest dimension of lesions, lesion volume, lesion volume/prostate volume, ISUP grade (biopsy), number of positive cores (Fig. 4a-g and Fig. S6a-f). Univariate and multivariate logistic regression analyses revealed that largest dimension of lesion (OR: 1.90, 97.5% CI: 1.27–3.16, p < 0.01), and number of positive cores (OR: 1.45, 97.5% CI: 1.03–2.19, p = 0.04) were independent risk factors for the occurrence of PSM (Table S1).

Subsequently, a Nomogram Model was constructed using the two significant variables (Fig. 4h). The ROC curve (AUC: 0.82, 95% CI: 0.72–0.92) and calibration curve for this model is shown in the Fig. 4i and 4j. Additionally, clinical impact and decision curve analysis validated that this model effectively identifies high-risk patients who ultimately develop PSM, providing substantial value for clinical decision-making (Fig. S6g-h).

Discussion

Despite numerous retrospective studies have identified multiple risk factors for PSM, there are relatively few studies on the relationship between tumor occurrence zones and PSM development [23, 24]. Our previous study reported TZ as an independent risk factor for PSM, however, the underlying causes of this phenomenon warrant further investigation [15]. In this study, multicenter patient sample data demonstrated that TZ remains a consistent high-risk factor for PSM in both pT2 and pT3 patients. Subsequently, we explored PSM risk factors in TZ patients stratified by pathological stage (pT2 and pT3). Clinical under-staging represents a critical factor for PSM in pT3 TZ cancers. For pT2 disease, preventing PSM is particularly crucial when managing apex TZ tumors with adverse features, warranting more stringent patient selection for NS procedures. Furthermore, we developed a predictive model specifically for the pT2 apex TZ subgroup, which shows potential for enhancing preoperative PSM risk stratification and facilitating personalized surgical planning.

Among all enrolled patients, those with higher pathological staging (pT3) were found to have a higher incidence of PSM. The incidence of PSM in TZ patients is higher than that in PZ patients, which is consistent with previous reports [15, 25]. Notably, TZ tumors exhibited a higher PSM rate than PZ tumors in both pT2 and pT3 disease. This finding contrasts with the conventional view that the elevated PSM risk in TZ tumors is primarily attributable to pT3 cases [26], indicating that certain pT2 TZ tumors also contribute significantly to margin positivity. We hypothesize that the mechanisms underlying PSM may differ between pT2 and pT3 tumors, prompting a stratified subgroup analysis to investigate distinct etiological factors.

In the pT3 cohort, clinical under-staging was more frequent among patients with PSM in TZ tumors than in PZ tumors. Further analysis revealed a significantly higher rate of pT3 under-staging in TZ tumors than in PZ tumors, consistent with prior studies [27]. This discrepancy is likely attributable to the more heterogeneous imaging (indistinct capsule margins surrounding the TZ and the lack of clear ECE) appearance of TZ cancers, which forms the basis for clinical staging [28].

Unexpectedly, there was no significant difference in PSM incidence between the under-staged and correctly-staged TZ tumors. Nevertheless, under-staged PSM cases exhibited better clinical characteristics than correctly-staged PSM and NSM cases. Based on previous experience, better clinical characteristics typically imply a lower incidence of PSM [29]. This finding indicates that under-staged is an additional risk factor for PSM in pT3 TZ tumors, independent of clinical features. This may occur when surgeons, after misjudging clinical staging, perform standard surgical procedures intended for cT3- patients on patients who are pT3+.

Among patients with PSM in pT2 disease, apex tumors remained the most frequent location. This finding is consistent with the literature, where the apex is reported as the most common site for PSM, accounting for 33% to 43.3% of cases [30, 31]. Further analysis localized the elevated PSM rate in pT2 TZ disease specifically to the apex region, which unexpectedly demonstrated a higher incidence than apex PZ tumors. This discrepancy may be attributed to the significantly more frequent selection of NS surgery for apex TZ tumors (59% vs. 19% in apex PZ), with NS techniques employed in 86% of apex TZ PSM

cases, strongly implicating inappropriate NS selection as a key predisposing factor. The pursuit of improved quality of life has driven the widespread adoption of NS techniques [11]. Although NS is considered safe for pT2 patients, a body of evidence calls for caution when applying these techniques to apex tumors [32, 33]. Consequently, surgeons typically adopt a prudent approach regarding NS surgery for apex PZ tumors. As a result, NS surgery in apex PZ tumors is performed on a highly selected group of patients with more favorable pathology. In contrast, the more medial anatomical location of TZ tumors often creates a subjective bias favoring NS procedures, which can override a comprehensive assessment of individual patient risks. The ill-defined surgical boundary of the anterior fibromuscular stroma compromises dissection, often leading to inadvertent prostatic capsule incision when operating close to the prostate for sphincter preservation [34, 35].

A pivotal and intriguing finding emerged from the analysis of patient clinical characteristics. In the TZ cohort, PSM patients exhibited significantly worse clinical features than NSM patients. Conversely, in the PZ cohort, the median clinical characteristics of PSM patients were only modestly higher than those of NSM patients. This suggests that for most pT2 PZ tumors, complete resection is generally achievable. The consequent prudent surgical selection in PZ results in minimal divergence in clinical profiles between PSM and NSM patients. Under such conditions of limited clinical disparity, the occurrence of a PSM appears more dependent on surgeon experience or other non-clinical, stochastic factors. In stark contrast, for TZ tumors, the inappropriate application of NS techniques in patients with adverse clinical features appears to directly drive PSM. This suboptimal patient selection consequently results in a TZ PSM cohort with markedly poorer clinical profiles than their NSM counterparts. This unexpected yet critical finding substantiates our proposed hypothesis regarding the distinct etiologies of PSM in pT2 disease.

Further analysis characterized high-risk pT2 apex TZ tumors. Multivariate analysis confirmed only the maximum tumor diameter and the number of positive biopsy cores as independent predictors of PSM. Tumor diameter is a valuable, reproducible, quantitative marker, validated in our prior work and by other studies, and was established here as an independent risk factor for PSM [27, 36]. Studies by Turan et al. and Hyeon et al. both demonstrated a positive correlation between the number of positive cores in biopsy specimens and the occurrence of PSM [37, 38]. Predictive models have been further developed to aid in preoperative risk prediction of PSM following RP, thereby facilitating individualized management for PCa patients [5, 24]. While predictive model involving all patients provided a universal paradigm, it hindered personalized preoperative PSM risk assessment for individual patients [15, 39]. Given the distinct clinical challenge of apex pT2 TZ tumors, we developed a dedicated nomogram to predict PSM risk by integrating two independent risk factors: maximum lesion diameter and the number of positive biopsy cores. These variables, derived from preoperative imaging and biopsy pathology, complement each other in quantifying tumor burden, thereby underscoring its pivotal role in PSM occurrence.

This study has several limitations. First, to align MRI lesions with actual lesions, we excluded PCa patients with PI-RADS scores < 4 and negative MRI results. Second, although this was a multicenter study, to minimize the impact of temporal variations on surgical approaches and technical concepts, we

included only the most recent patients from 2022 to 2023. This resulted in a smaller overall cohort and subgroup (pT2 apex TZ) patient numbers, thereby limiting the level of evidence for the risk model. Third, although all surgeons in this study possessed extensive professional experience and performed standard LRP procedures, there were variations in their specific implementation of NS techniques. This may have influenced the reported PSM incidence.

Conclusion

From the perspective of pathological staging (pT2 and pT3), this study investigated the causes of PSM in high-risk TZ patients. For pT3 TZ cancers, clinical under-staging is a critical factor leading to PSM. Accurate staging is crucial for reducing PSM in pT3 disease. In pT2 disease, apex TZ tumors with adverse clinical features had a high PSM rate due to inappropriate selection of a NS technique. For high-risk apex pT2 TZ tumors, the selection of NS requires stringent criteria and warrants extreme caution. A predictive model for PSM in this subgroup may provide valuable guidance.

Abbreviations

Abbreviations	Full names
DCA	decision curve analysis
ECE	Extracapsular Extension
ISUP	International Society of Urological Pathology
LRP	laparoscopic radical prostatectomy
Mp-MRI	multiparametric magnetic resonance imaging
NS	nerve-sparing surgery
NSM	Negative Surgical Margins
PCa	Prostate cancer
PI-RADS	Prostate Imaging Reporting and Data System
PSA	Prostate-specific antigen
PSM	positive surgical margins
PZ	peripheral zone
RP	Radical prostatectomy
SVI	Seminal Vesicle Invasion
TZ	transition zone

Declarations

Ethics approval and consent to participate

This study complies with the Helsinki Declaration. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Soochow University (No. 2022(424), 2022) and registered in the China Clinical Trial Registry (ChiCTR2300075944, 2023). Due to the retrospective nature of the study, informed consent was waived.

Consent for publication

All presentations of case reports have consent for publication.

Competing Interests

The authors report no conflicts of interest in this work.

Funding

This work was supported by the National Natural Science Foundation of China (No. 32200533 and No.82572292), the Natural Science Foundation of Jiangsu Province (BK20241796), and the Gusu Health Personnel Training Project of Suzhou City (No. GSWS2019033).

Author Contribution

X.C., H.X. and J.Z.: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Visualization. Z.H. and T.X.: Methodology, Investigation, Resources. C.L., and Z.W.: Software, Validation, Writing – Original Draft. Y.L.: Data Curation, Writing – Review & Editing, Supervision, Funding acquisition. J.H., Y.H., and X.W.: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding acquisition, Resources, Project administration. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

The authors declare that no additional acknowledgements are required.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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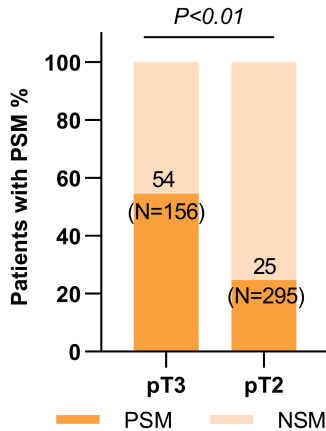
Figures

a.

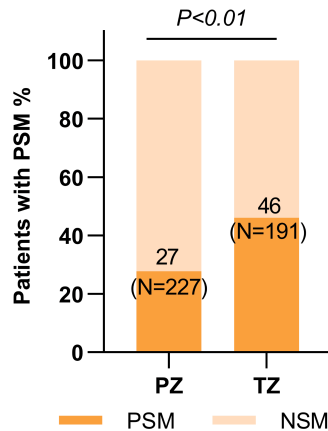
The patients with PSM in various T stage, n (%)									
Patients group	PZ		TZ		PZ+TZ		Total		Count
T stage	cT3	≤cT2	cT3	≤cT2	cT3	≤cT2	cT3	≤cT2	
pT3	26(5.8)	10(2.2)	14(3.1)	31(6.9)	3(0.7)	1(0.2)	43(9.5)	42(9.3)	85(18.8)
	34(7.5)	16(3.5)	5(1.1)	11(2.4)	3(0.7)	2(0.4)	42(9.3)	29(6.4)	71(15.7)
pT2	8(1.8)	19(4.2)	3(0.7)	40(8.9)	0(0)	3(0.7)	11(2.4)	62(13.7)	73(16.2)
	14(3.1)	100(22.2)	5(1.1)	82(18.2)	8(1.8)	13(2.9)	27(6.0)	195(43.2)	222(49.2)
Count	82(18.2)	145(32.2)	27(6.0)	164(36.4)	14()	19(4.2)	123(27.3)	328(72.7)	451(100)

■ PSM
 ■ NSM

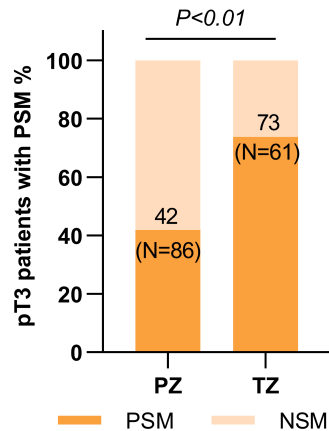
b.



c.



d.



e.

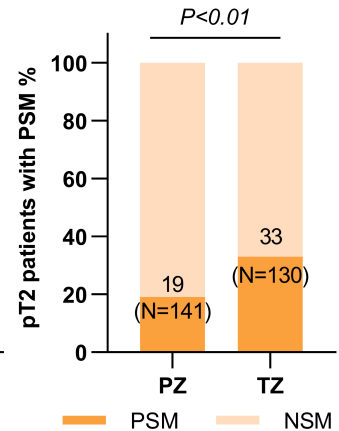


Figure 1

Comparison of PSM incidence across different cohorts. **(a)** PSM incidence table for patients with different T stages. **(b)** PSM occurrence in pT2 and pT3 cohorts. **(c)** PSM occurrence in PZ and TZ cohorts. PSM occurrence in PZ and TZ subgroups among **(d)** pT3 patients and **(e)** pT2 patients.

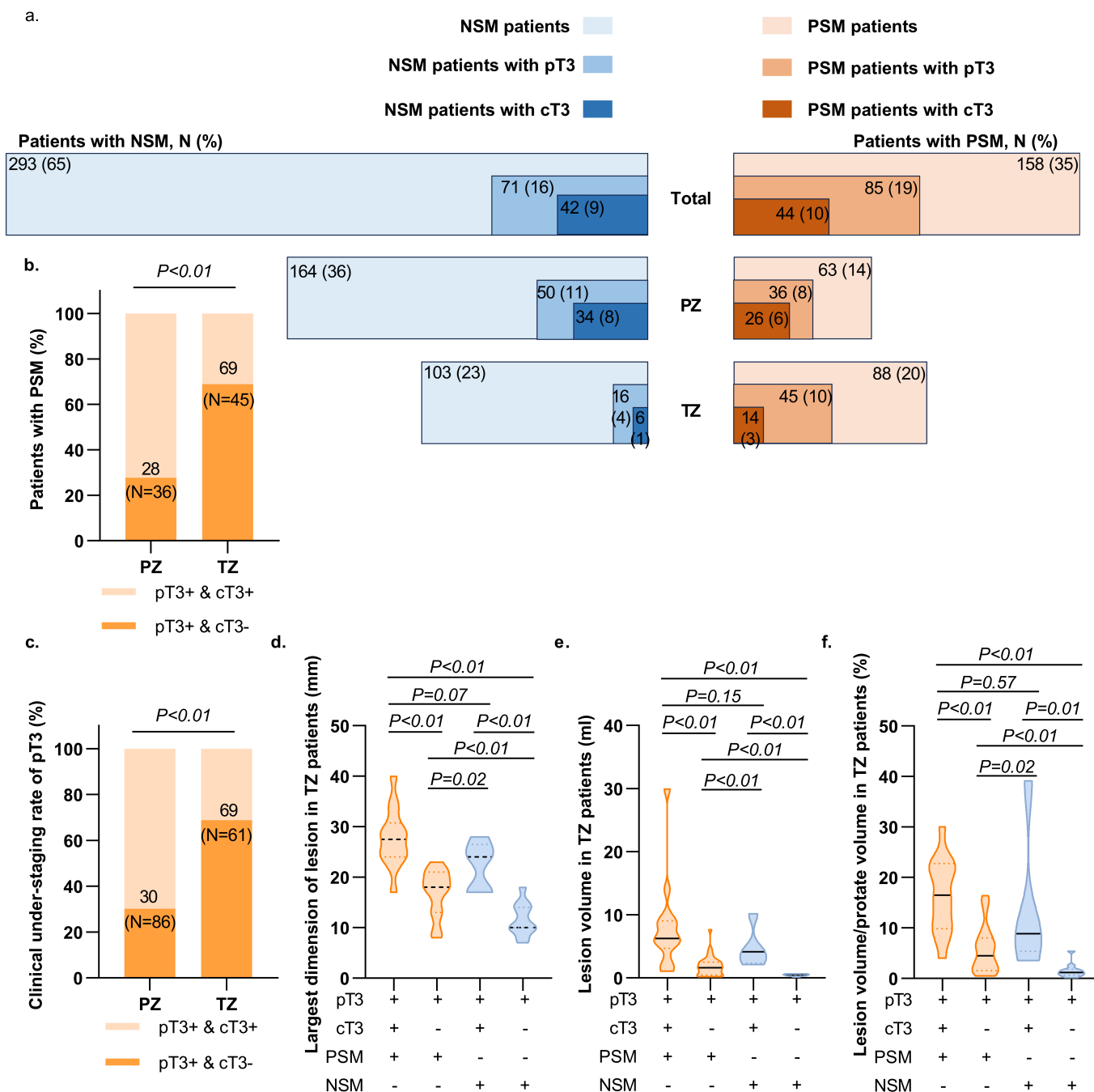


Figure 2

Comparative analysis of clinical under-staging between TZ and PZ in pT3 patients. **(a)** Distribution of pT3 and cT3 groups in PSM and NSM populations. The proportion of patients with clinical under-staging among TZ and PZ patients in **(b)** PSM cohort and **(c)** pT3 cohort. Compared to clinical under-staging patients, correctly-staged patients exhibited greater **(d)** largest dimension of lesion, **(e)** lesion volume, and **(f)** lesion volume/prostate volume.

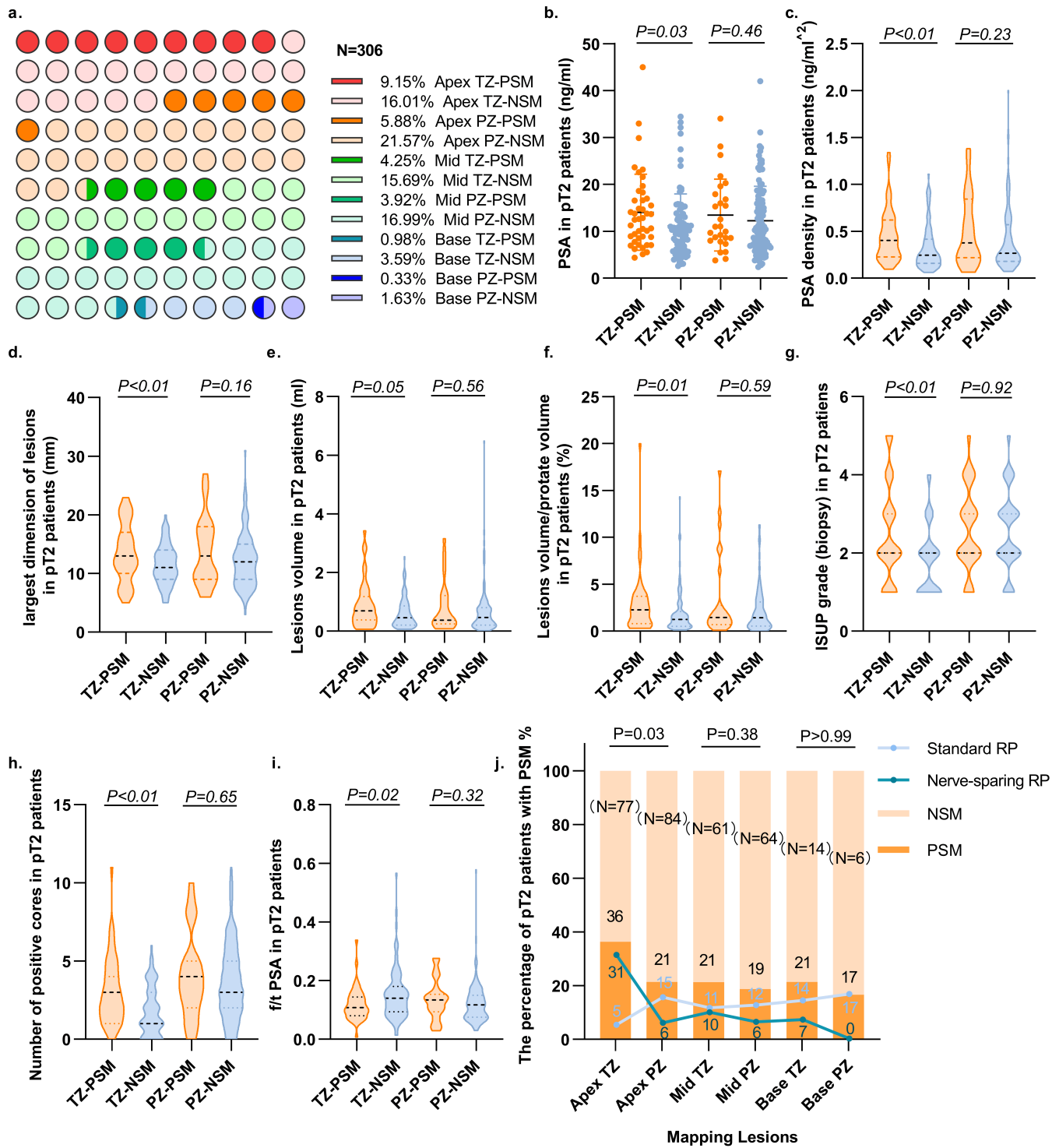


Figure 3

TZ tumors in the apex affect PSM occurrence in pT2 patients. **(a)** Distribution of NSM and PSM in TZ and PZ at different locations. Compared to TZ-NSM patients, TZ-PSM patients exhibited greater **(b)** PSA, **(c)** PSA density, **(d)** largest dimension of lesions, **(e)** lesions volume, **(f)** lesions volume/prostate volume, **(g)** IUSP grade (biopsy), **(h)** number of positive cores, and **(i)** f/t PSA. **(j)** The apex TZ group exhibited higher NS utilization rates and PSM occurrence rates.

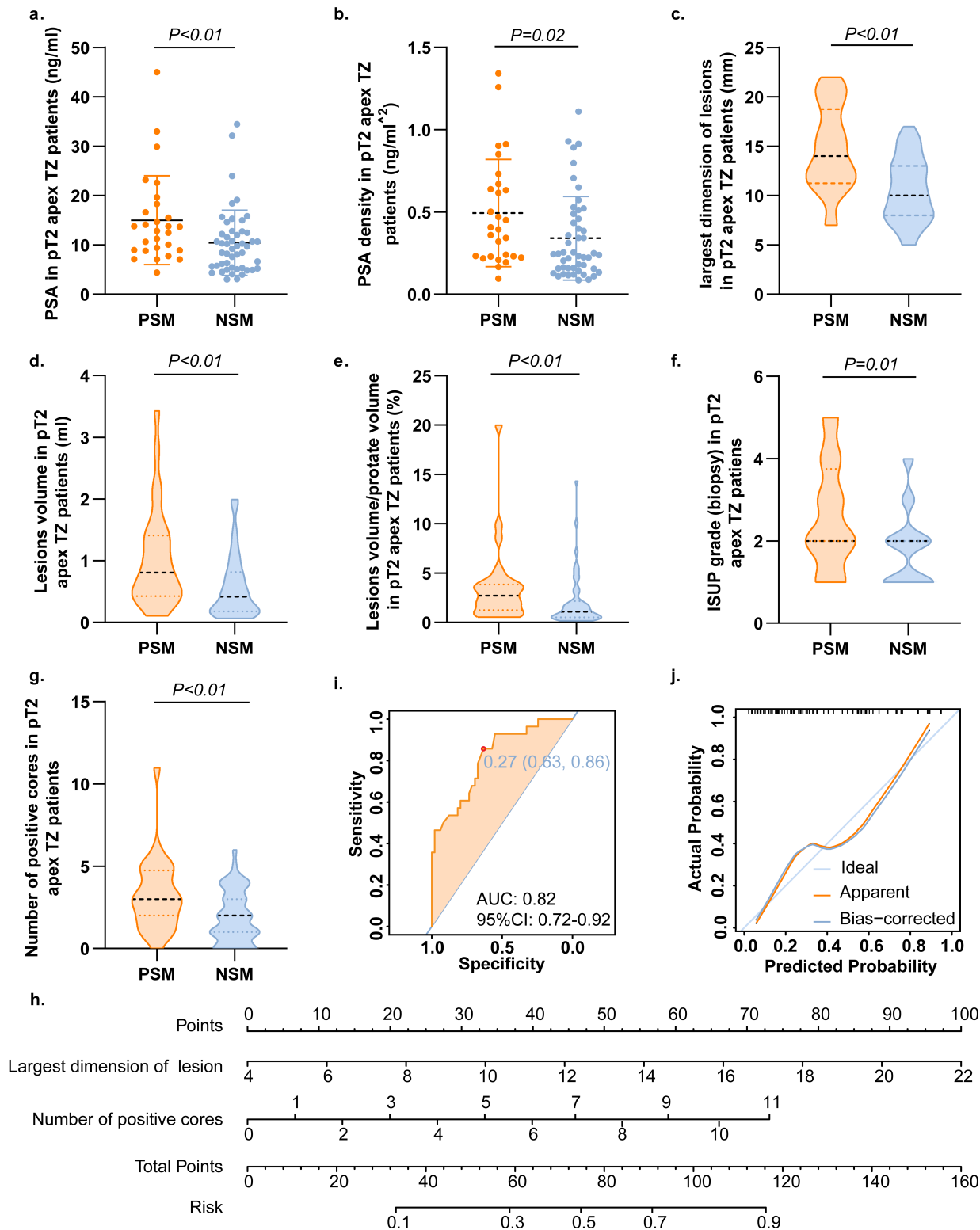


Figure 4

Factors associated with PSM and construction of PSM risk prediction model in pT2 apex TZ patients. Compared to NSM patients, PSM patients exhibited greater **(a)** PSA, **(b)** PSA density, **(c)** largest dimension of lesions, **(d)** lesions volume, **(e)** lesions volume/prostate volume, **(f)** IUSP grade (biopsy), and **(g)** number of positive cores. **(h)** Nomogram model for pT2 apex TZ patients. **(i)** ROC curve and **(j)** calibration curve for the nomogram model.

Supplementary Files

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