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Original Article

The Clinical Significance of the Positive Surgical Margin and Dominant Tumor Laterality Following Radical Prostatectomy: A Retrospective Study

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Abstract

Background and objectives: Positive surgical margin (PSM) after radical prostatectomy (RP) is an established factor associated with the outcome of biochemical recurrence (BCR). Dominant tumor is presumed to harbor the most aggressive biological behavior. The aim of this study was to evaluate the clinical significance of the PSM laterality and its correlation with dominant tumor. ***Methods:*** Excluding cases with multiple location PSM, 406 consecutive PSM patients after RP between 1993 and 2007 were retrospectively reviewed and included in this study. The BCR prognosis was estimated by the Kaplan-Meier survival analysis. ***Results:*** Of these 406 PSM cases, 115 cases (28.3%) had apex PSM, 272 cases (67.0%) had peripheral PSM, and 19 cases (4.7%) had bladder neck PSM. Among the 272 peripheral PSM cases, 117 cases (43.0%) were on the right side, 111 cases (40.8%) were on the left side, and 44 cases (16.2%) were on both sides of the prostate. For tumor dominancy, 87 cases (21.4%) were right dominant, and 70 cases (17.2%) were left dominant, whereas the remainder were non-laterality dominant. Similar clinicopathological and oncologic characteristics were observed between right and left PSM or dominant tumor. When compared to cases with same side PSM and dominant tumor, the cases with contralateral PSM to dominant tumor showed a significantly worse BCR prognosis in high-risk cases ($p < 0.001$). ***Conclusions:*** Our results indicated that the laterality of both PSM and tumor dominancy did not have any clinical significance. However, the significantly worse BCR prognosis of cases with a contralateral PSM to dominant tumor in the high-risk cases may suggest a more aggressive invasion ability, but not only due to an anatomical oppressive growth.

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Introduction

Positive surgical margin (PSM) after radical prostatectomy (RP) for local prostate cancer (PCa) is consistently reported as a strong predictor of postoperative biochemical recurrence (BCR).[1] The PSM rate in the contemporary RP series has been reported to vary from 11% to 38%,[2] with an additional ≥10% of patients with a high BCR risk, who had a close surgical margin (cancer cells coming within 0.1 mm from the surgical margin).[3] The BCR rate in the PSM cases has been reported to range from 42% to 64%,[4] thus indicating variability in the degree of the association of the margin status with the disease progression. Previously, extensive studies on PSM risk stratification were carried out, and most of the studies focused mainly on the location (apex, peripheral, bladder neck (BN), or anterior-posterior), number, length, and Gleason score (GS) of the PSM[5–10] of which, cases with PSM at the apex location (apex-PSM) were consistently reported to have a significantly better BCR-free survival similar to those cases with a negative surgical margin on the multivariate analysis.[11,12]

The clinical relevance of laterality for both PSM and tumor dominancy had been rarely investigated.[13–17] Previously, using a cohort of 226 PSM cases, Kang *et al*.[15] reported that patients with right-sided PSM were more likely to develop BCR than those with left-sided PSM on a multivariate analysis. However, no further evidence was reported that the laterality of PSM could have an impact on the PCa oncological out-

Keywords: Prostate cancer; Prostatectomy; Positive surgical margin; Dominant tumor; Laterality; Prognosis.

Abbreviations: BCR, biochemical recurrence; BN, bladder neck; GS, Gleason score; PCa, prostate cancer; PNI, perineural invasion; PSA, prostate-specific antigen; PSM, positive surgical margin; RP, radical prostatectomy; SRT, salvage radiotherapy.

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come. Herein, using a cohort of 406 PSM cases with a long-term follow-up, we compared the clinicopathological features and BCR outcome between the laterality of both PSM and dominant tumor with the aim to provide a comprehensive understanding of PSM laterality.

Materials and methods

Study population

The study was approved by the Institutional Review Board of Mass General Brigham and performed in accordance with the ethical standards as laid down in the Helsinki Declaration (Fortaleza revision, 2013). The cohort used for the present study was well described in our previous study.[7] Briefly, through the PCa database of the Department of Urology and Pathology, Massachusetts General Hospital in Boston, a total of 3,357 patients who underwent RP for localized PCa between 1993 and 2007 were retrospectively reviewed. With the exclusion criteria comprising neoadjuvant treatment or direct postoperative adjuvant therapy, positive lymph nodes, postoperative PSA persistence, or lost PSA follow-up, 2,796 cases still remained. Of these cases, 476 cases (17.0%) were identified with PSM. Since the main purpose of this study was to evaluate the clinicopathological and oncological prognostic impact of PSM laterality, to avoid any potential bias from different PSM locations,[1,18] 70 cases with multiple locations were excluded. Finally, a total of 406 PSM cases were included for further analysis. The RP specimens were inked, and the pathological assessments were done according to our routine protocol.[19] PSM was defined as an unequivocal presence of tumor cells at the inked margin of the RP specimen.[20] The laterality of tumor dominancy was determined by the tumor extension in four quadrants. All the cases included in this study were from a database with updated maintenance. GS was updated according to the 2014 International Society of Urological Pathology criteria by two reviewers (SW and CLW).[21] Postoperative BCR was defined as a post-nadir detectable serum PSA level of ≥0.2 ng/ml, followed by a confirmatory value. Salvage radiation therapy (SRT) was defined as radiation to the prostatic fossa (+/− LNs) in the setting of a newly detectable PSA. The Guidelines of Strengthening the Reporting of Observational studies in Epidemiology (STROBE) were complied.

Statistical analysis

Descriptive statistics of categorical variables focused on the frequencies and proportions. The medians and interquartile ranges (IQR) were reported for the continuous variables. Statistical analysis was performed using the Kruskal-Wallis H test for the continuous variables, and Pearson's Chi-squared test or Fisher's exact test was conducted for the categorical variables. Kaplan-Meier survival analysis was performed to estimate the probability of remaining free from BCR. The comparison of the survival distributions was performed with the log-rank test. All tests were two-sided with statistical significance set at $p < 0.05$. All statistical analyses were performed with Stata14 (College Station, TX, USA).

Results

Baseline characteristics

The clinicopathological characteristics of the 406 PSM cases is shown in Table 1. The median age at RP was 60 years old (IQR, 55–65), the median preoperative PSA was 5.8 ng/mL (IQR, 4.6–8.5), and the median prostate weight of the RP specimen was 38 grams (IQR, 32–48). Two hundred and eighty-one cases (69.2%) had organ-confined pT2 disease at surgery, 172 cases (42.4%) had a GS6, and 280 cases (69.0%) presented perineural invasion (PNI). Based on the PSM locations, 115 cases (28.3%) were from the apex, 272 cases (67.0%) from the peripheral region, and 19 cases (4.7%) were from the bladder neck. Among the 272 peripheral PSM cases, 117 cases (43.0%) were identified as right PSM, 111 cases (40.8%) were identified as left PSM, and 44 cases (16.2%) had bilateral PSM. Over a median follow-up of 12.6 years (IQR: 9.6–16.3), 176 men (43.4%) developed BCR after RP and the five-year BCR-free survival was 69.0%. Eighty-eight cases (21.7%) received SRT after the diagnosis of BCR.

Comparison of right PSM and left PSM

Cases with apex-PSM showed significantly favorable clinicopathological characteristics (lower percentage of these cases were pT3 stage, multifocal PSM, or developing BCR) when compared to cases from other groups divided by the laterality status (Table 1). Cases with bilateral PSM showed significantly unfavorable clinicopathological characteristics (more pT3 stage, and more BCR).

The laterality of PSM was well-associated with tumor dominancy. No other significant clinicopathological characteristic differences could be found between the cases with right PSM vs those cases with left PSM (Table 1). For BCR-free survival, patients with apex-PSM had significantly better BCR-free prognosis than cases with other PSM locations, including right PSM ($p = 0.020$), left PSM ($p = 0.006$), bilateral PSM ($p < 0.001$) and BN-PSM ($p = 0.022$) (Fig. 1a). No statistical significance of BCR-free survival was found between right PSM and left PSM ($p = 0.632$; data not shown).

Comparison of the right dominant tumor and left dominant tumor

Based on the laterality of the dominant tumor, we divided all cases into three groups: right dominant tumor was found in 87 cases (21.4%), left dominant tumor was found in 70 cases (17.2%), and the remaining 249 cases (61.4%) had non-laterality dominant tumor. Non-laterality dominant tumor cases showed a significantly higher PSA level and higher frequency of multifocal PSM when compared with either the left dominant or right dominant tumors. No significant difference was found when comparing the cases with right dominant tumor to cases with left dominant tumor (Table 2). For BCR-free survival, patients in the three different groups showed a similar prognosis ($p = 0.537$) (Fig. 1b).

Comparison of the same side PSM to dominant tumor and the contralateral PSM to dominant tumor

We found that not all PSM was identified from the same side as the dominant tumor. Among the 272 cases with peripheral PSM, 96 cases (35.9%) showed same side PSM to dominant tumor, 22 cases (8.1%) showed a contralateral PSM to dominant tumor (16 cases only had contralateral PSM, and 6 cases had both sides PSM), and the remaining 154 cases had non-laterality dominant PSM (Table 3). Both the non-laterality dominant tumor cases and cases with a contralateral PSM to dominant tumor showed a significantly high frequency of multifocal PSM than cases with same side PSM to dominant tumor (34.4%, 36.4%, and 7.8%, respectively; $p < 0.001$). Of the 22 cases with contralateral PSM to dominant tumor, 17 cases had GS≤3+4 and five cases had GS≥4+3, which had the similar tumor grade frequency of those cases with same side PSM and non-laterality dominant PSM (Table 3).

For BCR-free survival, the patients from the three different

Table 1. Clinicopathological characteristics of different PSM locations after radical prostatectomy

	Total	Apex-PSM N = 115 (28.3)	Peripheral N = 272 (67.0)			BN-PSM N = 19 (4.7)	*p1 (R vs L)*	*p2 (All)*
			R-PSM	L-PSM	RL-PSM			
Patients (%)	406 (100)	115 (28.3)	117 (28.8)	111 (27.3)	44 (10.8)	19 (4.7)		
Age (yr)	60 (55–65)	61 (56–65)	60 (54–64)	61 (56–65)	59 (53–64)	60 (55–63)	0.307	0.214
PSA (ng/ml)	5.8 (4.6–8.5)	5.8 (4.9–7.9)	5.9 (4.7–9.1)	5.5 (4.2–7.4)	6.4 (4.5–8.2)	8.9 (4.6–12)	0.146	0.206
Prostate weight (g)	38 (32–48)	42 (33–50)	39 (33–49)	39 (32–47)	34 (27–39)	34 (30–42)	0.674	0.003
Gleason Score (%)							0.540	0.063
3+3	172 (42.4)	47 (40.9)	59 (50.4)	46 (41.5)	12 (27.3)	8 (42.2)		
3+4	140 (34.5)	46 (40.0)	35 (29.9)	37 (33.3)	15 (34.1)	7 (36.8)		
4+3	38 (9.3)	8 (7.0)	12 (10.3)	13 (11.7)	3 (6.8)	2 (10.5)		
≥8	56 (13.8)	14 (12.1)	11 (9.40)	15 (13.5)	14 (31.8)	2 (10.5)		
Pathologic Stage (%)							0.677	0.047
pT2	281 (69.2)	90 (78.3)	79 (67.5)	72 (64.9)	25 (56.8)	15 (78.9)		
pT3	125 (30.8)	25 (21.7)	38 (32.5)	39 (35.1)	19 (43.2)	4 (21.1)		
Tumor dominancy							<0.001	<0.001
Right-dominant	87 (21.4)	22 (19.1)	52 (44.4)	8 (7.2)	2 (4.6)	3 (15.8)		
Left-dominant	70 (17.2)	12 (10.4)	8 (6.8)	44 (39.6)	4 (9.1)	2 (10.5)		
Non-laterality dominant	249 (61.4)	81 (70.5)	57 (48.8)	59 (53.2)	38 (86.3)	14 (73.7)		
PNI (%)							0.553	0.123
Negative	126 (31.0)	45 (39.1)	34 (29.1)	28 (25.2)	11 (25.0)	8 (42.1)		
Positive	280 (69.0)	70 (60.9)	83 (70.9)	83 (74.8)	33 (75.0)	11 (57.9)		
SRT (%)							0.363	0.064
Non-SRT	318 (78.3)	100 (87.0)	84 (71.8)	86 (77.5)	34 (77.3)	14 (73.7)		
SRT	88 (21.7)	15 (13.0)	33 (28.2)	25 (22.5)	10 (22.7)	5 (26.3)		
PSM status							0.831	<0.001
Single focal	335 (82.5)	113 (98.3)	104 (88.9)	100 (90.1)	0 (0)	18 (94.7)		
Multifocal	71 (17.5)	2 (1.7)	13 (11.1)	11 (9.9)	44 (100)	1 (5.3)		
No. BCR (%)	176 (43.4)	36 (31.3)	52 (44.4)	52 (46.9)	27 (61.4)	9 (47.4)	0.790	0.009
No. Metastasis (%)	34 (8.4)	5 (4.4)	10 (8.6)	11 (9.9)	6 (13.6)	2 (10.5)	0.820	0.255
No. Death (%)	65 (16.0)	22 (19.1)	13 (11.1)	19 (17.1)	8 (18.2)	3 (15.8)	0.252	0.490

PSM, positive surgical margin; R, Right; L, Left; BN, bladder neck; PSA, prostate specific antigen; PNI, perineural invasion; SRT, salvage radiotherapy; BCR, biochemical recurrence.

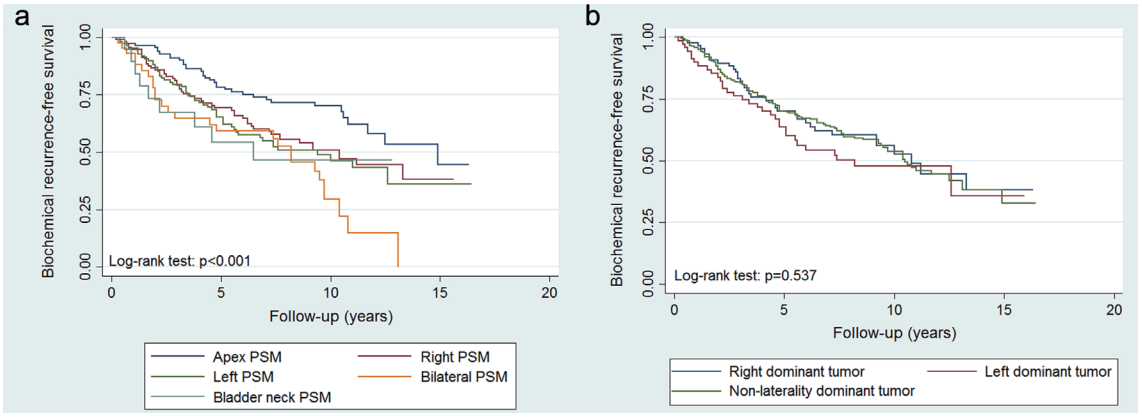

Fig. 1. Kaplan-Meier curves showing biochemical recurrence-free survival in all 406 PSM cases stratified by apex PSM vs right PSM vs left PSM vs bilateral PSM vs bladder neck PSM (a) and right dominant tumor vs left dominant tumor vs non-laterality dominant tumor (b).

groups showed a similar prognosis (p = 0.988) (Fig. 2a). Interestingly, when the prognosis was examined with the subgroups based on their GS, cases with a contralateral PSM to dominant tumor showed a significantly worse prognosis than the cases of the other two groups in the high-risk (GS≥4+3) subgroup (p < 0.001). On the contrary, the prognoses were similar among the three groups in the low to intermediate risk (GS≤3+4) subgroup (p = 0.464).

Discussion

Recently, the effect of tumor laterality on the disease out-

Table 2. Clinicopathological characteristics by prostate tumor dominancy of radical prostatectomy specimens

	Right-dominant tumor	Left-dominant tumor	Non-laterality dominant tumor	*p*
Patients (%)	87 (21.4)	70 (17.2)	249 (61.4)	
Age (yr)	61 (55–64)	61 (56–65)	60 (55–65)	0.685
PSA (ng/ml)	5.7 (4.6–7.5)	5.4 (4.0–7.0)	6.0 (4.7–9.4)	0.030
Prostate weight (g)	38 (33–50)	39 (31–47)	39 (32–47)	0.942
Gleason Score (%)				0.279
3+3	40 (49.8)	23 (32.9)	109 (43.8)	
3+4	29 (33.3)	24 (34.2)	87 (34.9)	
4+3	6 (6.9)	13 (18.6)	19 (7.6)	
≥8	12 (13.8)	10 (14.3)	34 (13.7)	
Pathologic Stage (%)				0.886
pT2	59 (67.8)	50 (71.4)	172 (69.1)	
pT3	28 (32.2)	20 (28.6)	77 (30.9)	
PNI (%)				0.348
Negative	23 (26.4)	19 (27.1)	84 (33.7)	
Positive	64 (73.6)	51 (72.9)	165 (66.3)	
SRT (%)				0.207
Non-SRT	65 (74.7)	51 (72.9)	202 (81.1)	
SRT	22 (25.3)	19 (27.1)	47 (18.9)	
PSM focal status				0.004
Single focal	79 (90.8)	63 (90.0)	193 (77.5)	
Multifocal	8 (9.2)	7 (10.0)	56 (22.5)	
No. BCR (%)	36 (41.4)	33 (47.1)	107 (42.3)	0.752
No. Metastasis (%)	6 (7.1)	8 (11.4)	20 (7.9)	0.561
No. Death (%)	10 (11.9)	10 (14.3)	45 (17.9)	0.340

PSM, positive surgical margin; PSA, prostate specific antigen; PNI, perineural invasion; SRT, salvage radiotherapy; BCR, Biochemical recurrence.

Table 3. Combination of PSM laterality and tumor dominancy

	All cases (n = 272)	GS ≤ 3 + 4 (n = 204)	GS ≥ 4 + 3 (n = 68)
Non-laterality dominant PSM	154	117 (76.0%)	37 (24.0%)#
IpsiPSM to dominant tumor	96	70 (72.9%)	26 (27.1%)
ContraPSM to dominant tumor	22	17 (77.3%)	5 (22.7%)
With Right dominant tumor and Left PSM	10	8	2
With Left dominant tumor and Right PSM	12	9	3
With only contraPSM	16	13	3
With contraPSM and IpsiPSM	6	4	2

PSM, positive surgical margin; IpsiPSM, Ipsilateral PSM (with only same side PSM); ContraPSM, Contralateral PSM (with only other side PSM or with both side PSM); #, 15 cases were with bilateral PSM.

come has been the topic of investigation in the genito-urologic field, including the kidney,[22] testis,[23] and the upper urinary tract (UTUC),[24] and suggests a potential association between tumor laterality and progression. However, laterality studies on PCa were rare and had inconsistent results.[13–17]

In our present study, with a cohort of 406 PSM patients after RP, we found that the frequency of right PSM and left PSM among the PCa patients was similar (43.0% and 40.8%, respectively). The laterality of PSM was positively correlated with the laterality of PCa dominance, while non-laterality dominant PCa carried similar occurrence of right PSM (48.8%) and left PSM (53.2%). Cases with either right PSM or left PSM showed similar clinicopathological features and oncological outcomes. Similar to our results, previously, using a set of 162 cases with laterality information in the peripheral area (posterior + anterior), Blute *et al*.[17] reported the findings of the right PSM rate of 47.5% (77/162), left PSM rate of 45.1% (73/162), and bilateral PSM rate of 7.4% (12/162). Contrary to our observation that cases with right PSM had a similar BCR prognosis as those with left PSM, Kang *et al*.[15] found that among all the PSM cases, when including PSM at different locations (apex, base, posterior, and anterior), cases with right PSM were more likely to have BCR progress when compared to those with left PSM (HR: 1.7; $p = 0.04$) by multivariate analysis. When further examining the data from their cohort, 45% of those with left PSM were found to be at the apex location, while only 30% of those with right PSM were found to be at the apex. Since it was well-established that cases with apex-PSM were associated with a significantly better BCR-free survival, similar to those with negative surgical margin on multivariate analysis,[1,7,11,12] we considered that the different frequency of apex-PSM would create bias of the results and induce the discrepancy.

In our current PSM cohort study, the frequency of dominant tumor laterality was also comparable (right and left dominant tumor were 21.4% and 17.2%, respectively), and cases with right dominant tumor showed similar clinicopathological features and oncological outcomes as those cases with left dominant tumor. Previously, Tareen *et al*.[13] reported that men with unilateral PCa showed more favorable oncological outcomes than those with bilateral PCa. On the contrary, Mouraviev *et al*.[14] reported that unilateral and bilateral PCa had a similar BCR prognosis. For the first time, our current study results provided data suggesting that the laterality of the dominant tumor did not have any impact on the disease progression, which was consistent with our findings on PSM laterality.

In general, PSM usually comes from the side with a dominant (more extensive) tumor. Interestingly, we found that 22 cases (8.1%) out of the 272 cases with peripheral PSM carried a contralateral PSM to the dominant tumor, 16 cases of them (72.7%) only had a contralateral PSM, while another six cases had bilateral PSM. Even though the BCR prognosis was the same among the three PSM groups in all cases, cases with contralateral PSM showed a significantly worse BCR prognosis than cases with same-side PSM and non-laterality dominant PSM cases in the high-risk PCa subgroup (GS≥4+3). Previously, it was reported that the extent length of PSM and GS on the PSM were independent BCR prognosticators.[9,10] Compared to same-side PSM, contralateral PSM could carry a worse oncological outcome because of the longer length, multifocal or higher GS on PSM. However, it would be difficult to explain why contralateral PSM also showed a significantly worse BCR than non-laterality dominant PSM in similar conditions (same multifocal frequency; same bilateral frequency). We understand that with only five cases that were identified as contralateral PSM in high-risk PCa, our

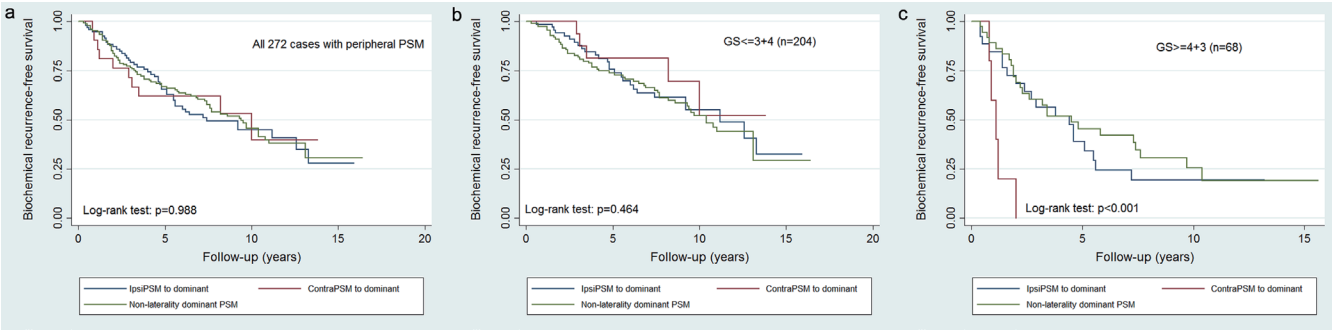

Fig. 2. Kaplan-Meier curves showing biochemical recurrence-free survival stratified by same side PSM to dominant tumor vs contralateral PSM to dominant tumor vs non-laterality dominant PSM in all 272 cases with peripheral PSM(a), 204 cases with peripheral PSM and low-risk PCa (GS≤3+4) (b) and 68 cases with peripheral PSM and high-risk PCa (GS≥4+3) (c).

study results may be overfitted. Nevertheless, it was clear that contralateral PSM to dominant tumor could carry more aggressive and invasive ability than same-side PSM, which could be mainly due to the oppressive and expansive growth. A contralateral PSM to the dominant tumor in high-risk PCa is worth additional attention for adjuvant treatment.

The present study was limited by its retrospective and non-randomized nature. Our study also lacked information on the length of the PSM and the GS at PSM, which each of these factors would be useful in further analysis. Furthermore, the significance of contralateral PSM to dominant tumor was limited by the small sample size and the possibility of overfitting; therefore, a further larger prospective study would be warranted.

Conclusions

Our results indicated that the laterality of both PSM and tumor dominancy did not have clinical significance. The significantly worse BCR prognosis of cases with a contralateral PSM to dominant tumor in high-risk cases could suggest a more aggressive invasion ability, but not only due to an anatomical oppressive growth. Our study results could help physicians to schedule optimal adjuvant therapy with the different PSM status.

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None.

Conflict of interest

Wu CL has been an editorial board member of the *Journal of Clinical and Translational Pathology* since 2021. The authors have no other conflict of interests to declare.

Author contributions

Design of the study (CLW, SW, SXL and GJW), data collection (SW, ML, JL, GJW, ZW and AOS), statistical analyses (SW and GJW), data interpretation (SW, SXL, GJW, ML, JL, GJW, ZW and AOS), drafting of the manuscript (SW, SXL and GJW), and revision of the manuscript (CLW, MLB, DMD and AFO). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study was approved by the Institutional Review Board of Mass General Brigham and performed in accordance with the ethical standards as laid down in the Helsinki Declaration (Fortaleza revision, 2013).

Data sharing statement

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

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