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Received: 8 November 2021 | Accepted: 14 March 2022

DOI: 10.1002/pros.24341

ORIGINAL ARTICLE

The Prostate WILEY

Impact of positive surgical margin length and Gleason grade at the margin on oncologic outcomes in patients with nonorgan-confined prostate cancer

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Abstract

Purpose: Positive surgical margins (PSM) represent a poor prognostic factor at radical prostatectomy (RP). To investigate the impact of PSM, its length, the focality and the Gleason grade at the PSM, on the oncologic outcomes in nonorgan-confined RP patients.

Methods: Within a high-volume center database, we identified patients who harbored non-organ-confined (pT3) prostate cancer (PCa) at RP between 2010 and 2016. Only patients without lymph node invasion were included. Kaplan–Meier analyses and multivariable Cox regression models were used to test the effect of PSM on biochemical recurrence (BCR), metastasis, and cancer-specific death after RP in patients without adjuvant radiotherapy.

Results: Overall, 3705 patients were identified. Of those, 27.2% ($n = 1007$) harbored PSM. At 96 months after RP, BCR-free, metastasis-free and cancer-specific survival was 41.6 versus 57.5%, 82.7 versus 88.6%, and 94.7 versus 98.5% for patients with versus without PSM (all $p < 0.001$). BCR-free, metastasis-free and cancer-specific survival rates at 96 months were 56.7 versus 26.5% ($p < 0.001$), 94.4 versus 67.4% ($p < 0.001$), and 100.0 versus 87.1% ($p < 0.01$) for Gleason pattern 3 versus ≥ 4 at the margin and 45.0 versus 27.8% ($p < 0.01$), 83.3 versus 82.3% ($p = 0.2$), and 95.2 versus 92.7% ($p = 0.3$) for <4 mm versus ≥4 mm length of margin. In multivariable Cox models PSM was an independent predictor for BCR (hazard ratio [HR]:1.53, $p < 0.001$) and cancer-specific death (HR:2.75, $p = 0.02$). In subgroups of patients with PSM only, Gleason ≥ 4 at the margin (HR:1.60, $p < 0.01$) and length of PSM (HR:1.02, $p < 0.05$) was an independent predictor of BCR.

Conclusion: PSM represents an independent predictor for worse oncologic outcome in nonorgan-confined PCa at RP. Gleason ≥ 4 at the margin was associated with the development of BCR, metastasis, and with cancer-specific death after RP. Next to

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margin status, Gleason at the margin and its length carry important information that should be reported for the specimen.

KEYWORDS
nonorgan confined, positive surgical margin, prostate cancer, PSM, radical prostatectomy

1 | INTRODUCTION

Positive surgical margins (PSM) represent a poor prognostic factor at radical prostatectomy (RP) for prostate cancer (PCa) patients.[1–3] Patients with nonorgan confined (pT3) are likely to harbor PSM. Recent studies report rates of PSM ranging from 37% to 61% in pT3 PCa patients.[2,4,5] Specifically, the lowest reported rates (37%) of PSM in pT3 patients derived from a robotically treated cohort by Patel and colleagues within a multi-institutional series.[5] Conversely, higher rates apply for national registries. Wright et al.[2] reported a PSM rate of 44% for pT3a patients within the Surveillance, Epidemiology, and End Results (SEER) database. Similar rates, compared with the one reported by Wright et al., were also recorded by Lightfoot et al.[4] within a robotically treated cohort for pT3a patients (43%) treated by a single high-volume surgeon. However, for patients with seminal vesicle invasion (pT3b) the authors recorded much higher PSM rates (61%).[4]

Recently, we reported that PSM negatively impacts survival in patients with non-organ confined PCa within the SEER database.[3] Moreover in organ-confined pT2 PCa the Gleason grade at the PSM and its length are poor risk factors for biochemical recurrence (BCR) after RP.[6]

Previously, Ploussard and colleagues reported that the PSM length >3 mm and multifocal PSM in non-organ confined prostate cancer are risk factors for BCR after RP.[7] Similarly, Brimo et al.[8] reported within a small cohort of 108 patients with nonorgan that a higher Gleason grade at the margins is associated with BCR. However, the predictive value of the Gleason grade at the PSM, its length, and the PSM focality in nonorgan confined pT3 disease on long-term oncologic outcomes remains still debatable.

To address this void, we tested the relationship between PSM and BCR, metastasis, and cancer-specific death. Specifically, we examined the relationship of PSM, the Gleason grade at the PSM, its length and focality, and BCR, metastasis and cancer-specific death after RP, within an institutional high-volume center database of contemporary exclusively nonorgan confined PCa RP patients.

2 | PATIENTS AND METHODS

2.1 | Study population

After Institutional Review Board approval, 5271 patients that harbored pathologic nonorgan confined PCa (pathologic stage T3) were treated with RP between 2010 and 2016 at a tertiary referral institution (Martini–Klinik Prostate Cancer Center, Hamburg-Eppendorf, Germany) were identified.

Exclusion criteria consisted of lymph node invasion ($n = 1459$) or unknown margin status ($n = 105$). These selection criteria yielded 3705 patients, which represent the focus of the current study.

2.2 | Surgical approach

Surgery was performed either as an open retropubic or robot-assisted laparoscopic approach as previously described.[9,10] Neurovascular bundle preservation was performed with the intraoperative frozen section (NEUROSAFE) technique as previously described.[10,11] In the case of PSM during the frozen section, a resection of the neurovascular bundle at the corresponding side was performed.

2.3 | Surgical margin parameters

Parameters describing the surgical margin status were retrieved from the pathology reports. In cases where a mixed Gleason pattern (i.e., 3 + 4) was recorded for a surgical margin, the predominant Gleason pattern was used for statistical analyses.

2.4 | Endpoints

BCR was defined as two consecutive PSA values ≥0.2 ng/ml after surgery. Time to BCR was calculated as the time from RP to BCR or last follow-up. Metastasis was defined as positive imaging following BCR. Imaging procedures consisted of bone scan and/or computed tomography and/or abdominal magnetic resonance imaging and/or 11C-choline positron emission tomography/computed tomography scan. Time to metastasis was also calculated as the time from RP to development of metastasis or last follow-up. Time to cancer-specific death was calculated as the time from RP to death or last follow-up. Cancer-specific death was defined as death attributed to PCa.

2.5 | Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges were reported for continuously coded variables. The χ^2 tested the statistical significance in proportions' differences. The Mann–Whitney U test examined the statistical significance of medians' differences, respectively.

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Kaplan–Meier analyses graphically depicted BCR-free, metastasis-free (MFS), and cancer-specific survival. Univariable and multivariable Cox regression models were fitted to test the relationship between PSM, Gleason at the PSM, PSM length, PSM focality and BCR, metastasis, and cancer-specific death, respectively. Patients with adjuvant radiotherapy ($n = 362$) were excluded from all survival analyses.

Specifically, the first set of Cox regression models tested the impact of PSM on BCR, the second set of Cox regression models tested the impact of PSM on metastasis development, the third set the relationship of PSM on cancer-specific death. Subsequently, a fourth and fifth Cox regression model tested the impact of the Gleason patterns at the PSM (Gleason pattern 3 vs. ≥4), its length (<4 mm vs. ≥4 mm), and focality (uni- vs. multifocal) on BCR and metastasis in the subgroup of patients with PSM. The adjustment was made for the covariates: age at surgery, year of surgery, preoperative PSA value, Gleason grade groups (GGG 1–2 vs. GGG 3 vs. GGG 4–5), pathologic tumor stage (pT3a vs. pT3b), and pathologic lymph node status (pN0 vs. pNx). R software environment for statistical computing and graphics (version 3.6.2) was used for all statistical analyses. All tests were two-sided with a level of significance set at $p < 0.05$.

3 | RESULTS

3.1 | Descriptive statistics

Overall, 3705 patients with pathologic nonorgan confined stage (pT3) were identified (Table 1). The median follow-up was 50 months (interquartile range 36.3–73.7 months). Of all, 27.2% ($n = 1,007$) harbored PSM. Patients with PSM had higher median PSA values (11.0 vs. 7.9 ng/ml, $p < 0.001$), higher proportion of Gleason grade group 4–5 (22.6 vs. 8.7%, $p < 0.001$) and more frequently harbored seminal vesicle infiltration (46.0 vs. 22.0%, $p < 0.001$), compared to patients with negative surgical margins. The mean and median length of PSM was 4.47 mm (standard deviation 0.2 mm) and 2 mm (interquartile range 0.5–5.7 mm). Most had unifocal PSM (77.0%) and most frequently a Gleason pattern of 3 at the margin was recorded (43.8%). 362 patients (9.8%) were treated with adjuvant radiotherapy.

3.2 | Effect of PSM on BCR

BCR-free survival (Figure 1A) at 96 months after RP was 41.6 versus 57.5% for patients with versus without PSM ($p < 0.001$). BCR-free survival rates at 96 months were 44.3 versus 30.8% ($p = 0.01$) for unifocal versus multifocal PSM (Figures 1B), 56.7 versus 26.5% ($p < 0.001$) for Gleason pattern 3 versus ≥4 at the margin (Figures 1C) and 45.0 versus 27.8% ($p < 0.01$) for <4 mm versus ≥4 mm length of margin (Figure 1D). In multivariable Cox regression models (Table 2), PSM (hazard ratio [HR]: 1.53, 95% confidence interval [CI] 1.33–1.77; $p < 0.001$), year of surgery (HR: 0.91, 95% CI 0.88–0.94; $p < 0.001$), higher PSA (HR: 1.01, 95% CI 1.01–1.02; $p < 0.001$), GGG 3 (HR: 2.45, 95% CI 2.13–2.83; $p < 0.001$), GGG 4–5 (HR: 3.62, 95% CI 3.01–4.36; $p < 0.001$), and pathologic stage T3b (HR: 1.78, 95% CI 1.56–2.03; $p < 0.001$), all represented independent predictors of BCR.

In subgroup analysis, focusing on patients with PSM only (Table 3), PSM length (HR: 1.02, 95% CI 1.01–1.04, $p < 0.05$) and Gleason ≥4 at the margin (HR: 1.60, 95% CI 1.62–2.21, $p < 0.01$) represented independent predictors of BCR. Conversely, PSM focality was no predictor ($p = 0.3$) of BCR.

3.3 | Effect of PSM on metastasis

At 96 months after RP, MFS rates were 82.7 versus 88.6% ($p < 0.001$, Figure 2A) for patients with versus without PSM. MFS rates at 96 months were 82.8 versus 84.0% ($p = 0.9$, Figure 2B) for unifocal versus multifocal PSM, 94.4 versus 67.4% ($p < 0.001$, Figure 2C) for Gleason pattern 3 versus ≥4 at the margin and 83.3 versus 82.3% ($p = 0.2$, Figure 2D) for <4 mm versus ≥4 mm length of PSM.

In multivariable Cox models predicting development of metastasis (Table 2), GGG 3 (HR: 5.09, 95% CI 3.48–7.42, $p < 0.001$), GGG 4–5 (HR: 10.7, 95% CI 7.07–16.2, $p < 0.001$), and pathologic stage T3b (HR: 2.04, 95% CI 1.55–2.69, $p < 0.001$) were independent predictors for metastasis. However, PSM (HR: 1.15, 95% CI 0.85–1.56, $p = 0.4$) failed to reach significance in prediction of metastasis.

In subgroup analysis, focusing on patients with PSM (Table 3), Gleason ≥4 at the margin ($p = 0.3$), PSM focality ($p = 0.2$), and PSM length ($p = 0.3$) were no predictors of metastasis.

3.4 | Effect of PSM on survival and cancer-specific survival

At 96 months after RP, cancer-specific survival rates were 94.7 versus 98.5% ($p < 0.001$, Figure 3A) for patients with versus without PSM. Cancer-specific survival rates at 96 months were, 94.4 versus 97.2% ($p = 0.4$, Figure 3B) for unifocal versus multifocal PSM, 100.0 versus 87.1% ($p < 0.01$, Figure 3C) for Gleason pattern 3 versus ≥4 at the margin and 95.2 versus 92.7% ($p = 0.3$, Figure 3D) for <4 mm versus ≥4 mm length of PSM.

Last but not least, in multivariable Cox models predicting cancer-specific death (Table 2), PSM (HR: 2.75, 95% CI 1.17–6.47, $p = 0.02$), year of surgery (HR: 0.65, 95% CI 0.48–0.89, $p = 0.01$), GGG 3 (HR: 12.9, 95% CI 1.53–25.6, $p = 0.02$), and GGG 4–5 (HR: 36.1, 95% CI 11.7–78.4, $p < 0.001$) were independent predictors for PCa-specific death.

4 | DISCUSSION

PSM represents a poor prognostic factor at RP in patients with PCa.[1–3] However, the impact of the Gleason pattern at the PSM, PSM length, and the PSM focality in pT3 patients on long-term

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TABLE 1 Descriptive characteristics of PCa patients that underwent RP between 2010 and 2016, stratified according to the surgical margins status

	Overall (*n* = 3705)	Negative SM (*n* = 2698, 72.8%)	PSM (*n* = 1007, 27.2%)	*p* Value
Age, median (IQR)	66.4 (60.8–70.6)	66.3 (60.6–70.6)	66.6 (61.5–70.8)	0.1
Year of surgery, median (IQR)	2013 (2011–2015)	2013 (2011–2015)	2013 (2011–2015)	0.9
PSA, ng/ml, median (IQR)	8.5 (5.8–13.0)	7.9 (5.6–11.6)	11.0 (6.7–18.7)	<0.001
Gleason Grade group, *n* (%)				
GGG 1–2	2077 (56.1)	1639 (60.7)	438 (43.5)	<0.001
GGG 3	1164 (31.4)	823 (30.5)	341 (33.9)	
GGG 4–5	464 (12.5)	236 (8.7)	228 (22.6)	
Pathologic stage, *n* (%)				
pT3a	2649 (71.5)	2105 (78.0)	544 (54.0)	<0.001
pT3b	1056 (28.5)	593 (22.0)	463 (46.0)	
Lymph node stage, *n* (%)				
N0	3452 (93.2)	2509 (93.0)	943 (93.6)	0.5
Nx	253 (6.8)	189 (7.0)	64 (6.4)	
Length of PSM, mm, mean (*SD*); median (IQR)			4.47 (0.2); 2 (0.5-5.7)	
PSM focality, *n* (%)				
Unifocal			775 (77.0)	
Multifocal			163 (16.2)	
Unknown			69 (6.8)	
Gleason at PSM, *n* (%)				
3			441 (43.8)	
≥4			407 (40.4)	
Unknown			159 (15.8)	

Abbreviations: GGG, Gleason grade group; IQR, interquartile range; PCa, prostate cancer; PSA, prostatic specific antigen; PSM, positive surgical margin; RP, radical prostatectomy; *SD*, standard deviation; SM, surgical margin.

oncologic outcomes is still under debate. Several previous studies assessed the impact of PSM, Gleason pattern at the PSM, PSM length, or PSM focality at RP and BCR.[1,7,12–18] However, the impact of these margin-specific characteristics on hard clinical endpoints, that is, development of metastasis or cancer-specific death is largely unknown. To address this void, we examined the relationship between PSM and BCR, metastasis and cancer-specific death within an institutional high-volume center database of contemporary non-organ confined PCa RP patients. Our analyses revealed several noteworthy findings.

First, overall we recorded a PSM rate of 27.2% for nonorgan confined PCa. These rates are favorable compared with previous reported PSM rates for pT3 PCa patients, where PSM ranges from 37% to 61%.[2,4,5]

Second, patients with PSM harbored worse BCR-free survival rates compared with patients with negative surgical margins. BCR-free survival at 96 months after RP was 41.6 versus 57.5% for patients with versus without PSM ($p < 0.001$). Additionally, PSM represented an independent predictor of BCR (HR 1.53) after multivariable adjustment. In subgroup analysis, focusing only on patients with PSM, multifocal PSMs, a Gleason pattern ≥4 at the margin and a PSM length ≥4 mm were all associated with worse BCR. However, in multivariable analysis, only the PSM length (HR: 1.02, $p < 0.05$) and a Gleason ≥4 at the margin (HR: 1.60, $p < 0.01$)

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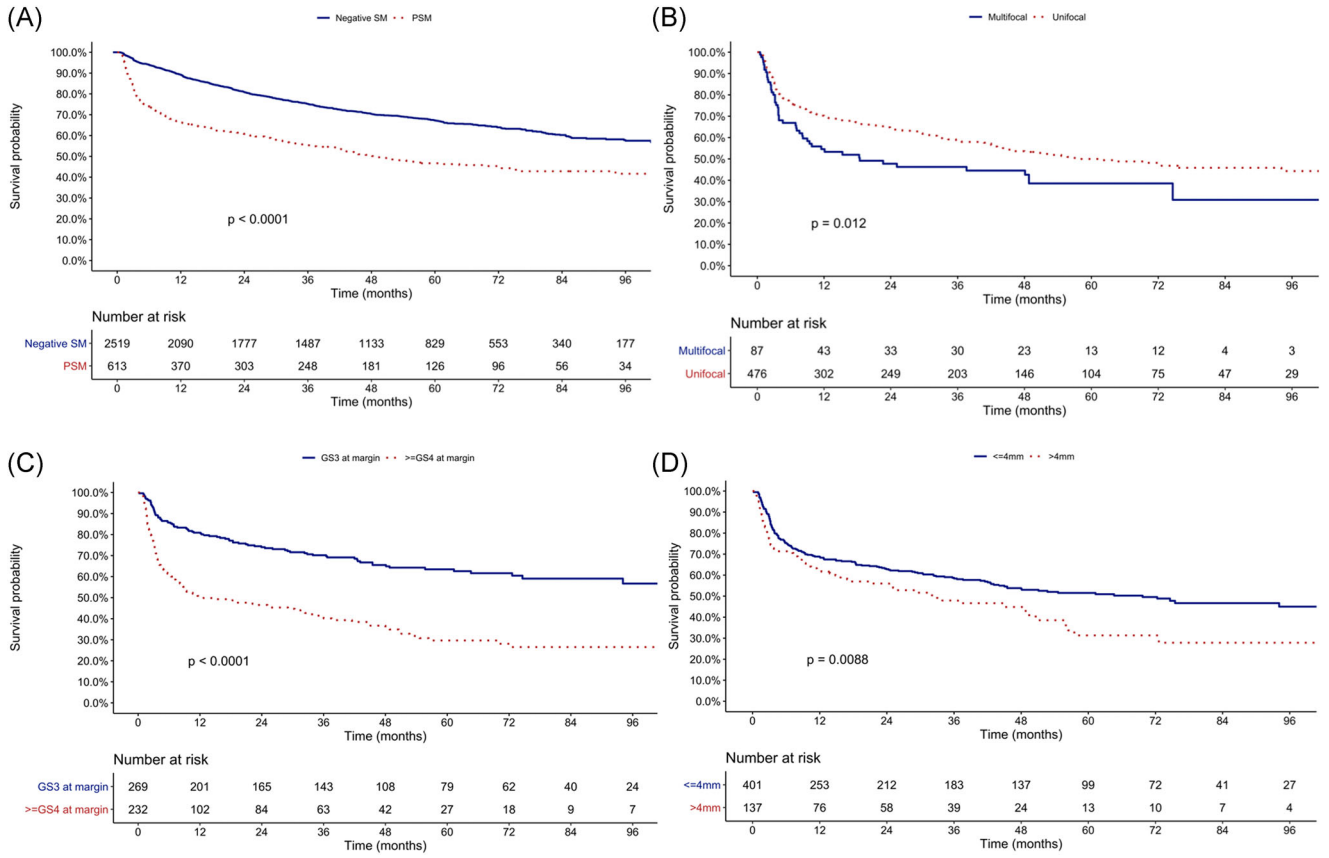


FIGURE 1 BCR-free survival stratified according to surgical margin status (A), PSM focality (B), PSM Gleason (C), and PSM length (d). BCR, biochemical recurrence; PSM, positive surgical margin [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariable Cox regression models predicting biochemical recurrence, metastasis, and cancer-specific death after radical prostatectomy

	BCR		Metastasis		Cancer-specific death	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Negative margin (reference)	-	-	-	-	-	-
PSM	1.53 (1.33–1.77)	<0.001	1.15 (0.85–1.56)	0.4	2.75 (1.17–6.47)	0.02
Year of surgery	0.91 (0.88–0.94)	<0.001	1.01 (0.94–1.09)	0.7	0.65 (0.48–0.89)	0.01
Age	0.99 (0.98–0.99)	0.04	0.98 (0.96–1.01)	0.1	0.94 (0.88–1.01)	0.1
Preoperative PSA	1.01 (1.01–1.02)	<0.001	0.99 (0.99–1.01)	0.6	0.97 (0.93–1.02)	0.2
pT3a (reference)	-	-	-	-	-	-
pT3b	1.78 (1.56–2.03)	<0.001	2.04 (1.55–2.69)	<0.001	2.14 (0.88–5.19)	0.1
GGG 1–2 (reference)	-	-	-	-	-	-
GGG 3	2.45 (2.13–2.83)	<0.001	5.09 (3.48–7.42)	<0.001	12.9 (1.53–25.6)	0.02
GGG 4–5	3.62 (3.01–4.36)	<0.001	10.7 (7.07–16.2)	<0.001	36.1 (11.7–78.4)	<0.001
pN0 (reference)	-	-	-	-	-	-
pNx	0.82 (0.62–1.09)	0.2	0.73 (0.36–1.48)	0.4	1.24 (0.16–9.71)	0.8

Abbreviations: CI, confidence interval; GGG, Gleason grade group; HR, hazard ratio; PSA, prostatic specific antigen, PSM, positive surgical margin.

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TABLE 3 Multivariable Cox regression models predicting biochemical recurrence and metastasis in prostate cancer patients with nonorgan confined disease and positive margins at radical prostatectomy

	BCR		Metastasis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Multifocal PSM (reference)	-	-	-	-
Unifocal PSM	0.85 (0.60–1.19)	0.3	1.60 (0.77–3.35)	0.2
Gleason 3 at the PSM (reference)	-	-	-	-
Gleason ≥4 at the PSM	1.60 (1.62–2.21)	<0.01	1.53 (0.70–3.34)	0.3
Length of PSM (mm)	1.02 (1.01–1.04)	<0.05	1.02 (0.98–1.06)	0.3
pT3a (reference)	-	-	-	-
pT3b	1.70 (1.29–2.22)	<0.001	2.13 (1.16–3.90)	0.01
GGG 1–2 (reference)	-	-	-	-
GGG 3	1.39 (0.99–1.95)	0.1	5.94 (1.90–18.6)	<0.01
GGG 4–5	2.17 (1.49–3.16)	<0.001	13.9 (4.29–45.6)	<0.001

Abbreviations: CI, confidence interval; GGG, Gleason grade group; HR, hazard ratio; PSM, positive surgical margin.

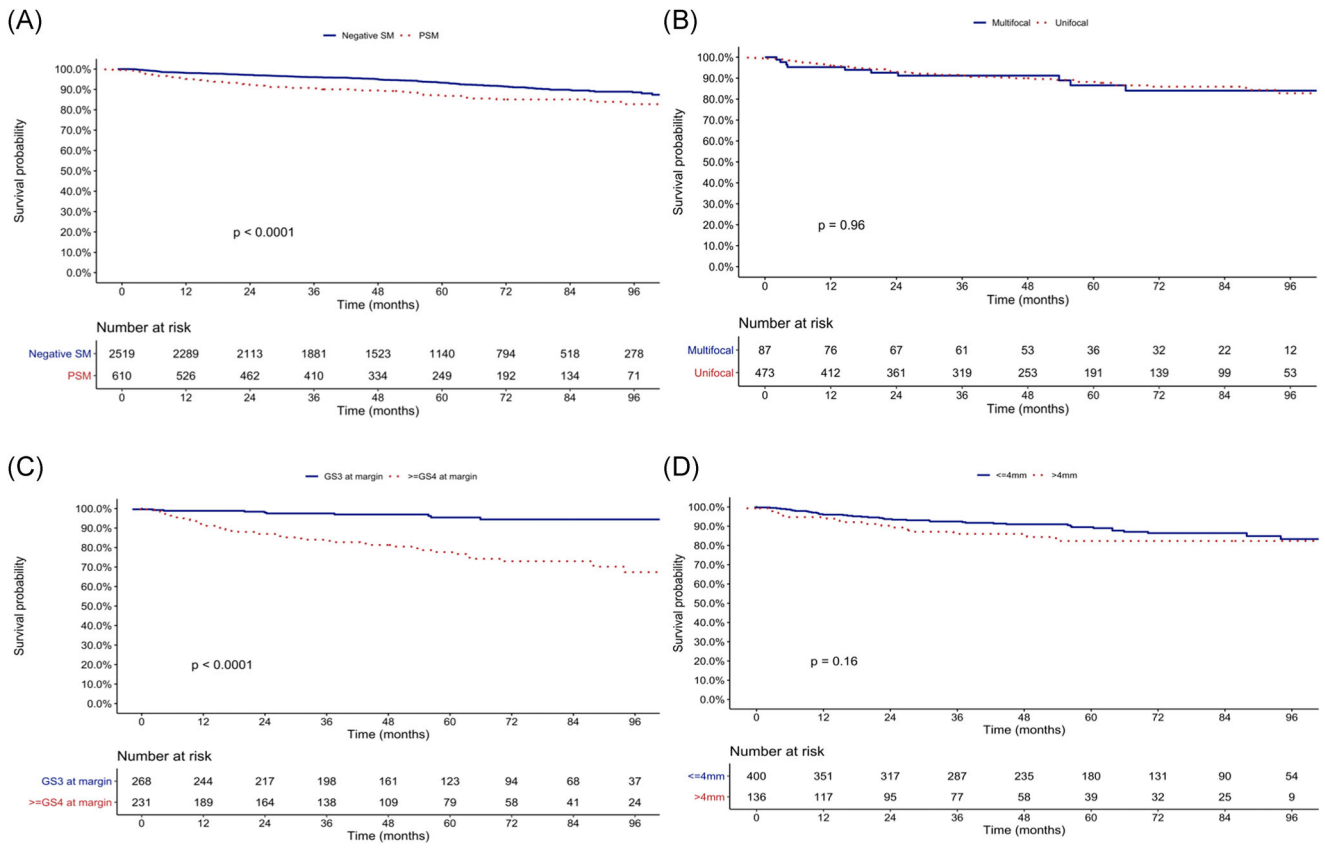


FIGURE 2 Metastasis-free survival stratified according to surgical margin status (A), PSM focality (B), PSM Gleason (C), and PSM length (D). PSM, positive surgical margin [Color figure can be viewed at wileyonlinelibrary.com]

represented independent predictors of BCR. These results corroborate the findings from Ploussard et al., who reported that the PSM length represents a risk factor for BCR in nonorgan confined PCa after RP.[7] Furthermore, our results underline the report from Brimo et al.[8] who reported that a higher Gleason grade at the margins is associated with BCR.[8]

Third, patients with PSM more frequently developed metastasis during the follow-up. At 96 months after RP, MFS rates were 82.7 versus 88.6% ($p < 0.001$) for patients with versus without PSM. However, in multivariable models PSM (HR: 1.15, $p = 0.4$) failed to reach significance in prediction of metastasis. These results are in line with a previous study within a cohort of patients treated with early

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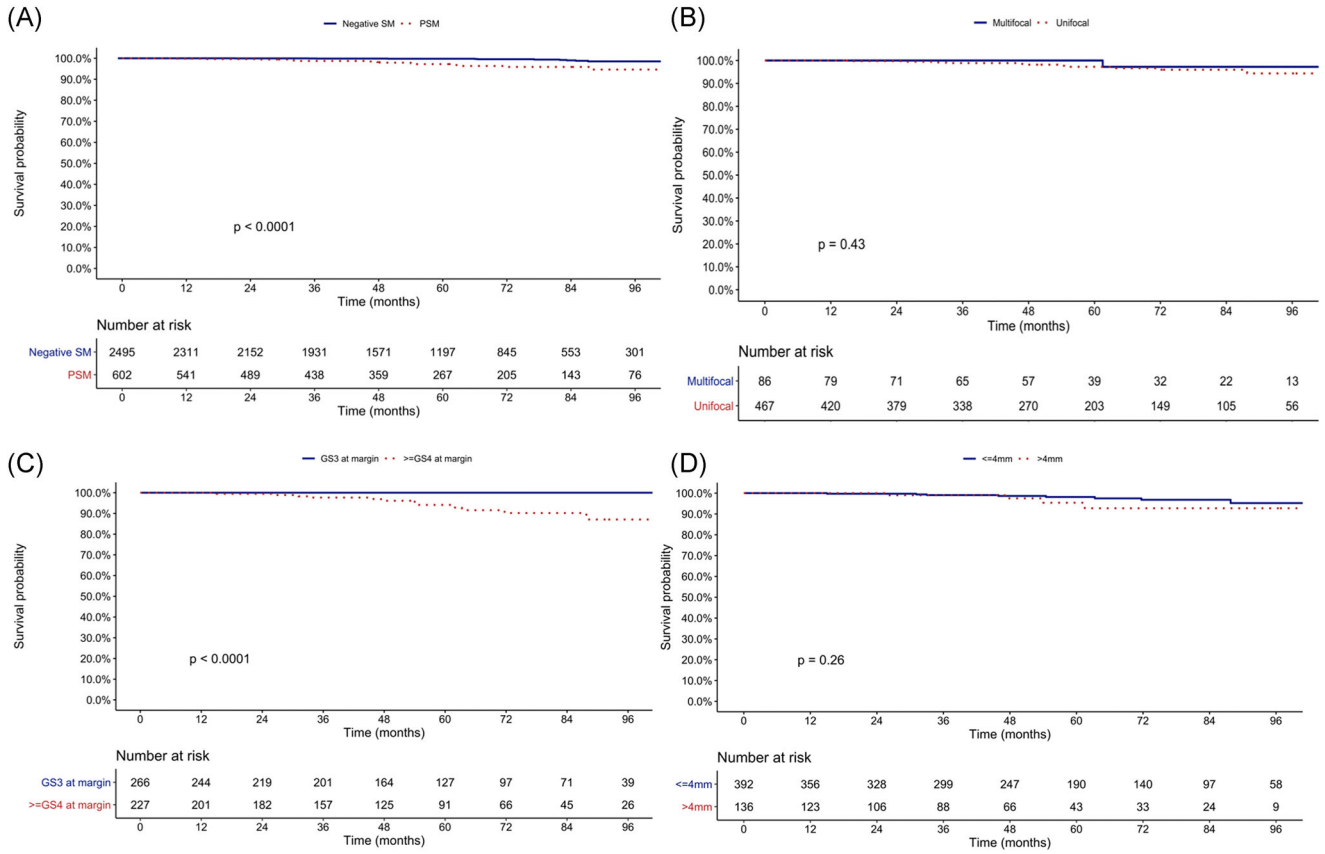


FIGURE 3 Cancer-specific survival stratified according to surgical margin status (A), PSM focality (B), PSM Gleason (C), and PSM length (D). PSM, positive surgical margin [Color figure can be viewed at wileyonlinelibrary.com]

salvage radiotherapy due to BCR after RP.[19] In this study, PSM was no independent predictor for development of metastasis, while the strongest predictor for metastasis following BCR was a higher Gleason Grade and seminal vesicle invasion at RP, which is in line with our findings. In subgroup analysis, focusing on patients with PSM, neither a Gleason ≥4 at the margin the length of the PSM or its focality were independent predictor for development of metastasis. Fourth, patients with PSM harbored worse long-term survival compared to patients without PSM. At 96 months after RP, cancer-specific survival rates were 94.7 versus 98.5% ($p < 0.001$) for patients with versus without PSM. Additionally, in multivariable models, PSM represented an independent predictor for cancer-specific death (HR: 2.75, $p = 0.02$). These results underline the above mentioned findings for BCR with a clinically more meaningful endpoint.

Last but not least, in subgroup analysis, focusing only on patients with PSM, patients with a higher Gleason pattern at the margin harbored worse survival. Cancer-specific survival rates at 96 months were, 100.0 versus 87.1% ($p < 0.01$) for Gleason pattern 3 versus ≥4 at the margin. Conversely, no differences in survival between unifocal and multifocal, as well as for PSM length <4 mm versus ≥4 mm were recorded.

Taken together, our results demonstrated that patients with non-organ confined PCa and PSM have worse BCR-free, MFS and cancer-specific survival after RP. Moreover, to the best of our knowledge we are the first that demonstrated that in patients with PSM and nonorgan confined PCa, a higher Gleason pattern at the PSM was associated with worse survival. This said, the PSM length and PSM Gleason pattern at RP should be routinely reported, which is in line with the recommendations of the 2009 International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens.[20]

Our study is not devoid of limitations. First and foremost, it shares limitations of all similar studies that relied on retrospective data. Moreover, our study only provides information from a high-volume PCa referral centers, where all RPs were performed by high-volume surgeons, which may differ from other centers. Additionally, the site of the PSM may also affect oncologic outcomes after RP, which was unavailable within the current database. Last but not least, our database did not contain information on adjuvant hormone therapy, which may have influenced oncologic outcomes.

5 | CONCLUSION

PSM represents an independent predictor for worse oncologic outcomes in non-organ-confined PCa at RP. Gleason ≥4 at the margin was associated with the development of BCR, metastasis, and with cancer-specific death after RP. Moreover, the length of PSM

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was an independent predictor for BCR. Next to margin status, Gleason at the margin and its length carry important information that should be reported for the specimen.

ACKNOWLEDGEMENTS

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

Derya Tilki certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: Preisser F, Heinze A, S. Abrams-Pompe R, et al. Impact of positive surgical margin length and Gleason grade at the margin on oncologic outcomes in patients with nonorgan-confined prostate cancer. *The Prostate*. 2022;82:949-956. doi:10.1002/pros.24341

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