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Impact of positive surgical margins on secondary treatment, palliative radiotherapy and prostate cancer-specific mortality. A population-based study of 13 198 patients

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Abstract

Background: The results of studies evaluating the impact of positive surgical margins on prostate cancer-specific mortality have been inconsistent. We, therefore, evaluated the impact of surgical margin status on subsequent secondary treatment, palliative radiotherapy, and prostate cancer-specific mortality.

Methods: A total of 14 837 men treated with radical prostatectomy (RP) during the period 2001 to 2015 were identified from the Cancer Registry of Norway. Of those, 13 198 (89%) patients had complete data on the preoperative prostate-specific antigen level, pathological T-category, Gleason score in the prostatectomy specimen, and margin status. Multivariable Cox proportional hazards models were used to evaluate the risk, and flexible parametric models for the cumulative incidence were fitted to predict the probabilities of secondary treatment (salvage radiotherapy or prophylactic breast radiation), palliative radiotherapy, and prostate cancer-specific mortality.

Results: After a median follow-up time of 5.2 years (3591 patients with ≥8 years of follow-up), positive surgical margins (PSMs) were independently predictive of secondary treatment (hazard ratio [HR] = 2.43, 95% confidence interval [CI] = 2.21-2.66) and palliative radiotherapy (HR = 1.45, 95% CI = 1.03-2.05). After 10 years, the absolute increased risk for palliative radiotherapy in patients with PSMs after RP varied between 0.1% in pT2 tumors with a Gleason score of 6, to 12% for pT3b tumors with a Gleason score of 9 to 10. PSMs were not independently associated with prostate cancer-specific mortality (HR = 1.14, 95% CI = 0.82-1.59).

Conclusion: PSMs were associated with increased application of secondary treatment and palliative radiotherapy but were not predictive of prostate cancer-specific mortality. As the use of palliative radiotherapy was only marginally increased in

patients with PSMs and the lowest-risk disease characteristics, avoiding PSMs may be of greatest prognostic relevance in patients with higher-risk disease characteristics.

KEYWORDS
mortality, prostate cancer, prostatectomy, radiotherapy, surgical margin

1 | INTRODUCTION

The presence of positive surgical margins (PSMs) after radical prostatectomy (RP) is associated with the risk of biochemical relapse and is considered a measure of surgical quality.[1] However, results from studies evaluating the possible unfavorable long-term effects of PSMs on prostate cancer-specific mortality have been inconsistent,[2,3] and the question of whether PSMs after prostate cancer surgery should be of concern has been discussed.[4]

Only a few large studies have examined the impact of PSMs on endpoints other than biochemical relapse, including local progression, castrate-resistant prostate cancer, and the development of the metastatic disease. Previously, Boorjian et al[5] reported that the presence of PSMs increased the risk for biochemical relapse, local progression and salvage treatment; however, no statistically significant increased risk for development of metastatic disease or prostate cancer-specific mortality was found. Similarly, Mithal et al[6] found a positive but nonsignificant association between PSMs and development of metastatic disease or castrate-resistant prostate cancer.

In the present population-based study, we elucidate the impact of PSMs on the following clinically relevant endpoints: secondary treatment indicating biochemical relapse (salvage radiotherapy or prophylactic breast radiation), palliative radiotherapy for advanced disease, and prostate cancer-specific mortality. Furthermore, we estimate the probabilities of secondary treatment, palliative radiotherapy and prostate cancer-specific mortality by time after surgery, key disease characteristics, and margin status and portray the results in illustrations that may aid in patient counseling.

2 | MATERIAL AND METHODS

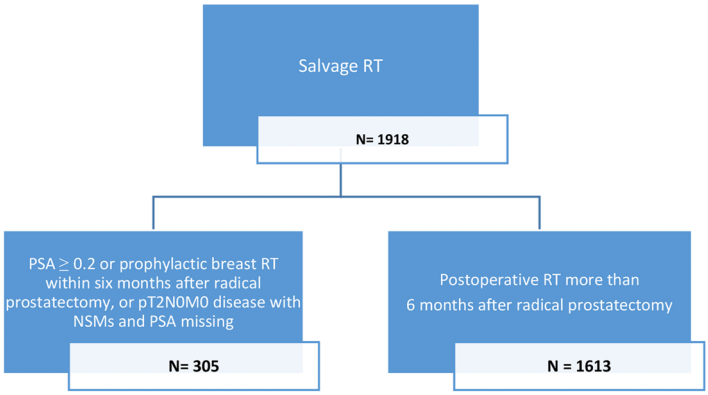
During the period 2001 to 2015, 14 837 patients below 75 years of age without evidence of distant metastases at diagnosis were treated by RP in Norway. As each pathology unit in Norway is obliged to submit a copy of the pathology report from every RP specimen examined to the Cancer Registry of Norway, the registry has almost complete coverage of performed prostatectomies.[7] The unique personal identification number secures patient identification. A total of 13 198 (89%) of these patients had available data on preoperative prostate-specific antigen (PSA) values, pathological T-category (pT-category), Gleason score in the RP specimen, and resection margin status. Patients treated with radiotherapy were identified from a radiotherapy database within the Cancer Registry. Secondary treatment, indicating biochemical relapse after RP, was defined as salvage radiotherapy or prophylactic radiation to the breast buds after RP. During the study period, prophylactic breast radiotherapy was used before antiandrogen treatment to prevent gynecomastia.[8] Information on the postoperative use of Gonadotropin-releasing hormone (GnRH) analogs was not available. Radiotherapy with a total radiation dose equivalent to the biological effects of ≥60 grays in 2 gray fractions initiated more than 6 months postoperatively was defined as salvage radiotherapy. Patients with evidence of a PSA value more than 0.2 or prophylactic breast radiation before postoperative pelvic radiotherapy were also allocated to the salvage radiotherapy group (Figure 1A, PSA data were available in approximately two-thirds of the patients treated with radiotherapy within 6 months after RP). Correspondingly, radiotherapy doses ≥60 grays that were administered less than 6 months after RP to patients without evidence of a PSA value more than 0.2 or prophylactic breast radiation were categorized as adjuvant radiotherapy (Figure 1B). Radiotherapy with doses below 60 grays was defined as palliative radiotherapy.

Uni- and multivariable Cox proportional hazards models were used to evaluate the risk of secondary treatment, palliative radiotherapy, and prostate cancer-specific mortality associated with the surgical margin status. The preoperative PSA value, pT-category, Gleason score in the prostatectomy specimen, and age were added as covariates in the multivariable model. In addition, to account for structural and time-dependent changes, hospital size (based on the number of radical prostatectomies performed annually) and time periods of surgery were included in the model. To exclude the possible effect of adjuvant radiotherapy on the results, separate analyses were performed after the exclusion of patients adjuvantly treated. The outcomes in patients with PSMs who received adjuvant radiotherapy were also compared to those of patients with PSMs who did not receive such treatment. Subgroup analyses including tumor size (available from 2006 to 2015) were also performed. To check for possible interactions, likelihood ratio tests were performed, as well as subgroup analyses stratified by age, pT-category and Gleason score. Flexible parametric models for the cumulative incidence were fitted to predict the probabilities of secondary treatment, palliative radiotherapy, and prostate cancer-specific mortality. For the first two endpoints, death from any cause was considered a competing risk, and for the last endpoint, death from other causes was treated as a competing risk. In addition to surgical margin status, these models included the key prognostic variables; pathological Gleason score and pT-category. Statistical analyses were performed using Stata software version 15.0.

3 | RESULTS

The median follow-up time of the study was 5.2 years (Q1-Q3 = 3.1-8.3 years, person-time = 78 234), and 3591 patients had

(A)



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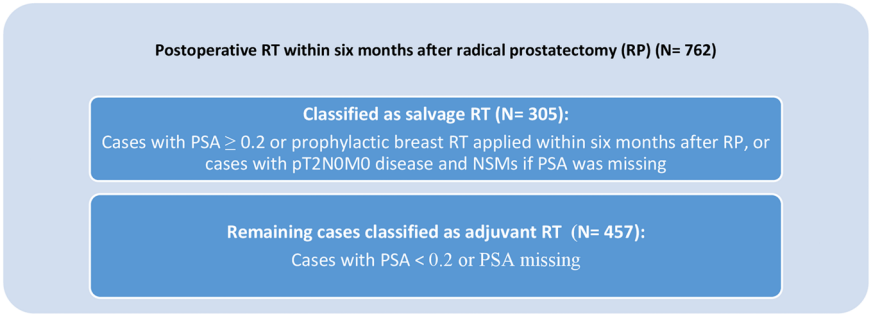

Postoperative RT within 6 months after radical prostatectomy		762 (100%)
Salvage RT (N=305)	Postoperative PSA ≥ 0.2	259 (34.0%)
	Treated with prophylactic breast RT before postoperative RT	34 (4.4%)
	pT2N0M0 disease with NSMs and postoperative PSA missing	12 (1.6%)
Adjuvant RT (N=457)	Postoperative PSA < 0.2	226 (29.7%)
	Postoperative PSA missing	231 (30.3%)

FIGURE 1 A, Definition of salvage radiotherapy (RT). B, Definition of adjuvant radiotherapy (RT) [Color figure can be viewed at wileyonlinelibrary.com]

more than 8 years of follow-up. The median age of the patients included in the study was 63 years (range = 38-74 years), and the median preoperative PSA was 8.1 (range = 0-99, Q1-Q3 = 6.0-11.6). Table 1 presents the characteristics of the patients by surgical margin status. PSMs were reported in 3478 (26.4%) of the 13 198 patients. The proportion of patients with PSMs decreased from 39.4% in the period 2001-2003 to 23.0% in the period 2013-2015, and significant decreases in the proportion of prostatectomy specimens with PSMs were observed for both pT2 and pT3 tumors ($P = .000$; Table 2).

During follow-up, 2112 (16.0%) patients received secondary treatment. Almost one in three patients who had PSMs and one in 10 patients with negative surgical margins (NSMs) received secondary treatment (Table 3). In total, 397 (11.4%) patients with PSMs and 60 (0.6%) with NSMs were treated with adjuvant radiotherapy. Furthermore, 152 patients received palliative radiotherapy, and in 167 cases, prostate cancer was recorded as the underlying cause of death. The median age at death was 70 years (range = 47-90 years). The 10- and 15-year prostate cancer-specific mortality rates (number of patients at risk at 10 years: 1884; at 15 years: 168) were 2.5% (NSMs: 1.8%, PSMs: 4.2%) and 6.6% (NSMs: 3.8%, PSMs: 11.4%), respectively. Correspondingly, the 10- and 15-year total mortality rates were 10.3% and 22.2%, respectively. The 10- and 15-year probabilities for palliative radiotherapy were 2.3% (NSMs: 1.5%, PSMs: 4.4%) and 3.8% (NSMs: 2.5%, PSMs: 6.6%). The corresponding figures for secondary treatment were 21.7% (NSMs: 14.5%, PSMs: 41.1%) and 23.8% (NSMs: 16.6%, PSMs: 43.1%; Kaplan-Meier estimates). Eighty-nine (58.6%) of the patients who received palliative radiotherapy had prostate cancer reported as their underlying cause of death, and 13 (8.6%) had another cause (12 patients) or missing (one patient) cause of death. The use of secondary treatment and palliative radiotherapy were strongly associated with an increased risk of prostate cancer death (hazard ratio [HR] = 3.1; confidence interval [CI] = 2.1-4.5 and HR = 73.6; CI = 50.2-108.0; Table 4).

PSMs increased the risk of secondary treatment (HR = 2.4, 95% CI = 2.2-2.7) and palliative radiotherapy (HR = 1.5, 95% CI = 1.0-2.1; Table 5A); however, they were not independently associated with prostate cancer-specific mortality (HR = 1.1, 95% CI = 0.8-1.6). Similar results were obtained using Fine and Gray competing risk regression analysis. The HRs were not noticeably altered by the exclusion of patients treated with adjuvant treatment or by the inclusion of adjuvant treatment in the model, and no statistically significant differences were found between patients with PSMs who received adjuvant treatment and those who did not receive adjuvant treatment (Table SA). Table 5B shows that secondary treatment was used relatively more often for tumors with PSMs than for tumors with NSMs in patients who were younger or had a lower

TABLE 1 Characteristics of 13 198 patients by surgical margin status, study period 2001 to 2015

	NSMs		PSMs		Total	
	N	%	N	%	N	%
Total	9 720	73.6	3 478	26.4	13 198	100.0
Period of surgery						
2001-2003	400	60.6	260	39.4	660	5.0
2004-2006	1 002	69.2	446	30.8	1 448	11.0
2007-2009	1 870	71.1	759	28.9	2 629	19.9
2010-2012	2 995	75.3	982	24.7	3 977	30.1
2013-2015	3 453	77.0	1 031	23.0	4 484	34.0
Age, y						
<60	2 368	74.7	802	25.3	3 170	24.0
60-64	2 809	74.8	948	25.2	3 757	28.5
65+	4 543	72.4	1 728	27.6	6 271	47.5
Preoperative PSA, ng/mL						
<10.0	6 704	78.2	1 872	21.8	8 576	65.0
10.0-19.9	2 495	68.2	1 166	31.8	3 661	27.7
≥20	521	54.2	440	45.8	961	7.3
Pathological stage						
pT2	6 973	82.1	1 523	17.9	8 496	64.4
pT3a	2 130	61.2	1 349	38.8	3 479	26.4
pT3b-pT4[a]	375	50.9	361	49.1	736	5.6
LN+	242	49.7	245	50.3	487	3.7
Gleason score from RP specimen						
6	2 160	80.2	533	19.8	2 693	20.4
7a	4 577	74.9	1 533	25.1	6 110	46.3
7b	2 007	71.3	807	28.7	2 814	21.3
8	623	65.3	331	34.7	954	7.2
9-10	353	56.3	274	43.7	627	4.8

Abbreviations: NSMs, negative surgical margins; PSA, prostate-specific antigen; PSMs, positive surgical margins; RP, radical prostatectomy.
[a]pT4: five cases.

pT-category/grade disease. No clear interactions were found in the analyses of palliative radiotherapy and prostate cancer-specific mortality. The preoperative PSA value was an independent predictor for secondary treatment but not for palliative radiotherapy or for prostate cancer-specific mortality. In the subgroup analyses, tumor size in the prostatectomy specimen was found to be predictive of secondary treatment ($P = .01$), palliative radiotherapy (nonsignificant, $P = .14$) and prostate cancer-specific mortality ($P = .01$); however tumor size had only a minor impact on the risk estimates for the association between surgical margin status and our study endpoints (data not shown). Likewise, the inclusion of geographical region (patients were allocated to the South-East-, West-, Central- or Northern-region based on their county of residence) in the multivariable analyses had only negligible effects on the risk estimates.

TABLE 2 Positive surgical margins (%) by period of surgery and pathological T-category

Period	pT2	pT3a	pT3b
2001-2003	135/477 (28.3)	110/162 (67.9)	11/17 (64.7)
2004-2006	260/1 120 (23.2)	138/242 (57.0)	39/74 (52.7)
2007-2009	369/1 805 (20.4)	280/618 (45.3)	85/157 (54.1)
2010-2012	361/2417 (14.9)	439/1 192 (36.8)	109/226 (48.2)
2013-2015	398/2 677 (14.9)	382/1 265(30.2)	113/257 (44.0)

TABLE 3 Secondary treatment, palliative radiotherapy (RT) and cause of death by surgical margin status in 13 198 patients, study period 2001 to 2015

	NSMs		PSMs		Total	
	N	%	N	%	N	%
Adjuvant RT	60	0.6	397	11.4	457	3.5
Secondary treatment	983	10.1	1129	32.5	2 112	16.0
Salvage RT only	801	8.2	971	27.9	1 772	13.4
Prophylactic breast and salvage RT	70	0.7	76	2.2	146	1.1
Prophylactic breast RT only	112	1.2	82	2.4	194	1.5
No known secondary treatment	8 677	89.3	1 952	56.1	10 629	80.5
Total	**9 720**	**100.0**	**3 478**	**100.0**	**13 198**	**100.0**
Palliative RT	67	0.7	85	2.4	152	1.2
Cause of death						
Prostate cancer	82	0.8	85	2.4	167	1.3
Other	349	3.6	151	4.3	500	3.8
Unknown	47	0.5	14	0.4	61	0.5

Abbreviations: NSMs, negative surgical margins; PSMs, positive surgical margins.

The probabilities for secondary treatment, palliative radiotherapy, and prostate cancer-specific mortality were strongly influenced by the pT-category and Gleason score. Figure 2 illustrates the probability of secondary treatment by pT-category, surgical margin status, and pathological Gleason score. At 10 years postoperatively, the probability for secondary treatment varied from 7% in patients with pT2 tumors with a Gleason score of 6 and NSMs to nearly 80% in patients with pT3b tumors with a Gleason score of 8 to 10 and PSMs. The probability of palliative radiotherapy within 10 years varied from 0.2% in patients with pT2 tumors with a Gleason of 6 and NSMs to nearly 35% in patients with pT3b tumors with a Gleason score of 9 to 10 and PSMs (Figure 3 and Table 6). Similarly, at 10 years after surgery, the probability of prostate cancer-specific mortality varied from 0.2% in patients with pT2 tumors with a Gleason score of 6 and NSMs to slightly above 35% in patients with pT3b tumors with a Gleason score of 9 to 10 cancer and PSMs. The absolute increased risk for receiving treatment with palliative

TABLE 4 Hazard ratios for prostate-specific death in patients that received secondary or palliative radiotherapy

	Secondary treatment	Palliative radiotherapy
Univariable (CI)	8.7 (6.2-12.1)	201.9 (145.7-279.6)
Multivariable (CI)[a]	3.1 (2.1-4.5)	73.6 (50.2-108.0)

Abbreviation: CI, confidence interval; PSA, prostate-specific antigen.
[a]Adjusted for age, period of surgery, preoperative PSA, pT-category, Gleason score in radical prostatectomy specimen, and hospital volume. Time dependent analysis.

TABLE 5A Hazard ratios for secondary treatment, palliative radiotherapy, prostate cancer-specific mortality, and all-cause mortality after radical prostatectomy

	Univariable (CI)		
	Secondary treatment	**Palliative radiotherapy**	**Prostate cancer mortality**
Surgical margins			
Negative (reference)	1.0	1.0	1.0
Positive	3.71 (3.41-4.04)	3.10 (2.25-4.27)	2.34 (1.72-3.19)
	Multivariable (CI)		
	Secondary treatment	**Palliative radiotherapy**	**Prostate cancer mortality**
Surgical margins			
Negative (reference)	1.0	1.0	1.0
Positive	2.43 (2.21-2.66)	1.45 (1.03-2.05)	1.14 (0.82-1.59)
Preoperative PSA			
<10	1.0	1.0	1.0
10-19	1.34 (1.22-1.47)	1.11 (0.79-1.57)	1.00 (0.72-1.40)
≥20	1.43 (1.24-1.65)	0.81 (0.43-1.53)	0.76 (0.41-1.39)
Pathological T-category			
pT2	1.0	1.0	1.0
pT3a	1.57 (1.41-1.74)	2.75 (1.78-4.26)	2.39 (1.58-3.62)
pT3b-T4	2.35 (2.03-2.72)	5.58 (3.40-9.16)	4.47 (2.77-7.19)
LN+	4.19 (3.52-4.99)	6.96 (3.66-13.2)	7.53 (4.17-13.6)
Gleason score			
3+3 = 6	1.0	1.0	1.0
3 + 4 = 7	1.62 (1.38-1.89)	3.28 (1.36-7.92)	3.91 (1.63-9.38)
4 + 3 = 7	3.22 (2.73-3.79)	8.97 (3.73-21.6)	9.35 (3.88-22.5)
8	4.44 (3.68-5.35)	15.3 (6.11-38.1)	22.2 (9.02-54.7)
9-10	4.78 (3.89-5.88)	34.0 (13.7-84.5)	44.5 (18.1-109)
Age at surgery, y			
<60	1.0	1.0	1.0
60-64	1.03 (0.91-1.16)	1.71 (1.08-2.70)	1.60 (1.04-2.49)
≥65	0.95 (0.85-1.06)	1.29 (0.83-2.01)	1.23 (0.80-1.88)
Period			
2001-2003	1.0	1.0	1.0
2004-2006	0.80 (0.67-0.96)	0.44 (0.27-0.74)	0.55 (0.32-0.95)
2007-2009	0.76 (0.65-0.90)	0.37 (0.22-0.62)	0.67 (0.39-1.16)
2010-2012	0.57 (0.48-0.67)	0.16 (0.09-0.30)	0.35 (0.18-0.68)
2013-2015	0.27 (0.22-0.33)	0.13 (0.05-0.32)	0.57 (0.24-1.37)
Hospital volume			
Low	1.0	1.0	1.0
Medium	0.89 (0.80-0.98)	1.08 (0.74-1.58)	1.12 (0.78-1.61)
High	0.71 (0.63-0.80)	1.09 (0.59-1.66)	0.91 (0.59-1.38)
Patients receiving adjuvant treatment excluded[a,b](CI)			
Negative (reference)	1.0	1.0	1.0
Positive	2.95 (2.70-3.24)	1.47 (1.03-2.10)	1.15 (0.81-1.62)

Abbreviation: CI, confidence interval; PSA, prostate-specific antigen.

[a]Adjusted for age, period of surgery, preoperative PSA value, pT- and N- category, Gleason score in radical prostatectomy specimen, and hospital volume.

[b]Follow-up starting six months after radical prostatectomy.

radiation within 10 years in patients with PSMs after RP compared to patients with NSMs varied between 0.1% in pT2 tumors with a Gleason score of 6 to approximately 12% for pT3b tumors with a Gleason score of 9 to 10 (Table 6). The nonsignificant 13% relative increase in prostate cancer-specific mortality among patients with PSMs compared to patients with NSMs was translated into an absolute increased risk of 0.1% in patients with the most indolent prostate tumors (pT2, Gleason score 6) and 5.0% in patients with the most aggressive tumors (pT3b, Gleason score 9-10) at 10 years after RP.

4 | DISCUSSION

The current population-based study demonstrates increased risks for secondary treatment and palliative radiotherapy when PSMs are present in the prostatectomy specimen. Ten years after prostatectomy, the largest increases in absolute risk for palliative radiotherapy among cases with PSMs compared with cases with NSMs were observed among patients with aggressive disease characteristics. However, PSMs were not independently associated with prostate cancer-specific mortality. In addition to the strongest predictor, the Gleason score in the

TABLE 5B Stratified analyses by age group, pT-category, and Gleason score group: hazard ratios for secondary treatment, palliative radiotherapy (RT), and prostate cancer-specific mortality in patients with positive surgical margins status versus patients with negative surgical margins after radical prostatectomy

		Secondary treatment (CI)	Palliative RT (CI)	Prostate cancer mortality (CI)
Age	<60	2.96 (2.48-3.52)	2.76 (1.30-5.85)	1.55 (0.79-3.03)
	60-64	2.45 (2.08-2.89)	1.04 (0.58-1.86)	0.85 (0.47-1.53)
	65+	2.16 (1.87-2.50)	1.29 (0.75-2.23)	1.12 (0.66-1.88)
pT-category	pT2	3.60 (3.14-4.13)	1.52 (0.75-3.06)	1.41 (0.73-2.69)
	pT3a	2.27 (1.94-2.65)	1.35 (0.77-2.37)	0.65 (0.37-1.15)
	pT3b-pT4	1.41 (1.11-1.79)	1.46 (0.75-2.86)	1.39 (0.70-2.75)
	LN+	1.45 (1.09-1.92)	2.24 (0.68-7.36)	1.76 (0.65-4.75)
Gleason score	<7b	3.79 (3.29-4.37)	1.56 (0.78-3.13)	1.11 (0.56-2.19)
	7b	1.98 (1.69-2.33)	1.46 (0.79-2.74)	0.83 (0.42-1.63)
	8	1.78 (1.40-2.26)	1.57 (0.68-3.59)	0.83 (0.40-1.74)
	9-10	1.39 (1.05-1.84)	1.15 (0.57-2.30)	1.44 (0.73-2.85)

Abbreviation: CI, confidence interval.

prostatectomy specimen, the pT-category was independently associated with palliative radiotherapy and prostate cancer-specific mortality. The preoperative PSA value was predictive for secondary treatment but was not associated with the use of palliative radiotherapy or prostate cancer-specific mortality.

The reported rates of PSMs in our nationwide study are in line with those reported in the previous studies[9] and were nearly halved throughout the study period. Earlier studies have shown that margin status is associated with surgical experience.[10-12] From 2001 to 2015 the number of radical prostatectomies performed annually in Norway increased from approximately 300 to more than 1800, and the average number per hospital department increased from approximately 15 to approximately 130. This development suggests that surgical quality has improved during the last decade. In recent years, the use of

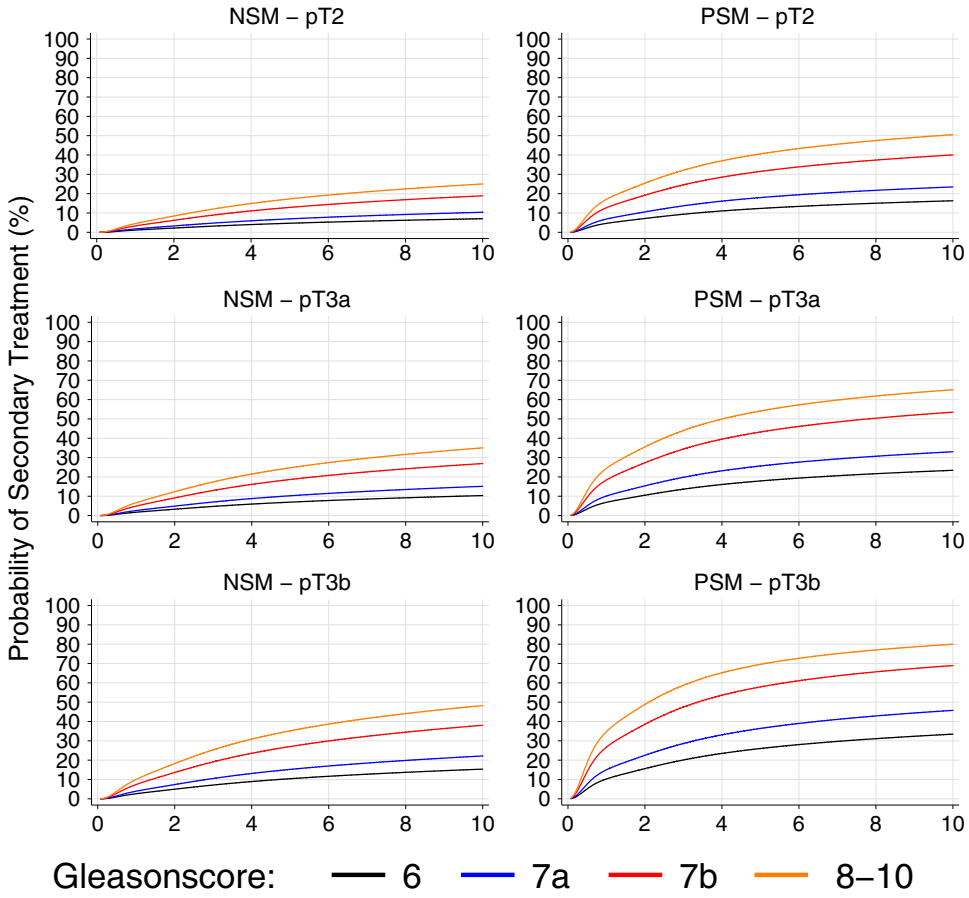

FIGURE 2 Probability of secondary treatment by time, pT-category, Gleason score in the prostatectomy specimen and surgical margin status [Color figure can be viewed at wileyonlinelibrary.com]

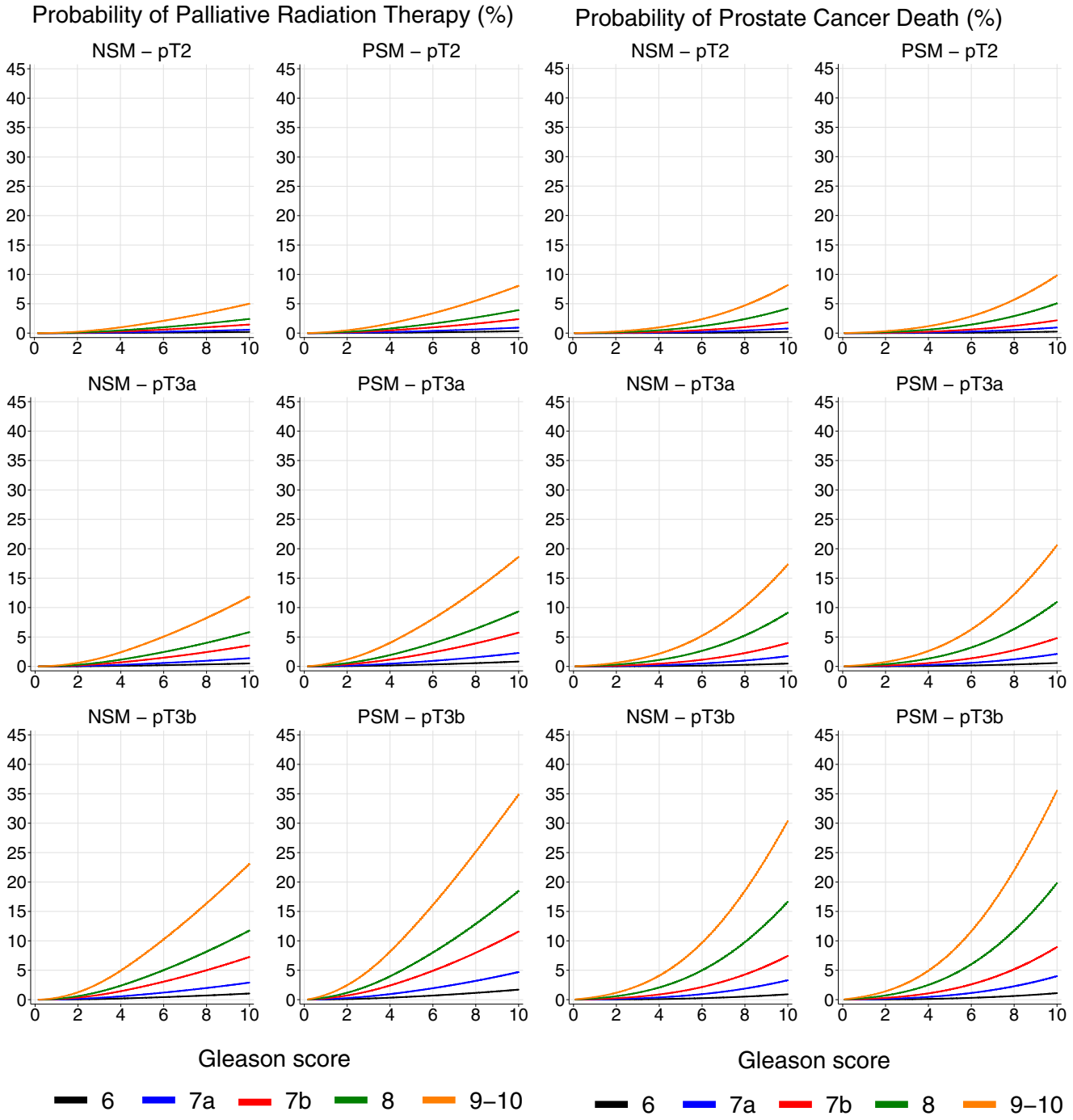

FIGURE 3 Probability of palliative radiotherapy and prostate cancer-specific mortality by time, pT-category, Gleason score in the prostatectomy specimen and surgical margin status [Color figure can be viewed at wileyonlinelibrary.com]

preoperative prostate magnetic resonance imaging (MRI) and multidisciplinary conferences may have also influenced the selection of patients for nerve-sparing surgery and reduced the amount of PSMs.[13]

Previous studies have been consistent regarding the positive relationship between PSMs and biochemical relapse.[14] However, as the probability of prostate cancer-specific mortality within the first 10 to 15 years after RP is low, only large studies or studies with long follow-up times have been able to show independent and statistically significant unfavorable effects of PSMs on prostate cancer-specific mortality.[3,15] A recent meta-analysis that included 32 cohort studies and involved 141 222 patients, concluded that PSMs are closely associated with a higher risk of prostate cancer-specific and overall mortality.[16] The present study is one of the largest studies to evaluate the association of PSMs and risk of later treatment for disease progression. Although we found a 45% relative increased risk for the application of palliative radiotherapy and a 13% relative increased risk for prostate cancer-specific mortality (not significant) among patients with PSMs, there was only a minor difference in

TABLE 6 Probabilities of palliative radiotherapy (RT) and prostate cancer death 10 years after radical prostatectomy (RP) by pathological T-category and Gleason score (GS)

		Probability of palliative RT 10 years after RP (%)			Probability of prostate cancer death 10 years after RP (%)		
		NSMs	PSMs	Absolute difference	NSMs	PSMs	Absolute difference
pT2	GS <6	0.2	0.3	0.1	0.2	0.3	0.1
	GS 7a	0.6	0.9	0.3	0.8	1.0	0.2
	GS 7b	1.5	2.4	0.9	1.8	2.2	0.4
	GS 8	2.4	3.9	1.5	4.2	5.1	0.9
	GS 9-10	5.0	8.1	3.1	8.2	9.8	1.6
pT3a	GS <6	0.5	0.8	0.3	0.5	0.6	0.1
	GS 7a	1.4	2.3	0.9	1.8	2.1	0.3
	GS 7b	3.6	5.7	1.1	4.0	4.8	0.8
	GS 8	5.8	9.3	3.5	9.1	11.0	1.9
	GS 9-10	11.8	18.6	6.8	17.3	20.6	3.3
pT3b-pT4	GS <6	1.0	1.7	0.7	0.9	1.1	0.1
	GS 7a	2.9	4.7	1.8	3.3	4.0	0.7
	GS 7b	7.3	11.6	4.3	7.4	9.0	1.6
	GS 8	11.8	18.5	6.7	16.7	19.8	3.1
	GS 9-10	23.1	34.9	11.8	30.4	35.5	5.1

Abbreviations: NSMs, negative surgical margins; PSMs, positive surgical margins.

absolute risk for palliative radiotherapy in patients with pT2 and low Gleason score tumors at 10 to 15 years after surgery. The prognostic importance of margin status among low-risk prostate cancer patients can thus be questioned. In contrast, among patients with the most aggressive tumors (pT3b, Gleason score 9-10), there was a 12% absolute increased risk for palliative radiotherapy and a 5% absolute increased risk for prostate cancer-specific mortality in cases with PSMs compared to cases with NSMs at 10 years after surgery. Although beneficial effects of postoperative radiotherapy may have impacted the results, achieving NSMs after surgery may, therefore, be of utmost prognostic relevance to patients with high-risk disease characteristics. This should be taken into consideration when discussing nerve-sparing surgery with the patient. However, as PSMs are associated with statistically significant increased risks of secondary treatment that may cause additional side effects, the presence of PSM should remain a quality measure.

There has been some uncertainty about the quality of death certificates in prostate cancer patients in Norway. A recent study evaluating the quality of death certificates in 764 men with prostate cancer from the county of Vestfold in Norway found that 10% (7/70) of patients younger than 75 years at death were incorrectly labeled as having prostate cancer as their underlying cause of death.[17] In our study, the median age at death for the patients that died during follow-up was 70 years. Consequently, these results suggest that misclassification of the cause of death is a minor problem in our study. However, 37 (8.5%) of the 436 prostate cancer patients who were reported as having another cause of death in the Vestfold study should have been reported as having prostate cancer as their underlying cause of death. Thus, the effect of misclassification leading to some dilution of the effects of PSMs on mortality cannot be excluded.[18] Therefore, the evaluation of secondary endpoints indicating disease progression provides important supplementary evidence in addition to the assessment of prostate cancer-specific mortality.

The current study has some limitations. Additional variables that have been shown to affect biochemical relapse, such as tumor location,[19] length of PSMs,[20] and Gleason score at the PSMs,[21] were not available. It is also possible that PSMs may be an additional indicator of the severity of disease not captured by the pT-category, Gleason score in the RP specimen, and PSA value. However, when performing a subgroup analysis that also included tumor size in the prostatectomy specimen, only minor changes in the risk estimates for the association between surgical margin status and our study endpoints were observed. Therefore, we believe that the effect of PSMs as an additional indicator of the severity of disease is minor. Furthermore, no central review of the pathology specimens was performed, and variations in practice and interpretation of margin status can be present and lead to misclassification. In addition, information on secondary treatments such as the use of GnRH analogs was not available. Moreover, the use of additional therapy with salvage radiotherapy, antiandrogen treatment, GnRH analogs, chemotherapy and more recently abiraterone or enzalutamide, administered at different stages of disease progression, may have worsened the ability to discriminate direct independent associations of margin status with our outcomes. Finally, longer follow-up may be beneficial for evaluation of the possible association between PSMs and prostate cancer-specific mortality.

The strengths of our study are that, unlike the results from single- or multi-institutional studies, our population-based data are less vulnerable to distortions related to local clinical practice. Furthermore, use of the national identification number ensures almost complete follow-up of all patients. Our study is also one of the first studies to incorporate palliative radiotherapy in the assessment of possible unfavorable effects of PSMs.

5 | CONCLUSIONS

PSMs were found to be significantly associated with the increased use of secondary treatment and palliative radiotherapy after RP. However, the favorable effects of NSMs at 10 years after surgery were minor for patients with the lowest-risk disease characteristics, and after a median follow-up time of 5.2 years, PSMs were not found to be predictive of prostate cancer-specific mortality. Thus, avoiding PSMs after surgery may be of greatest prognostic relevance to patients with higher-risk disease characteristics.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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