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ORIGINAL ARTICLE

Pre- and post-prostatectomy variables associated with pelvic post-operative radiotherapy in prostate cancer patients: a national registry-based study

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ABSTRACT

Background: In patients with prostate cancer (PCa), the lack of clear guidelines on the use of radiotherapy after radical prostatectomy (RP) invites unwanted variation of this treatment. We describe the hazard ratios and probabilities related to the use of post-RP radiotherapy.

Material and methods: Data were collected from the Cancer Registry of Norway and nine radiotherapy units. All patients were diagnosed with a non-metastatic PCa from January 2004 through June 2011. *Adjuvant radiotherapy* was defined as pelvic radiotherapy initiated <5 months after RP at a PSA <0.2 ng/ml. All other pelvic radiotherapy series were categorized as *salvage radiotherapy*, and, combined with adjuvant radiotherapy they were termed *post-RP radiotherapy*.

Results: Of 6840 prostatectomized patients, 1170 (17%) had undergone post-RP radiotherapy, mainly as salvage radiotherapy. The number of adjuvant radiotherapy series almost tripled from 2009. Based on pre-prostatectomy variables (PSA, Gleason score, and clinical risk group) and findings in the prostatectomy specimens (status of resection margins, pathological tumor category and Gleason's score), the probability of post-RP radiotherapy ranged respectively from 14% to 73%, and from 4% to 83%.

Conclusions: In our study, post-RP radiotherapy was applied in approximately one in six patients. Based on the combination of PCa-specific variables routinely available at the time of diagnosis, a patient's probability of post-RP radiotherapy can be determined *before* decision of primary treatment strategy, followed by probability determination based on histopathological variables emerging from the prostatectomy specimen.

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Prostate cancer (PCa) is the most frequent cancer among men in Europe [1]. In 2014, nearly 5000 men were diagnosed with PCa in Norway, and about 90% of these patients were diagnosed without distant metastases [2]. Radical prostatectomy (RP) is one of the curative treatment options for these patients [3,4]. If the histopathological examination of the prostatectomy specimen shows tumor growth beyond the prostate capsule and/or tumor involvement in the resection margin(s), adjuvant radiotherapy should be considered as an additional treatment option [3,4]. Only a minority of patients meeting the above criteria receive adjuvant radiotherapy [5–7]. Early salvage radiotherapy at the time of biochemical and local recurrence is an alternative strategy [3,8].

The combination of RP and pelvic radiotherapy is believed to increase the level and severity of adverse effects compared to definitive radiotherapy applied as a primary treatment. If a patient's probability of radiotherapy after RP could be estimated at the time of diagnosis, he may choose definitive radiotherapy as primary treatment instead of RP. The two treatment modalities seem to result in a similar five and 10-year survival period [9–11]. It is, however, relatively unknown whether, and to what degree, routinely available PCa-specific variables at the time of diagnosis are associated with the use of pelvic radiotherapy following RP.

With this background, the present study has two co-primary aims. First, to assess the use of curatively intended pelvic radiotherapy after RP in Norway. Second, to calculate the hazard ratios (HRs) related to post-RP radiotherapy and to determine the probability of receiving this additional treatment for PCa.

Material and methods

Patient selection

Patients eligible for this study were identified using the Cancer Registry of Norway (CRN). The patients were diagnosed with adenocarcinoma of the prostate from January 2004 through June 2011 and had undergone RP within one year of diagnosis (*MainGroup*). A research data file was established with information on the date of diagnosis, age, and PSA at the time of diagnosis, Gleason's score (GS) of biopsy,

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clinical tumor category (cT), and clinical risk group. For patients diagnosed in 2009 or later (*SubGroup2009*), results from the histopathological examination of the prostatectomy specimens were electronically recorded at the CRN. This information was added to the research file. The CRN also has a sub-registry with information about the radiotherapy series provided in all radiotherapy units in Norway. This sub-registry comprises data on, for example, date of initiating radiotherapy, intention to treat (curative or palliative), target region and total dose. All the irradiated patients had curatively intended pelvic radiotherapy initiated after RP at a delivered total dose of 60 Gy or more. PSAs at the start of radiotherapy were collected from the nine responsible radiotherapy units. There was no information on whether or not biochemical relapse was accompanied by a pelvic recurrence.

Data management

The patients were divided into clinical risk groups in accordance with the European Association of Urology (EAU) classification; lymph node status not included [4]. Gleason's score in biopsies and prostatectomy specimens were categorized following the recommendations of the International Society of Urological Pathology on Gleason grading of PCa [12]. The status of the resection margins was defined as "free" or "not free" without identification of the extent of possible tumor involvement. Radiotherapy series initiated less than five months after RP in patients with an undetectable PSA (<0.2 ng/ml) were categorized as *adjuvant radiotherapy*, and all other series were categorized as *salvage radiotherapy*. Due to low numbers, the treatment categories of adjuvant and salvage radiotherapy were mainly analyzed together as one combined group, termed *post-RP radiotherapy*.

Statistics

Continuous variables were assessed by medians and ranges with the Mann–Whitney test evaluating differences. Categorical variables were expressed as percentages with the chi-square test evaluating differences. Kaplan–Meier's estimates related to post-RP radiotherapy were established for all patients and stratified for PCa-specific variables, respectively, at the time of diagnosis and following the analysis of the prostatectomy specimen. The observation time was defined as the time between RP and the date of the first event; post-RP radiotherapy, emigration, death, or end of study (31 December 2012). Cox proportional hazards regression models provided HRs with 95% confidence interval (CI). The assumptions of proportionality were tested using Schoenfeld's residuals, and no evidence of non-proportionality was found. To estimate the probability of post-RP radiotherapy depending on combined significant covariates from the Cox regression analyses, a multivariate competing risk analysis was done, according to Hinchliffe and Lambert [13]. Death was treated as a competing risk, and the cause-specific hazard function for both post-RP radiotherapy and death was estimated and combined into estimates of cumulative incidence. Missing data were imputed using multiple imputation techniques. A $p < .05$ was considered statistically significant. All p values were from two-sided tests. The statistical programs for the different analyses were SPSS for PC version 21.0 and STATA version 14.1 (Chicago, IL, USA).

Ethics

The project was approved by the Regional Ethical Committee of the South-Eastern Health Region in Norway.

Results

Post-RP radiotherapy in patients diagnosed with PCa from January 2004 through June 2011 (MainGroup)

With a median observation time of 41 months (range: <1–108), a total of 1170 of 6840 prostatectomized men had undergone curatively intended pelvic radiotherapy after RP (Table 1). The nine-year Kaplan–Meyer estimate was 25% (95% CI: 22–27%) (Figure 1(a)).

In the irradiated patients, radiotherapy was initiated at a median time of 14 months (range: 1–102) since RP. Only 161 of the 1170 irradiated patients had undergone post-RP radiotherapy as adjuvant treatment; 54 patients (8%) were diagnosed before 2009 and 107 patients (23%) were diagnosed thereafter (data not shown). The median PSA at the start of post-RP radiotherapy was 0.4 ng/ml (range: <0.2–38.0).

The proportions of irradiated patients increased with rising PSA at the time of diagnosis, clinical tumor category (cT ≤ 2 vs. cT ≥ 3), biopsy-based GS, and clinical risk group. In the Cox regression analysis, the clinical tumor category (cT 2b, cT

Table 1. Patient characteristics.

	All patients $N = 6840$	RP[a] only $n = 5670$	Post-RP radiotherapy[b] $n = 1170$ (17%)	
Date of diagnosis				
Jan. 2004–Dec. 2008	3844	3143	701 (18%)	
Jan. 2009–June 2011	2996	2527	469 (16%)	
Age at diagnosis				
Median (range)	63 (39–86)	63 (39–86)	63 (45–77)	
<65	4322	3595	727 (13%)	
≥65	2518	2075	443 (18%)	
PSA at diagnosis (ng/ml)				
Median (range)	8.5 (1.0–604.0)	8.2 (1.0–604.0)	10.0 (1.7–241.0)	
<10	4259	3703	556 (13%)	
10–20	2078	1617	461 (22%)	
>20	503	350	153 (30%)	
Clinical tumor category (cT)				
≤2a	5139	4345	794 (15%)	16%[c]
2b ≤2	523	421	102 (20%)	
2c	645	541	104 (16%)	
≥3	533	363	170 (32%)	
Gleason's score				
≤6	3025	2684	341 (11%)	
7a	2287	1933	354 (15%)	
7b	872	635	237 (27%)	
8	513	329	184 (36%)	
9–10	143	89	54 (38%)	
Clinical risk group				
Low	1504	1379	122 (8%)	
Intermediate	3358	2816	542 (16%)	
High, localized	1426	1099	327 (23%)	
High, locally advanced	555	376	179 (32%)	

[a]Radical prostatectomy.
[b]Radiotherapy ≥60 Gy.
[c]Irradiated patients with cT2/all patients with cT2.

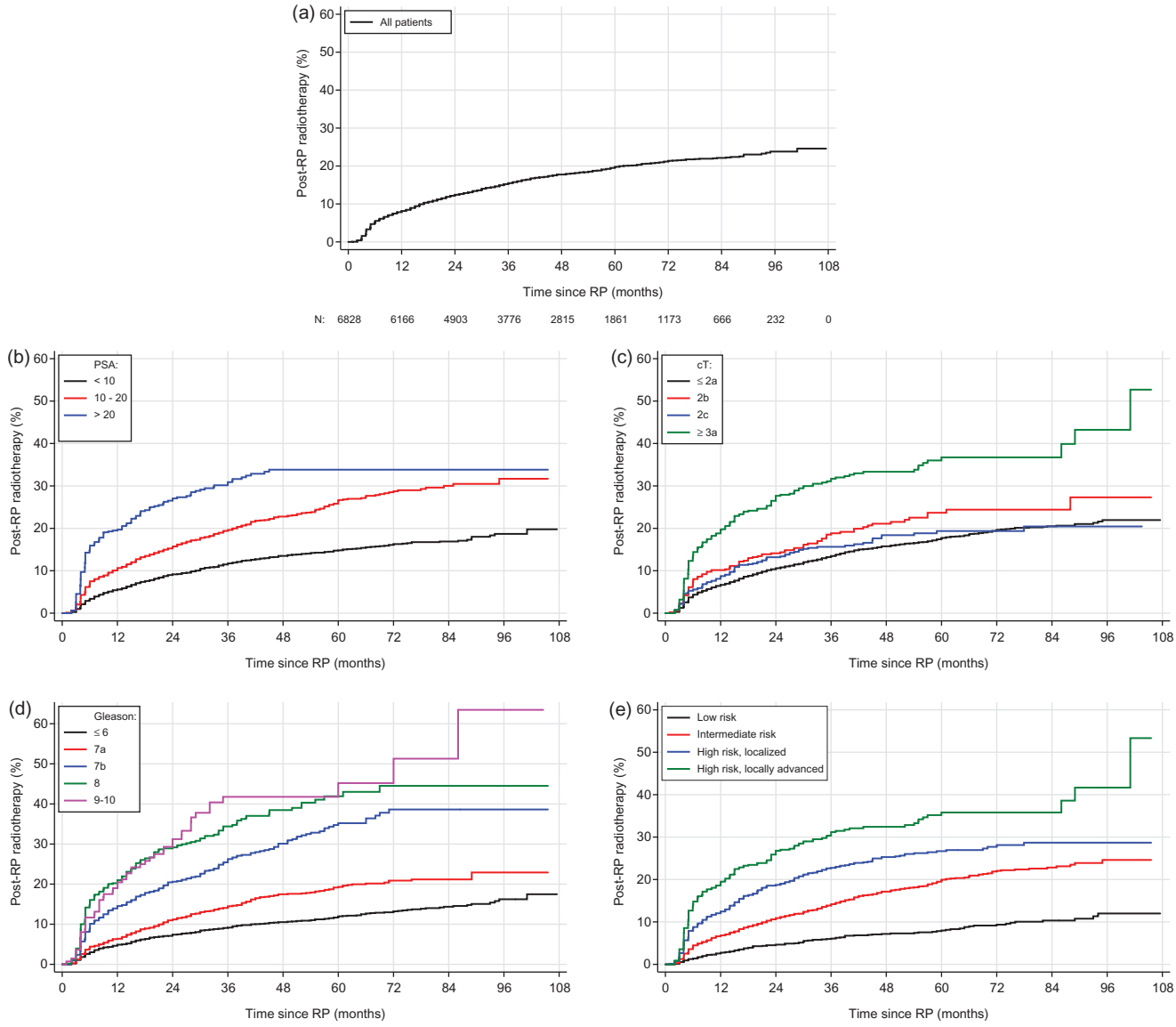

Figure 1. Nine-year Kaplan–Meier's estimates of post-prostatectomy radiotherapy based on pre-prostatectomy variables.

Table 2. Risk of post-prostatectomy radiotherapy based on pre-prostatectomy variables.

	HR[a]	95% CI[b]	*p* Value[c]
PSA at diagnosis (ng/ml)			
<10	Ref.	1.30, 1.72	<.01
10–20	1.50	1.52, 2.42	<.01
>20	1.92		
Clinical tumor category			
≤2a	Ref.		
2b	1.18	0.95, 1.46	.14
2c	0.81	0.62, 1.07	.15
≥3	1.42	0.69, 2.93	.34
Gleason's score			
≤6	Ref.		
7a	1.34	1.12, 1.60	<.01
7b	2.30	1.88, 2.80	<.01
8	2.83	2.19, 3.65	<.01
9–10	2.89	2.06, 4.07	<.01
Clinical risk group			
Low	Ref.		
Intermediate	1.35	1.05, 1.75	.02
High, localized	1.72	1.25, 2.39	<.01
High, locally advanced	1.74	0.82, 3.69	.15

[a]Hazard ratio.
[b]Confidence interval.
[c]Significant level: $p < .05$.

2c and cT ≥ 3) lost its statistical significance compared to the reference (cT ≤ 2a) (Table 2). The HRs were similar for GS 8 vs. GS 9–10 in the biopsies. The largest difference occurred between GS 7a and GS 7b. The Kaplan–Meier graphs display the findings from Tables 1 and 2 (Figure 1(a–e)).

Post-RP radiotherapy in patients diagnosed with PCa from January 2009 through June 2011 (SubGroup2009)

With a median follow-up time of 25 months (range: <1–47) after RP, 469 (16%) of 2996 patients in SubGroup2009 had undergone post-RP radiotherapy (Table 3). The use of post-RP radiotherapy increased with rising GS in the prostatectomy specimen, tumor growth beyond the prostate capsule (pT ≥ 3), and the presence of tumor involvement in resection margin(s). Post-RP radiotherapy was used in only 7% of patients with a prostate-confined (pT 2) tumor, compared with 27% in patients with an extra-prostatic tumor growth (pT ≥ 3). A total of 513 patients had both tumor involvement in the resection margin(s) and pT ≥ 3 (data not shown).

Table 3. Results from the histopathological examination of the prostatectomy specimens.

	All patients $N = 2996$	RP only $n = 2527$	Post-RP radiotherapy[a] $n = 469$ (16%)	
Pathological tumor category (pT)				
2a	391	360	31 (8%)	
2b } 2	161	143	18 (11%) } 7%[b]	
2c	1159	1087	72 (6%)	
≥3	1285	937	348 (27%)	
Gleason's score				
≤6	601	577	27 (4%)	
7a	1365	1222	143 (10%)	
7b	597	455	142 (24%)	
8	283	190	93 (33%)	
9–10	150	86	64 (43%)	
Status of resection margins				
Free	2183	2040	143 (7%)	
Not free	813	487	326 (40%)	

[a]Adjuvant ($n = 107$) or salvage radiotherapy ($n = 362$).
[b]Irradiated patients with pT2/all patients with pT2.

Table 4. Risk of post-prostatectomy radiotherapy based on variables in the prostatectomy specimen.

	HR[a]	95% CI[b]	p Value[c]
Pathological tumor category			
2a	Ref.		
2b	1.46	0.76, 2.77	.25
2c	0.74	0.46, 1.19	.21
≥3	1.88	1.21, 2.91	.01
Gleason's score			
≤6	Ref.		
7a	1.70	1.12, 2.58	.01
7b	3.39	2.22, 5.17	<.01
8	5.09	3.27, 7.92	<.01
9–10	5.29	3.31, 8.44	<.01
Status of resection margins			
Free	Ref.		
Not free	5.90	4.80, 7.26	<.01

[a]Hazard ratio.
[b]Confidence interval.
[c]Significant level: $p < .05$.

Only 261 of these (51%) had undergone post-RP radiotherapy; in 91 men this was provided as adjuvant radiotherapy. The HR among patients with pT ≥3 was almost double of that in patients with pT 2a (Table 4). Compared to the reference (GS ≤6), a five-fold increase of the hazard function was observed in patients with GS ≥8 in the prostatectomy specimen or tumor involvement in the resection margin(s). Again, there were similar HRs for GS 8 vs. GS 9–10 with the largest difference between GS 7a and GS 7b. Figure 2(a) visualizes the 20% (95% CI: 18–22%) Kaplan–Meier estimate related to post-RP radiotherapy for patients in SubGroup2009. Figure 2(b–d) depicts comparable estimates for patients stratified by findings in the prostatectomy specimen; pathological tumor category (pT), GS and status of resection margins.

Probability of post-RP radiotherapy

Based on the results from the multivariate competing risks analyses, the probability of post-RP radiotherapy was estimated for different levels of PCa-specific variables at the time of diagnosis and in the prostatectomy specimens (Table 5(a,b)). Within each clinical risk group, a rising biopsy-based GS increased the probability of post-RP radiotherapy with further increase along with rising PSA at time of diagnosis. The nine-year probability of receiving post-RP radiotherapy ranged from 14% in patients with a clinical low-risk tumor (cT ≤2a and PSA <10 ng/ml and GS ≤6) to 73% in those with the highest-risk PCa (cT ≥3 and PSA >20 ng/ml and GS 9–10). The comparable four-year probability based on PCa-specific variables in the prostatectomy specimens ranged from 4% (tumor-free resection margins and pT 2 and GS ≤6) to 83% (tumor involvement in resection margin(s) and pT ≥3 and GS 9–10). Figure 3(a,b) shows the time-dependent probability of post-RP radiotherapy related to the status of resection margins (tumor-involvement; no vs. yes) and GS. In general, patients with tumor involvement in resection margin(s) have a four-fold increased probability of post-RP radiotherapy compared to patients with tumor-free resection margins, the interval between RP and post-RP radiotherapy diminished along with increasing GS in the prostatectomy specimen.

Discussion

In our study, 1170 (17%) of 6840 patients had undergone post-RP radiotherapy. The nine-year Kaplan–Meier estimate was 25% (95% CI: 22–27%). Among the irradiated patients, the number receiving adjuvant radiotherapy almost tripled from 2009. As a new finding, we show that the combination of PCa-specific variables routinely available at the time of diagnosis enables the determination of an individual's probability of receiving post-RP radiotherapy, ranging from 14% to 73%. We have confirmed the impact of unfavorable PCa-specific variables in the prostatectomy specimen on the frequency of post-RP radiotherapy.

Guidelines on the use of adjuvant radiotherapy are vague [3,4]. Studies have shown reduced risk of biochemical failure after adjuvant radiotherapy in patients with extra-prostatic tumor growth and/or tumor involvement in the resection margin(s); however, no beneficial effect on survival has been shown [14,15]. On the other hand, a Cochrane report [16], Thompson et al. [17], and Gandaglia et al. [18], claim survival prolongation after a follow-up of 10 years or more, but only Wiegel et al. [14] provided a clear separation between adjuvant radiotherapy (shortly after RP at an undetectable PSA) and salvage radiotherapy (measurable PSA). Further, early salvage radiotherapy provided to patients with a very low PSA at the start of radiotherapy may be as effective as "true" adjuvant radiotherapy [19,20].

The potential radiotherapy-induced adverse effects in particular may also be an argument against the use of adjuvant radiotherapy. According to van Stam et al. [21], more frequent and more severe adverse effects occurred if post-RP radiotherapy was initiated within the first seven months after RP compared to radiotherapy initiated thereafter. Conversely, Hegarty et al. [22] did not show any influence of timing and adverse effects.

The uncertainties, particularly when regarding the lack of a clear benefit in PCa-specific survival, can explain the

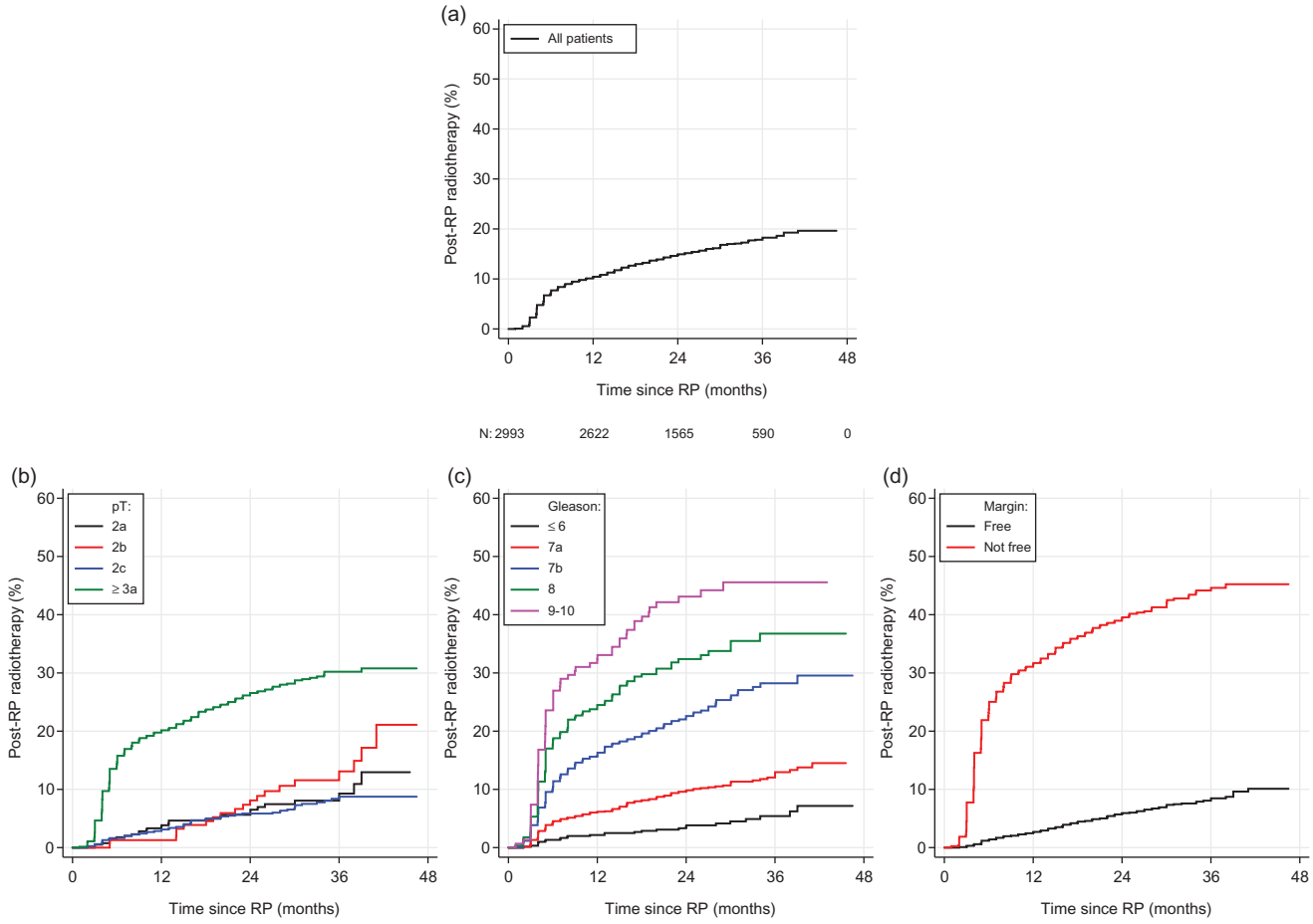

Figure 2. Four-year probability of post-prostatectomy radiotherapy based on findings in the prostatectomy specimen.

Table 5. Probability of post-prostatectomy radiotherapy based on combinations of pre-prostatectomy variables (a) or variables in the prostatectomy specimen (b).

(a)

Risk group[a]	Low	Intermediate		High, localized			High, locally advanced		
PSA (ng/ml)	<10	<10	10–20	<10	10–20	>20	<10	10–20	>20
GS[b] ≤6	14%	18%	24%	21%	27%	35%	28%	36%	46%
GS 7a	Irr.[c]	20%	27%	23%	30%	38%	32%	40%	50%
GS 7b	Irr.	30%	38%	34%	42%	52%	44%	54%	64%
GS 8	Irr.	Irr.	Irr.	41%	50%	60%	53%	62%	71%
GS 9–10	Irr.	Irr.	Irr.	44%	53%	63%	55%	65%	73%

(b)

Status of resection margins	Free		Not free	
Pathological tumor category (pT)	pT 2	pT ≥3	pT 2	pT ≥3
GS[a] ≤6	4%	8%	18%	34%
GS 7a	6%	12%	26%	46%
GS 7b	11%	21%	43%	68%
GS 8	15%	29%	56%	80%
GS 9–10	17%	32%	60%	83%

[a]In according to EAU classification [4].
[b]Gleason's score.
[c]Irrelevant.

modest use of adjuvant radiotherapy after RP internationally [5,7] and in our study. However, the increased use of adjuvant radiotherapy observed in this study since 2009 may be explained by a rising tendency to perform RP as the primary treatment option in patients with locally advanced PCa [23,24]. The increasing involvement of multidisciplinary teams in the decision on PCa treatment may additionally have contributed to this finding among our study population.

For several years, it has been accepted that the presence of at least one or two unfavorable histopathological findings in the prostatectomy specimen (extra-prostatic tumor growth and/or tumor involvement in the resection margins) increases the use of post-RP radiotherapy [25]. We confirm these

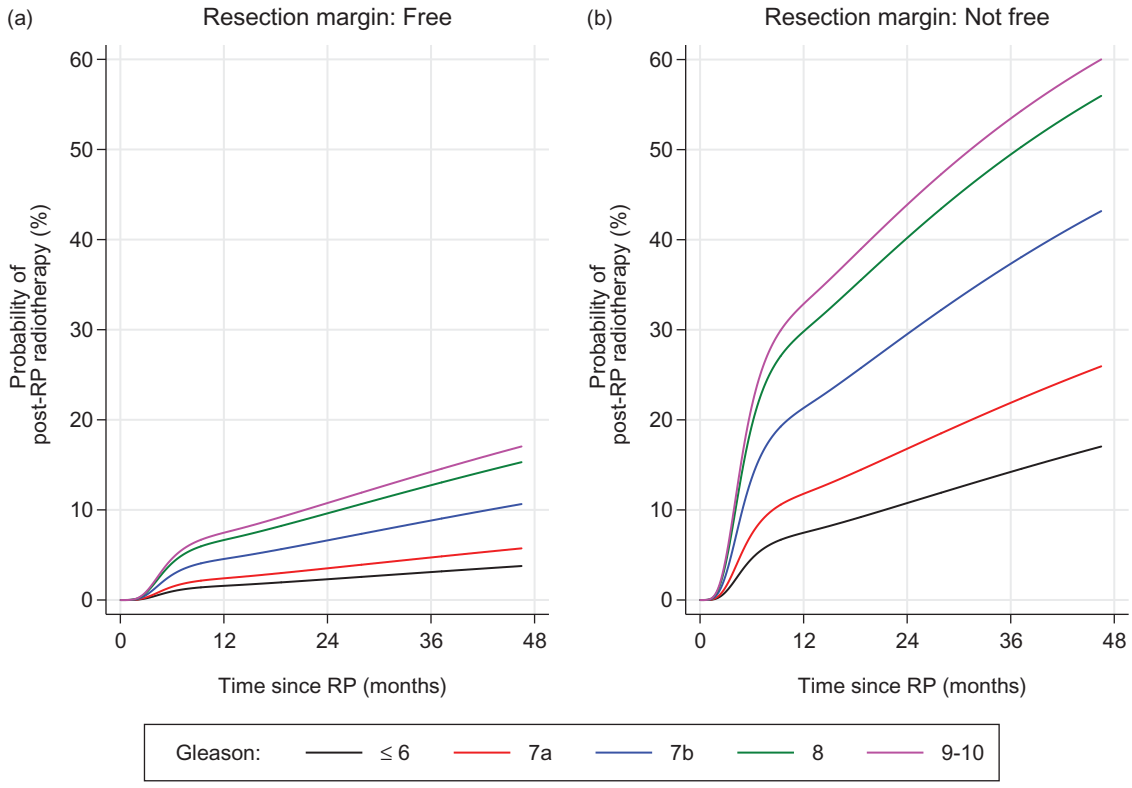

Figure 3. Four-year probability of post-prostatectomy radiotherapy related to status of the resection margins and Gleason's score in the prostatectomy specimen.

results by observing an increasing probability of receiving post-RP radiotherapy along with GS and tumor-involvement of the resection margin(s).

The most important, and to our knowledge new, finding in this study, is that the probability of post-RP radiotherapy can be determined based on PCa-specific variables routinely available at the time of diagnosis. Based on this, if confirmed in further studies, a patient can and should be informed about his individual probability of having this additional treatment to RP *before* the decision on primary treatment strategy. In that way, patients with clinical high-risk PCa, in particular, can consider definitive radiotherapy as their primary treatment and thus avoid potential adverse effects related to the combination of RP and radiotherapy. The ongoing SPCG-15 trial (RP vs. definitive radiotherapy with (neo-) adjuvant hormonal treatment in clinical high risk PCa) will shed more light upon treatment-related differences regarding survival and adverse effects.

This study has some limitations. First, the relevance of our endpoint "use of post-RP radiotherapy" can be debated on the background of the uncertainty of any major clinical benefit of this treatment. However, for the medical community, it is essential to be aware of the use of resource-demanding therapeutic strategies, radiotherapy being one of them, as a supplement to efficacy analyses. Second, our findings reflect the routine practice during nine years with vague guidelines as to the use of radiotherapy following RP; nationally these have only existed since 2009. Third, the combination of adjuvant and salvage radiotherapy termed as post-RP radiotherapy in most of the statistical analyses might be viewed as a limitation. The strength of this project is its national population-based study design.

Conclusions

During nine years of follow-up, one in six patients had undergone radiotherapy as an additional treatment to RP, mostly provided as salvage radiotherapy. The probability of post-RP radiotherapy can be calculated based on PCa-specific variables routinely available at the time of diagnosis and findings in the prostatectomy specimen. Each PCa patient should be informed about his individual probability of post-RP radiotherapy *before* the final decision of primary treatment strategy, and post-operatively based on the histopathology of the prostatectomy specimen.

Disclosure statement

None to declare.

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