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Original Article

Pathologically Node-Positive Prostate Carcinoma – Prevalence, Pattern of Care and Outcome From a Population-Based Study

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Abstract

Aims: To evaluate the prevalence, patterns of care and outcome of pathologically node-positive (pN+) prostate cancer (P-Ca) after radical prostatectomy from a provincial population database.

Patients and methods: Patients were identified from a provincial cancer registry and a genitourinary cancer outcomes unit (2005–2014). Of a total of 4723 patients who underwent radical prostatectomy, 167 patients with pN+ P-Ca were identified (28/2181 from 2005–2007 and 139/2542 from 2010–2014). Persistently elevated postoperative prostate-specific antigen (PSA) ≥ 0.2 ng/ml was noted in 52 (31%) patients, 23 (44.2%) of whom had salvage androgen deprivation therapy plus radiotherapy (ADT + RT), 25 (48%) were managed with ADT alone and four (7.8%) had no treatment. Of 115 patients with postoperative PSA <0.2 ng/ml, 47 (41%) had ADT alone and 50 (43.5%) had ADT + RT. Survival estimation was carried out using the Kaplan–Meier method. The association of prognostic factors with survival was evaluated using univariate and multivariate analysis and was limited to the newer cohort (2010–2014).

Results: The median age was 64 years; the median baseline PSA was 12.5 ng/mL (range 2.5–108.4). After a median follow-up of 48 months, overall survival at 5 and 10 years for the entire cohort were 89% and 81%, respectively, and distant metastasis-free survival (DMFS) at the same time points were 77% and 58%, respectively. For the newer cohort, 5-year overall survival and DMFS were 91.5% and 76%, respectively. On univariate analysis, persistently elevated post-operative PSA ≥0.2 ng/ml ($P = 0.0003$), seminal vesicle involvement ($P = 0.027$), ≥2 nodes ($P = 0.035$) and ADT alone ($P = 0.054$) had a poor prognostic impact on DMFS, whereas margin involvement had a marginally negative influence on overall survival ($P = 0.06$). On multivariate analysis, postoperative PSA ≥0.2 ng/ml (hazard ratio 4.4, 95% confidence interval 1.7–11.4; $P = 0.002$) continued to have a significant association with DMFS. On a sensitivity analysis, postoperative PSA ≥0.1 also had a significant association with DMFS on univariate and multivariate analysis (hazard ratio 3.69, 95% confidence interval 1.32–10.29; $P = 0.01$). Similarly, postoperative PSA ≥0.4 ng/ml had a significant association with DMFS (hazard ratio 3.87, 95% confidence interval 1.58–9.46, $P = 0.003$).

Conclusion: This study showed a notable difference in the proportion of pN+ P-Ca patients between two different time cohorts. A significant association of persistently elevated postoperative PSA with DMFS was noted in our study. This must be accounted for while tailoring postoperative treatment in pN+ P-Ca.

Key words: Androgen deprivation therapy; node-positive prostate cancer; patterns of care; persistently elevated postoperative PSA; radiotherapy

Introduction

Radical prostatectomy remains a highly efficacious treatment modality for localised prostate carcinoma (P-Ca) [1]. However, about 3–14% of patients with P-Ca have lymph node-positive disease (pN+) after radical prostatectomy [2–5]. The overall prognosis for this subset of patients remains guarded [6,7] and if left untreated, most of these patients will develop disease progression within 18–24 months of radical prostatectomy [8]. A randomised controlled study by Messing *et al.* [9] established the use of adjuvant androgen deprivation therapy (ADT) as the standard of care for patients with pN+ P-Ca. In addition, recent retrospective institutional series, and population-based studies, have shown the benefit of postoperative radiotherapy in pN+ patients, in terms of prolonging the biochemical relapse-free survival, cause-specific survival and overall survival [10,11]. The multi-institutional study by Abdollah *et al.* [12] has established the benefit of

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radiotherapy in two subsets of pN+ P-Ca: those with ≤2 positive nodes and Gleason 7–10, pT3b/4, or margin positive, and patients with 3–4 positive nodes regardless of any other high-risk pathological features. On the contrary, another analysis of the Surveillance, Epidemiology and End Results (SEER)–Medicare linked data failed to show any benefit from radiotherapy [13]. Amid such conflicting results, we reviewed our provincial population-based data to evaluate the prevalence, patterns of care and outcomes for pN+ P-Ca and to correlate treatment modalities with outcomes.

Patients and Methods

pN+ P-Ca patients in our province in two cohorts from 1 January 2005 to 31 December 2007 and from 1 January 2010 to 31 December 2014 were included in this study. Approval was obtained from the university research ethics board as well as the Data Access Committee of the provincial cancer registry. Patients were identified from the cancer registry and the provincial genitourinary cancer outcomes unit. For our study, we classified patients into two prostate-specific antigen (PSA) categories: persistently elevated postoperative PSA, which includes patients with elevated immediate postoperative PSA ≥ 0.2 ng/ml 4–8 weeks after surgery, which continued to be ≥ 0.2 ng/ml before the start of subsequent treatment (PSA group 1) and patients with immediate postoperative PSA < 0.2 ng/ml (PSA group 2) [14,15]. Any subsequent treatment for patients in PSA group 1 was deemed to be 'salvage' treatment. On the contrary, for patients in PSA group 2, treatment received within 6 months of prostatectomy was considered 'early adjuvant' therapy, whereas that after 6 months of surgery was considered 'delayed adjuvant' treatment. If patients in PSA group 2 had received treatment only after their PSA rose above 0.2 ng/ml, the treatment was considered as 'salvage' treatment. Follow-up of all patients was updated until 14 June 2017.

In total, 31 096 patients were diagnosed with P-Ca in our province during the study period. However, the genitourinary cancer outcomes unit did not have complete data for surgical pathology reports in non-referred patients during the years 2008 and 2009. Hence, we did not collect data for those 2 years, to avoid bias related to accrual of non-consecutive patients. This provided us with two time groups of patients to compare (2005–2007/old cohort; 2010–2014/new cohort). In total, 28 pN+ P-Ca were identified of 2181 patients undergoing radical prostatectomy between 2005 and 2007. Of 2542 patients who underwent radical prostatectomy between 2010 and 2014, 139 patients were pN+. The rate of pN+ P-Ca was 1.3% in the older cohort and 5.5% in the recent cohort. Preoperative computed tomography scans documented significant pelvic nodes in only 10 (6%) patients; 60 (36%) patients had stage 1c disease, 79 (47%) had stage 2, 17 (10%) stage 3a and 11 (7%) had stage 3b/4 disease. Trans-rectal ultrasound-guided needle biopsies were carried out in 165 (99%) patients. The most common preoperative Gleason sum score was 9 ($n = 66$; 40%). Preoperative risk stratification using the Genitourinary Radiation Oncologists of Canada (GUROC) scheme showed 44 (26%) patients in the intermediate-risk category and 121 (73%) patients in the high-risk category [16]. Preoperative risk stratification was unknown for two patients.

Surgical Details

In this study, 166 patients had radical prostatectomy. Radical cystoprostatectomy was carried out in one patient due to concurrent bladder cancer. Of note, 34 had neoadjuvant systemic treatment, of whom 30 had neoadjuvant ADT (three in the 2005–2007 cohort and 27 in the 2010–2014 cohort), whereas four patients had a combination of neoadjuvant ADT and chemotherapy (one in the 2005–2007 cohort and three in the 2010–2014 cohort). All patients had pelvic lymph node sampling or dissection during radical prostatectomy. The median number of dissected/sampled nodes was 6 (interquartile range [IQR] 3–11); about 40% patients had ≥7 nodes removed. There was no difference in the extent of lymph node sampling between the old (8.32 ± 6.99) and new (6.32 ± 5.21) cohorts ($P = 0.17$). Comparative evaluation of the two cohorts showed a 16% reduction in margin-positive surgeries in recent times (82% in 2005–2007 versus 66% in 2010–2014) despite a relatively higher proportion of high-risk patients undergoing radical prostatectomy in 2010–2014. Overall, 52 (31%) patients were in PSA group 1, whereas 115 (69%) patients belonged to PSA group 2. The difference in relative proportion of patients in PSA group 1 between the cohorts (21.4% in the old cohort versus 33% in the new cohort) was statistically insignificant ($P = 0.32$).

Postoperative Treatment

Among 52 patients in PSA group 1, 25 (48%) were managed with salvage ADT alone, 23 (44.2%) had a combination of ADT and radiotherapy (ADT + RT) and four (7.8%) had no treatment. Of 115 patients in PSA group 2, 47 (41%) had ADT alone and 50 (43.5%) had ADT + RT; no treatment was received by 18 (16.5%) patients. The treatment details based on time-cohort and PSA groups have been summarised in Figure 1. We observed a 10% increase in the use of postoperative combined modality treatment (ADT + RT) in 2010–2014 (45%) compared with 2005–2007 (35%). There was an 8% decline in the use of ADT alone in the recent cohort (42% versus 50%); the difference was, however, not significant ($P = 0.64$). In total, 72 patients were treated with ADT (with or without chemotherapy) and 73 patients were offered ADT + RT combination (Figure 1). Overall, six patients in the ADT + RT arm did not receive planned ADT and were finally treated with radiotherapy alone.

The median postoperative radiotherapy dose was 66 Gy (range 52.5–76 Gy). In most patients, radiotherapy was delivered over two phases. Phase I consisted of 40–46 Gy to the pelvis and prostate bed, followed by 16–30 Gy as a further boost to the prostate bed. Only 10 (14%) patients received radiotherapy to the prostate bed alone. Radiotherapy techniques included three-dimensional conformal radiotherapy in 33 patients, intensity-modulated

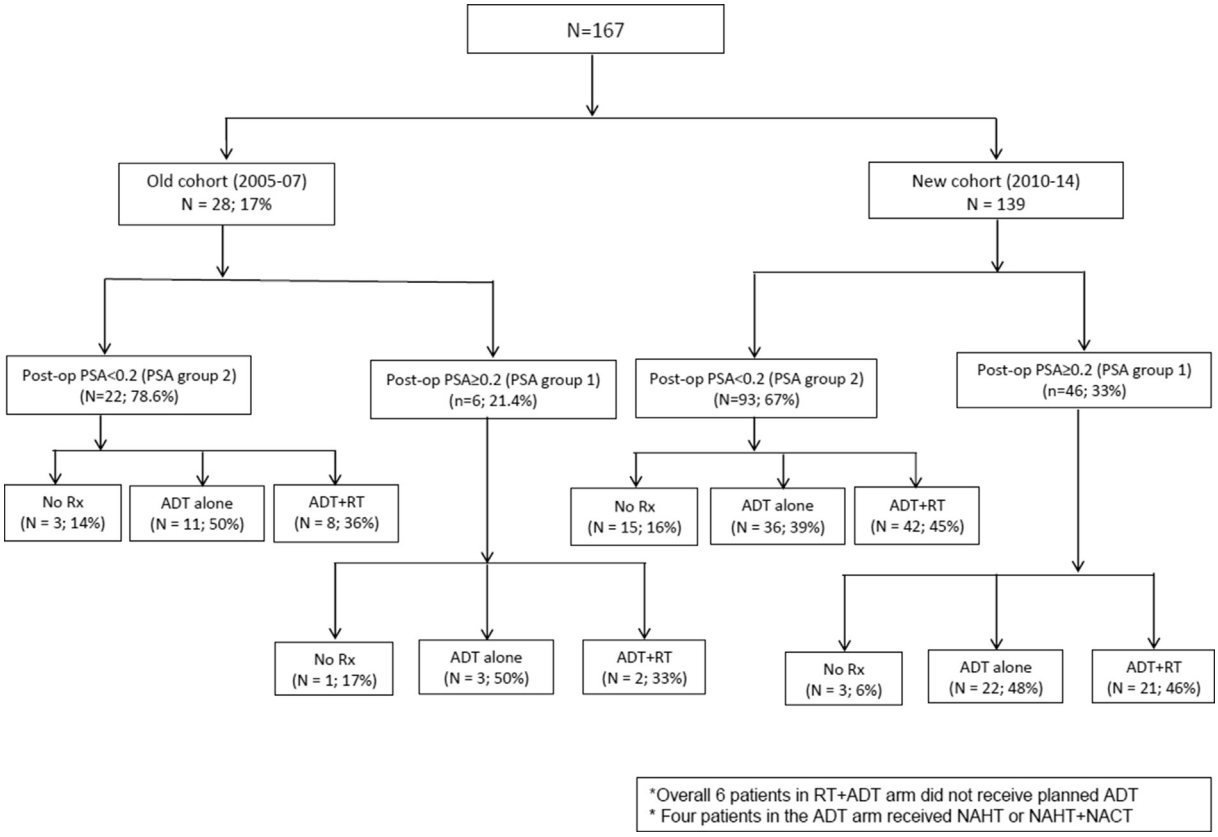

Fig 1. Treatment details of the patient cohort.

radiotherapy in eight patients, volumetric modulated arc therapy in 15 patients. A combination of techniques including three-dimensional conformal radiotherapy in phase I followed by intensity-modulated radiotherapy or volumetric modulated arc therapy in phase II was used in 22 patients. The median duration of ADT treatment was 9 months (range 3–60 months). The most common ADT regimen was goserelin or leuprolide with a combination of bicalutamide used for the initial month. No patient had orchiectomy in our study cohort.

Definition of Further Failures

All the failure events, including local, nodal or distant failures, were captured for statistical analysis. Local failure was defined as disease recurrence at the surgical resection margin, vesico-urethral anastomosis or prostate bed. Nodal failure was defined as a new or enlarging lymph node $\geq$1 cm on short axis on computed tomography scan of the pelvis or para-aortic nodal chain and all other sites of failure were considered distant metastasis. All information about events of death, including causes of death, were collected from the cancer registry.

Statistical Analysis

Descriptive statistics were used to calculate the incidence and prevalence of pN+ P-Ca and to describe the demographic characteristics of the study population. A comparison of categorical variables was carried out using the chi-squared test. For continuous variables, median values were reported with IQRs and mean values were compared using the *t*-test. Distant metastasis-free survival (DMFS) was defined as the period from the date of surgery to the date of distant metastasis or last follow-up. Overall survival was defined as the period from the date of surgery to death or last follow-up. Prostate cancer-specific survival (PCSS) was defined as the period from the date of surgery to death due to P-Ca or last follow-up. DMFS, PCSS and overall survival estimation were carried out using the Kaplan–Meier method and various clinic–demographic factors and treatment modalities were compared using the Log-rank test. Multivariate analysis with the Cox proportional hazard model was used to identify the association of various factors, including treatment with DMFS and overall survival. Univariate and multivariate analyses were restricted to patients in the recent cohort (2010–2014) to avoid bias related to comparing two different time cohorts. Patients who did not receive any treatment until the last date of follow-up were excluded from univariate and multivariate analyses. Six patients who had planned treatment of ADT + RT but could not have the planned ADT were still considered under the ADT + RT treatment group. Similarly, four patients who received chemotherapy with ADT were included in the ADT-alone group (as none of them received radiotherapy). All statistical analyses were carried out using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) and SPSS® v. 14.0 (IBM

Corp., New York, NY, USA), with a two-sided significance level set at $P < 0.05$.

Results

Postoperative Histopathology

The median age of the study population was 64 years (IQR 58–68 years); the median baseline PSA level was 12.5 ng/ (IQR 8.2–21.5; range 2.5–108.4). The most frequently observed postoperative Gleason score was 9 ($n = 88$; 53%) and the most common primary Gleason grade was 4 ($n = 127$; 76%). Most patients had pathological T3 tumour ($n = 151$; 91%); five (3%) patients had T4 and 11 (6%) patients had T2c tumour. Other postoperative histopathological details have been summarised in Table 1.

The mean and median follow-up durations for the entire study population were 54 and 48 months (IQR 34–68 months), respectively. For patients treated with ADT + RT, the median follow-up duration was 50.5 months (IQR 38–67 months), whereas for the ADT-alone group it was 49 months (IQR 31–69 months). The median follow-up duration for the 2010–2014 cohort was 43 months (IQR 31–64 months).

Table 1
Postoperative histopathological details for the study cohort ($n = 167$)

Parameters		Number of patients	% of patients
Tumour stage	T2c	11	6
	T3a	31	19
	T3b	120	72
	T4	5	3
Postoperative overall Gleason score	6	2	1
	7	60	36
	8	10	6
	9	88	53
	10	4	2.3
	Unknown	3	1.7
Postoperative primary Gleason grade	3	12	8
	4	127	76
	5	22	12
	Unknown	6	4
Bladder neck involvement	Yes	26	16
	No	141	84
Apex involvement	Yes	58	35
	No	109	65
High-grade prostatic intra-epithelial neoplasia	Yes	71	43
	No	96	57
Extra-prostatic extension	Yes	137	82
	No	30	18
Peri-neural invasion	Yes	124	74
	No	43	26
Lymphovascular space invasion	Yes	92	55
	No/unknown	75	45
Seminal vesicle involvement	Yes	124	74
	No/unknown	43	26
Number of positive nodes	One	107	64
	≥2	60	36
Extra-nodal extension	Yes	44	26
	No	123	74
Margin involvement	Yes	117	70
	No	50	30

Patterns of Failure

Among 72 patients treated with ADT alone, 33 (45.8%) had disease failure. The predominant site of failure was distant metastasis. Isolated distant metastasis was noted in 21 patients. Isolated local failure was noted in five patients. Of these five patients, two received further salvage radiotherapy to the pelvis and prostate bed: one patient had 46 Gy to the pelvis and prostate bed followed by a 20 Gy boost to the prostate bed, whereas the second patient received 44 Gy to the pelvis and prostate bed followed by a 26 Gy boost to the prostate bed. Isolated nodal failure was noted in three patients. All these three patients received salvage ADT alone. Combined nodal and distant failure was seen in two patients, combined local and distant failure was seen in one patient and combined local and nodal failure was seen in one patient.

Of 73 patients treated with the ADT + RT combination, disease failure was noted in eight patients (11%). Isolated distant metastasis was noted in six patients, whereas two patients had combined nodal and distant failure. There was no incidence of isolated local or nodal failure.

The incidence of local failure (7/72 versus 0/73) was significantly lower in patients treated with the ADT + RT combination compared with patients treated with ADT alone ($P = 0.006$). The rate of distant metastasis was also significantly lower in patients treated with ADT + RT (8/73; 11%) compared with those treated with ADT alone (24/72; 33%) ($P = 0.004$). The incidence of nodal failure, however, was not different between the ADT + RT (2/73, one in pelvic lymph nodes and the other in para-aortic lymph nodes) and ADT alone (6/72, five in pelvic lymph nodes, one in para-aortic lymph nodes) groups ($P = 0.14$).

Survival

Overall survival at 5 and 10 years for the entire cohort were 89% and 81%, respectively, and DMFS at 5 and 10 years were 77% and 58%, respectively. For the new cohort (2010–2014), 5-year overall survival and DMFS were 91.5% and 76%, respectively (Figure 2). PCSS at 5 and 10 years were 94% and 87%, respectively, for the entire cohort.

In the newer cohort, DMFS at 5 and 10 years were 55% and 23%, respectively, for patients in PSA group 1 (persistently elevated postoperative PSA ≥ 0.2 ng/ml) and 83% and 71%, respectively, for PSA group 2 (postoperative PSA < 0.2 ng/ml). Overall survival at 5 and 10 years for patients in PSA group 1 (persistently elevated postoperative PSA ≥ 0.2 ng/ml) were 89% and 81%, respectively, whereas they were 89.5% and 81%, respectively, for PSA group 2 (postoperative PSA < 0.2 ng/ml).

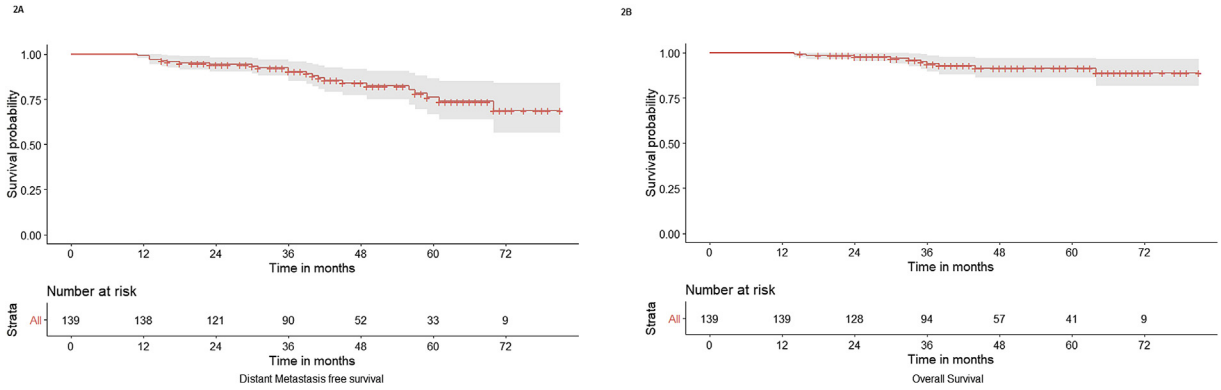

Fig 2. Distant metastasis-free survival (A) and overall survival (B) of the newer cohort (2010–2014).

Among 78 patients of the recent cohort who belonged to PSA group 2 and who received postoperative treatment, 44 underwent early adjuvant treatment, whereas 34 underwent delayed adjuvant or salvage treatment. The 5-year DMFS in the early adjuvant versus delayed adjuvant/salvage group was 92.6% versus 80.6% (Log-rank $P = 0.055$) and 5-year overall survival in the two groups were 97% and 87.1% (Log-rank $P = 0.113$), respectively. Patients of PSA group 2, treated with ADT + RT ($n = 42$), had a 5-year overall survival of 94.4% compared with 90.7% for those who received ADT alone ($n = 36$) ($P = 0.62$). The 5-year DMFS in the ADT + RT and ADT-alone groups were 96% and 79%, respectively ($P = 0.03$). In patients of PSA group 1 (2010–2014) who received postoperative treatment ($n = 43$), 5-year overall survival in the ADT + RT ($n = 21$) and ADT-alone ($n = 22$) groups were 92.3% and 86.6%, respectively ($P = 0.98$). Treatment with ADT + RT ($n = 21$) led to a 5-year DMFS of 53.3% compared with 42.4% with ADT alone ($n = 22$) ($P = 0.3$).

On univariate analysis for overall survival, we found a trend towards association of the presence of margin involvement with overall survival (5-year overall survival 89.2% versus 100%; $P = 0.06$).

Univariate analysis for DMFS revealed that persistently elevated postoperative PSA ≥0.2 ng/ml, seminal vesicle involvement and ≥2 positive lymph nodes had a significant association with DMFS (Table 2). Patients treated with ADT + RT had a trend towards superior 5-year DMFS (82.2% versus 68.3%, $P = 0.054$) (Figure 3). On multivariate analysis for DMFS, persistent postoperative PSA ≥0.2 ng/ml retained its significant association with DMFS (hazard ratio 4.4, 95% confidence interval 1.7–11.4, $P = 0.002$).

We carried out a sensitivity analysis for the impact of postoperative PSA on DMFS by changing the threshold for PSA group 1 to ≥0.4 ng/ml and ≥0.1 ng/ml, respectively. Persistently elevated postoperative PSA ≥0.4 ng/ml had a significant association with DMFS on both univariate and multivariate analysis (hazard ratio 3.87, 95% confidence interval 1.58–9.46, $P = 0.003$). Similarly, persistently postoperative PSA ≥0.1 ng/ml also had a significant association with DMFS on univariate and multivariate analysis (hazard ratio 3.69, 95% confidence interval 1.32–10.29, $P = 0.01$). There was no association of persistent postoperative PSA ≥0.1 ng/ml ($P = 0.3$) and ≥0.4 ng/ml ($P = 0.2$) with overall survival.

Discussion

The current study describes a rise in incidence of pN+ P-Ca cases over time in our province. The proportion of pN+ P-Ca in our series was 3.5%, ranging from 1.3% in 2005–2007 to 5.5% in 2010–2014, despite no significant difference in the extent of pelvic lymph node dissection. The difference could be ascribed to a higher proportion of high-risk patients undergoing surgery in recent times. This finding needs attention, considering significant variation in the proportion of pN+ P-Ca quoted in contemporary literature [5,17–19]. In a series of extended pelvic lymph node dissection by Abdollah *et al.* [18], the proportion of pN+ patients was 13.8%. Although the highest pN+ rates were observed in the earlier cohort (1990–1995), 10.6–15.6% of men treated in more recent years (2006–2010) still had node-positive disease. The median number of sampled lymph nodes in this study was 16. However, a recent study by McDonald *et al.* [5] described 3.4% pN+ patients of a total of 3642 patients undergoing radical prostatectomy, which is similar to our findings. In the McDonald *et al.* study, the median number of lymph nodes removed was 9 (5–14), which is congruent with our study. So, the extent of lymph node dissection might be a potential factor for the variation in yield of pN+ P-Ca, as shown by another study by Abdollah *et al.* [3].

Despite a relative conservative approach with pelvic lymph node dissection compared with studies by Da Pozzo *et al.* [10] and Briganti *et al.* [11], where the mean numbers of lymph nodes removed were 16 and 14, respectively, our survival figures are consistent with their results, which implies doubtful benefit of extended pelvic lymph node dissection. The other potential attributable factor could be robust use of adjuvant treatment and more frequent use of whole pelvic radiotherapy in our study. For example, the proportion of patients (44%) who received postoperative radiotherapy in our study is higher compared with other available literature [11–13,20]. On the contrary, the proportion of patients who had no adjunct treatment (13.5%) in

Table 2
Results of the univariate analysis for overall survival and distant metastasis-free survival (DMFS) for the recent cohort ($n = 139$)

Parameters	5-year overall survival % (95% CI)	*P*-value	5-year DMFS % (95% CI)	*P*-value
Age				
41–60 ($n = 45$)	97.8 (93.4–100)	0.2	61.6 (38–100)	0.09
60–79 ($n = 94$)	89 (82–96.7)		79.8 (69.9–91.2)	
Postoperative PSA				
PSA $<$ 0.2 ng/ml ($n = 93$)	92.3 (86.5–98.5)	0.5	87.5 (79.3–96.5)	*0.0003*
PSA $\geq$ 0.2 ng/ml ($n = 46$)	89.5 (76.5–100)		46.6 (27.3–80)	
Margin				
Positive ($n = 94$)	89.2 (81.7–97.3)	0.06	69.2 (56.9–84.1)	0.08
Negative ($n = 45$)	100		90.9 (81.4–100)	
Extra-prostatic extension				
Yes ($n = 117$)	91.7 (85.9–98)	0.9	73.5 (63.1–85.6)	0.3
No ($n = 22$)	92.8 (83.6–100)		93.8 (82.6–100)	
Seminal vesicle involvement				
Yes ($n = 99$)	91.9 (85.7–98.5)	0.826	69.8 (58.7–83)	*0.027*
No ($n = 37$)	93.9 (86.1–1)		100	
Lymphovascular space invasion				
Yes ($n = 78$)	91.9 (85.2–99.1)	0.6	72 (59.1–87.8)	0.3
No ($n = 55$)	92.5 (84.3–100)		80.5 (66.9–96.8)	
Peri-neural invasion				
Yes ($n = 107$)	90.8	0.6	72.9 (62.2–85.5)	0.7
No ($n = 32$)	91.3 (85.2–97.8)		92.1 (82.3–100)	
Number of positive nodes				
1 ($n = 86$)	92.9 (87–99.2)	0.5	84.7 (74.1–96.8)	*0.035*
$\geq$2 ($n = 53$)	89.5 (70.9–99.3)		63.8 (48.7–83.6)	
Extra-nodal extension				
Yes ($n = 22$)	91 (81.7–1)	0.7	74.8 (59.8–93.6)	0.61
No ($n = 117$)	92.8 (86.7–99.3)		75.2 (62.6–90.4)	
Treatment modality				
ADT alone ($n = 58$)	89.4 (80.9–98.8)	0.8	68.3 (54.9–85)	*0.054*
ADT + RT ($n = 63$)	93.9 (87.3–100)		82.2 (69.5–97.4)	

CI, confidence interval; PSA, prostate-specific antigen; ADT, androgen deprivation therapy; ADT + RT, androgen deprivation therapy plus radiotherapy. P value in italics shows statistically significant results.

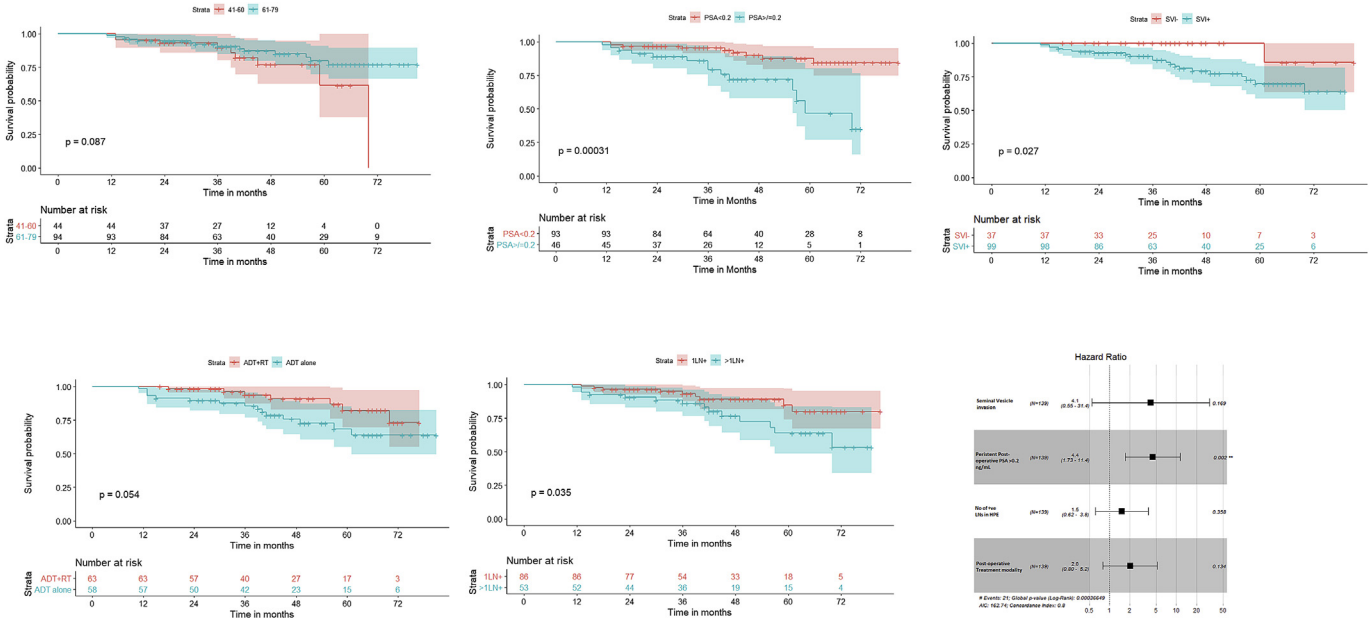

Fig 3. Prognostic factors that had a significant association with distant metastasis-free survival on univariate analysis (Log-rank) and multivariate forest plot with hazard ratios.

our study was substantially less than in other studies, such as 50.3% in the study by Wong *et al.* [20] using the National Cancer Database (NCDB) or approximately 46% in the Kaplan study of the SEER database [13]. We report more frequent use of whole-pelvis radiation followed by prostate bed boost as compared with other reports [10,19]. All of these factors might have resulted in optimal cancer specific survival (CSS) and overall survival in our study despite a relatively limited pelvic lymph node sampling.

In PSA group 1 of our new cohort, timing (early adjuvant versus delayed adjuvant and salvage) of postoperative treatment had no significant impact on overall survival, although there was a trend towards improved DMFS. This is in contrast to the study by Cozzarini *et al.* [21] who found improved CSS and time to distant progression in patients treated with early adjuvant radiotherapy in a cohort of 415 patients with mixed nodal status (pN0: 261/pN+: 154). In their series, patients were classified into two groups: those who underwent adjuvant early radiotherapy within 6 months and those who received late salvage radiotherapy for local failure or were actively monitored over time (without any evidence of relapse) with an aim to eliminate the potential bias related to the risk of harbouring occult distant metastasis at the time of referral for salvage radiotherapy.

Our study did not find any additional benefit of the ADT + RT combination compared with radiotherapy alone. The findings concur with those of the SEER database analysis by Kaplan *et al.* [13], where they found no additional benefit in overall mortality (5.09 versus 3.77 events per 100 person-years, $P = 0.153$) or cancer-specific mortality with the use of postoperative radiotherapy in 577 elderly (age $\geq$ 65 years) pN+ P-Ca patients irrespective of use of ADT and timing of postoperative radiotherapy. On the contrary, another population-based study by Wong *et al.* [20] reported superior overall survival with the use of ADT + RT (5-year overall survival of 88.8%) compared with ADT alone (82.9%) or no adjuvant treatment (85.2%). The discordance of results among different population-based studies could be related to differences in other prognostic factors, such as age, baseline risk categories, postoperative Gleason scores, proportion of patients with advanced disease (reflected by PSA > 10 ng/mL at baseline) among the study populations [22,23]. Moreover, P-Ca is an indolent malignancy and several patients continued to get second- or third-line treatment despite biochemical failure. This might abrogate any survival difference between ADT + RT versus the ADT-alone group.

Persistently elevated postoperative PSA $\geq$0.2 ng/ml was found to be associated with poor DMFS in our study. On sensitivity analysis, we found a similar association of postoperative PSA $\geq$0.1 ng/ml and $\geq$0.4 ng/ml with DMFS. These findings are compatible with other studies [5,24]. The study by McDonald *et al.* [5] showed postoperative PSA $\geq$ 0.2 ng/ml to be associated with poor metastasis-free survival (87% versus 99% at 5 years) on Log-rank test ($P = 0.001$). Additionally, Bianchi *et al.* [24] showed that patients with PSA persistence $\geq$ 0.1 ng/ml after radical prostatectomy had higher 8-year clinical recurrence and cancer specific mortality rates than those with undetectable PSA (69% versus 12% and 16% versus 4.2%, respectively; $P \leq 0.002$) in pN+ patients.

The strengths of the study include uniform ADT and radiotherapy protocols across the province, meticulous reporting of staging, risk stratification, clinicopathological and treatment details, failure and death status ensured by chart review of individual patient. However, the limitations of the study include inherent bias related to the retrospective nature, small patient population and a smaller number of events. The natural history of P-Ca is considerably long and events continue to unfold as time elapses after diagnosis or treatment [25]. This is more relevant in the context of patients being treated with ADT [26] and, of note, 87% of the patients in the newer cohort of our study underwent ADT with or without radiotherapy. Hence, the results of our study should be interpreted with caution.

Despite all these caveats, the current study shows a rise in the proportion of pN+ P-Ca patients in recent times. The study highlights that persistently elevated postoperative PSA is predictive of poor DMFS in patients with pN+ P-Ca and this should be considered while tailoring postoperative treatment in patients with pN+ P-Ca.

Conflicts of interest

G. Bahl receives honoraria from Sanofi and Bayer Health Care Pharmaceuticals.

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References

[1] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Van Der Kwast T, *et al.* EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent - Update 2013. *Eur Urol* 2014;65:124–137. https://doi.org/10.1016/j.eururo.2013.09.046.

[2] Briganti A, Larcher A, Abdollah F, Capitanio U, Gallina A, Suardi N, *et al.* Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol* 2012;61:480–487. https://doi.org/10.1016/j.eururo.2011.10.044.

[3] Abdollah F, Sun M, Thuret R, Budäus L, Jeldres C, Graefen M, *et al.* Decreasing rate and extent of lymph node staging in patients undergoing radical prostatectomy may undermine the rate of diagnosis of lymph node metastases in prostate cancer. *Eur Urol* 2010;58:882–892. https://doi.org/10.1016/j.eururo.2010.09.029.

[4] Abdollah F, Cozzarini C, Suardi N, Gallina A, Capitanio U, Bianchi M, *et al.* Indications for pelvic nodal treatment in prostate cancer should change. Validation of the Roach formula in a large extended nodal dissection series. *Int J Radiat*

Oncol Biol Phys 2012;83:624–629. https://doi.org/10.1016/j.ijrobp.2011.06.2014.

[5] McDonald ML, Howard LE, Aronson WJ, Terris MK, Cooperberg MR, Amling CL, *et al*. First postoperative PSA is associated with outcomes in patients with node positive prostate cancer: results from the SEARCH database. *Urol Oncol Semin Orig Investig* 2018;36:239.e17–239.e25. https://doi.org/10.1016/j.urolonc.2018.01.005.

[6] Cheng L, Zincke H, Blute ML, Bergstralh EJ, Scherer B, Bostwick DG. Risk of prostate carcinoma death in patients with lymph node metastasis. *Cancer* 2001;91:66–73.

[7] Boorjian SA, Thompson RH, Siddiqui S, Bagniewski S, Bergstralh EJ, Karnes RJ, *et al*. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol* 2007;178:864–870. https://doi.org/10.1016/j.juro.2007.05.048. Discussion 870–1.

[8] Spiess PE, Lee AK, Busby JE, Jordan JJ, Hernandez M, Burt K, *et al*. Surgically managed lymph node-positive prostate cancer: does delaying hormonal therapy worsen the outcome? *BJU Int* 2007;99:321–325. https://doi.org/10.1111/j.1464-410X.2006.06648.x.

[9] Messing EM, Manola J, Yao J, Kiernan M, Crawford D, Wilding G, *et al*. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472–479. https://doi.org/10.1016/S1470-2045(06)70700-8.

[10] Da Pozzo LF, Cozzarini C, Briganti A, Suardi N, Salonia A, Bertini R, *et al*. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol* 2009;55:1003–1011. https://doi.org/10.1016/j.eururo.2009.01.046.

[11] Briganti A, Karnes RJ, Da Pozzo LF, Cozzarini C, Capitanio U, Gallina A, *et al*. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pn+ prostate cancer: results of a matched analysis. *Int Braz J Urol* 2011;37:550–551. https://doi.org/10.1590/S1677-55382011000400025.

[12] Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, *et al*. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol* 2014;32:3939–3947. https://doi.org/10.1200/JCO.2013.54.7893.

[13] Kaplan JR, Kowalczyk KJ, Borza T, Gu X, Lipsitz SR, Nguyen PL, *et al*. Patterns of care and outcomes of radiotherapy for lymph node positivity after radical prostatectomy. *BJU Int* 2013;111:1208–1214. https://doi.org/10.1111/bju.12079.

[14] Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, *et al*. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27:2924–2930. https://doi.org/10.1200/JCO.2008.18.9563.

[15] Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, *et al*. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol* 2007;177:540–545. https://doi.org/10.1016/j.juro.2006.10.097.

[16] Rodrigues G, Lukka H, Warde P, Brundage M, Souhami L, Crook J, *et al*. The prostate cancer risk stratification project: database construction and risk stratification outcome analysis. *J Natl Compr Cancer Netw* 2014;12:60–69.

[17] Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, *et al*. EAU guidelines on prostate cancer. *Eur Urol* 2008;53:68–80. https://doi.org/10.1016/j.eururo.2007.09.002.

[18] Abdollah F, Suardi N, Gallina A, Bianchi M, Tutolo M, Passoni N, *et al*. Extended pelvic lymph node dissection in prostate cancer: a 20-year audit in a single center. *Ann Oncol* 2013;24:1459–1466. https://doi.org/10.1093/annonc/mdt120.

[19] Lawton CA, Winter K, Grignon D, Pilepich MV. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol* 2005;23:800–807. https://doi.org/10.1200/JCO.2005.08.141.

[20] Wong AT, Schwartz D, Osborn V, Safdieh J, Weiner J, Schreiber D. Adjuvant radiation with hormonal therapy is associated with improved survival in men with pathologically involved lymph nodes after radical surgery for prostate cancer. *Urol Oncol Semin Orig Investig* 2016;34:529. https://doi.org/10.1016/j.urolonc.2016.06.017. e15–20.

[21] Cozzarini C, Bolognesi A, Ceresoli GL, Fiorino C, Rossa A, Bertini R, *et al*. Role of postoperative radiotherapy after pelvic lymphadenectomy and radical retropubic prostatectomy: a single institute experience of 415 patients. *Int J Radiat Oncol Biol Phys* 2004;59:674–683. https://doi.org/10.1016/j.ijrobp.2003.12.001.

[22] Leibovici D, Spiess PE, Agarwal PK, Tu S-M, Pettaway CA, Hitzhusen K, *et al*. Prostate cancer progression in the presence of undetectable or low serum prostate-specific antigen level. *Cancer* 2007;109:198–204. https://doi.org/10.1002/cncr.22372.

[23] Carter HB, Epstein JI, Partin AW. Influence of age and prostate-specific antigen on the chance of curable prostate cancer among men with nonpalpable disease. *Urology* 1999;53:126–130.

[24] Bianchi L, Nini A, Bianchi M, Gandaglia G, Fossati N, Suardi N, *et al*. The role of prostate-specific antigen persistence after radical prostatectomy for the prediction of clinical progression and cancer-specific mortality in node-positive prostate cancer patients. *Eur Urol* 2016;69:1142–1148. https://doi.org/10.1016/j.eururo.2015.12.010.

[25] Antonarakis ES, Feng Z, Trock BJ, Humphreys EB, Carducci MA, Partin AW, *et al*. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int* 2012;109:32–39. https://doi.org/10.1111/j.1464-410X.2011.10422.x.

[26] Crawford ED, Petrylak D, Sartor O. Navigating the evolving therapeutic landscape in advanced prostate cancer. *Urol Oncol* 2017;35S:S1–S13. https://doi.org/10.1016/j.urolonc.2017.01.020.