SCANDINAVIAN JOURNAL OF UROLOGY
2020, VOL. 54, NO. 6, 475–480
https://doi.org/10.1080/21681805.2020.1817143

Taylor & Francis
Taylor & Francis Group

ARTICLE

Impact of biopsy perineural invasion on younger prostate cancer patients after radical prostatectomy

Sharron X. Lin[a]*, Yu Zheng[a,b]*, Shulin Wu[a,c], Michael L. Blute[a], Douglas M. Dahl[a] and Chin-Lee Wu[a,c]

[a]Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [b]Department of Urology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, China; [c]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

ABSTRACT

Objectives: To identify the potential indicators for higher-risk disease and poor outcome in younger prostate cancer (PCa) patients (age $\leq$ 50) who had undergone radical prostatectomy (RP) in the prostate-specific antigen (PSA) era.

Materials and Methods: A total of 186 PCa cases of age $\leq$ 50 who underwent RP between 2003 and 2010 at our center were included for study. High-risk disease after RP was defined as cases with pre-PSA $\geq$ 20 ng/ml and/or Gleason score (GS) $\geq$ 4 + 3 and/or pT stage $\geq$ 3. The poor outcome group was defined as cases with biochemical recurrence (BCR) and/or metastasis (Mets) and/or all-cause death. Multivariate logistic regression models were performed to identify independent risk factors for both high-risk disease and poor outcome.

Results: Among 186 younger PCa patients aged $\leq$ 50, 36 cases (19.5%) had high-risk disease and 24 cases (12.9%) had poor outcome. The presence of biopsy perineural invasion (BxPNI) was significantly associated with high-risk disease and showed a trend to correlate with worse outcome in univariate analysis. On multivariate logistic regression analysis, BxPNI was shown to be a significant independent risk factor with covariate of D'Amico for poor outcome ($p = 0.047$) and an independent risk factor with covariate of BxGPC for high-risk PCa excepting the variables to define high-risk disease ($p = 0.013$). Prognostically, cases with BxPNI showed a poor BCR-free survival in univariate analysis but did not reach significance ($p = 0.063$).

Conclusion: Our results show that BxPNI could be considered as a risk classification factor to identify the best candidates among younger PCa patients for further treatment and may also be used for developing active surveillance (AS) selection criteria for younger PCa patients.

Abbreviations: AS: Active surveillance; BCR: Biochemical recurrence; Bx: Biopsy; GPC: Greatest percentage of cancer involvement; GS: Gleason score; PCa: Prostate cancer; PNI: Perineural invasion; PSA: Prostate-specific antigen; RP: Radical prostatectomy

ARTICLE HISTORY
Received 18 May 2020
Revised 10 July 2020
Accepted 27 August 2020

KEYWORDS
Biopsy perineural invasion; younger age; high-risk prostate cancer; oncological outcome; prognosis; active surveillance; radical prostatectomy

Introduction

Prostate cancer (PCa) remains the most commonly diagnosed non-cutaneous cancer and the second leading cause of cancer-related death among men in the US and Europe [1]. For many years, PCa was considered as a disease of elderly men because the incidence of PCa showed a peak age around 65 years old with an ~80% rate [2]. It is known that man's androgen (A) levels drop dramatically after the age of 50 [3] and both androgen/androgen receptor (AR) play critical roles in the development and progression of PCa [4]. Although the incidence of patients diagnosed with PCa at an age equal or younger than 50 years old (age $\leq$ 50) was rare in the pre-PSA era (about 1%), the widespread use of PSA screening contributes markedly to a 5.0-fold increase in the detection of younger patients with PCa [5].

Contrary to the earlier findings of more aggressive tumor characteristics in younger patients, which more likely including distant metastasis and poor survival in the pre-PSA era [6–9], contemporary analyses found that younger PCa patients who underwent RP showed more favorable clinicopathological features and better oncological outcomes when compared to older men in the PSA era [10–15]. The natural history of early screening PCa vs early onset PCa is still poorly understood. It was speculated that early onset PCa could potentially be biologically different and represent a larger proportion of hereditary disease from cancer seen in older men [16]. Given the controversy regarding the prognostic impact on younger men, and considering their longer life expectancy, fewer comorbidities, expectation of favorable convalescence and the perception that they will ultimately

CONTACT Chin-Lee Wu cwu2@partners.org Department of Urology and Pathology, Massachusetts General Hospital, Harvard Medical School, Warren Building 225, 55 Fruit Street, Boston, 02114, MA, USA
*These authors contributed equally to this work.

require intervention, currently, radical prostatectomy (RP) remains as the standard treatment for localized PCa for younger patients, although the active surveillance (AS) treatment option has been highly recommended for indolent or low-risk PCa patients in recent years [17,18].

Intrinsic high-risk factors including PSA, pathologic T stage (pT) and RP Gleason score (GS) were well established and known to correlate with poor oncological outcomes [19]. Using PSA, clinical T stage (cT) and biopsy GS, D'Amico risk-group classification has been widely used for PCa risk stratification [20]. Perineural invasion found in biopsy specimens (BxPNI) was reported as an indicator of adverse pathological features and biochemical recurrence (BCR) after RP [21], however, the conclusion remains uncertain since the results in multivariate analysis from different study cohorts were inconsistent.

The aim of this study is to identify the clinical and pathological characteristics correlated with high-risk and poor oncological outcomes in a cohort of younger PCa patients at age equal or less than 50 years old (age $\leq$ 50) who underwent RP. Results from this study will help the selection of the younger men suffering from PCa who will benefit the most for advanced and aggressive treatment. In addition, our study result may also be helpful for selecting the best AS candidates diagnosed with PCa at a younger age.

Materials and methods

Following Institutional Review Board approval, using a PCa database of the Departments of Urology and Pathology at Massachusetts General Hospital between 2003–2010, 2093 localized PCa cases were reviewed after applying exclusion criteria including neoadjuvant treatment or direct postoperative adjuvant therapy, positive lymph nodes, postoperative PSA persistence or loss to PSA follow-up. Of these, 186 younger patients at age $\leq$ 50 years old (8.9%) were identified and were included in this study for further analysis.

Data collected for analysis included pre-surgery data: age at diagnosis, PSA, race, family history, cT, biopsy Gleason score (BxGS), BxPNI, number of positive biopsy cores (BxPCN), greatest percentage of tumor on biopsy core (BxGPC), D'Amico risk group category and post-surgery data: prostate weight, GS on RP specimen (RPGS), pT, positive surgical margin (PSM), PNI in RP specimen (RPPNI), as well as oncological outcome data: BCR was defined as a post-nadir detectable serum PSA level of $\geq$ 0.2 ng/ml, followed by a confirmatory value. Metastatic disease (Mets) was defined by the diagnosis of PCa recurrence in a lymph node or at a distant site by clinical impression and radiographic evidence. Information on death was taken from death certificates, patient charts or physician correspondence.

In this study, the high-risk group was defined as any case with PSA $\geq$ 20 ng/ml and/or RPGS $\geq$ 4 + 3 and/or pT $\geq$ 3; poor outcome was defined as any case with an outcome of BCR and/or metastasis and/or all-cause death.

Descriptive statistics of categorical variables focused on frequencies and proportions. Medians and interquartile ranges (IQR) were reported for continuous variables. Statistical analysis was performed using the Kruskal-Wallis H test for continuous variables and Pearson's Chi-squared test or Fisher's exact test for categorical variables. Univariate logistic regression models, as well as multivariate models fitted with selected variables which showed significance on univariate analysis were created to compute odds ratios for risk predictors. All tests were 2-sided with statistical significance set at $p < 0.05$. All statistical analyses were performed with Stata14 (College Station, TX).

Results

The association between pre-surgical or post-surgical clinicopathological features and the defined high-risk or poor outcome is shown in Table 1. In this cohort of 186 younger patients at age $\leq$ 50 who underwent RP, 36 cases (19.5%) were identified as high-risk, and 24 cases (12.9%) were identified as poor outcome (from 23 cases of BCR, five cases of Mets and two cases of all-cause death) with a median follow-up of 9.7 years. We found that high-risk cases were significantly associated with poor outcome ($p < 0.001$). Of the high-risk cases, all RP pathologic features and PSA were significantly adverse characteristics consisting with the definition, and BxGS, cT and D'Amico risk were significantly higher in this high-risk group. In addition, we found that in this younger age cohort, BxPNI (8.7% vs 38.9%, $p < 0.001$), BxPCN and BxGPC were significantly associated with high-risk. Furthermore, we found that cases with high-risk were associated significantly with BCR rate ($p < 0.001$), metastasis ($p = 0.005$) and all-cause death ($p = 0.037$). For outcome analysis, poor outcome is correlated significantly with higher PSA (6.1 vs 4.2 ng/ml, $p < 0.001$), intermediate to high D'Amico risk ($p = 0.002$) and higher BxGS ($p = 0.001$). Although not reaching statistical significance, BxPNI and cT showed a trend of association with poor outcome ($p = 0.055$).

When establishing the multivariate logistic regression model with the presurgical variables which showed statistical significances in univariate analysis, we excluded PSA, BxGS and D'Amico risk group, which were already included as high-risk definition to identify additional risk stratification factors. We found BxPNI and BxGPC showed significant association with high-risk disease ($p = 0.013$ and $p = 0.003$, respectively). For predicting poor oncological outcome, PSA, cT, BxGS, D'Amico risk and BxPNI were all significantly associated with poor outcome in univariate analysis. However, only D'Amico remained as an independent and significant predictor in multivariate analysis. To avoid any multicollinearity in the model, further analysis was performed after removing PSA, cT and BxGS, factors already included in the D'Amico risk classification. By this analysis, BxPNI showed as an independent predictor with covariate of D'Amico risk as shown in Tables 2 and 3 ($p = 0.047$).

The prognostic impact of BxPNI on BCR outcome was also tested in our study. As shown in Figure 1, BxPNI positive younger PCa patients showed a trend of unfavorable BCR-free survival in Kaplan-Meier survival analysis ($p = 0.063$).

Table 1. Clinical and pathologic characteristics of 186 patients age ≤50 who underwent RP between 2003 and 2010.

	Total	≤50 low-risk	≤50 high-risk	*p*	≤50 favorable outcome	≤50 poor outcome	*p*
Patients (%)	186 (100)	150 (80.5)	36 (19.5)		162 (87.1)	24 (12.9)	
Age (years) (IQR)	48 (46–50)	49 (47–50)	48 (45–49)	0.551	49 (46–50)	47 (44–49)	0.192
PSA (ng/ml) (IQR)	4.5 (2.8–6.4)	4.1 (2.6–5.9)	6.2 (5.1–11)	**0.001**	4.2 (2.7–6.0)	6.1 (5.3–11)	**<0.001**
Weight (g) (IQR)	36 (30–40)	35 (30–40)	36 (29–39)	0.916	35 (30–40)	36 (29–41)	0.882
Follow-up (years) (IQR)	9.7 (6.7–12)	9.6 (6.2–11)	11 (8.2–12)	**0.048**	9.7 (6.3–12)	11 (8.5–13)	0.055
Race (%)				0.300			1.000
White	169 (90.9)	137 (91.3)	32 (88.9)		146 (90.1)	23 (95.8)	
Black	10 (5.4)	7 (4.7)	3 (8.3)		9 (5.6)	1 (4.2)	
Hispanic	5 (2.7)	5 (3.3)	0 (0)		5 (3.1)	0 (0)	
Asian	2 (1.0)	1 (0.7)	1 (2.8)		2 (1.2)	0 (0)	
cT Stage (%)				**0.018**			0.055
cT1	159 (85.5)	133 (88.7)	26 (72.2)		142 (87.7)	17 (70.8)	
cT2	27 (14.5)	17 (11.3)	10 (27.8)		20 (12.3)	7 (29.2)	
D'Amico (%)				**0.001**			**0.002**
Low	134 (72.0)	115 (76.7)	19 (52.8)		123 (75.9)	11 (45.8)	
Intermediate	47 (25.3)	34 (22.7)	13 (36.1)		37 (22.8)	10 (41.7)	
High	5 (2.7)	1 (0.6)	4 (11.1)		2 (1.2)	3 (12.5)	
Family history (%)				1.000			0.630
No	133 (71.5)	107 (71.3)	26 (72.2)		117 (72.2)	16 (66.7)	
Yes	53 (28.5)	43 (28.7)	10 (27.8)		45 (27.8)	8 (33.3)	
BxGS (%)				**<0.001**			**0.001**
≤6	144 (77.4)	127 (84.7)	17 (47.2)		130 (74.5)	14 (60.4)	
3 + 4	32 (17.2)	22 (14.7)	10 (27.8)		28 (18.3)	4 (23.9)	
4 + 3	7 (3.8)	1 (0.6)	6 (16.7)		3 (4.8)	4 (10.5)	
≥8	3 (1.6)	0 (0)	3 (8.3)		1 (0.6)	2 (8.3)	
BxPNI (%)				**<0.001**			0.055
Negative	159 (85.5)	137 (91.3)	22 (61.1)		142 (87.7)	17 (70.8)	
Positive	27 (14.5)	13 (8.7)	14 (38.9)		20 (12.3)	7 (29.2)	
BxPCN (IQR)	2 (1–4)	2 (1–4)	3 (2–6)	**0.011**	2 (1–4)	2 (1–5)	0.898
BxGPC (IQR)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.5 (0.2–0.8)	**<0.001**	0.3 (0.1–0.6)	0.4 (0.2–0.7)	0.411
RP GS (%)				**<0.001**			**<0.001**
≤6	121 (65.0)	117 (78.0)	4 (11.1)		115 (71.0)	6 (25.0)	
3 + 4	52 (28.0)	33 (22.0)	19 (52.8)		42 (25.9)	10 (41.7)	
4 + 3	9 (4.8)	0 (0)	9 (25.0)		3 (1.9)	6 (25.0)	
≥8	4 (2.2)	0 (0)	4 (11.1)		2 (1.2)	2 (8.3)	
Pathologic Stage (%)				**<0.001**			0.331
pT2	161 (86.6)	150 (100)	11 (30.6)		142 (85.7)	19 (79.5)	
pT3	25 (13.4)	0 (0)	25 (69.4)		20 (14.3)	5 (20.5)	
Margin (%)				**<0.001**			**0.035**
Negative	155 (83.3)	136 (90.7)	19 (52.8)		139 (85.8)	16 (66.7)	
Positive	31 (16.7)	14 (9.3)	17 (47.2)		23 (14.2)	8 (33.3)	
PNI (%)				**<0.001**			**0.047**
Negative	93 (50.0)	85 (56.7)	8 (22.2)		86 (53.1)	7 (29.2)	
Positive	93 (50.0)	65 (43.3)	28 (77.8)		76 (46.9)	17 (70.8)	

Bold values denote statistical significance at the $p < 0.05$ level.

Discussion

Over the years, PCa has been considered as an aging disease of older men. Recently, understanding the clinicopathological characteristics and its associated oncological outcomes of younger PCa patients is of great interests since the entity has been increasing rapidly in the PSA era [22,23]. The previous knowledge from pre-PSA era showed that an early onset PCa could potentially be biologically different from PCa seen in older men and represent a larger proportion of hereditary disease [16]. Despite a steady increase in treating PCa with AS in recent years [18], younger PCa patients are often counseled towards active treatment because of their longer life expectancy, fewer comorbidities, expectation of favorable convalescence and the perceived likelihood that intervention will ultimately be required. Recently, a multicenter study reported a similar AS outcome in younger patients (age ≤ 60) as the older counterpart, providing the evidence to recommend AS for selected younger patients with low-risk PCa [24,25].

The prevalence of younger patients age ≤ 50 in our study cohort was 8.9%, which was similar to the results obtained from previous studies with the larger RP cohorts in the PSA era in the US. Parker et al. [13] reported a frequency of 9.3% of younger patients age < 50 in their 5195 RP cohort and Samadi et al. [26] reported a 10.9% frequency of younger patients age ≤ 50 in a 2495 RP cohort. In our study, about 20% of patients were identified as high-risk cases based on the well-known intrinsic high-risk factors. With a median 9.7 years follow-up, BCR was found in 12.4% of the patients ($n = 23$), metastasis was found in 2.7% of patients ($n = 5$), and all-cause death incidence was 1.1% of the entire cohort ($n = 2$). Based on these oncologic outcomes, about 13% of patients in our cohort were identified as the poor outcome group.

Between the high-risk group and low-risk group, we found no significant difference in the rate of America African (AA) patients (8.3% vs 4.7%) or positive family history (27.8% vs 28.7%). Previously, AA was associated with a significantly higher incidence in the younger age group [13]. In our cohort, only 10 AA cases were identified, however the rate of AA in high-risk group was much higher. Although family history was found previously in higher frequency among

Table 2. Univariate logistic analysis for high-risk disease and poor outcome of 186 cases age ≤50 who underwent RP between 2003 and 2010.

Univariate	High-risk			Poor outcome		
	OR	95% CI	p	OR	95% CI	p
Age (years)	0.95	0.84–1.07	0.426	0.91	0.80–1.05	0.187
PSA (ng/ml)	1.29	1.15–1.45	**<0.001**	1.11	1.03–1.20	**0.004**
Prostate weight (g)	1.00	0.97–1.04	0.907	1.00	0.96–1.04	0.873
Race						
White		ref			ref	
Black	1.83	0.45–7.49	0.398	0.71	0.09–5.83	0.746
Hispanic	n/a	n/a	n/a	n/a	n/a	n/a
Asian	4.28	0.26–70.2	0.308	n/a	n/a	n/a
cT						
≥cT2 vs cT1	3.01	1.24–7.31	**0.015**	2.92	1.07–7.92	**0.035**
D'Amico						
low		ref			ref	
Intermedium	2.31	1.04–5.16	**0.040**	3.02	1.19–7.67	**0.020**
High	24.2	2.57–228	**0.005**	16.8	2.53–111	**0.020**
Family history						
Pos vs Neg	0.96	0.43–2.15	0.916	1.30	0.52–3.25	0.574
Bx GS						
≤6		ref			ref	
3 + 4	3.40	1.38–8.38	**0.008**	1.33	0.41–4.33	0.414
4 + 3	44.8	5.08–395	**0.001**	12.4	2.51–61.0	**0.002**
≥8	n/a	n/a	n/a	18.6	1.58–218	**0.020**
BxPNI						
Pos vs Neg	6.71	2.78–16.1	**<0.001**	2.92	1.08–7.92	**0.035**
BxPCN	1.22	1.06–1.40	**0.006**	1.02	0.85–1.21	0.846
BxGPC	19.0	5.30–68.0	**<0.001**	1.91	0.45–8.15	0.381

High-risk included cases: (1) psa ≥20, (2) RP GS ≥4 + 3, (3) pT ≥3; Poor outcome included cases: (1) BCR, (2) Mets, (3) all cause death.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 3. Multivariate logistic analysis for high-risk disease and poor outcome of 186 cases age ≤50 who underwent RP between 2003 and 2010.

Multivariate	High-risk			Poor outcome		
	OR	95% CI	p	OR	95% CI	p
Age (years)	–	–	–	–	–	–
PSA (ng/ml)	definition	definition	/	collinearity	collinearity	/
Prostate weight (g)	–	–	–	–	–	–
Race						
White	ref			ref		
Black	–	–	–	–	–	–
Hispanic	–	–	–	–	–	–
Asian	–	–	–	–	–	–
cT				collinearity	collinearity	
≥cT2 vs cT1	1.73	0.63–4.78	0.287	/	/	/
D'Amico	definition	definition				
low	ref			ref		
Intermediate	/	/	/	2.97	1.15–7.64	**0.024**
High	/	/	/	17.1	2.49–117	**0.004**
Family history						
Pos vs Neg	–	–	–	–	–	–
Bx GS	definition	definition		collinearity	collinearity	
≤6	ref			ref		
3 + 4	/	/	/	/	/	/
4 + 3	/	/	/	/	/	/
≥8	/	/	/	/	/	/
BxPNI						
Pos vs Neg	3.89	1.33–11.6	**0.013**	2.90	1.02–8.30	**0.047**
BxPCN	0.92	0.75–1.13	0.426	–	–	–
BxGPC	11.2	2.25–56.0	**0.003**	–	–	–

High-risk included cases: (1) psa ≥20, (2) RP GS ≥4 + 3, (3) pT ≥3; Poor outcome included cases: (1) BCR, (2) Mets, (3) All cause death.
Bold values denote statistical significance at the $p < 0.05$ level.

younger PCa [27], its impact on separating high-risk disease from low-risk disease in younger patients was not found in our study. The prostate size was smaller (median of 36 gram)

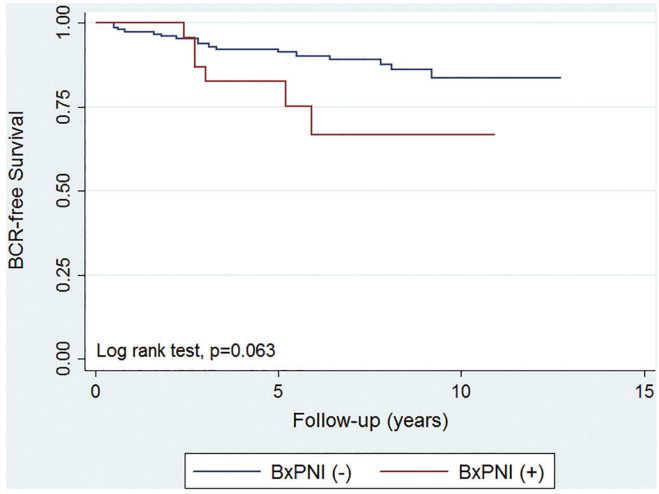

Figure 1. Kaplan–Meier curve showing biochemical recurrence-free survival stratified by BxPNI status.

in younger PCa patients and no significant differences were found between high-risk and low-risk groups, indicating that BPH which was often found among elderly men was an unlikely factor influencing the risk stratification in younger PCa patients.

In multivariate logistic regression model, BxPNI and BxGPC were shown as independent and significant predictors for high-risk group. Meanwhile, BxPNI and D'Amico risk were presented as independent and significant predictors for poor outcome. Previously, D'Amico risk was established as a significant prognostic indicator of BCR [28,29] and BxGPC has also been demonstrated to correlate with poor pathologic features and higher BCR following RP [30,31]. Interestingly, in our study, BxPNI is consistently shown to have a significant impact on the younger patients group. Previously, BxPNI has been associated with adverse RP pathologic features such as extraprostatic extension (EPE), seminal vascular invasion (SVI), positive surgical margin (PSM) and lymph node metastasis [21,32–34]. Our previous meta-analysis investigating the effect of BxPNI on BCR outcome after RP also showed that BxPNI could be a prognostic indicator [21]. In the current study, we found D'Amico risk was the only independent predictor of poor outcome after eliminating other significant covariates including PSA, cT, BxGS and BxPNI which showed significance in univariate analysis. Since D'Amico risk is characterized based on patients' PSA, cT and BxGS, in order to eliminate the possibility of multicollinearity in the model, we thought it was reasonable to use D'Amico risk in combination with only BxPNI in our analysis. We found that BxPNI remained as an independent predictor when competing with D'Aimco risk. When the prognostic impact of BxPNI was investigated with our younger patient cohort, BxPNI-positive cases only showed a trend of poor BCR-free survival but did not reach statistical significance. A future larger cohort study will be warranted to evaluate the association of the BxPNI and patient's oncological prognosis. Our study results demonstrated that BxPNI identified in younger PCa patients could be a strong indicator of high-risk disease and poor oncological outcome. Our data provided evidence and suggests that positive BxPNI diagnosis should raise concerns of more

aggressive disease and the consideration of relevant intervention for younger PCa patients.

It was reported that the steady growth of the prostate slowly accelerates approximately at age 50 [35], coordinating with an age-related decrease in the innervation of the prostate [36]. Previously, it was shown that the perineural space might provide the path for cancer cells to spread beyond the prostate with limited resistance [37]; PCa cells could interact actively with adjacent nerves [38,39]; and PCa cells in the perineural space were with higher biological activities, including increased proliferation and decreased apoptosis [38,40].

Our results indicated that, in the PSA era, only limited cases of younger patients age $\leq$ 50 harbored high-risk PCa and the majority of younger patients at age $\leq$ 50 showed favorable pathologic features and better oncological outcomes, therefore, these patients could be considered to be treated with the AS option after strict screening. The AS selection criteria of low-risk PCa varied from institution to institution and mostly included clinical stage T1c, PSA density less than 0.15 ng/ml, no Gleason pattern 4 or 5, fewer than three positive cores and 50% or less cancer per core [41]. Our finding of the association of BxPNI with aggressive PCa phenotype in younger patients suggest that the BxPNI may be an important indicator for aggressive PCa and should be considered as an additional AS selection criteria, especially among younger PCa patients. Our findings also supported the notion that microenvironments, including the muscle stroma, perineural invasion, hypoxia, and altered extracellular matrix environment by microvesicles may play an important role during PCa invasion progression and metastasis of lethal PCa [42].

The present study has its limitations. Our study is limited by its retrospective and non-randomized nature and since this study spans a longtime period, it could lead to potential misclassification. In addition, our study is limited by its relatively small sample size. Despite these limitations, this study has several strengths, including the study cohort having a longtime follow-up which could probably reveal differences in metastasis and overall mortality in younger patients. Furthermore, all patients in the current cohort were from the PSA era, making it possible to provide concrete data for understanding the nature history of early screening PCa in younger patients.

Conclusion

In summary, among the younger PCa patients aged $\leq$ 50 who underwent RP, about 20% of patients were with high-risk PCa and about 10% showed poor outcome. When compared with other well-established pre-surgery risk factors, BxPNI was correlated with both high-risk and poor outcome, indicating that BxPNI could be an important risk stratification factor in predicting high-risk PCa and poor outcome and for considering definitive treatments for younger PCa patients. Our study findings may also help to develop AS selection criteria for younger PCa patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA A Cancer J Clin. 2019;69(1):7–34.

[2] Zhou CK, Check DP, Lortet-Tieulent J, et al. Prostate cancer incidence in 43 populations worldwide: an analysis of time trends overall and by age group. Int J Cancer. 2016;138(6):1388–1400.

[3] Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev. 2005;26(6):833–876.

[4] Heinlein CA, Chang C. Androgen receptor in prostate cancer. Endocr Rev. 2004;25(2):276–308.

[5] Li J, German R, King J, et al. Recent trends in prostate cancer testing and incidence among men under age of 50. Cancer Epidemiol. 2012;36(2):122–127.

[6] Wilson JM, Kemp IW, Stein GJ. Cancer of the prostate. Do younger men have a poorer survival rate? Br J Urol. 1984;56(4):391–396.

[7] Tjaden HB, Culp DA, Flocks RH. Clinical Adenocarcinoma of the Prostate in Patients under 50 Years of Age. J Urol. 1965;93:618–621.

[8] Huben R, Natarajan N, Pontes E, et al. Carcinoma of prostate in men less than fifty years old. Data from American College of Surgeons' National Survey. Urology. 1982;20(6):585–588.

[9] Bleyer A, Spreafico F, Barr R. Prostate cancer in young men: an emerging young adult and older adolescent challenge. Cancer. 2020;126(1):46–57.

[10] 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(1):126–130.

[11] Loeb S, Hernandez DJ, Mangold LA, et al. Progression after radical prostatectomy for men in their thirties compared to older men. BJU Int. 2008;101(12):1503–1506.

[12] Khan MA, Han M, Partin AW, et al. Long-term cancer control of radical prostatectomy in men younger than 50 years of age: update 2003. Urology. 2003;62(1):86–91.

[13] Parker PM, Rice KR, Sterbis JR, et al. Prostate cancer in men less than the age of 50: a comparison of race and outcomes. Urology. 2011;78(1):110–115.

[14] Brassell SA, Rice KR, Parker PM, et al. Prostate cancer in men 70 years old or older, indolent or aggressive: clinicopathological analysis and outcomes. J Urol. 2011;185(1):132–137.

[15] Freedland SJ, Presti JC Jr., Kane CJ, et al. Do younger men have better biochemical outcomes after radical prostatectomy? Urology. 2004;63(3):518–522.

[16] Thorstenson A, Garmo H, Adolfsson J, et al. Cancer specific mortality in men diagnosed with prostate cancer before age 50 years: a nationwide population based study. J Urol. 2017;197(1):61–66.

[17] Mahran A, Turk A, Buzzy C, et al. Younger men with prostate cancer have lower risk of upgrading while on active surveillance: a meta-analysis and systematic review of the literature. Urology. 2018;121:11–18.

[18] Mahal BA, Butler S, Franco I, et al. Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010–2015. JAMA. 2019;321(7):704–706.

[19] Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. 2007;177(6):2106–2131.

[20] Shariat SF, Karakiewicz PI, Suardi N, et al. Comparison of nomograms with other methods for predicting outcomes in prostate cancer: a critical analysis of the literature. Clin Cancer Res. 2008;14(14):4400–4407.

[21] Wu S, Lin X, Lin SX, et al. Impact of biopsy perineural invasion on the outcomes of patients who underwent radical prostatectomy: a systematic review and meta-analysis. Scand J Urol. 2019;10:1–8.
[22] Hussein S, Satturwar S, Van der Kwast T. Young-age prostate cancer. J Clin Pathol. 2015;68(7):511–515.
[23] Salinas CA, Tsodikov A, Ishak-Howard M, et al. Prostate cancer in young men: an important clinical entity. Nat Rev Urol. 2014;11(6):317–323.
[24] Fang AM, Glaser ZA, Rais-Bahrami S. Increasing the use of active surveillance for prostate cancer in younger men. Cancer. 2019;125(19):3292–3295.
[25] Leapman MS, Cowan JE, Nguyen HG, et al. Active surveillance in younger men with prostate cancer. J Cin Oncol. 2017;35(17):1898–1904. 10
[26] Samadi DB, Sebrow D, Hobbs AR, et al. Clinicopathological, functional, and immediate oncologic outcome assessment in men aged $\leq$ 50 years with prostate cancer after robotic prostatectomy. Urol Oncol. 2017;35(1):30e17–30.e24.
[27] Lesko SM, Rosenberg L, Shapiro S. Family history and prostate cancer risk. Am J Epidemiol. 1996;144(11):1041–1047.
[28] Hernandez DJ, Nielsen ME, Han M, et al. Contemporary evaluation of the D'amico risk classification of prostate cancer. Urology. 2007;70(5):931–935.
[29] D'Amico AV, Tempany CM, Schultz D, et al. Comparing PSA outcome after radical prostatectomy or magnetic resonance imaging-guided partial prostatic irradiation in select patients with clinically localized adenocarcinoma of the prostate. Urology. 2003;62(6):1063–1067.
[30] Harnden P, Shelley MD, Naylor B, et al. Does the extent of carcinoma in prostatic biopsies predict prostate-specific antigen recurrence? A systematic review. Eur Urol. 2008;54(4):728–739.
[31] Bismar TA, Lewis JS Jr., Vollmer RT, et al. Multiple measures of carcinoma extent versus perineural invasion in prostate needle biopsy tissue in prediction of pathologic stage in a screening population. Am J Surg Pathol. 2003;27(4):432–440.
[32] Cozzi G, Rocco BM, Grasso A, et al. Perineural invasion as a predictor of extraprostatic extension of prostate cancer: a systematic review and meta-analysis. Scand J Urol. 2013;47(6):443–448.
[33] Kryvenko ON, Diaz M, Meier FA, et al. Findings in 12-core transrectal ultrasound-guided prostate needle biopsy that predict more advanced cancer at prostatectomy: analysis of 388 biopsy-prostatectomy pairs. Am J Clin Pathol. 2012;137(5):739–746.
[34] Stone NN, Stock RG, Parikh D, et al. Perineural invasion and seminal vesicle involvement predict pelvic lymph node metastasis in men with localized carcinoma of the prostate. J Urol. 1998;160(5):1722–1726.
[35] Swyer GI. Post-natal growth changes in the human prostate. J Anat. 1944;78(Pt 4):130–145.
[36] Chapple CR, Crowe R, Gilpin SA, et al. The innervation of the human prostate gland-the changes associated with benign enlargement. J Urol. 1991;146(6):1637–1644.
[37] Villers A, McNeal JE, Redwine EA, et al. The role of perineural space invasion in the local spread of prostatic adenocarcinoma. J Urol. 1989;142(3):763–768.
[38] Ayala GE, Dai H, Ittmann M, et al. Growth and survival mechanisms associated with perineural invasion in prostate cancer. Cancer Res. 2004;64(17):6082–6090.
[39] Ayala GE, Dai H, Tahir SA, et al. Stromal antiapoptotic paracrine loop in perineural invasion of prostatic carcinoma. Cancer Res. 2006;66(10):5159–5164.
[40] Fromont G, Godet J, Pires C, et al. Biological significance of perineural invasion (PNI) in prostate cancer. Prostate. 2012;72(5):542–548.
[41] Bastian PJ, Mangold LA, Epstein JI, et al. Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. Cancer. 2004;101(9):2001–2005.
[42] Harryman WL, Warfel NA, Nagle RB, et al. The tumor microenvironments of lethal prostate cancer. Adv Exp Med Biol. 2019;1210:149–170.