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Original Article

Absolute percentage of biopsied tissue positive for Gleason pattern 4 disease (APP4) appears predictive of disease control after high dose rate brachytherapy and external beam radiotherapy in intermediate risk prostate cancer

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ABSTRACT

Background and purpose: To identify if, in intermediate risk prostate cancer (IR-PCa), the absolute percentage of biopsied tissue positive for pattern 4 disease (APP4) may be a predictor of outcome.

Materials and methods: 411 patients with IR-PCa were retrospectively reviewed. APP4 was calculated based on biopsy reports. Multivariable competing risk analysis was then performed on optimized APP4 cutpoints to predict for biochemical failure (BF), androgen deprivation use for BF (ADT-BF) and development of metastases (MD).

Results: Median follow-up for the cohort was 5.2 (Inter Quartile Range: 2.9–6.6) years. Median baseline PSA was 7.3 (5.3–9.8) ng/mL. 234 (56.9%) patients had T1 and 177 (43.1%) had T2 disease. Median APP4 was 2.00 (0.75–7.50)%.

38 (9.3%) patients experienced BF. The optimal cutpoint of APP4 for BF was >3.3% with an area under the curve (AUC) of 0.66. 17 (4.1%) received ADT-BF. The ADT-BF cutpoint was >6.6% with an AUC of 0.72. Eight (2.0%) developed MD. The MD cutpoint was >17.5% with an AUC of 0.86.

Using APP4 >3.3 vs $\leq$ 3.3, log-transformed baseline PSA ln(PSA) (HR 2.5, 1.1–6.1; $p = 0.037$) and APP4 (HR 2.3, 1.1–4.7; $p = 0.031$) predicted for BF. Using APP4 >6.6 vs $\leq$ 6.6, ln(PSA) (HR 4.2, 1.4–12.4; $p = 0.010$) and APP4 (HR 3.7, 1.4–10.0; $p = 0.009$) were predictive of ADT-BF. APP4 >17.5 vs $\leq$ 17.5 alone was predictive of MD (HR 25.7, 4.9–135.3; $p < 0.001$).

Conclusion: APP4 cutpoints of >3.3%, >6.6% and >17.5% were strongly associated with increased risk of BF, ADT-BF and developing MD respectively. These findings may inform future practice when treating IR-PCa but require external validation.

With decreased screening among North American men, the number of patients presenting with high grade prostate cancer (PCa) has increased [1–3]. Beyond this, with an increased utilization of active surveillance, a growing percentage of patients treated for PCa today have intermediate risk disease [4,5].

To help guide management, patients with intermediate risk prostate cancer (IR-PCa) are often further subdivided into those with favorable and unfavorable IR-PCa [6,7]. This division often includes a distinction between patients with grade group (GG) 2 (Gleason 3+4) and GG 3 (Gleason 4+3) on pathology as patients with GG 3 disease have a worse prognosis [8,9].

However, the distinction between patients with GG 2 vs 3 is likely an inaccurate measure of the volume of high-grade Gleason

Abbreviations: PCa, prostate cancer; IR-PCa, intermediate risk prostate cancer; GG, grade group; APP4, absolute percentage of all biopsied tissue positive for pattern 4 disease; BF, biochemical failure; ADT-BF, androgen deprivation therapy use for biochemical failure; MD, development of metastatic disease; PG4, percentage of tumor that is Gleason 4 disease; HDR, high dose rate brachytherapy; EBRT, external beam radiotherapy; V100, volume of prostate receiving 100% of prescribed brachytherapy dose; ADT, androgen deprivation therapy; HR, hazard ratio; PSA, prostate specific antigen; Ln(PSA), natural logarithm transformed PSA value; ROC, receiver operator characteristic.

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pattern as it only reflects the relative proportion of pattern 3 and pattern 4 disease with no indication of the amount of pattern 4 disease that is present. For example, a patient with a high overall volume of Gleason pattern 4 PCa can be classified as GG 2 if there is an even higher percentage of pattern 3 disease. Conversely, a patient with low overall volume of pattern 4 PCa can be classified as having GG 3 disease, even if only one of 12 cores were involved.

Acknowledging this discrepancy in the current grading system, this study aimed to identify if the absolute percentage of all biopsied tissue positive for pattern 4 disease (APP4) may be a predictor of outcome. Furthermore, it aimed to determine the optimal cutoff values of APP4 to be considered for predicting three outcomes: biochemical failure (BF), androgen use for biochemical failure (ADT-BF) and development of metastatic disease (MD).

Materials and methods

Study design and data collection

After approval from the institutional research ethics board (291-2011), data for 546 consecutive patients with IR-PCa and treated with high dose rate brachytherapy (HDR) boost followed by external beam radiotherapy (EBRT) between June 2009 and December 2016 were collected. Post treatment, PSA was measured 6-monthly for the first 2 years and then 6-monthly to yearly thereafter. All patients received HDR at the study institution and were either discharged back to a regional cancer center or followed for a minimum of 4 years then discharged back to their family physician if 3 consecutive PSA measurements were stable at nadir. In patients discharged after 2015, a single PSA measurement of <0.4 after 4 years was used as criteria to discharge the patient [10].

Biopsy characteristics

Biopsies for patients included in this study were predominately performed using a trans-rectal approach under ultrasound guidance and a 12 core sampling technique. In a minority of cases, biopsies were performed in house using an ultrasound guided trans-perineal approach with 12 core sampling [11]. Biopsy specimens underwent routine central review by a uro-pathologist.

Treatment characteristics

All patients within the cohort received 15 Gy in 1 fraction, HDR boost to the prostate gland. For HDR treatments, the technique is described elsewhere [12,13]. In brief, patients underwent general anesthetic and, under real-time trans-rectal ultrasound, 12–18 catheters were placed within the gland. Sequential axial image sets were taken and used for contouring prostate, urethra and rectal volumes and catheter reconstruction. Plans were generated using Oncentra Prostate (Elekta AB, Stockholm, Sweden) and delivered prior to anesthetic reversal. Dosimetric constraints followed a standardized in-house protocol [12]. EBRT treatments were mainly hypofractionated intensity modulated radiotherapy-based plans (37.5 Gy in 15 fractions) generated and delivered to the prostate and proximal seminal vesicles at the host institution. Patients did have the option to receive EBRT at centers closer to their homes. In these cases, other fractionation regimens and planning techniques were sometimes utilized.

Statistical methods

Descriptive statistics were used to describe the cohort. For non-normally distributed continuous variables medians and interquartile ranges were used. For binomial and ordinal variables the absolute numeric count and proportion (percentage) were used. APP4 was calculated as the percentage of Gleason 4 disease within the tumor(s) multiplied by the percentage of total biopsied tissue positive for disease divided by 100 [(% of biopsy tissue positive for disease) × (percentage of disease that is pattern 4)/100%].

Multivariable Cox proportional sub-distribution hazards models were created for each of three outcomes: BF, ADT-BF and MD. Competing risks were accounted for using Fine and Gray's method [14]. For BF, time to event was calculated as time from date of HDR brachytherapy to date of last measured PSA value or BF as defined by the phoenix definition [15]. For ADT-BF, time to event was calculated as time from date of HDR brachytherapy to date of any last followup or date of ADT initiation. For MD, time to event was calculated as time from date of HDR to time of last followup or first radiographic evidence of disease.

In Cox proportional hazards modeling, patient age, volume of prostate receiving 100% of the prescribed dose (V100) and APP4 were treated as continuous variables, ADT use and tumor T-Stage (divided as T1 or T2) were treated as dichotomous variables. PSA at the time of diagnosis was normalized using a natural logarithm transformation and included in the model as a continuous variable ln(PSA). To avoid having interdependent variables, GG (used as an ordinal variable) was considered separately of %Gleason pattern 4 (PG4), APP4 (continuous variable) and APP4 cutpoints (dichotomous variable). When developing all models, only cases with complete information for all of the variables considered were used.

Optimum cutpoints of APP4 to predict for BF, ADT-BF and MD were calculated through maximization of the area under the receiver operating characteristic (ROC) curve. For this, criterion was based on the maximum value of Youden's J Index. Cumulative incidence was estimated using the Nelson–Aalen method for BF, ADT-BF and MD between groups and the log-rank test was used. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.) [16].

Results

Baseline cohort and treatment characteristics

411 patients had complete pathologic information and were analyzed. Patient, tumor and treatment characteristics for this cohort are given in Table 1. Median pre-treatment PSA was 7.3 (5.3–9.8) ng/mL. 234 (57%) patients had T1 and 177 (43%) had T2 disease. A median of 12 (10–12) biopsy cores were taken and a median of 5 (3–7) cores were positive for disease. Most patients (287; 70%) had Gleason GG 2 disease. By National Comprehensive Cancer Network (NCCN) classification, 156 (38%) had favorable and 255 (62%) had unfavorable intermediate risk disease. The median percentage of biopsy tissue positive for disease was 2 (0.75–7.35)%. A total of 71 (18%) patients received ADT for a median of 6.0 (3.0–6.0) months. All patients (100%) received a prescribed dose of 15 Gy HDR to the prostate, however EBRT dose varied slightly with the most common fractionation being 37.5 Gy in 15 fractions (391; 97%). In those with data available (n = 319) median prostate D90 at the time of implantation was 109.0 (107.2–110.4)Gy.

Follow-up and survival

Median followup for the cohort was 5.2 (2.9–6.6) years. Within this, biochemical follow-up was available for a median of 4.7 (2.6–6.3) years. Only 15 (4%) patients included in this analysis had less than one year of follow-up data available. In total 38 (9%) biochemical relapses were identified. Estimated cumulative incidence of BF at 4 years was 5 (3–8)%. This correlated with ADT-BF in 17 (4%) patients and MD in 8 (2%) patients. At 4 years estimated cumulative incidence of ADT-BF and MD was 2 (0–4)% and 0.6 (0.0–1.6)% respectively (Fig. 1).

Table 1
Patient, tumor and treatment characteristics for 411 patients receiving combined treatment with EBRT and HDR for intermediate risk prostate cancer.

	Median (IQR) or No. (%)
Age [years]	66 (61–71)
Baseline PSA [ng/mL]	7.3 (5.3–9.8)
T-Stage	
T1a	0 (0%)
T1b	0 (0%)
T1c	234 (57%)
T2a	116 (28%)
T2b	54 (13%)
T2c	7 (2%)
Grade Group	
2	287 (70%)
3	124 (30%)
% of biopsy tissue positive for cancer [%]	12 (5–22)
% of tumor showing Gleason 4 disease [%]	20 (10–55)
% of biopsy tissue showing Gleason 4 disease [%]	2.00 (0.75–7.35)
Use of androgen deprivation therapy	71 (18%)
Prostate V100 [%]	96.7 (95.8–97.3)
Prostate V150 [%]	35.2 (32.1–38.3)
Prostate V200 [%]	11.4 (9.7–13.2)
EBRT dose and fractionation	
25 Gy in 5 fractions	3 (1%)
37.5 Gy in 15 fractions	391 (95%)
45 Gy in 25 fractions	4 (1%)
46 Gy in 23 fractions	4 (1%)
Unknown/Missing	9 (2%)

Cox proportional hazards modeling of cohort

21 cases were excluded from the Cox proportional hazards models. Reasons for exclusion included missing records of ADT use and prostate V100. Full modeling information for all variables is available in Appendix A. On Cox proportional hazards modeling only ln(PSA) was found to be predictive of BF [Hazard Ratio (HR): 3.0 (95% Confidence Interval 1.3–7.0); $p = 0.012$). Of note, GG was not predictive [HR 3 vs 2: 1.4 (0.7–2.7); $p = 0.341$]. When using PG4 in place of GG, PG4 was also not predictive of BF [HR: 1.01 (0.99–1.02); $p = 0.34$] but ln(PSA) maintained its prognostic significance [HR: 3.0 (1.3–7.0); $p = 0.013$]. When APP4 was used instead of GG both ln(PSA) [HR: 2.8 (1.2–6.4); $p = 0.013$] and APP4 [HR: 1.04 (1.01–1.07); $p = 0.013$] were predictive of outcome.

When considering cumulative incidence of ADT-BF on Cox proportional hazards modeling only ln(PSA) was found to be predictive of outcome [HR: 5.6 (1.9–17.1); $p = 0.002$]. A trend toward GG as a predictor was noted [HR 3 vs 2: 2.5 (0.98–6.30); $p = 0.056$]. When analyzing PG4, both PG4 [HR: 1.02 (1.01–1.04); $p = 0.009$] and ln(PSA) [HR: 5.1 (1.6–16.1); $p = 0.005$] were predictive of ADT-BF. When APP4 was used, both ln(PSA) [HR: 5.0 (1.8–13.7); $p = 0.002$] and APP4 [HR: 1.05 (1.01–1.09); $p = 0.009$] predicted ADT-BF.

When considering cumulative incidence of MD on Cox proportional hazards modeling GG was found predictive of outcome [HR 3 vs 2: 6.0 (1.1–31.2); $p = 0.034$] and ln(PSA) was not [HR: 1.5 (0.1–15.7); $p = 0.758$]. When analyzing PG4, only PG4 [HR: 1.03 (1.00–1.06); $p = 0.037$] was predictive. When considering APP4, only APP4 was predictive of MD [HR: 1.11 (1.06–1.16); $p < 0.001$].

Cutpoints analysis

When analyzing the ROC curves (Appendix A), the optimal cutpoint for predicting BF with APP4 was calculated as >3.3% (Area under the ROC curve: 0.663; Efficiency: 0.629). For ADT-BF, the optimal APP4 cutpoint was calculated as >6.6% (0.716; 0.693). For MD, the optimal APP4 cutpoint was calculated as >17.5% (0.859; 0.787).

Outcomes by cutpoint of APP4

Fig. 2 shows the estimated cumulative incidence of BF for the corresponding optimized cutpoint of APP4 (>3.3% vs $\leq$ 3.3%). Cumulative incidence of BF at 4 years post treatment was estimated as 2 (0–4)% for values of APP4 $\leq$ 3.3% and 10 (7–16)% for values of APP4 >3.3% ($p < 0.001$).

Fig. 3 shows the estimated cumulative incidence of ADT-BF for the corresponding optimized cutpoint of APP4 (>6.6% vs $\leq$ 6.6%). Cumulative incidence of ADT-BF at 4 years post treatment was estimated as 2 (0–30% for values of APP4 $\leq$ 6.6% and 10 (3–16)% for APP4 >6.6% ($p < 0.001$).

Fig. 4 shows the estimated cumulative incidence of MD for the corresponding optimized cutpoint of APP4 (>17.5% vs $\leq$ 17.5%). Cumulative incidence of MD at 4 years post treatment was estimated as 0.4 (0.0–1.1)% for values of APP4 $\leq$ 17.5% and 5.2 (0.0–10.5)% for APP4 >17.5% ($p < 0.001$).

Revised Cox proportional hazards model using cutpoints

Cox proportional hazards were calculated for each of the optimized cutpoints and ratios are summarized in Table 2. In all models the optimized cutpoint of APP4 for each endpoint was found to be significantly predictive of outcome. When considering cumulative incidence of BF, the HR for APP4 >3.3% vs $\leq$ 3.3% was 2.3 (1.1–4.7; $p = 0.031$). Ln(PSA) was also predictive [HR: 2.5 (1.1–6.1); $p = 0.037$] of BF. When considering cumulative incidence ADT-BF the HR for APP4 >6.6% vs $\leq$ 6.6% was 3.7 (1.4–10.0; $p = 0.009$). Again, ln(PSA) was predictive [HR: 4.2 (1.4–12.4); $p = 0.010$]. Finally, when considering cumulative incidence of MD, the hazard radio for APP4 >17.5% vs $\leq$ 17.5% was 25.7 (4.9–135.3; $p < 0.001$). Here ln(PSA) was not predictive of outcome [HR: 1.4 (0.1–13.9); $p = 0.783$].

Discussion

The current study identified APP4 cutpoints for predicting increased risk of BF (>3.3%), ADT-BF (>6.6%) and MD (>17.5%) in a large cohort of patients all treated with radical intent HDR brachytherapy followed by EBRT. Cutpoints were highly predictive of their respective outcomes.

On review of the literature, a study of Turkish patients by Kir et al. was identified that also explored the utility of APP4 in prostate cancer biopsy specimens [17]. Within their cohort, 216 patients had GG 1 and 156 patients had GG 2 disease; 80 of these had >6% Gleason pattern 4. On multivariate analysis, APP4 was predictive of BF after radical prostatectomy. This is in agreement with the present study despite the difference in treatment technique and biochemical failure definition. However, the difference observed in BF between patients with biopsy specimens containing <6% APP4 vs 6–25% was not statistically significant. This appears to be in contradiction to the present study. However, a likely explanation is their limited power to show a difference (52 patients had 6–25% APP4).

The present study did not include GG 1 disease and was able to show differences between this relatively large, homogeneous group of patients with IR-PCa. Furthermore, all tumors were graded using the updated Gleason grading system thereby making this analysis applicable to current pathological specimens [18].

Within the present analysis, APP4 was adopted as the variable of interest as GG was not found predictive of BF or ADT-BF. It is possible that with longer follow-up, GG would predict for BF as, in other series, GG 3 vs 2 has been shown to have higher incidence of BF and up to a 3 times increased risk of death from prostate cancer [8,9,19–21]. In this cohort, having GG 3 disease was still associated with an increased risk of MD (HR: 6). However, the APP4

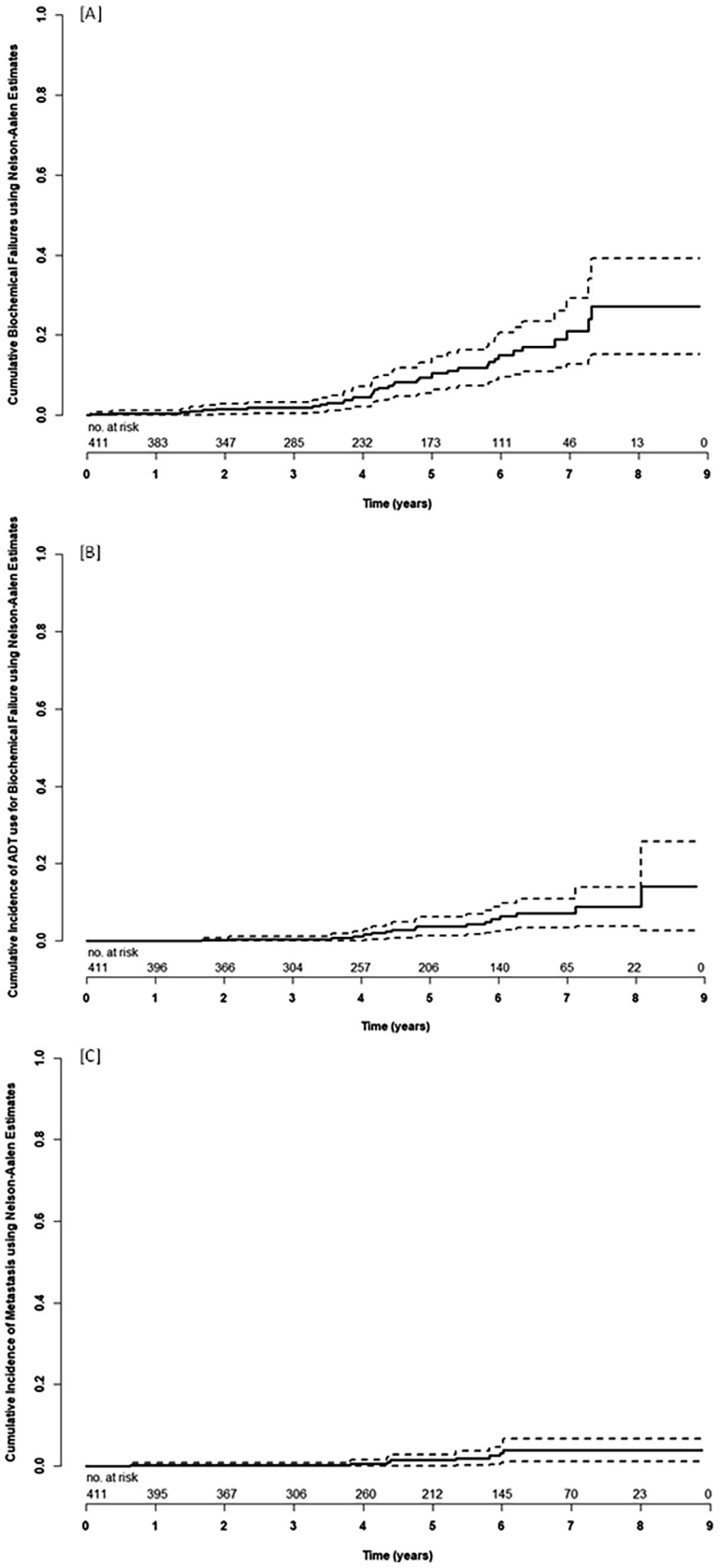

Fig. 1. Nelson–Aalen estimated cumulative incidence (black solid line) and 95% confidence interval of the estimate (black broken line) of [a] biochemical relapse, [b] ADT use and [c] development of metastatic disease for all patients included in the analysis.

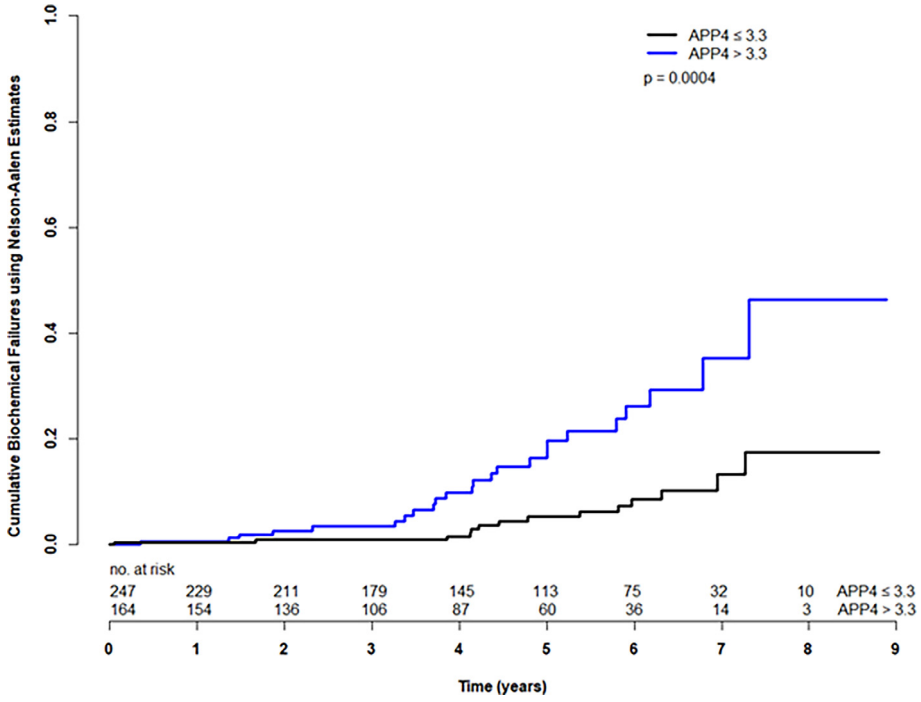

Fig. 2. Nelson–Aalen estimated cumulative incidence of biochemical failure for all patients with absolute percentage of all biopsy tissue positive for pattern 4 disease >3.3% (blue solid line) vs $\leq$ 3.3% (black solid line).

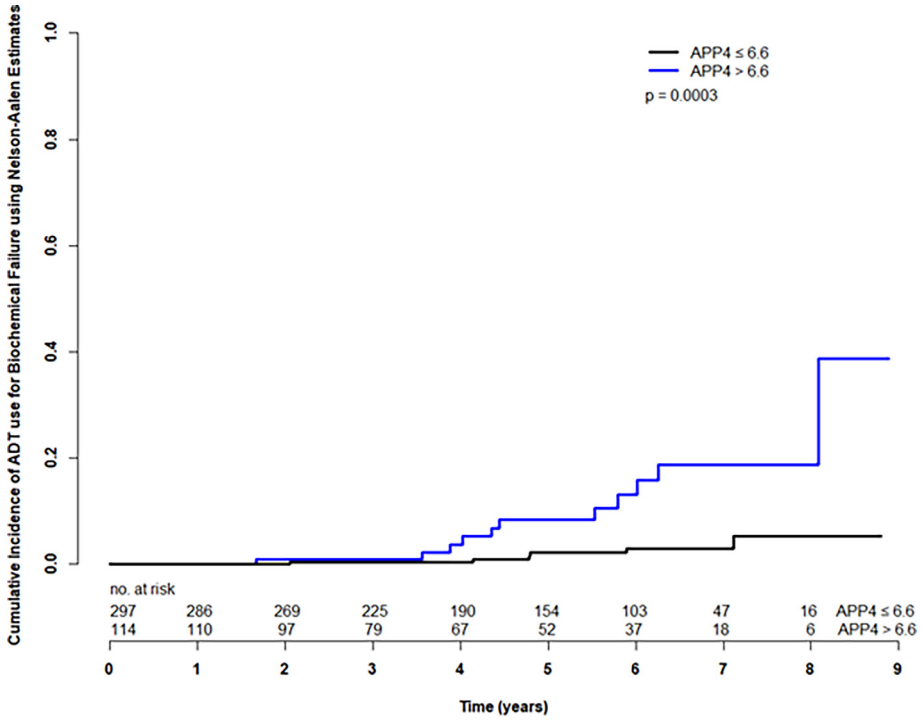

Fig. 3. Nelson–Aalen estimated cumulative incidence of ADT use for biochemical failure for all patients with absolute percentage of all biopsy tissue positive for pattern 4 disease >6.6% (blue solid line) vs $\leq$ 6.6% (black solid line).

cutpoint of 17.5% appeared to be a stronger predictor (HR: 25.7). This suggests that perhaps APP4 may be the underlying factor that accounts for the differences between outcomes in GG 3 vs 2 disease.

This association of APP4 with MD is a significant finding and infers that APP4 may have implications on predicting overall survival outcomes in prostate cancer. In a recent study, Xie et al. analyzed data from over 21,000 patients with prostate cancer enrolled in clinical trials [22]. They found that a strong correlation between overall survival and development of MD. Given this, if validation studies are able to confirm the prognostic utility of APP4, a clinically relevant cutpoint for APP4 of 15 (17.5 rounded down for simplicity of use in the clinic) should be considered for possible intensification of therapy. This could be in the form of ADT with

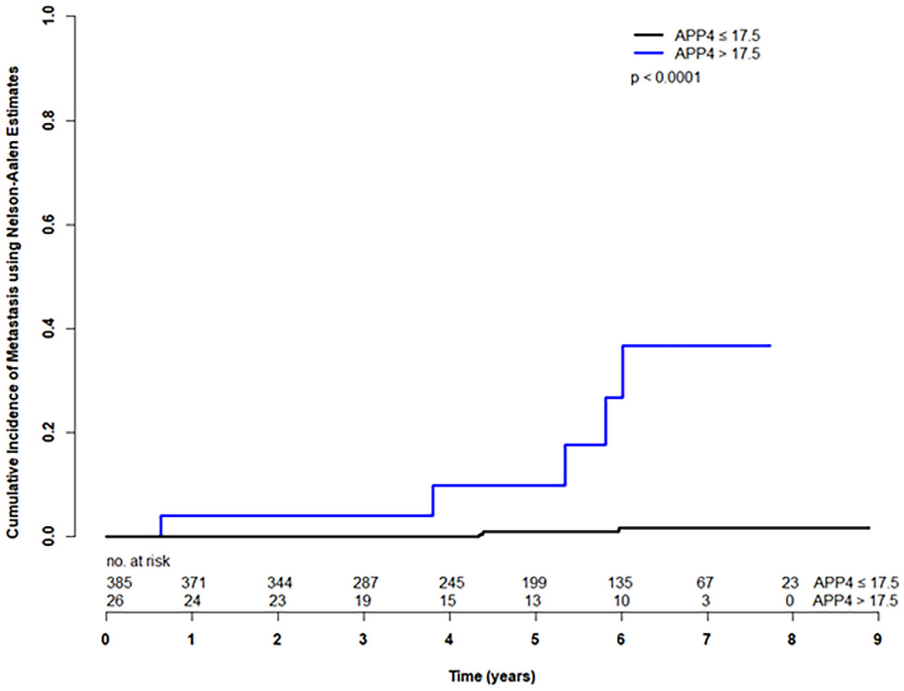

Fig. 4. Nelson–Aalen estimated cumulative incidence of development of metastatic disease for all patients with absolute percentage of all biopsy tissue positive for pattern 4 disease >17.5% (blue solid line) vs ≤ 17.5% (black solid line).

Table 2
Cox proportional hazards ratio with 95% confidence interval (95% CI) and associated *p*-value for each variable tested when considering the absolute percentage of all biopsied tissue positive for Gleason pattern 4 disease (APP4).

	HR (95% CI; p-value)
Biochemical relapse	
Baseline PSA (ln) [ng/mL]	2.5 (1.1–6.2; 0.037)
APP4: >3.3% vs ≤ 3.3%	2.3 (1.1–4.7; 0.031)
T-Stage: T2 vs T1	1.2 (0.6–2.5; 0.572)
Age [years]	1.0 (1.0–1.1; 0.485)
ADT Use: "yes" vs "no"	0.9 (0.3–2.6; 0.815)
Prostate V100 [%]	1.0 (1.0–1.1; 0.588)
ADT use for relapse	
Baseline PSA (ln) [ng/mL]	4.2 (1.4–12.4; 0.010)
APP4: >6.6% vs ≤ 6.6%	3.7 (1.4–10.0; 0.009)
T-Stage: T2 vs T1	1.0 (0.4–2.5; 0.928)
Age [years]	1.1 (1.0–1.1; 0.118)
ADT Use: "yes" vs "no"	1.0 (0.3–3.5; 0.989)
Prostate V100 [%]	1.0 (0.8–1.3; 0.686)
Metastatic disease	
Baseline PSA (ln) [ng/mL]	1.4 (0.1–13.9; 0.783)
APP4: >17.5% vs ≤ 17.5%	25.7 (4.9–135.3; <0.001)
T-Stage: T2 vs T1	0.5 (0.1–2.8; 0.437)
Age [years]	1.0 (0.9–1.1; 0.990)
ADT Use: "yes" vs "no"	1.9 (0.3–14.0; 0.538)
Prostate V100 [%]	1.3 (0.9–2.0; 0.198)

or without elective nodal irradiation. Finally, with further study, there may be role for PSMA imaging for further risk stratification in patients with high APP4 [23,24].

Another variable that has been previously reported on as predictive of outcomes in prostate cancer is PG4 [25,26]. In a series of 350 patients with Gleason 7 disease, Choy et al. found patients with 21–50% PG4 disease to have a 2.2 times risk of BF over 1–20% PG4 [21]. In another report Sauter et al. showed differences in BF rates between patients with 0–25%, 26–50%, 51–75% and 76–100% PG4 [27]. In this analysis, PG4 when used as a continuous variable in Cox proportional hazards modeling was not predictive of BF. PG4 had a weaker association with ADT-BF (HR: 1.02) and MD (HR: 1.03) than APP4 (HR: 1.05 and 1.11 respectively). This appears intuitive as APP4 integrates the proportion of tissue biopsied that is positive for disease, something also shown to be predictive of outcome [28].

Within the Cox proportional hazards models, T-Stage was not found to be a significant predictor of outcome. This appears to contradict previous reports [29–31]. A possible explanation is 85% of patients had either T1c or T2a disease. With very few (7) T2c glands it is expected that there would be little dependency of outcome on T-Stage and is consistent with the results seen by Liauw et al. in high risk patients where T1-T2 disease had similar freedom from biochemical failure [32].

In this analysis, ADT use also did not appear to modify outcome. This again appears contradictory to some prior reports [33,34]. However, in patients with IR-PCa receiving dose escalated radiotherapy, this point has been debated [35,36]. Furthermore, only 18% of patients received ADT in this cohort and the practices around the use of ADT prior to treatment were inconsistent. Across this cohort, the most common reason for ADT use was for hormonal downsizing of the gland. Given this, the result could be anticipated.

In the present study, while using APP4 as continuous variables and as cutpoints, ln(PSA) was highly predictive of biochemical relapse (HR 2.8 and 2.5) and subsequent ADT use for biochemical failure (HR 5.0 and 4.2). It was also predictive of these outcomes when GG or PG4 was used instead of APP4. However, ln(PSA) was not predictive of metastatic disease in any scenario. The inability of baseline PSA to predict for metastatic disease is consistent with previously reported literature [37,38]. However, this appears counter-intuitive given its utility as a predictor for biochemical failure and subsequent ADT use for biochemical failure. There are likely several factors which contribute to this finding. First, it is likely that given the relatively short follow-up, many of the patients who biochemically failed had not developed clinically

detectable metastatic disease. Next, high grade tumors with low PSA have been previously shown to have high prostate cancer specific mortality and would be anticipated to have early development of metastatic disease [39]. The presence of such patients in the study cohort likely explains these findings. Analysis of APP4 specifically in these patients in a larger cohort with adequate power to review outcomes should be considered.

A limitation of this study was the lack of gland volume data. There is a possibility that APP4 is subject to biopsy sampling error which should be correlated with the gland volume at the time of biopsy. Unfortunately, these data were unavailable at the time of analysis as most biopsies were performed outside of the investigating center and ultrasound reporting practices of gland volume were inconsistent. Furthermore, data collection was retrospective and potentially subject to follow-up bias where patients were more likely to be followed by an oncologist if clinical suspicions of biochemical relapse was present. Also, the overall median follow-up in this cohort was short (5.2 years). Hence, the ability of APP4 to predict for late treatment failure cannot be inferred from these results. Finally, the data included in this study are single institutional and for a single treatment paradigm; the results require validation in an external cohort and with other treatment modalities.

Conclusions

APP4 cutpoints of >3.3%, >6.6% and >17.5% were strongly associated with increased risk of BF, ADT-BF and developing MD respectively. Although these findings are preliminary and require validation in an external cohort, they may inform future practice when treating patients with IR-PCa.

Conflicts of interest

This project was funded in part by departmental funding from the University of Toronto, Department of Radiation Oncology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.007.

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