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Original Research

A low prostate specific antigen predicts a worse outcome in high but not in low/intermediate-grade prostate cancer☆

Christian D. Fankhauser [a,b,c,d,*,1], Matthew G. Parry [b,e,f,1], Adnan Ali [a,g], Thomas E. Cowling [b,f], Julie Nossiter [b,e,f], Arun Sujenthiran [b,e], Brendan Berry [b,e,f], Melanie Morris [b,e,f], Ajay Aggarwal [b,e,f,h], Heather Payne [b,i], Jan van der Meulen [b,e,f], Noel W. Clarke [a,b,j]

[a] *Department of Urology, The Christie NHS Foundation Trust, Manchester, UK*
[b] *National Prostate Cancer Audit, Royal College of Surgeons of England, London, UK*
[c] *University of Zurich, Zurich, Switzerland*
[d] *Department of Urology, Luzerner Kantonsspital, Lucerne, Switzerland*
[e] *Clinical Effectiveness Unit, The Royal College of Surgeons of England, London, United Kingdom*
[f] *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, GU Cancer/FASTMAN Research Group, Manchester University, Manchester, United Kingdom*
[g] *GU Cancer/FASTMAN Research Group, Manchester University, Manchester, United Kingdom*
[h] *Department of Radiotherapy, Guy's and St Thomas' NHS Foundation Trust*
[i] *Department of Clinical Oncology University College London Hospital NHS Trust, London, United Kingdom*
[j] *Department of Urology, Salford Royal NHS Foundation Trust, Manchester, UK*

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KEYWORDS
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Abstract ***Objective:*** The relationship between prostate-specific antigen (PSA) and prostate cancer (PCa) grade was traditionally thought to be linear but recent reports suggest this is not true in high-grade cancers. We aimed to compare the association between PSA and PCa-specific mortality (PCSM) in clinically localised low/intermediate and high-grade PCa. ***Subjects/patients and methods:*** Retrospective cohort study using the National Prostate Cancer Audit database in England of men treated with external beam radiotherapy (EBRT), EBRT

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* *Corresponding author*: The Christie NHS Foundation Trust. Wilmslow Road. Withington. Manchester. M20 4BX, UK. fax: +44 161 446 3365.
E-mail address: cdfankhauser@gmail.com (C.D. Fankhauser).
@CDFANKHAUSER (C.D. Fankhauser)

[1] Contributed equally.

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therapy;
Prostate-specific antigen

and brachytherapy boost (EBRT + BT), radical prostatectomy or no radical local treatment between 2014 and 2018. Multivariable competing-risk regression was used to examine the association between PSA, Gleason, and PCSM. Multivariable restricted cubic spline regression was used to explore the non-linear associations of PSA and PCSM.

Results: 102,089 men were included, of whom 71,138 had low/intermediate-grade and 22,425 had high-grade PCa. In high-grade, 4-year PCSM was higher with PSA ≤5 than PSA 5.1–10 for men treated with EBRT (hazard ratio 1.96 (95% confidence interval 1.15–3.34) or no radical local treatment (hazard ratio 1.99 (95% confidence interval 1.33–2.98). Restricted cubic spline regression showed that PSA and PCSM have a non-linear association in high-grade but a linear association in low/intermediate-grade PCa.

Conclusion: The low-PSA/high-grade combination in M0 PCa treated with EBRT has a higher PCSM than those with high-grade and intermediate PSA levels. In high-grade disease, the PSA association was non-linear; by contrast, low/intermediate-grade had a linear relationship. This confirms a more aggressive biology in low PSA secreting high-grade PCa and a worse outcome following treatment.

1. Introduction

Recent studies of high-grade localised prostate cancer (PCa) have shown a *J*-shaped rather than a linear association between prostate-specific antigen (PSA) levels at diagnosis and oncological outcome following treatment [1–5]. This suggests that men with high-grade PCa who are treated with standard of care interventions have a worse prognosis when their PSA is low compared to high-grade cases with intermediate PSA levels [1]. The reasons for this are incompletely understood, although limited gene expression data suggest altered neuroendocrine/small-cell and androgen receptor signalling in such men, which might account for a more aggressive biopotential and resistance to standard therapies [6–8]. The aim of this study was to analyse the association between PSA and PCa-specific mortality (PCSM) in a national population using data from the National Prostate Cancer Audit in England (the NPCA (www.npca.org)) using data stratified by grade and local/systemic treatment in men with clinically localised PCa to assess the effects of treatment in this patient group.

2. Material and methods

2.1. Patient population

Men diagnosed with clinically localised PCa (T1-4N0M0) between 1st April 2014 and 31st March 2018 were identified within the NPCA. This national population-based dataset has, since 2014, collected and reported data annually on the diagnosis and treatment of all prostate cancers in England [9]. Sources include the English Cancer Registry [10], the National Radiotherapy Dataset (RTDS), Hospital Episode Statistics (HES) data, and the UK Office for National Statistics mortality data, all linked at patient level [11].

The International Classification of Diseases 10th revision code 'C61' was used to identify patients having PCa within the English Cancer Registry. High-grade, clinically localised PCa was defined as a pre-treatment Gleason score of 8 or above and low/intermediate-grade as a Gleason score of 7 or below. Pre-treatment Gleason score, TNM-stage and PSA levels at diagnosis were available from the English Cancer Registry.

Men were grouped according to the treatment received: no radical local treatment, radical prostatectomy (RP), external beam radiotherapy (EBRT) and EBRT with a brachytherapy boost (EBRT + BT). The standard of care in England for high-risk clinically localised PCa is for EBRT to be combined with androgen deprivation therapy (ADT), referred to herein as EBRT. The Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th Revision (OPCS-4) code 'M61' within the HES record was used to identify the men who underwent RP. The RTDS OPCS-4 code 'X671' was used to identify men receiving EBRT to the prostate. Men were considered to have undergone EBRT + BT if a brachytherapy episode was identified in the RTDS, if specific OPCS-4 code combinations were identified in HES (M706 + X653 + Y363; M706 + X653; M712 + X653) or if a recognised EBRT regimen for brachytherapy boost was identified in the RTDS (36–39 Gray (Gy) in 15 fractions, 43–47 Gy in 22–25 fractions and 50.2 Gy in 28 fractions). The use, product and duration of ADT were not available.

Age at diagnosis and patient ethnicity (white, Asian, black and 'other') were recorded in the English Cancer Registry. Patient comorbidity was measured using the Royal College of Surgeons Charlson Score based on the International Classification of Diseases 10th revision

codes given in each patient's HES records up to a year before diagnosis [12]. HES data were used to supplement patient ethnicity information. Socioeconomic deprivation status was determined for patients from the English 2012 Index of Multiple Deprivation on the basis of their area of residence, divided according to quintiles of the national distribution [13].

2.2. Outcome definition

The Office for National Statistics provided the dates of death. PCSM was defined as any death where PCa was identified on the death certificate as part of the sequence leading to death.

2.3. Statistical analysis

We calculated cumulative incidence of PCSM for each treatment group stratified by PSA level ($\leq$5, 5.1–10, 10.1–20 and $>$ 20 ng/mL). We considered death from a cause other than PCa as a competing event when analysing PCSM. Follow-up started on the day of treatment for RP, EBRT and EBRT + BT groups or on the day of diagnosis for the men who received no radical local treatment. Follow-up ended on 31st December 2018 up to a maximum of four years.

A multivariate Fine and Gray competing-risk analysis was used to estimate subdistribution hazard ratios (HRs) with 95% confidence intervals (CIs) to compare PCSM rates between PSA groups for each treatment category (no radical local treatment, RP, EBRT and EBRT + BT) [14]. Survival time was censored on the date of death if death was from a competing cause. An interaction term was included between PSA level and PCa grade (high versus low/intermediate). Wald tests were performed to test interaction. The proportional hazards assumption was examined using Schoenfeld residuals. We also included PSA as a continuous variable using a multivariable Cox proportional hazards restricted cubic spline regression analysis with three to seven interior knots to allow for non-linear associations. The number of knots to be included in the final model was chosen to minimise the Akaike Information Criterion [15] and knot location was based on Harrell's recommended percentiles [16]. The lowest Akaike Information Criterion was seen with 5 knots.

All regression analyses included age, ethnicity (white, Asian, black or other), number of comorbidities (0, 1, 2 or more), socioeconomic deprivation status (national quintiles), pre-treatment T-stage (T1/2 and T3/4) and year of diagnosis. Radiotherapy dose and the use of pelvic lymph node irradiation were also included within the regression models for the EBRT group. Patients with missing Gleason score were excluded from our analysis; other missing data were imputed using multiple imputations by chained equations and 10 imputed data sets were created, for which study estimates were combined using Rubin's rules [17]. All statistical analysis was conducted using Stata version 15.1 (StataCorp, College Station, Texas, USA).

3. Results

We identified 102,147 men diagnosed with clinically localised PCa during the study period. Exclusions were made if any treatment date predated the diagnosis date (n = 58), giving a final cohort of 102,089, of whom 71,138 had low/intermediate-grade and 22,425 high-grade PCa as defined above with a median follow-up of 31 months from diagnosis (Table 1). Gleason grade was missing in 8526 and PSA was missing in 23,149 men; the proportion of men with missing PSA was similar for men with low/intermediate or high-grade PCa but it was higher if Gleason grade was also missing (Supplementary table 1).

Of the 71,138 men with low/intermediate-grade disease, 28,835 (40.5%) men did not receive radical local treatment whereas 18,665 (26.2%), 22,177 (31.2%) and 1461 (2.1%) men were treated with RP, EBRT and EBRT + BT, respectively. Of the 22,425 men with high-grade disease, 5448 (24.3%) men did not receive radical local treatment whereas 4184 (18.7%), 11,790 (52.6%) and 1003 (4.5%) men were treated with RP, EBRT and EBRT + BT, respectively. Among men with high-grade PCa, there were 551 PCa deaths in men not receiving radical local treatment compared to 215, 18 and 11 PCa deaths in the EBRT, RP and EBRT + BT groups, respectively (Fig. 1). For reference, there were 770 non-PCa deaths in men who did not receive radical local treatment compared to 436, 59 and 15 PCa deaths in the EBRT, RP and EBRT + BT groups, respectively. Given the low event numbers in the RP and EBRT + BT cohorts, regression analyses were only completed for patients who did not receive radical local treatment and for those having EBRT.

In men with high-grade PCa who received no radical local treatment, the 4-year cumulative PCSM was 19.4%, 12.5%, 11.1% and 19.7% for PSA groups $\leq$5, 5.1–10, 10.1–20 and $>$ 20 ng/mL, respectively (Table 2). PCSM was higher in men with PSA $\leq$5 ng/mL than in men with a PSA 5.1–10 ng/mL (HR 1.99 95% CI 1.33–2.98). By contrast, this pattern was not seen in men with low/intermediate-grade PCa who did not receive radical local treatment. In this group, PCSM increased in a linear fashion with increasing PSA. The 4-year cumulative PCSM here was 0.5%, 0.8%, 2.3% and 5.1% for PSA groups $\leq$5, 5.1–10, 10.1–20 and $>$ 20 ng/mL, respectively. A Wald test confirmed that PCa grade was an effect modifier of the association between PSA and PCSM for men who did not receive radical local treatment ($P < 0.001$).

Table 1
Characteristics of men with localised prostate cancer stratified by grade.

	Low/intermediate-grade		High-grade		Missing grade		Total	
	No.	%	No.	%	No.	%	No.	%
Age (years)								
<60	11,512	16.2	1722	7.7	327	3.8	13,561	13.3
60–69	28,786	40.5	7186	32	1098	12.9	37,070	36.3
70–79	26,808	37.7	10,477	46.7	2248	26.4	39,533	38.7
≥80	4032	5.7	3040	13.6	4853	56.9	11,925	11.7
Number of comorbidities (RCS Charlson score)								
0	55,864	78.5	16,988	75.8	6097	71.5	78,949	77.3
1	10,761	15.1	3665	16.3	1341	15.7	15,767	15.4
≥2	4513	6.3	1772	7.9	1088	12.8	7373	7.2
Ethnicity								
White	62,116	92.1	19,973	93.5	7653	94.3	89,742	92.6
Asian/Asian British	1321	2	411	1.9	154	1.9	1886	1.9
Black/Black British	2885	4.3	666	3.1	205	2.5	3756	3.9
Other	1109	1.6	312	1.5	102	1.3	1523	1.6
Missing	62,116	92.1	19,973	93.5	7653	94.3	89,742	92.6
Deprivation status (national quintiles)								
1 (least deprived)	17,044	24	5280	23.5	1902	22.3	24,226	23.7
2	17,729	24.9	5600	25	2107	24.7	25,436	24.9
3	14,726	20.7	4771	21.3	1866	21.9	21,363	20.9
4	12,180	17.1	3722	16.6	1491	17.5	17,393	17
5 (most deprived)	9459	13.3	3052	13.6	1160	13.6	13,671	13.4
PSA (ng/ml)								
≤5	8565	15.5	1215	6.8	371	6.3	10,151	12.9
5.1–10	25,766	46.7	5108	28.6	1090	18.5	31,964	40.5
10–20	13,662	24.8	5167	28.9	1182	20.1	20,011	25.3
>20	7201	13	6371	35.7	3242	55.1	16,814	21.3
Missing	15,944		4564		2641		23,149	
T-stage								
T1	14,588	20.6	1667	7.5	714	9.4	16,969	16.8
T2	38,132	53.8	7607	34.2	3166	41.9	48,905	48.6
T3	17,915	25.3	12,222	54.9	3136	41.5	33,273	33
T4	279	0.4	750	3.4	547	7.2	1576	1.6
Missing	224		179		963		1366	
Diagnosis year								
2014	12,110	17	3562	15.9	1673	19.6	17,345	17
2015	17,629	24.8	5398	24.1	2116	24.8	25,143	24.6
2016	18,022	25.3	5894	26.3	2010	23.6	25,926	25.4
2017	18,487	26	5931	26.4	2157	25.3	26,575	26
2018	4890	6.9	1640	7.3	570	6.7	7100	7
Local treatment								
No local treatment	28,835	40.5	5448	24.3	7349	86.2	41,632	40.8
RP	18,665	26.2	4184	18.7	138	1.6	22,987	22.5
EBRT	22,177	31.2	11,790	52.6	982	11.5	34,949	34.2
EBRT + BT	1461	2.1	1003	4.5	57	0.7	2521	2.5

In men with high-grade PCa treated with EBRT, the 4-year cumulative PCSM was 7.8%, 3.8%, 2.0% and 4.8% for PSA groups ≤5, 5.1–10, 10.1–20 and > 20 ng/mL, respectively. PCSM was higher in men with PSA ≤5 ng/mL than in men with a PSA 5.1–10 ng/mL (HR 1.96 95% CI 1.15–3.34). This pattern was not seen in men with low/intermediate-grade PCa treated with EBRT, where PCSM increased in a linear fashion with increasing PSA. The 4-year cumulative PCSM in the patients having low/intermediate-grade PCa with EBRT was 0.5%, 0.5%, 0.8% and 1.4% for PSA groups ≤5, 5.1–10, 10.1–20 and > 20 ng/mL, respectively. A Wald test provided only borderline evidence to suggest that grade of PCa was an effect modifier on the association between PSA and PCSM for this group of men treated with EBRT, but interaction could not be confirmed ($P = 0.152$) (Table 2).

In men with high-grade PCa treated with EBRT + BT, the 4-year cumulative PCSM was 3.8%, 1.9%, 9.8% and 6.4% for PSA groups ≤5, 5.1–10, 10.1–20 and > 20 ng/mL, respectively. In men with high-grade PCa treated with RP, the 4-year cumulative PCSM was 0.9%, 1.6%, 1.5% and 2.9%% for PSA groups ≤5, 5.1–10, 10.1–20 and > 20 ng/mL, respectively.

Results from the restricted cubic spline regression analysis are shown in Fig. 2. This confirms that there is a

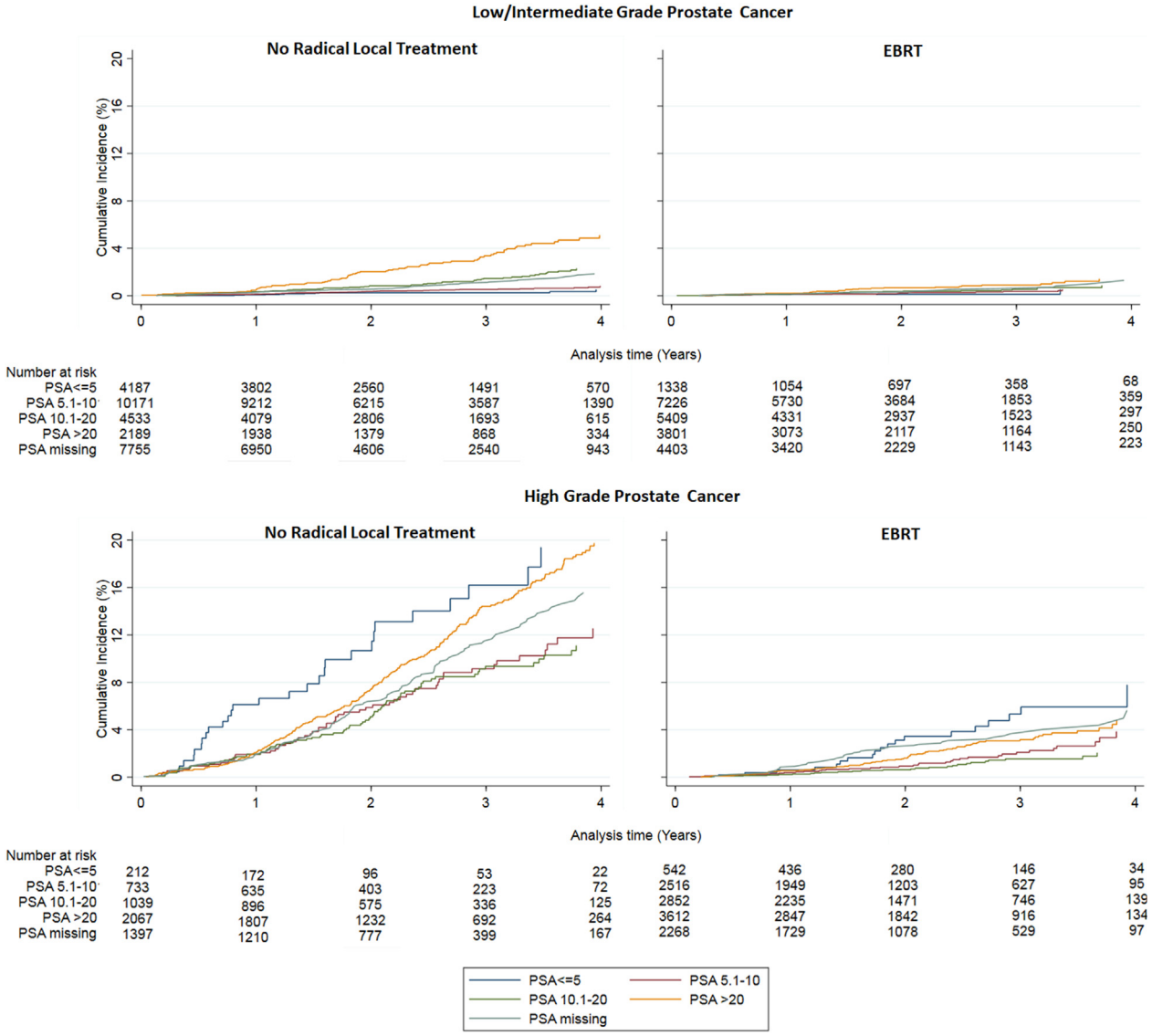

Fig. 1. Prostate cancer specific mortality stratified by PSA according to grade (low/intermediate-grade: Gleason 7 or less in top row and high-grade: Gleason 8 or more in bottom row) and the treatment received (no local treatment in left column and EBRT in right column). EBRT, external beam radiotherapy; PSA, prostate-specific antigen.

non-linear association between PSA and PCSM in men with low PSA secreting high-grade PCa. However, in low/intermediate-grade disease, the pattern was different, with an increasing rate of PCSM as the PSA increased.

4. Discussion

The national level data presented herein, which is collected and reported annually, suggest that men who low PSA secreting high-grade PCa have a less favourable outcome than men with high-grade disease producing intermediate and high PSA levels. The data relating to surgery suggest that the rate of failure using this modality might be lower, but the numbers studied and the length of follow-up are inadequate for definitive interpretation, although this trend in the data does warrant further investigation.

Our results add to the existing data on the relationship between PSA levels and oncological outcomes in PCa [1–5]. The first description of a poorer outcome in men with high-grade PCa but low PSA was reported using data from the Surveillance, Epidemiology and End Results program [2]. This observation was confirmed by the same group of authors by adding 494,793 men clinical data from the National Cancer Data Base [1]. In addition, the authors observed a linear association between PSA and oncological outcomes in low/intermediate-grade PCa. Similar to our UK cohort, the authors used a large sample size with only a limited follow-up of 49 and 25 months.

Further among 4960 men from the Decipher Genomic Resource Information Database, a higher expression of neuroendocrine/small-cell markers was observed in high-grade PCa with low PSA compared to

Table 2
Prostate cancer specific mortality in men with localised prostate cancer according to PSA stratified by cancer grade and the treatment received.

	No radical local treatment			EBRT		
	4-year Cumulative Incidence % (95% CI)	Adjusted HR (95% CI)	*P* value	4-year Cumulative Incidence % (95% CI)	Adjusted HR (95% CI)	*P* value
Low/intermediate-grade						
≤5	0.5 (0.2–1.0)	1.06 (0.62–1.81)		0.5 (0.1–2.0)	1.03 (0.31–3.42)	
5.1–10	0.8 (0.6–1.1)	1	**<0.001**	0.5 (0.3–0.9)	1	0.118
10.1–20	2.3 (1.7–3.0)	**2.08 (1.48–2.92)**		0.8 (0.5–1.4)	1.15 (0.63–2.10)	
>20	5.1 (3.9–6.5)	**4.09 (2.94–5.68)**		1.4 (0.9–2.1)	**1.92 (1.13–3.25)**	
High-grade						
≤5	19.4 (12.7–27.1)	**1.99 (1.33–2.98)**		7.8 (4.0–13.1)	**1.96 (1.15–3.34)**	
5.1–10	12.5 (9.3–16.3)	1	**<0.001**	3.8 (2.4–5.8)	1	**0.002**
10.1–20	11.1 (8.7–13.8)	0.97 (0.74–1.28)		2.0 (1.3–3.1)	0.67 (0.41–1.10)	
>20	19.7 (17.4–22.1)	**1.59 (1.26–2.02)**		4.8 (3.5–6.3)	1.24 (0.83–1.84)	

high-grade PSA without PSA <2.5 ng/mL [1]. The poor outcomes of men with high-grade PCA and very low PSA levels of 2.5 ng/mL was further confirmed in two prostatectomy cohorts [4,5]. With a longer follow-up of 13 years, which is substantially longer than all previously discussed reports, our group modelled PSA as a continuous variable using data from 4908 men in the Health Professionals Follow-up Study (HPFS). Our analyses revealed that there is no single cut-off for PSA but rather a subgroup of patients with high-grade PCa with a PSA of around 5–10 ng/mL with the best oncological outcome whereas lower or higher PSA levels were associated with poorer outcomes.

The current manuscript supports previous findings and adjustments for important confounders including socioeconomic status. The large size of this national dataset strengthens the prior observation that clinically localised PCa has a non-linear association with PSA in both low/intermediate and high-grade PCa. However, in the latter, the observed relationship is the opposite of that seen with low/intermediate-grade disease given that the lowest PSA values are associated with a much higher PCSM ('J-shaped'). The results raise important questions about the biology and natural history of low PSA secreting high-grade PCa. In addition, the observed non-linear association of PSA and high-grade disease with PCSM is relevant to identifying patients whose response to standard therapy is much worse, highlighting the need to test alternative treatment approaches in this setting and to continue to focus outcome-based research on better biomarkers, improved prognostic/predictive models and new approaches to treatment.

Whilst our data are unable to explain fully the true basis of the adverse association of high-grade and low PSA PCa, our results do re-emphasise that our contemporary treatment strategies are sub-optimal and that there is an imperative to plan new studies addressing novel detection and treatment and to re-visit our 'standard' approaches in this area of oncology. The biology underpinning our observations is incompletely understood but low PSA secreting high-grade PCa clearly has a more aggressive biopotential, further exemplified by the greater preponderance for local progression and metastases to the viscera in these tumour types [18]. This may significant implications for the management of PCa. Further studies are required to assess how low PSA secreting high-grade PCa could be detected without PSA screening e.g. new screening methods like magnetic resonance imaging. In addition, neoadjuvant treatment options [19] and local treatment should be studied in clinical trials. Last, the need for genetic counselling and PSA-based or imaging-based follow-up should be investigated.

There are limitations and strengths in this analysis. The NPCA cohort had a relatively short follow-up, but notwithstanding this, the study size was large and there were a significant number of early PCa deaths recorded. Furthermore, our observation regarding survival is recapitulated in results from similar M0 patients in the STAMPEDE trial who were treated with ADT and EBRT [20]. The registration of the cause of death is a legal requirement in England and Wales; nevertheless, the misclassification of PCSM might also be present in the NPCA data set: previous reports comparing the causes of death as registered on death certificates with those in autopsy reports showed disagreements in up to a third of cases [21]. However, this potential pitfall should not have influenced our results as we compared data within and not between different treatment modalities. The lacking information about the use and duration of ADT represent another limitation as the time point (neoadjuvant/concomitant/adjuvant) and duration of ADT impact oncological outcomes [22,23]. Of mention is the large proportion of men with localised high-grade PCa who did not receive local treatment in our cohort, probably because of older age and frailty. Of the newly presenting men with high-risk disease in England, a substantial proportion were very elderly and with multiple comorbidities precluding more aggressive treatment [24].

A further reason to avoid comparison between treatment groups reflects unmeasured confounding

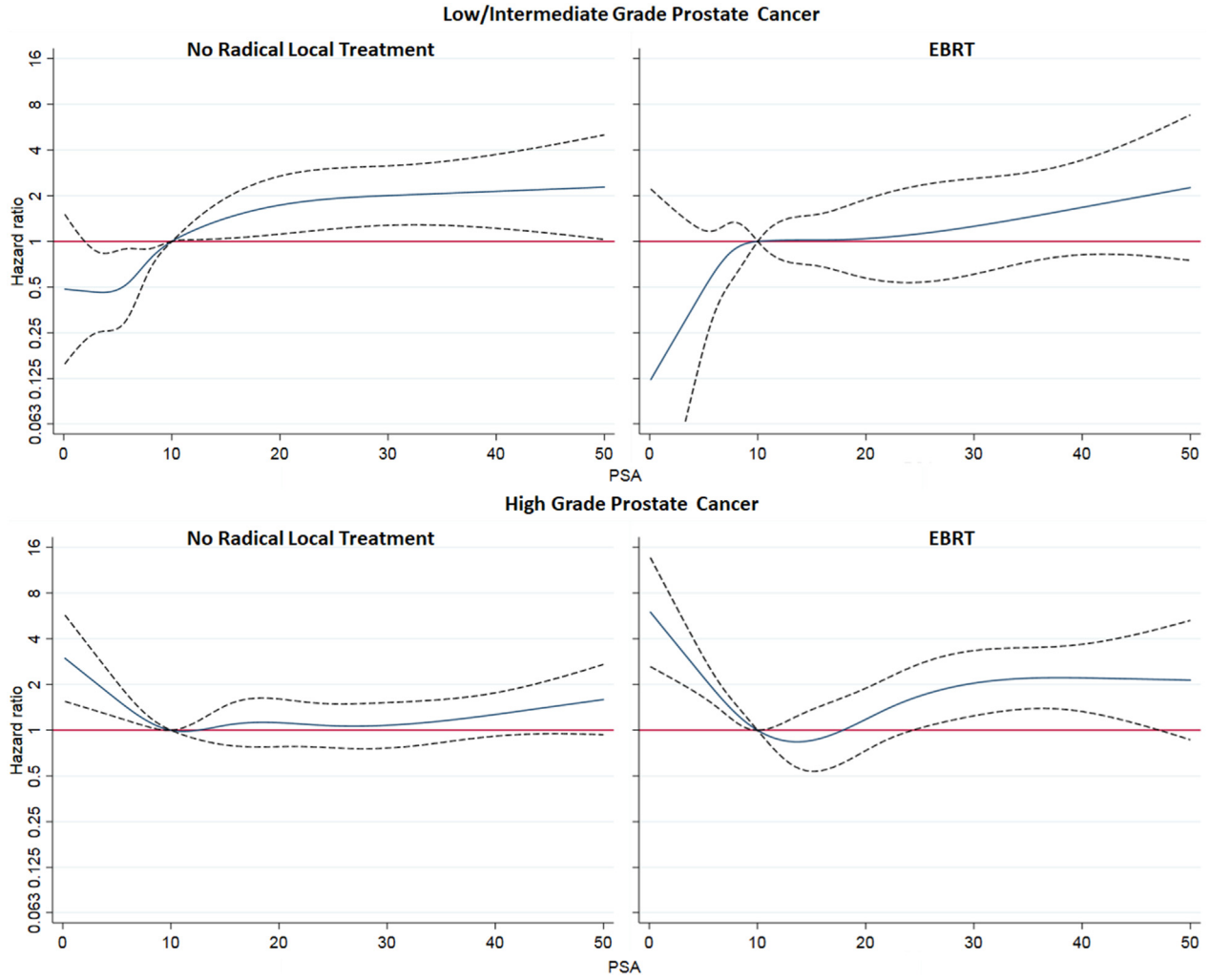

Fig. 2. The relationship between prostate-specific antigen (PSA) and prostate cancer specific mortality for men with low/intermediate-grade (Gleason Score ≤7: top row) and high-grade (Gleason Score ≥8: bottom row) and localised prostate cancer using restricted cubic splines stratified by no local treatment (left side) and external beam radiation therapy (EBRT) (right side). The solid blue curve represents point estimates, and the dotted lines represent the 95% confidence intervals. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

because of missing or unmeasurable data in our dataset. This includes the absence of tumour volume and local T-stage, PCa family history or PSA which all may represent potential confounders influencing the outcomes after RP or EBRT. Reasons for a high proportion of missing PSA values could either be the clinician treating a patient without a PSA value or the omission of PSA entries into the database. However, we feel that in current practice, it would be highly unlikely that a treating clinician would proceed with any PCa treatment without having first measured the PSA. Our view is, therefore, that missing PSA are more likely to a failure to enter the PSA by staff coders in the coding process.

Strength of our analysis is the use of high-quality 'real-world' data on a national scale and the concomitant use of contemporary treatment options with adjustment for important confounders in patient subgroups. Multi-modal treatment is not currently practised routinely in RP patients treated in the England, whereas multi-modal therapy is a standard of care for those treated with EBRT. Currently, treatment of high-risk PCa differs between regions as demonstrated in a recent comparison of the Surveillance, Epidemiology and End Results program and NPCA data showing that RP were more frequently used in the United States whereas in England EBRT is more commonly applied [25]. Thus, the data in this sense are paradoxical and unexplained. Further commentary relating to this would need to be the subject of future reports.

A further positive factor is that 95% of men diagnosed with PCa in England undergo treatment in the NHS, where radical surgery and EBRT is centralised to high volume multi-disciplinary treatment centres whose outcomes are monitored annually by the NPCA. The contemporary study period (2014–2018) also adds

confidence that modern diagnostic, staging, and treatment methods were used. With any large database, data accuracy relies on the clinical coding in routinely collected electronic administrative hospital systems. The accuracy of the routine HES data utilised by the NPCA data has been shown to be high when compared to data extracted from clinical notes and it is as high as 90% for procedure codes [26].

5. Conclusion

In conclusion, the association between PSA and PCSM may not be non-linear and low PSA secreting high-grade PCa tumours have a more aggressive phenotype. This has potential implications for future PCa detection, treatment and post treatment monitoring. The data regarding treatment of low PSA secreting high-grade PCa with surgery are inadequate for definitive comment but the data trend suggest that further study in this area is required to establish clearly whether treatment with surgery in this setting might improve outcomes.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.12.017.

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