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Clinical features of neuroendocrine prostate cancer

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Abstract

Background: Neuroendocrine prostate cancer (NEPC) is an aggressive variant of prostate cancer that may arise *de novo* or in patients previously treated with hormonal therapies for prostate adenocarcinoma as a mechanism of resistance. Despite being important to recognise, the clinical features of NEPC are poorly defined and could help guide when to perform a biopsy to look for NEPC histologic transformation.

Methods: We reviewed baseline, treatment and outcome data of 87 patients with metastatic prostate cancer and tumour biopsy confirming NEPC histology. Forty-seven (54.0%) NEPC cases presented *de novo*, and 40 (46.0%) were therapy-related (t-NEPC). Thirty-six (41.4%) were

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Conflict of interest statement

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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.2019.08.011.

classified as pure small-cell carcinoma, and 51 (58.6%) demonstrated mixed features with both small-cell carcinoma and adenocarcinoma present. Genomic data were available for 47 patients.

Results: The median age at time of NEPC was 68.1 years, median prostate-specific antigen (PSA) was 1.20 ng/ml (0.14 ng/mL small-cell carcinoma, 1.55 ng/mL mixed carcinoma) and sites of metastases included bone (72.6%), lymph node (47.0%), and viscera (65.5%). Median time from adenocarcinoma to t-NEPC diagnosis was 39.7 months (range, 24.5–93.8) with a median of two lines of prior systemic therapy. Platinum chemotherapy was used to treat 57.5% of patients, with a median progression-free survival of 3.9 months. Small-cell carcinoma was associated with worse overall survival (OS) than mixed histology (8.9 months from NEPC diagnosis versus 26.1 months, $P < 0.001$). Median OS of *de novo* NEPC was shorter than that of t-NEPC (16.8 months from prostate cancer diagnosis versus 53.5 months, $P = 0.043$). An average PSA rise per month of ≤0.7 ng/ml before t-NEPC; elevated lactate dehydrogenase levels, *RB1* and *TP53* loss and liver metastases were poor prognostic features.

Conclusions: We describe the clinical features of a cohort of patients with NEPC. These characteristics may inform future diagnostic strategies.

Keywords

Neuroendocrine prostate cancer; Aggressive variant; Small-cell carcinoma; Treatment resistance

1. Introduction

Prostate cancer is the most common cause of cancer in men in the United States and Europe and the second leading cause of cancer death [1]. The vast majority of patients present with prostate adenocarcinoma, a tumour type that displays morphologic characteristics reminiscent of luminal prostate cells, is driven by androgen and is typically associated with elevated serum prostate-specific antigen (PSA). Rarely, patients may present with *de novo* small-cell carcinoma of the prostate, a poorly differentiated neuroendocrine carcinoma with similar histology as small-cell lung cancer (SCLC) and other small-cell carcinomas [2,3]. These patients are typically treated with platinum-based chemotherapy using SCLC regimens [4–6]. It has been recently recognised that small-cell prostate cancer may also develop in later stages of prostate cancer progression in up to 15–20% of patients treated with hormonal therapies for prostate adenocarcinoma [7–10]. This histologic transformation occurs as a mechanism of treatment resistance [7,11]. Because there is a disease spectrum as patients evolve from prostate adenocarcinoma to small-cell carcinoma, either pure or mixed histologic features may be seen within this continuum. Therefore, the term ‘neuroendocrine prostate cancer (NEPC)’ is commonly used to encompass both small-cell carcinoma and mixed tumours with both prostate adenocarcinoma and small-cell morphologies present [3]. Patients developing treatment-related NEPC (t-NEPC) are also considered for similar platinum chemotherapy regimens [5,12]. Because of these important clinical implications, the National Comprehensive Cancer Network (NCCN) guidelines were recently updated to include consideration of metastatic biopsy in any patient with castration-resistant prostate cancer (CRPC) to look for t-NEPC transformation [6]. The clinical features of *de novo* NEPC and t-NEPC are poorly defined and may help further guide when to perform a biopsy, patient counselling and therapy choice. Defining clinical features, potentially in combination

with recently identified NEPC molecular features (e.g. *RB1* and *TP53* loss) [7,8,10,13,14], may also inform the development of inclusion criteria for new clinical trials geared towards this aggressive prostate cancer subtype.

2. Materials and methods

2.1. Patient cohort

Patients with metastatic prostate cancer and a metastatic biopsy confirming pathologic features of NEPC were retrospectively identified at Weill Cornell Medicine (WCM) between 2004 and 2017. NEPC was defined by the presence of either pure small-cell carcinoma (by tumour morphology) or mixed histology with both adenocarcinoma and small-cell/neuroendocrine carcinoma present (mixed) using published criteria [5] (Supplementary Table S1 and Fig. S1). Patients with NEPC were further classified as either *de novo* if at the time of NEPC diagnosis they had no prior diagnosis or treatment for prostate adenocarcinoma or *therapy-related* if they had received prior androgen deprivation therapy (ADT) for a previous diagnosis of prostate adenocarcinoma.

The choice of systemic therapies after the diagnosis of NEPC was at the discretion of the treating physician and according to pathological findings and clinical features and included ADT, potent androgen receptor (AR)–targeted therapies (e.g. enzalutamide, abiraterone), chemotherapy (e.g. docetaxel, cabazitaxel, platinum) and investigational agents. Treatments were administered continuously until evidence of progression disease or unacceptable toxicity or for a planned number of cycles in the case of chemotherapy according to regime-specific protocols. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. The protocol was approved by the WCM Institutional Review Board (IRB#1305013903 and IRB#0905010441).

Clinical and demographic information was collected by medical record review.

When available, metastatic tumour genomic status of select genes (i.e. *AR*, *TP53*, *RB1*, *BRCA2*, *BRCA1*, *ATM*) was collected from review of whole-exome sequencing (WES) data obtained through a Clinical Laboratory Improvement Amendments/Clinical Laboratory Evaluation Program (CLIA/CLEP) compliant tumour/normal WES assay (EXaCT-1; IPM-Exome-pipeline, version 0.9) [15,16]. In addition, for cases with adequate fresh/frozen tissue, RNA sequencing data were evaluated to assess the expression of AR-signalling genes and integrated NEPC score. The AR score was calculated based on the expression levels of 30 genes and methods previously described [10,17]. The NEPC score is a panel of 70 genes described in the study by Beltran *et al.* [10].

2.2. Outcomes

The primary aim was to evaluate NEPC overall survival (OS) calculated from the time of initial prostate cancer diagnosis, of metastatic disease and of NEPC diagnosis and time to progression on different treatments. Patients still alive at the time of the last follow-up were censored.

2.3. Statistical analysis

Clinical characteristics at the time of biopsy confirming NEPC were reported, including sites of metastases and laboratory values. PSA values in the preceding six months were used to estimate the average monthly increase in PSA. Clinical, where available, and genomic characteristics were compared across *de novo* versus t-NEPC and mixed versus small-cell carcinoma.

Kaplan-Meier estimates and log-rank tests were used to compare *de novo* NEPC with t-NEPC.

3. RESULTS

3.1. Clinical characteristics of NEPC

Eighty-seven patients with metastatic prostate cancer and metastatic biopsy confirming NEPC histology [51 (58.6%) mixed carcinoma, 36 (41.4%) small-cell carcinoma] were identified. Forty-seven (54.0%) patients presented *de novo* NEPC, and 40 (46.0%) presented t-NEPC (Fig. 1). Serum PSA at the time of NEPC diagnosis was available in 61 (70.1%) patients, and at least one PSA in the six months before NEPC diagnosis was available in 28 (32.2%) patients.

The median age at the time of NEPC diagnosis was 68.1 years (interquartile range [IQR]: 59.6–75.3; 67.2 [56.5–74.5] for *de novo*; 69.5 [61.8–77.2] for t-NEPC, $P = 0.065$). Median PSA was 1.20 ng/ml (IQR: 0.05–13.4; 0.21 [0.04–3.49] *de novo*; 3.34 [0.16–15.4] t-NEPC, $P = 0.085$). For patients with t-NEPC, the average percent PSA rise per month before t-NEPC biopsy diagnosis was 16%. Serum chromogranin A (CGA) and lactate dehydrogenase (LDH) were elevated in 48.3% (14/29) and 62.5% (20/32) of patients with NEPC, respectively.

Thirty-nine (44.8%) patients with NEPC had presented with metastases at the time of their initial prostate cancer diagnosis (57.4% *de novo* NEPC, 30.0% t-NEPC), and another 48 patients had clinically localised prostate cancer with a median time to metastatic disease of 26.5 months (IQR: 3.96–69.4). For patients who had localised disease, 21 of 48 (43.8%) underwent prostatectomy (6/20 of localised *de novo* cases), 25 of 48 (52.1%) received radiotherapy (11/20 of localised *de novo* cases), 8 of 48 (16.3%) received both prostatectomy and radiotherapy (all adenocarcinoma before t-NEPC) and 11 of 48 received chemotherapy in addition to radiation (all *de novo* NEPC); two patients did not have their primary tumour treated. For patients with t-NEPC, primary tumours were of high-grade Gleason score ≥8 adenocarcinomas in 66.7% of cases; on retrospective review, 58.6% had evidence of neuroendocrine differentiation in their primary tumour (61% mixed with Gleason 9–10). The remaining cases were two Gleason score 6 (3 + 3) and nine Gleason score 7 [55.6% (4 + 3) and 44.4% (3 + 4)]. Clinical and pathological features of patients with NEPC at the time of their prostate cancer diagnosis are included in Table 1.

We did not identify significant clinical differences between patients with *de novo* NEPC ($n = 47$) with a diagnosis of mixed ($n = 26$) versus pure small-cell carcinoma ($n = 21$), other than

a higher incidence of radiotherapy treatment in patients with small-cell carcinoma [13/21 (61.9%) versus 6/26 (23.1%), $P = 0.016$] (Table 2).

3.2. Survival outcomes by clinicopathological features of NEPC and response to different treatments

The median OS for patients with NEPC calculated from the time of initial prostate cancer diagnosis was 54.4 months (95% confidence interval [CI]: 38.8–118.3 months; Fig. 2A). OS from the time of metastatic disease was 25.4 months, and OS from the time of NEPC biopsy diagnosis was 16.8 months (95% CI: 10.3–25.3 months; Fig. 2B).

Within NEPC, we observed a significant difference in OS between those with mixed histology versus those with small-cell carcinoma (median OS from prostate cancer diagnosis: 71.6 months mixed versus 22.0 months small-cell [log-rank $P = 0.030$]; OS from metastatic disease: 33.5 months mixed versus 15.9 months small-cell [log-rank $P = 0.006$]; OS from NEPC diagnosis: 26.1 months mixed versus 8.9 months small-cell [log-rank $P < 0.001$]) (Fig. 2C and D). In addition, the median OS time from the time of initial prostate cancer diagnosis of patients with NEPC who presented *de novo* NEPC ($n = 53$) was shorter than those who presented t-NEPC ($n = 34$) (median OS from prostate cancer diagnosis: 16.8 months *de novo* versus 53.5 months *therapy-related* [log-rank $P = 0.043$]), although OS did not differ from the time of metastatic disease (log-rank $P = 0.60$) or the time of NEPC diagnosis (log-rank $P = 0.19$) (Fig. 2E and F). A histology of small-cell carcinoma, average PSA rise per month of ≤ 0.7 ng/ml, elevated LDH level and presence of liver metastasis before t-NEPC diagnosis were clinical factors significantly associated with worse outcomes in patients with t-NEPC (Table 3).

Among the 47 patients with NEPC that presented *de novo*, 30 (63.8%) were treated with primary ADT and 7 (14.8%) subsequently went on to receive abiraterone or enzalutamide. These patients all had mixed histology at diagnosis. Sixty-six percent (31/47) of *de novo* patients received chemotherapy alone. The most common first-line chemotherapy regimens included platinum doublet ($n = 25$; 4 with taxane, 21 with etoposide) or docetaxel ($n = 3$), and second-line regimens included platinum alone ($n = 1$), platinum doublet with etoposide ($n = 4$) or docetaxel ($n = 4$).

Among *de novo* patients, median radiographic progression-free survival (PFS) on first-line therapy was 4.89 months [95% CI: 3.84–8.49] overall, 3.84 months [95% CI: 3.57–11.48] for platinum, 3.92 months [95% CI: 3.84–not reached (nr)] for taxane; 7.93 months [95% CI: 7.02–nr] for ARPI. Median PFS on second-line therapy was 2.33 months [95% CI: 2.00–3.02] overall, 2.52 months [95% CI: 1.31–nr] for platinum and 2.0 months [95% CI: 1.31–nr] for ARPI.

Among the 40 patients with t-NEPC, the median number of prior lines of systemic therapy before t-NEPC diagnosis was two [IQR: 1–3]. Median PFS on prior abiraterone or enzalutamide ($n = 6$) was 5.16 months [95% CI: 3.05-nr]. After t-NEPC diagnosis, median PFS on subsequent androgen receptor pathway inhibition (ARPI) ($n = 11$) was 3.07 months [95% CI: 1.77–nr]. Patients were treated with chemotherapy including platinum alone ($n = 3$), platinum doublet ($n = 17$; 3 with taxane, 14 with etoposide) or docetaxel ($n = 4$). Five

patients did not receive any treatment after t-NEPC diagnosis. Second-line therapies included platinum doublet (n = 15; 12 with taxane, 3 with etoposide) or docetaxel (n = 4). Median PFS on platinum after NEPC diagnosis (any line of therapy) was 4.82 months [95% CI: 3.41–10.52] and 4.82 months [95% CI: nr–nr] for taxane therapy [alone (n = 8) and in combination with platinum (n = 15)].

3.3. Molecular landscape of neuroendocrine prostate cancer cases and treatment outcomes

Genomic data were available for 47 (54.0%) patients [24 (51%) *de novo*, 23 (49%) *therapy-related*] patients. The incidence of molecular alterations involving *AR*, *RB1*, *TP53*, DNA repair genes and AR-signalling gene expression score and NEPC score were similar in *de novo* versus t-NEPC (Table 1), as well as in small-cell carcinoma versus mixed tumours (Table 2).

In addition, we performed a comparison between NEPC subtypes and previously published adenocarcinoma cases (Fig. 3) [10,18]. As expected based on prior studies [8,10,19,20], NEPC tumours displayed a lower frequency of *AR* somatic alterations (12.8% versus 61.2%, $P < 0.001$) and had lower AR signalling (mean 0.21 versus 0.42, $P < 0.001$) and a higher frequency of *RB1* loss (76.6% versus 48.5%, $P = 0.002$) and *TP53* alterations (68.1% versus 50.5%, $P = 0.066$) than castration-resistant adenocarcinoma (Supplementary Table 2). Although the numbers were small, there were no significant differences in the frequency of these molecular features identified between *de novo* NEPC and t-NEPC or between pure and mixed tumours. After adjustment for the presence of liver metastases, only *RB1* and *TP53* co-occurrence was significantly associated with worse OS from the time of NEPC diagnosis in a univariate analysis of each molecular alteration (Table 4).

Moreover, we examined the impact of molecular alterations on response to different treatments and found that patients with *de novo* NEPC or t-NEPC treated with abiraterone or enzalutamide either before or after NEPC diagnosis showed no association between *AR* aberration and outcomes after treatment (PFS log-rank $P = 0.28$, OS $P = 0.15$), while patients with NEPC harbouring *RB1* and *TP53* alterations concurrently had a shorter PFS than those without both alterations ($P < 0.0001$), although OS did not significantly differ ($P = 0.18$).

In platinum-treated NEPC, there was no significant difference in outcome in AR-aberrant compared to AR-normal patients ($P = 0.12$ for PFS and $P = 0.062$ for OS), or with RB1 and TP53 alterations concurrently versus without ($P = 0.053$ for PFS and $P = 0.049$ for OS).

No significant impact of molecular factors on clinical outcome was observed in patients treated with taxane chemotherapy.

3.4. Exploratory castration-resistant prostate cancer patterns of early transformation to t-NEPC

We went back and reviewed the clinical features of 34 patients with t-NEPC at the time they had developed CRPC, before a diagnosis of t-NEPC was suspected clinically to warrant biopsy (Fig. 4). At the time of CRPC, median time from diagnosis of localised prostate

cancer was 32.6 months (IQR: 17.0–74.3 months), median time from progression after ADT treatment was 8.3 months (IQR: 4.12–17.8 months), median PSA was 2.0 ng/ml (IQR: 0.16–8.75), serum CGA was elevated above normal (>95 ng/ml) in 85.7% of cases (IQR: 177–533) and 24% of patients had liver metastases. Although we did not find that PSA changed significantly from CRPC to t-NEPC, patients who eventually developed t-NEPC had a progressive increase in serum neuroendocrine markers including CGA from initial diagnosis to CRPC ($P = 0.029$) and from CRPC to t-NEPC ($P = 0.018$), as well as neuron-specific enolase (NSE) (initial diagnosis to CRPC, $P = 0.086$; CRPC to t-NEPC, $P = 0.022$).

4. Discussion

NEPC is an aggressive subtype of prostate cancer that may arise *de novo* or manifest in the later stages of prostate cancer as a mechanism of treatment resistance. Patients with NEPC are often treated with chemo-therapy including platinum, given their pathologic and molecular similarities with SCLC [6,10,12]. In this study, we reviewed the clinical and pathological features of a cohort of patients with NEPC to provide insights into prognosis and other clinical variables that may aid in clinical management.

Aparicio *et al.* [12,13] have previously defined clinical features of aggressive variant prostate cancer, features similar to small-cell carcinoma (i.e. visceral or lytic bone metastases, bulky tumour, low PSA, short response to ADT) but without requiring biopsy, as inclusion criteria for platinum-based chemotherapy trials. Our study corroborated these findings and found that patients with pathologically confirmed NEPC harboured frequent visceral metastases, low PSA levels and frequent loss of *RB1* and *TP53* genes (suggesting less AR-driven disease). Platinum chemotherapy has also been investigated in patients with CRPC with or without neuroendocrine features, showing a moderate efficacy in terms of objective response rate, PSA response and PFS and a modest toxicity [12,21,22].

While patients with *de novo* versus t-NEPC as well as mixed versus small-cell seem to harbour similar molecular features based on interrogation of common alterations in a subset of our cases, we highlight distinguishing clinical features and response to systemic therapies. Particularly, we identified a worse outcome in patients with *de novo* diagnosis of NEPC and a histology of pure small-cell carcinoma versus mixed NEPC. Patients with NEPC were unlikely to benefit from AR pathway inhibitors, and our data suggest that they may respond less well to AR inhibitors even before t-NEPC diagnosis.

Notably, the explanation for this reduced survival on ARPI in the castration-resistant state may be attributed to the presence of clinical and molecular features (e.g. liver metastases, low PSA rise, neuroendocrine markers, *TP53* or *RB1* alterations) in patients before a confirmed clinical diagnosis of t-NEPC, as evidenced in our exploratory analysis. Similarly, Aggarwal *et al.* [23] also found in their cohort, including three patients with adenocarcinoma that later converted to t-NEPC, that molecular alterations such as lack of *AR* enhancer gain and loss of *RB1* may be detected before t-NEPC. Overall, these data suggest that early detection of individuals developing t-NEPC may help guide therapy choice away from hormonal agents and potentially towards more aggressive strategies for early intervention.

The identification of aggressive variants of prostate cancer, including when to perform a biopsy to look for NEPC or when to use platinum chemotherapy based on clinical features, remains challenging, and there is currently a lack of consensus [24]. Based on accumulating data, t-NEPC may be suspected in patients who develop rapidly progressive disease, unusual sites or pattern of metastases and/or progression in the setting of a low or modestly rising PSA. Better refinement and quantification of PSA kinetics in relation to radio-graphic progression requires further study, as this may better help identify patients with CRPC developing non–AR-driven disease. Metastatic tumour biopsies in this setting and potential molecular profiling could inform their proper management. Pure small-cell carcinomas may need to be managed more aggressively than mixed NEPC cases.

We recognise several limitations of our study including the retrospective non-randomised design, modest sample size, limited number of analysed metastatic biopsies with molecular data available and lack of complete clinical information for all cases. In addition, there is an introduction of bias from patient selection, as the choice of therapy was at the discretion of the treating physician, and, in some cases, patients received multiple therapies with possible cross-resistance phenomenon, thereby making it more complicated to assess treatment response. Finally, we only considered the most common genomic alterations of NEPC, but we could potentially evaluate several other molecular alterations and their clinical impact to obtain a comprehensive landscape of NEPC.

Despite these limitations, our findings provide new insights into the clinical hallmarks of NEPC, a distinct and aggressive subgroup of prostate cancer, that may be useful to improve the diagnosis and management of patients with prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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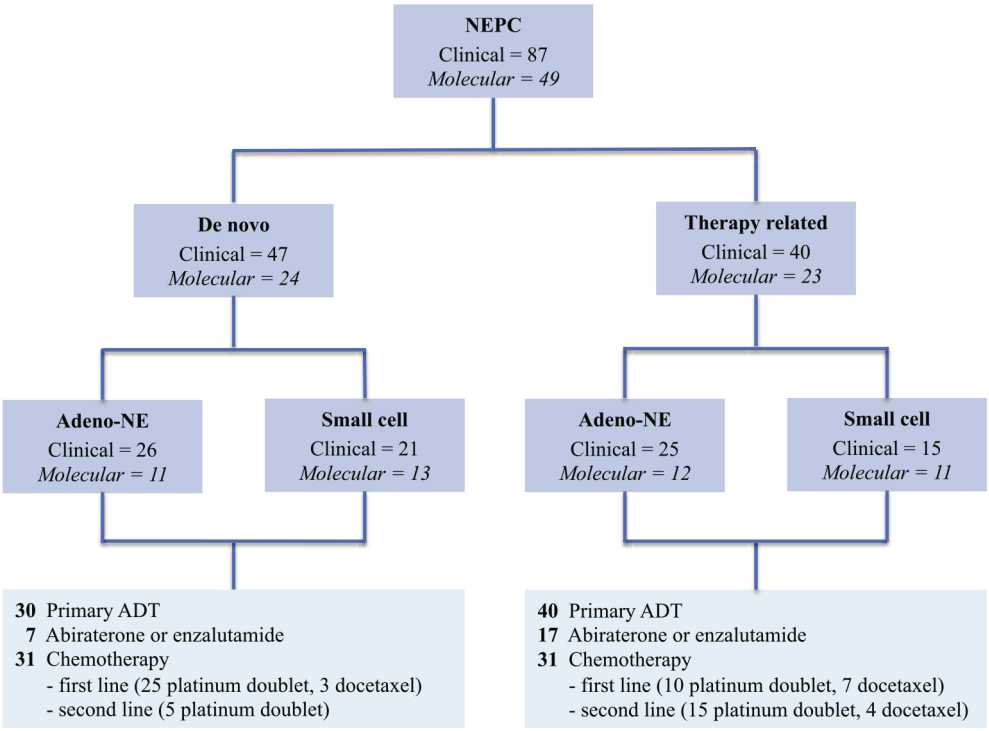

Fig. 1.

Flow chart of evaluable clinical and molecular profiling in patients with NEPC. NEPC, neuroendocrine prostate cancer; ADT, androgen deprivation therapy.

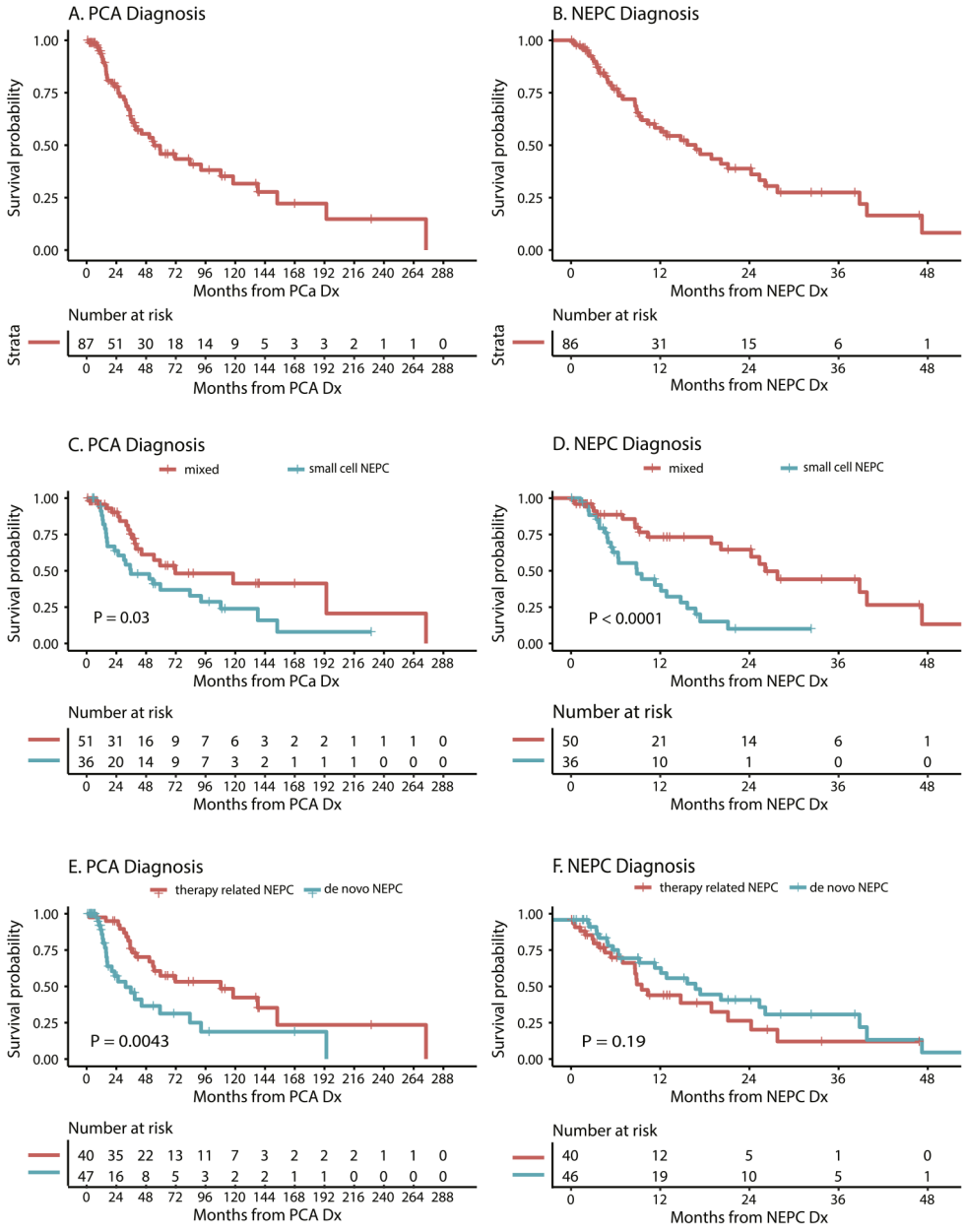

Fig. 2. Overall survival (OS) in a cohort of patients with NEPC.

OS from diagnosis of prostate cancer (PCA) (A) and from diagnosis of NEPC (B). OS in mixed versus small-cell carcinoma from diagnosis of PCA (C) and from diagnosis of NEPC (D). OS in *de novo* versus *therapy-related* NEPC from diagnosis of PCA (E) and from diagnosis of NEPC (F). In the X axis of survival curves, different time scales are used for A, C and E compared with B, D and F panels because of significant different time intervals between OS from PCA diagnosis and OS from NEPC diagnosis. NEPC, neuroendocrine prostate cancer.

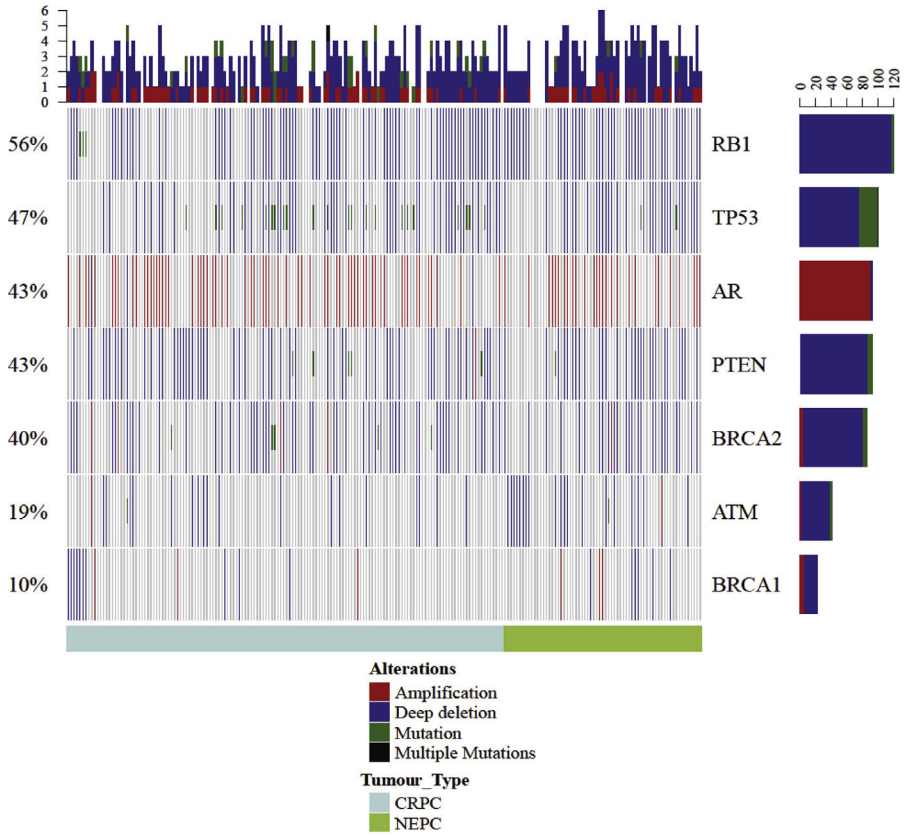

Fig. 3. Genomic landscape of NEPC and CRPC adenocarcinoma cases detected by whole-exome sequencing.

Genomic aberrations (point mutations and copy number variations) were for selected genes including *AR*, *TP53*, *RB1*, DNA repair pathway (*BRCA1*, *BRCA2*, *ATM*) and *PTEN*. NEPC, neuroendocrine prostate cancer; CRPC, castration-resistant prostate cancer.

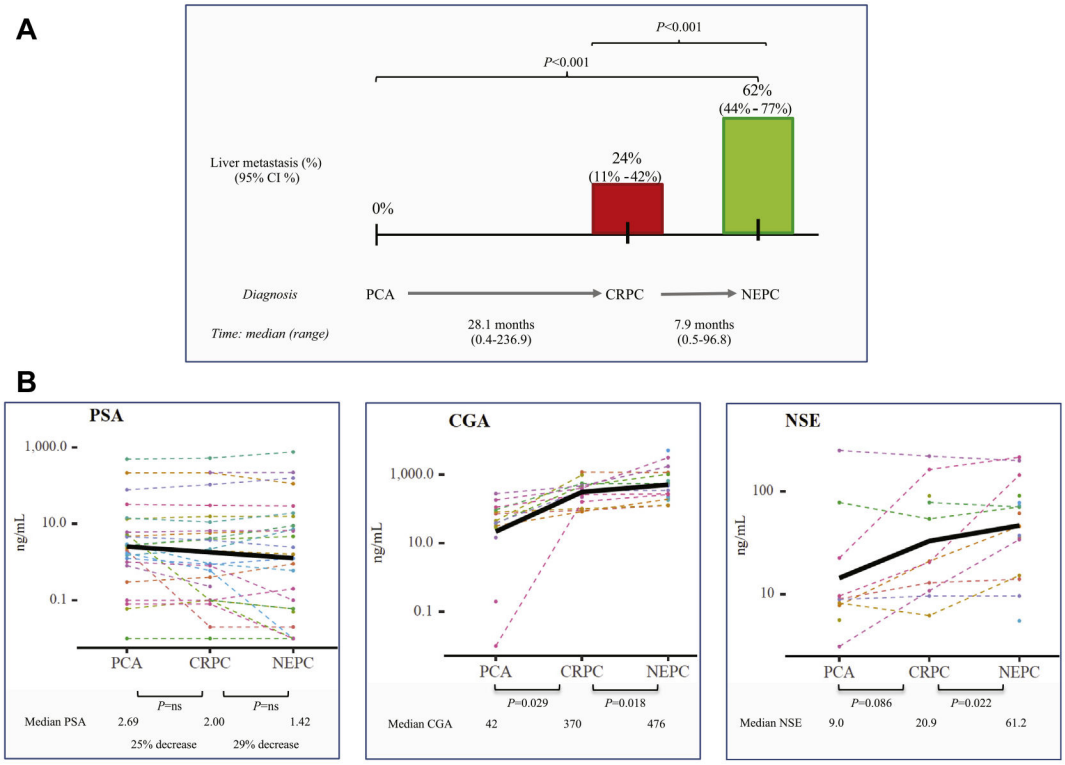

Fig. 4. Exploratory CRPC adenocarcinoma patterns of early transformation into NEPC.

Frequency of liver metastasis (A) and laboratory values (PSA, CGA, NSE) (B) at different time points from diagnosis of prostate cancer (PCA) through the castration-resistant state (CRPC) to the appearance of NEPC. NEPC, neuroendocrine prostate cancer; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; CGA, chromogranin A; NSE, neuron-specific enolase.

Table 1

Clinicopathological characteristics of patients with NEPC.

Characteristics	All *n* = 87	De novo *n* = 47	Therapy-related *n* = 40	P value
Age, years, median [interquartile range]	68.1 [59.6, 75.3]	67.2 [56.5, 74.5]	69.4 [61.8, 77.2]	0.11
NEPC Clinical Classification:				0.65
Mixed	51 (58.6%)	26 (55.3%)	25 (62.5%)	
Small-cell carcinoma	36 (41.4%)	21 (44.7%)	15 (37.5%)	
Radical radiotherapy				0.038
No	42 (48.3%)	28 (59.6%)	14 (35.0%)	
Yes	45 (51.7%)	19 (40.4%)	26 (65.0%)	
Prostatectomy				1.00
No	62 (71.3%)	33 (70.2%)	29 (72.5%)	
Yes	25 (28.7%)	14 (29.8%)	11 (27.5%)	
T staging				0.069
T1	2 (8.70%)	2 (18.2%)	0 (0.00%)	
T2	6 (26.1%)	1 (9.09%)	5 (41.7%)	
T3	13 (56.5%)	6 (54.5%)	7 (58.3%)	
T4	2 (8.70%)	2 (18.2%)	0 (0.00%)	
N staging				0.89
N0	16 (69.6%)	7 (63.6%)	9 (75.0%)	
N1	4 (17.4%)	2 (18.2%)	2 (16.7%)	
N2	1 (4.35%)	1 (9.09%)	0 (0.00%)	
Nx	2 (8.70%)	1 (9.09%)	1 (8.33%)	
Gleason score				1.00
< 8	21 (33.3%)	10 (34.5%)	11 (32.4%)	
≥ 8	42 (66.7%)	19 (65.5%)	23 (67.6%)	
Mets at PCA diagnosis				0.019
No	48 (55.2%)	20 (42.6%)	28 (70.0%)	
Yes	39 (44.8%)	27 (57.4%)	12 (30.0%)	
Mets at NEPC dx				0.044

Characteristics	All	De novo	Therapy-related	P value
	n = 87	*n* = 47	*n* = 40	
No	14(16.1%)	11 (23.4%)	3 (7.50%)	
Yes	72 (82.8%)	35 (74.5%)	37 (92.5%)	
Missing	1 (1.15%)	1 (2.13%)	0 (0.00%)	
Liver mets at NEPC dx				0.044
No	14 (16.1%)	11 (23.4%)	3 (7.50%)	
Yes	72 (82.8%)	35 (74.5%)	37 (92.5%)	
Missing	1 (1.15%)	1 (2.13%)	0 (0.00%)	
Time from PCA to mets dx, months, median [interquartile range]	26.5 [3.96, 69.4]	5.21 [0.75, 14.9]	40.1 [29.6, 107]	<0.001
Time from PCA to NEPC dx, months, median [interquartile range]	12.2 [1.33,48.9]	2.26 [0.00, 11.8]	39.7 [24.5, 93.8]	<0.001
Time from mets to NEPC dx, months, median [interquartile]	0.16 [0.00, 9.79]	0.00 [0.00, 6.50]	4.72 [0.00, 15.5]	0.008
Type of treatment				
Primary ADT	70 (100%)	30 (42.9%)	40 (57.1%)	
Second-generation AR-directed therapy	24 (100%)	7 (29.2%)	17 (70.8%)	
Chemotherapy	76 (100%)	37 (46.7%)	39 (51.3%)	0.110
PSA at NEPC dx, ng/mL, median [interquartile range]	1.20 [0.05, 13.4]	0.21 [0.04, 3.49]	3.34 [0.16, 15.4]	0.085
PSA rise per month, ng/mL	0.68 (5.39)	−1.06 (2.98)	1.98 (6.44)	0.11
PSA rise % per month, ng/mL	127 (135)	142 (205)	116(37.5)	0.67
LDH at NEPC dx, U/L				0.17
< 192[#]	18 (39.1%)	11 (52.4%)	7 (28.0%)	
≥ 192	28 (60.9%)	10 (47.6%)	18 (72.0%)	
CGA at NEPC dx, ng/mL				0.73
< 95[#]	19 (43.2%)	8 (38.1%)	11 (47.8%)	
≥ 95	25 (56.8%)	13 (61.9%)	12 (52.2%)	
Available biopsy				0.70
Yes	47 (54.0%)	24 (51.1%)	23 (57.5%)	
No	40 (46.0%)	23 (48.9%)	17 (42.5%)	
AR alteration				0.42
No	41 (87.2%)	22 (91.7%)	19 (82.6%)	
Yes	6 (12.8%)	2 (8.33%)	4 (17.4%)	
RB1 alteration				0.19

Characteristics	All *n* = 87	De novo *n* = 47	Therapy-related *n* = 40	P value
No	11 (23.4%)	8 (33.3%)	3 (13.0%)	
Yes	36 (76.6%)	16 (66.7%)	20 (87.0%)	
TP53 alteration				0.60
No	15 (31.9%)	9 (37.5%)	6 (26.1%)	
Yes	32 (68.1%)	15 (62.5%)	17 (73.9%)	
Co-occurrence of *RB1/TP53*				0.096
No	19 (40.4%)	13 (54.2%)	6 (26.1%)	
Yes	28 (59.6%)	11 (45.8%)	17 (73.9%)	
DNA repair any alteration[ǂ]				0.54
No	36 (76.6%)	17 (70.8%)	19 (82.6%)	
Yes	11 (23.4%)	7 (29.2%)	4 (17.4%)	
DNA repair somatic alteration				0.70
No	40 (85.1%)	21 (87.5%)	19 (82.6%)	
Yes	7 (14.9%)	3 (12.5%)	4 (17.4%)	
DNA repair germline alteration				0.19
No	41 (87.2%)	19 (79.2%)	22 (95.7%)	
Yes	6 (12.8%)	5 (20.8%)	1 (4.35%)	
NEPC score	0.41 (0.27)	0.45 (0.26)	0.37 (0.29)	0.52
AR score	0.21 (0.15)	0.22 (0.16)	0.21 (0.15)	0.91

Abbreviations. AR, androgen receptor; ATM, ataxia telangiectasia–mutated gene; BRCA, breast cancer gene; CGA, chromogranin A; dx, diagnosis; LDH, lactate dehydrogenase; mets, metastasis; mixed, mixed features with both small-cell carcinoma and adenocarcinoma present; NEPC, neuroendocrine prostate cancer; PCA, prostate cancer; PSA, prostate-specific antigen; RB1, retinoblastoma 1; TP53, tumour protein p53.

[ǂ]DNA repair alterations included BRCA1 and BRCA2 mutation or deletion, and ATM mutation.

[#]Upper normal limit.

Table 2

Clinicopathological characteristics of *de novo* patients with NEPC.

Characteristics	All *n* = 47	Mixed *n* = 26	Small-cell *n* = 21	P
Age, years, median [range]	67.2 [56.5, 74.5]	68.7 [54.6, 75.9]	65.9 [56.7, 70.5]	0.43
Radical radiotherapy				0.016
No	28 (59.6%)	20 (76.9%)	8 (38.1%)	
Yes	19 (40.4%)	6 (23.1%)	13 (61.9%)	
Prostatectomy				0.26
No	33 (70.2%)	16 (61.5%)	17(81.0%)	
Yes	14 (29.8%)	10 (38.5%)	4 (19.0%)	
T staging				0.036
T1	2 (18.2%)	0 (0.00%)	2 (100%)	
T2	1 (9.09%)	1 (11.1%)	0 (0.00%)	
T3	6 (54.5%)	6 (66.7%)	0 (0.00%)	
T4	2 (18.2%)	2 (22.2%)	0 (0.00%)	
N staging				0.36
N0	7 (63.6%)	6 (66.7%)	1 (50.0%)	
N1	2 (18.2%)	2 (22.2%)	0 (0.00%)	
N2	1 (9.09%)	1 (11.1%)	0 (0.00%)	
Nx	1 (9.09%)	0 (0.00%)	1 (50.0%)	
Gleason score				0.69
< 8	10 (34.5%)	5 (29.4%)	5 (41.7%)	
≥ 8	19 (65.5%)	12 (70.6%)	7 (58.3%)	
Mets at PCA diagnosis				0.80
No	20 (42.6%)	12 (46.2%)	8 (38.1%)	
Yes	27 (57.4%)	14 (53.8%)	13 (61.9%)	
Mets at NEPC dx				0.081
No	11 (23.4%)	9 (34.6%)	2 (9.52%)	
Yes	35 (74.5%)	17 (65.4%)	18 (85.7%)	
Missing	1 (2.13%)	0 (0.00%)	1 (4.76%)	

Characteristics	All *n* = 47	Mixed *n* = 26	Small-cell *n* = 21	P
Liver mets at NEPC dx				0.081
No	11 (23.4%)	9 (34.6%)	2 (9.52%)	
Yes	35 (74.5%)	17 (65.4%)	18 (85.7%)	
Missing	1 (2.13%)	0 (0.00%)	1 (4.76%)	
Time from PCA to mets dx, months, median [range]	5.21 [0.75, 14.9]	7.70 [1.03, 13.2]	3.84 [0.54, 14.1]	0.42
Time from PCA to NEPC dx, months, median [range]	2.26 [0.00, 11.8]	0.74 [0.00, 9.84]	7.54 [0.23, 21.4]	0.20
Time from mets to NEPC dx, months, median [range]	0.00 [0.00, 6.50]	0.00 [−0.74, 0.08]	0.44 [0.00, 7.93]	0.040
PSA at NEPC dx, ng/mL, median [range]	0.21 [0.04, 3.49]	1.55 [0.01, 12.2]	0.14 [0.05, 0.96]	0.42
PSA rise per month, ng/mL	−1.06 (2.98)	−1.64 (3.57)	0.11 (0.43)	0.21
PSA rise % per month, ng/mL	142 (205)	79.7 (37.3)	265 (347)	0.36
LDH at NEPC dx, U/L				0.39
< 192[#]	11 (52.4%)	6 (66.7%)	5 (41.7%)	
≥ 192	10 (47.6%)	3 (33.3%)	7 (58.3%)	
CGA at NEPC dx, ng/mL				0.067
< 95[#]	8 (38.1%)	1 (11.1%)	7 (58.3%)	
≥ 95	13 (61.9%)	8 (88.9%)	5 (41.7%)	
Available biopsy				0.30
Yes	24 (51.1%)	11 (42.3%)	13 (61.9%)	
No	23 (48.9%)	15 (57.7%)	8 (38.1%)	
AR alteration				0.48
No	22 (91.7%)	11 (100%)	11 (84.6%)	
Yes	2 (8.33%)	0 (0.00%)	2 (15.4%)	
RB1 alteration				0.082
No	8 (33.3%)	6 (54.5%)	2 (15.4%)	
Yes	16 (66.7%)	5 (45.5%)	11 (84.6%)	
TP53 alteration				1.00
No	9 (37.5%)	4 (36.4%)	5 (38.5%)	
Yes	15 (62.5%)	7 (63.6%)	8 (61.5%)	
Co-occurrence of *RB1/TP53*				0.66
No	13 (54.2%)	7 (63.6%)	6 (46.2%)	

Characteristics	All *n* = 47	Mixed *n* = 26	Small-cell *n* = 21	P
Yes	11 (45.8%)	4 (36.4%)	7 (53.8%)	
DNA repair somatic alteration[≠]				0.58
No	21 (87.5%)	9 (81.8%)	12 (92.3%)	
Yes	3 (12.5%)	2 (18.2%)	1 (7.69%)	
DNA repair germline alteration				0.63
No	19 (79.2%)	8 (72.7%)	11 (84.6%)	
Yes	5 (20.8%)	3 (27.3%)	2 (15.4%)	
DNA repair any alteration				0.66
No	17 (70.8%)	7 (63.6%)	10 (76.9%)	
Yes	7 (29.2%)	4 (36.4%)	3 (23.1%)	
NEPC score	0.45 (0.26)	0.46 (0.26)	0.45 (0.29)	0.99
AR score	0.22 (0.16)	0.28 (0.11)	0.16 (0.20)	0.36

Abbreviations. AR, androgen receptor; ATM, ataxia telangiectasia–mutated gene; BRCA, breast cancer gene; CGA, chromogranin A; dx, diagnosis; LDH, lactate dehydrogenase; mets, metastasis; mixed, mixed features with both small-cell and adenocarcinoma present; NEPC, neuroendocrine prostate cancer; PCA, prostate cancer; PSA, prostate-specific antigen; RB1, retinoblastoma 1; TP53, tumour protein p53.

[≠]DNA repair alterations included BRCA1 and BRCA2 mutation or deletion, and ATM mutation.

[#]Upper normal limit.

Table 3

Univariate Cox regression analysis for overall survival in patients with NEPC.

Variable	Hazard ratio (95% CI)	P value
De novo (yes versus no)	0.67 [0.37–1.22]	0.19
Histology of small-cell carcinoma (yes versus no)	3.49 [1.8–6.76]	<0.001
Radical radiotherapy (yes versus no)	1.71 [0.91–3.2]	0.097
Prostatectomy (yes versus no)	0.82 [0.43–1.57]	0.55
Gleason score (<8 versus ≥ 8)	0.76 [0.35–1.66]	0.49
Mets at dx (yes versus no)	1.45 [0.79–2.64]	0.23
PSA at NEPC dx	1 [1–1.01]	0.33
PSA rise per month	1.1 [1–1.22]	0.056
PSA rise % per month	1 [1–1.01]	0.021
Serum LDH at NEPC dx	1 [1–1.01]	0.003
Serum CGA at NEPC dx	0.89 [0.4–2]	0.79
NSE at NEPC dx	1.01 [1–1.02]	0.10
CEA at NEPC dx	1 [1–1]	0.53
Haemoglobin at NEPC dx	0.79 [0.62–1.01]	0.062
Serum albumin at NEPC dx	0.44 [0.16–1.22]	0.11
Alkaline phosphatase at NEPC dx	1.01 [1–1.01]	0.033
Serum testosterone at NEPC dx	1 [0.99–1]	0.29
Presence of liver mets at NEPC dx (yes versus no)	3.57 [1.27–10.07]	0.016
AR alteration (yes versus no)	0.56 [0.17–1.89]	0.35
RB1 alteration (yes versus no)	1.88 [0.73–4.84]	0.19
TP53 alteration (yes versus no)	2.09 [0.85–5.13]	0.11
DNA repair any alteration$^{\neq}$ (yes versus no)	1.07 [0.42–2.7]	0.89
DNA repair somatic alteration$^{\neq}$ (yes versus no)	1.05 [0.36–3.07]	0.94
DNA repair germline alteration (yes versus no)	0.63 [0.15–2.72]	0.54
NEPC score	0.62 [0.06–6.8]	0.70
AR score	0.12 [0–9.74]	0.34

Abbreviations. AR, Androgen receptor; ATM, ataxia telangiectasia–mutated gene; BRCA, breast cancer gene; CEA, carcinoembryonic antigen; CGA, chromogranin A; diagnosis; LDH, lactate dehydrogenase; mets, metastasis; NEPC, neuroendocrine prostate cancer; NSE, neuron-specific enolase; PSA, prostate-specific antigen; RB1, retinoblastoma 1; TP53, tumour protein p53.

[‡] DNA repair alterations included BRCA1 and BRCA2 mutation or deletion, and ATM mutation.

Table 4

Univariate Cox regression analysis for overall survival in NEPC patients with a single molecular alteration as predictor of interest, adjusting for liver metastasis at NEPC diagnosis.

Molecular alteration	Hazard ratio (95% CI)	P value
AR somatic alteration	0.59 [0.18–1.98]	0.39
RB1 somatic alteration	3.29 [1.21–8.93]	0.019
TP53 somatic alteration	2.62 [0.99–6.9]	0.052
Any DNA repair alteration *	1.83 [0.71–4.66]	0.21
Somatic DNA repair alteration	3.42 [1.09–10.69]	0.035
Germline DNA repair alteration	0.83 [0.19–3.58]	0.80
NEPC score	0.62 [0.06–6.8]	0.70
AR score	0.12 [0–9.74]	0.34

Abbreviations. AR, Androgen receptor; ATM, ataxia telangiectasia–mutated gene; BRCA, breast cancer gene; CEA, carcinoembryonic antigen; CGA, chromogranin A; diagnosis; LDH, lactate dehydrogenase; mets, metastasis; NEPC, neuroendocrine prostate cancer; NSE, neuron-specific enolase; PSA, prostate-specific antigen; RB1, retinoblastoma 1; TP53, tumour protein p53.

* DNA repair alterations included BRCA1 and BRCA2 mutation or deletion, and ATM mutation.