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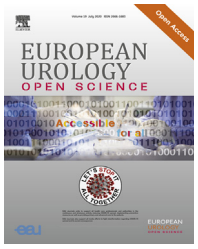

European Association of Urology

Prostate Cancer

Combined Longitudinal Clinical and Autopsy Phenomic Assessment in Lethal Metastatic Prostate Cancer: Recommendations for Advancing Precision Medicine

Juho Jasu [a], *Teemu Tolonen* [a,b], *Emmanuel S. Antonarakis* [c], *Himisha Beltran* [d], *Susan Halabi* [e], *Mario A. Eisenberger* [c], *Michael A. Carducci* [c], *Yohann Loriot* [f], *Kim Van der Eecken* [g], *Martijn Lolkema* [h], *Charles J. Ryan* [i], *Sinja Taavitsainen* [a], *Silke Gillessen* [j,k,l], *Gunilla Högnäs* [a], *Timo Talvitie* [a], *Robert J. Taylor* [m], *Antti Koskenalho* [a], *Piet Ost* [n,o], *Teemu J. Murtola* [a,p], *Irina Rinta-Kiikka* [a,q], *Teuvo Tammela* [a,p], *Anssi Auvinen* [a,r], *Paula Kujala* [b], *Thomas J. Smith* [c,s], *Pirkko-Liisa Kellokumpu-Lehtinen* [a], *William B. Isaacs* [t], *Matti Nykter* [a], *Juha Kesseli* [a], *G. Steven Bova* [a,*]

[a] *Faculty of Medicine and Health Technology, Prostate Cancer Research Center, Tampere University and Tays Cancer Center, Tampere, FI-33014, Finland;* [b] *Fimlab Laboratories, Department of Pathology, Tampere University Hospital, Tampere, Finland;* [c] *Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA;* [d] *Dana Farber Cancer Institute, Boston, MA, USA;* [e] *Duke University Medical Center, Department of Biostatistics and Bioinformatics, Durham, NC, USA;* [f] *Department of Medical Oncology, Gustave Roussy, Villejuif, France;* [g] *Department of Medical and Forensic Pathology, Ghent University, Ghent, Belgium;* [h] *Department of Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands;* [i] *Department of Medicine, Division of Oncology, University of Minnesota, Minneapolis, MN, USA;* [j] *Institute of Oncology of Southern Switzerland, Bellinzona, Switzerland;* [k] *Faculty of Biosciences, Università della Svizzera Italiana, Lugano, Switzerland;* [l] *Faculty of Cancer Science, University of Manchester, UK;* [m] *Independent consultant, Portland, ME, USA;* [n] *Department of Radiation Oncology, Iridium Netwerk, Wilrijk (Antwerp), Belgium;* [o] *Department of Human Structure and Repair, Ghent University, Ghent, Belgium;* [p] *TAYS Cancer Center, Department of Urology, Tampere, Finland;* [q] *TAYS Cancer Center, Department of Radiology, Tampere, Finland;* [r] *Faculty of Social Sciences, Unit of Health Sciences, Tampere University, Tampere, Finland;* [s] *Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA;* [t] *Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA*

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Abstract

Background: Systematic identification of data essential for outcome prediction in metastatic prostate cancer (mPC) would accelerate development of precision oncology.
Objective: To identify novel phenotypes and features associated with mPC outcome, and to identify biomarker and data requirements to be tested in future precision oncology trials.
Design, setting, and participants: We analyzed deep longitudinal clinical, neuroendocrine expression, and autopsy data of 33 men who died from mPC between 1995 and 2004 (PELICAN33), and related findings to mPC biomarkers reported in the literature.
Intervention: Thirty-three men prospectively consented to participate in an integrated clinical-molecular rapid autopsy study of mPC.

* Corresponding author. Prostate Cancer Research Center, Tampere University, Faculty of Medicine and Health Technology, PO Box 100, 33014 Tampere, Finland. Tel. +3582945211.
E-mail address: steve.bova@tuni.fi (G.S. Bova).

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Outcome
Text mining
Precision medicine

Outcome measurements and statistical analysis: Data exploration with correction for multiple testing and survival analysis from the time of diagnosis to time to death and time to first occurrence of severe pain as outcomes were carried out. The effect of seven complications on the modeled probability of dying within 2 yr after presenting with the complication was evaluated using logistic regression.
Results and limitations: Feature exploration revealed novel phenotypes related to mPC outcome. Four complications (pleural effusion, severe anemia, severe or controlled pain, and bone fracture) predict the likelihood of death within 2 yr. Men with Gleason grade group 5 cancers developed severe pain sooner than those with lower-grade tumors. Surprisingly, neuroendocrine (NE) differentiation was frequently observed in the setting of high serum prostate-specific antigen (PSA) levels ($\geq$30 ng/ml). In 4/33 patients, no controlled (requiring analgesics) or severe pain was detected, and strikingly, 14/15 metastatic sites studied in these men did not express NE markers, suggesting an inverse relationship between NE differentiation and pain in mPC. Intracranial subdural metastasis is common (36%) and is usually clinically undetected. Categorization of "skeletal-related events" complications used in recent studies likely obscures the understanding of spinal cord compression and fracture. Early death from prostate cancer was identified in a subgroup of men with a low longitudinal PSA bandwidth. Cachexia is common (body mass index $<$0.89 in 24/31 patients) but limited to the last year of life. Biomarker review identified 30 categories of mPC biomarkers in need of winnowing in future trials. All findings require validation in larger cohorts, preferably alongside data from this study.
Conclusions: The study identified novel outcome subgroups for future validation and provides "vision for mPC precision oncology 2020–2050" draft recommendations for future data collection and biomarker studies.
Patient summary: To better understand variation in metastatic prostate cancer behavior, we assembled and analyzed longitudinal clinical and autopsy records in 33 men. We identified novel outcomes, phenotypes, and aspects of disease burden to be tested and refined in future trials.

1. Introduction

Recent advances in cancer genomics and adoption of electronic health records together provide opportunities for development of precision oncology [1–3]. However, it is not known what clinical data are essential for reaching this goal.

To expand upon recent clinical data collection recommendations [4] and to hasten improvement of outcome predictors [5], we performed an exploratory analysis of all available clinical, histological, and autopsy data including neuroendocrine marker data in 33 men enrolled in a rapid autopsy study of metastatic prostate cancer (mPC). We also analyzed relevant literature-reported biomarker associations between clinical findings and features predicting disease trajectory. We combined these results to propose a framework for future data recording that encompasses both clinical observational studies and intervention trials in the context of recent advanced prostate cancer (PC) trial data recommendations [4,6] and guidelines [7–9]. Broader and better harmonized collection of phenotype data, with associated identification of best-performing biomarkers, will hasten progress toward improved outcomes.

We have made all study data available and encourage others to add data from other cohorts to improve upon this starting point. By examining the landscape of features at baseline and longitudinally in high-risk PC in their fullest available context, this report aims to improve future precision oncology approaches for patients with PC.

The current study focuses on new clinical longitudinal phenotypic characterization and includes a new analysis of previously published neuroendocrine expression data, but does not include any new analysis of previously reported whole genome sequence data in ten men included in this cohort [10–12]. Additional molecular analysis in this cohort is anticipated in future studies.

2. Patients and methods

2.1. PELICAN comprehensive phenotyping study

2.1.1. Patients

We curated all available clinical records from a series of 33 men who provided informed consent to participate in the Johns Hopkins Medicine Institutional Review Board-approved (NA_00003925) Project to ELIminate lethal CANcer (PELICAN) integrated clinical-molecular autopsy

study of lethal mPC. This study was the first integrated clinical-molecular autopsy study initiated at Johns Hopkins Hospital, and informed the development of subsequent autopsy studies in pancreatic and other cancers [13]. The study was initiated in 1994; the first PELICAN study patient underwent autopsy in 1995 and the last of 33 patients in 2004. Cohort accrual was stopped in 2005 due to insufficient funds. Twelve additional consented patients did not undergo autopsy because they died after study termination.

2.1.2. Clinical phenotyping methods

A total of 23 892 pages of medical history and surveys were collected from the 33 patients for this "PELICAN33 phenotyping study." All available medical records from January 1969 to September 2004 were curated, including available records prior to PC diagnosis and records such as treatment start and stop dates and laboratory values preserved by some of the study patients.

Each encounter record was linked to all related records (drug records, laboratory values, radiation therapy records, etc.) relevant to the same encounter, forming a detailed clinical timeline linked to medical record page numbers, enabling rigorous verification of study data. Incomplete and erroneous clinical data in records were tracked, and examples of these are presented in Supplementary Tables 1 and 2. Pictographs common in paper records but lost in electronic records are also documented (Supplementary Fig. 1).

In this report, the term "feature" is used to define any observable characteristics, whereas the related term "phenotype" is used to define features or combinations of features related to PC biology. A total of 171 features were curated across all records for each patient (Supplementary Table 3). For 59/171 "longitudinal" features, data points on a clinical timeline form a matrix of 10 116 total values analyzed for the total group of 33 patients. For the other 112/171 "discrete" features, a single value is analyzed per patient. Some features such as prostatitis are analyzed as discrete (ever occurred/never occurred) values because not all occurrences could be placed on the clinical timeline.

The raw text of each inpatient and outpatient encounter record was used in 2011–2013 for a natural language processing (NLP) study focused on the detection of pain in clinical records [14], where spot checking of the text of records was used to validate pain findings by NLP. For the current study, mentions of patient pain status were manually curated for all records using the same four classes of pain as used in the prior study [14]: severe pain (pain that is noted to be severe, with a number of 8–10 if expressed on a scale from 0–10), controlled pain (pain that is in control due to the use of analgesics), some pain (nonsevere pain that is not in control with analgesics or no analgesics are in use at the time), and no pain. All "severe pain" instances previously detected by NLP [14] and by the new fully manual curation were individually evaluated by two of the authors (J.J. and G.S.B.), and the differences in these two approaches were analyzed and resolved. The manually curated pain data were used in the analyses of complications in the current study.

The Body mass index (BMI, body weight in kg/[height in m]^2) ratio between the time of death and diagnosis was calculated based on available body weight and height values. BMI ratio was calculated using the following formula: (last BMI value)/(BMI closest to the time of diagnosis). The last available measurements were used for BMI at the time of death. For 29/33 (88%) patients, the last weight measurement was measured at autopsy, and for others, within the last 2 mo prior to death.

Gleason grade was obtained from PC diagnostic biopsy (Bx) and radical prostatectomy records. Available Bx and prostatectomy slides were whole-slide imaged, and the digitized slides were regraded by a genitourinary pathologist (T. Tolonen). Primary tumor histomorphology was typical prostate adenocarcinoma in all 33 cases [15], with no evidence of neuroendocrine features on primary tumor hematoxylin and eosin–stained sections. Neuroendocrine differentiation (NED) data from metastatic sites previously reported by Sainio et al [16] (available for 31/33 patients) were used in the integrated analysis with longitudinal serum PSA values. Small cell cancer morphology was identified in mPC tissue in one of 33 PELICAN33 cases (A23).

2.1.3. Statistical methods

We performed pairwise association exploration between 43 features using Fisher's exact test, with adjustment for multiple testing done using the Benjamini-Hochberg [17] method (Supplementary Table 4). To optimize detection of meaningful differences, low-frequency features, summary features used in descriptive statistics, features better studied by other methods, and a feature lacking comprehensive survey responses were excluded from this exploratory analysis (Supplementary Table 3).

Six of 171 features (PSA, hemoglobin, BMI, BMI ratio, Gleason grade group [GG], and perineural invasion) were selected for survival analysis from the time of diagnosis to the time to death and time to first occurrence of severe pain as outcomes based on known or putative association with PC outcome. For each feature analyzed by survival analysis, patients were partitioned into high- and low-value groups using the median as the threshold for continuous-scale features. For example, the median PSA at the time of diagnosis was 26.9 ng/ml, so the high-value group consisted of patients who had a PSA of $>$26.9 ng/ml at the time of diagnosis. The survival function estimates were calculated using the Kaplan-Meier estimate and the significance of differences was quantified using the log-rank test. A Cox model was used for multivariate analysis of the same six features.

A logistic regression model was used to evaluate the effect of seven complications common among mPC patients (fractures, spinal cord compression, deep vein thrombosis (DVT), severe anemia [Hb $\leq$7.9 g/dl], pleural effusion, urinary obstruction, and severe or controlled pain [defined as pain requiring use of analgesics]) on the modeled probability of dying within 2 yr after presenting with the complication. Longitudinal data were available for all seven complications. Data from all 33 men were used to fit the model. There were a total of 148 data points: time of diagnosis and all subsequent instances of a new complication. Owing to the limited size of the study cohort, splitting into training and validation data subsets was not advisable, and hence significant findings must be tested further in additional cohorts (see the Discussion section). The logistic regression model with the lowest Akaike information criterion was selected using backward stepwise variable selection. Classification was performed by thresholding the modeled probability at 0.5. Coefficients with confidence intervals, p values (chi-square), prediction accuracy, sensitivity, specificity, and likelihood ratio for a positive result (LR+) were calculated. Bootstrap confidence intervals were calculated for prediction accuracy, sensitivity, and specificity using adjusted bootstrap percentile method with 100 000 bootstrap samples. Receiver operating characteristic (ROC) curve plotting the true positive and false positive rates and area under the curve (AUC) were calculated to describe the performance of the final model; 95% confidence intervals (CIs) for the AUC were calculated with 2000 stratified bootstrap replicates. We tested the generalizability of the model by performing leave-one-patient-out cross-validation and tested whether performance of the model changed in predicting the outcome for the excluded patient. AUC, sensitivity, and specificity were calculated.

2.2. Compilation of known or putative clinical features associated with high-risk prostate cancer

We selected biomarker studies supporting the ability to define a high risk of metastasis in men with clinically localized PC, or the ability to predict survival in men diagnosed with metastatic disease. The current version of this list was compiled through iterative literature searches and discussion among study authors, and is available for review and subsequent improvement (see the Results and Discussion sections).

The criterion for inclusion is that the biomarker appears potentially useful for patient selection or treatment.

2.3. Synthesis: recommendations for information management in future precision oncology trials in mPC

Results from the phenomic analysis in 33 men (2.1) and biomarker review (2.2) were analyzed together to produce draft recommendations for information management to support future precision oncology trials in high-risk prostate cancer contained in Supplementary Table 5 and presented in the Discussion section.

3. Results

3.1. PELICAN comprehensive clinical phenotyping

3.1.1. Cohort description

The study data included 207.1 person-years' experience of 33 men between diagnosis and death from mPC (mean 6.3, median 5.5, range 0.8–15.4 yr). Summaries of key clinical features are shown in Supplementary Tables 6–9.

3.1.2. Metastatic spread and causes of death

Study patients' ages at diagnosis and death, comorbidities, complications, sites of metastasis, and causes of death are listed in Supplementary Table 9. These features vary widely, including age at diagnosis (median 63 yr, range 39–82 yr), and years between diagnosis and death (6 yr, 1–15 yr).

Metastatic PC was listed in the autopsy report as the underlying cause of death in all cases except for patient A13, whose proximate cause of death was sepsis and peritonitis caused by a perforated sigmoid colon due to corticosteroid treatment of mPC, and therefore his underlying cause of death is listed as mPC. In 16/33 (48%) of cases, mPC was the sole listed cause of death. Additionally, more proximate causes of death were listed in 17/33 (52%) cases, including pneumonia (various types; 11/33, 33%) and single cases (1/33, 3%) of sepsis and peritonitis, pericardial tamponade, terminal gastric aspiration, pulmonary embolism (PE), diffuse alveolar damage, pyelonephritis, pleural effusion, renal failure, perforated sigmoid colon, and malignant pericardial effusion. Other comorbid conditions present but not listed in the cause of death are listed in Supplementary Table 9.

3.1.3. Univariate analysis of survival time

Median survival was 47 mo (95% CI 43–96) for patients with International Society of Urological Pathology (ISUP) GG 5 adenocarcinoma and 81 mo (95% CI 55–161; two-sided log-rank $p = 0.044$) for those with ISUP GG ≤ 4 (Fig. 1A). ISUP GG 5 was also associated with shorter time until the first recording of severe pain: 35 mo (95% CI 16 mo to cannot be estimated [NE]) versus 54 mo (95% CI 42 mo to NE) for ISUP GG ≤ 4 (two-sided log-rank $p = 0.0032$; Fig. 1B). The other five features tested (PSA, hemoglobin, BMI, BMI ratio, and perineural invasion) were not associated with overall survival (OS) or survival until the first record of severe pain. A multivariable proportional hazard model did not detect significant associations beyond the association of OS with ISUP GG and PSA.

3.1.4. Analysis of complications

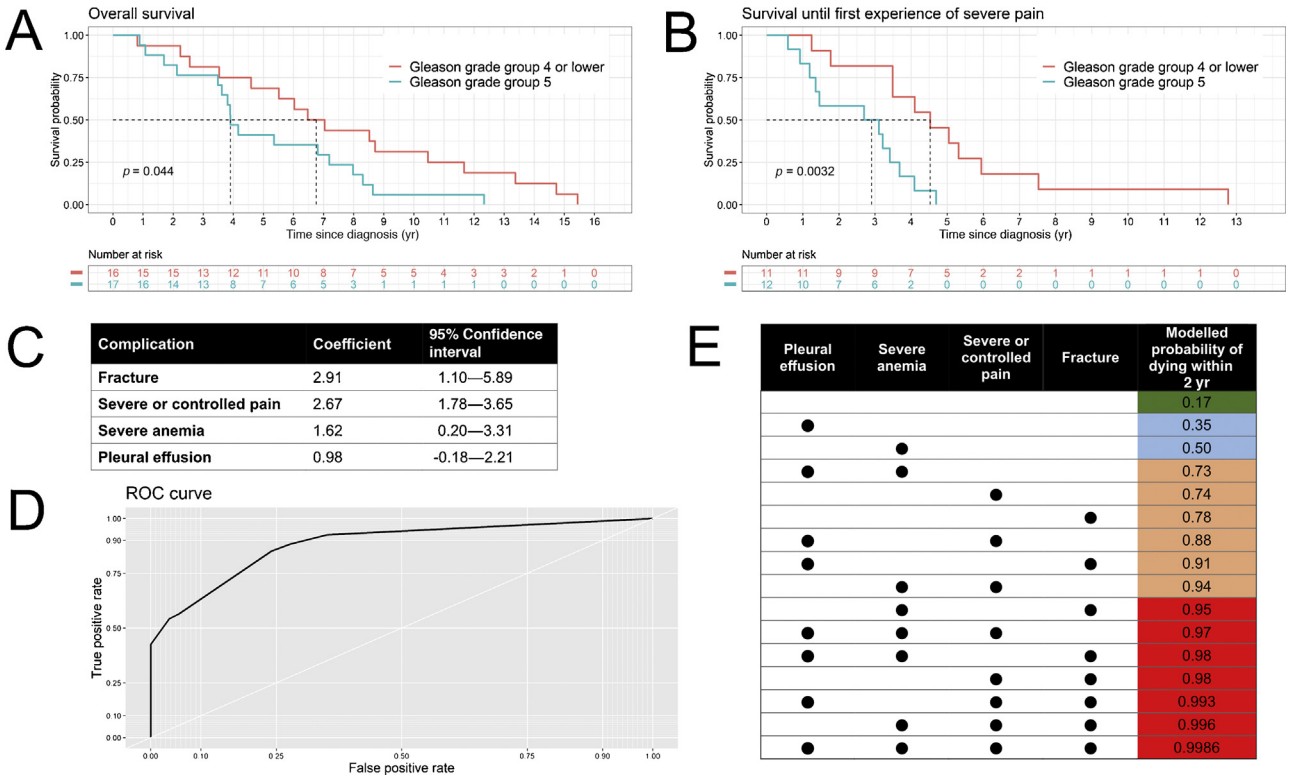
A logistic regression model showed that fractures, severe or controlled pain, severe anemia (Hb ≤ 7.9 g/dl), and pleural effusion were associated with the probability of death within 2 yr after the occurrence of the most recent complication (Fig. 1C). The modeled probability of dying within 2 yr after the occurrence of the most recent complication varied greatly, with a fracture increasing the probability the most: the modeled probability of dying within 2 yr after having a fracture with no history of any of the other three complications was 0.78 (Fig. 1E). Prediction accuracy is 0.82 (95% CI 0.74–0.86), sensitivity is 0.89 (95% CI 0.81–0.94), specificity is 0.70 (95% CI 0.54–0.81), LR+ is 3.02, and the AUC for the ROC curve is 0.88 (95% CI 0.83–0.93; Fig. 1D). In a leave-one-patient-out cross-validation, reassuringly, the AUC was 0.81 (95% CI 0.73–0.88), sensitivity 0.88, and specificity 0.70.

3.1.5. Patterns of longitudinal serum PSA

A total of 1423 serum PSA values were available for the 33 men between 1987 and 2004, with a median of 39 (range two to 129) PSA values for each man. Two main patterns of longitudinal serum total PSA over the course of mPC are apparent (Fig. 2A). In four "lower PSA bandwidth" (LPSAB) patients, serum PSA never rose above 51 ng/ml, and all 29 patients in the "high PSA bandwidth" (HPSAB) group had at least one PSA value of >200 ng/ml. In the LPSAB group, the lifetime highest PSA median was 28.7 ng/ml (minimum 20.7, maximum 51) and the last PSA median of 17.2 ng/ml (minimum 0.05, maximum 24.5). In the HPSAB group, the lifetime highest PSA median was 1026.2 ng/ml (minimum 206.9, maximum 9940) and the last PSA median was 757 ng/ml (minimum 60.7, maximum 9940). We explored differences between the LPSAB and HPSAB patient groups. LPSAB group patients had fewer non-bone, non–lymph node metastatic sites than HPSAB group patients (LPSAB median 0.5, mean 2, minimum 0, maximum 7 vs HPSAB median 3, mean 3.17, minimum 0, maximum 6; Supplementary Table 10); and LPSAB group patients also had shorter OS between diagnosis and death (LPSAB median 20 mo, mean 29, minimum 11, maximum 66 vs HPSAB median 78 mo, mean 82, minimum 10, maximum 185, log-rank $p = 0.003$). Thus, patients in the LPSAB group were likely diagnosed later in the mPC disease process and died with a lower burden of disease than HPSAB group patients, as measured by the number of non-bone, non–lymph node sites involved (Supplementary material).

3.1.6. Neuroendocrine differentiation

Of 27 patients in the HPSAB group, five (19%) had strong expression of at least one NED marker and seven (26%) had focal expression of both NED markers. In the LPSAB group, A23 fits the expected pattern of a neuroendocrine PC tumor, with small cell morphological features in metastases and NED (Fig. 2), while the three other LPSAB cases (75%) show either no (A26) or only focal (A5 and A13) NED, suggesting



Complication	Coefficient	95% Confidence interval
Fracture	2.91	1.10—5.89
Severe or controlled pain	2.67	1.78—3.65
Severe anemia	1.62	0.20—3.31
Pleural effusion	0.98	-0.18—2.21

Pleural effusion	Severe anemia	Severe or controlled pain	Fracture	Modelled probability of dying within 2 yr
				0.17
●				0.35
	●			0.50
●	●			0.73
		●		0.74
			●	0.78
●		●		0.88
●			●	0.91
	●	●		0.94
	●		●	0.95
●	●	●		0.97
●	●		●	0.98
		●	●	0.98
●		●	●	0.993
	●	●	●	0.996
●	●	●	●	0.9986

Fig. 1 – Features associated with survival and impact of complications on survival in metastatic prostate cancer. (A) Overall survival is shorter in men with International Society of Urological Pathology (ISUP) grade group (GG) 5 histomorphology. (B) ISUP GG 5 is also associated with significantly shorter time to the first record of severe pain in the 23 patients who experienced severe pain. (C) Four cancer-related complications that were included in the logistic regression model selected after stepwise selection using Akaike information criterion. The model predicts the likelihood of dying within the next 2 yr when presenting with a new complication. Severe anemia is defined as Hb ≤7.9 g/dl. (D) ROC curve plotting the true and false positive rates with different thresholds applied to the output of the logistic regression model. AUC, which is used to evaluate the performance of the model, is 0.88. (E) Modeled probabilities for dying within 2 yr when presenting with specific combinations of complications. AUC = area under the curve; ROC = receiver operating characteristic.

that these three cases could fall into the recently described DNPC subtype of mPC (Supplementary material) [18]. Surprisingly, five of 27 cases in the HPSAB group had metastases with strong expression of at least one NED marker, indicating that NED and androgen signaling sufficient for high PSA expression are not mutually exclusive in a potentially novel subgroup of mPC cases.

3.1.7. *Relationships between clinical features*

Exploration of relationships between the 43 selected clinical features is detailed in Supplementary Table 11. A number of potentially useful associations were identified that did not stand up to correction for multiple testing may merit testing together with data from other well-curated cohorts.

3.1.8. *Details of most common clinically important complications of mPC*

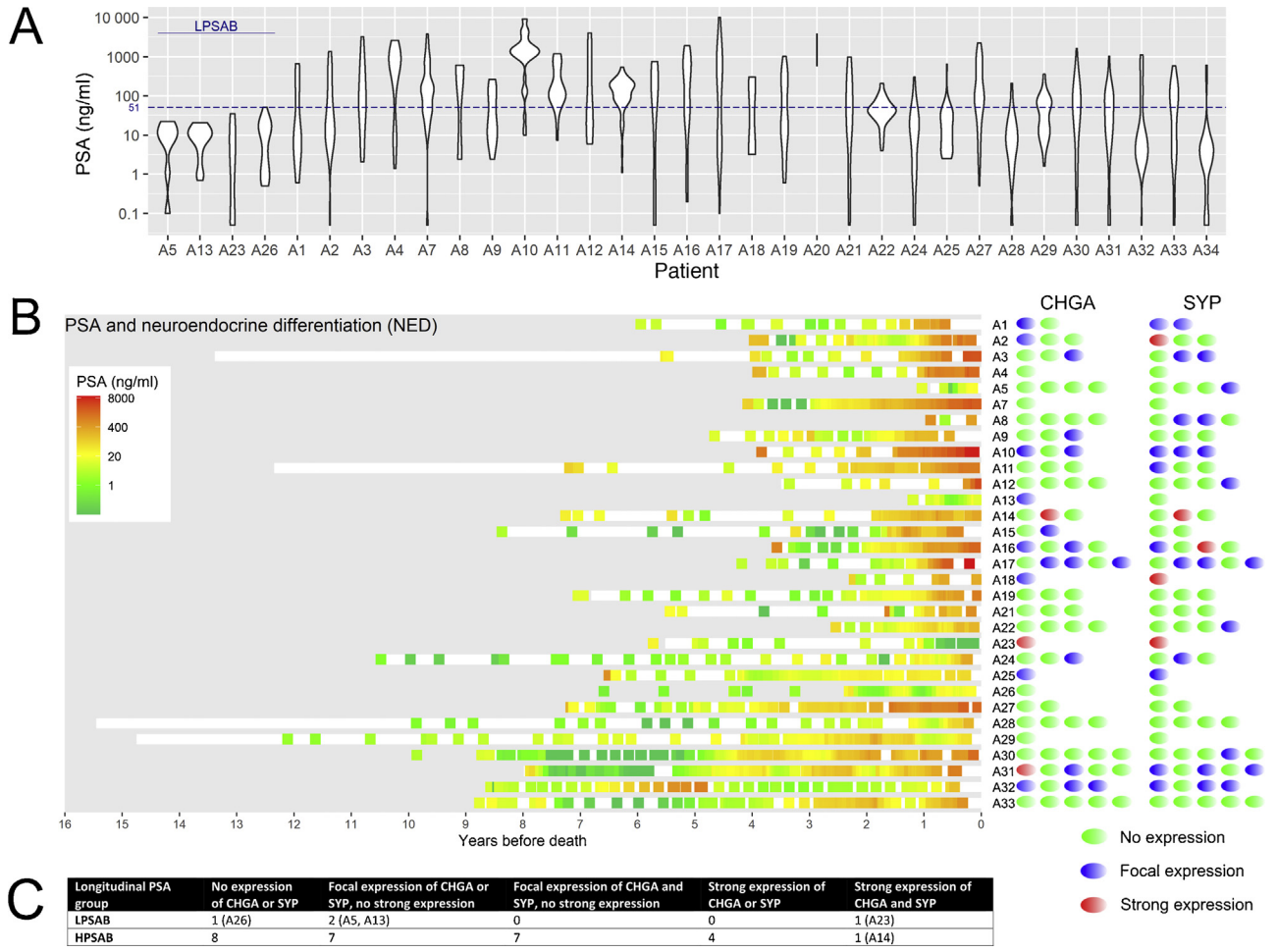
Complications experienced by two or more of the 33 patients are listed in Figure 3A and occurred mostly during the last 2 yr of life. Time of occurrence and relation to PSA level are shown for nine features in Figure 3B. Spinal cord compression and severe anemia tended to occur in patients with a very high PSA level. Urinary obstruction (both upper and lower urinary tract obstruction combined) was the only complication, with events distributed relatively evenly from PC diagnosis to death.

3.1.9. *Bone fractures and spinal cord compression*

Many studies combine spinal cord compression, fractures, radiation to the bone, and surgery to the bone to analyze the occurrence of these four "skeletal-related events" as a single entity. Our data made it possible to study these as separate features (Supplementary Table 12). Radiation to the bone was very common with a total of 65 occurrences for 26 patients, nine of whom never had a fracture or spinal cord compression, suggesting that considerable variation in outcome could be better understood through analysis of the four skeletal-related event complications separately.

Fractures occurred in 12 of 33 (36%) patients between diagnosis and death, and all but one occurred less than 2 yr before death. Vertebral fracture was the most common type of fracture, with six in total, followed by three fractures of the proximal femur. No specific inducing trauma was noted (eg, falling) in the medical records for any of these fractures.

Spinal cord compression occurred in 13/33 (39%) patients (Supplementary Table 13). The thoracic spine was the most common site of cord compression. Central spinal cord compression was present in ten of these 13 patients, and compression at two or more levels was



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Longitudinal PSA group	No expression of CHGA or SYP	Focal expression of CHGA or SYP, no strong expression	Focal expression of CHGA and SYP, no strong expression	Strong expression of CHGA or SYP	Strong expression of CHGA and SYP
LPSAB	1 (A26)	2 (A5, A13)	0	0	1 (A23)
HPSAB	8	7	7	4	1 (A14)

Fig. 2 – HPSAB and LPSAB patterns of longitudinal serum PSA and neuroendocrine differentiation. (A) Longitudinal serum PSA violin plots. Width is proportional to the number of PSA measurements available at each value. Four patients (A5, A13, A23, and A26) in whom serum PSA did not rise above 51 ng/ml form an LPSAB group. All 29 patients in the HPSAB group had at least one PSA value over 200 ng/ml. (B) PSA longitudinal timeline together with immunostain-based neuroendocrine differentiation (NED) data from specific metastases at autopsy [16]. The white bar for each patient starts at the time of diagnosis. No neuroendocrine staining data were available for patients A20 and A34. Each oval dot to the right represents separate metastatic sites tested for the two NED markers chromogranin A (CHGA) and Synaptophysin (SYP). Over 10% of cells showing positivity to the marker was classified to have strong expression, 1–10% to have focal expression, and 0% to have no expression. (C) Comparison of NED immunostaining results in the LPSAB and HPSAB groups. HPSAB = higher PSA bandwidth; LPSAB = lower PSA bandwidth; PSA = prostate-specific antigen.

present in 75% of instances. Of the 13 patients with spinal cord compression, only five had a vertebral fracture (Supplementary Table 12). There was also one patient, A32, who had a vertebral fracture but no spinal cord compression.

3.1.10. *Pain*

Remarkably, for four patients (A28, A29, A30, and A33), no severe or controlled pain was detected, and notably these patients also had almost no NED expression (only A30 had focal Synaptophysin [SYP] expression; none of the patients had CHGA expression). All four patients are in the HPSAB group, and no patients without severe or controlled pain were found in the LPSAB group.

Detection of pain varied depending on the type of data extraction used (Fig. 3C and D). Our prior NLP [14] in this cohort found significantly more instances in the "pain" category (see the Patients and methods section) than were found using manual text curation in the current study, and manual text curation identified more records tagged with controlled pain than the prior NLP study. We formally compared prior NLP and current manual pain curation results. Any records flagged with the phenotype of severe pain by either manual curator or NLP were re-evaluated by two of the authors (J.J. and G.S.B.), and the comparative pain phenotyping results are shown in Supplementary Tables 14 and 15. Examples of curation discrepancies between NLP and manual curation are shown in Supplementary Table 16.

3.1.11. *Pulmonary embolism (PE)*

Ten patients were found to have PE at autopsy: there were seven patients with peripheral pulmonary thromboemboli, single cases of peripheral pulmonary vascular tumor emboli (A1) and suture emboli (A13), and one case of central pulmonary (saddle) thromboembolus (A21). Only one patient (A1) was diagnosed with PE during life. This took place 38 mo before death, and the patient was also

A

Complication	Number of patients	Complication	Number of patients	Complication	Number of patients	Complication	Number of patients
Fever	26 (79%)	Constipation	13 (39%)	Dyspnea	8 (24%)	Impotence	4 (12%)
Pneumonia	22 (67%)	Fracture	12 (36%)	Leukopenia	8 (24%)	Anasarca	3 (9%)
Pleural effusion	20 (67%)	Dehydration	12 (36%)	Deep vein thrombosis	7 (21%)	Syncopal episode	3 (9%)
Moderate or severe urinary obstruction	17 (52%)	Generalized weakness	11 (33%)	Neutropenia	7 (21%)	Subdural hematoma	2 (6%)
Severe anemia	16 (48%)	Confusion	10 (30%)	Sepsis	7 (21%)	Hydrocele	2 (6%)
Hematuria	16 (48%)	Pulmonary embolism	10 (30%)	Hypokalemia	6 (18%)	Nephrostomy tube obstruction	2 (6%)
Urinary tract infection	14 (42%)	Neuropathy	9 (27%)	Vertigo	5 (15%)	Bowel obstruction	2 (6%)
Spinal cord compression	13 (39%)	Thrombocytopenia	9 (27%)	Granulocytopenia	4 (12%)		

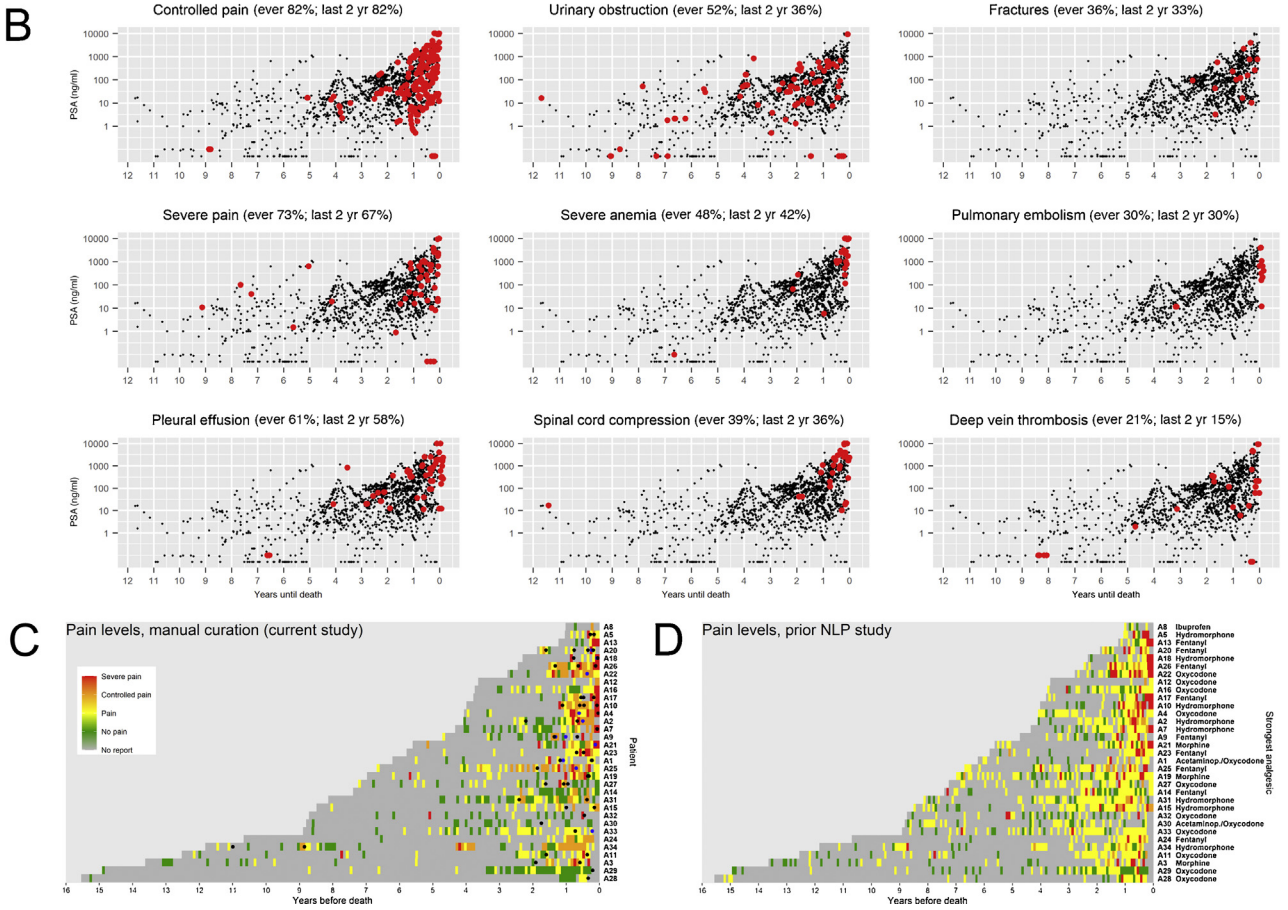

Fig. 3 – Frequency and timing of complications of metastatic prostate cancer and associated PSA levels. (A) Complications experienced by at least two of the 33 patients. (B) Incidence of nine common complications by PSA and time until death, ordered from the highest to the lowest overall frequency. Black dots represent all PSA values available for the 33 patients. For each occurrence of a complication in a patient, the nearest available PSA dot from the same study patient is marked red. First percentage in brackets is the likelihood of the complication developing at any time, and the second is the likelihood of the complication developing within the last 2 survival years. (C and D) Pain levels according to fully manual curation and prior natural language processing (NLP), from the study of Heintzelman et al [14]. The strongest analgesic [30] used by each patient is marked after the patient ID. Levels of pain and need for analgesics varied. Opioids were used by 32 out of 33 patients. In Figure 3C, time of treatment with palliative external beam radiotherapy is signified with black dots and administration of systemic radioisotopes with blue dots. NLP found more instances of pain than manual curation, but manual curation found more instances of controlled pain, which is the most complicated pain level to curate in our four-level scale. PSA = prostate-specific antigen.

diagnosed with DVT at the time. The nine other patients diagnosed with PE at autopsy did not have DVT diagnosed during life or at autopsy.

3.1.12. *Subdural metastases*

Twelve patients had subdural metastases at autopsy. During the last year of life, six of 12 patients had cranial computed tomography (CT) or magnetic resonance imaging (MRI) performed. Five underwent cranial CT, only one of which was positive for subdural metastases. Four underwent cranial MRI, three of which were positive. Three patients with subdural metastases developed neurological deficits, with the subdural metastases being the most likely etiology. These included cranial nerve findings (A31), upper and

Table 1 – Biomarkers supporting the ability to define the high risk of metastasis in men with PC clinically confined to the prostate, or the ability to predict survival in men already diagnosed with metastatic disease

Feature	Important or recent association with mPC outcome or biology	Utility or prospective utility as predictive marker in individual mPC patients and status in the current study
Histomorphology	Higher Gleason score and the greatest percentage of a biopsy core involved by cancer associated with worse PSA-free and clinical recurrence–free survival, and CSS [31]; high Gleason score associated with shorter OS [32]; higher percentage of cancer volume in needle biopsy specimens associated with worse CSS and OS in localized prostate cancer patients with external beam radiotherapy [33]; biopsy perineural invasion associated with worse biochemical recurrence prognosis in patients with local prostate cancer after radical prostatectomy [34]; higher number of perineurally invaded nerves associated with worse PFS [35]; lymphovascular invasion identified in radical prostatectomy associated with worse biochemical PFS, MFS, and OS after radical prostatectomy [36]; expression of Tenascin-C associated with worse OS [37]	No single histomorphological feature is currently sufficient to accurately determine the risk of recurrence or likelihood of cure [31]; image analysis combined with machine learning has been reported to outperform pathologists in some tasks in recent studies [38].
Small cell carcinoma	Pure small cell carcinoma histology associated with worse OS than mixed small cell carcinoma and adenocarcinoma histology in metastatic tumor biopsies, with OS calculated both from the time of PC diagnosis and the time of diagnosis of metastatic disease [39]; detection of treatment-emergent small cell neuroendocrine PC associated with worse OS in patients with prior AR-targeting therapy for mCRPC [40]	Pure small cell carcinomas may need to be managed more aggressively than mixed NEPC cases [39].
NED prostate cancer tissue and serum markers	High serum chromogranin A (CHGA) and neuron-specific enolase (NSE) associated with worse PFS and OS in mCRPC patients [39,41]; immunohistochemical CHGA expression associated with worse PFS and OS in patients receiving ADT early after diagnosis of PC [42]; *SRRM4* gene expression associated with worse OS [43]	Generally, NED is more common in high-grade and high-stage PC and, especially after ADT, during tumor progression and in CRPC [44]; altered renal function and treatment with proton pump inhibitors may induce high serum CHGA levels, so interpretation must be done cautiously in patients with these situations [44]; on SRRM4, studies needed on whether (1) SRRM4 expression is associated with other neuroendocrine carcinoma in patients, (2) anticancer therapies induce SRRM4 expression in these patients, and (3) SRRM4 drives tumor progression to neuroendocrine carcinoma through reprogramming RNA splicing gene networks [43].
Local (seminal vesicle or bladder invasion) or regional (pelvic lymph node) metastatic spread	Local metastatic spread associated with worse PFS [36]; regional metastatic spread associated with worse CSS [45]	Noninvasive detection of seminal vesicle, bladder, and pelvic lymph node mPC status by imaging would be useful to patients, but there are still problems regarding accuracy [46].
Distant metastasis (any metastasis that is not local or regional)	Distant metastases associated with worse OS and visceral metastases more than bone metastases [47]; distant metastases associated with worse CSS than local metastases or nonmetastatic cancer [45]	Neither older nor more recent noninvasive mPC imaging methods have been fully integrated with longitudinal precision medicine trials to date. Comparisons of digital bone scan [48], PET CT [49], whole-body MRI [50], and other methods are needed. Integrated studies of these methods in trials of stereotactic ablative radiotherapy of individual metastases [51] are needed.
Serum PSA Note: serum PSA referred to here and in the PELICAN33 study is total PSA or tPSA (see also PSA isoforms below)	Nonmetastatic PC: high initial PSA associated with worse BRFS, MFS, and CSS [52]; postradiation therapy with ADT PSA decline after 3 mo associated with better BRFS and CSS in intermediate and high-risk patients and with better OS in high-risk patients with localized PC [53]; PSA slope $\geq$0.05 3–12 mo after radical prostatectomy associated with worse MFS [54] Nonmetastatic castration-resistant PC: high PSA and PSA velocity associated with worse bone MFS and OS in non-mPC with rising PSA despite ADT [55] Metastatic hormone-sensitive PC: PSA of $\geq$4 ng/ml 7 mo after androgen deprivation started associated with worse OS in mPC patients [56] Metastatic castration-resistant PC: Postchemotherapy PSA decline after 3 mo associated with better OS in mCRPC patients [57]; low PSA at death associated with shorter time from diagnosis to death in patients with mCRPC [58]	PSA currently is used as a nonspecific indicator of response. Utility in tracking disease burden in individuals is relatively unstudied; PSA may remain low despite mPC, especially in patients with neuroendocrine PC [39] (see Results of the current study); PSA response appears to vary depending on therapy mechanism of action [59,60]. Also, PSA may rise initially after chemotherapy, and then fall. Berthold et al [61] reported 103/873 patients having an initial PSA increase after starting chemotherapy, 23 patients even satisfying criteria for PSA progression, but later having a PSA response (defined as PSA being $<$50% of the baseline value). Of these 103 patients, 50% of PSA responses occurred within the first two cycles and 80% within the first four cycles (ie, 12 wk) of chemotherapy. Note that discussing methods with your laboratory and keeping records of the specific total PSA assay method, calibration method, and breadth of the standard curve used may be important for comparative tPSA evaluation in future studies. According to the literature, current laboratory standard methods do not typically include calibration standards above 100 ng/ml [62,63].

Table 1 (*Continued*)

Feature	Important or recent association with mPC outcome or biology	Utility or prospective utility as predictive marker in individual mPC patients and status in the current study
Germline predisposition and other somatic mutations in high-risk prostate cancer	Germline variants detected in a surprisingly high number (12.2%) of all metastatic cancers in MET500 cohort [64]; in mPC, germline mutations of BRCA1/2 and ATM associated with worse OS [65]; HSD3B1 c.1245 CC germline genotype associated with worse OS in mCRPC patients starting first-line abiraterone/enzalutamide treatment [66]; germline variants of anoctamin 7 (ANO7) associated with high-grade PC, and high expression associated with worse OS [67] and better response to docetaxel in mCRPC [68]; clinical utility of DNA-damaging chemotherapy in mPCs containing somatic defects in DNA repair genes demonstrated in recent years [26]; somatic tumor RB1 mutation associated with poor survival recently [69]	Utility of germline analysis in predicting actionable somatic tumor variants has not been tested to our knowledge. Detection of somatic mutations of DNA repair genes currently in use as predictive biomarkers for response to DNA-damaging chemotherapy such as olaparib. Multiplex analysis of whole genome somatic genomic defects and outcome is needed in mPC cohorts to evaluate relative utility of specific genomic biomarkers.
Pain	Bone pain associated with worse OS in patients with mCRPC [70]; more pain associated with worse OS in patients with mCRPC [71]; achieving a pain response to treatment associated with better OS [57]; in current study, Gleason grade pattern and time to first severe pain linked, needs to be validated	Bone pain is associated with increased risk of skeletal-related events [70]. Testing pain as a specific outcome variable is indicated.
SREs, including pathological fracture, spinal cord compression, radiation to bone, or surgery to bone	SREs associated with worse OS in patients with mCRPC [72]	Howard et al [72] showed SREs' association with increased mortality and suggested testing medications to reduce SREs in future studies. The current study suggests that SREs are a useful summary feature, but that underlying patient-specific data on fracture, spinal cord compression, and radiation or surgery to reduce bone pain should be tabulated to enable more fine-grained associations with biology in future studies
Body mass index (BMI)	BMI of $<25\ kg/m^2$ associated with worse CSS and OS in patients with advanced CRPC [73]	A lower BMI may reflect cachexia. Alternatively, higher protein and calorie reserves may help obese men to better withstand the cachexia-producing effects of advancing CRPC [73].
Hemoglobin (Hb)	Low Hb associated with worse PFS, CSS, and OS in mHSPC patients [74]; low Hb associated with worse PFS and OS in mCRPC patients [75]	Since red cell transfusion or erythropoiesis-stimulating agents are used for treatment of chemotherapy-related anemia in patients receiving chemotherapy [76,77], studies needed to further optimize Hb while minimizing thromboembolic risk. In the current study, 16/33 patients experienced severe anemia (Hb $\leq$7.9 g/dl) at least once (Supplementary Fig. 4). See the Results section for findings related to PE and DVT in the current study.
Alkaline phosphatase (AP)	High AP associated with worse PFS and OS in mHSPC patients [78]; high bone-specific AP associated with worse OS in mCRPC patients [79]	Bone-specific AP is increased in men using ADT and is further elevated by bone metastases [80]; elevated total (nonspecific) AP might reflect micrometastases despite negative findings on conventional imaging. Total AP could be used to select patients who may benefit more from intensive therapy such as upfront docetaxel or abiraterone in addition to ADT [78]. Alkaline phosphatase and bone-specific alkaline phosphatase need to be competed together with other biomarkers in future prioritization competitions. In the current study, alkaline phosphatase values are available but showed no discernible trend. No bone-specific alkaline phosphatase values were present in the current study. In the current study, a minimum of 2, maximum of 105, and median of 33 AP values were available. An increasing AP toward death was usually seen in those with sufficient values, but some had a peak in AP earlier, with a decreasing AP at death.
Lactate dehydrogenase (LDH)	High LDH associated with worse PFS and OS in mPC patients, independently associated with worse OS in mCRPC and mHSPC patients [81]	As LDH was associated with worse OS in patients with mHSPC, pretreatment LDH values might be a useful biomarker in the choice of treatment even in early metastatic PC and could be used to select patients who may benefit more from intensive therapy such as upfront docetaxel or abiraterone in addition to ADT [81]. LDH needs to be competed with other biomarkers in future trials.
Albumin and prealbumin	Low albumin associated with worse OS in patients with skeletal mPC [82]; low pretreatment prealbumin associated with worse PSA PFS, radiological PFS, and OS in patients with mCRPC treated with abiraterone acetate [83]	Prealbumin might be useful in evaluating nutritional status and help clinicians decide whether nutritional support or supplementation is needed. Biological half-life is approximately 2.5 d, compared with 20 d of albumin [83]. Needs to be competed with other biomarkers and related to cachexia phenotypes detailed in the current study.

Table 1 (*Continued*)

Feature	Important or recent association with mPC outcome or biology	Utility or prospective utility as predictive marker in individual mPC patients and status in the current study
Fibrinogen (plasma) and d-dimer	High fibrinogen associated with worse PFS, CSS, and OS in patients treated with ADT [84], possibly through increased DVT; low fibrinogen and d-dimer levels are indicators of DIC [85]	Deserve competition with other biomarkers in future studies.
Performance status (PS)	Worsened PS associated with worse OS in patients with mCRPC [32,47,57] and used as part of Halabi et al's [86] prognostic model	In the Advanced Prostate Cancer Consensus Conference 2017, 62% of panelists considered patients with metastatic disease not suitable for docetaxel treatment if PS was $\geq$2 for reasons other than cancer [87]. ECOG PS has been criticized, and the use of a wider range of scoring and assessment tools has been encouraged [88].
Physical activity	Physical activity associated with better CSS and OS [89]	Physical activity should be encouraged and tracked [90] using exercise trackers, and should be included in future trials as covariate.
C-reactive protein (CRP)	High pretreatment CRP associated with worse PFS, CSS, and OS [91]	As several diseases increase CRP, one should be careful while considering CRP as a predictor of survival in cancer patients [91]. It should be competed against and prioritized compared with other biomarkers in future studies.
Interleukin 6 (IL-6)	High IL-6 associated with worse CSS [92]; high IL-6 associated with worse OS in mCRPC [93]	Personalized medicine approaches might make it possible to identify PC patients who will likely respond to anti–IL-6 therapies [94]
Metabolic syndrome (MetS)	MetS has been associated with worse PFS [95]. Note that determining MetS status requires tracking of waist circumference, triglycerides, HDL-C, blood pressure, fasting plasma glucose. PDW, and CRP tracked with MetS, but their individual value not assessed	Existing mPC treatment methods influences development of MetS [95]. In future trials, MetS status should specifically be tracked, and efforts to reduce MetS should be recorded. PDW and CRP should be tested as important covariates with potential capacity to improve treatment selection.
Neutrophil-lymphocyte ratio (NLR)	High pretreatment NLR associated with worse BRFS, PFS, and OS [96]; high pretreatment dNLR associated with worse BRFS and OS [97]	Previous studies and studies in patients with other cancers have suggested that the prognostic value of NLR is higher in more advanced cancer. It may prove useful in risk classification [96]; is quick, easy. and cheap to test; and deserves competition with other biomarkers in future studies.
Platelet-lymphocyte ratio (PLR)	High pretreatment PLR associated with worse PFS, CSS, and OS [96]	PLR may prove useful in risk classification [96]; is quick, easy, and cheap to test; and deserves competition with other biomarkers in future studies.
Prostate-specific membrane antigen (PSMA) and PSMA-PET-CT	Expression of PSMA in CTCs associated with worse PSA progression-free survival, treatment response, and OS in CRPC patients [98]	PSMA-PET-CT scanning is more accurate than the conventional method of CT + bone scan for detecting metastases [99]. Its overall value should be determined by comparison with other biomarkers. PSMA expression was found to be increased in patients who had a history of enzalutamide treatment; AR-signaling–targeted therapies possibly induce PSMA expression [98]. Low PSMA expression in mCRPC in patients with discordant FDG-avid disease was found to have poor prognosis in a small study [100].
Prostate MRI results	Multiparametric MRI (mpMRI) is currently in use as an alternative to biopsy in trials of PC active surveillance [101]; no studies of initial mpMRI results and OS or PFS are yet available	Prostate MRI and mpMRI at diagnosis should be analyzed together with precision oncology studies wherever possible.
Circulating tumor cells (CTCs)	A high number of CTCs, both before and after treatment, associated with worse OS in CRPC patients receiving chemotherapy [102]; high pretreatment number of CTCs associated with worse PFS and OS in patients with mCRPC starting second-line endocrine therapy [103]	There is an increase in CTCs at 10–12 wk after the start of abiraterone acetate or enzalutamide associated with worse PFS and OS in patients with mCRPC starting second-line endocrine therapy [103]. Comparative utility of CTCs and liquid biopsy is needed.
Androgen-receptor splice variants (AR-V)	AR-V7 positivity in CTCs associated with worse PFS and OS in patients with mCRPC [104–106]; there is some debate and demand for more studies [107–110]; whole blood AR transcripts of full length and AR-V1 associated with worse PSA PFS and OS in CRPC patients [111]	Utility in individual patients is debated. Head to head comparisons of AR-V7 detection methods and comparison with other biomarkers needed to learn its place.
Plasma and other body fluid cell-free DNA (cfDNA) and circulating tumor DNA	High prechemotherapy cfDNA associated with worse radiological PFS and OS in patients with mCRPC receiving first- and second-line taxane chemotherapy [112]	A decline in cfDNA concentration during the first 3–9 wk after initiation of taxane therapy was seen in patients deriving benefit from taxane chemotherapy [112]. Nuances of value of ctDNA signals in blood and cerebrospinal fluid in mPC are shown in our recent study [11], strongly supporting inclusion in future autopsy and precision oncology trials.
miRNA in body fluids	Clinical significance of miRNA is currently being explored; current findings are more focused on diagnosis and risk classification, but levels of some miRNAs have already been associated with changes in survival [113,114]	In clinical practice, miRNA is yet to be used as a biomarker for diagnosis or prognosis in prostate cancer [115]. There are no commercially available miRNA signatures [116]. Nonetheless, it deserves competition with other biomarkers in future studies.

Table 1 (*Continued*)

Feature	Important or recent association with mPC outcome or biology	Utility or prospective utility as predictive marker in individual mPC patients and status in the current study
Tumor-derived extracellular vesicles (tdEVs or exosomes)	A high number of tdEVs associated with worse OS in CRPC patients with progressing disease [117]	It deserves competition with other biomarkers in future studies.
PSA (KLK3) isoforms and human kallikrein-related peptidase 2 (hK2; KLK2)	A 4K score combining high hK2 prior to RP associated with worse MFS in men with Gleason grade group 4–5 or seminal vesicle invasion at RP [118]	No studies have yet been reported in mPC.
Sarcosine	High serum sarcosine associated with worse PFS and OS in patients with mCRPC [119]	It deserves competition with other biomarkers in future studies.
Bone mineral density (BMD)	no studies of BMD and survival in mPC found; bone mineral density is known to decrease while on ADT [120].	Baseline BMD at study entry could hypothetically be used to guide antiandrogen therapy least likely to lead to SREs or to inform the use of denosumab.

ADT = androgen deprivation therapy; AR = androgen receptor; BRFS = biochemical recurrence-free survival; CRPC = castration-resistant prostate cancer; CSS = cancer-specific survival; CT = computed tomography; CTC = circulating tumor cell; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ECOG PS = Eastern Cooperative Oncology Group performance status; FDG = fluorodeoxyglucose; HDL-C = high-density lipoprotein cholesterol; MFS = metastasis-free survival; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; mPC = non-androgen-deprived metastatic prostate cancer; MRI = magnetic resonance imaging; NED = neuroendocrine differentiation; NEPC = neuroendocrine PC; OS = overall survival; PC = prostate cancer; PDW = platelet distribution width; PE = pulmonary embolism; PET = positron emission tomography; PFS = progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SRE = skeletal-related event; tdEV = tumor-derived extracellular vesicles, also called exosomes.
Biomarkers are listed in approximate decreasing order of strength of current evidence and frequency of current use.
Note that terms related to hormone status in prostate cancer are used as much as possible in the way they appear in the specific references cited. However, all uses of the term "hormone-refractory prostate cancer" have been replaced by the more recent term CRPC [121].

lower extremity weakness (A7), and a generalized tonic-clonic seizure after bilateral subdural hematomas developed (A2).

3.1.13. *Cachexia*

Using the international consensus definition of cancer cachexia from Fearon et al [19], all patients experienced at least one interval of cachexia. The ratio of BMI near the time of diagnosis of PC to BMI in the perimortem period ("BMI ratio") varied between 0.51 and 1.11 (median 0.82; Supplementary Fig. 2). Severe cachexia (BMI ratio $\leq$0.75) occurred in 11/31 (35%) and moderate cachexia (BMI ratio 0.76–0.89) occurred in 13/31 (42%) patients. Weights were generally stable until the last year of life, when a decreasing trend often emerged, with marked variation in the degree of final cachexia evident by BMI ratio reflected in upper arm soft tissues (Supplementary Fig. 3). The anatomic pattern of metastasis among the 11 men with severe cachexia did not differ significantly from the 11 men on the other end of the cachexia spectrum, and specifically, distribution of liver and/or adrenal metastases was not significantly different in these two groups. Notably, six of 31 (19%) patients gained weight during the 1–3 mo prior to death, likely due to fluid retention secondary to heart or renal failure, hypoalbuminemia, and increased corticosteroid use in the perimortem period. None of the six patients were found to have ascites at autopsy.

3.2. *Literature review of features distinguishing clinical aspects of high-risk PC and recent ICHOM data recommendations*

Table 1 attempts to list all features associated with outcome in high-risk patients in aggregate, listing utility or prospective utility in the management of individual patients (precision medicine) together with pertinent results from the current PELICAN33 study. The table is available for community curation and improvement (for details, please contact the corresponding author with "PELICAN33 Table 1" in the subject line).

A working group convened by the International Consortium for Health Outcome Measurement (ICHOM) produced a useful data collection reference guide for trials in patients with advanced PC [4]. We reviewed version 2.3.1 of these recommendations (2017) together with the PELICAN33 results and biomarker review, and found several areas where we believe that the recommendations can be improved in future versions. The areas for potential improvement are detailed in Supplementary Table 5 and summarized in the Supplementary material. The table is available for community curation and improvement (for details, please contact the corresponding author with "PELICAN33 Table A5" in the subject line).

4. Discussion

Can the results of this study help steer the PC research field to a more productive period? Between 1990 and 2019, the number of PC research articles published annually increased from 1012 to >7000 [21] and annual global cancer

research funding increased more than fivefold [22–25]. Some findings from this period of growth have been translated to benefit patients [26,27], but most of the published observations from 1990 to 2019 are poorly contextualized and largely unable to help individual patients or improve understanding of cancer biology. Now would be a good time for the cancer research community to take action to assure that future clinical and research data collection and reporting will be more likely to result in improved outcomes in patients. This research report is an attempt to inspire a specific process for achieving this result.

There is no substitute for the power of comprehensive combined clinical and autopsy studies as sources of ground truth, especially in clinical trials, and it is a failure of the research community not to recognize this. Although autopsy studies have been added at several institutions in recent years [28], systematic support for these efforts is largely absent. When recruiting for PELICAN33, we found that most patients with metastatic cancer intuitively understand the need for autopsy studies. They consented to participate because they wanted to help others, and they acknowledged benefit from participation by providing some measures of purpose to their suffering. The results reported here, coupled with our recent report linking clinical outcome with cancer evolution [11], make it clear that clinicians, researchers, and funding agencies should acknowledge a critical need for high-quality autopsy studies as an essential part of the transition to precision oncology. We are not implying that all mPC patients need to be a part of an autopsy study. We argue that an as-yet undetermined threshold number of autopsies must be conducted to refine what is learned in precision oncology trials.

The key to improving outcomes in men with mPC is to identify the most reliable way to rapidly separate effective from ineffective treatments, guided by a refined set of predictive biomarkers. The mPC clinical research field is currently awash with clinical and laboratory biomarkers of outcome, very few of which have been compared and prioritized. The research community regularly reports new biomarkers [29], but there has been no successful effort to determine which among these reported biomarkers are best and in what situations. We encourage the research community to cut the Gordian knot of complexity by working to update and improve the current versions of Table 1 (candidate biomarkers) and Supplementary Table 5 (vision for mPC precision oncology 2020–2050). By adopting some or all of the biomarkers and data recommendations, and fully sharing trial and molecular data, we can make far more rapid progress. The PELICAN33 data used for the current study, which are deposited in the European Genome Archive, represent an important first step in that process.

Although the current study is limited to 33 patients, it nonetheless demonstrates that accrual of high-quality longitudinal cohorts including autopsy analysis will be central to progress advancing precision oncology. The fact that the patients in PELICAN33 underwent autopsy between 1995 and 2004, prior to introduction of abiraterone and enzalutamide, is a positive attribute because the current study can provide a basis for comparison of phenotypic outcomes in future autopsy cohorts including patients treated with abiraterone, enzalutamide, and other more recently developed therapies.

5. Conclusions

In 2020 alone, an estimated 375 304 deaths from mPC occurred worldwide [20]. Despite this considerable toll, to our knowledge this report is the first comprehensive analysis of the clinical experience, histological data, and diagnostic autopsy findings in a cohort of men with mPC or, in fact, any lethal cancer. Despite the small cohort size of 33 patients, our novel findings include new candidate predictors of outcome (four complications that predict death within 2 yr, association between ISUP GG, and time to severe pain), new phenotypes (PSA bandwidth groups, NED subtypes, possible inverse association between mPC NED and pain, cachexia timing, and BMI change subgroups), as well as new insights into disease burden (subdural metastases are common but often clinically undetected, and the importance of distinguishing fracture and spinal cord compression when monitoring trial results). All these require validation in additional cohorts. Some of the findings could have been obtained with longitudinal clinical data alone, but the NED-related findings and the extent of disease/comorbidity findings depend entirely on the analysis of metastatic tissue from multiple sites, both of which effectively require autopsy data (Supplementary material). These results strongly suggest that larger longitudinal integrated phenomic studies of this type should be carried out.

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Study concept and design: Bova, Jasu.
Acquisition of data: Bova, Jasu, Koskenalho, Kesseli, Tolonen, Eisenberger, Carducci, Isaacs.
Analysis and interpretation of data: Jasu, Tolonen, Antonarakis, Beltran, Halabi, Eisenberger, Carducci, Loriot, Van der Eecken, Lolkema, Ryan, Taavitsainen, Gillessen, Högnäs, Talvitie, Taylor, Koskenalho, Murtola, Tammela, Auvinen, Kujala, Smith, Kellokumpu-Lehtinen, Isaacs, Nykter, Kesseli, Bova.
Drafting of the manuscript: Bova, Jasu, Kesseli.
Critical revision of the manuscript for important intellectual content: Jasu, Tolonen, Antonarakis, Beltran, Halabi, Eisenberger, Carducci, Loriot, Van der Eecken, Lolkema, Ryan, Taavitsainen, Gillessen, Högnäs, Talvitie, Taylor, Koskenalho, Ost, Murtola, Rinta-Kiikka, Tammela, Auvinen, Kujala, Smith, Kellokumpu-Lehtinen, Isaacs, Nykter, Kesseli, Bova.
Statistical analysis: Bova, Jasu, Kesseli, Halabi, Auvinen.
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Appendix A. Supplementary data

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