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Prostate Cancer

Prognostic Stratification of pN1 Prostate Cancer After Radical Prostatectomy: A Competing Risk Analysis from a Multi-institutional Cohort

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Abstract

Background and objective: Lymph node–positive (pN1) prostate cancer (PCa) is a heterogeneous disease, and a clear definition of prognostic groups is urgently needed. We aimed to assess cancer-related mortality (CRM) in different prognostic groups of pN1 patients, created based on the pathological PCa characteristics and number of positive lymph nodes (LN+).
Methods: We conducted a retrospective, multicentre cohort study including 894 patients with pN1 disease treated at 15 European high-volume centres. Independent predictors for CRM were identified and pooled. A prognostic model was constructed for the prediction of CRM, accounting for death from other causes as a competing risk. The 10-yr cumulative risk of mortality was assessed.
Key findings and limitations: Our model was based on pT stage (pT2-3a vs pT3b-4), surgical margin (SM) status (positive vs negative), and number of LN+ (1–4 vs >4), and included three prognostic groups. The favourable-prognosis group

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includes patients with pT2-3a and one to four LN+, or pT3b-4 with negative SM status. The intermediate-prognosis group included patients with pT2-3a disease and more than four LN+, or pT3b-4 disease, one to four LN+, and positive SM status. Patients in the poor-prognosis group had all three high-risk factors present. The C-index of this model was 0.73. The 10-yr cumulative CRM rates were 12% (95% confidence interval: 7.3–16%), 32% (24–40%), and 58% (40–76%), respectively, with significant differences between groups (hazard ratio 2.2–6.4, $p < 0.005$).

Conclusions and clinical implications: The pN1 patient population is extremely heterogeneous, with an increased risk of death from PCa rather than death from other causes. In this group of patients, primary cancer characteristics (pT stage, number of LN+, and SM status) still represent the driving factors of CRM.

Patient summary: Men with positive lymph nodes on pathology have an increased risk of dying from prostate cancer, rather than from other causes. Our proposed model stratifies patients into groups with different cancer-related prognosis and may aid in personalised clinical decision-making in a postoperative setting.

1. Introduction

The presence of lymph node invasion (pN1) after radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND) is generally considered to be associated with a poor prognosis. A systematic review revealed heterogeneity of the pN1 population with 10-yr cancer-specific survival rates ranging widely from 72% to 98% [1]. However, oncological outcomes vary widely and seem to depend on the number of positive lymph nodes (LN+), unfavourable primary tumour characteristics, patient age, and adjuvant treatment modalities [2–8]. In several previous reports, authors attempted to evaluate the importance of unfavourable primary tumour characteristics and aggregate these to identify prognostic groups that predict cancer-related mortality (CRM) [3,9–11]. These studies revealed heterogeneity of the pN1 population, with 8- and 10-yr cancer-specific mortality rates ranging widely from 1.4% to 28%. Most retrospective analyses in this setting aimed to identify a subgroup of patients with a favourable prognosis where adjuvant treatment can be postponed safely. In this regard, current European Association of Urology (EAU) guidelines recommend offering observation to a patient with two or fewer LN+ and a postoperative prostate-specific antigen (PSA) level of <0.1 ng/ml [12]. Even though multiple studies tried to identify prognostic factors to guide pN1 management, it remains unclear which patients have an increased risk of dying from prostate cancer (PCa) rather than from other causes. Incorporation of such data into clinical prognostic groups would be essential to improve our knowledge of the natural history of pN1 patients, who deserve more personalised clinical decision-making in the post-RP setting.

We hypothesised that node-positive patients after RP have different risks of CRM depending on the combination of unfavourable primary cancer characteristics, as well as the number of LN+. The objectives of our study were to assess the cumulative CRM and other cause mortality (OCM) in a pN1 patient cohort, and to identify patient groups with different CRM risks. This prognostic model is based on significant unfavourable pathological cancer characteristics and the number of LN+.

2. Patients and methods

2.1. Patient population

The European Multicenter Prostate Cancer Clinical and Translational Research Group (EMPaCT) database contains retrospectively collected data of 9508 consecutive patients with EAU-recommended criteria for high-risk localised or locally advanced PCa (PSA >20 ng/ml or cT stage T3–4 or Gleason score 8–10) who were treated with RP and PLND in 15 tertiary centres from 1987 to 2017. T stage was based on a digital rectal examination. Random biopsies were taken in the vast majority of patients, supplemented with targeted biopsies only if the tumour was palpable or visible on transrectal ultrasound. Preoperative staging was done using conventional imaging (computed tomography [CT] of chest-abdomen and bone scan). In the EMPaCT database, only cN0 patients were included. We identified 2251 consecutive patients with pN1 PCa. From this cohort, the dataset was defined excluding patients with missing information for at least one of the following variables: age, PSA, pathological International Society of Urological Pathology (pISUP) grade group (GG), pathological T stage (pT), surgical margin (SM) status, and number of LN+ or follow-ups. Patient selection is shown in Supplementary Fig. 1. Cause of death was based on a review of patient records and/or death certificates for each individual case. The time to CRM was defined as the time between RP and death attributed to PCa or cancer-related complications. This study was approved by institutional review boards or independent ethics committees.

2.2. Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables, and medians with interquartile

range (IQR) for continuous variables. The cumulative incidence function was used to estimate cancer-specific survival. The Kaplan-Meier method was used to estimate overall survival. The year of surgery and age were included as covariates in our model. Clustering by centre was accounted for by means of a random centre effect. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The Fine and Gray model was used for data analysis, accounting for the death from other causes as a competing risk. First, a multivariable model of independent predictors of CRM was developed using a forward model building procedure. Based on the predictors selected in this model, groups were defined as the unique combinations of pT stage (pT2-3a vs pT3b-4), pISUP (GG 1–3 vs GG 4–5), SM status (negative vs positive), and LN+ (one to four vs more than four). Using pairwise testing, predictors were combined in prognostic groups. Overlapping groups were collapsed until significant differences between all were reported. All analyses were performed correcting for neoadjuvant treatment and year of surgery. The discriminative performance of the different models was quantified using the C-index proposed by Wolbers et al [13] for the competing risk setting. The C-index was determined for a model with all possible combinations, as well as for the final model with different risk groups. A subanalysis of patients without neoadjuvant treatment and surgery after 2005 was performed. An exploratory analysis was performed to investigate the impact of adjuvant treatment regimens on survival in each risk group. Analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC, USA) with a two-sided significance level of $p < 0.05$.

3. Results

A total of 894 patients were identified for the final analysis. Of this cohort, 348 (39%) patients had pT3b-4 disease, 162 (18%) patients had more than four LN+ at ePLND, while 60% ($n = 540$) had positive SM status at final pathology. Of all patients, 22% ($n = 201$) received neoadjuvant hormonal therapy. The median follow-up was 63 mo (IQR 25–110) for the complete cohort. During the follow-up period, 189 deaths were registered, of which 111 were reported as PCa related. Of all patients, 220 (42%) received adjuvant radiotherapy (aRT) and 268 (53%) received adjuvant androgen deprivation therapy (ADT). Two out of three patients (66.1%) had an ISUP score of 4–5. Patient characteristics are summarised in Table 1.

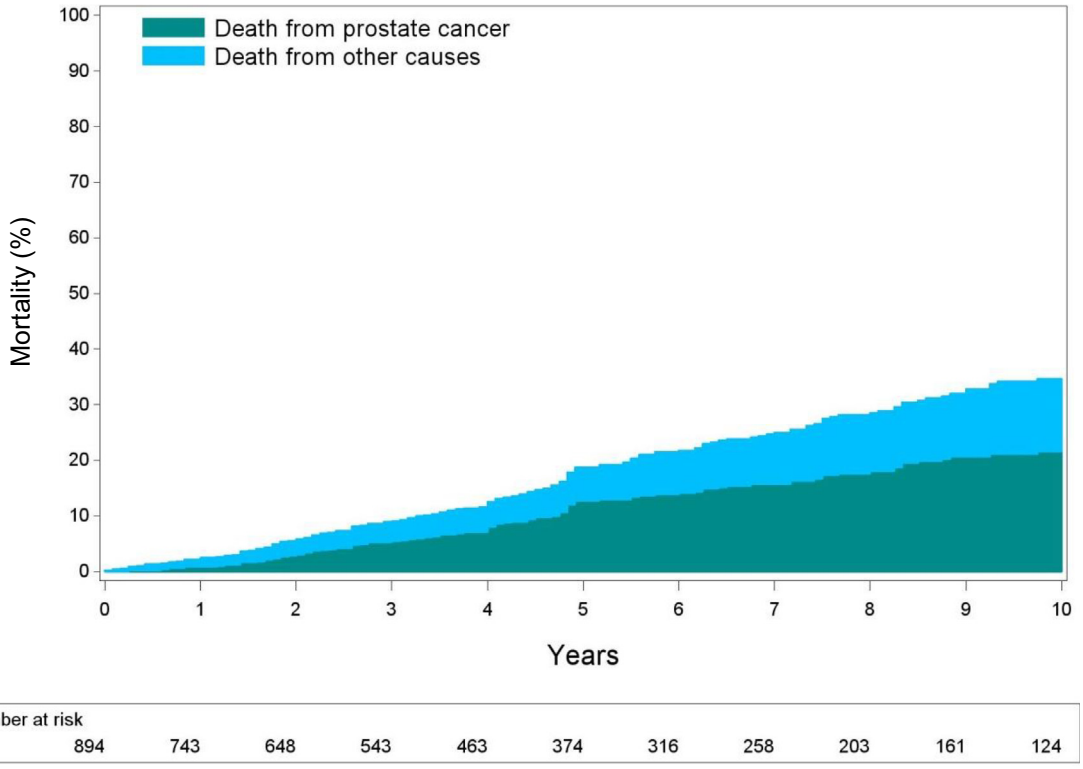
A multivariable analysis for the detection of independent predictors of CRM (Supplementary Tables 1 and 2) showed a significant influence of pT stage (HR 2.2, 95% CI [1.4–3.3]; $p = 0.0002$), LN+ (HR 2.5, 95% CI [1.6–3.9]; $p < 0.002$), and SM status (HR 1.8, 95% CI [1.1–2.8]; $p = 0.012$). Afterwards, a model with all potential combinations was created (C-index of 0.74; Supplementary Fig. 2). Pairwise testing of these combinations and collapsing groups with equal risk led to the configuration of three prognostic groups, and were labelled as favourable (pT2-3a and one to four LN+ [independent of SM status] or pT3b-4 and negative SM status [independent of LN+]), intermediate (pT2-3a and more than four LN+ [independent of SM status] or pT3b-4 and positive SM status and one to four LN+), or poor (pT3b-4 and positive SM status and more than four LN+) prognostic subgroups (Supplementary Table 3).

Table 1 – Patients' characteristics

Patient characteristics ($n = 894$)	Results
Age (yr), median (IQR)	65 (59–70)
PSA (ng/ml), *n* (%)	
0.1–10	243 (27)
10–20	200 (22)
>20	451 (51)
Clinical stage, *n* (%)	
cT1	85 (9.5)
cT2	198 (22)
cT3–4	490 (55)
Unknown	121 (14)
Biopsy ISUP GG, *n* (%)	
1	174 (20)
2	84 (9.4)
3	126 (14)
4	255 (29)
5	234 (26)
Unknown	21 (2.4)
Year of surgery, *n* (%)	
≤2005	409 (46)
Pathological stage, *n* (%)	
pT2	127 (14)
pT3a	419 (47)
pT3b-4	348 (39)
Pathological ISUP GG, *n* (%)	
1	83 (9.3)
2	91 (10)
3	129 (14)
4	193 (22)
5	398 (45)
Surgical margins, *n* (%)	
Negative	354 (40)
Number of LNs removed, median (IQR)	17 (11–24)
Number of positive LNs, median (IQR)	2 (1–4)
Number of positive LNs, *n* (%)	
1–2	573 (64)
3–4	159 (18)
>4	162 (18)
Follow-up, median (IQR)	63 (25–110)
Cancer-related death, *n* (%)	111 (12)
Other cause death, *n* (%)	78 (8.7)
Adjuvant treatment, *n* (%)	
None	147 (16)
RT alone	130 (15)
ADT alone	178 (20)
RT + ADT	90 (10)
Unknown	349 (39)
Neoadjuvant hormonal treatment, *n* (%)	
No	649 (73)
Yes	201 (23)
Unknown	44 (4.9)

ADT = androgen deprivation therapy; IQR = interquartile range; ISUP GG = International Society of Urological Pathology grade group; LN = lymph node; PSA = prostate-specific antigen; RT = radiotherapy.

Fig. 1 shows the cumulative incidence of CRM and OCM in the entire study cohort ($n = 894$). The cumulative 10-yr CRM and OCM rates were 22% (95% CI: 18–26) and 13% (95% CI: 9.8–15), respectively. The cumulative 10-yr overall mortality (OM) rate was 35% (95% CI: 30–40). The rates of 10-yr CRM risk in the three prognostic groups were 12%, 32%, and 58%, respectively (Fig. 2), with significant differences between all groups (HR 2.2–6.4, $p \leq 0.005$; Supplementary Table 4). This model had a C-index of 0.73. The 10-yr OCM rates were 12%, 16%, and 9.6%, respectively (Fig. 3). The subanalysis on patients without neoadjuvant



Years	CRD	OCM	OM
2, % (95% CI)	3.1 (1.9–4.4)	2.3 (1.5–3.1)	5.8 (4.1–7.5)
5, % (95% CI)	13 (10–16)	6.0 (4.4–7.5)	19 (16–22)
10, % (95% CI)	22 (18–26)	13 (9.8–15)	35 (30–40)

Fig. 1 – Cumulative prostate cancer mortality and other cause mortality. CI = confidence interval; CRD = cancer-related death; OCM = other cause mortality; OM = overall mortality.

ADT showed similar results in the overall cohort as well as in the model with the three risk groups, with C-indices of 0.70 and 0.69, respectively (Supplementary Tables 1 and 4). An overview of CRM, OCM, and OM of both the subgroups as well as the general population can be found in Table 2.

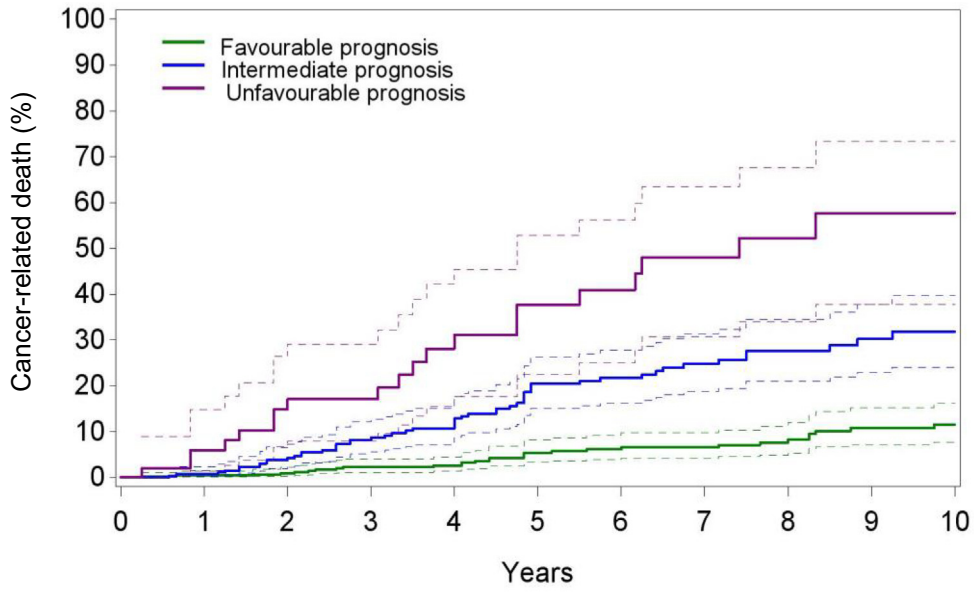
A multivariable competing-risk model was applied to assess the differential role of adjuvant treatment (none vs ADT alone vs radiotherapy [RT] alone vs RT + ADT) in the different prognostic subgroups. No statistical effect of adjuvant treatments was seen in these groups (Supplementary Table 5).

4. Discussion

In this study, we present the cumulative 10-yr CRM and OCM in a large RP series of almost 900 pN1 patients. Moreover, we stratified patients into groups with a significantly different risk of CRM according to unfavourable PCa characteristics and the number of LN+. Our analyses revealed several noteworthy findings.

First, we confirm that patients with pN1 indeed constitute a heterogeneous population with different risks of CRM. Our model demonstrated 10-yr CRM rates ranging between 12% and 58% in three prognostic risk groups. Our study is not the first to present such large variability in mortality in node-positive patients: Abdollah et al [9] reported 1.4–28% 8-yr CRM in five risk groups; similarly, Moschini et al [10] showed 10-yr CRM rates ranging from 5.9% to 27% in three risk groups. A recent publication by Marra et al [14] reported overall survival rates between 89% and 94%, and stratified patients into a high-risk group benefiting from aRT and a low-intermediate-risk group not benefiting from aRT. Our proposed stratification model seems capable of more accurately identifying patients with different risks of progression. An overview of these models is shown in Supplementary Table 6.

Second, the model demonstrated that pT3b-4 stage, positive SM status, and the number of LN+ are the main predictors of a poor prognosis. Overall, this supports previously published findings [15]. It is noteworthy, however, that the pISUP GG fell out of the model. This can probably be explained by the patient characteristics of our cohort. As the EMPaCT database included only clinically high-risk PCa patients, we observed that the vast majority (>65%) of included patients had pISUP GG of 4–5. The fact that pT stage and positive SM status are such important drivers of CRM is consistent with the hypothesis that death from PCa is probably driven mostly by the characteristics of the



Number at risk											
Favourable prognosis	537	435	388	327	285	238	205	168	138	116	96
Intermediate prognosis	303	264	225	184	156	119	97	80	57	40	25
Unfavourable prognosis	54	44	35	32	22	17	14	10	8	5	3

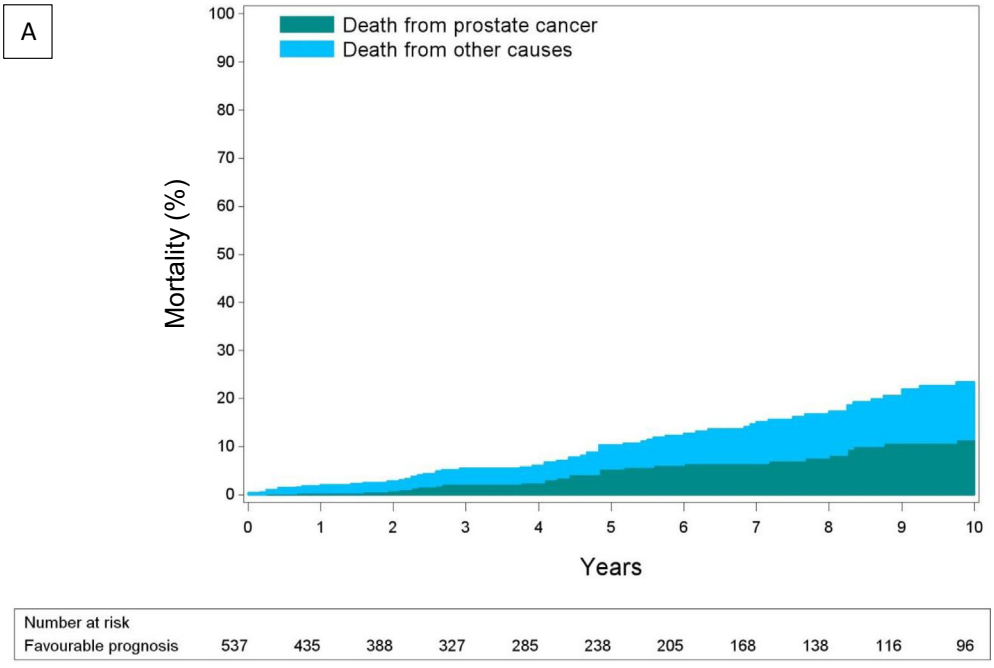
Years	Favourable prognosis	Intermediate prognosis	Unfavourable prognosis
2, % (95% CI)	0.91 (0.019–1.8)	4.2 (1.8–6.7)	17 (6.2–28)
5, % (95% CI)	5.3 (2.9–7.8)	20 (15–26)	38 (22–53)
10, % (95% CI)	12 (7.3–16)	32 (24–40)	58 (40–76)

Fig. 2 – Cancer-related death, divided by prognostic group. CI = confidence interval.

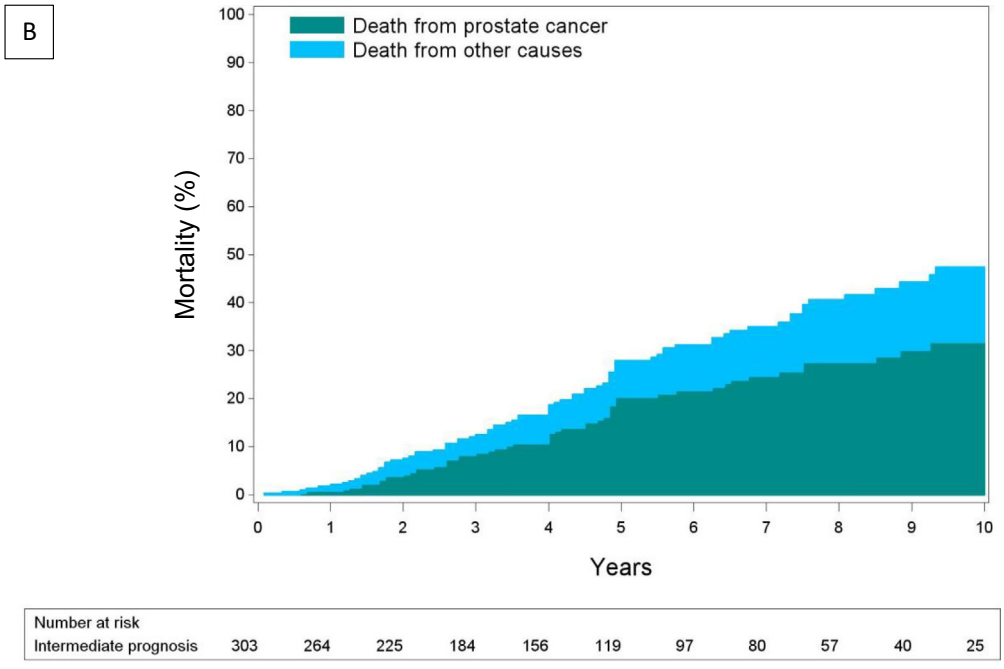
primary tumour. This statement is fully endorsed by the fact that patients with a high lymphatic metastatic tumour burden (more than four LN+) are represented in all three different prognostic subgroups. One could state that survival of patients with pT2-3a disease depends on the number of LN+, while the prognosis of patients with pT3b-4 disease depends mostly on the SM status (with the exception of patients with both positive SM status and more than four LN+).

Third, our analyses revealed that, overall, patients with pN1 disease are at an increased risk of dying from PCa rather than from other causes. Overall, the 10-yr CRM rate was 22%, while the OCM rate was 13%. Eggener et al [2] demonstrated similar trends of an increased risk of CRM compared with OCM in the pN1 population after RP. A CRM rate higher than the OCM rate was also reported by Rider et al [16] in a population-based cohort study of non-curatively treated patients. However, in their study, the definition of "regionally metastatic" PCa patients (T4 or N1 or PSA 50–100 ng/ml) does not accurately represent the true pN1 population, so comparison with our findings is difficult. In our study, men in the favourable-prognosis group had a similar risk of dying from other causes than from PCa (both 12%). This is more or less similar to that in patients with pN0 in the EMPaCT database (10-yr CRM: 8.1%). However, in the intermediate- and unfavourable-prognosis patient groups, CRM was two- and six-fold higher than OCM (32% vs 16% and 58% vs 9.6%, respectively). Importantly, 10-yr CRM gradually increased in each prognostic group, while the difference in OCM was marginal and even decreased slightly towards the unfavourable-prognosis group.

Fourth, one can argue that the use of pN1 prognosis groups is outdated as the current EAU guidelines do not recommend routinely performing an ePLND or even using nomograms anymore [12]. Despite these new recommendations, our model shows important counselling possibilities for patients with pN1 disease regarding adjuvant treatment options. It is known that patients with haematogenous metastases (bone or visceral) have a worse prognosis than those with lymph node–only metastatic disease [17] and that the ways of metastasis development are partially independent [18]. However, since most patients develop locoregional lymph node metastases first, it remains important to critically evaluate pN status if the risk is sufficiently high. Current EAU guidelines suggest staging of newly diagnosed high-risk PCa patients using prostate-specific membrane antigen positron emission tomography (PSMA PET)/CT if available [12]. In case of positive nuclear imaging, one can

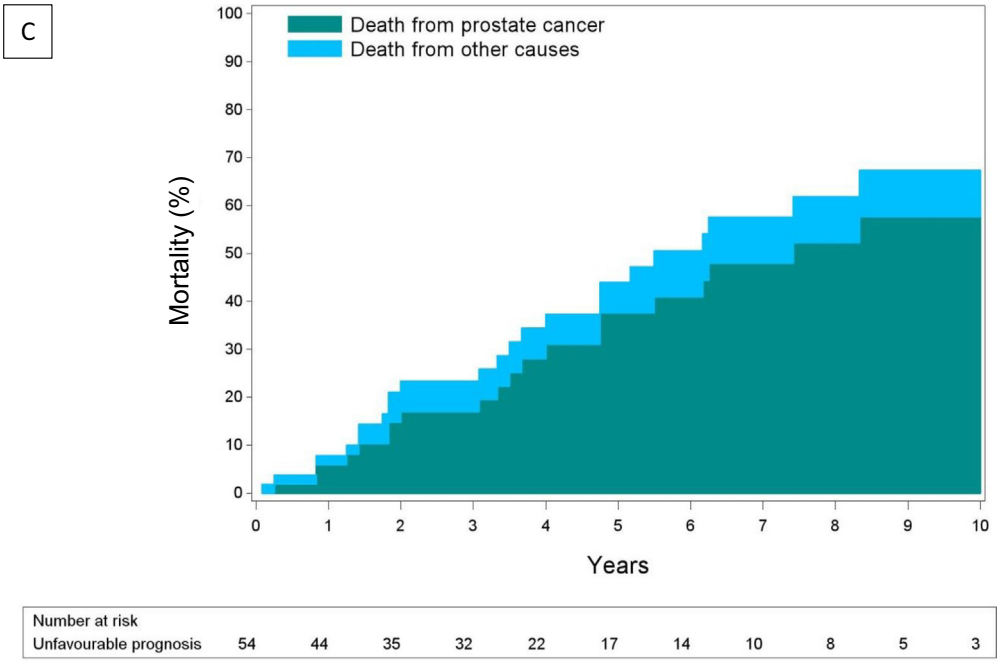


Years	CRD	OCM	OM
2, % (95% CI)	0.91 (0.019–1.8)	1.9 (0.66–3.1)	2.8 (1.3–4.3)
5, % (95% CI)	5.3 (2.9–7.8)	5.0 (2.7–7.2)	10 (7.1–14)
10, % (95% CI)	12 (7.3–16)	12 (7.6–16)	23 (18–29)



Years	CRD	OCM	OM
2, % (95% CI)	4.2 (1.8–6.7)	3.4 (1.2–5.5)	7.6 (4.4–11)
5, % (95% CI)	20 (15–26)	7.6 (4.1–11)	28 (22–34)
10, % (95% CI)	32 (24–40)	16 (9.5–22)	47 (39–56)

Fig. 3 – Cumulative prostate cancer mortality and other cause mortality, by prognostic group: (A) favourable prognosis, (B) intermediate prognosis, and (C) unfavourable prognosis. CI = confidence interval; CRD = cancer-related death; OCM = other-cause mortality; OM = overall mortality.



Years	CRD	OCM	OM
2, % (95% CI)	17 (6.2–28)	6.3 (0–13)	23 (11–36)
5, % (95% CI)	38 (22–53)	6.3 (0–13)	44 (28–60)
10, % (95% CI)	58 (40–76)	9.6 (0.39–19)	67 (50–85)

Fig. 3 (*continued*)

Table 2 – Patients' characteristics and mortality rates in three risk-groups

	Favourable prognosis (*n* = 537)	Intermediate prognosis (*n* = 303)	Unfavourable prognosis (*n* = 54)	All patients (*n* = 894)
	pT2-3a, SM–, –4 LN+ (*n* = 224)	pT2-3a, SM–, >4 LN+ (*n* = 40)	pT3b-4, SM+, >4 LN+ (*n* = 54)	
	pT2-3a, SM+, 1–4 LN+ (*n* = 223)	pT2-3a, SM+, >4 LN+ (*n* = 59)		
	pT3b-4, SM–, 1–4 LN+ (*n* = 81)	pT3b-4, SM+, 1–4 LN+ (*n* = 204)		
	pT3b-4, SM–, >4 LN+ (*n* = 9)			
Age (yr), median (IQR)	65 (59–70)	65 (60–70)	65 (60–70)	65 (59–70)
PSA (ng/ml), median (IQR)	16 (8.5–29)	28 (13–59)	30 (13–64)	20 (9.6–39)
Adjuvant treatment, *n* (%)				
None	103 (19)	40 (13)	4 (7.4)	147 (16)
RT alone	87 (16)	37 (12)	6 (11)	130 (15)
ADT alone	56 (10)	101 (33)	21 (39)	178 (20)
RT + ADT	28 (5.2)	56 (18)	6 (11)	90 (10)
Unknown	263 (49)	69 (23)	17 (31)	349 (39)
Follow-up (mo), median (IQR)	53 (19–97)	48 (23–86)	45.5 (22–81)	63 (25–110)
Mortality rate, *n* (%)	74 (14)	85 (28)	23 (43)	189 (21)
CRM, % (95% CI)				
2 yr	0.91 (0.02–1.8)	4.2 (1.8–6.7)	17 (6.2–28)	3.1 (1.9–4.4)
5 yr	5.3 (2.9–7.8)	20 (15–26)	38 (22–53)	13 (10–16)
10 yr	12 (7.3–16)	32 (24–40)	58 (40–76)	22 (18–26)
OCM, % (95% CI)				
2 yr	1.9 (0.66–3.1)	3.4 (1.2–5.5)	6.3 (0–13)	2.3 (1.5–3.1)
5 yr	5.0 (2.7–7.2)	7.6 (4.1–11)	6.3 (0–13)	6.0 (4.4–7.5)
10 yr	12 (7.6–16)	16 (9.5–22)	9.6 (0.4–19)	13 (9.8–15)
OM, % (95% CI)				
2 yr	2.8 (1.3–4.3)	7.6 (4.4–11)	23 (11–36)	5.8 (4.1–7.5)
5 yr	10 (7.1–14)	28 (22–37)	44 (28–60)	19 (16–22)
10 yr	23 (18–29)	47 (39–56)	67 (50–85)	35 (30–40)

ADT = androgen deprivation therapy; CI = confidence interval; CRM = cancer related mortality; IQR = interquartile range; LN+ = number of positive lymph nodes; OCM = other cause mortality; OM = overall mortality; PSA = prostate specific antigen; RT = radiotherapy; SM = surgical margin.

assume that the patient is indeed (pathologically) node positive. In case of negative imaging, however, LN+ cannot be excluded as smaller lymph nodes can be missed [19]. In order to reduce the number of unnecessary ePLND procedures in PSMA PET–negative patients while aiming for optimal nodal staging, novel nomograms including next-

generation imaging findings have been developed [20]. These nomograms are ideally suited to guide the ePLND informed decision-making together with the patient.

While we know that pN1 patients with miN1 disease have worse prognosis than those with miN0 [21], our cohort consists of high-risk PCa patients with cN0 on conventional imaging. Many of these patients would probably have had miN1 disease on PSMA PET. Furthermore, while PSMA PET/CT staging is recommended and has even shown to improve outcome due to better stratification [22], this is not yet routinely available in all centres. These patients will still be surgical candidates. As our model uses only postoperative risk factors, this remains of clinical relevance for urologists. We, however, believe that our findings should be validated in a PSMA PET–staged population.

Current EAU guidelines state three possible treatment options for pN1 patients: (1) adjuvant ADT, (2) aRT + ADT, or (3) observation if unmeasurable postoperative PSA and two or fewer LN+ [12]. The therapeutic effect of adjuvant treatment is driven mainly by intensification of local control in the presence of unfavourable primary tumour characteristics [23]. Our results indirectly support these findings. As stated above, our results provide a strong basis for new treatment recommendations based on a more personalised approach. Even though these prognostic groups should be validated externally before being used in routine clinical practice, patients in the three prognostic groups should not be treated in a similar way. Our exploratory analysis of adjuvant treatment options provides us with some guidance. The favourable-prognosis group could probably be managed expectantly with regular PSA follow-up. Adjuvant treatments do not seem to provide any benefit (potentially even worsen survival). In case of biochemical recurrence, salvage treatment is feasible. Patients in the unfavourable group should receive PSMA PET/CT (if not yet received) and probably be treated as metastatic hormone-sensitive PCa patients. In case of negative imaging, adjuvant locoregional RT could still be considered. Making treatment decisions for patients in the intermediate-prognosis group is particularly challenging. However, these patients may be especially well suited for enhanced local control through a combination of locoregional RT and ADT. Recent data from the PART trial suggest a benefit from the inclusion of the para-aortic lymph node field [24]. This intensified aRT schedule might be of particular interest/benefit for these patients. The proposed treatment strategies for each prognostic group should be explored further and validated in large-scale prospective clinical trials.

Altogether, our findings demonstrate that most pN1 patients have a higher risk of dying from PCa than from other causes. Our findings are in line with previously published studies investigating adjuvant or salvage treatment options [4,9,15,25]. The proposed model shows the ability to stratify patients into different prognostic groups with good performance (C-index of 0.73). Our results support the view that not all pN1 patients are affected by systemic disease, as can be seen through the low long-term CRM in the favourable subgroup. Application of this model in clinical practice could optimise patient selection for treatment (de)intensification, thereby likely improving cancer-related outcomes and avoiding adverse events associated with unnecessary or ineffective treatment options.

The main limitations of our study are the retrospective design (with all associated biases), a considerable number of missing data, exclusion of cN1 patients in the initial cohort, and the lack of standardised postsurgical treatment regimens. Even though patients were staged using standard-of-care imaging (no PSMA PET/CT was available), there is a possibility of underestimating cN1 and potentially even cM1 patients. Furthermore, the patient accrual period was longer, leading to heterogeneity in follow-up treatment. This leads to varying follow-up periods (median of 63 mo), resulting in the fact that 10-yr outcomes should be interpreted with caution. In addition, our study did not include a central pathology review. This results in a lack of, for example, information about LN+ size and variant histology (eg, cribriform growth pattern). Information about PSA persistence was not available. Furthermore, some subgroups have included a limited number of patients.

Despite these limitations, our study has some important strengths. It is the largest and the first surgical series to provide information on CRM and OCM in the pN1 population using a competing-risk analysis. All patients were treated at tertiary referral centres with dedicated uro-oncological staff, reflecting state-of-the-art management at the time. Our model stratifies patients into different prognostic groups based on significant tumour features going from favourable up to unfavourable prognoses. This is different from previous studies where only a favourable subgroup was identified. Our suggested model is easy to use, demonstrates good performance, and can be proposed in any situation of pN1 disease.

5. Conclusions

This study demonstrated that patients with pN1 are at an increased risk of dying from PCa than from other causes. However, the pN1 population is extremely heterogeneous and the risk of cancer-related death is still mainly driven by (unfavourable) primary tumour characteristics rather than by the number of LN+. From this perspective, our prognostic stratification model allows us to visualise different subgroup prognoses based on the combination of pathological T stage, SM status, and the number of LN+. These subgroups allow us to incorporate pN1 prognostic groups in future trials, tailoring adjuvant treatment options to individual patient risks.

Author contributions: Steven Joniau had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

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