Independent Validation of a Risk Stratification Model Predicting Survival in Patients with Metastatic Hormone-Sensitive Prostate Cancer

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Key Words: Prognostic model, Overall survival, Metastatic prostate cancer, Systemic therapy, Chemotherapy.

Abstract. Background/Aim: The aim of this study was to analyze the survival predictions obtained from an online nomogram, originally developed in two US patient cohorts with metastatic hormone-sensitive prostate cancer, because clinical practice and survival outcomes may vary on an international level. Materials and Methods: A retrospective single-institution study of 197 patients, managed according to Norwegian guidelines, was performed. Model-predicted survival was assessed online and compared to observed survival. Results: The median overall survival was 32.7 months. The nomogram predicted 3-year survival probabilities of 3-72% and 5-year probabilities of 0-54% in individual patients. Regarding 3-year prediction, the median was 47% (observed 3-year survival: 45%). The corresponding 5-year figures were 30% (nomogram) and 25% (observed). In univariate Cox regression, predicted 3-year and 5-year likelihood of survival were associated with observed survival of the study population (both $p<0.001$). Conclusion: The survival predictions from the US nomogram were correlated with observed survival in this Norwegian validation study.

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Men with metastatic hormone-sensitive prostate cancer (mHSPC) have recently gained access to more efficacious up-front systemic treatment (1). Both controlled randomized clinical trials and real-world studies have shown improved survival with androgen deprivation therapy (ADT) combined with docetaxel compared to the previous standard of ADT alone (2-7). Also, newer androgen receptor signaling inhibitors (ARSI) and ARSI treatment plus docetaxel have resulted in promising outcomes (8, 9). Despite such advances, mHSPC remains a heterogeneous disease with highly variable survival. Factors such as tumor biology (e.g. Gleason score or grade group) and pattern of metastases (e.g. visceral *vs.* bone only) impact on response duration and survival, and patient characteristics such as comorbidity and age may modify decision making and selection of first-line systemic treatment (10). Risk stratification models are useful when counseling men with newly diagnosed mHSPC. Labe et al. developed and validated a model based on information from the National Cancer Database (NCDB, training dataset) and the Surveillance, Epidemiology, and End Results (SEER) database (validation dataset) (11). The NCDB dataset included the time period 2010-2014 (n=13,818; SEER: 2010-2015; n=9,318). A nomogram was created, which may be used to predict 3- and 5-year survival (online calculation: https://tinyurl.com/prostate-met). Nomogram components included grade group, T stage, N stage, metastases (visceral, bone only, non-regional lymph node), prostate-specific antigen (PSA), race and age. In order to assess the model in a different geographical region, we performed an independent validation study (Norway as compared to USA). Due to differences between healthcare systems and recommended treatment, survival outcomes and risk stratification may vary in international comparisons.

Patients and Methods

The study resembled previous validation approaches by our group (12, 13) and utilized a continuously maintained single-institution database, which collects data from unselected Norwegian patients with mHSPC managed in routine clinical practice since 2006 in line with national treatment guidelines. Systemic therapy was discussed in a multidisciplinary urology tumor board and tailored to disease burden and biology, organ function and patient preferences. Staging consisted of computed tomography (CT) and isotope bone scans or magnetic resonance imaging (MRI) of the spine and pelvic bones. If clinically relevant, other modalities were added to clarify patterns of metastases.

Labe *et al.* (11) developed a web platform for data entry and display of predicted survival (3- and 5-year probabilities; https://tinyurl.com/prostate-met), which was utilized in our study. Both 3- and 5-year predictions were tabulated. Complete baseline information was available for all patients. Overall survival (time to death) from the day of diagnosis of mHSPC was calculated employing the Kaplan–Meier method (SPSS 27; IBM Corp., Armonk, NY, USA). The minimum follow-up was 37 months, because 3-yr survival data had to be available. The median follow-up of all 22 censored patients was 60 months. Date of death was known in all other patients. To ensure sufficient group sizes, three strata were analyzed (low, medium, high survival rates). Cox regression was employed to assess the correlation between survival and nomogram-predicted likelihood of 3- and 5-year survival (continuous variables), respectively. The database was created for the purpose of regional quality-of-care analyses, has already been utilized and does not require additional approval by the local Ethics Committee (REK Nord).

Results

The online calculator was employed to obtain survival predictions for all 197 patients in our single-institution database. The median patient age was 72 years (Table I). A typical patient had *de novo* metastatic disease, bone only metastases and a grade group 4 or 5 primary tumor. The median overall survival was 32.7 months. The nomogram predicted 3-year survival probabilities of 3-72% and 5-year probabilities of 0-54% in individual patients. Regarding 3-year prediction, the median was 47% (observed 3-year survival: 45%). The corresponding 5-year figures were 30% (nomogram) and 25% (observed). In univariate Cox regression, predicted 3-year and 5-year likelihood of survival were associated with observed survival of the study population (both $p<0.001$). The Kaplan-Meier curves of the 3-year survival analysis are shown in Figure 1, while Figure 2 shows the 5-year results (both statistically significant).

Discussion

The purpose of this study was the additional validation of a recent prognostic model predicting survival of men with mHSPC. The original nomogram development and validation study (11) included to large US cohorts (NCDB, SEER). In the NCDB dataset, 84% of patients had bone only metastases (74% in our study). Stage T1 was recorded in 35% (10% in our study). White patients represented 78% of the cohort (100% in our study). Grade group 5 was more common in the NCDB dataset (59% *vs.* 47%). Differences such as less advanced T stage may translate into longer survival of patients in the NCDB dataset, but this effect is probably offset by the higher proportion of patients with unfavorable grade group. The main difference between the datasets lies in the size of the cohorts. In order to improve the statistical power of our study, we

allowed for inclusion of patients who were treated earlier or later than their US counterparts. The availability of 3-year survival data in living patients was the minimum requirement for inclusion in our study. When interpreting the median overall survival of 32.7 months, it is important to consider that only 4% of the patients had received docetaxel plus ADT. The vast majority were treated in the historical ADT only era. These patients also lacked access to some of the survival-prolonging agents for metastatic castration-resistant disease, which became available during the time period of the study (7). In our recent study of docetaxel plus ADT for mHSPC median survival was 56 months (6).

Overall, as also illustrated in the Figures, the nomogram provided useful risk stratification. Perfect concordance between predicted and observed survival was not observed, particularly in the best of the three prognostic strata. Our approach with three approximately equally sized strata was chosen to ensure better statistical power than other possible classifications with a larger number of prognostic groups. Whether the differences between predicted and observed survival arise from the small study size, different time periods, or principally different diagnostic and therapeutic approaches in Norway is difficult to estimate. Additional studies from other countries are required to shed more light on this issue.

Future research may also include additional prognostic factors, which were not available in the NCDB dataset, and thus are not included in the nomogram. For example, performance status, anemia, serum alkaline phosphatase, lactate dehydrogenase or C-reactive protein may represent promising candidates (14). In addition, early response to treatment (magnitude of PSA decline, depth of response)

after 3 or 7 months may provide information about the durability of the effect and future course of the disease (15, 16).

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Figure 1. Actuarial overall survival for three different strata, *p*<0.001 (pooled over all strata). Group size: n=68, 63 and 66, respectively. Poor prognosis: predicted 3-year rate <40%. Intermediate prognosis: predicted 3-year rate 40-53%. Good prognosis: predicted 3-year rate >53%. Observed 3-year rates for the three strata: 35, 44 and 52%, respectively. Median survival: 25.0, 32.3 and 38.3 months, respectively.

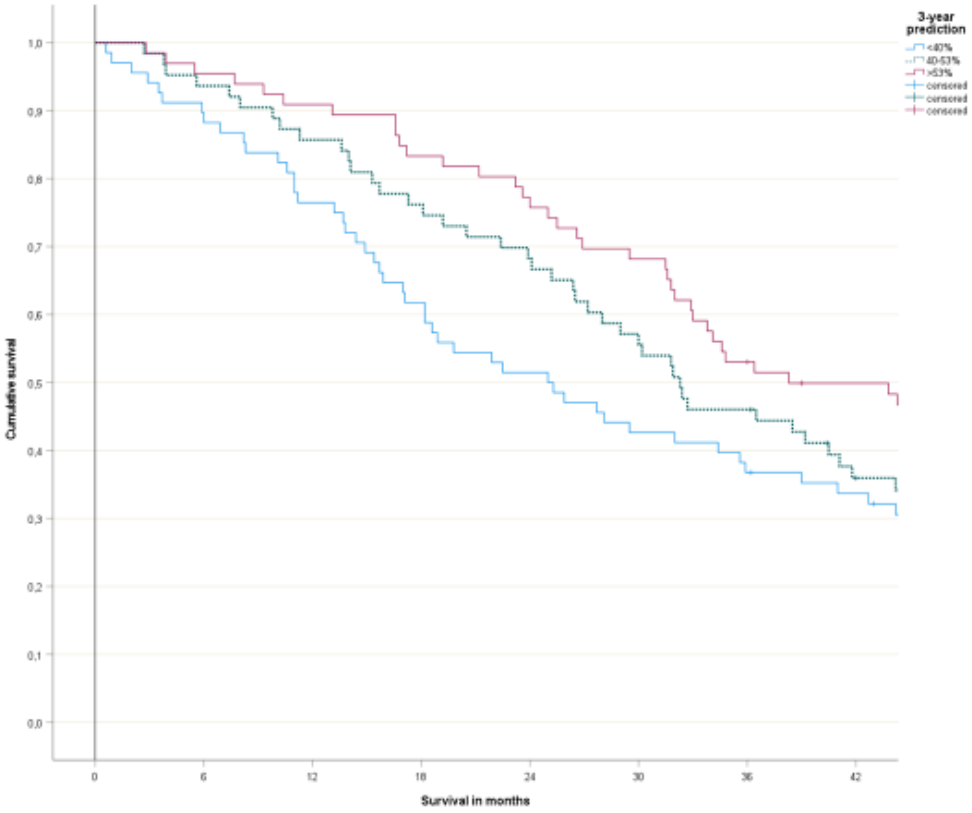

Figure 2. Actuarial overall survival for three different strata, $p<0.001$ (pooled over all strata). Group size: n=53, 81 and 63, respectively. Poor prognosis: predicted 5-year rate <21%. Intermediate prognosis: predicted 5-year rate 21-36%. Good prognosis: predicted 5-year rate >36%. Observed 5-year rates for the three strata: 12, 24 and 32%, respectively. Median survival: 21.9, 32.4 and 38.3 months, respectively.

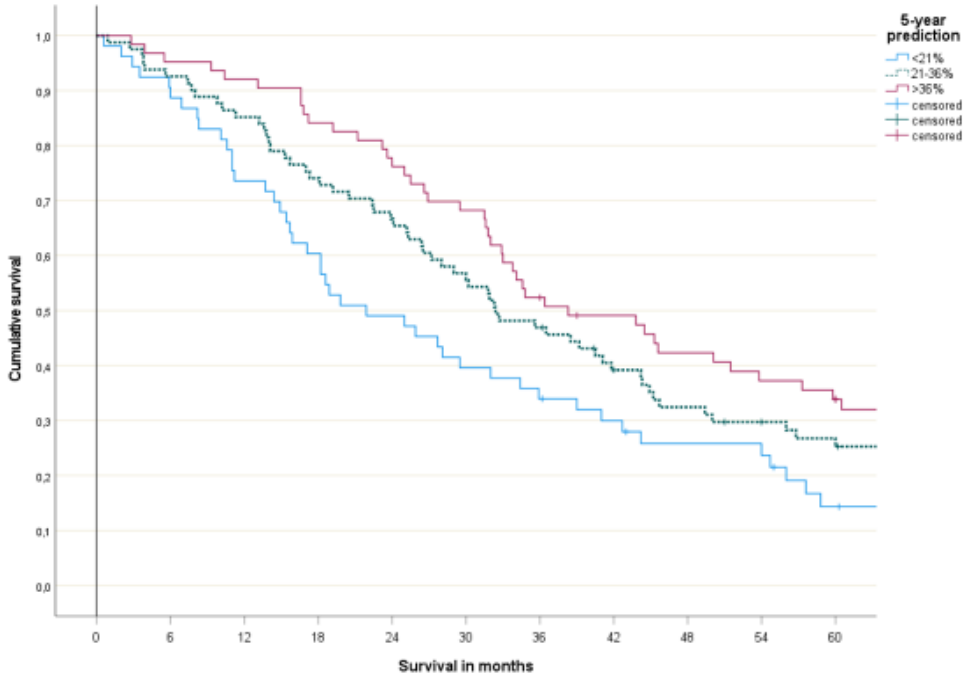

Table I. Baseline characteristics in 197 patients

Parameter	n	%
Caucasian race	197	100
Age		
<50 years	1	1
50s	17	9
60s	57	29
70s	90	46
≥80	32	16
Disease presentation		
De novo metastatic disease	115	58
Initially non-metastatic disease	82	42
Pattern of metastases		
Bone only metastases	146	74
Visceral metastases	11	6
Non-regional lymphatic metastases	40	20
Histology, grade group		
1	23	12
2	31	16
3	19	10
4	32	16
5	92	47
Stage		
T1	20	10
T2	57	29
T3	83	42
T4	37	19
N0	75	38
N1	59	30
Nx	63	32
Prostate-specific antigen (PSA)		
<10 µg/L	32	16

10-20 µg/L	19	10
>20 µg/L	146	74
Treatment		
Upfront docetaxel	7	4
Median values		
Median age, range (years)	72	48-90
Median PSA, range (µg/L)	51	0.2-10,300