



# External validation of a nomogram for the prediction of 10-year life expectancy in candidates for radical prostatectomy

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## Abstract

**Purpose** Accurate life expectancy prediction is essential in decision-making concerning treatment of clinically localized prostate cancer (PCa). Nomogram predictions are more precise and reproducible than clinician's estimations. The most accurate nomogram addressing 10-year life expectancy in PCa patients has not been externally validated to date. Therefore, we aimed to evaluate the performance of this nomogram in a contemporary external cohort.

**Patients and methods** For this, we enrolled all consecutive patients, who underwent radical prostatectomy at a single institution between 2005 and 2007. Age at surgery and Charlson Comorbidity Index (CCI) were assessed. PCa-related deaths and patients under 55 years were excluded as indicated by the nomogram. The prediction of 10-year life expectancy was calculated according to the nomogram and compared to actual survival data. Calibration and discrimination were assessed using calibration plots.

**Results** Overall, 1597 patients were evaluated, with a median age of 64 years (range 55–78 years) at surgery and a median follow-up of 134.4 months (range 0.1–161.7 months). Median CCI was 0 (range 0–10). At 10 years, 134 patients (8.4%) had died of other causes than PCa. The nomogram showed moderate discrimination capacities on receiver-operator characteristic analysis (c-index: 0.64). On calibration curves, the nomogram underestimated the actual life expectancy.

**Conclusion** The performance accuracy of this prediction model was moderate and underestimated 10-year life expectancy of contemporary PCa patients. In conclusion, prediction of life expectancy remains challenging with a continued need for more precise tools.

**Keywords** Prostate cancer · Life expectancy · External validation · Prediction model · Nomogram

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Sophie Knipper and David Pröwrock contributed equally to this work.

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## Introduction

Prostate cancer (PCa) is one of the most common male malignancies worldwide. Since the regular use of prostate-specific antigen (PSA) screening in the early 90s, the diagnosis shifted towards earlier stages and PSA-based diagnosis has become the standard of care in industrialized countries [1]. Because of this development, the proportion of patients diagnosed with early detected cancer has increased substantially, leading to a high eligibility for immediate or deferred local treatment, i.e., radical prostatectomy, radiation therapy, or active surveillance [2]. For this, all major current guidelines consider a life expectancy (LE) of at least 10 years mandatory for any survival benefit of local treatment in PCa [3–6]. However, no specific tool for the prediction of LE as crucial element in decision-making is either mentioned or recommended.

Prediction of LE is challenging, especially in PCa patients who might be diagnosed via screening and tend to live longer than the “non-cancer” population [7]. Several prediction models have been developed addressing this issue [8–10]. The model with the highest predictive accuracy was published in 2007 by Walz et al. [11, 12]. It examines the risk of non-cancer mortality (other-cause mortality, OCM) within 10 years of receiving definitive therapy, and included age, treatment type, and Charlson Comorbidity Index (CCI). However, since no external validation has been presented so far, we sought to test the performance of this nomogram in an external cohort.

## Patients and methods

### Study cohort

A total of 3141 consecutive patients treated with radical prostatectomy (RP) for localized PCa in a single high-volume European centre between 2005 and 2007 were included in this study. The majority of these patients were diagnosed due to an elevated PSA and reflect a referral population without structured screening program.

Patients with missing or incomplete data on 10-year follow-up were excluded. In addition, PCa-related deaths were also excluded, as the Walz nomogram aims on overall survival (OS) prediction independent from the effect of PCa-specific mortality (CSM). Only patients over 55 years were included as the Walz nomogram was designed for this patient group. Age at surgery and comorbidities coded in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) were assessed. These allow defining the Charlson Comorbidity Index (CCI) at the time of treatment which can predict the risk of mortality according to the existing comorbidities [13]. Questionnaires and death reports of the national cancer registry were used annually for follow-up. In case of uncertainty of the cause of death, patients' relatives and referring physicians were contacted directly. All data were prospectively stored in an institutional database (FileMaker Pro 10; FileMaker, Inc., Santa Clara, CA, USA). The study was approved by our internal study board.

### Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. Kaplan–Meier plots graphically depicted the other-cause mortality of the cohort. Nomogram predictions of the 10-year life expectancy were compared with actual follow-up. For this, we tested both, the discrimination, i.e., how well the prediction

model discriminates between different patients, and the calibration, i.e., if the prediction model can approximate as close as possible to the actual number of events, of the nomogram [14].

The discrimination was tested using the Heagerty's concordance index (c-index), which is similar to an area under the receiver-operating characteristics curve (AUC) and applicable to time to event data [15]. It describes the probability that, given two randomly drawn patients, the patient who experienced an event (e.g., death) had a higher risk score than a patient who had not experienced the event. The maximum c-index value is 1.0, which indicates perfect prediction, while 0.5 indicates the probability of correctly predicting the outcomes by random chance, i.e., tossing a coin.

Calibration of the nomogram was assessed by comparing its predicted probability of death with actual death. Sensitivity analyses relied on a subgroup of patients without secondary treatment, as described in the original publication [11]. All statistical tests performed were two sided, and *p* values < 0.05 were considered statistically significant. Statistical analyses were performed using R version 3.3.4 (R Foundation for Statistical Computing, Vienna, Austria; <https://www.r-project.org>).

## Results

Overall, 3141 patients underwent RP between 2005 and 2007 at University-Hospital Hamburg, Germany. Of those, 57 (1.8%) died of PCa within 10 years of RP, for 141 patients no follow-up data were available, and 346 patients were under 55 years old. This resulted in a cohort of 2597 men. Of those, 1597 patients had a follow-up of at least 10 years or died during this time of other causes than PCa. Table 1 lists the characteristics of patients included in this validation and those of the original cohort used to develop the nomogram.

The median age at surgery, median follow-up, and median CCI were 64 years (range 55–78 years), 134.4 months (range 0.1–161.7 months), and 0 (range 0–10), respectively (Table 1). Of those, 134 (8.4%) patients had died at 10 years. Moreover, 381 patients received secondary treatments, such as adjuvant or salvage radiation.

In Kaplan–Meier analyses, the 10-year survival probability was 91.6% [95% confidence interval (CI) 90.3–93.0%]. After stratification according to CCI, the 10-year survival probability rates were 94.1% (CI 92.8–95.5%) for CCI 0, 87.7% (CI 83.3–92.3%) for CCI 1, and 81.2% (CI 76.0–86.7%) in CCI ≥ 2, respectively (*p* < 0.0001, Figs. 1 and 2).

In the validation of the Walz nomogram, the concordance-index (c-index) on receiver-operator characteristics analysis was 0.64, showing a moderate discrimination capacity of the prediction model in this external cohort.

**Table 1** Characteristics of current validation cohort of 1,597 radical prostatectomy patients treated between 2005 and 2007 in a single European institution in comparison to the original development cohort of the Walz nomogram

Variable	Current validation cohort		Original development cohort (radical prostatectomy patients only)	
	No.	%	No.	%
Total patients	1597	100	5955	100
Age at treatment (years)				
Mean	64.0		64.2	
Median	64		64	
Range	55–78		55–89	
< 60	310	19.4	1188	19.9
60–69	1114	69.8	3886	65.3
≥ 70	173	10.8	881	14.8
Charlson Comorbidity Index				
Mean	0.5		1.1	
Median	0		1	
Range	0–10		0–11	
0	1887	74.3	2704	45.4
1	203	12.7	1397	23.5
2	139	8.7	1,024	17.2
3	33	2.1	472	7.9
4	20	1.3	221	3.7
5	4	0.3	77	1.3
6	8	0.5	40	0.7
≥ 7	3	0.1	29	0.4
Follow-up time, months				
Mean	129.1		88.8	
Median	134.4		84	
Range	0.1–161.7		0.1–186	
Deaths (overall)	170	11.9	903	15.2
Deaths (at 10 years)	134	8.4		
Overall survival probability				
10 years		91.6		81.1

Deaths are related to other causes than prostate cancer

On calibration curves, the model underestimated the actual life expectancy (Fig. 3).

In sensitivity analyses, including the subgroup of patients without secondary treatment ( $n = 1216$ , Supplementary Table 1), virtually, the same results were observed. Specifically, in Kaplan–Meier analyses, the 10-year survival probability was 93.0% (CI 91.7–94.5%). When using this subgroup for validation of the Walz nomogram, the c-index on receiver-operator characteristics analysis was 0.62 (Supplementary Fig. 1).

## Discussion

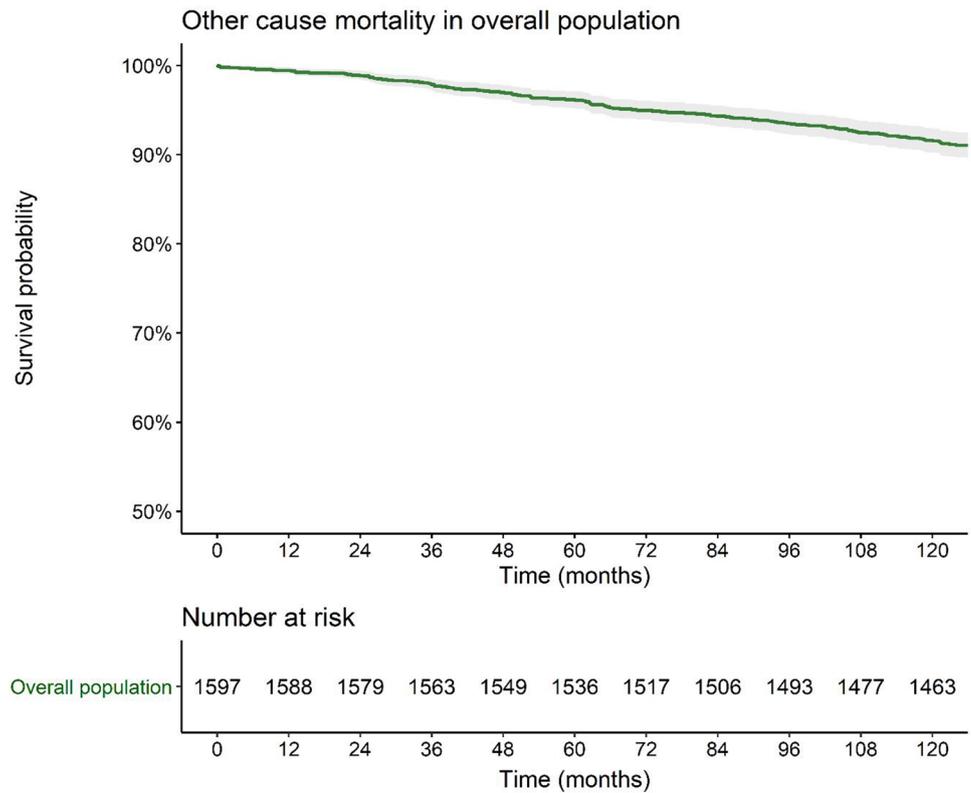
Life expectancy (LE) is of utmost importance in decision-making regarding treatment choice in localized PCa and guidelines generally recommend an LE of at least 10 years to consider local therapy [3–5]. However, none of the guidelines suggest a specific tool to predict LE, presumably due to the lack of validated predictions tools. Several analyses described the importance of comorbidities and age in terms of survival probability [16, 17]. Thus, in 2007, Walz and colleagues conducted a prediction model for the risk of 10-year non-cancer mortality after receiving local treatment. A population of 9131 Canadian men treated by RP ( $n = 5955$ ) or RT ( $n = 3176$ ) between 1989 and 2000 was used to design and test their model. All supposed PCa-related deaths were excluded. The discrimination of the model including age, treatment type, and CCI, was 0.84 in their internal validation [11]. This is the model with the highest predictive accuracy addressing LE in PCa patients published to date [7]. Furthermore, it was developed on radical prostatectomy candidates in contrast to the other nomograms in this field [18]. In addition, it is easy to use as it only includes age and CCI.

To the best of our knowledge, this prediction model has never been validated externally. External validation is important, however, since the generalizability of the reported predictive accuracy remains unknown otherwise. Differences in patient population, especially related to the geographic region, country, or continent, as well as historical cohorts, are potential confounders that might disturb the performance of a nomogram when applied to a different and contemporary cohort of patients [19]. Furthermore, since overall LE is constantly increasing in most western countries, prediction models developed on historical patients addressing this endpoint might underestimate the current survival probabilities. In theory, in a stable nomogram, such differences should result in minimal predictive accuracy variations, as a truly generalizable nomogram should adjust properly for any such differences [19].

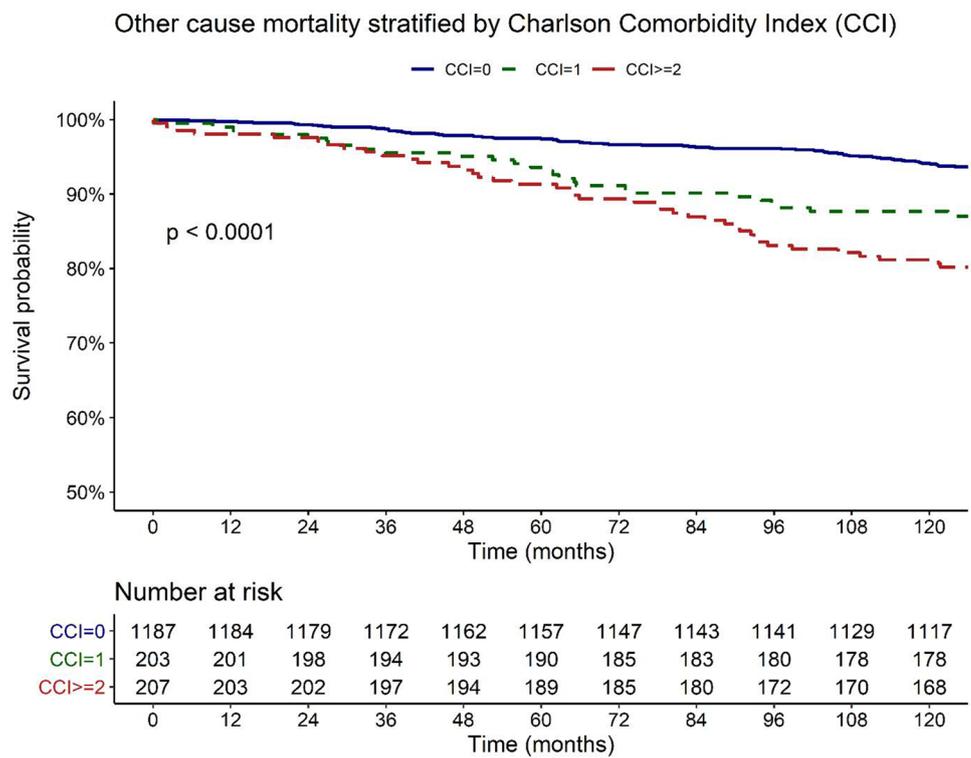
In consequence, we focused on a contemporary European patient population with an actual follow-up of 10 years after RP to ascertain an external validation of the Walz nomogram. Our analyses demonstrated several noteworthy findings.

The c-index on receiver-operator characteristics analysis was 0.64, showing a moderate discrimination capacity of the Walz Nomogram in our external cohort. This might have several underlying reasons. First, the nomogram was conducted in a general Canadian population, including patients treated from 1989 to 2000. Our validation cohort, however, is a European single-institution cohort, with patients undergoing treatment between 2005 and 2007.

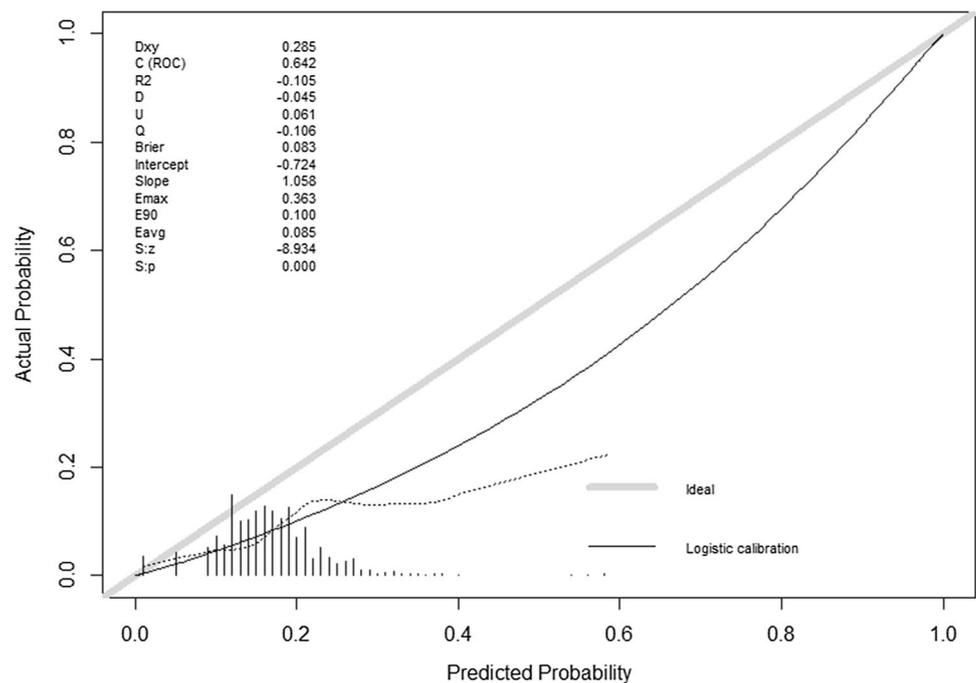
**Fig. 1** Kaplan–Meier plot graphically depicting the probability of other cause mortality (green line) with 95% confidence intervals (shadows) in 1597 radical prostatectomy patients treated between 2005 and 2007 in a single European institution



**Fig. 2** Kaplan–Meier plot graphically depicting other cause mortality stratified by Charlson Comorbidity Index (CCI) in 1597 radical prostatectomy patients treated between 2005 and 2007 in a single European institution



**Fig. 3** Calibration plot depicting the agreement between observed and predicted probability of 10-year survival after radical prostatectomy in the validation cohort for the Walz nomogram. The grey line is the ideal agreement of predicted and actual probability of survival



Second, men who received secondary treatment for PCa were excluded in the nomogram development to exclude the effect of PCa-specific mortality, as information on cause-specific mortality was not available for these patients [11]. The determination of cause of death differs between the original and the validation cohort. However, we strongly believe for both ways to lead to a very reliable estimation of cause of death. In the development cohort, the information on death occurrence was based on health insurance data including complete data on every secondary treatment of PCa. Since no patient dies of PCa without secondary treatment in case of recurrence after RP or RT, consistent identification of cause of death other than prostate cancer was ascertained. In our population, however, cause-specific mortality was available for all patients, including those with secondary treatment. Since estimation of life expectancy is needed in preoperative counselling, when possible postoperative secondary treatment is not entirely predictable, we believe our cohort to be clinically more relevant. However, we additionally relied on sensitivity analyses that only included patients without secondary PCa treatment showing virtually the same results.

Third, predictive accuracy of the nomogram might be negatively affected by two aspects: one, the follow-up of the original development cohort and our validation cohort was different (84 vs. 134 months); two, as Vickers and colleagues demonstrated, length of follow-up itself can impact the predictive accuracy of a nomogram with a decrease in accuracy with longer follow-up [14]. Since our cohort consists of patients with a long follow-up (median: 134 months), the c-index counterintuitively might be lower than in a cohort with shorter follow-up.

On calibration curves, the nomogram underestimated actual life expectancy. In the population used for the prediction model by Walz and colleagues, the median CCI was 1 (range 0–11) with a median age of 64 years (range 55–89). In our cohort, however, patients had a median CCI of 0 (range 0–10), indicating an overall healthier population. In addition, contemporary diagnostics, staging, and therapeutics of many diseases might have changed and prolonged the life expectancy per se.

Several other prediction models on LE have been published, specifically being conducted for PCa patients. In 1996, Albertsen and colleagues examined a cohort of PCa patients 65–75 years old diagnosed between 1971 and 1976. They tested three different comorbidity indices (the Kaplan–Feinstein index, the Charlson Comorbidity Index, and the index on coexisting disease) on the risk of mortality and demonstrated the importance of comorbidity in LE predictions [8]. Based on their findings, they provided a formula to predict LE. In an external validation, a c-index of 0.71 was reported for this model [10]. Another model was presented by Tewari et al. in 2004. They developed comprehensive lookup tables for estimating 10-year overall survival probability stratified by patient age, race, readily available clinical variables, comorbidities, and treatment type by matching a cohort of 1611 men with clinically localized PCa with 4538 age, race, and comorbidity matched controls. In their validation, a c-index of 0.63 was reported for the cancer-specific survival model and 0.69 for the overall survival model [9]. The external validation showed a c-index of 0.70 [10]. In 2006, Cowen et al. performed an external validation of the

Albertsen and Tewari models and additionally presented a new model. It incorporated numerous factors, such as age, CCI, performance status, angina history, blood pressure, body mass index, tobacco use, marital status, PSA, Gleason score, clinical stage, treatment type, and treatment year. Discrimination of their 10-year survival prediction model was modest with a c-index of 0.73. Moreover, an external validation has not been published so far [10]. In 2016, Kent et al. published a prediction model of other-cause mortality in localized PCa patients using adjusted United States Social Security Administration tables with comorbidities from a United Kingdom actuarial life expectancy model. On external validation with patients from the Prostate Cancer Outcomes Study, discrimination of their 10-year survival model was also modest with a c-index of 0.72 [18]. Another approach was published by Maritto et al. by estimating LE by comorbidity-adjusted life tables and health-adjusted age [20]. However, since the life tables are not specific on PCa patients, this might be a limitation [7].

Despite the suboptimal predictive accuracy of the above-mentioned nomograms, prediction models based on survival data of PCa patients potentially remain the best tools in estimating LE in those men. Although several life tables predicting survival are easily accessible, they are not specific for localized PCa patients. Compared to the general population, PCa patients have been shown to live longer due to a different health-conscious behaviour [7]. Similarly, clinician-predicted LE estimation is readily available in daily practice and has been assessed by comparing clinician-predicted survival to actual survival of PCa patients [21, 22]. However, LE estimation by clinicians was found to be inconsistent and inaccurate, as well as unrelated to the level of training or experience [7]. In addition, nomograms have shown to outperform clinicians' predictions of various endpoints in PCa patients [23]. Thus, nomogram predictions remain the best available tool in predicting LE in PCa patients by generating reproducible results.

Several inherent limitations of the Walz nomogram need to be mentioned. First, the prediction model includes treatment modality. This seems appealing, but, by incorporating any presumed survival advantage associated with RP, the biases of the treatment selection are also included in the model. Since, generally, RP patients live longer than RT patients due to a healthier population, the initially reported good discrimination might be caused by the inclusion of this variable [7]. Another influencing factor of the model might be the CCI itself. Originally, it was based on a sample of 559 patients admitted to a hospital in New York City in 1987 [24]. The accuracy and applicability of this model to contemporary outpatients might be difficult to ascertain [25]. However, the CCI is a widely accepted and easy to use tool,

which has been assessed and validated in various publications in PCa patients [13, 16, 17].

Further limitations of our study need to be mentioned. Since only patients with complete 10-year follow-up could be included in this validation cohort, a large proportion of patients were excluded, thus potentially raising the likelihood of bias. However, the exclusion should be considered a random and, therefore, the leftover 1,597 patients are still representative of our population.

In conclusion, the available prediction models on 10-year life expectancy of radical prostatectomy candidates are of suboptimal accuracy. Our study underlines the importance of external validation by showing the substantial difference of predictive accuracy in our patients compared to the original development cohort. In consequence, predictive tools may not be expected to be reliable unless reproducibility is proven by external validation.

## Conclusion

In this first external validation of the Walz nomogram in a cohort of European men undergoing radical prostatectomy, the performance accuracy of this prediction model was moderate and underestimated 10-year life expectancy of contemporary PCa patients. In conclusion, prediction of life expectancy remains challenging with a continued need for more precise tools.

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**Author contributions** Protocol/project development: MG and SK. Data collection or management: DP and SK. Data analysis: SK and ZT. Manuscript writing/editing: SK, DP, HH, DT, PK, and MG.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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