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ORIGINAL ARTICLE

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Long-term overall survival of radical prostatectomy patients is often superior to the general population: A comparison using life-table data

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Abstract

Background: To examine overall survival rates within a large cohort of German prostate cancer (PCa) patients and to compare these with life-expectancy (LE) predictions derived from German life tables. We hypothesized that the advantage of good general health in radical prostatectomy (RP) patients combined with favorable cancer outcomes might lead to even higher overall survival rates over 10 years compared to the LE of a general population.

Methods: A total of 6483 patients were treated with RP between 1992 and 2007 at the Martini-Klinik Prostate Cancer Center. Preoperative risk classification was performed according to D'Amico. Postoperative risk classification was performed according to the Cancer of the Prostate Risk Assessment score (CAPRA-S). A simulated cohort was created that resembled the exact age distribution of the RP population using Monte Carlo simulation which was based on data derived from official male German life tables (1992–2017). Markov chain was used to represent natural age progression of the simulated cohort. Kaplan–Meier plots were created to display the differences between 10-year observed overall survival (OS) and the simulated, predicted LE.

Results: For D'Amico low risk and intermediate risk, 10-year OS was 12.0% and 9.2% above predicted LE in the simulated cohort, respectively. For D'Amico high risk, OS was virtually the same as predicted LE (0.8% difference in favor of RP treated patients). For CAPRA-S low and intermediate risk, OS was 11.8% and 9.7% above predicted LE. For CAPRA-S high risk, OS was virtually the same as predicted LE (0.3% difference in favor of the simulated cohort).

Conclusions: Low- and intermediate risk PCa patients treated with RP can expect a very favorable overall survival, that even exceeds LE predictions. High risk patients' overall survival perfectly aligns with LE predictions.

KEYWORDS

life table, life-expectancy, prostate cancer, radical prostatectomy, survival

1 | INTRODUCTION

Excellent curative management options for prostate cancer (PCa) are available and a large part of treated patients can expect a favorable oncological outcome.[1] For the near future, a further increase of long-term survival rates after active treatment in PCa patients is expected.[2] However, since PCa is more common in the elderly population, and furthermore, usually progresses at slower rates compared to other malignancies, patient age and estimated life-expectancy (LE) are important factors that have to be taken into consideration in the clinical decision-making process.[3] Patients with a long LE can expect to benefit most from active treatment, while patients with a short LE may benefit less, or even may not benefit at all.[4] Therefore, when deciding for active treatment, a LE of over 10 years is deemed necessary.[5] In this regard, one of the advocated European Association of Urology (EAU) guideline recommendations is the use of life tables to evaluate the patients' LE. Without taking into account individual comorbidities or other health-related assessments, life tables are suitable to narrow down the estimated LE, since they resemble national population samples. Radical prostatectomy (RP) is an invasive approach, that is usually more frequently performed in patients with a good general health, as opposed to patients treated with other, less invasive methods.[6] Therefore, RP treated patients may represent a population that exhibits more favorable health compared to individuals of same age within a general population. This may ultimately translate into higher overall survival rates compared to life tables' derived LE predictions.[7] We tested this hypothesis in German PCa patients treated with RP in a center of excellence and compared survival rates to corresponding German life tables.

2 | PATIENTS AND METHODS

After approval of the institutional review board, we identified 7012 PCa patients in our institutional database who received RP, with or without pelvic lymph node dissection (PLND), between 1992 and 2007. We excluded 261 patients with pathological T-stage 4 (pT4) and/or distant metastasis (M1). Furthermore, 268 patients with missing or inconclusive pT-stage, Gleason grade groups (GGG), missing patient age or missing follow-up data were excluded. After applying these exclusion criteria, a total of 6483 patients were included in this retrospective single-center study. All RP's and PLND's were performed by staff urologists in a standardized manner, as previously described.[8] Dedicated uro-pathologists assessed all specimen and reported pathological results according to the Gleason System and the TNM classification. Preoperative risk classification was performed according to D'Amico low, intermediate and high risk groups.[9] Postoperative risk classification was performed according to the Cancer of the Prostate Risk Assessment score (CAPRA-S).[10,11] CAPRA-S scores were further by stratified by low- (CAPRA-S 0–2), intermediate- (CAPRA-S 3–5), and high (CAPRA-S 6 or more) risk of recurrence.

2.1 | Statistical analyses

Univariable Kaplan–Meier plots were created to illustrate observed overall survival (OS) outcomes over 10 years. Furthermore, Monte Carlo simulation was performed to create a simulated cohort that resembled the exact age composition of the RP-treated population, according to previous methodology.[7] Using official male German life table data from the years 1992 to 2017,[12] a Markov chain representing natural age progression for the simulated cohort was computed, in which each simulated patient could either survive or die within each of the 10 simulated year intervals. Consequently, the model computed a 10-year LE prediction for a simulated cohort that was based on the exact ages of actual RP treated patients. The predicted LE of the simulated cohort was then included in Kaplan–Meier plots and compared with OS rates.

R software environment for statistical computing and graphics (version 3.4.0 for MAC OS X; http://www.r-project.org/) was used for all statistical analyses.[13] Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. The χ^2 and Log-rank tested the statistical significance in proportions and survival differences. All tests were two-sided with a level of significance set at $p < .05$.

3 | RESULTS

Median follow-up was 144 months (IQR: 92.5–180.10). Median age of the overall cohort was 63 years (IQR: 59–67). Considering preoperative patient characteristics, D'Amico low (38.7%) and intermediate (36.9%) risk groups were predominantly exhibited in the overall cohort. Considering postoperative patient characteristics, the majority of patients (58.3%) exhibited a low risk of recurrence, as determined by a score of 0–2 in the CAPRA-S.

3.1 | Survival analyses according to preoperative characteristics

When taking into account the overall population of 6483 RP treated patients between 1992 and 2017, regardless of risk stratification, OS at 10 years was 90.7%. For this population, a simulated cohort of 6483 patients was created, that exactly resembled the age distribution of the real cohort. For this simulated cohort, predicted LE for 10 years was 81.2%. Therefore, the calculated difference between OS and predicted LE was 9.5%, in favor of RP treated patients (Figure 1). The more favorable OS of RP treated patients was also exhibited when stratifying the overall cohort into two different age subgroups according to overall median age at diagnosis (63 years). In these analyses, in the subgroup of patients aged 63 or younger as well as in the subgroup of patients over 63 years, a more favorable OS than predicted by LE was recorded. However, the older subgroup exhibited larger differences between OS and predicted LE at

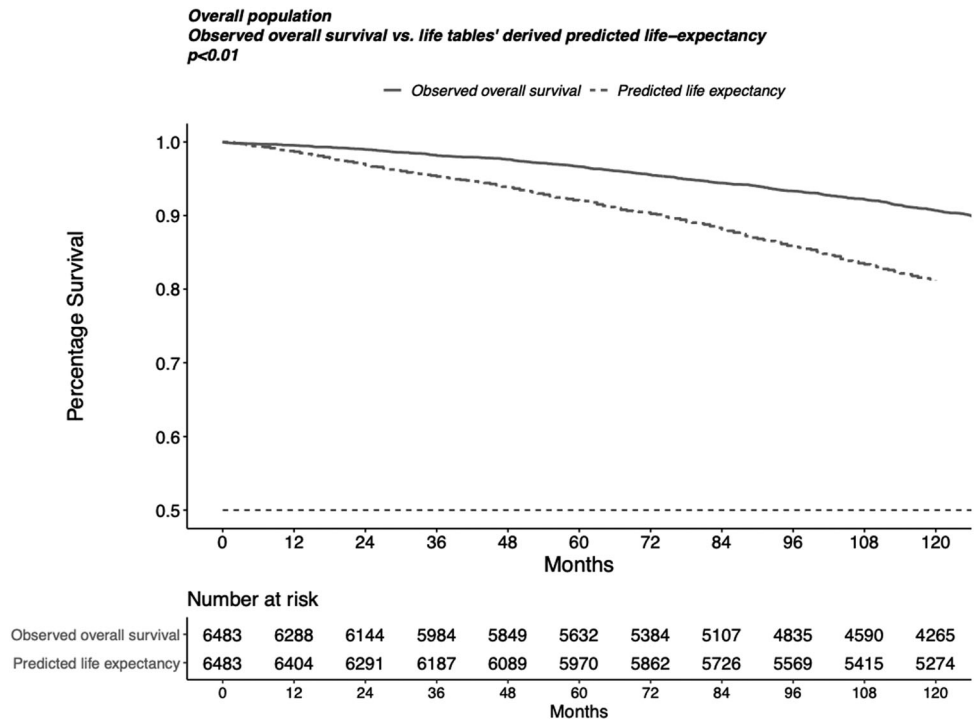

FIGURE 1 Ten-year observed overall survival rates of prostate cancer patients treated with radical prostatectomy in a single institution between 1992 and 2007 compared to predicted life expectancy from a simulated cohort that resembles exact same age distribution and which is based on German life table data from 1992 to 2017

10 years than their younger counterparts (15.5% difference for the subgroup of patients over 63 years and 5.9% for the subgroup of patients aged 63 years or younger, Figure S1). To complement the age-stratified analyses, we also performed a further analysis only relying on D'Amico intermediate risk patients. Here, the difference between OS and predicted LE was also larger in the older subgroup. Specifically, for patients aged 63 years or younger, the difference between OS and predicted LE was 4.6%, in favor of RP treated patients, while for patients over 63 years, the difference was 13.8%, also in favor of RP.

In the next step of the analyses, differences between OS and predicted LE stratified by D'Amico risk groups were calculated, following the same methodology in 5420 patients with complete preoperative tumor information (Figure 2). For D'Amico low risk patients ($n = 2508$), OS at 10 years was 93.2% compared to a predicted LE of 81.2%, which resulted in a difference of 12.0%, in favor of RP treated patients. For D'Amico intermediate risk patients ($n = 2395$), OS at 10 years was 89.8% compared to a predicted LE of 80.6%, which resulted in a difference of 9.2%, in favor of RP treated patients. For D'Amico high risk patients ($n = 517$), OS at 10 years was 82.6% compared to a predicted LE of 81.8%, which resulted in a difference of 0.8%, in favor of RP treated patients (Table 1).

3.2 | Survival analyses according to postoperative characteristics

In the next step of the analyses, postoperative tumor characteristics were stratified by CAPRA-S score in 6279 patients with complete postoperative data. For individual CAPRA-S scores, OS compared to respective predicted LE at 10 years was always above predicted LE in all scores from 0 to 6. From a CAPRA-S score of 7 and onwards, OS rates were always beneath predicted LE, with a maximum negative difference of 15.4% for patients with a CAPRA-S score of 9 or higher (Table 2). Thereafter, CAPRA-S was grouped by scores from 0 to 2 (low risk for recurrence, $n = 3779$), 3 to 5 (intermediate risk for recurrence, $n = 1752$), and 6 or more (high risk for recurrence, $n = 766$). OS and respective predicted LE for these groupings were plotted (Figure 3) and differences at 10 years were calculated.

Specifically, for CAPRA-S low risk, OS at 10 years was 93.1% and predicted LE was 81.3%, which resulted in a difference of 11.8% in favor of RP treated patients. For CAPRA-S intermediate risk patients, OS at 10 years was 90.9% and predicted LE was 81.2%, which resulted in a difference of 9.7%, in favor of RP treated patients. For CAPRA-S high risk patients ($n = 766$), OS at 10 years was 79.1% and predicted LE was 79.4%, which resulted in a difference of 0.3%, in favor of the simulated cohort.

In the final step of the analyses, two subgroups with presumably worst tumor characteristics were identified, and analyses were repeated. The first subgroup consisted of patients with pT3a-b tumor, GGG 4–5 and positive surgical margins. The second subgroup consisted of all pN1 patients. For the first subgroup (Figure 4A, $n = 65$), OS at 10 years was 56.7% and predicted LE was 81.5%, which resulted in a difference of 24.8% in favor of the simulated cohort. For the second subgroup (Figure 4B, $n = 234$), OS at 10 years was 71.8% and predicted LE was 82.5%, which resulted in a difference of 10.7% in favor of the simulated cohort.

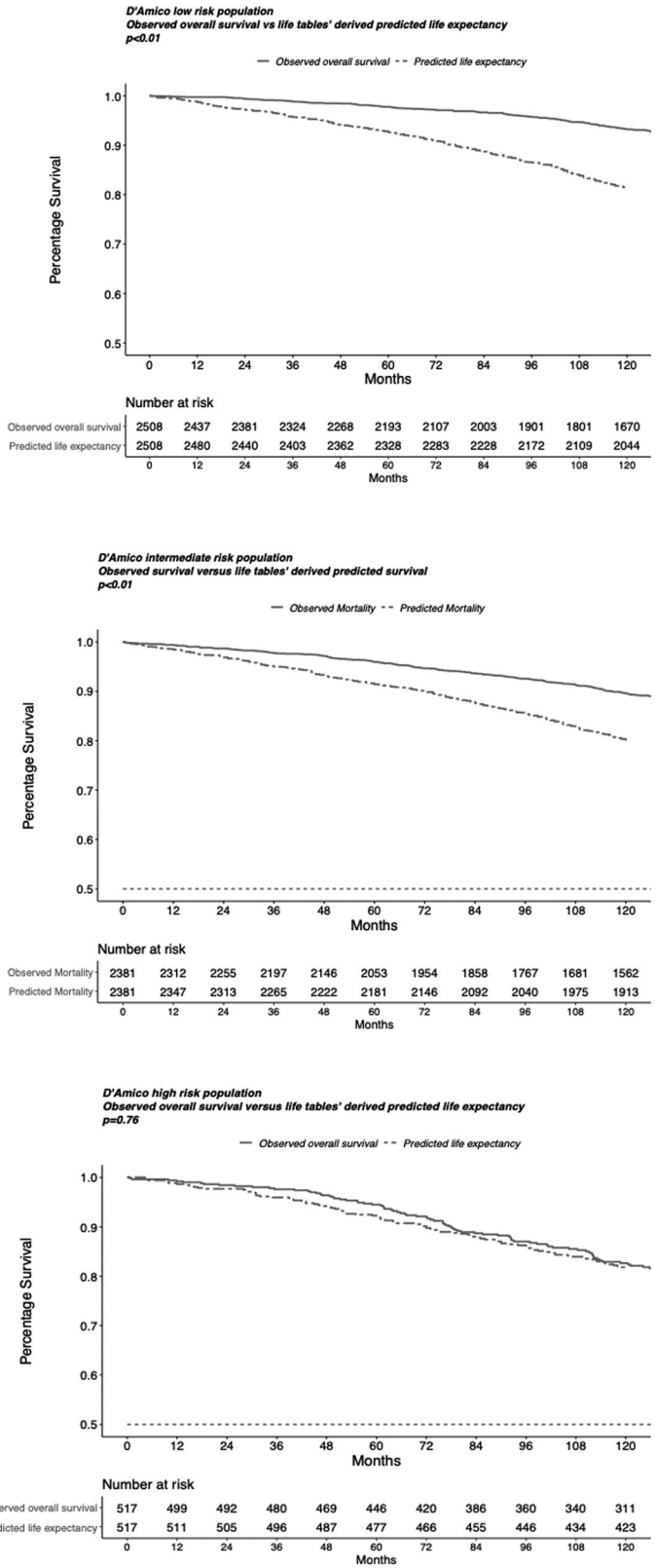

FIGURE 2 Ten-year observed overall survival rates of D'Amico low-, intermediate- and high-risk prostate cancer patients treated with radical prostatectomy in a single institution between 1992 and 2007 compared to predicted life expectancy from a simulated cohort that resembles exact same age distribution and which is based on German life table data from 1992 to 2017

TABLE 1 Patient characteristics of 6483 prostate cancer patients treated with radical prostatectomy from 1992 to 2007 in a single German institution

RP-treated population 1992–2007 ($n = 6483$)	Value
Age (years), median (IQR)	63 (59–67)
PSA (ng/ml), median (IQR)	6.5 (4.6–10.0)
D'Amico risk group, *n* (%)	
Low risk	2508 (38.7)
Intermediate risk	2395 (36.9)
High risk	517 (8.0)
Unknown	1063 (16.4)
CAPRA-S, *n* (%)	
0–2 (low)	3779 (58.3)
3–5 (intermediate)	1752 (27.0)
6 or more (high)	766 (11.8)
RP Gleason grade group, *n* (%)	
GGG 1	2664 (41.1)
GGG 2	2904 (44.8)
GGG 3	763 (11.8)
GGG 4	53 (0.8)
GGG 5	99 (1.5)
pT stage, *n* (%)	
pT2	4472 (69)
pT3a	1324 (20.4)
pT3b	687 (10.6)
pN stage, *n* (%)	
pN0	3008 (46.4)
pN1	234 (3.6)
pNX	3236 (49.9)
Surgical margin status, *n* (%)	
R0	5293 (81.6)
R1	1177 (18.2)
Rx	3 (0)

Abbreviations: GGG, Gleason grade group; IQR, interquartile range; RP, radical prostatectomy.

TABLE 2 Differences between observed overall survival and German life tables' derived predicted life expectancy at 10 years in a prostate cancer population treated with radical prostatectomy at a single German institution

CAPRA-S	Observed survival	Predicted life expectancy	Difference
0	93.1%	83.1%	+10.0%
1	93.3%	81.4%	+11.9%
2	93.0%	81.1%	+11.9%
3	92.3%	81.5%	+10.8%
4	90.2%	83.4%	+6.8%
5	88.3%	81.2%	+7.1%
6	89.4%	82.4%	+7.0%
7	77.5%	87.8%	−10.3%
8	72.8%	84.6%	−11.8%
9 or more	68.7%	84.1%	−15.4%

Note: Stratification was performed by Cancer of the Prostate Risk Assessment (CAPRA-S) score.

4 | DISCUSSION

We assumed that PCa patients treated with RP may represent a selected population that exhibits a favorable general health status, which might even be superior compared to the general population. Based on this assumption, we hypothesized, that RP treated patients exhibit higher OS compared to the general population. We tested our hypothesis in RP treated patients at our institution from 1992 to 2007 and compared 10-year OS rates to predicted LE in a simulated cohort model. This model was derived from official German life tables from 1992 to 2017 and was based on the exact same age distribution of the RP treated patients. Our analyses yielded several noteworthy findings.

First, when considering the overall cohort, a higher 10-year OS of RP treated patients was exhibited when compared to the predicted LE of the simulated cohort for the same time period. This survival advantage was in effect from the very beginning of the follow-up and even further increased with longer follow-up time (9.5% survival advantage at 10 years). Furthermore, the OS advantage of RP treated patients compared to predicted LE increased with higher patient age. Specifically, the predicted LE underestimated OS only by 5.9% in patients aged 63 or younger. Conversely, for patients older than 63 years, the predicted LE underestimated OS by 15.5%. This finding implies that the effect of better general health of RP treated patients compared to the German population is indeed even more striking in elderly patients. To account for potential confounding by differences in PCa characteristics between these two artificially created age subgroups of >63 years and ≤63 years, we repeated analyses also in the largest available D'Amico subgroup (intermediate risk). Also in this analysis, virtually the same findings could be encountered, which further strengthens our findings.

Second, the OS advantage of RP treated patients over predicted LE of the is also even more striking in patients with favorable cancer features. For example, when considering preoperative risk stratification using D'Amico risk groups, low risk patients exhibited a survival advantage of 12.0% at 10 years. This survival advantage was also confirmed when considering postoperative risk stratification using CAPRA-S. For CAPRA-S low risk patients, OS exceeded predicted LE of the simulated cohort at 10 years virtually to same extents as seen in D'Amico low risk patients (11.8%).

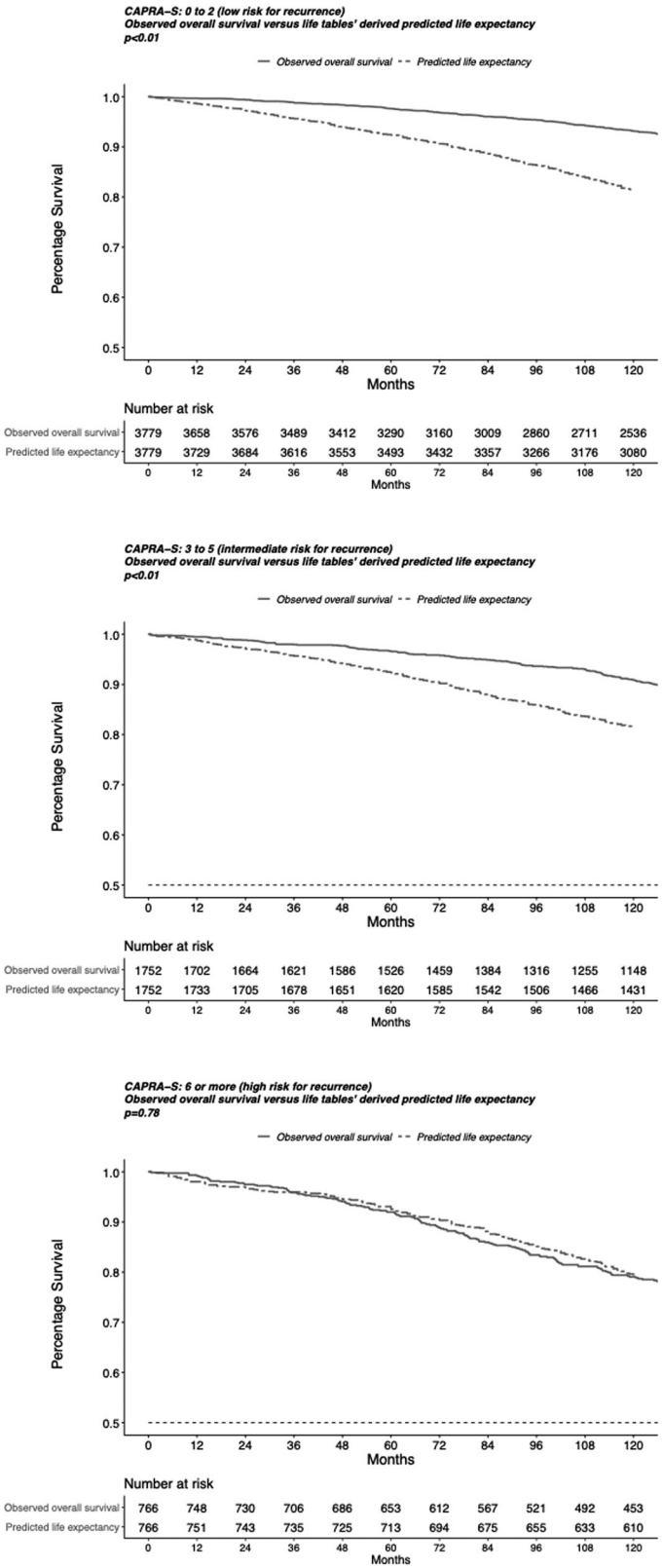

FIGURE 3 Ten-year observed overall survival rates of "Cancer of the Prostate risk assessment–post surgical" (CAPRA-S) low, intermediate and high risk patients treated with radical prostatectomy in a single institution between 1992 and 2007 compared to predicted life expectancy from a simulated cohort that resembles exact same age distribution and which is based on German life table data from 1992 to 2017

Third, as opposed to patients with favorable cancer risk features, the observed OS advantage decreased and eventually even ceased to exist in patients with aggressive cancer risk features. While the 10-year OS for D'Amico high risk patients and CAPRA-S high risk patients was at least comparable to the simulated LE of the general population, a certain subgroup of patients fell below the values of the simulated cohort. For example, when considering individual CAPRA-S scores (0–9 or higher) and not per risk group, patients with CAPRA-S score of 7 and onwards always fell below the simulated LE at 10 years by at least 10% and eventually reached a value difference

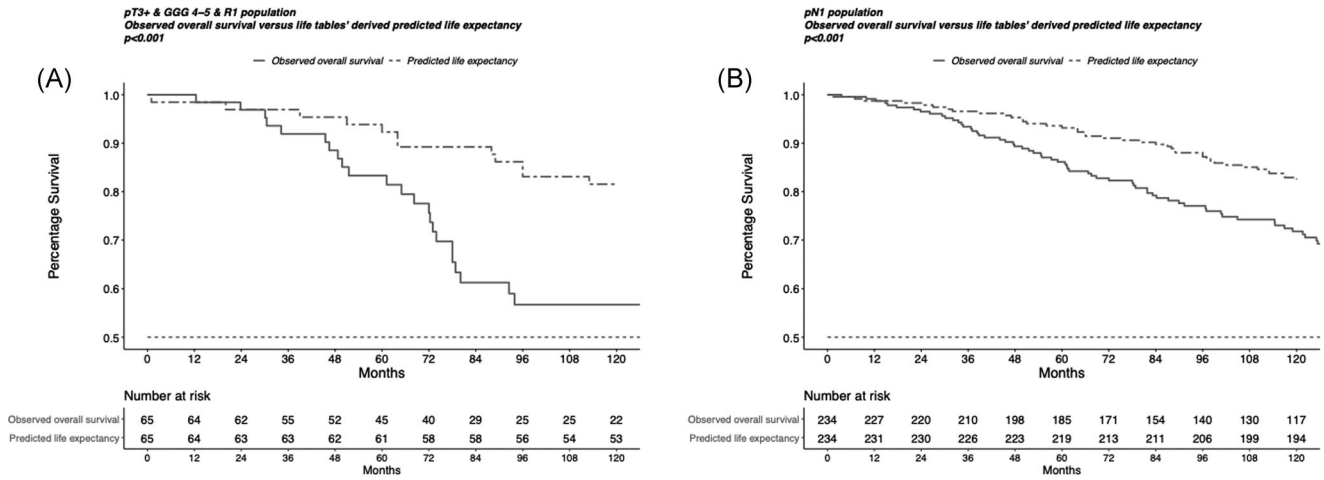

FIGURE 4 Ten-year observed overall survival rates of a subgroup of prostate cancer patients with pT3a-b, Gleason Grade Group 4–5 and positive surgical margins (A) and patients with positive lymph nodes (B) treated with radical prostatectomy and pelvic lymph node dissection in a single institution between 1992 and 2007 compared to predicted life expectancy from a simulated cohort that resembles exact same age distribution and which is based on German life table data from 1992 to 2017

of 15.4% in patients with CAPRA-S score of 9 or higher. Even more distinct survival differences were exhibited when considering a subgroup of patients where highest rates of cancer specific mortality were assumed (pT3a-b, GGG 4–5, positive surgical margin). Ultimately, these patients had the worst OS at 10 years and fell below predicted LE by 24.8%. These findings suggest that the impact of cancer specific mortality in these individuals outweighs other cause mortality, that is often in effect in in RP treated patients.[14]

Preisser et al. previously demonstrated the feasibility of using life table information to compare OS of a treated population to a simulated cohort based on national population data.[7] In their work, North American patients who underwent RP within the Surveillance, Epidemiology and End Results database were compared to Social Security Administration life tables LE estimations. Using this methodology, Preisser et al.[8] were the first to report a certain underestimation of predicted LE for RP patients. However, since North American patients cannot be directly compared to European patients, neither in terms of PCa survival nor in general population LE and general health, a separate analysis in European patients was deemed necessary.[15–17] To the best of our knowledge, we are the first to use this methodology within a large RP treated, consecutive European PCa cohort. Our findings depict a favorable general health and excellent LE of German patients undergoing RP, which ultimately suggests good patient selection.

In this regard, the EAU and also the German S3 Guidelines recommend to perform active treatment for PCa only in patients with favorable general health and a residual LE of more than 10 years.[5,18,19] However, since age is not the only prognosticator of survival, further factors should play a role in the assessment of PCa patients. For example, to assess the general health status of elderly patients, the Geriatric-8 assessment tool may be considered.[20] Furthermore, the role of comorbidity, as assessed by the Charlson-Comorbidity Index[21] or by the Cumulative Illness Score Rating-Geriatrics CISR-G,[22] should receive attention in the decision making process for active treatment. Other authors advocate the use of a combination of life table data with comorbidity data.[23] Apart from these tools, that are of use in all areas of medicine and oncology, also specific nomograms for predicting LE in the setting of PCa have been advocated earlier.[24,25] Nevertheless, it has to be taken into account that such nomograms and assessment tools are often complex and require a multitude of inputs, that are not always readily available for clinicians at the time of consultation. Furthermore, these tools are—in contrast to life tables—usually not updated regularly and might be based on historic data. Therefore, the power of life tables relies within their availability, contemporaneity and simplicity.

Taken together, we confirmed that German RP treated patients exhibit superior survival compared to the predicted LE of an age-adjusted simulated cohort that is based upon the general German population. However, this statement is only valid for patients who do not bear very aggressive tumor characteristics. The methodology of using Monte Carlo simulation and Markov Chain on life table data is a powerful tool to evaluate the true impact of a specific disease and its treatment on potential life years lost compared to the LE of the general, nation-specific population. It would be interesting to apply this methodology also in other nations and populations, to confirm our findings and to prove if the survival advantage in RP treated patients compared to the underlying population continues to stay in effect.

Our findings have to be interpreted in the context of potential limitations. First, the presented cohort was treated between 1992 and 2007, which may be regarded as a historic cohort. However, the need for a complete 10-year follow-up dictated the patient selection. Second, the superior observed survival of the overall cohort compared to the simulated cohort might be biased by the presence of a high number of patients with favorable cancer characteristics. Third, the lack of consistent and comparable comorbidity data such as the

CCI or the CISR-G precludes further insights in the general health status of our cohort. Finally, German life tables do not account for differences in race/ethnicity when providing age-based life expectancy estimations, therefore, no adjustment for this variable could be performed. However, the same limitation also applies to life tables from other countries with even more distinct heterogeneity regardig race/ethnicity within the general population, such as the United States, Canada, Switzerland, France or South Africa.[26–28]

5 | CONCLUSION

German low- and intermediate risk PCa patients treated with RP can expect a very favorable overall survival, that even exceeds LE predictions. High risk patients' overall survival aligns with LE predictions, but may also fall below predictions in specific subgroups with distinctly worse tumor characteristics.

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CONFLICT OF INTERESTS

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Christoph Würnschimmel, Pierre I. Karakiewicz, Derya Tilki. *Acquisition of data*: Christoph Würnschimmel and Derya Tilki. *Analysis and interpretation of data*: Christoph Würnschimmel and Zhe Tian. *Drafting of the manuscript*: Christoph Würnschimmel and Derya Tilki. *Critical revision*: Wenzel, Wang, Huland, Graefen. *Statistical analysis*: Christoph Würnschimmel and Derya Tilki. *Supervision*: Derya Tilki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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