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# Prostate cancer prognosis in men with other malignancies prior to radical prostatectomy

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**Abstract**

**Objectives:** Cancer survivors are often diagnosed with subsequent prostate cancer. To improve medical care of these patients, we examined the oncological outcomes in men with prostate cancer and a cancer history.

**Patients and methods:** We retrospectively analyzed data from 25,422 prostate cancer patients, who underwent a radical prostatectomy between 1992 and 2016. Patients with other malignancies were identified using medical records and self-administrated questionnaires. Cox regression and Kaplan Meier analysis of a propensity score-matched patient cohort were performed to examine biochemical recurrence-free survival, metastasis-free survival, overall survival and prostate cancer-specific survival. Competing risk analysis was used to estimate other-cause mortality, other cancer-specific mortality, and prostate cancer-specific mortality. Statistical analysis was performed using R.

**Results:** Of all patients, 6.4% were diagnosed with other malignancy prior to radical prostatectomy. Patients with tumor history were older (median: 66 years vs. 64 years., $P < 0{,}001$) and showed a higher tumor volume (median: 4.0 ml vs. 3.6 ml, $P = 0.02$) than patients without. The risk of biochemical recurrence and metastasis development after radical prostatectomy was similar. All-cause mortality was significantly increased (hazard ratio 2.0; 95% confidence interval 1.7−2.4), while prostate cancer-specific mortality was lower (hazard ratio 0.4; 95% confidence interval 0.23−0.87) in patients with additional malignancy. In a propensity score-matched cohort overall survival was significantly adverse ($P < 0.001$) and prostate cancer-specific survival was higher ($P = 0.003$) in patients with other malignancy prior to surgery.

**Conclusion:** A higher other-cause mortality in men with tumor history should be concerned in the decision-making for medical care of prostate cancer patients in favor of reserved care strategies. 

*Keywords:* Prostate cancer; Multiple primary neoplasms; Radical prostatectomy; Cancer-specific mortality; All-cause mortality; Competing risk

*Abbreviations:* RP, radical prostatectomy; PCa, prostate cancer; BCR, biochemical recurrence; MFS, metastasis-free survival; OS, overall survival; PCaS, prostate cancer-specific survival; OCM, other-cause mortality; OCaM, other-cancer mortality; PCaM, prostate cancer mortality; IQR, inter quartile range; HR, hazard ratio; CI, confidence interval

## 1. Introduction

The development of multiple primary neoplasms is no longer a rarity due to medical progress and constantly growing life expectancy. Since their description by Billroth in 1882 [1] the incidence of second and higher order tumors has increased with the growing population of cancer survivors, who additionally have an extended risk of developing

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malignancies compared to the general population [2]. Almost every 10th tumor patient is affected by another malignancy in his course of life [3,4]. Each sixth tumor in the United States already appears to be a second or higher order neoplasia [5]. A further increase in patients with multiple primary neoplasms in the future is likely and poses new problems for the medical care of those affected.

Also, men with prostate cancer (PCa) have to deal with multiple primary tumors. In fact, PCa is one of the most common neoplasms that can be detected after previous tumors [4]. These antecedent malignancies are observed in nearly 10% of the PCa patients [6] and constitute not only a competitive health disorder with impact on life expectancy [7,8]. Also, an influence on the tumor biology of the PCa in the context of common etiology and the medical care of the first tumor is possible [9−13]. In particular hereditary mutations in breast cancer genes are associated with the formation of multiple primary neoplasms and more aggressive tumors of the prostate [14].

Concerning the unclear consequences of PCa on the patient's life expectancy and quality of life, it is crucial to examine the impact of anamnestic tumor disease on the prognosis of subsequent PCa.

To our knowledge only few studies have dealt with this question and the results of these investigations do not allow to make a statement on the prognosis of PCa after previous tumor disease. Therefore, we analyzed the clinical outcome of PCa patients with and without other malignancies prior to radical prostatectomy (RP).

## 2. Patients and methods

### 2.1. Patient population

We retrospectively analyzed 25,422 patients with histologically confirmed adenocarcinoma of the prostate, who underwent a RP between 1992 and 2016. We excluded patients without follow-up information and patients with salvage RP leading to a cohort of 24,316 patients. RP was performed using an open retropubic or robot-assisted laparoscopic approach, as previously described [15,16]. Patients with another malignancy prior to RP were identified using patient information from medical records and self-administrated questionnaires. Requirement for PCa surgery was a completed definite treatment of the primary cancer with no evidence of disease persistence or recurrence in oncological follow-up. Exceptions were made in the case of malignant diseases with favorable natural courses, for example, chronic lymphocytic leukemia (low stages), basalioma, and spindle cell carcinoma of the skin. A favorable prognosis related to the primary cancer was predicted by the treating medical oncologist in a multidisciplinary tumorboard after review of current follow-up evaluation (e.g., imaging, colonoscopy for colorectal cancer). Required failure-free survival varied according to the primary cancer entity.

### 2.2. Statistical analysis

The Kruskal-Wallis test and the Pearson's Chi-squared test were used for univariate analyses to test for statistical differences of the distribution of the median and for independence of categorical probability distributions among patients with other malignancy prior to RP or PCa only.

Cox proportional hazard multivariable analysis was performed to calculate the hazard and significance on biochemical recurrence (BCR), metastasis development, all-cause mortality (ACM), and PCa-specific mortality (PCaM).

A propensity score matching analysis was performed to estimate BCR-free survival, metastasis-free survival), overall survival (OS), and prostate cancer-specific survival (PCaS) using the Kaplan Meier method and the log-rank test.

A competing risk model was fitted to estimate the cumulative incidence functions for other-cause mortality (OCM), other cancer-specific mortality (OCaM), and PCaM. Statistical analysis was performed using R [17].

## 3. Results

### 3.1. Patients

Of all patients, 6.4% were diagnosed with other malignancy prior to RP. Cancer of the skin (34%), colorectal cancer (15%), bladder cancer (11%), kidney cancer (11%), lung cancer (4%), head and neck cancer (4%). and other entities (21%) were observed (Supplementary Table 1). Patients with other malignancy prior to RP were older (median: 66 years vs. 64 years, $P < 0.001$) and had higher tumor volume (median: 4.0 ml vs. 3.6 ml, $P = 0.02$), but showed no differences in the distribution of D'Amico risk groups, preoperative PSA level, pT-stage, pathological Gleason score, and pN-status (Table 1). Median follow-up since surgery was 61 months (interquartile range: 35.8−108).

### 3.2. Cox proportional hazard

The risk of BCR (hazard ratio [HR] 1.04; 95% confidence interval [CI] 0.92−1.17, $P$= 0.53) and metastasis development (HR 0.91; 95% CI 0.7−1.18, $P = 0.47$) after RP was similar between patients with other malignancy prior to RP and patients with PCa only (Supplementary Table 2). ACM including OCM and OCaM was significantly increased (HR 2.0; 95% CI 1.7−2.4, $P < 0.001$), while PCaM was significantly lower (HR 0.4; 95% CI 0.23−0.87, $P = 0.017$) in patients with additional malignancy (Table 2).

### 3.3. Competing risks

OCM, OCaM, and PCaM at 60 months were 2.7%, 2.6%, and 0.2% for patients with other malignancy prior to RP and 1.7%, 0.3%, 0.7% for patients with PCa only (Fig. 1).

Table 1
Patient and tumor characteristics in men with other cancer prior to RP and PCa only

| Parameter | Overall | PCa only | Other cancer prior to RP | *P* value |
|---|---|---|---|---|
| Patients, *n* (%) | 24,316 | 22,764 (93.6) | 1,552 (6.4) | |
| D'Amico risk, *n* (%) | | | | |
| Low | 7,695 (32.8) | 7,222 (32.9) | 473 (31.5) | 0.41 |
| Intermediate | 11,240 (47.9) | 10,520 (47.9) | 720 (48) | |
| High | 4,545 (19.4) | 4,238 (19.3) | 304 (20.3) | |
| Age at surgery (yr.) | | | | |
| Median | 64 | 64 | 66 | <0.001 |
| IQR | 59−69 | 59−68 | 62−70 | |
| Range | 33−81 | 33−81 | 41−80 | |
| Tumor volume (ml) | | | | |
| Median | 3.7 | 3.6 | 4 | 0.02 |
| IQR | 1.8−7.2 | 1.8−7.2 | 2.0−7.5 | |
| Range | 0.001−136 | 0.001−136 | 0.001−73.9 | |
| Preoperative PSA value (ng/ml) | | | | |
| Median | 7 | 7 | 7.2 | 0.54 |
| IQR | 4.9−10.7 | 4.9−10.6 | 4.8−10.7 | |
| Range | 0−911 | 0.0−911 | 0.0−168 | |
| Gleason score, *n* (%) | | | | |
| 3 + 3 | 4,911 (20.2) | 4,622 (20.3) | 289 (18.7) | 0.07 |
| 3 + 4 | 13,663 (56.3) | 12,801 (56.3) | 862 (55.7) | |
| 4 + 3 | 4,070 (16.8) | 3,798 (16.7) | 272 (17.6) | |
| ≥4 + 4 | 1,624 (6.7) | 1,500 (6.6) | 124 (8) | |
| pN-status, *n* (%) | | | | |
| Nx | 6,879 (28.3) | 6,439 (28.3) | 440 (28.4) | 0.71 |
| N0 | 15,371 (63.3) | 14,400 (63.4) | 971 (62.7) | |
| N+ | 2,017 (8.3) | 1,880 (8.3) | 137 (8.9) | |
| pT-stage, *n* (%) | | | | |
| pT2 | 16,073 (66.2) | 15,080 (66.3) | 993 (64.1) | 0.2 |
| pT3a | 5,067 (20.9) | 4,720 (20.8) | 347 (22.4) | |
| pT3b/pT4 | 3,151 (13) | 2,943 (12.9) | 208 (13.4) | |
| Surgical margin, *n* (%) | | | | |
| Negative | 19,799 (81.5) | 18,544 (81.5) | 1,255 (81.1) | 0.64 |
| Positive | 4,489 (18.5) | 4,196 (18.5) | 293 (18.9) | |
| BCR, *n* (median time*, mo.) | 4,623 (19.0) | 4,314 (19.1) | 309 (17.1) | 0.35 |
| Metastasis, *n* (median time*, mo.) | 915 (31.9) | 854 (31.7) | 61 (33.3) | 0.72 |
| Other-cause death, *n* (median time*, mo.) | 801 (75.9) | 724 (75.9) | 77 (70.5) | <0.001 |
| Other cancer-specific death, *n* (median time*, mo.) | 191 (72.2) | 118 (69.4) | 73 (73.7) | <0.001 |
| PCa-specific death, *n* (median time*, mo.) | 310 (75.6) | 299 (75.0) | 11 (115.3) | 0.04 |

BCR = biochemical recurrence; PCa = prostate cancer; RP = radical prostatectomy.
* Since RP.

### 3.4. Propensity score-matched analysis

Kaplan Meier estimates in a propensity score-matched patient cohort (Supplementary Table 3) were used to compare patients with other cancer prior to RP ($n = 1532$) and PCa only ($n = 3,064$). Median follow-up was 61 months. No differences in BCR-free survival ($P = 0.71$, Fig. 2A) and metastasis-free survival ($P = 0.91$, Fig. 2B) were found. OS was adverse ($P < 0.001$, Fig. 2C) and PCaS showed a benefit ($P < 0.001$, Fig. 2D) for patients with other cancer diagnosis prior to RP. Probabilities for OS at 120 months were 84.7% (95% CI: 81.8−87.7) and 90.0% (95% CI: 88.3−91.8) and for PCaS at 120 months were 99.0% (95% CI: 98.0−100.0) and 97.1% (95% CI: 96.2−98.1) for other cancer prior to RP and PCa only, respectively.

### 3.5. Competing risk analysis in other cancer types

PCa-specific death was registered in patients with bladder cancer (3/165), kidney cancer (3/157), skin cancer (3/509), colorectal cancer (2/229), and in other/unknown cancer (1/116) with probabilities of PCaM of 1.9%, 1.6%, 0.6%, 0.5%, and 3.6%, respectively (Supplementary Figure 1, Supplementary Table 1). Probabilities for OCaM at 120 months were highest in pancreas cancer (33.4%),

Table 2
Cox regression multivariable analysis predicting ACM and PCaM

| | ACM | | | PCaM | | |
|---|---|---|---|---|---|---|
| Parameter | HR | CI, 95% | *P* value | HR | CI, 95% | *P* value |
| Year of surgery | 0.95 | 9376−0.96 | <0.001 | 0.92 | 0.9−0.94 | <0.001 |
| Age at surgery | 1.05 | 1.04−1.06 | <0.001 | 1.0 | 0.98−1.02 | 0.94 |
| PSA value preoperative | 1.0 | 0.99−1.0 | 0.42 | 0.99 | 0.99−1.0 | 0.05 |
| pT-stage | | | | | | |
| pT3a vs. pT2 | 1.15 | 0.98−1.34 | 0.09 | 1.22 | 0.73−1.71 | 0.60 |
| pT3b/pT4 vs. pT2 | 1.77 | 1.47−2.12 | <0.001 | 2.85 | 1.9−4.27 | <0.001 |
| pN-status | | | | | | |
| pNx vs. pN0 | 1.03 | 0.89−1.19 | 0.68 | 1.03 | 0.7−1.5 | 0.9 |
| pN+ vs. pN0 | 1.34 | 1.1−1.64 | 0.004 | 1.3 | 0.97−1.75 | 0.08 |
| Gleason score | | | | | | |
| 3 + 4 vs. 3 + 3 | 1.16 | 0.99−1.35 | 0.07 | 2.06 | 1.15−3.69 | 0.02 |
| 4 + 3 vs. 3 + 3 | 1.71 | 1.39−2.1 | <0.001 | 5.07 | 2.74−9.37 | <0.001 |
| ≥4 + 4 vs. 3 + 3 | 3.38 | 2.64−4.35 | <0.001 | 13.4 | 7.04−25.67 | <0.001 |
| Surgical margin | | | | | | |
| Negative vs. positive | 1.36 | 1.19−1.56 | <0.001 | 1.65 | 1.29−2.12 | <0.001 |
| Radiation therapy | | | | | | |
| Adjuvant vs. no | 0.56 | 0.41−0.77 | <0.001 | 0.38 | 0.22−0.64 | <0.001 |
| Salvage vs. no | 0.67 | 0.56−0.79 | <0.001 | 0.86 | 0.65−1.13 | 0.27 |
| Hormone therapy | | | | | | |
| Yes vs. no | 1.5 | 1.28−1.75 | <0.001 | 5.76 | 4.19−7.9 | <0.001 |
| Other cancer prior to RP | | | | | | |
| Yes vs. no | 2.03 | 1.71−2.4 | <0.001 | 0.44 | 0.23−0.87 | 0.017 |

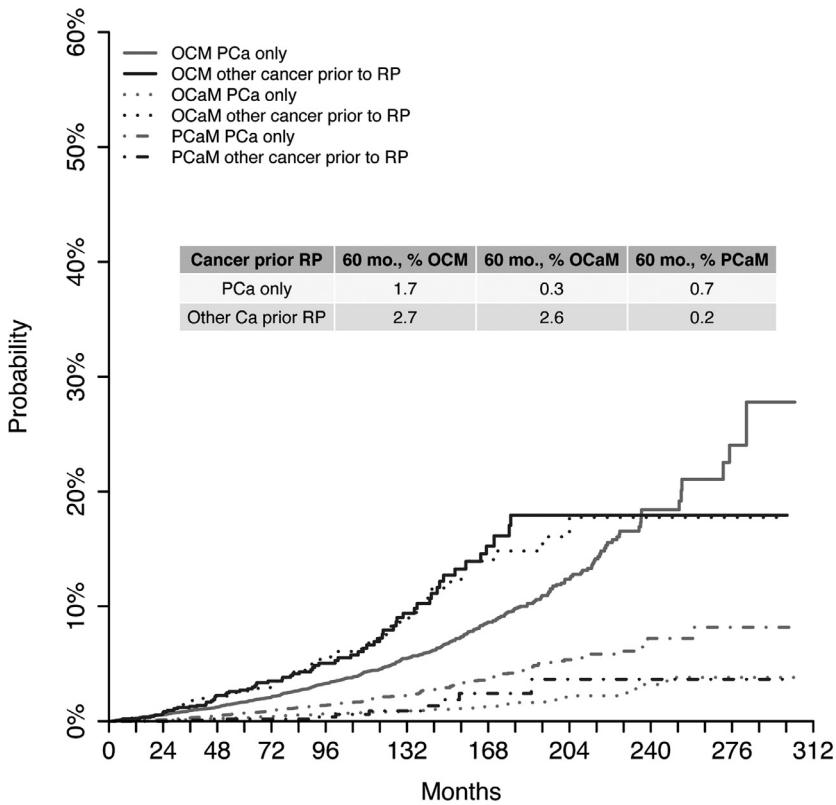


Fig. 1. Competing risk analysis comparing OCM, OCaM, and PCaM between patients with other malignancy prior to RP and PCa only. OCaM = other cancer-specific mortality; OCM = other-cause mortality; PCaM = PCa-specific mortality.

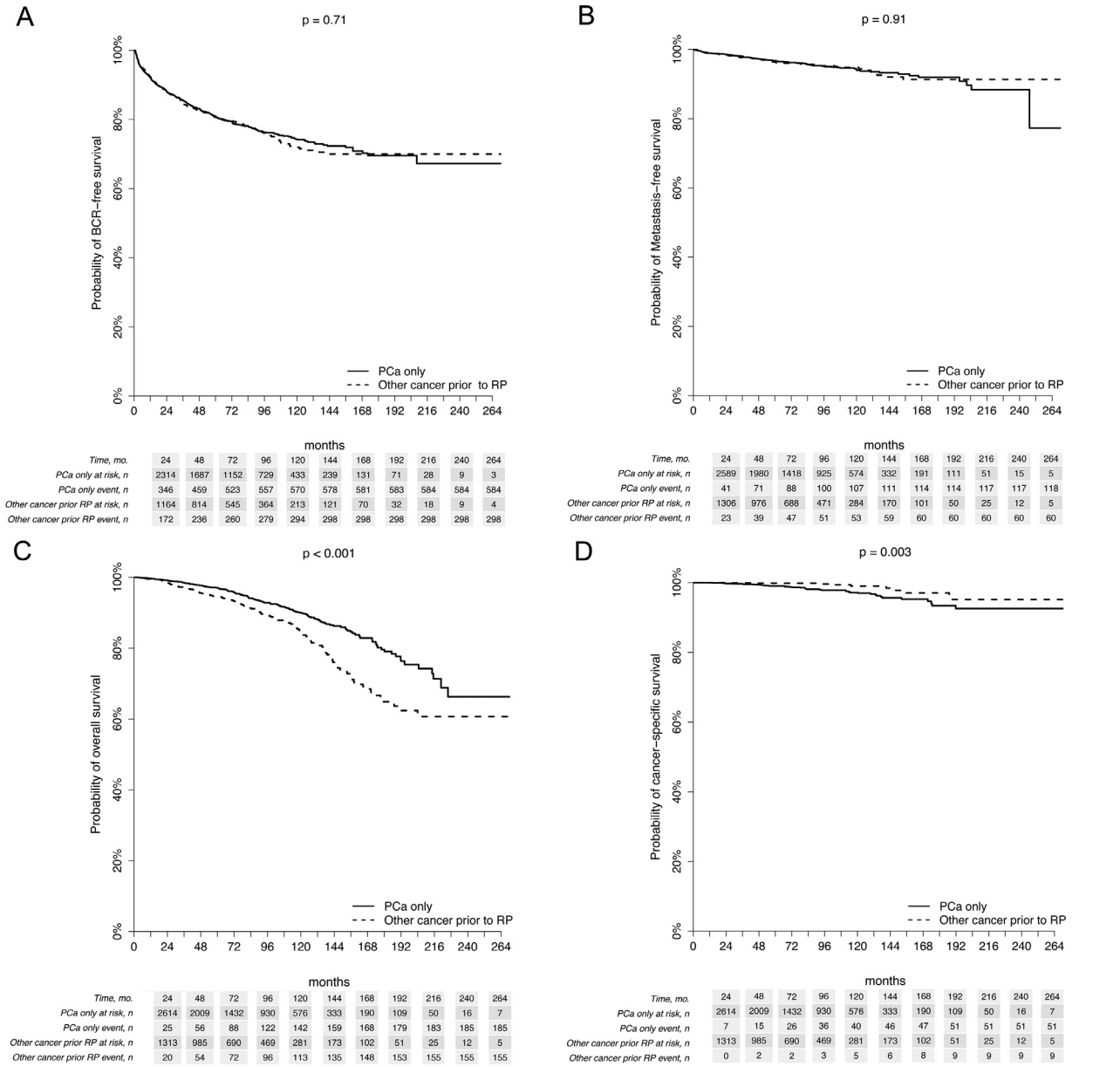


Fig. 2. Kaplan Meier analysis for BCR-free survival (A), MFS (B), OS (C), and PCaS (D). BCR = biochemical recurrence; MFS = metastasis-free survival; OS = overall survival; PCaS = prostate cancer-specific survival.

lung cancer (30.0%), stomach cancer (18.6%), leukemia (18.3%), testis cancer (14.6%), and colorectal cancer (9.1%) (Supplementary Figure 1, Supplementary Table 1).

### 3.6. Subset analysis

A subset analysis excluding 333 cases with nonmelanotic skin cancer (e.g., spindle cell carcinoma or basalioma) confirms the higher OCM and the lower PCaM of patients with tumor history (Supplementary Table 4 and Supplementary Figures 2 and 3).

## 4. Discussion

Information on prevalence of malignancies in the medical history of PCa patients vary widely between studies. While Liskow et al. [18] observed preexisting neoplasms in 4.1% of PCa patients, Hemelrijck et al. [6] found earlier malignancies in about 10% of these men. Further investigations determined prevalence rates of 6% to 9% [19–22]. Differences in period of investigation, detection of temporally distant malignancies, and patient population should be kept in mind as factors for these variations in prevalence. Especially, the latter could explain a lower frequency in our

study, since in particular patients with a lower rate of comorbidities are considered for a surgical treatment. Nonetheless the high incidence of PCa in western countries should be taken into account. This may lead to a high number of PCa patients with further malignant neoplasms in their medical history. This observation may be a result of increasing survival rates following cancer treatment due to medical progress and the additional increased risk of developing malignancies in cancer survivors [2]. Germany has one of the highest survival rates for cancer in Europe [23] and especially age-related tumors such as PCa are likely to occur after an earlier primary tumor disease as a result of increasing life expectancy and demographic change.

In contrast to other studies, our findings suggest that previous tumor diseases have no impact on PCa characteristics. Kawakami et al. [24] found that PCa patients with other malignancies showed more favorable disease characteristics than those without further tumors. Dinh et al. [21] observed an increased frequency of high-risk cancers in men with history of tumor disease. Also, Liskow et al. [18] and Mirabeau-Beale et al. [25] found a higher amount of Gleason scores ≥8 in these patients. However, the previous study group also considered the higher age of PCa patients as a potential reason for deviant Gleason patterns. That supports the results of our study. Additionally, the prostate tumors of these patients had a larger volume. These observations may be due to later medical care. A delay of diagnosis and in particular therapeutic intervention as a result of higher morbidity may explain these findings. This assumption is supported by the observation of less frequent use of definitive therapies [21] and more watchful waiting and active surveillance in PCa patients with tumor history [25]. Also, mutations in cancer predisposing genes may be a cause of the development of multiple primary neoplasms and deviations in tumor biology. Such a connection between the occurrence of multiple tumors and the characteristics of PCa could not be demonstrated in our study, which may be due to the rarity of these syndromes. Only 11% of PCa patients with multiple primary neoplasms actually have pathologic germline mutations in cancer predisposing genes [26] and not all of them are highly penetrant with great influence on tumor biology.

Taking into account the higher age and larger tumor volume of patients with a history of tumor disease, the reduction in PCaM of these men, which has been demonstrated in this study and by Mirabeau-Beale et al. (2014) [25], seems only plausible in relation to the simultaneous increase in ACM. This could be explained by the existence of residual malignancies or comorbidities after curative cancer treatment leading to the observed increase in OCM. Patients selected for RP in curative intend usually have low OCM with a life expectancy of more than 10 to 15 years. However, if patients have been treated for another malignant disease in curative intent prior to PCa diagnosis, OCM increases substantially to more than 5% with the majority of non−PCa-specific deaths attributable to former tumors. Also Froehner et al. [27] found that about 40% of non−PCa-specific deaths after RP can be attributed to second cancers. The observed increase in PCaS with simultaneous reduction in OS, which also Lim et al. [20] showed in patients with multiple primary neoplasms, can be explained by this increase in OCM, too. The decrease in PCaM and the gain in PCaS are most likely of statistical nature due to extended probability of early non−PCa-specific death.

For clinical practice, these results call for increased attention to the chance of developing PCa in male cancer survivors. Men at risk should be made aware of a healthy lifestyle and avoidance of carcinogenic agents. In addition to these primary preventive measures, a recommendation of PCa screening, an advance of the age limit for early diagnosis and an extension of the diagnostic procedures may be thought of. An individual risk-benefit assessment remains indispensable to avoid overdiagnosis since the detection of a subsequent PCa does not necessarily entail therapeutic consequences. Higher morbidity in patients with multiple primary neoplasms seems to reduce the benefit of a RP and is simultaneously associated with an increased risk of developing complications after surgery [28]. To avoid overtreatment, patients with tumor history may be offered a nondefinitive therapy for their PCa, if medical indication and patient's consent are given. A comparison of conservative strategies and definitive therapeutic approaches in PCa patients with previous malignancies in the context of clinical trials appears to be useful for further addressing these issues.

Limitation of this study is the retrospective design. Recall bias and limited information from the patient records, especially concerning the time of diagnosis of the earlier malignancy, complicate the assessment of the chronical order of the diseases. Nevertheless, prospective collection of data in our established, internally reviewed-based clinical database and the long-standing optimization of such processes ensure reliable data analyses. In addition to patient information from medical records and self-administrated questionnaires data from national cancer registry was evaluated. The long investigation period from 1992 to 2016 may lead to corruption as a result of changes and developments in the medical care of PCa within this time. For this reason, we added the year of surgery as potential confounding factor as surrogate in multivariable analyses. Finally, possible limitations regarding external validity should be taken into account. Limited comparability between our patient population and the entirety of PCa patients must be kept in mind, because of the specialization on curative intended and operative therapy procedures. To provide comparability between our analysis and the results of other studies, which mostly lack information about nonmelanotic skin cancer, we excluded these patients ($n = 333$) from the data set and repeated the analysis. Except the loss of statistical significance in Cox proportional hazard analysis predicting PCaM for patients with and without other cancer prior to RP ($P = 0.057$, Supplementary Table 4), no noticeable changes were found (Supplementary Figures 2 and 3).

In conclusion, this study has shown that a primary tumor disease prior to PCa surgery is associated with a lower risk for PCa-specific death. This observation most likely results of an increased chance to die from other causes or from the initial malignant disease despite completed treatment and no evidence of recurrent disease in follow-up. These findings should be taken into account in the process of decision-making in the medical care of PCa patients.

## Declaration of interest

None.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.04.007.

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