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PREDICTING FIFTEEN-YEAR CANCER-SPECIFIC MORTALITY BASED ON THE PATHOLOGICAL FEATURES OF PROSTATE CANCER

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Abstract

Purpose—Long-term prostate cancer-specific mortality (PCSM) after radical prostatectomy is poorly defined in the era of widespread screening. An understanding of the treated natural history of screen-detected cancers and the pathological risk factors for PCSM are needed for treatment decision-making.

Methods—Using Fine and Gray competing risk regression analysis, the clinical and pathological data and follow-up information of 11,521 patients treated by radical prostatectomy at four academic centers from 1987 to 2005 were modeled to predict PCSM. The model was validated on 12,389 patients treated at a separate institution during the same period.

Results—The overall 15-year PCSM was 7%. Primary and secondary pathological Gleason grade 4–5 ($P < 0.001$ for both), seminal vesicle invasion ($P < 0.001$), and year of surgery ($P = 0.002$) were significant predictors of PCSM. A nomogram predicting 15-year PCSM based on standard pathological parameters was accurate and discriminating with an externally-validated concordance index of 0.92. Stratified by patient age, 15-year PCSM for Gleason score ≤ 6, 3+4, 4+3, and 8–10 ranged from 0.2–1.2%, 4.2–6.5%, 6.6–11%, and 26–37%, respectively. The 15-year PCSM risks ranged from 0.8–1.5%, 2.9–10%, 15–27%, and 22–30% for organ-confined

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cancer, extraprostatic extension, seminal vesicle invasion, and lymph node metastasis, respectively. Only 3 of 9557 patients with organ-confined, Gleason score ≤ 6 cancers have died from prostate cancer.

Conclusions—The presence of poorly differentiated cancer and seminal vesicle invasion are the prime determinants of PCSM after radical prostatectomy. The risk of PCSM can be predicted with unprecedented accuracy once the pathological features of prostate cancer are known.

Keywords

prostatic neoplasms; prostatectomy; models; statistical; treatment outcome

INTRODUCTION

Prostate cancer has a protracted natural history. In the absence of definitive local therapy, the 15-year prostate cancer-specific mortality (PCSM) is approximately 20%.[1] This risk may be substantially less among men living in regions where screening with prostate-specific antigen (PSA) is prevalent, given the 5–11 year lead-time with screening.[2] Prognostic studies to date have thus relied on a biochemical recurrence (BCR) endpoint.[3] However, BCR is not a surrogate endpoint for PCSM as a rising PSA may pose little threat to the longevity of many patients. Ideally, treatment decision-making should be based, in part, on accurate estimates of PCSM. Nomograms that predict PCSM are needed.

We recently developed a nomogram that predicts the 15-year PCSM after radical prostatectomy based on PSA, biopsy Gleason score, clinical stage).[4] Treatment outcome can be predicted with improved accuracy using pathological stage and Gleason score.[3] To more rigorously guide treatment decision-making, we endeavored to construct a nomogram for PCSM based on the pathological features of prostate cancer.

METHODS

Between 1987 and 2005, 11,521 consecutive patients with localized prostate cancer were treated by radical prostatectomy at Cleveland Clinic (Cleveland, OH), Memorial Sloan-Kettering Cancer Center (New York, NY), University of Michigan (Ann, Arbor, MI), and Baylor College of Medicine (Houston, TX). These patients served as the modeling cohort for nomogram development. For external validation of the nomogram, 12,389 patients similarly treated at Johns Hopkins University (Baltimore, MD) during the same time period were used. We excluded patients who received prior androgen deprivation therapy or radiation therapy.

Surgical specimens were evaluated by genitourinary pathologists at each institution. Pathological stage was assigned according to the American Joint Committee on Cancer criteria.[5] Secondary therapy was uncommonly administered in the absence of BCR. Death was attributed to prostate cancer if, upon review of the medical record, there was evidence of progressive metastases and prostate cancer was listed as the cause of death on the death certificate. In the modeling and validation cohorts, the median follow-up was 56 months

(interquartile range [IQR]: 24–93) and 96 months (IQR: 60–144), respectively. Overall, a total of 6818 and 1650 survivors had greater than 10 and 15 years of follow-up, respectively.

For construction of the nomogram, Fine and Gray competing risk regression analysis was used to model clinical parameters and follow-up data.[6] The PSA before radical prostatectomy and year of surgery were modeled with restricted cubic splines because of suspected nonlinear effects. Primary and secondary pathological Gleason grades were modeled as binary categorical variables (≤ 3 and ≥ 4). All decisions with respect to variable coding were made *a priori* without knowledge of their association with PCSM.

For external validation of the model, we assessed its discrimination using the concordance (c-) index and calibration by comparing the predicted probability of PCSM and the cumulative incidence of PCSM.[7] All statistical analyses were performed using S-Plus software (S-plus 2000; Insightful Corp, Redmond, WA) with additional functions (called “Design” and “cmprsk”) added.

RESULTS

The clinical features of the modeling and validation cohorts are summarized in Table 1. Overall, 347 patients died from prostate cancer and 1127 died from other causes. In the modeling and validation cohorts, the 15-year PCSM was 7% and 4%, respectively and the 15-year all-cause mortality was 33% and 16%, respectively. Overall, 108 (31%) PCSM events occurred in patients treated after 1995, when the stage migration effect of PSA screening appears to have stabilized[4].

In multivariable analysis, primary and secondary Gleason grade 4–5 ($P < 0.001$ for both), seminal vesicle invasion ($P < 0.001$), and year of surgery ($P = 0.002$) were the only parameters significantly associated with PCSM in the modeling cohort. A nomogram based on 8 standard parameters was developed to predict the 15-year PCSM (Figure 1a). The year of surgery is included in the model and the predictions are adjusted for treatment year; the graphical version of the nomogram assumes the patient is treated in 2005 (the most recent year in this cohort). The nomogram was accurate and discriminating with an externally-validated concordance index of 0.92 and predictions closely approximated the actual outcome at 15 years (Figure 1b). The nomogram predictions were similarly robust when applied to patients treated in the early (1987–1994) and later (1995–2005) PSA era (c-index 0.89 and 0.93, respectively).

The estimated 10-, 15-, and 20-year PCSM was analyzed for all 23,910 patients in this study based on pathological grade and stage (Table 2). For patients with Gleason ≤ 6 cancer, PCSM was negligible (1.2% or less) and was substantially less than the risk of death from competing causes, regardless of age at diagnosis (Figure 2). In contrast, PCSM for men with pathological Gleason 8–10 cancer was generally 31% or greater among the sub-groups analyzed, which was substantially greater than the risk of death from competing causes. PCSM for men with pathological Gleason 7 was intermediate between Gleason ≤ 6 and Gleason 8–10. There were no substantial differences in the 15-year PCSM between Gleason

3+4 (4.2–6.5%) and Gleason 4+3 (6.6–11%), as the 95% confidence intervals were overlapping at all the time-points analyzed.

A similar pattern was seen when long-term PCSM was analyzed by pathological stage (Figure 3). PCSM was negligible for men with organ-confined cancer (0.8–1.5%) and a substantially increased risk of PCSM was observed for those with seminal vesicle invasion or lymph node metastasis (22–42%), particularly for those younger than 70 years at diagnosis. The presence of isolated extraprostatic extension did not portend a particularly poor prognosis as PCSM for men younger than 70 years was 2.9–7%, which was generally substantially less than the risk of death from competing causes (6.6–24%). Patients with organ-confined, pathological Gleason ≤ 6 cancer had a particularly favorable prognosis as only 3 deaths from prostate cancer were observed among 9557 men treated.

DISCUSSION

Radical prostatectomy is widely used for the treatment of localized prostate cancer. There is conclusive evidence that radical prostatectomy compared to surveillance reduces PCSM among men with non-screen-detected cancers.[1] For men with screen-detected prostate cancer, the risk of PCSM has been difficult to predict due to the stage migration caused by screening. This study is the largest series of patients treated by radical prostatectomy in the PSA era and represents a major re-evaluation of the key prognostic factors in prostate cancer. The presence of pathological Gleason score 8–10 cancer and seminal vesicle invasion are the prime determinants of PCSM and a nomogram based on these and other parameters predicts 15-year PCSM with exceptional accuracy. This nomogram should be useful for patient counseling about prognosis and the need for secondary therapy. The study also provides important information about the treated natural history of prostate cancer and identifies the cancers that pose the greatest (and least) threat to survival.

The costs of screening in terms of over diagnosis and over-treatment were made apparent in a recent European screening trial; an estimated 48 men require treatment to prevent 1 death from prostate cancer at 10 years.[8] The results of our study help to sharpen the focus of therapy for men with screen-detected prostate cancers.

Patients with pathological Gleason score 8–10, seminal vesicle invasion or lymph node metastasis are at a substantially increased risk of PCSM compared to those without these features. However, the 15-year PCSM in these high-risk men was lower than expected, ranging from 22–37%. This finding is significant as men with these pathological features were thought to be incurable (based on the 70–85% reported rates of BCR),[9, 10] and previously considered by some to be unsuitable candidates for radical prostatectomy. While it is not known how these high-risk patients would have fared without local therapy, studies of similar patients treated without curative intent suggest substantially higher risks of PCSM.[11, 12] This suggests the greatest relative benefit of surgery compared to surveillance is for men with aggressive cancers, even those unlikely to be cured by surgery alone based on a BCR endpoint. For these men, combining surgery with the judicious use of adjuvant or salvage therapy is likely to have the greatest impact on reducing PCSM.

Currently, the majority of men who undergo radical prostatectomy have organ-confined and/or pathological Gleason score 6 cancers. These men have a negligible risk of PCSM. With the recent revision of the Gleason grading system, non-organ-confined, pathological Gleason ≤ 6 cancers are now a profoundly uncommon occurrence.[13] Thus, we may have observed even fewer cancer-specific deaths among these men had the surgical specimens been subjected to a contemporary pathological review. Radical prostatectomy is highly effective for well-differentiated cancers, but may be unnecessary in many of these men, as a similar cancer-specific survival may have been achieved without immediate radical therapy. These results provocatively call into question the need for any immediate treatment in men with pathological well-differentiated cancers, provided they can be accurately determined at the time of diagnosis. The 10-year prostate cancer-specific survival was 97.2% for a low-risk cohort of men on active surveillance in a recent study.[14] However, very few healthy, young men with low-risk cancers are managed by this approach due to concerns that clinical grading and staging may initially underestimate the threat posed by one's cancer.

Numerous investigators have shown the risk of PCSM for patients with BCR can be predicted using the rate of rise of the PSA level (known as the PSA doubling time [DT]).[15, 16] However, PSADT is useful only for patients who have manifested BCR, and a waiting period of 6–24 months is required to obtain sufficient PSA measurements to accurately calculate PSADT. These factors limit the clinical utility of PSADT to determine the need for additional local therapy, as the critical periods for treatment decisions are the immediate postoperative period or when the PSA level first begins to increase. Postoperative radiation therapy is most effective when given in the adjuvant setting or as salvage therapy when the serum PSA first reaches detectable levels.[17–19] As such, the nomogram is anticipated to be useful for selecting men for postoperative radiation therapy who are at substantial risk of PCSM.

An extraordinary finding of our study was the high level of accuracy of the nomogram using standard pathological parameters, which is unprecedented for predictive models in oncology; the c-index of 0.92 indicates that its performance approaches that of a perfectly discriminating model. The c-index of a similar model we developed based on pre-treatment clinical stage and biopsy Gleason score was 0.82, highlighting the inaccuracy of clinical versus pathological stage and grade.[4] Decisions regarding treatment for localized prostate cancer rely on clinical stage and grade. Our study suggests that novel biomarkers, imaging, and/or improved biopsy sampling should focus on predicting the pathological grade and stage of prostate cancer, as PCSM can be accurately predicted once the pathological features of prostate cancer are known. This should lead to improved patient selection for active surveillance for low-risk cancers and multimodal therapy for aggressive cancers.

Using PCSM as the endpoint of our study, the relative importance of other prognostic factors implicated in BCR is placed into appropriate context. A plot of 10-year BCR probability by a previously published nomogram with 15-year PCSM by this nomogram shows only a slight increased risk of PCSM men with a 10–50% BCR probability compared to those with a 10-year BCR probability < 5% (Figure 4). The risk of PCSM is substantially increased only when the risk of BCR is 50% or greater, and the majority (70%) of these patients has pathological Gleason 8–10 cancer, seminal vesicle invasion, and/or lymph node

metastasis. The relative lack of importance of many factors implicated in BCR for PCSM highlights the limitation of using the former as an endpoint. Factors other than aggressive tumor biology may increase the risk of BCR. For example, positive surgical margins are caused, in part, by technical errors,[20] and appear to increase the risk of local recurrence.[21] However, they were not significantly associated with PCSM in our study. The low risk of PCSM in men with isolated extraprostatic extension and positive surgical margins calls into question the need for adjuvant radiation therapy, despite evidence from a randomized trial of improved overall and metastasis-free survival compared to a (largely) observational strategy.[17] Salvage radiation therapy administered at the earliest sign of BCR appears to be a reasonable alternative to adjuvant radiation therapy in these men.[18]

The year of surgery was significantly associated with PCSM, with contemporary patients having an improved prognosis. Possible explanations for this finding include the stage migration induced by widespread PSA screening, the recognition and application of effective secondary therapy,[17, 22] technical improvements in radical prostatectomy,[23] and era-specific changes in histological grading.[13] Recent changes to the Gleason scoring system result in re-classification of many low-grade tumors to high-grade tumors. This strengthens our findings in terms of the low lethality of contemporary low-grade cancers and the favorable outcomes achieved with radical prostatectomy despite the presence of poorly differentiated cancer. The predictions of the model are anticipated to be valid when applied to patients treated after 2005 as we have previously shown the effect of year of surgery has stabilized since 1998.[4]

Our study has several limitations. The nomogram predicts the probability of PCSM within 15 years, but patients appear to be at risk of PCSM for up to 20 years after treatment.[24] A recent study of patients treated without curative intent in the pre-PSA era has suggested an acceleration in PCSM after 15 years,[25] although a contradictory finding was reported in a separate study.[11] Long-term PCSM was low among patients in our study, but we do not know how these patients would have fared without radical therapy. Likewise, we are unable to compare the effectiveness of radical prostatectomy to other therapies. Our model considers only PCSM and does not consider health-related quality-of-life.[26] We also did not consider all potential important prognostic parameters such as PSA velocity,[27] though it did not improve the accuracy of our preoperative nomogram.[4] Lastly, the nomogram is based on men treated at high-volume centers and thus may not be as accurate for men treated in other settings. However, this is also an advantage as high-volume centers are more likely to have experienced genitourinary pathologists and thus, a more accurate assessment of the pathological grade and stage.

In summary, pathological Gleason 8–10 cancer and seminal vesicle invasion are the prime determinants of PCSM after radical prostatectomy. The risk of PCSM in men with organ-confined, well-differentiated cancers is negligible. PCSM can be accurately predicted by a nomogram based on the clinical and pathological features of prostate cancer. By focusing on PCSM, this study represents a critical re-appraisal of the key prognostic factors in prostate cancer and is the most meaningful analysis of the treated natural history of screen-detected prostate cancer after radical prostatectomy.

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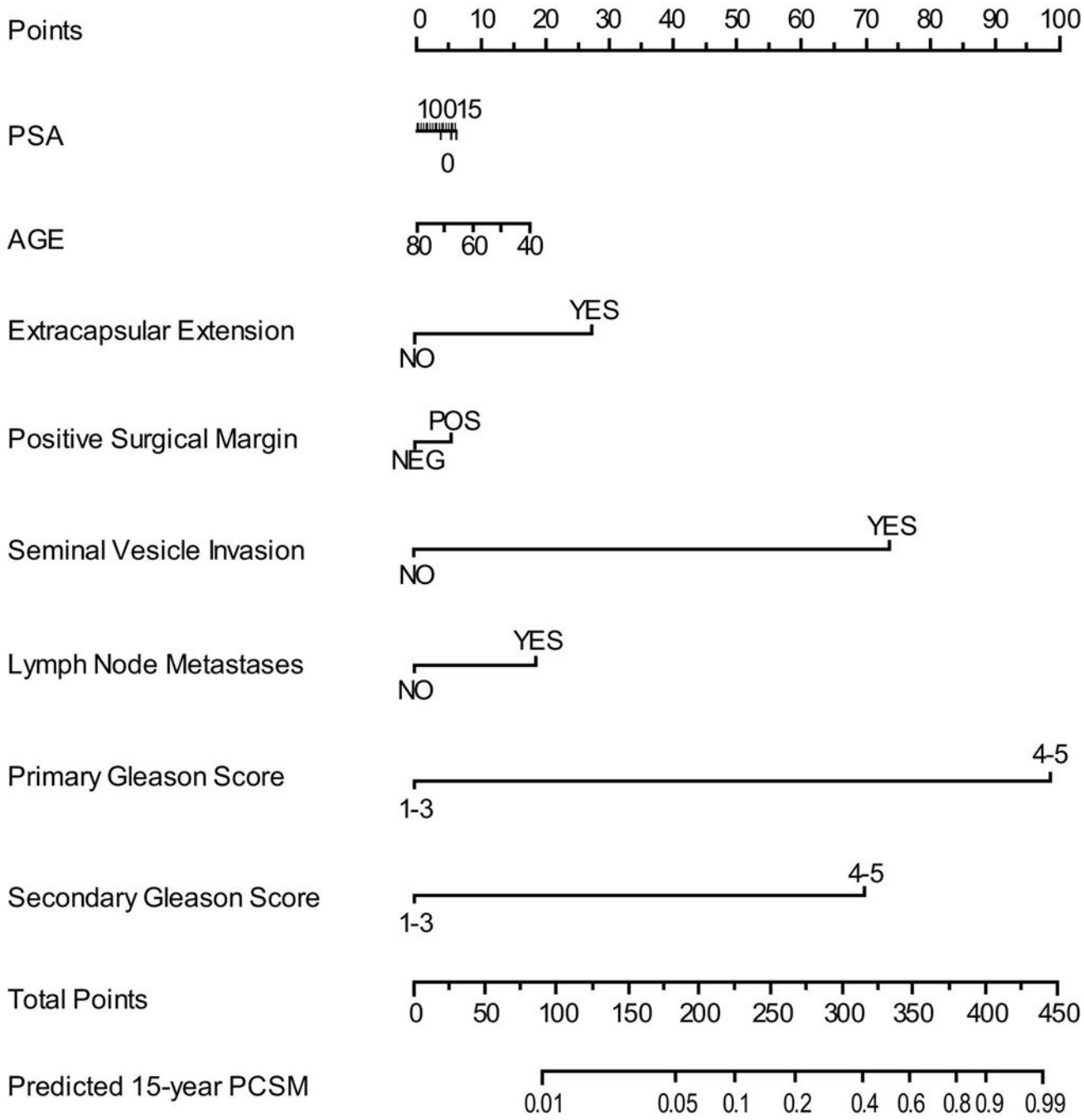

Figure 1.

(A) Nomogram predicting 15-year prostate cancer–specific mortality after radical prostatectomy based on the preoperative prostate-specific antigen level and the pathological features of prostate cancer. (B) Calibration of the nomogram. Dashed line indicates reference line where an ideal nomogram would lie. Instructions: Locate the patient's primary Gleason grade on the respective axis. Draw a straight line up to the Points axis to determine how many points toward prostate cancer–specific mortality he receives for his primary Gleason grade. Repeat this process for the other three parameters. Sum the points and locate

this number on the Total Points axis. Draw a straight line down to find the patient's probability of dying as a result of prostate cancer within 15 years of treatment.

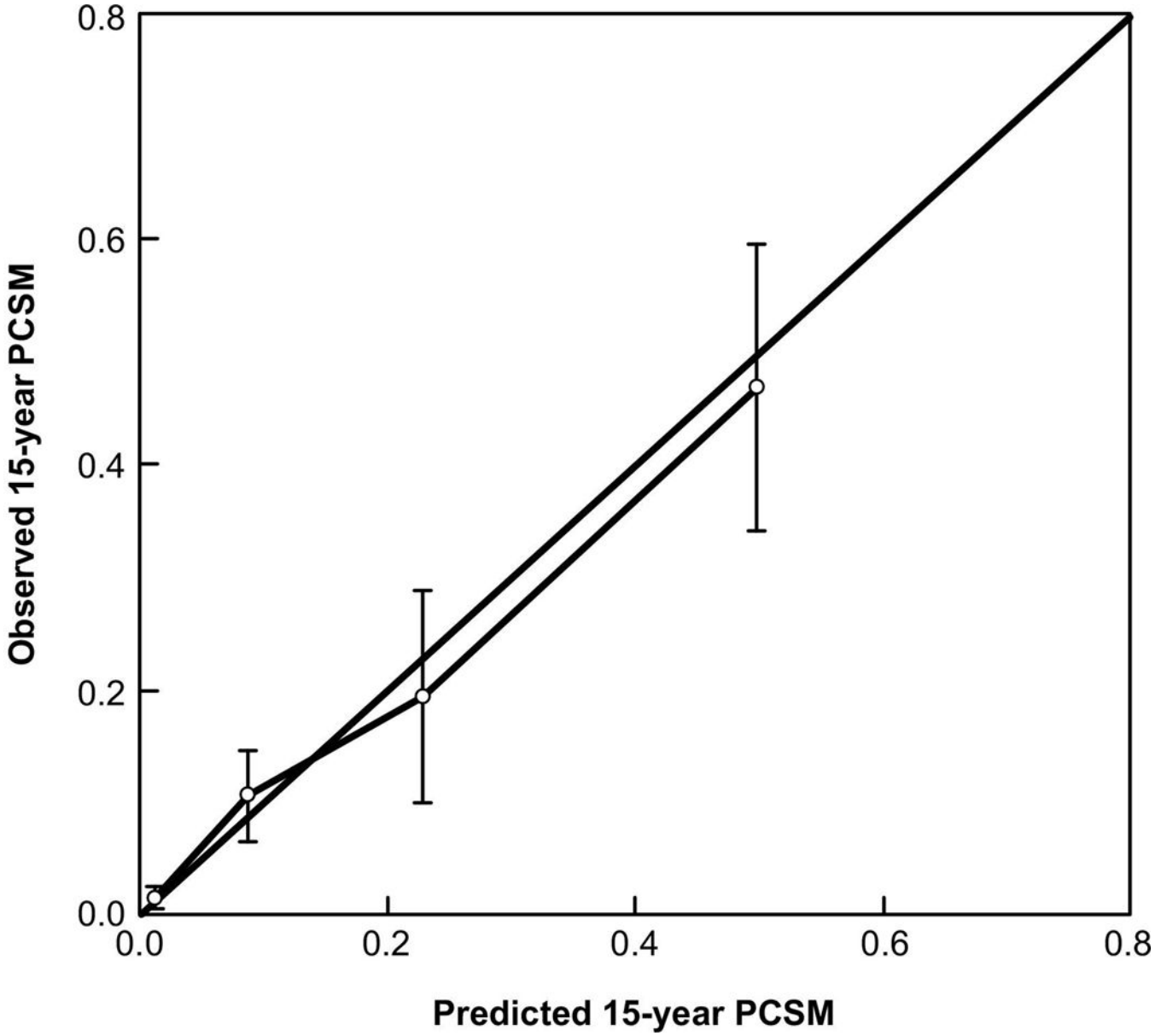

Figure 2.
Prostate cancer-specific mortality (black) and mortality from competing causes (gray) stratified by pathological Gleason score and patient age at diagnosis.

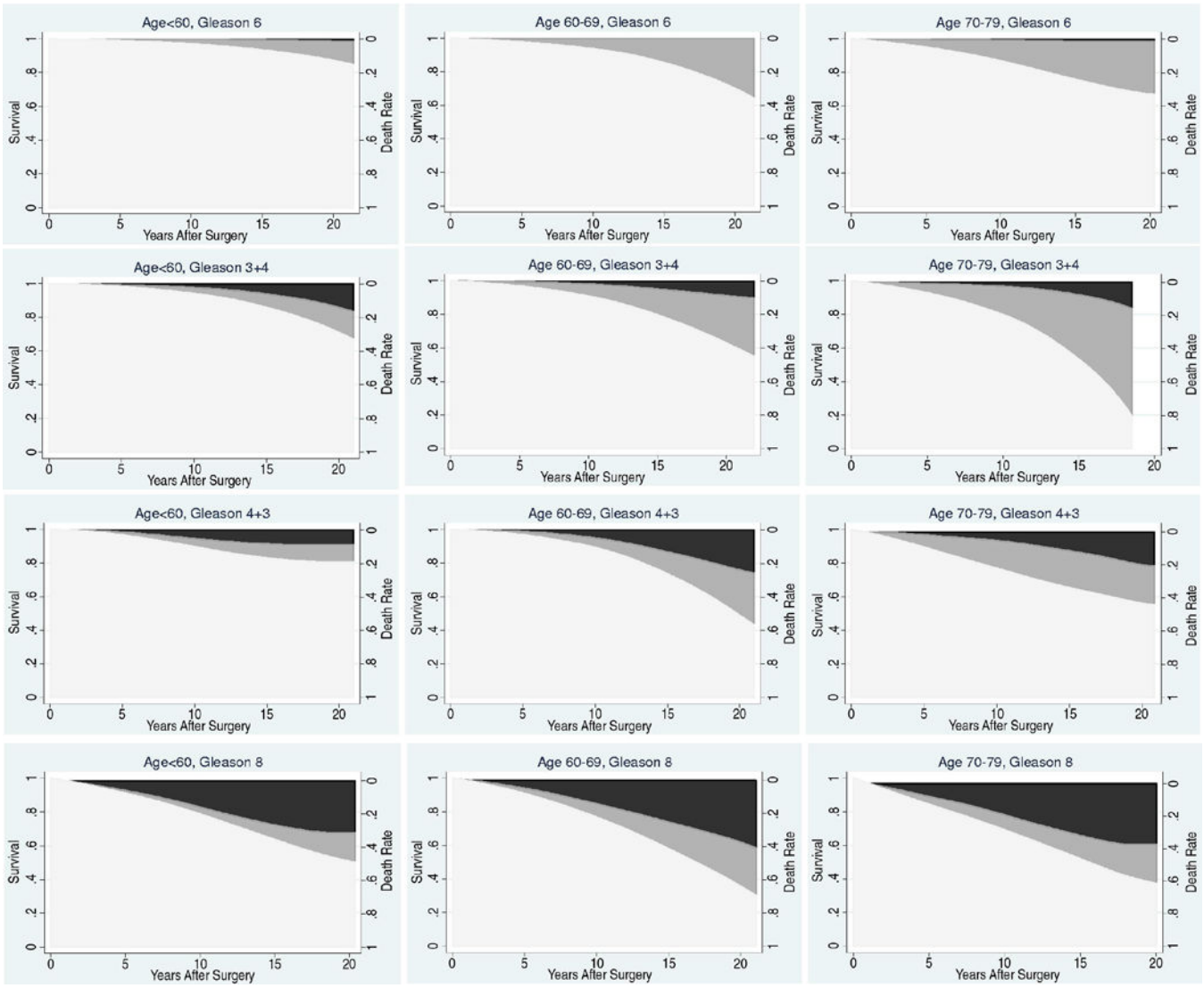

Figure 3.

Prostate cancer-specific mortality (black) and mortality from competing causes (gray) stratified by pathological stage and patient age at diagnosis.

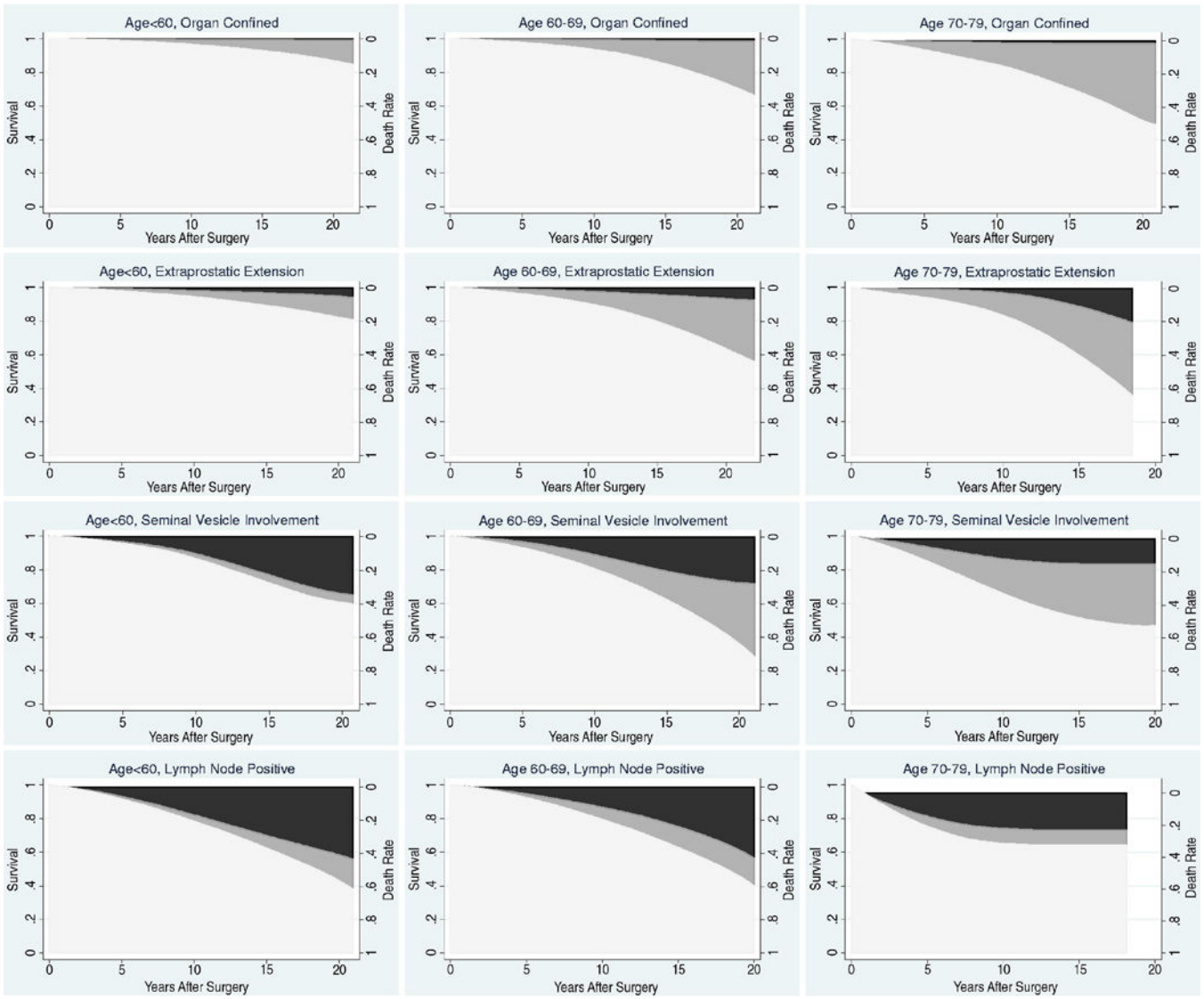

Figure 4.

Scatter plot comparing the 10-year PSA progression-free probability by a previously published nomogram (x-axis) with the 15-year prostate cancer-specific mortality probability by the current nomogram (y-axis).

Table 1

Clinical and pathological characteristics of patients in the modeling and validation cohorts.

	Modeling Cohort	Validation Cohort
Number of Patients	11,521	12,389
Median age, year (interquartile range)	60 (56–65)	58 (54–63)
Year of surgery (%)		
1987–1992	1073 (9)	1345 (11)
1993–1998	3169 (28)	3899 (31)
1999–2005	7279 (63)	7145 (58)
Median PSA, ng/ml (interquartile range)	6.0 (4.4–8.8)	5.9 (4.2–8.6)
Pathological Gleason score (%)		
Gleason 2–6	4305 (37)	7771 (62)
Gleason 7 (3+4)	4866 (42)	2939 (24)
Gleason 7 (4+3)	1303 (11)	953 (8)
Gleason 8–10	631 (6)	726 (6)
Pathological stage (%)		
Organ-confined	8051 (70)	7997 (64)
Extraprostatic extension*	2322 (20)	3589 (29)
Seminal vesicle invasion**	668 (6)	480 (4)
Lymph node metastasis	359 (3)	318 (3)
Positive surgical margins (%)	2607 (23)	1646 (13)
Median follow-up, months (interquartile range)	56 (24–93)	95 (60–139)
Prostate cancer-specific mortality (%)	157 (1.4)	190 (1.6)
Mortality from competing causes (%)	621 (5)	506 (4)
15-year prostate cancer-specific mortality (95% CI)	7% (6–9)	4% (3–5)
15-year all-cause mortality (95% CI)	33% (30–36)	16% (14–17)

* Extraprostatic extension without evidence of seminal vesicle invasion or lymph node metastasis

** Seminal vesicle invasion without evidence of lymph node metastasis

Table 2

Probability of death from prostate cancer and competing causes after radical prostatectomy among 23,910 men in the combined modeling and validation cohorts, stratified by pathological Gleason score, pathological stage, and age at diagnosis.

	10-Year		15-Year		20-Year	
	PCSM	**MCC**	**PCSM**	**MCC**	**PCSM**	**MCC**
Age < 60 years						
Gleason ≤ 6	0.1 (0.03–0.3)	2.4 (2–3)	0.6 (0.2–1.5)	6.0 (4.5–8)	1.2 (0.4–3)	11 (7–17)
Gleason 3+4	2.2 (1.5–3.3)	3.2 (2.4–4.4)	4.7 (3–6.8)	6.5 (4.6–8.8)	16 (7.2–29)	14 (8–23)
Gleason 4+3	5.6 (3.4–8.7)	4.9 (3–7.6)	9 (5.5–14)	10 (5.4–16)	9 (5.5–14)	10 (5.4–16)
Gleason 8–10	15 (11–20)	3.3 (1.7–5.9)	31 (23–39)	6.5 (3.5–11)	31 (23–39)	16 (6.5–28)
Age 60–69 years						
Gleason ≤ 6	0.1 (0.03–0.2)	6 (4.6–6.4)	0.2 (0.01–0.6)	12 (10–14)	0.2 (0.01–0.6)	33 (23–42)
Gleason 3+4	1.7 (1.1–2.5)	6.3 (5.2–7.6)	4.2 (2.8–5.9)	14 (12–17)	9.0 (4.8–15)	32 (19–45)
Gleason 4+3	4.4 (2.6–7.1)	4.7 (3–6.9)	11 (6.9–16)	11 (6.9–16)	23 (13–34)	34 (9–62)
Gleason 8–10	13 (9.7–17)	7.2 (4.8–10)	26 (20–32)	16 (11–21)	39 (25–53)	26 (17–36)
Age 70–79 years						
Gleason ≤ 6	0	11 (6.7–17)	1.2 (0.1–5.8)	22 (13–32)	1.2 (0.1–5.8)	30 (17–44)
Gleason 3+4	1.3 (0.4–3.6)	16 (11–22)	6.5 (1.9–15)	33 (22–44)	17 (2–44)	61 (29–82)
Gleason 4+3	6.6 (2–15)	18 (9.7–29)	6.6 (2–15)	23 (11–37)	18 (3–45)	23 (11–37)
Gleason 8–10	18 (9–31)	11 (4–22)	37 (17–57)	11 (4–22)	37 (17–57)	21 (5–46)
Age < 60 years						
Organ-confined	0.5 (0.3–8.4)	2.6 (2.1–3.2	0.8 (0.3–1.6)	6.8 (5–9)	0.8 (0.3–1.6)	12 (6.3–19)
Extraprostatic extension	1.7 (0.1–2.5)	3.6 (2.7–4.6)	2.9 (2–4.2)	6.6 (5–8.5)	7 (2–16)	12 (8.2–16)
Seminal vesicle invasion	8.4 (5.2–12)	2.3 (0.9–4.8)	27 (18–37)	5.3 (2.3–10)	33 (19–47)	5.3 (2.3–10)
Lymph node metastasis	18 (13–24)	2.8 (1.2–5.9)	30 (22–38)	6.5 (3.1–12)	41 (27–55)	16 (5.6–31)
Age 60–69 years						
Organ-confined	0.5 (0.3–8.7)	5 (4.2–5.8)	1 (0.5–1.8)	12 (9.7–14)	1.4 (0.7–2.7)	29 (19–40)
Extraprostatic extension	1.9 (1.3–2.7)	6.6 (5.5–7.9)	3.9 (2.8–5.3)	14 (12–16)	6.6 (4.1–9.9)	34 (24–43)

	10-Year		15-Year		20-Year	
	PCSM	**MCC**	**PCSM**	**MCC**	**PCSM**	**MCC**
Seminal vesicle invasion	8.8 (5.8–12)	8.5 (5.6–12)	22 (15–29)	16 (11–23)	26 (18–36)	47 (17–72)
Lymph node metastasis	12 (7.7–17)	7.2 (4–12)	22 (15–30)	13 (8–20)	42 (26–57)	16 (9–26)
Age 70–79 years						
Organ-confined	1.4 (0.4–4)	14 (9.2–19)	1.5 (0.4–4)	18 (12–25)	1.5 (0.4–4)	43 (17–68)
Extraprostatic extension	0.5 (0.1–2.6)	12 (7.3–18)	10 (4–19)	27 (18–38)	20 (7–39)	41 (26–56)
Seminal vesicle invasion	13 (6–23)	22 (13–34)	15 (7–26)	36 (18–55)	15 (7–26)	36 (18–55)
Lymph node metastasis	23 (8–43)	10 (1.5–27)	23 (8–43)	10 (1.5–27)	23 (8–43)	10 (1.5–27)

*Figures in parenthesis represent 95% confidence interval of probability estimate

Abbreviations: PCSM, prostate cancer-specific mortality; MCC, mortality from competing causes