Biology of Human Tumors

Clinical Cancer Research

Overdetection of Recurrence after Radical Prostatectomy: Estimates Based on Patient and Tumor Characteristics

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Abstract

Purpose: Prostate-specific antigen recurrence (PSA-R) after radical prostatectomy (RP) can occur years before metastasis. This study estimates the chance that an untreated PSA-R would not progress to clinical metastasis within the patient's lifetime, that is, that recurrence is overdetected.

Experimental Design: Times from PSA-R to metastasis were estimated from patients with RP treated at Johns Hopkins University (Baltimore, MD) who did not receive salvage treatment ($n = 441$) at PSA-R. Times to other-cause death were based on U.S. life tables adjusted to reflect other-cause survival among RP cases in the Surveillance, Epidemiology, and End Results (SEER) registry. We used competing risks simulation to estimate lower bounds on the chance that other-cause death would precede clinical metastasis for patients with disease characteristics at diagnosis based on the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database ($n = 4,455$).

Results: Cumulative incidence of PSA-R in CaPSURE was 13.6% at 5 years and 19.9% at 10 years. The risk of other-cause death among patients with RP in SEER was 60% lower than the age-matched U.S. population. At least 9.1% of patients with PSA-R <5 years after RP and at least 15.6% of patients with PSA-R 5 to 10 years after RP were overdetected. At least 31.4% of patients over the age of 70 years at diagnosis, who recurred <10 years of diagnosis, were overdetected.

Conclusions: This analysis indicates that PSA-R after RP may be overdetected, with risk depending on patient age and tumor characteristics. The potential for overdetection of recurrence confirms the need for approaches to determine whether and when to initiate salvage therapies. *Clin Cancer Res; 20(20); 5302–10. ©2014 AACR.*

Introduction

Overdetection and overtreatment of prostate cancer have been persistent concerns since the beginning of the prostate-specific antigen (PSA) era. To date, attention has focused on the issue of overdiagnosis caused by PSA screening, namely the detection by screening of prostate cancer in men who would never have been diagnosed or developed symptoms without screening. However, the advent of the PSA test ushered in an era not only of prediagnosis PSA screening but also of postdiagnosis PSA surveillance or monitoring. Similar to PSA screening for prostate cancer, the goal of PSA monitoring is to detect prostate cancer recurrence early so that salvage treatment has a better chance of improving disease-specific outcomes and prolonging survival.

Although PSA monitoring is now a standard component of care for patients with prostate cancer, its benefits have not been formally established in randomized studies. A comparison of cases with PSA recurrence (i.e., a detectable or rising PSA level) after radical prostatectomy (RP) who were treated with salvage radiotherapy compared with those not treated suggested a strong benefit and found that salvage therapy reduced the risk of metastasis by almost two thirds (1). A recent review of the literature regarding management of biochemical recurrence concluded that salvage radiotherapy can provide durable responses in a sizeable percentage of men, particularly when given early (2). However, an accompanying editorial (3) noted that is it still not clear which patients will benefit. In a sizeable fraction of patients, PSA recurrence occurs many years before disease would metastasize; studies of the natural history of disease progression following RP have suggested that the median interval from PSA recurrence to metastasis among men not treated at PSA recurrence is 8 to 10 years (4–6). Given this long interval, a potentially large fraction of men who experience PSA recurrence may be destined to die of other causes before their cancer progresses to a metastatic state. Indeed, another study (7) of patients with PSA recurrence

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Translational Relevance

Early treatment of prostate cancer recurrence after radical prostatectomy (RP) based on detectable or rising prostate-specific antigen (PSA) may reduce the risk of metastasis, yet even without salvage treatment many patients will die of other causes before metastatic disease manifests clinically. Overdetection of recurrence is the detection of recurrent disease that would not progress to clinical metastasis in the absence of salvage therapy. We combine high-quality data on natural history of progression to clinical metastasis and survival for patients with prostate cancer following RP to quantify the risk that noncancer death will precede metastasis. The results provide important information for patients with rising PSA after prostatectomy who are deciding whether to initiate salvage treatment.

after RP found that only 11.7% experienced systemic progression during 15 years of follow-up but 17% died of other causes.

Overdetection of recurrence occurs when a patient is considered to have recurrent disease on the basis of PSA alone but, in the absence of treatment, would not progress to clinically metastatic disease in his lifetime. For such a patient, secondary treatment cannot provide benefit. Moreover, the most common secondary therapies, hormonal therapy and salvage radiation, have been associated with increased incidence of bone fractures (8, 9) and cardiovascular disease (10–12) as well as urinary incontinence and rectal bleeding (2, 13).

The frequency of overdetection of recurrence has not been studied, but it could be significant, particularly among older patients who have higher risks of other-cause death. Knowledge of the magnitude of the problem could have implications for secondary treatment policies. Recent studies have identified clinical and pathologic factors that may stratify patients with PSA recurrence into groups with higher versus lower risk of disease-specific mortality (1, 6, 7, 14), but assessing overdetection of recurrence also requires considering the competing risk of other-cause death.

In this article, we adapt a method used to estimate overdiagnosis in the context of early detection (15) to quantify the frequency with which recurrence is overdetected after RP. Specifically, we use data from a well-studied cohort of patients treated with RP at Johns Hopkins University (JHU; Baltimore, MD) who experienced PSA recurrence (1, 4, 5) to analyze times from PSA recurrence to metastasis in the absence of salvage treatment. We then calculate the chance that recurrence is overdetected as the likelihood that progression to metastasis is preceded by other-cause death, which we estimate using data from U.S. life tables and the Surveillance, Epidemiology, and End Results (SEER) program. Ultimately, we estimate a lower bound on the likelihood of overdetection and extrapolate this to a more representative population of patients with RP using a competing risks simulation model. The results provide the first quantitative assessment of the frequency with which prostate cancer recurrence is overdetected as a result of PSA monitoring following primary surgery.

Materials and Methods

Overview

Our approach is designed to estimate the chance that other-cause death will precede prostate cancer metastasis in a representative cohort of cases with PSA recurrence following RP. Figure 1 illustrates our approach, which uses simulation modeling to project results based on observed data using a virtual case population. For each member of this population, we generate (i) clinical and pathologic features at diagnosis, (ii) a time from RP to PSA recurrence, (iii) a time from PSA recurrence to metastasis in the absence of salvage treatment, and (iv) a time from PSA recurrence to other-cause death. We define a case as overdetected at recurrence if other-cause death precedes progression to metastasis, and we calculate the frequency of overdetection at recurrence as the fraction of the PSA-recurrent population for whom the time to other-cause death is shorter than the time to metastasis in the absence of salvage treatment.

Data sources

Our model uses data from (i) the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database (16), (ii) a JHU cohort of patients with PSA recurrence after RP (1) who were followed for progression to metastasis, and (iii) U.S. life tables to inform time to other-cause death (17) adjusted using relative survival from the SEER registry.

To facilitate extrapolation to more general patients with RP, CaPSURE data (16) are first used to set clinical and pathologic characteristics at diagnosis [i.e., age, PSA, and pathologic Gleason score (GS), and stage]. CaPSURE is a longitudinal, observational database accruing approximately 1,000 variables, including clinical and pathologic characteristics at diagnosis and postdiagnosis PSA levels from more than 14,000 men enrolled in 40 participating urologic practice sites. We include cases diagnosed after 1994 because PSA screening rates in the population had more or less stabilized by this time. Only cases who received RP without neoadjuvant or adjuvant hormone or radiotherapy are considered. PSA recurrence is defined as two consecutive PSA levels greater than or equal to 0.2 ng/mL. To model time from RP to PSA recurrence, we fit a Cox regression model to the CaPSURE data, censoring other-cause deaths and adjusting for age, log(PSA), and pathologic GS and stage at diagnosis.

The JHU cohort is our primary source of information on the natural history of disease progression after PSA recurrence. For consistency with the model of time from RP to PSA recurrence, we only include patients who received RP after January 1994. The JHU cohort includes 1,071 men with RP after January 1994 who progressed to PSA recurrence (defined as two consecutive PSA levels greater than or equal to 0.2 ng/mL). We fit GS-specific Cox regression models to data on time from PSA recurrence to metastasis

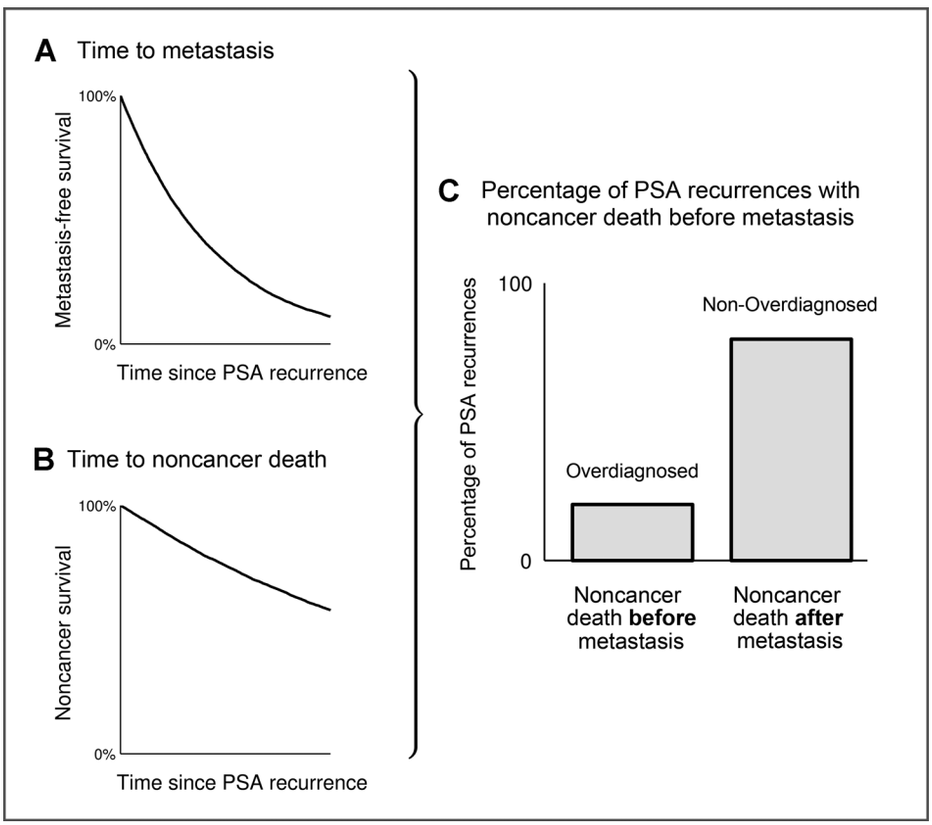

Figure 1. Schematic showing how the frequency of overdetection of recurrence may be estimated. A, the survival curve for the time from PSA recurrence to metastasis in the absence of other-cause death. B, the survival curve for the time from PSA recurrence to other-cause death. Overdiagnosis of PSA recurrence occurs when an individual dies of other causes before the point of metastasis and is represented by the smaller bar in C. The computation of overdiagnosis of recurrence requires complete follow-up for metastasis and other-cause death; in practice, we compute a lower bound on this quantity due to limited follow-up for metastasis.

adjusting for time from RP to PSA recurrence and an indicator of use of salvage therapy. The fitted model is used to predict time from PSA recurrence to metastasis in the absence of salvage treatment.

Competing risks of other-cause death are based on U.S. life tables (17) given age at treatment and birth year. However, contemporary patients receiving RP as first-line therapy tend to be healthier than the general population because they are mostly screen detected (18) and because patients who choose to undergo RP and are generally stronger and more able to tolerate a surgical procedure (19). To capture this survival advantage, we apply a hazard ratio (HR) to the age-specific death rates from the standard life table when we generate time to other-cause death. The HR is derived by comparing the annual observed versus expected (for an age-matched population) deaths for non-metastatic RP cases diagnosed in SEER between 1994 and 2007. Details are presented in Supplementary Appendix 2. As a sensitivity analysis, we repeat our analysis using a range of values for this HR to account for uncertainty in the risk of other-cause death among contemporary RP cases.

Simulation model

The simulation model generates a virtual population of 1 million patients by sampling age, log(PSA), GS, and stage from patients in the CaPSURE data. Then, given each patient's age and clinicopathologic characteristics, we simulate time from RP to PSA recurrence based on the Cox model fit to the CaPSURE cases and, independently, time from RP to other-cause death. For cases who survive to PSA recurrence, we project times to metastasis based on the GS-specific Cox models fit to the JHU cohort in the absence of salvage treatment. The steps involved in simulating these outcomes are provided in Supplementary Appendix 1.

Ideally, we would then compute the fraction of PSA-recurrent cases for whom the interval to other-cause death is shorter than the interval to metastasis in the absence of treatment. However, in practice, we compute a lower bound for this quantity to avoid extrapolating beyond the range of observed times to metastasis in the JHU dataset, which has relatively sparse data after 10 years of follow-up. Supplementary Appendix 3 provides details of how the lower bound is computed and how this approach avoids extrapolation.

We compute the lower bound on the frequency of over-detection of recurrence within groups defined by age and clinicopathologic characteristics and time from RP to PSA recurrence. Uncertainty intervals around point estimates are generated via repeated simulations with parameter values for the Cox models randomly sampled from 95% confidence intervals (CI) around the model coefficients.

We also conduct two sensitivity analyses to the estimated risks of other-cause death and metastatic progression after PSA recurrence. Our baseline analysis bases the risk of other-cause death on cases treated with RP in the SEER registry and the risk of metastasis on patients treated at JHU who did not

receive salvage therapy following PSA recurrence. We recognize that this may be a selected cohort with disease characteristics and outcomes that are not reflective of the general population. For example, those patients who did not receive salvage treatment after PSA recurrence may have had less aggressive disease or more comorbid illness than those who were treated. The sensitivity analysis alters the projected risks of progression based on the Cox regression model by a multiplicative factor reflecting both lower and higher risks than those in the baseline analysis. Similarly, we consider a range of multiplicative factors on the other-cause death risks reflecting cohorts that are both more and less healthy than the SEER RP population.

Results

The CaPSURE cohort consisted of 4,455 cases initially treated with RP in the absence of neoadjuvant or adjuvant hormone or radiotherapy between January 1994 and March 2009 with clinical T-stage <T4, N-stage N0 or NX, and M-stage M0 or MX. Among these cases, 464 (10.4%) were recorded as having a subsequent PSA recurrence and 421 (9.5%) patients recurred within 5 years. Average age at RP was 61.0 (range, 39–80) years, and median follow-up was 3.7 years (range, 5 days–15.4 years). The cumulative incidence of PSA recurrence was 13.6% at 5 years and 19.9% at 10 years. Table 1 summarizes characteristics of the CaPSURE cohort.

The JHU cohort included 1,071 men with RP who were diagnosed between January 1994 and September 2011 and who progressed to PSA recurrence. Average age at RP was 58.7 (range, 39–74) years, and median follow-up was 7.0 (range, 1.0–18.0) years. The cumulative incidence of metastasis was 12.7% at 5 years and 15.6% at 10 years. Of the 1,071 men who progressed to PSA recurrence, 441 (41.2%) had no record of salvage therapy following recurrence. Table 2 summarizes characteristics of the JHU cohort.

Table 3 presents Cox model results for time from RP to PSA recurrence. Table 3 shows strong associations between time to PSA recurrence and log(PSA), GS, and stage, confirming prior prognostic studies in this and other RP cohorts (20–22). Also, Table 3 presents GS-specific Cox model results for time from PSA recurrence to metastasis. Table 3 shows a strong association with time to PSA recurrence for GS 7 and GS ≥8. Each additional year of recurrence-free survival reduces the risk of metastasis following recurrence by 14% (95% CI, 5%–22%) for GS 7 and by 21% (95% CI, 3%–36%) for GS ≥8. These results replicate prior studies of the factors predicting metastasis (5) and disease-specific death (6) among cases with PSA recurrence after RP.

Our comparison of the risk of other-cause death among SEER RP cases and the expected risk of other-cause death in the age-matched population showed that HR = 0.4 approximates the reduction in observed mortality relative to expected mortality up to 10 years after RP (Supplementary Appendix 2: Tables S1–S3 and Supplementary Fig. S1). Given this HR for the risk of other-cause death, the projected cumulative incidence of PSA recurrence within 5 years and 5 to 10 years after RP closely matches the corresponding value for the CaPSURE cohort (Table 4).

Table 1. Characteristics of CaPSURE cohort diagnosed between January 1994 and March 2009, treated with RP, and followed for PSA recurrence ($n = 4,455$)

Characteristics	No. of patients	Percentage
Age		
<40	1	0.0
40–49	233	5.2
50–59	1,589	35.7
60–69	2,163	48.6
≥70	469	10.5
Year of diagnosis		
1994–1996	807	18.1
1997–1999	352	7.9
2000–2002	1,701	38.2
2003–2005	1,257	28.2
2006–2008	336	7.5
2009–2012	2	0.0
GS at diagnosis		
≤6	3,140	70.5
7	1,039	23.3
≥8	193	4.3
Missing	83	1.9
PSA at diagnosis		
0–2.5	293	6.6
2.51–4.0	481	10.8
4.1–6.0	1,698	38.1
6.1–10.0	1,202	27.0
≥10	618	13.9
Missing	163	3.7
Clinical Stage		
≤T2a	3,383	75.9
>T2a	1,040	23.3
Missing	32	0.7

Table 4 presents projected lower bounds on the frequency of overdetection of recurrence separately for men with PSA recurrence within 5 years and 5 to 10 years after RP. The lower bounds are strongly dependent on the interval from RP to PSA recurrence. Among men with PSA recurrence within 5 years after RP, the model projects that at least 9.1% (95% CI, 7.6%–10.6%) are overdetected, and among men with PSA recurrence 5 to 10 years after RP, the model projects that at least 15.6% (95% CI, 12.7%–18.5%) are overdetected. In addition, the lower bounds are highly dependent on age at diagnosis; for example, among cases with PSA recurrence within 5 years after RP, at least 2.8%, 4.9%, 10.3%, and 16.4% of cases of ages 40–49, 50–59, 60–69, and ≥70 years are overdetected, respectively.

Our sensitivity analysis to the risk of metastatic progression revealed that results were fairly robust across the range of multiplicative factors assumed (Table 5). Increasing the

Table 2. Characteristics of JHU cohort diagnosed between January 1994 and September 2011, treated with RP, and observed to have PSA recurrence

	All cases (n = 1,071)		No salvage therapy (N = 441)		Salvage therapy (n = 604)	
Characteristics	**No. of patients**	**Percentage**	**No. of patients**	**Percentage**	**No. of patients**	**Percentage**
Age at diagnosis (y)						
40–49	82	7.7	30	6.8	52	8.6
50–59	487	45.5	203	46.0	274	45.4
60–69	480	44.8	195	44.2	269	44.5
≥70	21	2.0	13	3.0	8	1.3
Year of diagnosis						
1994–1996	229	21.4	106	9.9	123	11.5
1997–1999	227	21.2	89	8.3	138	12.9
2000–2002	228	21.3	97	9.1	131	12.2
2003–2005	172	16.1	74	6.9	98	9.2
2006–2008	148	13.8	61	5.7	87	8.1
2009–2012	41	3.8	14	1.3	27	2.5
RP GS						
≤6	228	21.3	120	27.2	104	17.2
7	601	56.1	238	54.0	353	58.4
≥8	242	22.6	83	18.8	147	24.2
PSA at diagnosis, ng/mL						
0–2.5	31	2.9	14	3.2	14	2.3
2.51–4	79	7.4	36	8.2	42	7.0
4.1–6.0	287	26.8	115	26.1	166	27.5
6.1–10.0	361	33.7	146	33.1	205	33.9
≥10	313	29.2	130	29.5	177	29.3
Pathologic stage						
≤T2a	301	28.1	132	29.9	162	26.8
>T2a	770	71.9	309	70.1	442	73.2
Time to PSA recurrence, y						
≤3	670	62.6	251	56.9	396	65.6
>3	401	37.4	190	43.1	208	34.4

risk of metastasis by a factor of 2, the lower bound on the percentage overdetected was 7.9% (95% CI, 6.4%–9.4%) for PSA recurrence within 5 years and 13.7% (95% CI, 10.8%–16.5%) for PSA recurrence within 5 to 10 years. Using a factor of 0.25, the lower bound on the percentage overdetected was 11.6% (95% CI, 9.8%–13.4%) for PSA recurrence within 5 years and 17.8% (95% CI, 14.6%–20.9%) for PSA recurrence 5 to 10 years after RP. As expected, increasing the risk of metastasis reduced the projected frequency of overdetection. Results were also sensitive across a range of multiplicative factors on the risk of other-cause death (Table 6). As expected, a risk of other-cause death that was considerably lower than the risk used in our baseline analysis, representing a much healthier cohort, yielded a lower frequency for the overdetection of recurrence than a risk that was considerably higher.

Discussion

In this article, we investigate whether the lengthy intervals from PSA recurrence to metastasis suggested by previous studies might potentially lead to a setting in which men would be classified as having disease recurrence and become candidates for salvage therapy, but their disease would never progress to clinical metastasis. When patients are labeled as having progressive or recurrent disease solely on the basis of detectable or rising PSA, and this event can occur many years before overt metastasis, this creates the potential for overdetection of recurrent prostate cancer. Our objective has been to determine whether and, if so, how frequently PSA recurrence might be overdetected in the sense that it would not be followed by systemic progression within the patient's lifetime. We used observed data from established cohorts to develop a model of what might be expected in a general case population (mimicking the CaPSURE case population) developing PSA recurrence after prostatectomy and not receiving salvage treatment (with metastasis rates mimicking the JHU cohort). The projected times to metastasis and other-cause death are all based on this probabilistic model and not directly on the observed datasets.

It is important to recognize that our investigation addresses only one aspect of PSA recurrence and this

Table 3. Cox proportional hazard regression models for CaPSURE cohort (time from RP to PSA recurrence) and JHU cohort (time from PSA recurrence to clinical metastasis)

Time period (source)	Covariate	HR (95% CI)	*P*
Treatment to PSA recurrence (CaPSURE)	Age, y	1.01 (0.99–1.02)	0.299
	log(PSA) [log(ng/mL)]	2.45 (2.15–2.78)	<0.001
	GS		
	≤6	Ref.	
	7	1.59 (1.28–1.96)	<0.001
	≥8	3.23 (2.37–4.41)	<0.001
	Stage		
	≤T2a	Ref.	
	>T2a	1.35 (1.10–1.64)	0.004
PSA recurrence to metastasis GS ≤ 6 (JHU)	Time to PSA recurrence, y	0.99 (0.79–1.25)	0.963
	Treatment		
	No salvage	Ref.	
	Salvage	0.44 (0.12–1.71)	0.239
PSA recurrence to metastasis GS = 7 (JHU)	Time to PSA recurrence, y	0.86 (0.78–0.95)	0.003
	Treatment		
	No salvage	Ref.	
	Salvage	0.30 (0.20–0.44)	<0.001
PSA recurrence to metastasis GS ≥ 8 (JHU)	Time to PSA recurrence, y	0.79 (0.64–0.97)	0.027
	Treatment		
	No salvage	Ref.	
	Salvage	0.18 (0.10–0.32)	<0.001

pertains to a potential harm associated with early treatment of an overdetected recurrence. This harm does not apply to all cases of PSA recurrence but only to a subset of these cases and must be considered in the context of the potential for benefit associated with early salvage treatment in non-overdetected cases. Indeed, one might argue that, overall, the long-term toxicity from modern salvage radiotherapy may be a small price to pay for the protection it affords from the endpoint of clinical metastasis. We do not go so far as to make judgments about the tradeoffs involved in the decision to treat a PSA recurrence (we will address these in a later study); we simply point out that there is a tradeoff to consider, particularly in older men whose PSA recurrence occurs years after their primary surgery.

Estimating the frequency of overdetection of recurrence requires information on metastasis among men not treated after PSA recurrence and other-cause death among men with PSA recurrence. Previous studies (4–7) have analyzed metastatic progression and prostate cancer mortality in RP cases who were not treated at the time of PSA recurrence. These studies found that time to PSA recurrence, GS, and PSA doubling time is predictive of metastatic progression and death. However, in these studies, calculations of PSA doubling time included PSA measurements taken after PSA recurrence. Because we predict overdetection of recurrence only using information available at the time of PSA recurrence, we included only time to PSA recurrence and pathologic GS in our prediction of time to metastatic progression.

Recognizing that contemporary RP cases are likely to be healthier than the general population, we used survival data from the SEER registry to adjust the risks of other-cause death relative to those in the age-matched population. Examining deaths over 10 years after diagnosis (using cases diagnosed 1994–2007), we determined that the risk was approximately 60% lower and applied a HR of 0.4 to standard life tables in generating our results. However, we also investigated sensitivity of frequencies of overdetection of recurrence to this value.

Rather than extrapolating beyond our follow-up period to analyze time from PSA recurrence to metastasis, we developed a lower bound on the frequency of overdetection of recurrence. This lower bound requires specification of a value T that represents the maximum follow-up time for which sufficient data on time to metastasis are available. In our dataset, the longest observed time to metastasis was 14 years, but we set T to 10 because there were very few observations between 10 and 14 years. We caution that results may be sensitive to different choices of T. We considered values of 8 and 9 years for T and obtained corresponding lower bounds of 6.9% and 7.8% among cases with PSA recurrence occurring within 5 years after RP. Thus, it seems that the lower the value of T, the lower the estimated bound on the frequency of overdetection of recurrence.

The limitations of our analysis relate primarily to limitations of the datasets used. Our datasets are limited mostly by their selectiveness. Although the CaPSURE data reflect prostate care in a community setting, the CaPSURE population

Table 4. Cumulative incidence of PSA recurrence projected by the model and lower bound on the frequency of overdetection of recurrence

	PSA recurrence within 5 years		PSA recurrence within 5–10 years	
Characteristics	Percentage with PSA recurrence	Lower bound on percent overdetected	Percentage with PSA recurrence	Lower bound on percent overdetected
Overall	13.3 (12.7–14.0)	9.1 (7.6–10.6)	5.7 (5.3–6.2)	15.6 (12.7–18.5)
Age at diagnosis, y				
40–49	11.2 (8.5–13.9)	2.8 (0.1–5.5)	4.7 (2.9–6.5)	3.7 (0.2–7.2)
50–59	11.8 (10.8–12.8)	4.9 (2.8–7.0)	5.2 (4.4–5.9)	9.1 (4.9–13.2)
60–69	14.0 (13.0–15.0)	10.3 (8.1–12.6)	6.1 (5.4–6.8)	17.2 (12.8–21.6)
≥70	17.1 (14.9–19.3)	16.4 (11.2–21.6)	6.2 (4.8–7.7)	31.4 (20.6–42.2)
GS				
≤6	10.3 (9.6–11.0)	10.7 (8.5–12.9)	4.8 (4.3–5.3)	15.7 (11.9–19.4)
7	18.5 (17.0–20.1)	7.8 (5.2–10.3)	7.3 (6.2–8.4)	15.7 (10.6–20.9)
≥8	37.2 (32.7–41.7)	5.1 (1.6–8.6)	12.0 (8.9–15.1)	14.9 (5.2–24.6)
PSA at diagnosis, ng/mL				
0–2.5	3.8 (2.4–5.3)	9.7 (1.7–17.7)	1.8 (0.8–2.8)	13.8 (6.2–21.4)
2.51–4	6.7 (5.2–8.2)	8.8 (2.6–15.0)	3.5 (2.4–4.6)	12.3 (1.8–22.8)
4.1–6.0	10.4 (9.5–11.4)	8.6 (5.8–11.3)	4.6 (4.0–5.2)	15.5 (10.5–20.5)
6.1–10.0	14.5 (13.3–15.8)	9.0 (6.2–11.7)	6.5 (5.6–7.5)	15.5 (10.1–20.8)
≥10	28.9 (26.6–31.3)	9.8 (6.9–12.6)	10.5 (9.0–12.1)	17.0 (10.7–23.2)
Stage				
≤T2a	11.7 (11.0–12.4)	9.5 (7.6–11.4)	5.2 (4.7–5.7)	15.4 (11.9–18.9)
>T2a	18.7 (17.2–20.3)	8.2 (5.7–10.7)	7.2 (6.2–8.2)	16.2 (10.7–21.6)

NOTE: Other-cause death is generated by applying a HR of 0.4 to the standard life table.

consists of patients treated at a specific group of clinics and may differ from the general RP population with respect to some clinical and pathologic characteristics. Both the CaPSURE and the JHU datasets include cases diagnosed as far back as 1994 and may not reflect the risk profiles of contemporary diagnoses. However, it is necessary to include these cases to enable sufficient follow-up postdiagnosis for ascertainment of outcomes. Our data on time from PSA recurrence to metastasis is also subject to selection in that cases were treated at a single center (JHU) and were not randomized to be treated (or not) at the time of PSA recurrence. Despite these limitations, this dataset has become an authoritative source of information on the natural history of metastasis following PSA failure. It is possible that the baseline hazard of metastasis in this cohort is not representative of the general population of patients with PSA recurrence after RP. If it is lower than would be expected in the general population, then our estimates of overdetection of recurrence will be inflated. However, even if we double the metastasis risk following PSA recurrence, we still find that the risk of overdetection of recurrence is at least 7.9% for cases with PSA recurrence within 5 years after RP and at least 13.7% for cases with PSA recurrence 5 to 10 years after RP.

Table 5. Sensitivity analysis for postrecurrence risk of metastasis with different HRs relative to those estimated based on the JHU cohort with PSA recurrence who did not get salvage treatment

HR applied on JHU cohort	Lower bound on percent overdetected if PSA recurrence within 5 years after RP (%)	Lower bound on percent overdetected if PSA recurrence within 5–10 years after RP (%)
2.00	7.9 (6.4–9.4)	13.7 (10.8–16.5)
1.50	8.7 (7.3–10.2)	14.5 (11.6–17.4)
1.25	8.9 (7.4–10.5)	15.4 (12.4–18.3)
1.00	9.1 (7.6–10.6)	15.6 (12.6–18.5)
0.75	10.3 (8.7–11.8)	16.5 (13.7–19.2)
0.50	10.8 (9.2–12.4)	16.9 (13.8–20.1)
0.25	11.6 (9.8–13.4)	17.8 (14.6–20.9)

Table 6. Sensitivity analysis for other-cause death with different HRs relative to U.S. life tables

	Recurrence in 5 years		Recurrence in 5–10 years	
HR	Percentage with PSA recurrence	Lower bound on percent overdetected	Percentage with PSA recurrence	Lower bound on percent overdetected
1.0	13.0 (12.4–13.7)	20.2 (18.0–22.5)	5.1 (4.7–5.6)	31.4 (27.3–35.5)
0.9	13.1 (12.4–13.7)	18.7 (16.6–20.8)	5.2 (4.8–5.6)	29.2 (25.3–33.0)
0.8	13.1 (12.5–13.8)	16.7 (14.7–18.7)	5.4 (4.9–5.8)	28.1 (24.4–31.9)
0.7	13.2 (12.5–13.8)	15.4 (13.5–17.3)	5.4 (5.0–5.9)	25.3 (21.7–28.9)
0.6	13.3 (12.6–13.9)	13.1 (11.3–15.0)	5.5 (5.0–5.9)	22.6 (19.2–26.1)
0.5	13.3 (12.7–14.0)	11.4 (9.7–13.2)	5.6 (5.1–6.1)	19.4 (16.3–22.5)
0.4	13.3 (12.7–14.0)	9.1 (7.6–10.6)	5.7 (5.3–6.2)	15.6 (12.6–18.5)
0.3	13.5 (12.8–14.1)	7.0 (5.7–8.4)	5.8 (5.3–6.2)	11.9 (9.3–14.5)
0.2	13.5(12.8–14.2)	4.8 (3.6–6.0)	5.9 (5.5–6.4)	7.9 (5.7–10.1)
0.1	13.6 (12.9–14.2)	2.4 (2.0–3.2)	6.1 (5.6–6.5)	4.7 (3.0–6.4)

NOTE: HR for risk of metastasis is as estimated from JHU untreated PSA-recurrent cohort.

The notion that recurrent prostate cancer may be overdetected may be unfamiliar; however, the lengthy natural history that is characteristic of many prostate cancer cases strongly suggests that this could be a common phenomenon and one that may be important in decision making about secondary treatment. Indeed, the factors that seem to correlate positively with the chance that recurrence may have been overdetected (advanced age and low GS) are exactly those that correlate positively with a low risk of prostate cancer death after diagnosis. It may be of value for low-risk patients facing a decision about primary treatment to know that, if their disease was to recur, it might not need to be retreated in the future.

In conclusion, PSA recurrence after RP is almost certainly an indicator of persistent disease but has only limited power in determining the fate of the patient. Other factors, such as initial grade of disease, its stage, the PSA velocity or doubling time, and the general health of the patient, are very important and must be considered in balancing the morbidity of treating PSA recurrence with observation. On the basis of the datasets used in this study, we estimate that approximately 1 in 10 PSA recurrences or more will never be followed by metastatic progression within the patient's lifetime. These patients would be better off left untreated, as least until further information about metastatic potential (e.g., more reliable estimates of PSA doubling time based on longer follow-up) can be collected and assessed. For patients with high risks of overdetection of recurrence, a period of surveillance in the postrecurrence setting could lead to postponing or preventing unnecessary reductions in quality of life associated with standard salvage therapies. We conclude that, just as in the case of screening, any benefits of early detection of recurrent disease must be weighed against the potential harms of overtreatment.

Disclosure of Potential Conflicts of Interest

B.J. Trock reports receiving a commercial research grant from Myriad Genetics and has provided expert testimony on diabetes treatment for Sonacare Medical, LLC. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute, the National Institutes of Health, or the Centers for Disease Control and Prevention.

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