

Intermediate End Point for Prostate Cancer–Specific Mortality Following Salvage Hormonal Therapy for Prostate-Specific Antigen Failure

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Background: Whether the prostate-specific antigen (PSA) response to salvage hormonal therapy can act as an intermediate end point for prostate cancer–specific mortality (PCSM) remains unclear. Therefore, we evaluated whether PSA response, defined as the absolute value of the ratio of the rate of PSA change after salvage hormonal therapy to the rate of PSA change before salvage therapy, is associated with the time to PCSM following salvage hormonal therapy. **Methods:** A single-institution and two pooled multi-institution databases containing baseline, treatment, and follow-up information on men who received salvage hormonal therapy for PSA failure following surgery or radiation therapy from January 1, 1988, to January 1, 2002, formed the study (n = 199) and validation cohorts (n = 1255), respectively. The ability of PSA response and its constituents (i.e., pre–salvage hormonal therapy PSA slope and post–salvage hormonal therapy PSA slope) to predict time to PCSM following salvage hormonal therapy was assessed using Cox regression analysis. For illustrative purposes, PSA response was analyzed as a dichotomous variable with a breakpoint for the ratio of PSA response of 1. All statistical tests were two-sided. **Results:** PSA response was statistically significantly associated with time to PCSM following salvage hormonal therapy in both the study ($P_{\text{Cox}} = .0014$) and validation ($P_{\text{Cox}} < .001$) cohorts; however, its constituents were not (pre–salvage hormonal therapy PSA slope: $P_{\text{Cox-study}} = .97$, $P_{\text{Cox-validation}} = .57$; post–salvage hormonal therapy PSA slope: $P_{\text{Cox-study}} = .27$, $P_{\text{Cox-validation}} = .31$). Patients with a PSA response that was less than or equal to 1 had a statistically significantly shorter time to PCSM than patients with a PSA response of greater than 1 in both the study (hazard ratio [HR] = 3.6, 95% confidence interval [CI] = 1.3 to 10.3; $P_{\text{Cox}} = .01$) and validation (HR = 12.8, 95% CI = 6.2 to 26.3; $P_{\text{Cox}} < .001$) cohorts. **Conclusion:** The PSA response to salvage hormonal therapy can serve as an intermediate end point for PCSM in patients with a rising PSA level following surgery or radiation therapy. [J Natl Cancer Inst 2004;96:509–15]

Elevated prostate-specific antigen (PSA) levels are generally used to identify patients with prostate cancer. Rising PSA levels also define disease recurrence after initial therapy with radical prostatectomy or external beam radiation therapy (1) and often trigger the start of secondary therapy (2). The most widely practiced secondary therapy is some form of salvage hormonal therapy, which nearly always reduces the serum PSA level.

Although the PSA level declines in almost all patients following the initiation of salvage hormonal therapy, the rates of the initial rise in PSA level prior to and of the subsequent decline in PSA following salvage hormonal therapy vary among patients.

Given this variability in response and given the fact that PSA doubling time (PSA-DT) following surgery or radiation therapy and prior to the initiation of salvage hormonal therapy is the single most important known factor that can predict a patient’s risk of developing bone metastases as well as the risk of prostate cancer–specific mortality, it is possible that PSA response, defined as the absolute value of the ratio of the post– to the pre–salvage hormonal therapy PSA slope, is associated with the time to PCSM following salvage hormonal therapy. In this study, PSA response and its constituents (i.e., pre–salvage hormonal therapy PSA slope and post–salvage hormonal therapy PSA slope) were first evaluated using a Cox regression analysis of time to PCSM (3) applied to a single-institution database of radiation-managed patients to generate a hypothesis regarding the possible prognostic significance of PSA response for PCSM. The hypothesis was then tested using a validation cohort that included patients initially treated with surgery or radiation therapy at 44 institutions within the United States (4,5).

PATIENTS AND METHODS

Patient Selection and Initial Treatment

A single-institution Harvard affiliate (Saint Anne’s Hospital, Fall River, MA) database and two pooled multi-institution databases—Cancer of the Prostate Strategic Urologic Research Endeavor (4) and the Center for Prostate Disease Research (5)—containing baseline, treatment, and follow-up information on men who received salvage hormonal therapy for PSA failure following surgery or radiation therapy from January 1, 1988, to

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January 1, 2002, formed the study (n = 199) and validation (n = 1255) cohorts, respectively. An approved and signed Internal Review Board informed consent form was obtained from each participant prior to study entry.

To be eligible for participation in this study, patients treated surgically were permitted to have received up to 3 months of neoadjuvant hormonal therapy because the 5-year results of a randomized trial (6) have shown no statistically significant association between adding 3 months of neoadjuvant hormonal therapy to radical prostatectomy and PSA outcome. However, patients whose initial therapy included external beam radiation therapy were excluded from the study if they also received neoadjuvant, concurrent, and/or adjuvant hormonal therapy because of the survival benefit found when adding hormonal therapy to radiation therapy in the setting of a randomized trial (7). The median ages of the patients treated in the study and validation cohorts at the time of initial therapy were 71.3 years (range = 41.7–86.8 years) and 66.8 years (range = 43.7–85.7 years), respectively. The distribution of pretreatment clinical characteristics of the study and validation cohorts are shown in Table 1.

Staging

At initial presentation, all patients had their clinical stage evaluated, which involved providing a medical history and undergoing a physical examination, including a digital rectal examination, determination of serum PSA level, and a transrectal ultrasound-guided needle biopsy of the prostate with Gleason

score histologic grading (8). The biopsy was performed with an 18-gauge Tru-Cut needle (Travenol Laboratories, Deerfield, IL) via a transrectal approach. Before 1996, patients had a computerized tomographic scan of the pelvis and a bone scan. However, after 1996, patients with a pretreatment PSA level of less than 10 ng/mL and a biopsy Gleason score of 6 or lower did not undergo radiologic staging because of the less than 1% chance that these tests would reveal metastatic disease (9).

Clinical stage was determined from the results of the digital rectal examination and was assigned according to the 2002 American Joint Commission on Cancer (AJCC) staging system (10). Radiologic and biopsy information were not used to determine clinical stage. PSA levels were measured using the Hybritech (San Diego, CA), Tosoh (Foster City, CA), or Abbott (Chicago, IL) assay.

Follow-up and Salvage Hormonal Therapy

The median follow-up times for the entire study and for the validation cohorts were 7.5 years (range = 1.8–14.3 years) and 7.4 years (range = 1.5–14.5 years), respectively; follow-up started on the first day of initial local treatment. Before PSA-defined recurrence, as specified by the American Society for Therapeutic Radiology and Oncology consensus criteria (11), patients had a serum PSA measurement and digital rectal examination every 3 months after surgery or radiation therapy for 2 years, then every 6 months for an additional 3 years, and then annually thereafter.

After PSA-defined recurrence, PSA levels were measured at the discretion of the treating physician at a median of 3 months (range = 0.5–6 months). Patients were restaged at the time of PSA-defined recurrence and again within 1 month of initiating salvage hormonal therapy with a bone scan and computed tomography or magnetic resonance imaging of the pelvis. Patients who had radiologic evidence of metastasis to regional lymph nodes or to bone at the time of PSA-defined recurrence or within 1 month prior to initiating salvage hormonal therapy were excluded. The median follow-up after the start of salvage hormonal therapy for the 199 study and 1255 validation patients was 3.2 years (range = 0.3–11.0 years) and 3.3 years (range = 0.3–11.4 years), respectively. Salvage hormonal therapy was initiated between the time of PSA failure and before the patient became clinically symptomatic or had a positive bone scan, on the basis of both the treating physician's discretion and the patient's request. Salvage hormonal therapy most commonly consisted of a luteinizing hormone–releasing hormone agonist with (16%) or without (80%) a nonsteroidal anti-androgen, orchiectomy (2%), or nonsteroidal anti-androgen monotherapy (2%).

Among patients in the study cohort, all of whom were treated with radiation therapy, there were 58 deaths, 40 of which were prostate cancer–specific. In the validation cohort, which included both surgically treated and radiation-treated patients, there were 79 deaths, 29 of which were prostate cancer–specific. Determination of the cause of death was made from death certificates.

Statistical Analysis

PSA response. Both the pre- and post-salvage hormonal therapy PSA slopes were calculated assuming first-order kinetics and using at least three PSA values, each separated in time by at least 3 months, with a PSA increase of at least 0.2 ng/mL between PSA values. If a patient had one or two consecutive

Table 1. Distribution of pretreatment clinical characteristics of the 199 study cohort and 1255 validation cohort patients*

Clinical characteristics	Study cohort, % n = 199	Validation cohort (excluded patients), % n = 1255	P†
PSA, ng/mL			
≤4	5	11 (15)‡	<.001
4.1–10	35	45 (48)‡	
10.1–20	25	26 (21)‡	
>20	35	18 (16)‡	
Biopsy Gleason score			
≤6	45	58 (55)‡	<.001
7	35	30 (31)‡	
8–10	20	12 (14)‡	
2002 AJCC tumor category			
T1c	16	38 (39)‡	<.001
T2a	27	26 (26)‡	
T2b	17	19 (18)‡	
T2c	29	8 (9)‡	
T3a	7	6 (6)‡	
T3b	4	2 (2)‡	
T4	0	1 (1)‡	
Age, y§			
<50	1	2	<.001
50–59	3	16	
60–69	33	49	
70–74	38	22	
75–79	22	9	
≥80	5	2	

*PSA = prostate-specific antigen. AJCC = American Joint Commission on Cancer (10). Percentages may not add up to 100 due to rounding.

†P values were calculated for the comparison of distributions of the clinical characteristics between the study and validation cohorts using the chi-square test.

‡Percentage of patients with inadequate PSA data to calculate the PSA response to salvage hormonal therapy.

§Age at the time of initial therapy.

increases in his PSA level from an undetectable PSA level (i.e., <0.2 ng/mL) following surgery or from the PSA nadir following radiation therapy but before initiation of salvage hormonal therapy, PSA response could not be calculated; thus, such patients were excluded from the analysis. Similarly, if a patient did not have at least three PSA values available for analysis following salvage hormonal therapy and before initiation of the next salvage hormonal therapy series, then PSA response could not be calculated; such patients were also excluded from the analysis.

All patients in the study cohort had adequate PSA data to calculate PSA response; however, not all patients in the validation cohort had adequate PSA data. Therefore, to assess whether excluded patients were different from included patients in the validation cohort, a comparison using a chi-square test was performed for the baseline PSA level, biopsy Gleason score, and clinical 2002 AJCC tumor category (T-category) distributions and pre- and post-salvage hormonal therapy PSA slope among the included and excluded patients in the validation cohort.

Calculation of the PSA-DT. Unlike patients treated surgically, patients treated with radiation therapy do not necessarily have an undetectable PSA level (i.e., <0.2 ng/mL); however, they often have a finite nadir PSA level, which is typically less than 1.0 ng/mL within 2 years of radiation therapy. Therefore, to be certain that the magnitude of the PSA-DT would be the same for patients treated with surgery and those treated with radiation therapy who experienced the same absolute increase in PSA level, the nadir PSA level was subtracted from the post-radiation PSA level before the PSA-DT was determined.

The PSA-DT was calculated assuming first-order kinetics and by using a minimum of three PSA measurements, each separated by a minimum of 3 months and each with an increase in PSA level of more than 0.2 ng/mL. Therefore, the minimum PSA level that was used to calculate the PSA-DT needed to be more than 0.2 ng/mL for all study patients. If a patient had one or two consecutive increases in his PSA level from an undetectable PSA level (<0.2 ng/mL) after surgery or from the PSA nadir after radiation therapy but before initiation of salvage hormonal therapy, his PSA-DT could not be calculated; thus, such patients were excluded from the analysis. An example of the PSA measurements used to calculate the PSA-DT for patients treated with surgery and with radiation therapy follows. For example, if one assumes that serum PSA levels are obtained at 6-month intervals and that a surgically managed patient has consecutive 6-month PSA values of less than 0.2 (or 0), 0.3, 0.6, and 1.2 ng/mL, then the PSA-DT is approximately 6 months. Similarly, if PSA levels are obtained at the same time intervals and a radiation-managed patient has consecutive 6-month PSA values of 0.6 (nadir), 0.9, 1.2, and 1.8 ng/mL, then without correcting for the nadir of 0.6, the PSA-DT is approximately 12 months. However, if the PSA nadir of 0.6 is subtracted from each post-radiation PSA value, then the PSA-DT for patients treated with surgery and for those treated with radiation is the same (i.e., 6 months).

Assessing the prognostic significance of the PSA response. The ability of the constituents of the PSA response (i.e., pre-salvage hormonal therapy PSA slope and post-salvage hormonal therapy PSA slope) and PSA response to predict time to PCSM following salvage hormonal therapy was tested using a Cox regression analysis (3) in both the study and validation cohorts. PSA response and its constituents were treated as continuous variables for the purpose of the Cox regression analyses. In addition, the pre-salvage hormonal therapy PSA-DT was also

analyzed as a continuous variable in conjunction with PSA response and the post-salvage hormonal therapy PSA slope using a Cox regression analysis for the end point of time to PCSM following salvage hormonal therapy. To investigate whether the time interval from the first appearance of a rising PSA level following surgery or radiation therapy to the initiation of salvage hormonal therapy predicted for time to PCSM following salvage hormonal therapy, this time interval was analyzed as a continuous variable in conjunction with PSA response using a Cox regression analysis.

The PSA response data used in these analyses met the assumptions for using the Cox model, and the PSA response hazard ratios (12) were calculated with their associated 95% confidence intervals (CIs) from the Cox model. The 95% confidence intervals for estimates of prostate cancer-specific mortality were calculated using a bootstrapping technique (13) with 1000 replications. For the purpose of illustration, cumulative incidence plots (14) of PCSM, stratified by the absolute value of PSA response of greater than 1 compared with that of a PSA response of less than or equal to 1 and the post-surgery or post-radiation PSA-DT of less than 3 months versus 3 months or longer, were displayed. The categories selected to illustrate the prognostic significance of the PSA response and the PSA-DT were based on clinically meaningful end points. Specifically, PSA levels will generally fall at a rate that is faster than the rate of rise (i.e., PSA response is greater than 1) following salvage hormonal therapy unless a substantial burden of hormone-insensitive disease exists (i.e., PSA response is smaller than or equal to 1), as illustrated in Fig. 1. The categories of less than 3 months versus 3 months or longer for the PSA-DT were selected on the basis of evidence that supports a nearly 20-fold increase in risk of PCSM for patients with a PSA-DT of less than 3 months compared with that for patients with a PSA-DT of 3 months or longer (15).

Comparisons of PCSM estimates following salvage hormonal therapy were assessed for statistical significance using a two-

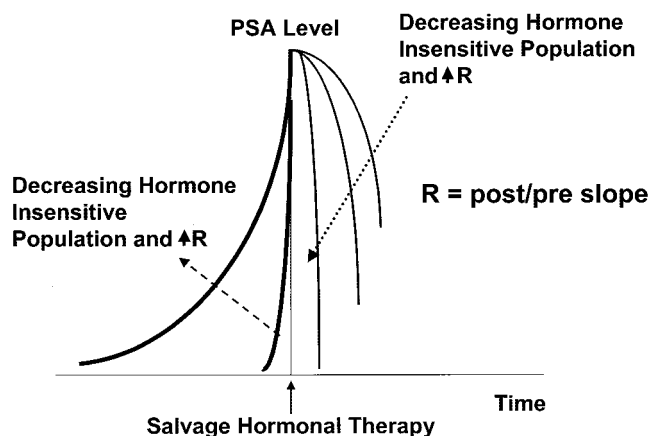


Fig. 1. Absolute value of the prostate-specific antigen (PSA) response (R) increases as the value of the pre-salvage hormonal therapy PSA slope (**thick lines**) decreases (i.e., a slower rise in PSA levels) and/or the value of the post-salvage hormonal therapy PSA slope (**thin lines**) increases (i.e., a faster decline in PSA levels). A patient with a large value for the pre-salvage hormonal therapy PSA slope (i.e., fast rise in PSA prior to salvage hormonal therapy) or a small value for the post-salvage hormonal therapy PSA slope (i.e., slow decline in PSA following salvage hormonal therapy) would be likely to have residual and/or recurrent prostate cancer that is not responsive to salvage hormonal therapy (i.e., hormone-insensitive).

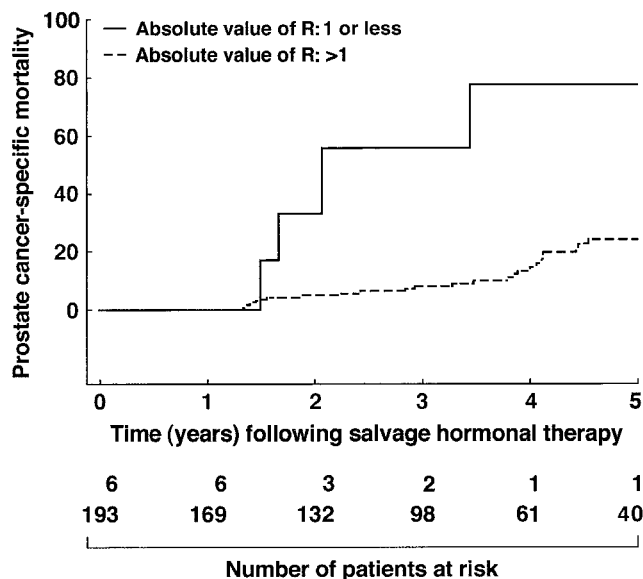


Fig. 2. Prostate cancer-specific mortality (PCSM) for 199 patients in the study cohort, stratified by the absolute value of the prostate-specific antigen (PSA) response (R) to salvage hormonal therapy. A two-sided log-rank test was used to compare estimates of PCSM following salvage hormonal therapy for each PSA response group. $P_{\text{Cox}} = .01$ for an absolute value for PSA response of less than or equal to 1 compared with an absolute value for PSA response of greater than 1. For an absolute value for PSA response of less than or equal to 1, the PCSM at 3 and 5 years was 56% (95% confidence interval [CI] = 12% to 99%) and 78% (95% CI = 40% to 100%), respectively. For an absolute value for PSA response of greater than 1, the PCSM at 3 and 5 years was 8% (95% CI = 4% to 11%) and 24% (95% CI = 15% to 33%), respectively.

sided log-rank test and reported at 3 and 5 years with 95% confidence intervals. Comparisons of the distribution of pretreatment clinical characteristics between the study and validation cohorts were performed using a chi-square test. All statistical tests were two-sided.

RESULTS

Prognostic Significance of the PSA Response

Patients who were excluded from the analysis because of inadequate PSA data needed to calculate a PSA response had a baseline PSA distribution ($P_{\text{chi-square}} = .09$), a biopsy Gleason score distribution ($P_{\text{chi-square}} = .18$), and a clinical 2002 AJCC T-category distribution ($P_{\text{chi-square}} = .92$) that were not statistically significantly different from those of the patients who were included in the analysis (Table 1). Patients who had only two PSA values before the start of salvage hormonal therapy did not have slopes that were statistically significantly higher ($P_{\text{chi-square}} = .86$) than those who had three PSA values available; likewise, patients with only two post-salvage hormonal therapy PSA values did not have slopes whose absolute value was statistically significantly smaller ($P_{\text{chi-square}} = .76$) than patients with three PSA values. For included patients, PSA response was statistically significantly associated with time to PCSM in both the study ($P_{\text{Cox}} = .0014$) and validation cohorts ($P_{\text{Cox}} < .001$), whereas the pre-salvage hormonal therapy PSA slope ($P_{\text{Cox}} = .97$ for the study cohort and $P_{\text{Cox}} = .57$ for the validation cohort) and the post-salvage hormonal therapy PSA slope ($P_{\text{Cox}} = .27$ for the study cohort and $P_{\text{Cox}} = .31$ for the validation cohort) were not associated with time to PCSM. In particular, following

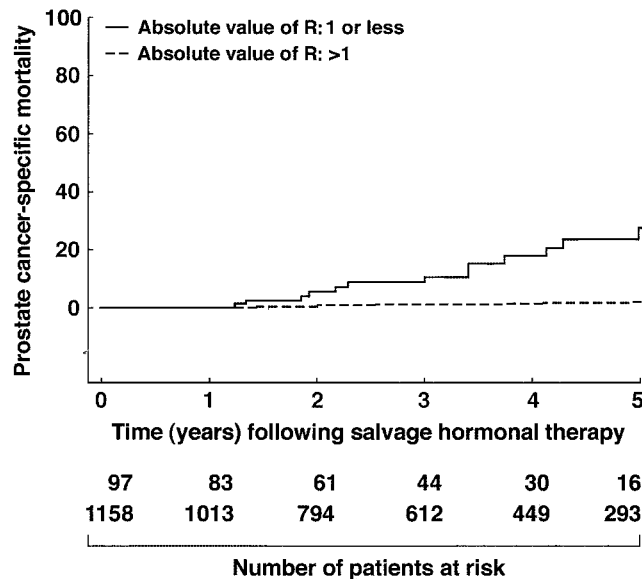


Fig. 3. Prostate cancer-specific mortality (PCSM) for 1255 patients in the validation cohort, stratified by the absolute value of the prostate-specific antigen (PSA) response (R) to salvage hormonal therapy. A two-sided log-rank test was used to compare estimates of PCSM following salvage hormonal therapy for each PSA response group. $P_{\text{Cox}} < .001$ for an absolute value for PSA response of less than or equal to 1 compared with an absolute value for PSA response of greater than 1. For an absolute value for PSA response of less than or equal to 1, the PCSM at 3 and 5 years was 11% (95% confidence interval [CI] = 3% to 19%) and 28% (95% CI = 14% to 42%), respectively. For an absolute value for PSA response of greater than 1, the PCSM at 3 and 5 years was 1% (95% CI = 0.5% to 2%) and 2% (95% CI = 0.8% to 3%), respectively.

salvage hormonal therapy, patients with a PSA response of less than or equal to 1 had a statistically significantly shorter time to PCSM than patients with a PSA response of greater than 1 in both the study cohort (hazard ratio [HR] = 3.6, 95% CI = 1.3 to 10.3; $P_{\text{Cox}} = .01$) and surgically treated and radiation-treated patients in the validation cohort (HR = 12.8, 95% CI = 6.2 to 26.3; $P_{\text{Cox}} < .001$).

As shown in Fig. 2, estimated PCSM following salvage hormonal therapy was statistically significantly lower ($P_{\text{log-rank}} = .01$) for patients in the study cohort whose PSA response was greater than 1 than for those patients whose PSA response was less than or equal to 1. Similarly, estimated PCSM following salvage hormonal therapy was statistically significantly lower ($P_{\text{log-rank}} < .001$) for patients in the validation cohort whose post-treatment PSA response was greater than 1 compared with patients whose PSA response was less than or equal to 1 (Fig. 3). The lower absolute value of PCSM for a given PSA response in the validation cohort compared with that in the study cohort reflects the statistically significantly more favorable ($P_{\text{chi-square}} < .001$) distributions of PSA level, biopsy Gleason score, and clinical T-category at the time of initial therapy (Table 1).

PSA-DT and PSA Response

For the patients in the validation cohort for whom PSA response and PSA-DT were available (i.e., the included patients; $n = 1255$), both PSA response ($P_{\text{Cox}} < .001$) and the pre-salvage hormonal therapy PSA-DT ($P_{\text{Cox}} = .04$) were statistically significantly associated with time to PCSM following salvage hormonal therapy, whereas the post-salvage hormonal therapy PSA slope ($P_{\text{Cox}} = .69$) was not statistically significantly associated

with time to PCSM following salvage hormonal therapy. Among patients in the validation cohort who had a post-surgery or post-radiation PSA-DT of less than 3 months ($n = 154$), estimated PCSM following salvage hormonal therapy, stratified by PSA response, was statistically significantly lower for patients with a PSA response of greater than 1 compared with that for patients with a PSA response of less than or equal to 1 ($P_{\text{log-rank}} = .04$) (Fig. 4). Similar statistically significant findings ($P_{\text{log-rank}} < .001$) for PSA response were found for patients with a post-surgery or post-radiation PSA-DT of 3 months or longer (Fig. 5).

The prognostic information that PSA response provided, in addition to the post-surgery or post-radiation PSA-DT, is shown in Table 2. In particular, as the PSA response increased, indicating a more rapid decline in PSA levels following salvage hormonal therapy and/or a more protracted rise in PSA levels prior to the initiation of salvage hormonal therapy, the estimated PCSM declined independent of the value of the pre-salvage hormonal therapy post-surgery or post-radiation PSA-DT.

Timing of Salvage Hormonal Therapy and PSA Response

PSA response remained statistically significantly associated with time to PCSM following salvage hormonal therapy in both the study ($P_{\text{Cox}} = .005$) and validation ($P_{\text{Cox}} < .001$) cohorts when assessed in conjunction with the time interval from the first appearance of a rising PSA level following surgery or radiation therapy to the initiation of salvage hormonal therapy. However, the timing of salvage hormonal therapy did not predict for the time to PCSM following salvage hormonal therapy in either the study ($P_{\text{Cox}} = .68$) or validation ($P_{\text{Cox}} = .78$) cohorts.

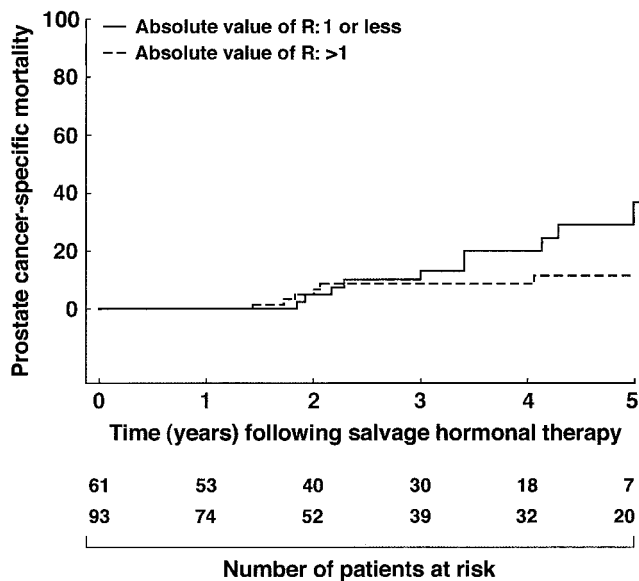


Fig. 4. Prostate cancer-specific mortality (PCSM) for the 154 patients with a prostate-specific antigen doubling time (PSA-DT) of less than 3 months in the validation cohort, stratified by the absolute value of the PSA response (R) to salvage hormonal therapy. A two-sided log-rank test was used to compare estimates of PCSM following salvage hormonal therapy for each PSA response group. $P_{\text{Cox}} = .04$ for an absolute value for PSA response of less than or equal to 1 compared with an absolute value for PSA response of greater than 1. For an absolute value for PSA response of less than or equal to 1, the PCSM at 3 and 5 years was 13% (95% confidence interval [CI] = 2% to 23%) and 37% (95% CI = 16% to 58%), respectively. For an absolute value for PSA response of greater than 1, the PCSM at 3 and 5 years was 9% (95% CI = 1% to 16%) and 11% (95% CI = 3% to 20%), respectively.

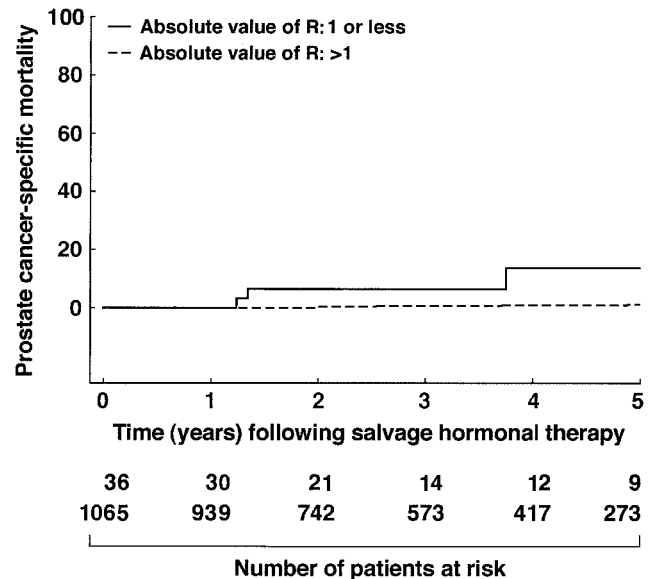


Fig. 5. Prostate cancer-specific mortality (PCSM) for the 1101 patients with a prostate-specific antigen doubling time (PSA-DT) of 3 months or longer in the validation cohort, stratified by the absolute value of the PSA response (R) to salvage hormonal therapy. A two-sided log-rank test was used to compare estimates of PCSM following salvage hormonal therapy for each PSA response group. $P_{\text{Cox}} < .001$ for an absolute value for PSA response of less than or equal to 1 compared with an absolute value of PSA response of greater than 1. For an absolute value for PSA response of less than or equal to 1, the PCSM at 3 and 5 years was 7% (95% confidence interval [CI] = 0% to 16%) and 14% (95% CI = 0% to 30%), respectively. For an absolute value for PSA response of greater than 1, the PCSM at 3 and 5 years was 0.7% (95% CI = 0.1% to 1.3%) and 1% (95% CI = 0.3% to 2%), respectively.

DISCUSSION

The most rapidly growing population of prostate cancer patients in the United States comprises men with a rising PSA level following surgery or external beam radiation therapy performed with curative intent for men with clinically localized prostate cancer (1). Recent studies (15–21) have determined that this patient population is heterogeneous with regard to the risk of developing bone metastases (16–20) and PCSM (15,21) and that the single most important known factor that can predict a patient's risk of both of these end points following PSA failure is the post-surgery or post-radiation PSA-DT. Specifically, a PSA-DT that is less than 3 months or the specific value of the PSA-DT when it is 3 months or longer has been shown to be a surrogate for determining whether a patient will experience

Table 2. Five-year estimates of prostate cancer-specific mortality following salvage hormonal therapy*

Absolute value of PSA response	5-year estimates of prostate cancer-specific mortality	
	PSA-DT <3 months, % (95% CI)	PSA-DT ≥3 months, % (95% CI)
≤1	37 (16 to 58)	14 (0 to 30)
>1–2	17 (0 to 36)	7 (0 to 15)
>2–3	16 (0 to 32)	3 (0 to 7)
>3	0 (0 to 0)	1 (0 to 4)

*Stratified by the pre-hormonal therapy prostate-specific antigen doubling time (PSA-DT) and the magnitude of the PSA response to salvage hormonal therapy for patients in the validation cohort. CI = confidence interval.

PCSM following PSA failure after primary management with surgery or external-beam radiation therapy (15).

In our study, the PSA response to salvage hormonal therapy and its constituents (i.e., pre-salvage hormonal therapy PSA slope and post-salvage hormonal therapy PSA slope) were evaluated using a Cox regression analysis (3). Because some patients in the validation cohort did not have adequate PSA data to calculate a PSA response, a comparison of the baseline distributions of PSA level, biopsy Gleason score, and clinical T-category between the included and excluded patients was performed. This comparison did not reveal any statistically significant differences between the two groups of patients, and the absolute differences within any one PSA level, biopsy Gleason score, or T-category among included and excluded patients was less than 5% (Table 1). In addition, patients who had only two PSA values before the start of salvage hormonal therapy did not have slopes that were statistically significantly higher than those who had three PSA values available; likewise, patients with only two post-salvage hormonal therapy PSA values did not have slopes whose absolute value was statistically significantly smaller than patients with three PSA values. As a result, the lack of a statistically significant difference between the included and excluded groups of patients with respect to baseline prognostic factors and the pre- and post-salvage hormonal therapy PSA slope suggested that the exclusion of these patients should not have had an impact on the findings of the study.

The main finding of this study was that, in both the study and validation cohorts, PSA response was statistically significantly associated with the time to PCSM following salvage hormonal therapy (Figs. 2 and 3), whereas the pre-salvage hormonal therapy and post-salvage hormonal therapy PSA slopes were not. Only the pre-salvage hormonal therapy PSA-DT, calculated by adjusting for the nadir value in radiation-managed patients, provided statistically independent information in predicting time to PCSM in addition to that already provided by PSA response following salvage hormonal therapy when analyzed using a Cox regression multivariable analysis and controlling for the value of PSA response (Figs. 4 and 5). The PSA response hazard ratio was smaller for the study as compared with the validation cohort. This can be explained by the higher baseline prostate cancer-specific mortality estimate in the study as compared with the validation cohort (Figs. 2 and 3), reflecting the more adverse features present in the study cohort at baseline (Table 1).

Clinically, rapid rises in PSA levels or a short post-surgery or post-radiation PSA-DT before the initiation of salvage hormonal therapy and slow declines in PSA levels following administration of salvage hormonal therapy suggest that the recurrent and/or residual prostate cancer cells responsible for the PSA recurrence are, in part, hormone insensitive (Fig. 1). Therefore, combining salvage hormonal therapy with an effective therapeutic intervention that targets hormone-insensitive prostate cancer would be expected to produce a more rapid decline in PSA levels (i.e., a larger value for the PSA response) and a subsequent lengthening of the time to PCSM than with salvage hormonal therapy alone. In this study, the statistically significant association of PSA response with the time to PCSM following salvage hormonal therapy provides support for a clinical trial in which PSA response could be used as an intermediate end point for PCSM.

Specifically, despite the use of all currently available salvage therapies (e.g., chemotherapy, immunotherapy, bisphosphonate therapy, and alternative therapy), clinical trials of effective sys-

temic therapies are needed for patients with short PSA-DTs (i.e., <3 months) following surgery or radiation therapy, whose median survival has been shown to be relatively short (i.e., 6 years) following PSA failure (15). In one randomized study (22) of newly diagnosed patients with minimal metastatic prostate cancer, median survival ranged from 4.25 to 4.33 years following orchiectomy with or without flutamide, respectively. This observation suggests that patients with a PSA-DT of less than 3 months have occult micrometastatic disease that is likely to be documented on bone scan in a relatively short amount of time (i.e., 1.67–1.75 years) following PSA failure. Therefore, for these patients, salvage hormonal therapy given at the time of PSA failure could be justified to delay the imminent sequelae of metastatic bone disease (15). Moreover, for these patients, a randomized clinical trial of salvage hormonal therapy plus a novel therapy that targets hormone-insensitive disease versus salvage hormonal therapy plus placebo could be evaluated based on the distribution of the PSA response between the two treatment arms. If a significant difference exists in PSA response, then it would be expected that this should translate into a significant difference in prostate cancer-specific mortality. Such a study design would expedite the discovery of effective agents in the treatment of men with PSA-recurrent prostate cancer, in whom currently available salvage therapies have had no measurable impact on survival (15).

Potential limitations of this study need to be considered. First, although all study patients who received salvage hormonal therapy had a negative bone scan within 1 month of initiating treatment, the exact point during the time course of the rising PSA levels at which salvage hormonal therapy was initiated was left to the discretion of the treating physician. Therefore, if salvage hormonal therapy is shown to prolong survival when given at the time of PSA-defined recurrence rather than at a later time, but prior to the documentation of a positive bone scan, then it would be necessary to reassess the association between PSA response and time to PCSM following salvage hormonal therapy in a setting where all men received salvage hormonal therapy at the time of the PSA-defined recurrence.

This study did not find that the time interval from the first rise in PSA level to the initiation of salvage hormonal therapy added statistically independent information in predicting time to PCSM in addition to that already provided by PSA response following salvage hormonal therapy when the data were analyzed using a Cox regression multivariable analysis and controlling for the value of the PSA response. Although these data provide some evidence that the timing of salvage hormonal therapy may not be an important predictor of time to PCSM following salvage hormonal therapy, only a randomized clinical trial that controls for all known and unknown confounding factors can assess the true relationship between the timing of salvage hormonal therapy and the time to PCSM following salvage hormonal therapy.

A second limitation is that the type of PSA response that novel therapies can produce will vary and may not occur on the same time scale as salvage hormonal therapy. That is, with regard to response type, some agents may be cytotoxic (7) while others may be cytostatic (23). Specifically, as depicted in Fig. 6, the improved PSA response would be expected to translate into a prolongation of the time to PCSM following novel therapy for both cytotoxic and cytostatic agents because of the elimination or growth retardation, respectively, of PSA-producing recurrent disease. However, novel agents that decrease serum PSA levels

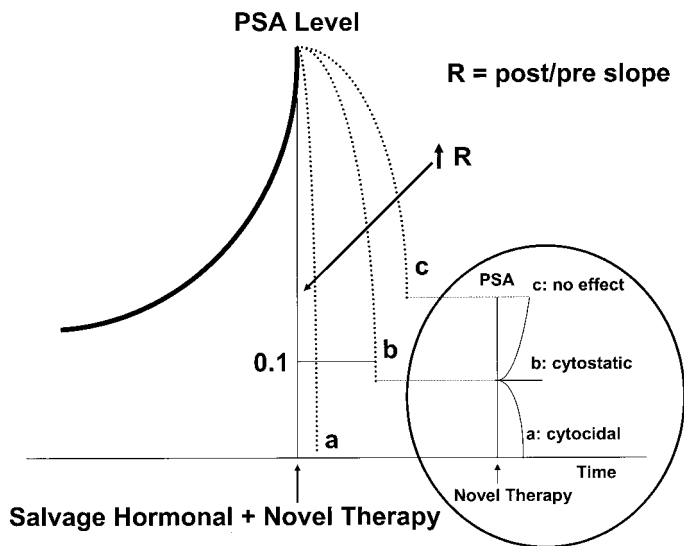


Fig. 6. Effect of salvage hormonal therapy plus a novel therapy on prostate-specific antigen (PSA) response (R). As the post-salvage hormonal therapy plus novel therapy PSA slope increases (i.e., a faster decline in PSA), the absolute value of the PSA response increases and is the largest when the novel agent has a cytotoxic effect on the residual and/or recurrent prostate cancer; whereas the absolute value of the PSA response is the smallest when the novel agent has no effect on the residual and/or recurrent prostate cancer. The expected effect of different classes of novel therapy on the PSA level, arising from the hormone-insensitive residual and/or recurrent prostate cancer, is shown in the circle.

without causing a cytotoxic or cytostatic effect could not be studied using PSA response as an intermediate end point for PCSM because the PSA response in that setting would not be an indication of the drug's ability to eliminate the residual and/or recurrent prostate cancer.

A third limitation is that adequate sampling of the serum PSA level extending over a reasonable time period following salvage hormonal therapy plus a novel therapy would be necessary to ensure that the impact of the novel therapy on the serum PSA levels could be adequately assessed. Based on the time scale over which cytotoxic chemotherapy has been shown to impact serum PSA (24), obtaining PSA levels for 3–6 months on a monthly basis following salvage hormonal therapy plus a novel therapy would be a reasonable approach.

In conclusion, the PSA response to salvage hormonal therapy was statistically significantly associated with the time to PCSM following salvage hormonal therapy in both the study and validation cohorts. These data provide evidence to support the use of the PSA response to salvage hormonal therapy as an intermediate end point for PCSM for patients with a rising PSA following surgery or radiation therapy.

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