Published in final edited form as:
BJU Int. 2012 January ; 109(1): 32–39. doi:10.1111/j.1464-410X.2011.10422.x.

The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up

Emmanuel S. Antonarakis, **Zhaoyong Feng**[*], **Bruce J. Trock**[*], **Elizabeth B. Humphreys**[*], **Michael A. Carducci**, **Alan W. Partin**[*], **Patrick C. Walsh**[*], and **Mario A. Eisenberger**
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231

[*] Brady Urological Institute, Johns Hopkins University, Baltimore, MD 21287, USA

Abstract

- To describe metastasis-free survival (MFS) in men with prostate-specific antigen (PSA) recurrence following radical prostatectomy, and to define clinical prognostic factors modifying metastatic risk.
- We conducted a retrospective analysis of 450 men treated with prostatectomy at a tertiary hospital between July 1981 and July 2010 who developed PSA recurrence (≥0.2 ng/mL) and never received adjuvant or salvage therapy before the development of metastatic disease.
- We estimated MFS using the Kaplan–Meier method, and investigated factors influencing the risk of metastasis using Cox proportional hazards regression.
- Median follow-up after prostatectomy was 8.0 years, and after biochemical recurrence was 4.0 years. At last follow-up, 134 of 450 patients (29.8%) had developed metastases, while median MFS was 10.0 years.
- Using multivariable regressions, two variables emerged as independently predictive of MFS: PSA doubling time (<3.0 vs 3.0–8.9 vs 9.0–14.9 vs ≥15.0 months) and Gleason score (≤6 vs 7 vs 8–10).
- Using these stratifications of Gleason score and PSA doubling time, tables were constructed to predict median, 5- and 10-year MFS after PSA recurrence. In different patient subsets, median MFS ranged from 1 to 15 years.
- In men undergoing prostatectomy, MFS after PSA recurrence is variable and is most strongly influenced by PSA doubling time and Gleason score. These parameters serve to stratify men into different risk groups with respect to metastatic progression.
- Our findings may provide the background for appropriate selection of patients, treatments and endpoints for clinical trials.

Keywords

metastasis-free survival; natural history; prostate cancer; PSA recurrence

Correspondence: E. S. Antonarakis, Prostate Cancer Research Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, CRB1-1M45, Baltimore, MD 21231, USA. eantona1@jhmi.edu.

CONFLICT OF INTEREST

This work is original, and was presented orally at the 2009 ASCO Genitourinary Cancer Symposium and at the 2009 ASCO Annual Meeting. The authors indicate no financial or other conflicts of interest.

INTRODUCTION

Prostate cancer is the most common male malignancy, with 217–730 new cases in the USA in 2010 [1]. Although radical prostatectomy can cure appropriately selected patients with localized disease, 20–40% will experience recurrence within 10 years [2]. Due to the universal availability and high sensitivity of PSA testing, most patients with disease relapse after prostatectomy present with a detectable PSA without local or distant recurrence. Once PSA progression has occurred, the disease is often incurable although survival may be extensive [3].

Management of PSA-recurrent prostate cancer remains controversial [4,5]. Treatment options include continuous androgen deprivation therapy (ADT) initiated upon PSA recurrence [6,7], deferred ADT reserved until metastatic progression [8,9], intermittent ADT [10,11] or clinical trial participation [12]. A subset of patients with PSA recurrence may benefit from salvage pelvic irradiation [13]. Understanding the factors that influence risk of metastatic progression is crucial in choosing optimal-risk-based therapies.

To describe the natural history for such patients, we previously studied 304 men with PSA recurrence after prostatectomy, of whom 131 had sufficient data to allow calculation of PSA doubling time (PSADT) [14]. No patient received additional therapy until metastatic progression. In that analysis, the median time from biochemical recurrence to metastasis, overall, was 8 years. Given this protracted course, we identified three variables stratifying patients into different risk groups for metastatic progression: surgical Gleason score, time from surgery to biochemical recurrence, and PSADT. Since this publication over one decade ago, other series have confirmed that a rapid PSADT is a strong risk factor for metastasis [15,16]. However, these series either involved small patient numbers or included men who received adjuvant/salvage therapies before developing metastases.

To further elucidate the natural history of untreated biochemically recurrent prostate cancer and to confirm risk factors for metastasis, we sought to update our original analysis using an expanded cohort of 642 men (of whom 450 had PSADT data) with longer follow-up. To our knowledge, this is the largest reported cohort of its type. Our ultimate aim is to distinguish those patients with PSA recurrence that require early aggressive therapy from those in whom a conservative approach may be reasonable, and to guide the design of prospective clinical trials in this patient population.

PATIENTS AND METHODS

PATIENTS

Of all men undergoing radical prostatectomy at Johns Hopkins Hospital between July 1981 and July 2010, 1973 developed biochemical recurrence (defined as a postoperative PSA ≥0.2 ng/mL). After eliminating patients who received adjuvant/neoadjuvant or salvage therapies before the detection of metastases (n = 798), and excluding patients with other missing information (n = 533), 642 men remained (Fig. 1). Only 450 men had sufficient data to allow calculation of PSADT, and these patients alone formed our cohort. Patients were followed through December 2010.

This was a retrospective analysis of prospectively collected data from a large cohort of men undergoing prostatectomy for localized disease. Data came from the Johns Hopkins Master Prostatectomy Database which stores clinical, pathological and demographic information under a consent waiver allowing its use for research without disclosing patient identifiers.

The database is approved by the Johns Hopkins institutional review board, and meets the requirements of the Health Insurance Portability and Accountability Act.

After prostatectomy, patients were generally followed with PSA measurements and rectal examinations every 3 months for the first year, every 6 months for the second year and every 12 months thereafter. Upon biochemical recurrence, PSA was measured approximately every 6 months, and imaging with CT and radionuclide bone scan was generally performed at baseline and then annually (or sooner if symptoms developed, e.g. bone pain). Because many patients did not receive regular postoperative evaluations at Johns Hopkins, follow-up protocols were not always uniform. Metastatic disease was defined as the presence of osseous metastases on bone scan, or visceral (liver, lung, brain) or extra-pelvic nodal metastases on CT scan. Magnetic resonance imaging was sometimes used to re-evaluate indeterminate lesions. Metastasis-free survival (MFS) was defined as the time interval from biochemical recurrence to initial metastasis. Patients were captured at the time of their first positive scan or censored at the time of their last confirmed negative scan. Deaths occurring before metastasis were also censored.

PSADT CALCULATION

PSADT was calculated using the log of 2 divided by the slope of the linear regression line of the log of PSA value against time (in months). All PSA values ≥0.2 ng/mL obtained within 24 months after biochemical recurrence were used. A minimum of two PSA levels collected ≥3 months apart were required. Because no patient received salvage therapy upon biochemical recurrence, PSADT determinations were not influenced by treatment.

STATISTICAL ANALYSIS

Comparisons between patient subgroups were performed using chi-squared tests for categorical data and *t* tests for continuous data. Age at surgery, preoperative PSA level (logarithmically transformed) and time to PSA recurrence were considered continuous variables. Race (white, non-white), clinical stage (T1, T2, T3), Gleason sum (4–6, 7, 8–10), pathological stage (organ-confined, extracapsular extension, seminal vesicle invasion, lymph node involvement), surgical margin status (positive, negative) and PSADT (<3, 3–8.9, 9–14.9, ≥15 months) were considered categorical variables.

Risk factors for metastasis were examined using Cox proportional hazards models. Univariate exploratory analyses showed that grouping Gleason score as ≤6 vs 7 vs 8–10 and time to biochemical recurrence as ≤3 vs >3 years maximized the likelihood ratio chi-squared for metastasis; these groupings were used in the multivariable model. For multivariable analysis, Cox proportional hazards regression was used. Variables entered into the model included age, race, preoperative PSA, clinical stage, Gleason score, extraprostatic extension, seminal vesicle invasion, lymph node involvement, surgical margin status, time to biochemical recurrence and PSADT. MFS probabilities were estimated for the whole cohort and within strata of prognostic factors using Kaplan–Meier methodology, and survival curve differences were evaluated using the log-rank test. Kaplan–Meier analyses used the time of PSA recurrence as time zero.

The predictive performance of the Cox model was assessed using the concordance (*C*) index. The *C* index was calculated with bootstrap correction for overfitting, after internal validation with 1000 bootstrap replications. Median, 5- and 10-year MFS estimates were derived from Kaplan–Meier curves, and 95% CIs were calculated using Greenwood's formula [17]. In some subgroups, the upper confidence limit for median survival was not computable and was represented as $>t_{max}$, where t_{max} was the maximum survival time

observed for that subgroup. The significance level was 0.05 for all statistical tests, and analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Clinical features of the 450 men with PSA-recurrent prostate cancer forming our cohort are summarized in Table 1. Most patients had pathologically non-organ-confined disease and Gleason scores ≥7. Median follow-up after surgery was 8.0 years, and after biochemical recurrence was 4.0 years. Median time from surgery to biochemical recurrence was 3.0 years. At last follow-up, 134 of 450 patients (29.8%) had developed metastases. The characteristics of these patients are shown in Table 1. Sites of the first documented metastasis included bone in 121 patients (90.3%), extra-pelvic lymph nodes in six patients (4.5%), lung in three patients (2.2%), liver in three patients (2.2%) and brain in one patient (0.8%). The median (range) PSA at the time of initial metastasis was 31.4 (0.2–798.5) ng/mL.

Median MFS after PSA recurrence was 10.0 years (95% CI 8.0–14.0 years) (Fig. 2). Five- and 10-year MFS probabilities were 67.3% (95% CI 61.4–72.4%) and 48.2% (95% CI 40.1–55.8%), respectively. Univariate proportional hazards models showed significant associations with MFS for race, Gleason sum, seminal vesicle invasion, lymph node involvement, time to biochemical recurrence and PSADT (Table 2). On multivariable analysis, only Gleason sum (≤6 vs 7 vs 8–10) and PSADT (<3.0 vs 3.0–8.9 vs 9.0–14.9 vs ≥15 months) emerged as statistically significant independent predictors of metastasis (Table 2). When PSADT was considered as a continuous variable, it remained a significant predictor of MFS on multivariable analysis (hazard ratio 0.98, 95% CI 0.96–0.99, $P < 0.001$).

To identify clinically relevant patient subgroups, we explored various PSADT cut-points by dividing patients into groups based on 3-month PSADT increments: <3.0, 3.0–5.9, 6.0–8.9, 9.0–11.9, 12.0–14.9, 15.0–17.9, 18.0–20.9 and 21.0–23.9 months. Patients with PSADT ≥24 months were combined into one group. PSADT groups were then examined in multivariable analysis and groups with statistically similar hazard ratios were combined. This resulted in four PSADT categories: <3.0, 3.0–8.9, 9.0–14.9 and ≥15 months. The bootstrapped concordance index (*C*) of the multivariable model using PSADT as a categorical variable to estimate MFS was 0.84. Notably, when PSADT was treated as a continuous variable, the bootstrapped *C* index of the multivariable model was 0.85, suggesting that predictive accuracy was not lost by using these artificial subdivisions of PSADT.

Figure 3 shows MFS curves stratified by the two statistically significant predictive variables. In addition, estimates of median, 5- and 10-year MFS (segregated by these two variables) are provided in Table 3. As shown, risk of metastatic progression is highest for men with Gleason scores 8–10 (vs lower Gleason scores) and PSADT <3.0 (vs longer PSADTs). Metastatic risk diminishes incrementally for patients in successively higher PSADT subgroups, with lowest risk conferred on those with PSADT ≥15 months.

To evaluate whether inclusion only of patients with PSADT information may have biased our estimation of MFS, we compared baseline characteristics between men with and without PSADT data. To this end, considering all patients with PSA recurrence ($n = 642$), those with ($n = 450$) and without ($n = 192$) available PSADT data did not differ significantly with respect to race ($P = 0.41$), preoperative PSA ($P = 0.21$), Gleason score ($P = 0.19$), surgical margin status ($P = 0.34$) or time to PSA recurrence ($P = 0.29$). Interestingly, patients with PSADT information were older at the time of prostatectomy (mean 59.9 vs 58.7 years; $P = 0.03$) and had higher rates of non-organ-confined disease (81.3% vs 71.9%; $P = 0.02$),

perhaps suggesting that MFS estimates may have even been underestimated in the present study.

DISCUSSION

Prostate cancer recurrence, heralded by a rising PSA after local therapy, represents a challenging dilemma. Although treatment with ADT is the standard for metastatic disease [18,19], optimal management of PSA recurrent disease is unclear [4,5,9]. Therefore, identifying and treating patients at highest risk of metastasis would probably have the greatest impact on patient outcomes, especially since most prostate cancer deaths occur in men with metastatic disease. Moreover, the interval from prostatectomy to metastasis itself predicts cancer-specific mortality [8,14].

We and others have previously shown that the natural history of untreated PSA recurrent disease is extensive but variable [3,14–16]. In our initial report [14], we studied 304 patients with post-prostatectomy biochemical recurrence, of whom 131 had PSADT information. The present updated analysis includes more patients (450 vs 131) with longer post-surgical follow-up (median, 8.0 vs 5.0 years), showing that median MFS after biochemical recurrence was 10.0 years overall. We show that two risk factors are independently predictive of MFS (PSADT and Gleason score, but not time to PSA recurrence) and have used these two parameters to construct tables enabling crude stratification by metastatic risk for patients with different PSADTs and Gleason scores. Importantly, the increased sample size of the present analysis has allowed us to examine four categories of PSADT (<3.0 vs 3.0–8.9 vs 9.0–14.9 vs ≥15.0 months), not just two categories (<10.0 vs ≥10.0 months) as in our original report. Our updated tables suggest that risk of metastatic progression after biochemical recurrence is variable and can be further characterized by knowledge of the PSADT and Gleason score, with median MFS ranging from 1.0 year in the highest risk group to 15.0 years in the lowest risk group (Table 3). Finally, although the absolute number of patients in this analysis is small, this represents the largest such data set in the medical literature.

Examination of multivariable regression results reveals that PSADT is the strongest predictor of metastasis. Since first recognized as an important prognostic factor 18 years ago [20], multiple studies have confirmed that PSADT is a predictor not only of clinical progression and metastasis [16,21,22] but also of prostate-cancer-specific mortality [3,13,23,24]. Moreover, the prognostic importance of PSADT in patients with biochemical recurrence is independent of the type of local therapy (prostatectomy or radiotherapy). However, optimal PSADT cut-points for differential stratification of patients remain uncertain. Previous reports suggested cut-points of ≤3 vs >3 months [24], ≤6 vs >6 months [16], ≤10 vs >10 months [14] and ≤12 vs >12 months [23]. In this analysis, to explore multiple PSADT cut-points in an unbiased way (and to improve upon our initial study [14]), we stratified patients into groups by 3-month intervals and identified three PSADT cut-points comprising four risk groups. However, since the relationship between PSADT and metastasis is probably continuous rather than discrete, this may explain why others have found different subdivisions of PSADT also stratifying patients into distinct risk groups.

Higher Gleason score was another significant predictor of metastasis. This is in keeping with results of other studies showing that Gleason score is significantly associated with risk of metastasis [16] and death from prostate cancer [2,25]. Again, there is no uniformity regarding optimal cut-points in Gleason score that best discriminate between high and low risk populations, and this may partially relate to methods of Gleason score assignment by pathologists. Additionally, some have suggested that Gleason score may not help risk-stratify patients after accounting for PSADT [26]. In our study, metastatic risk was highest

for patients with Gleason 8–10 but was also elevated for men with Gleason 7 (compared with those with Gleason ≤6). Although differences in metastatic risk between Gleason 7 and ≤6 did not reach statistical significance in multivariable analysis ($P = 0.067$), examination of Table 3 reveals that the 95% CIs from the 5- and 10-year MFS estimates do not overlap, supporting our decision to represent Gleason score in three categories.

Interestingly, although the interval from surgery to PSA relapse was predictive of metastasis in the univariate analysis, this was not true in the multivariable model. In our initial study [14], we reported that men with PSA recurrence ≤2 years after surgery were at highest risk of metastasis. While some studies confirmed this observation suggesting that a shorter time to PSA relapse was associated with increased risk of clinical progression and cancer-specific mortality [27–29], other studies did not find this association [21,23,25]. One possible explanation for this is that time to PSA relapse is closely related to (or even determined by) PSADT, so that this prognostic factor loses its significance after accounting for PSADT.

Using an overlapping cohort of men with biochemical recurrence from the same database, our group previously investigated factors influencing prostate-cancer-specific mortality [3]. In that analysis of 379 men followed for 6.8 years, 10-year prostate-cancer-specific survival was 73% overall but varied widely between the highest and lowest risk subgroups. Parameters determining cancer-specific survival in that study included PSADT, Gleason score and time to PSA recurrence. Therefore, the present analysis can be considered a companion study to the Freedland analysis [3] but now reporting MFS. Evaluation of MFS may be more relevant in informing the design of clinical trials in men with biochemically recurrent disease, because this endpoint requires shorter follow-up and is not affected by therapies administered after metastatic progression.

This study has several limitations. First, our analysis excludes patients receiving adjuvant or salvage therapies between prostatectomy and metastatic progression. This introduces bias because it retrospectively removes patients non-randomly, possibly eliminating those with worse prognosis and therefore artificially overestimating MFS. Second, the overall numbers of patients and events (metastatic progressions) in this data set are small, especially at longer follow-up times. Consequently, estimates of median, 5- and 10-year MFS within groups defined by PSADT and Gleason score may lack precision and often have wide CIs (Table 3). This should be taken into consideration by physicians using these data to characterize metastatic risk. Third, these results represent a single-institution cohort. In addition, the number of non-white patients is small (15%) and may not reflect the true racial mix of patients with prostate cancer. Therefore, these results require external validation, preferably using multicentre databases including more African-Americans and other ethnic minorities. Fourth, although Gleason sum and PSADT both appear to contribute independently to MFS, these factors are probably highly correlated, making it difficult to determine the true independent contribution of each. Last, stratifications of the two prognostic variables were based on optimal cut-points (i.e. cut-points that maximized the survival difference), an approach known to be associated with increased type I error and the possibility of overfitting [30].

Our results provide the conceptual framework for understanding the timing and risk factors for metastatic progression in men with PSA recurrence but should not be used to routinely counsel patients or guide clinical practice. These data may be used (with acknowledgement of their limitations) to aid in the rational selection of patients, treatments and endpoints for clinical trials involving men with biochemically relapsed disease. The duration of follow-up required in such studies may now be more clearly defined, especially if MFS is considered as a putative endpoint. Finally, the present study provides further evidence that PSADT is

the strongest prognosticator of metastasis in men with biochemical relapse, suggesting that this parameter should be calculated in all such patients.

In summary, we have shown using the largest published cohort of surgically treated patients with biochemical recurrence and no additional treatments after prostatectomy that MFS is extensive but variable. Using PSADT and Gleason sum, tables have been constructed providing crude estimates of metastatic risk for distinct patient subsets. This information may provide a basis for designing prospective clinical trials in men with PSA recurrent prostate cancer.

Acknowledgments

SOURCE OF FUNDING

This study was supported by the NIH/NCI SPORE Grant P50CA58236, the Prostate Cancer Foundation and the DOD Prostate Cancer Research Program. The study sponsors did not contribute in any way to the design, conduct, data collection or data analysis.

Abbreviations

ADT	androgen deprivation therapy
PSADT	PSA doubling time
MFS	metastasis-free survival

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60:277–300. [PubMed: 20610543]
2. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol. 2004; 172:910–14. [PubMed: 15310996]
3. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA. 2005; 294:433–9. [PubMed: 16046649]
4. Moul JW, Banez LL, Freedland SJ. Rising PSA in nonmetastatic prostate cancer. Oncology. 2007; 21:1436–45. [PubMed: 18077992]
5. Sandler HM, Eisenberger MA. Assessing and treating patients with increasing prostate specific antigen following radical prostatectomy. J Urol. 2007; 178:S20–4. [PubMed: 17644123]
6. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006; 7:472–9. [PubMed: 16750497]
7. Tenenholz TC, Shields C, Ramesh VR, Tercilla O, Hagan MP. Survival benefit for early hormone ablation in biochemically recurrent prostate cancer. Urol Oncol. 2007; 25:101–9. [PubMed: 17349523]
8. Makarov DV, Humphreys EB, Mangold LA, et al. The natural history of men treated with deferred androgen deprivation therapy in whom metastatic prostate cancer developed following radical prostatectomy. J Urol. 2008; 179:156–61. [PubMed: 18001801]
9. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2007; 25:1596–1605. [PubMed: 17404365]
10. Abrahamsson PA. Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: a systematic review of the literature. Eur Urol. 2010; 57:49–59. [PubMed: 19683858]

11. Yu EY, Gulati R, Telesca D, et al. Duration of first off-treatment interval is prognostic for time to castration resistance and death in men with biochemical relapse of prostate cancer treated on a prospective trial of intermittent androgen deprivation. J Clin Oncol. 2010; 28:2668–73. [PubMed: 20421544]
12. Scher HI, Eisenberger M, D'Amico AV, et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol. 2004; 22:537–56. [PubMed: 14752077]
13. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA. 2008; 299:2760–9. [PubMed: 18560003]
14. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999; 281:1591–7. [PubMed: 10235151]
15. Slovin SF, Wilton AS, Heller G, Scher HI. Time to detectable metastatic disease in patients with rising prostate-specific antigen values following surgery or radiation therapy. Clin Cancer Res. 2005; 11:8669–73. [PubMed: 16361552]
16. Okotie OT, Aronson WJ, Wieder JA, et al. Predictors of metastatic disease in men with biochemical failure following radical prostatectomy. J Urol. 2004; 171:2260–4. [PubMed: 15126798]
17. Kalbfleisch, JD.; Prentice, RL. The Statistical Analysis of Failure Time Data. New York: Wiley; 1980. p. 14-165.
18. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med. 1989; 321:419–24. [PubMed: 2503724]
19. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med. 1998; 339:1036–42. [PubMed: 9761805]
20. D'Amico AV, Hanks GE. Linear regressive analysis using prostate-specific antigen doubling time for predicting tumor biology and clinical outcome in prostate cancer. Cancer. 1993; 72:2638–43. [PubMed: 7691393]
21. Patel A, Dorey F, Franklin J, deKernion JB. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol. 1997; 158:1441–5. [PubMed: 9302139]
22. Zagars GK, Pollack A. Kinetics of serum prostate-specific antigen after external beam radiation for clinically localized prostate cancer. Radiother Oncol. 1997; 44:213–21. [PubMed: 9380819]
23. D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. J Clin Oncol. 2002; 20:4567–73. [PubMed: 12454114]
24. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst. 2003; 95:1376–83. [PubMed: 13130113]
25. Kim-Sing C, Pickles T. Prostate Cohort Outcomes Initiative. Intervention after PSA failure: examination of intervention time and subsequent outcomes from a prospective patient database. Int J Radiat Oncol Biol Phys. 2004; 60:463–9. [PubMed: 15380580]
26. Tollefson MK, Slezak JM, Leibovich BC, Zincke H, Blute ML. Stratification of patient risk based on prostate-specific antigen doubling time after radical retropubic prostatectomy. Mayo Clin Proc. 2007; 82:422–7. [PubMed: 17418069]
27. Chang SL, Freedland SJ, Terris MK, et al. Freedom from a detectable ultrasensitive prostate-specific antigen at two years after radical prostatectomy predicts a favorable clinical outcome: analysis of the SEARCH database. Urology. 2010; 75:439–44. [PubMed: 19819536]
28. Hanlon AL, Diratzouian H, Hanks GE. Post-treatment prostate-specific antigen nadir highly predictive of distant failure and death from prostate cancer. Int J Radiat Oncol Biol Phys. 2002; 53:297–303. [PubMed: 12023133]

29. Buyyounouski MK, Hanlon AL, Horwitz EM, Pollack A. Interval to biochemical failure highly prognostic for distant metastasis and prostate cancer-specific mortality after radiotherapy. Int J Radiat Oncol Biol Phys. 2008; 70:59–66. [PubMed: 17919840]

30. Keegan PE, Maththews JNS, Lunec J, Neal DE. Statistical problems with ‘optimal’ thresholds in studies of new prognostic factors in urology. BJU Int. 2000; 85:392–7. [PubMed: 10691812]

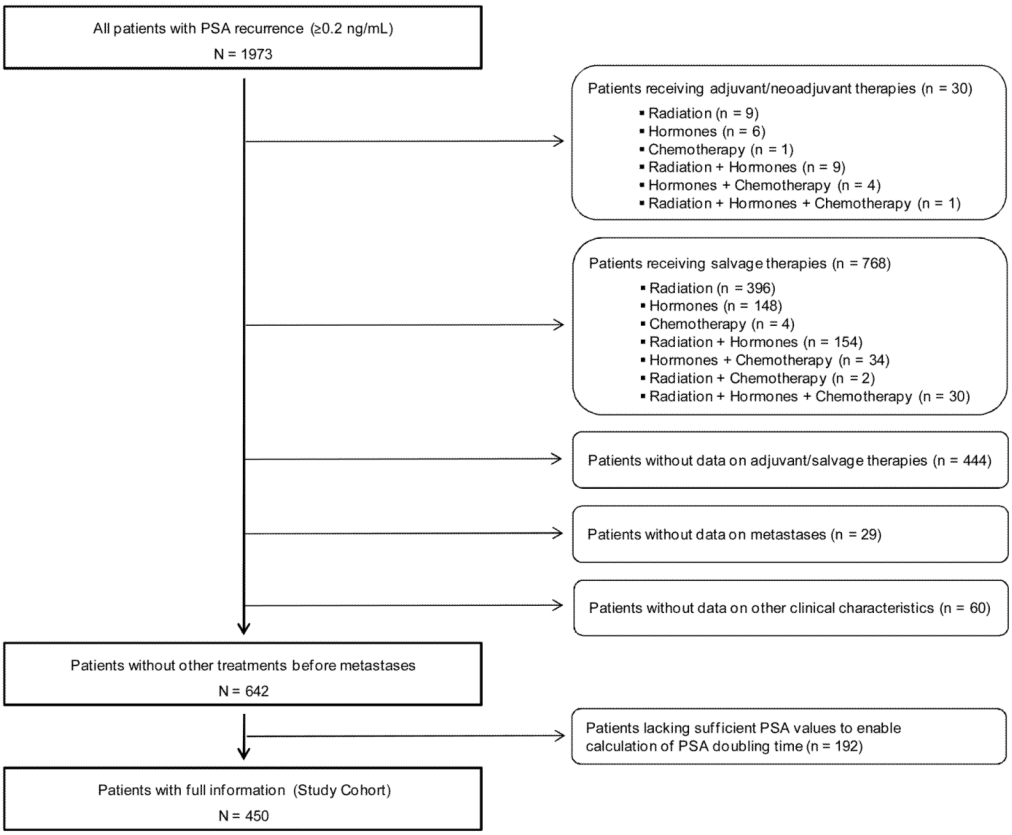


FIG. 1.
Consort diagram.

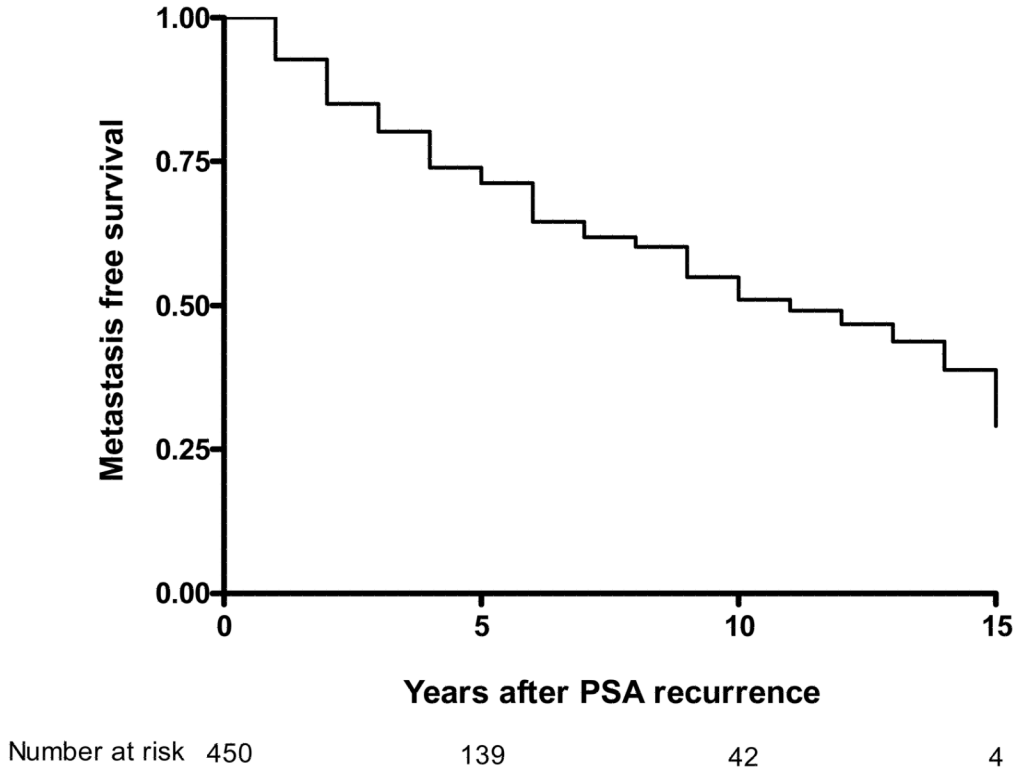
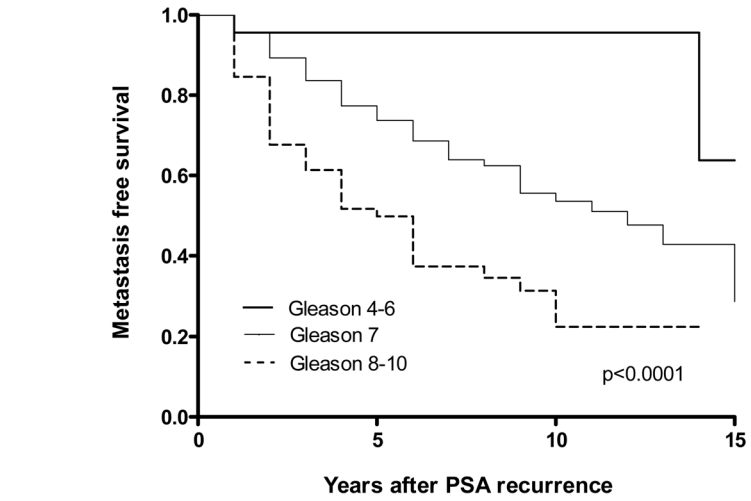
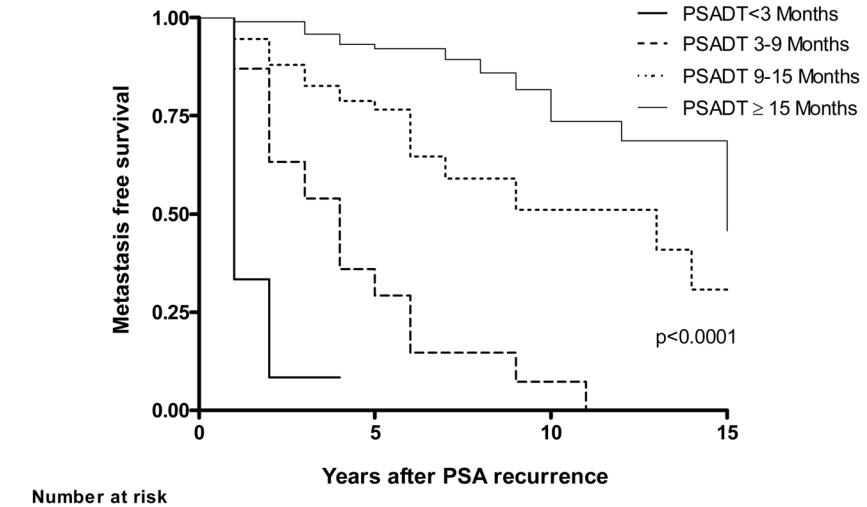


FIG. 2.
Kaplan–Meier estimate of overall MFS following PSA recurrence after radical prostatectomy, for the entire cohort of 450 men.



Number at risk				
Gleason score 4-6	88	26	6	1
Gleason score 7	239	85	29	3
Gleason score 8-10	123	28	7	0



Number at risk				
PSADT < 3 Month	46	0	0	0
PSADT 3-9 Month	106	16	2	0
PSADT 9-15 Month	86	37	11	1
PSADT ≥ 15 Month	212	86	30	3

FIG. 3.

Kaplan–Meier estimates of MFS, stratified by (a) pathological Gleason sum and (b) PSA doubling time.

TABLE 1

Characteristics of the 450 men with PSA recurrence after radical prostatectomy, encompassing a study period from July 1981 to July 2010

Characteristic	All patients (*N* = 450)	Men with metastases[a] (*N* = 134)	Men without metastases[a] (*N* = 316)
Age at surgery, years			
Mean (SD)	60.0 (5.8)	60.1 (5.3)	59.9 (6.1)
Race, *n* (%)			
White	382 (84.9)	126 (94.0)	256 (81.0)
Non-white	68 (15.1)	8 (6.0)	60 (19.0)
Preoperative PSA, ng/mL			
Median (range)	8.5 (0.7–151.0)	9.7 (1.2–129.0)	8.0 (0.7–151.0)
Clinical stage, *n* (%)			
T1	171 (37.9)	32 (23.5)	139 (44.0)
T2	267 (59.4)	93 (69.7)	174 (55.1)
T3	12 (2.7)	9 (6.8)	3 (0.9)
Pathological Gleason sum, *n* (%)			
4–6	88 (19.6)	5 (3.7)	83 (26.3)
7	239 (53.1)	66 (49.3)	173 (54.7)
8–10	123 (27.3)	63 (47.0)	60 (19.0)
Pathological stage, *n* (%)			
Organ-confined disease	84 (18.7)	11 (8.2)	73 (23.1)
Extraprostatic extension	209 (46.4)	41 (30.6)	168 (53.2)
Seminal vesicle invasion	63 (14.0)	31 (23.1)	32 (10.1)
Lymph node involvement	94 (20.9)	51 (38.1)	43 (13.6)
Surgical margin status, *n* (%)			
Positive	156 (34.6)	45 (33.6)	111 (35.0)
Negative	294 (65.4)	89 (66.4)	205 (65.0)
PSA doubling time, *n* (%)			
<3.0 months	46 (10.2)	29 (21.6)	17 (5.4)
3.0–8.9 months	106 (23.6)	57 (42.5)	49 (15.5)
9.0–14.9 months	86 (19.1)	25 (18.7)	61 (19.3)
≥15 months	212 (47.1)	23 (17.2)	189 (59.8)

[a] At the time of last follow-up.

TABLE 2

Cox proportional hazards models for predicting MFS after PSA recurrence following radical prostatectomy, using data from 450 men encompassing the study period from July 1981 and July 2010

	Univariate model		Multivariable model	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age at surgery, years (continuous)	0.99 (0.96–1.02)	0.713	1.01 (0.98–1.04)	0.464
Race				
White	1 [reference]		1 [reference]	
Non-white	0.4 (0.2–0.8)	0.010	0.5 (0.2–1.1)	0.086
Preoperative PSA, ng/mL (continuous)	1.00 (0.99–1.01)	0.567	0.99 (0.98–1.01)	0.424
Pathological Gleason sum				
4–6	1 [reference]		1 [reference]	
7	4.3 (1.7–10.7)	0.002	2.4 (0.9–6.2)	0.067
8–10	10.9 (4.4–27.1)	<0.001	4.5 (1.7–11.9)	0.002
Pathological stage				
Organ-confined disease	1 [reference]		1 [reference]	
Extraprostatic extension	1.2 (0.6–2.3)	0.658	0.6 (0.3–1.3)	0.240
Seminal vesicle invasion	3.0 (1.5–6.0)	0.002	1.3 (0.6–2.8)	0.434
Lymph node involvement	3.1 (1.6–6.0)	0.001	1.1 (0.5–2.2)	0.811
Surgical margin status				
Negative	1 [reference]		1 [reference]	
Positive	0.8 (0.6–1.1)	0.198	0.9 (0.6–1.4)	0.829
Time to PSA recurrence				
≤ 3 years	1 [reference]		1 [reference]	
> 3 years	0.4 (0.3–0.6)	<0.001	1.0 (0.6–1.5)	0.964
PSA doubling time				
≥ 15 months	1 [reference]		1 [reference]	
9.0–14.9 months	2.7 (1.6–4.8)	0.005	2.5 (1.4–4.5)	0.002
3.0–8.9 months	11.6 (7.0–19.3)	<0.001	8.0 (4.5–14.1)	<0.001
< 3.0 months	47.4 (25.2–89.0)	<0.001	33.3 (16.4–67.4)	<0.001

HR, hazard ratio.

TABLE 3

MFS after PSA recurrence according to pathological Gleason score and PSA doubling time

	Pathological Gleason score 8–10 (*n* = 123)	Pathological Gleason score 7 (*n* = 239)	Pathological Gleason score 4–6 (*n* = 88)	PSADT <3 months (*n* = 46)	PSADT 3–9 months (*n* = 106)	PSADT 9–15 months (*n* = 86)	PSADT ≥15 months (*n* = 212)
Median MFS, years (95% CI)	4 (2, 6)	11 (9, >17)	>15 (14, >15)	1 (0, 1)	4 (2, 4)	13 (6, >15)	15 (15, >17)
Metastasis- free rate at 5 years, % (95% CI)	43 (32, 54)	71 (63, 78)	94 (86, 98)	5(1, 21)[a]	27 (16, 39)	77 (63, 86)	91 (85, 95)
Metastasis- free rate at 10 years, % (95% CI)	19 (9, 33)	52 (41, 62)	94 (86, 98)	N/A	7 (1, 22)	51 (34, 66)	72 (59, 83)

In each subgroup, the median MFS as well as the 5- and 10-year probabilities of MFS from the time of PSA recurrence are shown. *n*, number of men in each subgroup. N/A, not applicable.

[a] Last subject censored at 4 years.