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The Natural History of Men Treated With Deferred Androgen Deprivation Therapy in Whom Metastatic Prostate Cancer Developed Following Radical Prostatectomy

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Abstract

Purpose—We report on the natural history and factors influencing the prognosis of a cohort of hormone naïve, prostate specific antigen era patients in whom metastatic prostate cancer developed after radical prostatectomy who were followed closely and treated with deferred androgen deprivation therapy at the time of metastasis.

Materials and Methods—A total of 3,096 men underwent radical prostatectomy performed by a single surgeon at Johns Hopkins Hospital between 1987 and 2005. Of these men 422 had prostate specific antigen failure. Distant metastasis developed in 123 patients, of whom 91 with complete data formed the study cohort initially treated during the prostate specific antigen era (1987 to 2005) and receiving androgen deprivation therapy after documented metastasis. A total of 41 men died of prostate cancer. Median survival times were estimated by Kaplan-Meier analysis. Prognostic impact was estimated as the hazard ratio derived from the Cox proportional hazards model.

Results—Median followup from radical prostatectomy was 120 months (range 24 to 216). Kaplan-Meier median (range) times to failure were 24 months (12 to 144) from radical prostatectomy to prostate specific antigen failure, 36 months (0 to 132) from prostate specific antigen failure to metastasis, 84 months (12 to 180) from metastasis to death and 168 months (24 to 216) from radical prostatectomy to death. Statistically significant univariate risk factors for prostate cancer specific mortality at the time of metastasis were pain at diagnosis of metastases ($p = 0.002$), time from radical prostatectomy to metastasis ($p = 0.024$) and prostate specific antigen doubling time less than 3 months during the 24 months before metastasis ($p = 0.016$). Multivariable analysis demonstrated independent predictors of prostate cancer specific mortality at the time of metastasis, namely pain (HR 3.5, $p = 0.003$) and prostate specific antigen doubling time less than 3 months (HR 3.4, $p = 0.017$).

Conclusions—Men treated with deferred androgen deprivation therapy for the development of metastasis after radical prostatectomy may have a long life span, 169 months after radical prostatectomy (range 24 to 216). The presence of pain and short prostate specific antigen doubling time predicted an unfavorable outcome.

Keywords

prostatic neoplasms; prostatectomy; neoplasm metastasis; androgens; pain

Radical prostatectomy has been demonstrated to be an effective treatment for prostate cancer, especially when the disease is organ confined.^{1–3} As our experience with treating men with RP has increased, we have also learned that many men who are not cured by surgery still may have good outcomes even when evidence of increasing PSA develops.^{4–6} Androgen signaling events have for many years been known to control CaP cell growth and differentiation, and androgen deprivation therapy has long been a mainstay for the treatment of advanced CaP.^{7,8}

In the last several years the pattern of practice of ADT for CaP in most of the Western world has been characterized by implementation of treatment before evidence of metastasis. Practitioners frequently extrapolate the benefits of ADT determined in advanced disease^{9–11} and apply those same principles to patients with PSA recurrence after RP.¹² However, the efficacy of immediate administration of ADT after PSA recurrence vs deferring ADT until evidence of metastatic disease has not been well established and is a subject of great controversy,¹³ while the deleterious effects of long-term ADT are well-known.¹⁴ We demonstrate CaP specific survival and analyze factors influencing it in a contemporary group of hormone naïve men with metastasis (stage D2) after RP, followed closely from the time of PSA increase.

MATERIALS AND METHODS

From January 1987 to July 2005 during a median followup of 120 months (range 24 to 216), 422 of 3,096 men (14%) who had undergone RP by a single surgeon (PCW) at Johns Hopkins Hospital experienced biochemical recurrence, defined as a single postoperative PSA of 0.2 ng/ml or higher. Of these men 123 (4%) had evidence of metastatic disease (visible on bone scan, computerized tomography or magnetic resonance imaging). A total of 32 patients were excluded from analysis for several reasons. There were 21 patients who received ADT before metastasis and 5 had missing data on ADT. Patients were censored at last followup, excluding 6 who were lost to followup after the diagnosis of metastasis. This resulted in a study population of 91 patients, all of whom first received ADT at the time of clinically evident distant metastasis. A total of 18 (20%) patients were given external beam radiation therapy after RP. There were 15 patients who received salvage XRT and 3 who received adjuvant XRT. A total of 41 men died of CaP and 5 died of other causes. Race was categorized using patient reported data and is reported for baseline demographic information purposes only. Because our study population was predominantly white, we did not include race in any statistical analyses (table 1). The institutional review board at Johns Hopkins

approved this study and, when required, written informed consent was obtained from all study participants.

Followup

Patients were followed postoperatively with PSA determinations and rectal examinations every 3 months for the first year, semiannually for the second year and annually thereafter. After biochemical progression PSA was measured semiannually and bone scans were recommended to be performed yearly. At every visit a pain history was elicited and if present a bone scan was performed out of sequence. Pain was documented as present only if the examining physician noted pain in the record. Absence of pain was recorded if the physician noted no pain on examination or the patient was noted to be without complaints. Pain data were recorded as missing if there was no documentation of pain or patient well-being. Comorbidities (DM, CAD) at the diagnosis of metastasis were recorded, as well as hematocrit documented within 12 months of the diagnosis of metastasis. The location of metastasis, axial vs appendicular or visceral, was noted as well as Eastern Cooperative Oncology Group performance status (as recorded by the examining physician or calculated based on information from the physician's note). If standard criteria used to determine ECOG performance status were missing or unclear, then performance status was treated as missing.

All 91 patients received ADT at the documentation of metastasis. Following progression after ADT, patients returned to the care of their primary oncologist for treatment and followup, and the manner and method by which ADT was administered were left to their discretion. PCSM was defined as death in any patient with metastasis showing any progression following ADT. Because of the limited number of nonCaP deaths (5) in this cohort, PCSM approached all-cause mortality, so data are only reported for PCSM. When the 5 men with nonCaP deaths were excluded vs censored at the time of death, the results of the multivariable analyses did not materially change. Therefore, these men were censored at the time of death and included in the analyses.

Determination of PSADT

Prostate specific antigen doubling time was calculated using the natural log of 2 (0.693) divided by the slope of the linear regression of logPSA vs time. We calculated PSADT using 2 different methods including all PSA values within 24 months after biochemical recurrence (greater than 0.2 ng/ml)⁵ and including all PSA values within 24 months before radiographic documentation of metastasis. Patients (9 for PSADT in the 24 months after biochemical recurrence, 1 for PSADT in the 24 months before metastasis) with a negative or undefined PSADT (no PSA increase) were assigned a value of 1,000 months for ease of calculations. All PSA values were taken before subsequent ADT, which might have affected PSADT calculation.

Statistical Methods

PSADTs were dichotomized as 3 or more months vs less than 3 months and time from surgery to metastasis was dichotomized as 5 or less years vs more than 5 years because a binary variable has easier clinical interpretation. These forms have also been prognostic in

previous studies.^{5,6} Median failure times were estimated with the Kaplan-Meier method. Potential prognostic factors for time from radiographic documentation of metastasis to CaP specific mortality were examined using log rank tests and univariate proportional hazards regression. Variables exhibiting $p \leq 0.15$ in univariate analyses were entered manually in Cox proportional hazards models in a forward stepwise fashion. Variable retention was based on the likelihood ratio test and change in estimated hazard ratios for variables already present. Final models were developed using multiple imputation and imputing missing values with a Markov Chain Monte Carlo (MCMC) method with 5 imputations, implemented in PROC MI and PROC MIANALYZE in SAS®. Imputation of missing values for the model variables is based on dependent variables in the model (survival time and death status), variables are correlated with model variables and variables correlated with the missingness of model variables. The proportional hazards assumption was verified for candidate prognostic factors by plotting Martingale residuals vs survival time and the Kolmogorov supremum test.¹⁵ Statistical analyses were performed using SAS® v9.1.

RESULTS

The clinical and pathological characteristics of the 91 patients analyzed in this study are shown in table 1. Most patients had clinically palpable, pathologically extraprostatic, high Gleason grade disease. Median preoperative PSA in these patients was 10.2 ng/ml (range 1.5 to 129, IQR 6.4 to 19). Median followup from RP was 120 months (range 24 to 216). Kaplan-Meier median failure times were 24 months (range 12 to 144) from RP to PSA failure, 32 months (range 2 to 129) from PSA failure to metastasis, 132 months (range 12 to 204) from PSA failure to death, 82 months (range 7 to 181) from metastasis to death and 168 months (range 24 to 216) from RP to death (fig. 1).

Median PSA at the time of metastasis was 31.4 ng/ml (range 0 to 679, IQR 9.1 to 92.7, table 2). One patient with a PSA of 0 ng/ml had an isolated lung metastasis discovered during an evaluation for cough, verified by bronchoscopic biopsy. The median number of PSA values obtained from PSA failure to metastasis was 4 (range 0 to 12). Median PSADT calculated from the time of PSA recurrence was 5.8 vs 5.0 months during the 24 months before the documentation of metastasis. Most patients had few comorbidities in that 3% had DM, 18% had CAD and 93% exhibited a performance status of 0 to 1. Of the patients 67% presented with appendicular or soft tissue visceral metastasis and 34% presented with pain (table 2).

Several variables were statistically significant prognostic factors for PCSM in univariate Cox proportional hazards analysis such as pain at diagnosis of metastases (HR 2.97, 95% CI 1.45–6.06, $p = 0.002$), time from RP to metastasis (continuous variable) (HR 0.99, 95% CI 0.98–0.998, $p = 0.024$), hematocrit at metastasis (HR 0.83, 95% CI 0.7–0.96, $p = 0.007$) and PSADT during the 24 months before metastasis (categorical variable less than 3 months) (HR 3.01, 95% CI 1.26–7.91, $p = 0.016$, table 3). Kaplan-Meier analysis revealed similar findings (fig. 2). Figure 2A, shows a log rank test revealing patients with no pain had a survival advantage compared to those with pain ($p = 0.002$). A similar survival advantage was seen in those with PSADTs of 3 or more months in figure 2B, ($p = 0.009$) and in those in whom metastasis took more than 5 years to develop ($p = 0.041$, fig. 2C).

A multivariable Cox proportional hazards model demonstrated that the independent predictors of PCSM are pain at diagnosis of metastasis (HR 7.9, 95% CI 2.5–24.7, $p < 0.001$) and PSADT before metastasis less than 3 months (HR 4.6, 95% CI 1.7–12.4, $p = 0.003$, table 4). Only 53 patients had data available for both covariates. We repeated the modeling process using multiple imputation to simulate missing data, resulting in an analysis representing all 91 patients. This analysis also resulted in a final model with pain at diagnosis of metastasis (HR 3.5, 95% CI 1.6–7.7, $p = 0.003$) and PSADT before metastasis of less than 3 months (HR 3.4, 95% CI 1.3–8.5, $p = 0.017$) (table 4). Testing Martingale residuals revealed no departure from the proportional hazards assumption ($p = 0.379$ and 0.548 for pain and PSADT before metastasis, respectively).¹⁵ PSADT determined in the 24 months immediately after PSA failure (HR 1.0, $p = 0.371$) and time from RP to metastasis (HR 1.0, $p = 0.804$) were not independent predictors of PCSM. Hematocrit obtained within 12 months before or after metastasis was not evaluated in a multivariable model because only 30 patients had data available. Kaplan-Meier analysis stratifying patients simultaneously by pain and short PSADT confirms the prominent role of pain as a predictor of PCSM ($p < 0.001$). The groups in order of longest to shortest survival are men without pain and with a long PSADT, then men without pain with a short PSADT, then men with pain and a long PSADT, and finally men with pain and a short PSADT (fig. 3).

DISCUSSION

The natural history of CaP following biochemical recurrence can be long,^{5,6} as can the natural history of CaP after the development of metastasis.⁵ While the timing of ADT is controversial, to our knowledge there are no studies describing the natural history of men treated with deferred ADT after the development of a PSA increase after RP. Nor are there studies evaluating the role of early vs deferred administration of ADT after the development of biochemical recurrence.¹³ Current practice patterns suggest that most patients in the United States receive ADT soon after PSA increase, before the development of metastatic disease. As a result the proportion of patients presenting with hormone naïve, metastatic CaP has decreased substantially in the last 2 decades.^{12,16}

Here we describe a contemporary cohort of patients in whom metastatic CaP developed after RP, and who were treated with close observation and deferred ADT. We demonstrate that the survival of these hormone naïve patients can be long, and that the presence of pain and a short PSADT during the 24 months preceding metastasis are independent risk factors for PCSM in this cohort. We also found no independent association between absolute PSA at diagnosis of metastasis and PCSM. The wide range of PSA levels at metastasis demonstrates the difficulty in relying solely on this test as a predictor of metastasis and under-scores the need to perform bone scans routinely, even in men with low PSA.

Eisenberger et al examined prognostic factors in men presenting with stage D2 CaP enrolled in a National Cancer Institute Intergroup sponsored double-blind, placebo controlled, prospective randomized trial comparing treatment of hormone naïve patients with leuprolide alone vs leuprolide plus flutamide.¹⁷ Multivariable analysis demonstrated that the extent of bone involvement on bone scan, presence of pain, anorexia and DM were independent prognostic factors for PCSM. In that cohort the median time from diagnosis of unstaged

prostate cancer to study entry was 6 weeks, implying these men already had metastatic CaP at presentation.¹⁷ The survival of contemporary patients with stage D2 CaP is markedly different from those of the prePSA and early PSA periods. This is due in large part to lead time bias from earlier detection of CaP.

The first outcomes data for men with metastasis after RP were published by Pound et al.⁵ In a subset of 103 men with metastasis after RP from 1982 to 1997 there were 44 men who died of CaP. Analysis revealed that time from surgery to the development of metastasis was the only significant independent risk factor for PCSM.

In our cohort of men in whom metastasis developed after RP, which incorporates many patients diagnosed after 1987 from the series evaluated by Pound et al,⁵ time to the development of metastasis is also significant in univariate analysis but is not independently prognostic in multivariable analyses including pain and PSADT 24 months before diagnosis of metastasis. Our cohort also has longer followup than the study by Pound et al and is more relevant to patients treated in the modern era, as PSA screening and followup were routinely available at Johns Hopkins Hospital by 1987. Our results differed from those observed in the trial by Eisenberger et al¹⁷ in that disease severity (determined by extent of bone scan involvement), anorexia at the time of diagnosis and performance status were not statistically significant risk factors for PCSM.¹⁶ Too few patients had data available on hematocrit or history of diabetes to evaluate their prognostic influence.

Our study has several limitations. It is a single center, retrospective analysis of a small number of patients. There were 21 patients who received ADT before the documentation of metastasis who were excluded from analysis. These patients may have received early ADT because they had more aggressive disease than those who received deferred ADT. In addition, this population of men who have undergone RP enjoys overall better health than patients from previous eras, such as those in the Intergroup trial who had stage D2 disease at initial diagnosis.¹⁶ This could be due to the selection bias for surgical candidates (only relatively healthy men can tolerate surgery), the schedule of frequent followup for surgical patients or a possible¹⁸ (although controversial¹⁹) protective effect of surgical control of the primary tumor on PCSM. Our study also evaluates patients who ultimately had metastasis after surgical treatment, who thus have highly aggressive disease. The prognostic factors that we identified are determined at the time of, not before, metastasis. Thus, our results may not be generalizable to evaluating risk for the average patient at the time of CaP diagnosis, after RP or at the time of biochemical failure. Finally, prognostic factor data were missing for a number of patients, requiring the use of multiple imputation for a more valid analysis. However, it is encouraging that the multivariate analyses identified the same 2 prognostic factors in analyses with and without multiple imputation, suggesting that these are not chance associations.

The data we present here do not specifically evaluate the difference between immediate and deferred ADT. However, they do demonstrate that hormone naïve patients with metastasis after RP, when closely followed in the interval after biochemical failure, may have an excellent response to deferred ADT and a long survival. When treating patients who may survive longer than a decade after surgery, the complications of ADT become

significant.^{14,20} We have identified prognostic factors (presence of pain and short PSADT at the time of metastasis) which predict worse outcome. Patients with these negative prognostic indicators may benefit from therapies in addition to ADT at the time of metastasis.

CONCLUSIONS

Optimal timing for the initiation of ADT remains controversial. Our data in patients followed from the time of RP indicate that deferred ADT initiated at the radiographic documentation of metastasis may still be associated with long survival time. The outcome of stage D2 CaP in a contemporary series is different from the pre or early PSA era. PSADT immediately before the development of metastasis and the presence of pain are important predictors of PCSM.

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
CAD	coronary artery disease
CaP	prostate cancer
DM	diabetes mellitus
ECOG	Eastern Cooperative Oncology Group
IQR	interquartile range
PCSM	prostate cancer specific mortality
PSA	prostate specific antigen
PSADT	prostate specific antigen doubling time
RP	radical prostatectomy
XRT	external beam radiotherapy

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FIG. 1.
Median (range) failure times in hormone naïve men with metastasis after radical prostatectomy

FIG. 2.

A, prostate cancer specific survival by pain at metastasis. B, prostate cancer specific survival by PSADT at metastasis. C, prostate cancer specific survival by time to metastasis.

No. Patients				
No pain, long PSADT	30	19	7	4
No pain, short PSADT	7	5	2	--
Pain, long PSADT	13	8	--	--
Pain, short PSADT	3	--	--	--

FIG. 3.
Prostate cancer specific survival by pain and PSADT at metastasis

TABLE 1

Clinical and pathological characteristics of men with metastasis after RP

No. pts	91	
Median pt age at surgery (range), (IQR)	60	(38–75), (57–64)
No. white race (%)	89	(97.8)
Median preop ng/ml PSA (range), (IQR)	10.2	(1.5–129), * (6.4–19)
No. biopsy Gleason score (%):		
2–6	35	(40)
7 (3 + 4)	22	(25)
4 + 3 or Greater	30	(34)
No. clinical stage (%):		
T1b	2	(2)
T1c	11	(12)
T2a	29	(32)
T2b	30	(33)
T2c	8	(9)
T3a	10	(11)
D0	1	(1)
No. pathological Gleason score (%):		
2–6	4	(4)
7 (3 + 4)	20	(22)
4 + 3 or Greater	67	(73)
No. pos margins (%)	31	(34)
No. extraprostatic extension (%)	82	(90)
No. seminal vesicle invasion (%)	44	(48)
No. lymph node involvement (%)	42	(47)
Median yrs followup after RP (range)	10	(2–18)
Median time to failure (range):		
Mos RP to PSA failure	24	(12–144)
Mos PSA failure to metastasis	32	(2–129)
Mos metastasis to death	82	(7–181)
Median mos RP to death (range)	168	(24–216)

* Includes data from 89 patients.

TABLE 2

Clinical characteristics of men at diagnosis of metastasis after RP

		1987–2005	No. With Data
Median ng/ml PSA at metastasis (range), (IQR)	31.4	(0–679), (9.1–92.7)	76
Median PSADT		5.8	60
Median PSADT at metastasis		5.0	59
Median hematocrit at metastasis (range), (IQR)	41.8	(27.2–47.1), (40–43.8)	30
No. comorbid DM (%)		2 (3)	80
No. comorbid CAD (%)		14 (18)	80
No. presence of appendicular metastases (%)		51 (67)	76
No. presence of pain (%)		25 (34)	74
No. ECOG performance status (%):			75
0		46 (61)	
1		24 (32)	
2		4 (5)	
3		1 (3)	
4		0	

TABLE 3

Univariate Cox proportional hazards model predicting PCSM for men with metastasis after RP

	HR	95% CI	p Value	No. With Data
Time from RP to metastasis	0.99	0.98–0.998	0.024	91
Time to PSA failure	0.99	0.97–1.00	0.100	91
Log (preop PSA)	1.07	0.75–1.53	0.704	89
Age	1.03	0.95–1.06	0.897	91
Preop Gleason grade 4 + 3 or greater	1.44	0.67–3.09	0.340	87
Pathological Gleason grade 4 + 3 or greater	1.92	0.92–3.99	0.083	91
Organ confined disease	0.73	0.22–2.36	0.594	91
Pos surgical margins	1.36	0.73–2.52	0.334	91
PSADT at PSA failure less than 3 mos	1.45	0.57–3.57	0.441	60
PSADT before metastasis less than 3 mos	3.01	1.26–7.19	0.016	59
ECOG performance status greater than 1	1.36	0.41–4.50	0.621	75
Presence of pain	2.97	1.45–6.06	0.002	74
Presence of appendicular metastases	1.42	0.65–3.12	0.378	76
Comorbid CAD	1.21	0.42–3.50	0.716	80
Absolute PSA at metastasis 100 ng/ml or greater	1.54	0.67–3.48	0.294	76

TABLE 4

Multivariate Cox proportional hazards models of risk factors for PCSM in men with metastasis after RP

Prognostic Factor	HR (95% CI)	p Value
Model deleting subjects with missing data (53 subjects, 20 deaths):		
Presence of pain at metastasis (yes vs no)	7.9 (2.5–24.7)	< 0.001
PSADT before metastasis (less than 3 vs 3 or more mos)	4.6 (1.7–12.4)	0.003
Model with missing data simulated by multiple imputation (91 subjects, 41 deaths):		
Presence of pain at metastasis (yes vs no)	3.5 (1.6–7.7)	0.003
PSADT before metastasis (less than 3 vs 3 or more mos)	3.4 (1.3–8.5)	0.017