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Management of Patients with Biochemical Recurrence after Local Therapy for Prostate Cancer

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Abstract

Nearly three quarters of a million American men who have been treated with prostatectomy and/or radiation therapy are experiencing an increasing prostate-specific antigen (PSA) level, a condition known as biochemical recurrence (BCR). Post localized therapy, some of these men will develop distant metastases with time, but many years may pass before signs of clinical progression appear. While androgen deprivation therapy remains a reasonable option for some men with BCR, deferring androgen ablation or offering non-hormonal therapies may be appropriate in patients where the risk of clinical/metastatic progression and prostate cancer specific death is low. Drug development in this space is a challenge because of the heterogeneous and prolonged natural history of biochemically recurrent prostate cancer, as well as the lack of short-term, validated surrogate endpoints for overall survival. In this setting, where randomized clinical trials have not provided definitive evidence of improvements in overall survival, a risk-stratified approach, informed by the patient's PSA kinetics, comorbidities and personal preferences, is recommended to determine the best management approach.

Keywords

Rising prostate specific antigen; prostate cancer; hormonal therapy; androgen deprivation therapy; biochemical recurrence

Introduction

Approximately 239,000 men will be diagnosed with prostate cancer in 2013, but 88% of these men will ultimately die from ischemic heart disease, or other non-prostate cancer causes.^{1,2} An estimated 60,000 – 70,000 men are diagnosed in the United States each year with biochemical recurrence (BCR), a state defined as rising PSA following radical prostatectomy or radiation treatment,³ and overall, three-quarters of a million men are estimated to be living with rising PSA following local therapy without evidence of overt metastatic disease.⁴

The optimal management of patients with non-metastatic, hormone naïve, biochemically relapsed prostate cancer remains largely unestablished at this time because of the lack of prospective randomized trials designed to address standards of care.⁵ Treatment decisions

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remain largely intuitive at the present time. Recognizing the deficiency, we will attempt to describe a logical risk-based approach for therapeutic considerations and clinical research in this relatively common subset of patients. Our approach is based on the extensive data on the natural history of these patients at the Johns Hopkins Hospital. We will discuss this and other existing datasets and define potential risk-benefit ratios of existing modalities of treatment.

Definitions of Biochemical Recurrence

The definition of BCR after local therapy varies based on the primary modality of treatment employed. After surgery, PSA levels >0.2 ng/mL or >0.4 ng/mL, and rising are often considered evidence of BCR.³ However, in 2007, the American Urological Association (AUA) reported on a review of more than 13,000 citations referencing biochemical recurrence in prostate cancer patients and found 54 different definitions of BCR following surgery and 99 different definitions of BCR following radiation therapy.⁶ The lack of consistently applied definitions of BCR limits the interpretation of data on natural history and some of the therapeutic considerations in these patients. Such inconsistencies are especially challenging for the interpretation and design of clinical trials.

Biochemical recurrence following radical prostatectomy

Among the 54 definitions of BCR following prostatectomy discovered by the AUA researchers, the most common was a PSA of >0.2 ng/mL or a close variation. The authors, who were also members of the AUA Prostate Guideline Update Panel,⁶ recommended that practitioners use a single definition of BCR after RP as follows:

“It is recommended that biochemical (PSA) recurrence following radical prostatectomy be defined as a serum PSA of 0.2 ng/mL or greater, with a second confirmatory level of PSA of >0.2 ng/mL. The first postoperative PSA should be obtained between 6 weeks and 3 months following therapy. The date of failure should be defined as the date of the *first* detectable PSA level once this value has been confirmed.”

In establishing this recommended definition, however, the panel added two caveats:

1. The higher levels of PSA (greater than 0.2 ng/mL) would have much greater specificity for clinical and/or radiographic recurrence and progression, but the authors justified the use of 0.2 ng/mL by arguing it had “provided high sensitivity for recurrence as well as the greatest generalizability.”
2. This definition is not an effective predictor of death from prostate cancer, suggesting that prognosis should be based on nomograms that consider Gleason score and PSA kinetics, although available nomograms have not been prospectively validated.

The panel acknowledged the appropriateness of reporting biochemical outcomes using additional PSA thresholds. Although some researchers who have designed clinical trials enrolling BCR patients have adopted this AUA definition,⁷ other researchers use 0.4 ng/mL and rising as the eligibility criterion, arguing that the higher value is more specific for future risk of clinical and radiologic progression.⁸ For trial purposes, the authors consider PSA levels >0.4 ng/mL and rising as evidence of BCR after surgery.

Biochemical recurrence following radiation

The AUA researchers found 99 definitions of BCR following radiation therapy, among which the most common was the American Society of Therapeutic Radiology and Oncology (ASTRO) definition: “the mid-point between PSA nadir and the first of three consecutive

risers in PSA.”⁶ Despite a recommendation by the AUA for its adoption, the ASTRO definition is problematic both because it requires backdating the time of biochemical recurrence and because of its failure to use the PSA level at nadir as a risk factor. The Phoenix definition (“nadir + 2 ng/mL, with the failure date defined as the date the rise in PSA is noted”) offers greater accuracy in predicting future clinical failures as compared with the ASTRO definition.^{9–11} However, the Phoenix definition provides substantially lower estimates of BCR at five years and substantially higher estimates of BCR at 10 years than the ASTRO definition.¹² The choice of definition can impact the findings of adjuvant treatment trials; the ASTRO definition would be likely to show a greater number of people experiencing BCR after treatment. The AUA retains its recommendation to use the ASTRO definition of BCR following RT alone (no hormonal therapy), whereas the Phoenix definition can be applied after RT with or without hormonal therapy, and avoids the need for backdating. As a result the Phoenix definition has gained wider acceptance in determining BCR for clinical decisions. Patients whose PSA dynamics meet the Phoenix definition and who have evidence of rapid PSADT may initiate treatment while patients with evidence of slow PSADT may defer further therapy. To ensure comparability with future trial results, it is important to continue to use the Phoenix definition to set criteria for trial entry for patients with BCR after radiation.

Natural history of prostate cancer patients experiencing biochemical recurrence following surgery or radiation therapy

The natural history of prostate cancer patients at Johns Hopkins Hospital (JHH) with evidence of BCR after radical prostatectomy has been extensively reported over the past decade. In 1999, Pound et al. first described the natural history of 304 men who had undergone radical prostatectomy at Johns Hopkins between April 1982 and April 1997, who demonstrated subsequent evidence of BCR (PSA ≥ 0.2 ng/mL), and who did not receive androgen deprivation therapy until there was evidence of metastatic disease. The researchers found that the median time from BCR to metastasis in all patients was eight years and the median time from metastasis to death was five years.¹³ In this report, time to biochemical progression, pathological Gleason score, and PSA doubling time (PSADT, more or less than 10 months) were significant predictors of metastasis-free survival (MFS) over three, five, and seven-year periods. Freedland et al. published a study in 2005 describing cancer-specific mortality of the same Johns Hopkins prostate cancer cohort, with five additional years of follow up. Of 379 patients who had experienced BCR, 66 died from prostate cancer, and the overall median survival had not been reached after 16 years. This analysis uncovered that the same three factors—PSADT (<3 , 3.0–8.9, and 9–14.9, and >15 months), Gleason score (≤ 7 vs. 8–10), and time from surgery to BCR (<3 vs. >3 years)—were significant predictors of prostate cancer specific mortality.¹⁴ In the most recent analysis of this same cohort, Antonarakis et al. provided updated information on the natural history and markers predictive of MFS in an expanded cohort of patients from the JHH database including 450 men with BCR after RP, and reported that median overall MFS was 10 years after BCR (Table 1).¹⁵ However Antonarakis et al. also found that only two of the predictors reported previously were significantly predictive of MFS: PSADT (<3 , 3 to 8.9, and 9–14.9, and ≥ 15 months) and Gleason score (≤ 6 vs. 7 vs. 8–10) (Table 2). In this updated analysis, time to BCR was not a significant predictor of metastasis. Several other analyses identified PSADT as a primary predictor of metastasis free survival and prostate cancer specific mortality (Table 2).

A study published by Zhou et al. in 2005 described the natural history of 498 patients treated with RP at other institutions, including the University of California at San Francisco (the CaPSURE database), military hospitals, and the Virginia Mason Medical Center (the Department of Defense Center for Prostate Disease Research Multicenter National Prostate

Cancer Database).¹⁶ Zhou et al. reported that only PSADT and not time to BCR or Gleason score were significant predictors of time to prostate-cancer-specific mortality. Both continuous and categorical (PSADT <3 vs. >3 months) models confirmed these results. Zhou et al. also studied 661 patients who had undergone primary radiation therapy (RT), and reported that PSADT is a significant predictor of time to prostate-cancer-specific mortality for RT patients in both the continuous and categorical models. Gleason score was also a significant predictor in the continuous model and in the categorical model for Gleason scores of 8–10, but not for lower Gleason scores.¹⁶

Diagnostic evaluation after PSA recurrence

At this time there are no clear-cut guidelines regarding the frequency of follow up, PSA determinations and frequency of imaging procedures. These are dependent on various factors including physicians' routines, patients' requests and other clinical and co-morbid states. The JHH series described above relied on PSA measurement every 6 months in the first year followed by yearly PSAs and bone scans and physical exams which include a digital rectal exam. Patients with rapid PSA doubling times (< 3 months) are seen more frequently than patients with longer PSA doubling times. At JHH, technetium-99m bone scans and CT scans of the abdomen and pelvis are scheduled annually in patients with PSADT >3 months unless there are symptoms to suggest the need for additional work up, except for those in clinical trials where the frequency and type of follow ups are determined by the study. Based on clinical history of the patient, evaluation (endorectal MRI or ultrasound) and possible biopsy of the prostate bed may also be considered if local relapse is suspected on DRE. Potential treatment objectives and therapeutic options, risk stratified by PSADT, are listed in Table 3.

Salvage radiation for biochemical recurrence

Although adjuvant radiotherapy immediately following radical prostatectomy in patients with high risk disease has been shown to reduce the risk of biochemical recurrence in three trials and to lengthen metastasis free survival and overall survival in one of the three trials,^{17–19} there have been no prospective studies of radiation deferred until biochemical recurrence, known as salvage radiotherapy (SRT).

A retrospective analysis of 1540 prostate cancer patients in 17 tertiary care hospitals showed that salvage radiation prolonged the time to PSA recurrence in men with lower Gleason (4–7) scores and increased PSADT (>6 months). These men, with more indolent disease, may have local-only recurrence and are those expected to benefit most from salvage radiation. Men with higher Gleason scores and shorter PSADT also benefited from salvage radiation, but to a lesser degree.²⁰ Paradoxically, a second retrospective study of 635 patients who underwent prostatectomy at JHH suggests that SRT improves prostate-cancer-specific survival only in men with PSADT < 6 months and only if SRT was administered within 2 years from biochemical recurrence.²¹ Although morbidities including gastrointestinal and genitourinary dysfunction are not uncommon, the incidence of severe toxicities reported was low.^{17,22,23} Long term toxicities include urethral strictures and radiation cystitis in approximately 4 to 8% of patients.^{24,25} On the basis of both of these studies, salvage radiation is offered to patients who have PSA recurrence following radical prostatectomy, who have the greatest likelihood of benefit.

Salvage Prostatectomy Post Radiation

Local persistence of prostate cancer is found in 40% to 70% of prostatic biopsies in men who have undergone radiation therapy^{26,27} and 30% to 50% men experience biochemical recurrence following radiation therapy.^{28,29} Local disease growth following radiation has

been associated with decreased time to metastatic progression and increased prostate cancer specific mortality^{30,31} and may also be associated with urological morbidity including hematuria, bladder outlet obstruction and chronic pain.³² Salvage prostatectomy is the only salvage therapy for radiation failure shown to provide long-term cancer control with a 10-year cancer-specific survival of 70 to 77%.^{33,34} The likelihood of benefit from salvage prostatectomy correlates with the original likelihood of cure had surgery been the preferred option. Patients with PSA less than 10 ng/ml show significantly better disease-free progression than patients with higher PSA values.³³ Salvage radiation is indicated only if there is biopsy proven local recurrence without evidence of nodal or distant metastases. Further the Gleason score for the repeat biopsy should be the same or lower than the original Gleason score. A negative post-radiation biopsy, on the other hand, creates clinical uncertainty. Options include clinical trials, ADT, or observation, or more aggressive workup including endorectal MRI and/or MR spectroscopy, or a repeat biopsy.

Due to fibrosis arising from radiation, a high perioperative morbidity is associated with salvage radical prostatectomy with urinary incontinence rate of 32% and major complications including rectal injury or anastomotic injury in 17–32% of cases.²⁹ High levels of morbidity combined with the challenging nature of the procedure mean that highly-experienced surgeons are crucial to success and low morbidity, and the procedure should be considered only for patients without radiographic evidence of metastases, PSA below 10 ng/ml, and favorable pre-radiation characteristics.

Hormonal therapy for biochemically-recurrent prostate cancer

The use of hormonal therapy in treating prostate cancer patients has increased substantially over the past two decades. Between 1990 and 2007, for example, the use of adjuvant ADT has increased 3 to 5-fold with brachytherapy and external beam radiation and high risk patients are increasingly receiving multi-modal therapy, often including ADT.³⁵ For patients with evidence of BCR, however, the impact of androgen deprivation therapy (ADT) on overall survival and quality of life remains unestablished primarily due to the lack of data derived from well-designed controlled trials.²⁵ The evidence available is primarily based on retrospective analyses or extrapolation of studies in distinct patient populations. The CaPSURE database indicates that of 620 men who underwent primary therapy with radical prostatectomy, and of the 430 men who underwent primary therapy with external beam radiation (during the period 1989–2004), ADT was employed as the next salvage therapy for 59% and 93% of the men, respectively.³⁶

Early initiation of ADT is associated with a decline of PSA, frequently below detectable levels, and delayed time to metastases.^{37,38} The impact of early initiation of ADT in patients without evidence of metastasis on overall survival, prostate cancer specific survival and quality of life has not been subjected to randomized controlled trials. A retrospective review of 248 men who had undergone radiation therapy and who experienced biochemical recurrence and had PSADT > 12 months, the use of hormones at time of biochemical recurrence prolonged metastasis free survival. No similar benefit was seen in men with PSADT > 12 months.³⁹ These results were confirmed according to the CaPSURE database from 1988–2002.⁴⁰ A third large retrospective analysis included men treated with ADT treatment at different PSA levels following RP (adjuvant, PSA of 0.4 ng/mL, PSA of 1 ng/mL, and PSA of 2 ng/mL, and at radiographic progression). Adjuvant ADT treatment was associated with a benefit in cancer-specific survival (98% vs 95%, $p = 0.009$) but not in overall survival. That benefit of ADT is lost, however, when ADT initiation was triggered by BCR of 0.4 or 1.0 or 2.0 ng/mL, with non-significant trends showing longer time to metastatic disease and better cancer specific survival for the untreated groups, though that

effect may be an artifact of the patient population in the retrospective analysis.⁴¹ No definitive statements can be made based on the retrospective nature of the analyses.

Three ongoing clinical trials are exploring the timing of adjuvant ADT initiation after following radiation: Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer (RADICALS); the Australian and New Zealand Timing of Androgen Deprivation trial (TOAD, NCT00110162) and the Canadian Early vs. Late Androgen Ablation Therapy trial (ELAAT, NCT0043975) and should provide important information regarding the benefits of ADT in patients with BCR.

Continuous versus intermittent administration of ADT

A second decision arises for patients and their physicians who decide to use ADT: whether to administer ADT continuously or to use a cyclical process called intermittent androgen deprivation (IAD). IAD employs ADT treatment until a maximum PSA response is achieved, and then suspends treatment. ADT is then reinitiated when the PSA reaches a predetermined level, usually between 4 and 10 ng/mL. Intermittent administration of ADT is used in the hope of prolonging time to castration resistance, decreasing acute and chronic side effects for patients who could be on hormonal therapy for extended periods, and minimizing costs.

Two phase III clinical trials, with a total enrollment of more than 2,000 men with biochemically recurrent prostate cancer, have found IAD to be non-inferior to continuous androgen deprivation (CAD) with respect to overall survival. A multi-center, international trial randomized 1,386 men experiencing BCR following RT (with or without prior RP) into IAD and CAD arms. The IAD arm received eight months of ADT followed by withdrawal, and then repeated the 8-month cycle when PSA reached 10 ng/mL. Overall survival for the IAD arm was non-inferior to the CAD arm after a median follow-up of 6.9 years. The IAD arm had more prostate cancer-related deaths (122 vs. 97 deaths) but fewer non-cancer related deaths (134 vs. 146 deaths). Median overall survival was 8.8 years on the IAD arm and 9.1 years on the CAD arm for a hazard ratio of 1.02 (95% CI 0.86–1.21). Testosterone levels recovered during each off-treatment period and bone mass loss, hot flashes, fatigue, and erectile dysfunction were reduced, and libido was increased in the IAD arm.⁴² Based on the lack of difference in overall survival, lower cost, and improvement in quality of life in the IAD arm, the authors recommend that physicians who choose to administer ADT to BCR patients use intermittent androgen deprivation.

A second phase III trial enrolling 425 southern European men with biochemical recurrence and 191 men with metastatic disease, found no difference in overall survival between IAD and CAD. The overall survival hazard ratio for the BCR subgroup was 0.86 (95% CI 0.65–1.14) in favor of CAD but the difference was not significant. For the metastatic subgroup the overall survival hazard ratio was 1.26 (95% CI 0.90 – 1.78), but was also not significant. Better sexual function was reported by men in the IAD arm, however was not reported separately for the BCR subgroup.^{43,44} The role of IAD for metastatic disease was also studied using a non-inferiority design with 1,500 patients (Southwest Oncology Group Study - S9346). In contrast to the European study, S9346 reported an overall survival advantage of 9.2 years for CAD vs. 7.1 years for IAD. However IAD was not definitively shown to be non-inferior to CAD in that study.³⁴ In sum, the use of IAD is not as well supported in metastatic disease as it is in biochemically recurrent disease and the timing and methodology and patient selection for IAD remain controversial.⁴⁵ Further research is exploring the association between ADT outcomes and predictive markers such as PSADT that may help guide treatment.⁴⁶

Concerns about adverse effects of androgen deprivation therapy

Given the long periods of metastasis free survival experienced by BCR patients, they may undergo prolonged treatment with ADT and experience potential long-term side effects. These potential side effects, including sexual dysfunction and loss of libido, memory loss, poor metabolic health,^{47,48} cardiovascular disease,⁴⁹ fracture risk and bone loss⁵⁰ are important considerations in the decision making process on when to initiate ADT, and whether to use intermittent or continuous ADT. Increased rates of diabetes and cardiovascular disease associated with ADT may be explained, in part, by significantly higher rates of poor metabolic health including insulin resistance experienced by men with BCR and/or metastatic prostate cancer who have been treated with ADT for at least 12 months, as compared with age-matched men with BCR not being treated with ADT.⁴⁷ This is not surprising because cross-sectional studies have shown that men with low testosterone have higher prevalence of insulin resistance and in some cases metabolic syndrome after controlling for other risk factors.⁵¹

In 2010, the U.S. Food and Drug Administration asked manufacturers of GnRH agonists to add new warnings to labeling that would alert patients and their health care professionals to the potential risk of heart disease and diabetes in men treated with these medications. A 2006 study by Keating, O'Malley, and Smith confirmed that patients prescribed GnRH agonists experienced increased risk of incident diabetes (adjusted hazard ratio [HR], 1.44; $P < 0.001$), coronary heart disease (adjusted HR, 1.16; $P < 0.001$), myocardial infarction (adjusted HR, 1.11; $P < 0.03$), and sudden cardiac death (adjusted HR, 1.16; $P < 0.004$).⁵²

Drug development endpoints for biochemically-recurrent prostate cancer patients

The heterogeneous and prolonged natural history of BCR and the lack of validated endpoints make drug development challenging for this patient population. Lengthy and highly variable periods of time before metastasis and death mean that the trials often must last for a decade or more before clinically relevant endpoints are reached. While the use of metastasis-free survival as a primary endpoint is most likely a clinically relevant endpoint it has not been shown to be a surrogate for overall survival.⁵³ Clinical trials comparing no treatment or a placebo vs a therapeutic intervention are quite challenging; most patients and physicians are reluctant to continue protocol-assigned treatment (treatment vs. placebo) until metastases develop. Further, researchers are limited by the lack of early biomarkers that are predictive of clinically relevant outcomes. The use of PSA dynamics (such as PSADT, PSA slope, PSA velocity) is of unestablished clinical significance, and is often highly variable as observed even on placebo arms of trials.⁵⁴ In addition, the impact of modulating PSA kinetics on clinically defined endpoints (such as metastasis-free survival) remains uncertain.⁵⁵

Treatment-induced changes in PSADT or other measures of PSA kinetics are even more problematic as endpoints because of the high variability of these measures. In three separate randomized controlled trials, patients on the placebo arms experienced a significant increase in PSADT: 73% of placebo patients experiencing greater than 100% increase in PSADT and 31% experienced $> 200\%$ in a study of rosiglitazone,⁵⁶ 78% of placebo patients experienced a lengthening of PSADT in a study of atrasentan;⁵⁷ and 20% of placebo patients experienced $> 200\%$ increase of PSADT in a study of celecoxib.⁷ For trials involving patients with biochemical recurrence to provide clinically meaningful results, far more information is needed on the natural history and variation of PSADT in that patient population.⁵⁴ Despite these challenges, trials in this patient population can provide important information on drug activity, pharmacokinetics and pharmacodynamics.

The ultimate treatment for BCR patients would be one that delays metastasis and death from prostate cancer without significant morbidity such as those associated with long term pharmacological castration. The long-term impact of shorter courses (6 to 18 months) of ADT combined with other approaches such as immunotherapy, anti-angiogenesis, or novel hormonal agents which aim to eradicate micrometastatic disease are being developed. A currently emphasized potential relevant endpoint is the observation of an undetectable PSA over time following an initial treatment course post-prostatectomy. Although an undetectable PSA has never been shown to be associated with longer metastasis free survival or overall survival, this potential endpoint is being actively evaluated in clinical trials designed to screen potential candidate treatments for subsequent randomized studies in the phase III setting. This novel endpoint is now being used in the design of upcoming trials with androgen receptor targeted approaches that combine GnRH agonists/antagonists with other hormonal agents (e.g., abiraterone, enzalutamide) in an attempt to completely inhibit androgen signaling.

Conclusion

Risk stratification based on PSADT and Gleason score is the primary determinant of metastatic progression and prostate cancer specific mortality and should help determine the frequency of diagnostic evaluation and timing of treatment initiation. From both a clinical and trial design perspective, determination of biochemical recurrence should be made using the AUA definition after prostatectomy and the Phoenix definition after radiation. It is important to emphasize that clinical trials remain the gold standard especially at this time when newer effective compounds and modalities have been approved in patients with more advanced disease.

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Key Points

- Nearly three quarters of a million American men who have been treated with prostatectomy and/or radiation therapy are experiencing an increasing prostate-specific antigen (PSA) level, a condition known as biochemical recurrence (BCR)
- Post localized therapy, some of these men will develop distant metastases with time, but many years may pass before signs of clinical progression appear.
- While androgen deprivation therapy remains a reasonable option for some men with BCR, deferring androgen ablation or offering non-hormonal therapies may be appropriate in patients where the risk of clinical/metastatic progression and prostate cancer specific death is low.
- Drug development in this space is a challenge because of the heterogeneous and prolonged natural history of biochemically recurrent prostate cancer, as well as the lack of short-term, validated surrogate endpoints for overall survival.

Table 1Metastasis free survival after PSA recurrence following radical prostatectomy¹⁵

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

Data From Antonarakis, E. S. et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU international* 2011; 109: 32–39.

Table 2

Selected studies summarizing predictors of the natural history of prostate cancer after biochemical recurrence

Study	N (BCR/ Total# RP and/or RT)	End point (# with M1/ # PCSD)	MFS by PSADT subgroup HR or MFS (95% CI)	PCSM by PSADT subgroup HR or mortality (95% CI)	OS by PSADT subgroup HR (95% CI)	Significant predictors
Primary Treatment: Radical Prostatectomy						
Pound et al., 1999 ¹³	304/1997	MFS (103 M1 pts of 304)	PSADT <10 mo. predictive of MFS (p<0.001)	na	na	PSADT, Gleason score, time to BCR
D'Amico et al., 2003 ⁵⁸	611/5918	PCSM, OS (154 ACD and 111 PCSD for RT +PR)	na	<3 mo. HR 62.9 18.8–210.1 >3 mo. HR 0.61 (0.51–0.73)	<3 mo. HR 18.2 (8.9– 37.2) >3 mo. HR 0.84 (0.78–0.90)	PSADT
Freedland et al., 2005 ¹⁴	379/na	PCSM (66 PCSD of 379)	na	<3.0 mo: HR 27.5 (CI 10.7– 70.9) 3.0–8.9 mo: HR 8.8 (CI 3.7–20.5) 9.0–14.9 mo: HR 2.44 (CI 0.9–6.8) 15.0 mo: HR 1 (ref)	na	PSADT, Gleason score, time to BCR
Zhou et al., 2005 ¹⁶	498/8669 (RT+RP)	PCSM (25 PCSD of 498)	na	<3 mo. PCSM 31% (17– 45%) 3 mo. PCSM 1% (0– 2%)	na	PSADT
Antonarakis et al., 2012 ¹⁵	450/na	MFS (134 M1 pts of 450)	Median MFS: <3.0 mo: 1 mo (CI 0–1) 3.0–8.9 mo: 4 mo. (CI 2–4) 9.0–14.9 mo: 13 mo. (CI 6–>15) 15.0 mo: 15 mo. (CI 15–>17)	na	na	PSADT, Gleason score
Antonarakis et al., 2011 ⁵⁹	346/na	MFS, OS (39 M1 pts of 190 with MFS data) (63 PCSD of 346)	<3 mo: HR 7.77 (CI 2.65– 22.76) 3–8 mo: HR 1.95 (CI 1.04–3.66) 9 mo: HR 1 (ref)	na	<3 mo: HR 27.4 (8.70– 86.38) 3–8 mo: HR 6.16 (3.00–12.64) 9 mo: HR 1 (ref)	PSADT
Primary Treatment: Radiotherapy						
D'Amico et al., 2002 ⁶⁰	94/381	PCSM (20 PCSD of 94)	na	12 mo. predictive of time to PCSD (p=0.003)	PSADT 12 mo. predictive of time to ACD (p=0.02)	PSADT, Delayed use of ADT
D'Amico et al., 2003 ⁵⁸	840/2751	PCSM, OS (154 ACD and 111 PCSD for RT +PR)	na	<3 mo. HR 12.2 (7.5–20.1) >3 mo. HR 0.83 (0.78–0.87)	<3 mo. HR 4.8 (3.4–7.0) >3 mo. HR 0.95 (0.93– 0.98)	PSADT
Zhou et al., 2005 ¹⁶	661/8669 (RT+RP)	PCSM (77 PCSD of 661)	na	<3 mo. PCSM 75% (59– 92%) 3 mo. PCSM 35% (24–47)	na	PSADT, Gleason score
Buyyounouski et al., 2007 ⁶¹	211/1578	MFS, PCSM (53 M1 pts of 211) (29 PCSD on 211)	<3 mo. MFS HR 2.87 (p=0.001) 3 mo. MFS HR 1 (ref)	na	na	IBF alone for PCSM; IBF, Gleason score, PSA nadir, PSADT for MFS

RP = radical prostatectomy, RT = radiation therapy, DM=Distant metastasis MFS = metastasis free survival, PCSD=prostate cancer specific deaths, ACD = any cause death, PCSM = prostate-cancer-specific mortality, M1= metastatic disease, OS = overall survival, PSADT = PSA doubling time, BCR = biochemical recurrence, IBF= interval to biochemical failure, na = not available

Table 3

Potential treatment objectives and therapeutic options for patients risk stratified according to PSADT.¹⁴

	PSADT < 9 months	PSADT > 9 months
Primary Treatment Objectives	Prevent progression and increase overall survival	Delay progression while limiting cumulative toxicity
Treatment Options	<ul style="list-style-type: none"> • More proactive and early implementation of androgen deprivation – intermittent or continuous based on close monitoring of PSA/PSADT. • Clinical trials (with more aggressive approaches) 	<ul style="list-style-type: none"> • Androgen deprivation, preferably intermittent, employed at relatively high thresholds. • Clinical trials (natural compounds, immunotherapy, antimetastatic, targeted compounds, immunotherapy, etc.)