Rising prostate specific antigen (PSA) during follow-up of prostate cancer patients – what to do?

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Introduction

The natural history of a rising prostate specific antigen (PSA) varies strongly with different stages of prostate cancer. The speed of rise has been shown to be indicative of clinical progression at various rates and at various times in the different clinical situations to be described in this article. Therapeutic options vary markedly as to whether a rise of PSA occurs in locally confined prostate cancer managed by potentially curative options such as radical prostatectomy or watchful waiting and, as a sign of progression under endocrine treatment of advanced disease. The present article will address natural history and management options in these conditions.

Watchful waiting

Watchful waiting describes a situation where prostate cancer is diagnosed but treatment is delayed either until progression occurs (delayed palliation) or with the option of applying potentially curative management (active surveillance). Locally confined prostate cancer may have a very slow rate of progression. Over diagnosis defined as the diagnosis of prostate cancer that will never be diagnosed during the lifetime of its carrier is prevalent specifically with the application of PSA driven diagnostic testing. The issue of over diagnosis has recently been reviewed [1]. The European Randomized Study of Screening for Prostate Cancer (ERSPC) offers a unique opportunity to determine the rate of over diagnosis according to variables such as age, frequency of testing and underlying prevalence. This has been done for the Rotterdam section of ERSPC [2].

Rationale for watchful waiting

Ideally, over diagnosed men should be identified and excluded from treatment, this is at present impossible. In the Rotterdam randomized study of screening, men in the age group of 55–75 years are invited and a 4-year interval is applied. The resulting rate of over diagnosis calculated by using the MISCAN technique is 54%. This is related to a lead-time of 10.3 years and a doubling of the lifetime risk (Table 1). Obviously, in this situation it is necessary to apply all available prognostic information to separate those cases that are over diagnosed and therefore may not require treatment.

Table 1
Lead-time and overdiagnosis by screening in ERSPC Rotterdam (after Draisma et al. 2003 [2])

Screening	Mean lead-time, years	Overdetection	
		% of detection	% increase lifetime risk
Single screen test			
at 55y	12.3	27	6
at 65y	9.5	47	38
at 75y	6.0	56	47
Screening with regular interval			
55–67y, annual	12.3	50	80
55–67y, 4-year interval	11.2	48	65
55–75y, 4-year interval	10.3	54	105

In areas where PSA-driven early diagnosis is prevalent such as Northern America and parts of Europe, this should also be reflected in a rising ratio of incidence and mortality of prostate cancer. This is in fact the case. Table 2 shows the incidence and mortality of prostate cancer in different areas of the world [3]. The ratio of 2.0 as reported for Eastern Asia was common in most European countries. In Northern America most likely due to the use of systematic screening, the ratio has risen to 7.6. This indicates that only 1 in 7.6 men diagnosed with prostate cancer is likely to die of this disease.

Table 2
Incidence and mortality of prostate cancer in different areas of the world (Globocan 2002). Ref: www.clip.iarc.fr

	Incidence			Mortality			Ratio Incidence/mortality (ASR)
	Cases (N)	Crude rate	ASR (w)	Deaths	Crude rate	ASR (w)	
World	679,023	21.7	25.3	221,002	7.1	8.2	3.1
Southern Africa	4778	19.3	40.5	2648	10.7	22.4	1.8
Eastern Asia	29,472	3.9	3.8	14,535	1.9	1.9	2.0
Northern Europe	46,974	100.4	57.5	16,771	35.9	19.7	2.9
Northern America	257,943	163.7	119.9	36,447	23.1	15.9	7.6

The natural history of locally confined prostate cancer

A number of observational studies are available which offer long-term observations of the natural course of prostate cancer up to the moment of clinical progression and the institution of palliative treatment [4–8]. All studies have one feature in common: they identify groups of men with extremely low rates of progression (5–15%) over 10–20 year periods in relation to favorable prognostic factors such as low PSA values, a slow rise of PSA and a favorable grade of differentiation or Gleason score. However, up to now these separations are insufficiently accurate for clinical decision making as has been shown by a recent attempt to establish a nomogram for watchful waiting which showed overall accuracy of predicting minimal disease of only 0.64–0.79% (ROC analysis) [9]. Obviously, the development of more accurate prognosticators has top priority in this field. As long as such information is not available, watchful waiting is the only clinical option, which may avoid over-treatment if it can be shown to be safe and acceptable.

The only information on clinical progression of clinically diagnosed locally confined prostate cancer from a randomized study is available through the Scandinavian randomized study of watchful waiting compared with radical prostatectomy (SPG4 study which was recently updated) [8]. Three hundred forty eight patients were randomized to a watchful waiting arm in which treatment was applied only after clinical progression occurred. The rate of systemic progression was 25.4% and 14.9% of the men died of prostate cancer after 10 years with a median follow-up of 8.2 years. Radical prostatectomy produced a modest but significant advantage of 5.3% and 5% in prostate cancer specific and overall mortality. These are the best available data on surveillance with palliative intent.

Active surveillance

In clinical application, PSA can be used as a single determination, for example at the time of diagnosis of progression after radical prostatectomy or as a continuous variable. PSA kinetics are commonly applied as PSA-velocity (PSAV) which is the increase of PSA in ng/mL/year or as the PSA doubling time (PSADT), the reciprocal value of PSA slope. Both options have been used alone or together with molecular sub-forms such as free-PSA (FPSA), or as the ratio of PSA divided by prostatic volume (PSA density, PSAD) to design a predictive nomogram [9]. Prognostic determinants of progression in a watchful waiting situation including PSA and PSA kinetics have recently been reviewed [10]. Six studies of watchful waiting are discussed in this review. Recently important data have been added which are discussed below.

In an early study of watchful waiting applied to 113 patients with a median age of 75 years and a follow-up time of 14 months, McLaren et al. [11] observed that PSA doubling time was a significant predicator of clinical progression (Fig. 1). Approximately 40% of T1 patients and 51% of T2 patients had clinical progression at 2 years increasing to 60% at 3 years. The correlation with PSA doubling time was con-

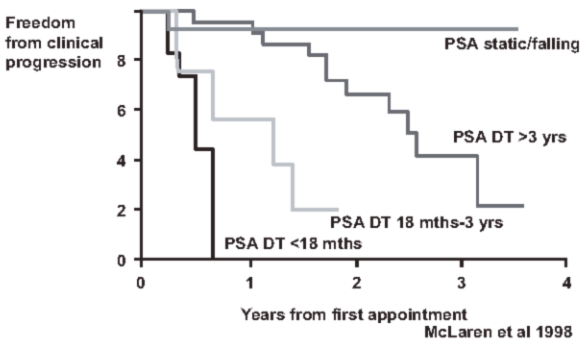

Fig. 1. PSA doubling time as a predictor of disease activity during watchful waiting ($n = 113$) [11].

firmed at multivariate analysis. With a PSADT <18 months 50% of patients progressed within 6 months. This series was collected prior to the clinical use of PSA-driven diagnostic testing. It probably reflects a more advanced state of disease than more recent series. Still, the observations are relevant and seem to be in-line with more recent data.

Choo et al. [12] reported on a watchful waiting study of 231 men who had a 6 month follow-up (median 45) and 3 PSA measurements at least (median 8). Doubling times of less than 2 years, 2–5 years, 5–10 years, 10–20 years, 20–50 years, and more than 50 years were seen in 11.3, 28.1, 18.2, 11.3, 6.9, and 24.5% of the 231 cases. 42% of men had a PSA doubling time in excess of 10 years.

Another recent study showed that a yearly rise of PSA of 2.0 ng/mL prior to radical prostatectomy was a powerful predictor of outcome after radical prostatectomy [13]. Klotz and co-workers [14] calculated that in men with a PSA below 8 at baseline, a PSA velocity of 2.0 ng/mL translates into a PSA doubling time of less than 3 years. They recommended this cut-off value as an inclusion criterion for a large randomized study of watchful waiting.

Carter et al. further investigating 114 prostate cancer cases and 388 men without prostate cancer in the Baltimore longitudinal study of ageing (BLSA) found that a PSA velocity of 0.2 or higher was a strong predictor of prostate cancer mortality 15–20 years earlier [15]. The original observation that PSA increase over time calculated as PSA velocity predicts the development of clinical cancer with poor outcome was reported by Carter et al. [16] again based on data from the BLSA. The group showed that a PSA velocity of 0.75% was predictive of aggressive cancer. Five years prior to the occurrence of an exponential rise however, the subjects with prostate cancer could not be differentiated from controls.

Most recently, the group from Johns Hopkins reported on a prospective study of active surveillance in 281 men of whom 189 had been followed for more than 1 year [17]. By predefined criteria 66 (35%) experienced clinical progression after a median time of 1.6 years, 10 were treated without experiencing progression, prostate cancer deaths were not observed, 18 were lost to follow-up and 93 remained on active surveillance with a median follow-up of 2.8 years. Only PSA velocity and % free PSA with a cut-off of 20% were significant predictors.

The available data clearly do not allow prediction of outcome at the time of diagnosis. However, parameters obtained during follow-up of untreated men with localized disease and favorable prognostic factors provide information that allows to make appropriate treatment choices at the appropriate time. Criteria for applying watchful waiting and follow-up schemes are still subject to discussion. A randomized trial is planned in North America [13].

Prediction of positive bone scans

Bone metastases are rare in men with locally confined disease and low PSA levels. Several studies attempt to quantify this relationship. These studies are important for daily clinical use and, considering the high cost of bone scans, also have significant impact with respect to the cost of care of locally confined cancer under active surveillance. As early as 1993 Oesterling et al. [18] recommended that bone scans should not be carried out with PSA values below 10 ng/mL. Yap et al. studied 244 men with localized disease and a median follow-up of 30 months. In this series, with a PSA threshold of 15 ng/mL the probability of a negative bone scan below this cut-off point was estimated to be 88–100%. The authors could not establish the timing of bone scans if men presented with a PSA of more than 15 ng/mL [19]. Gleave et al. found that of 490 cases of newly diagnosed locally confined prostate cancer only 6% had positive bone scans [20]. A positive bone scan was not found in 290 patients with PSA levels below 10 ng/mL. With PSA levels of 10–20 ng/mL or above 20 ng/mL respectively, positive bone scans were seen in 4.5 and 21% of cases. The risk of a positive bone scan was 8% for men who had PSA values of 20–50 ng/mL. As evidenced by the data, PSA above 20 ng/mL is a poor predictor of a positive bone scan. Dotan et al. [21] evaluated the predictive factors of a positive bone scan after radical prostatectomy. They included pre-operative PSA, time to biochemical progression, pathological findings at radical prostatectomy, PSA directly prior to the bone scan (trigger PSA) and PSA kinetics. The results were incorporated into a predictive model. In the multivariate analysis only PSA slope, PSA velocity and trigger PSA predicted a positive bone scan. The overfit corrected concordance index was 0.93. This highly discriminating nomogram can be used to predict positive bone scans with rising PSA values after radical prostatectomy.

Table 3 gives a summary of some of the relevant reports on relating PSA to positive bone scans in men under observation [22,23].

O' Sullivan et al. [24] concluded from their study of 420 patients, primarily managed by active surveillance, that isotope bone scans are unnecessary in prostate cancer with PSA levels of less or equal

Table 3
Prediction of positive bone scans in men with rising PSA after radical prosatectomy[a]

	Patients with PSA progression	Bone scans (N)		Predictors
		Neg	Pos	
Dotan et al. [21]	414	354	60	PSA slope, PSAV, Trigger PSA (multivariate, nomogram has concordance of 93%)
Gomez et al. [22]	153	34	10	Mean PSA 5.2 versus 30.7 for neg vs pos bone scans (p, 0.001)
Okotie et al. [23]	128	86	11	PSADT < or > 6 mo, 26% vs 3%, PSA ⩽ 10 – **no** positive scans

[a] PSAV: PSA velocity; PSADT: PSA doubling time.

20 ng/mL, stage less than T4 and Gleason score less than 8, unless Gleason score is a major pattern in a Gleason 7 cancer on biopsy. The observations are based on 187 scans of which 67 were positive for metastatic disease [24].

Conclusions on watchful waiting

Watchful waiting needs to be differentiated into delayed palliation, which is usually applied to men who are not eligible for potentially curative management for whatever reason (age, poor health, patient request) and active surveillance. Active surveillance is applied as a measure to prevent over-treatment of over-diagnosed cases in the PSA screening era. While it is certain that over-diagnosis lies in the 50% range if PSA-based detection regimens are applied, patients falling within this group of over-detected cases cannot be safely identified. Follow-up regimens utilizing biopsy-related prognostic factors and PSA kinetics are therefore used for the follow-up of these cases with the goal of applying potentially curative management if signs of progression occur (active surveillance). Such regimens are evaluated within prospective phase II studies, a large phase III study is planned in North America. For the time being, the risk taken by applying watchful waiting to men with low risk prostate cancer seems to compare favorably with the risks of over-treatment in this group of men.

Rising PSA after radical prostatectomy or radiotherapy

A rise of PSA to a confirmed value of 0.1 or 0.2 from previously non-measurable levels is generally considered as PSA progression after radical prostatectomy. After radiotherapy, the so-called ' ASTRO criteria' are applied. These require 3 consecutive rises of PSA to establish PSA progression. The date is then found by backdating to the second of the series of 3 rising PSA values.

The natural history of a rising PSA after radical prostatectomy

The study by Pound et al. [25] gives detailed information on the time to different steps of progression with a rise of PSA after radical prostatectomy. The median time from PSA progression to metastatic disease was 96 months in 34% of all patients who experienced this event. The time for metastases to death amounted to 60 months. PSA doubling time, Gleason score and time to PSA recurrence were significant prognostic factors.

Table 4 reviews recent reports on biochemical progression-free survival 5 and 10 years after radical prostatectomy and radiotherapy. In these series, 10-year progression rates are in the range of 32 to 60%. More recent data reported from radical prostatectomy series are more favorable, as a multicenter international validation study of the preoperative nomogram for prostate cancer recurrence after radical prostatectomy has shown [26].

Table 4
Biochemical failure after radical therapy for clinically localised prostate cancer

	Biochemical progression-free survival, %	
	5-year	10-year
Radical prostatectomy		
Pound et al. [25]	80	68
Amling et al. [27]	76	59
Radiotherapy		
Middleton et al. [28]	32–93	40–64
Shipley et al. [29]	66	–

Management of a rising PSA after potentially curative treatment

The extremely long natural history from a rise of PSA to metastatic disease and potential death as well as the low rate of these events in untreated men again seems to encourage a policy of delayed treatment.

However, the issue of early versus delayed treatment in this particular group is unresolved. Recent randomized studies using the anti-androgen bicalutamide in an adjuvant setting after radical prostatectomy suggests an advantage in terms of time to progression in the active treatment group [30,31]. Whether these differences will translate into advantages in cancer specific and overall survival remains uncertain at this time. Considering the natural history of the disease and the selection criteria applied, the difference between placebo and bicalutamide treatment is bound to be very small and to require a very long observation time.

Several studies have addressed the issue of radiotherapy applied to men with a rising PSA after radical prostatectomy. Unfortunately, a randomized study is not available. Delay of treatment until a palpable lesion is present seems to lead to poor results of radiotherapy. Imaging studies fail to diagnose recurrences at a sufficiently early stage. On the other hand, applying radiotherapy in men with a rising PSA without having strong evidence for a local recurrence will necessarily include men who do not have a local recurrence but who suffer from distant metastases leading to a rise of PSA. Obviously, in these men radiotherapy will be applied without scoring the desired success while the patient will still be confronted with the side effects of radiotherapy.

Recently a large multicentre study of radiotherapy in men with a rising PSA after radical prostatectomy was reported [32]. Five hundred and one patients were recruited from five different centers. The outcome was studied after a median follow-up of 45 months. Two hundred and fifty patients (50%) experienced disease progression, 10% developed distant metastases and 4% died of prostate cancer. The 4-year disease-free probability was 45% (95% confidence intervals 40%–50%). A careful analysis of predicators of disease progression was carried out. The results are summarized in Table 5

Missing table: 5!. A high Gleason score, a surprisingly low PSA value of more than 2 ng/mL, positive surgical margins, seminal vesicle invasion and a PSA doubling time equal or less than 10 months were significant predictive factors. In this study, the median time to PSA progression after radical prostatectomy was only 2.2 years. This is different compared to longer median times to progression observed by other authors. Van den Ouden et al. [33] found an average time to PSA progression of 58 months. The short time of PSA progression in-line with the findings of Pound et al suggests that a considerable proportion of men included in this multi-center study may have suffered from occult metastatic disease which is present at the time of radiotherapy associated with a faster and earlier rise of PSA. The results of the multi-center study will obviously be influenced strongly by patient selection.

Endocrine treatment is another option which is frequently applied. Very long treatment periods result and the long-term side effects are largely unknown [34]. Still endocrine treatment is indicated in symptomatic patients. Symptoms may include the anxiety resulting from the knowledge of a rising PSA. Here lies an important task for the treating urologist and physician in explaining the potential long duration of the natural history of a rising PSA. Men who present with a Gleason score of 7 or higher, PSA recurrence earlier than 2 years after radical prostatectomy or a short postoperative PSA doubling time may be candidates for early endocrine management. D' Amico et al have shown that a PSA doubling time as short as 3 months was significantly associated with prostate cancer-specific mortality. With respect to PSA doubling times of more than 3 months, a hazard ratio of 19.6 with 95% confidence intervals of 12.5–30.9 was found [35]. The author in his own practice would consider endocrine treatment in men with a PSA doubling time of less than 2 years.

There is an urgent need to find surrogate endpoints for locally confined prostate cancer in order to facilitate future studies. These are seriously hampered by the long duration of follow-up which is necessary to reach major traditional endpoints such as prostate cancer specific and overall survival. Recently a study of PSA as a potential surrogate endpoint was undertaken. Unfortunately, using the meta-analytic approach to this problem, surrogacy of PSA could not be established [36].

The only comparative study of early endocrine treatment versus delayed endocrine treatment in men with a rising PSA after radical prostatectomy carried out in 1352 men does not show an advantage in metastases-free survival after a follow-up up to 10 years [37]. Once again, this is an observational and not a randomized study.

Conclusions, rising PSA after potentially curative management

The natural history of a PSA rise after radical prostatectomy is well understood. On average it takes as long as 8 years to the occurrence of metastatic disease and 3 years to death of prostate cancer, which will only occur in a fraction of these men. Unfortunately, randomized studies establishing either radiotherapy or endocrine

treatment in this setting are unavailable. Prognostic factors can be used to predict those men at increased risk of metastatic progression and death. These include PSA kinetics, prognostic factors obtainable prior to treatment and the time from radical prostatectomy to the rise of PSA. Endocrine treatment will delay clinical progression; an effect with respect to prostate cancer-specific and overall survival has not been established. The potential side effects of long-term treatment need to be matched against the potential advantages of delaying metastases. Adverse prognostic factors and symptoms should provide indications for endocrine treatment. The role of radiotherapy remains dubious in spite of recent evidence from a multi-center study. If one follows the results of this study, radiotherapy should be applied to men who have a rising PSA below 2.0 ng/mL [31].

Rising PSA under endocrine treatment

A rising PSA under endocrine treatment indicates progression to hormone unresponsive disease. In a large randomized study, death occurred in 70% of men who had PSA progression after a median time of 1.98 years [38]. In the same study confirmed or unconfirmed doublings of PSA above nadir, an unconfirmed rise of 100%, as well as a 50% and 20% rise were all significant predictors of survival. Sensitivity and specificity cut-offs are given. However, surrogacy could not be established. Treatment of progression to hormone unresponsive disease will be dealt with elsewhere in this chapter. The critical decision is whether to apply taxane-based chemotherapy early before the occurrence of symptomatic metastases.

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