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CLINICAL INVESTIGATION **Prostate**

PSA DOUBLING TIME KINETICS DURING PROSTATE CANCER BIOCHEMICAL RELAPSE AFTER EXTERNAL BEAM RADIATION THERAPY

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Purpose: To investigate whether prostate-specific antigen PSA doubling time (PSADT) is constant in men with biochemical prostate cancer relapse after external beam radiotherapy (EBRT).
Methods and Materials: A total of 513 men treated radically with EBRT, with or without androgen ablation (AA), between 1993 and 2000, developed biochemical relapse. The slope of the ln (PSA) vs. time graph is calculated for the first two values after PSA nadir (first slope), the last two recorded PSAs (last slope), and all values excluding the first and final PSA (mid slope). Differences in these slopes were compared statistically with subgroup analysis for AA and secondary intervention.
Results: For men treated with EBRT and AA first slope was faster than either mid slope ($p = 0.031$) or last slope ($p < 0.001$). Men treated with EBRT alone had no change in PSADT over time unless they subsequently received secondary intervention. This group had a more rapid last slope compared with mid slope ($p < 0.001$).
Conclusions: PSA initially rises more rapidly after AA cessation, probably because of testosterone recovery. A subgroup of patients, who received secondary intervention after treatment with radiotherapy alone, showed a change in PSADT, to a faster velocity. This greater than constant exponential PSA growth is presumably the catalyst for secondary intervention. Otherwise, PSADT did not change during prostate cancer biochemical relapse. **© 2005 Elsevier Inc.**

Prostate cancer, Prostate-specific antigen, PSA doubling time, Biochemical relapse, Radiotherapy.

INTRODUCTION

Prostate-specific antigen (PSA) monitoring is integral to the follow-up of patients after either external beam radiotherapy (EBRT) or radical prostatectomy (RP). PSA rise is associated with both local and distant recurrence, but it is often not initially possible to find evidence of either. The interpretation of an increasing PSA is therefore difficult.

PSA doubling time (PSADT) is a useful prognostic variable (1). A fast PSADT is associated with distant recurrence and prostate-specific mortality and it has been suggested that PSADT itself could be used as a surrogate end point for mortality (2).

After the PSA level has started to rise, it has been assumed that its increase is exponential with a constant rate over time, and that PSADT is therefore constant. There are few published data to support this.

Patients treated with medical androgen ablation (AA) attain a lower PSA nadir post-EBRT. When AA treatment is stopped, the testosterone increases over a variable period. After stopping lutenizing hormone releasing hormone analogue (LHRH) treatment, 93% of patients reach a testosterone level of 5 nmol/L (135 ng/dL), 80% of them within a year (3). This may lead to a "testosterone bounce," an often rapid but self-limiting increase in PSA not associated with metastatic disease. Unfortunately, this can occasionally fit published criteria for biochemical relapse (4).

In radical prostatectomy specimens, tumor volume is loosely correlated with serum PSA (5). It is not clear after EBRT whether the level of PSA remains a direct measure of tumor bulk. *In vitro*, exponential growth of tumor is uncommon and doubling time often slows progressively in a Gompertzian fashion, presumably because of the tumor outgrowing its nutritional supply as it grows (6). Patel *et al.* compared the slope of the ln (PSA) vs. time graph using the first two PSA values after radical prostatectomy, with the

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slope using at least 4 PSA values. The PSADT appeared to be faster over the earlier period, suggesting a nonconstant exponential growth (7).

Conversely, it is clear that the PSADT is faster in the context of metastatic disease (1). It is conceivable that, as local disease spreads and metastatic foci grow, the PSADT might speed up sharply.

In trials of systemic therapy for prostate cancer, only a small proportion of patients has measurable disease either clinically or radiologically. An alternative to the conventional end points (complete response, partial response, stable disease, and progressive disease) is therefore needed. It has been suggested that a 50% decrease in PSA would be a useful endpoint (8), but a decrease in PSADT alone has been used to assess response with less active agents. It is therefore important to characterize the natural history of PSADT in prostate cancer relapse.

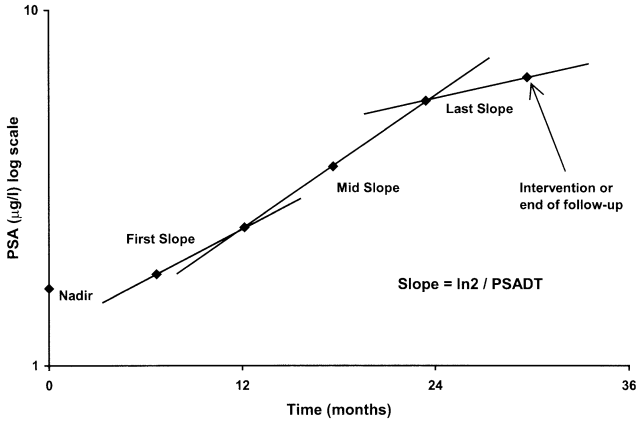

Fig 1. Schematic graph of In (PSA) vs. time to illustrate calculations for first slope, mid slope, and last slope. PSADT = prostate specific antigen doubling time.

METHODS AND MATERIALS

The British Columbia Cancer Agency Prostate Cohort Outcomes Initiative prospectively records the serial PSA values of 1,838 men treated with radical EBRT between June 1994 and January 2001. All patients give written consent to undergo treatment.

Patients are seen every 6 months for 3 years after completion of EBRT, then annually. A digital rectal examination is performed at each visit and a PSA blood test taken (Abbott Laboratories, Montreal, Quebec, Canada; MEIA polymonoclonal sandwich until 1997, mono-monoclonal sandwich since 1997). PSA blood results from outside laboratories are also obtained retrospectively. Men with a rising PSA or suspicion of relapse clinically are investigated as appropriate, including prostate biopsy, computed tomography scanning, or bone scans.

A proportion of men considered to be at "high risk" receives a combination of neoadjuvant, concurrent, and adjuvant AA therapy. This includes patients with one or more adverse features (PSA >15, Gleason sum ≥ 7, T3 or T4 tumors). The duration of AA has increased stepwise over the period.

For the purpose of this study, patients are considered to have had a biochemical relapse if they satisfy either the Vancouver or American Society for Therapeutic Radiology and Oncology (ASTRO) definitions for biochemical relapse. These are:

- Vancouver: At least two consecutive rises with at least one PSA value ≥ 1.5 ng/mL, with the relapse timed at midway between the last nadir and the first of the two rises. Additionally, relapse is scored if a patient receives therapeutic intervention (9).
- ASTRO: At least three consecutive rises, with relapse being timed at midway between the nadir and the first of the three rises. In addition, any secondary therapeutic intervention is scored as a relapse at the time of intervention (4).

Men whose PSA does not reach a nadir <4 are assumed to be refractory to primary radiotherapy treatment and are not included in the analysis.

In this analysis, PSA values are used from the first after the nadir until the last before further oncologic intervention. This might be in the form of androgen suppression or palliative radiotherapy. For those remaining on follow-up with no further treatment, all PSA values, including the most recent, are used. The second of two PSA recordings less than 2 months apart is excluded.

Least squares regression analysis is used to calculate the slope of the ln (PSA) vs. time graph and PSADT is calculated using the formula:

$$\text{PSADT} = \text{In } 2/\text{Slope} \quad (1)$$

Three pairs of slope and PSADT are calculated:

- the first two PSA values after nadir (first PSADT and first slope)
- The last two PSA values available, or before intervention (last PSADT and last slope)
- All PSA values excluding the first point after nadir and the final available PSA (mid PSADT and mid slope)

This method is shown in Fig. 1.

Men require at least three eligible PSA values to calculate first slope and last slope and be included in the analysis.

Statistical analysis

First slope, mid slope, and last slope are compared using a paired samples *t*-test for the hormone- and non–hormone-treated groups separately.

Whether the patients have a secondary intervention is analyzed as a subgroup.

RESULTS

Of 1,838 patients treated with EBRT between June 1994 and January 2001, 705 (38%) had a biochemical relapse defined either by the Vancouver (623) or ASTRO (616) criteria. Twenty-eight patients were excluded because of primary treatment failure and 164 (23%) of these men had less than three PSA values after their nadir, leaving 513 patients for analysis in the study. For 114 patients with three PSA values, only the first and last PSADT and slope can be calculated. This is summarized in Fig. 2. The median number of PSA values post nadir for analysis is five.

The median age of the study patients was 71 years, and their mean age was 70.4 years. The pretreatment staging