Biochemical failure: role for early hormonal therapy

C.L. AMLING
Naval Medical Center, San Diego, California, USA

PSA-only recurrence is a common problem in prostate cancer, with an estimated 30 000–60 000 cases presenting each year. A PSA-only recurrence is defined as the reappearance of significant PSA levels after radical prostatectomy or radiation therapy; however, the levels required to diagnose PSA-only recurrence vary among institutions and range mostly from 0.2 to 0.4 ng/mL. Extensive clinical review has prompted suggestions of using a 0.4 ng/mL as the threshold [1].

However, not all detectable PSA levels indicate clinically relevant disease. Often PSA levels are increased at the margins and apex, or in benign prostatic tissue after radical prostatectomy, while detectable urinary levels have been found in patients undergoing radical retropubic prostatectomy or from ectopic (urethral, bladder, spleen, perivesical) prostatic tissue. In the case of radiation therapy, the ASTRO definition of PSA failure is used [2], although the nadir PSA level is also a good indicator of success or failure, with recommended reference values of <0.2–0.5 ng/mL [3].

When a patient develops a PSA-only recurrence it should first be determined whether it is a local or distant recurrence. Standard imaging techniques are often of little use in reliably diagnosing localized tumours in the pelvis or other localizations. ^{111}In-capromab pendetide-based ProstaScint® scans are also rarely useful, although some studies suggest that they may better predict responses to radiotherapy [4]. Other variables used to establish the significance of a PSA-only recurrence include the time to recurrence (within or after 1–2 years) and the rate of change of PSA. The Center for Prostate Disease Recurrence (CPDR) data show that disease-free survival markedly differs in patients with a PSA-doubling time of > or <12 months (Fig. 1). Overall, the main factors that help to distinguish between local and distant recurrences are summarized in Table 1.

For the use of radiation therapy after radical prostatectomy, most studies support waiting until there is an increase in PSA. The results from a major South-west Oncology Group (SWOG) trial that may help to clarify the issue of immediate postoperative vs delayed radiation at the time of PSA recurrence are pending. For those who receive salvage radiotherapy for PSA recurrence, studies seem to suggest a positive role for radiation therapy with doses of at least 6600 cGy, and treatment is more effective at the lowest PSA levels (Fig. 2) [5].

Hormonal therapy has been suggested as one treatment approach for PSA-only recurrence, but no definite information on timing is available, and decisions should be balanced with quality-of-life considerations. Pros and cons for early and delayed hormonal therapy have been proposed; few trials have shown a survival benefit for early treatment, while major trials have shown no benefit. However, a major Medical Research Council (MRC) study showed a benefit of early hormonal therapy in preventing overall and prostate cancer-related death in men with advanced prostate cancer (Fig. 3) [6]. Early treatment was also associated with reduced risks for spinal cord compression, ureteric obstruction, extraskeletal metastasis and requirements for TURP (Fig. 4) [6].

Local	Distant
Gleason score <7	Gleason score >7
Seminal vesicles negative	Seminal vesicles positive
Nodes negative	Nodes positive
PSA >1 year	PSA <1 year
PSA velocity <0.75 ng/mL	PSA velocity >0.75 ng/mL
PSA doubling >6 months	PSA doubling <6 months

TABLE 1
Local vs distant recurrence; the main indicators

FIG. 1. Progression to metastatic disease in relation to PSA doubling time according to the CPDR database.

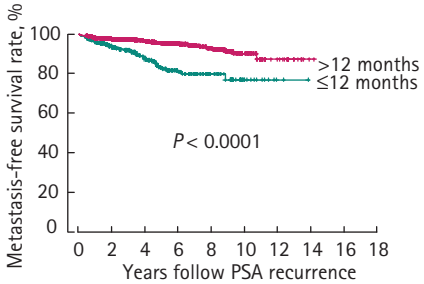


FIG. 2. Cumulative disease-free survival after radiation therapy in patients with PSA levels of > or <2 ng/mL. Reproduced with permission from [5].

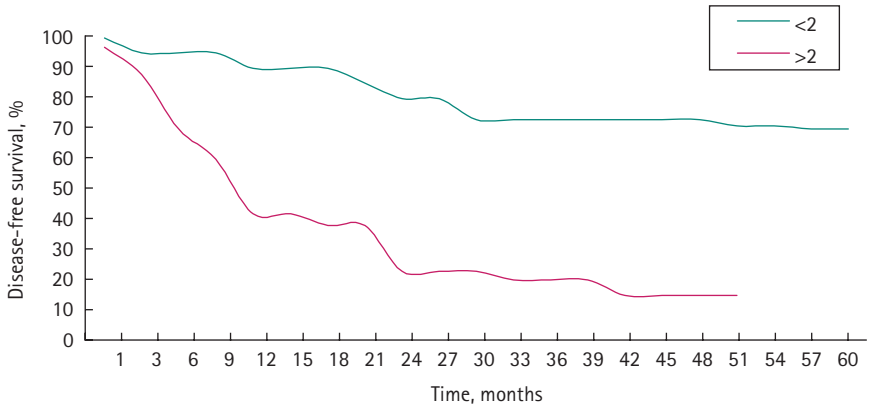


*FIG. 3. All-cause and prostate cancer-related deaths (top) and cumulative disease-free survival (bottom) in patients receiving immediate or delayed hormone therapy *P < 0.01 and P < 0.001 vs immediate treatment. Reproduced with permission from [6].*

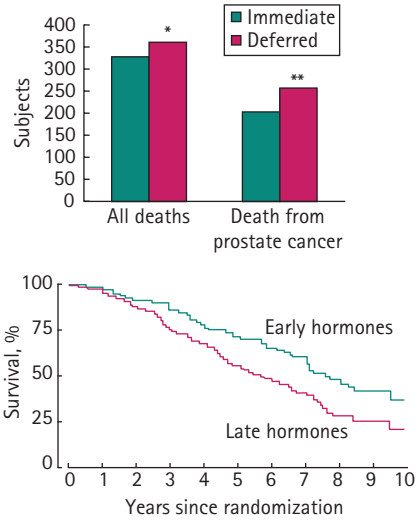
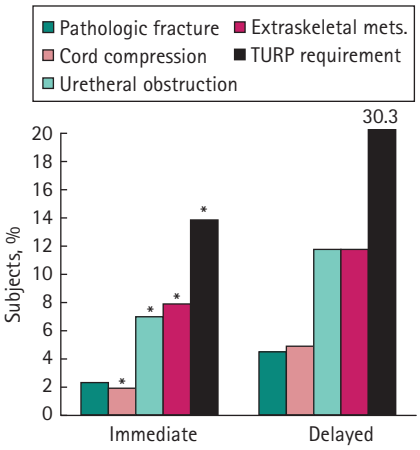


*FIG. 4. The incidence of complications in patients receiving immediate or delayed hormone therapy. *P < 0.05 vs delayed treatment. Reproduced with permission from [6].*



REFERENCES

1 **Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H.** Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? *J Urol* 2001; **165**: 1146–51

2 **American Society for Therapeutic Radiology and Oncology Consensus Panel.** Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997; **37**: 1035–41

3 **Critz FA, Levinson AK, Williams WH, Holladay CT, Griffin VD.** Holladay DA. Prostate specific antigen nadir achieved by men apparently cured of prostate cancer by radiotherapy. *J Urol* 1999; **161**: 1199–203

4 **Kahn D, Williams RD, Haseman MK, Reed NL, Miller SJ, Gerstbrein J.** Radioimmunoscintigraphy with In-111-labeled capromab pendetide predicts prostate cancer response to salvage radiotherapy after failed radical prostatectomy. *J Clin Oncol* 1998; **16**: 284–9

5 **Forman JD, Velasco J.** Therapeutic radiation in patients with a rising post-prostatectomy PSA level. *Oncology* 1998; **12**: 33–9

6 **The Medical Research Council Prostate Cancer Working Party Investigators Group.** Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. *Br J Urol* 1997; **79**: 235–46

Correspondence: C.L. Amling, Naval Medical Center, San Diego, California, USA.
e-mail: clamling@nmcsd.med.navy.mil