What Does Failure After Surgery or Radiation Mean?

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Abstract

Objective: The accurate definition of what constitutes treatment failure after surgery and radiotherapy for localised prostate cancer is critical to patient management. The current post-radiotherapy (post-RT) standard is the 2006 ASTRO definition of an increase of 2 ng/ml above the nadir level. After radical prostatectomy (RP) one definition is the detection of prostate-specific antigen (PSA) at or above 0.2 ng/ml following surgery, although some might argue that any detectable PSA is a sign of treatment failure.

Diagnosis and Treatment: The localisation of the origin of the PSA rise is difficult, and imaging and/or biopsy is often unhelpful. Postsurgical recurrence is present in the pelvis in a significant proportion of patients. Prostate/seminal vesical biopsy can be helpful in the post-irradiation setting, but the utility of cross-sectional imaging of the primary site is limited. PSA kinetics can be helpful in identifying aggressive disease, but PSA bounce must be considered, particularly after brachytherapy and high dose RT. Treatment responses are seen in patients, particularly when the PSA is <0.2 ng/ml and the interval to PSA failure is >18 months, but side effects can be significant.

Conclusions: The natural history of progression after failure is often prolonged. Most importantly, a significant number of men who fail treatment will not die of prostate cancer. This should be borne in mind when considering salvage therapy to the primary with interventional procedures, or systemic treatment with adjuvant hormonal and/or other therapies. Treatment can help some patients, but there is considerable associated morbidity in many cases. In the post-treatment failure scenario, it is critically important to consider the risk–benefit ratio for individual patients.

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1. Defining treatment failure

The critical answer to the question lies in the definition of treatment failure, because subsequent management of patients is predicated on this. It is therefore of fundamental importance that clear definitions are established to plan therapy and to interpret the outcomes of salvage treatment. Only
when the treatment failure has been defined and the nature of that failure determined as accurately as possible it is possible to direct therapy appropriately and safely.

1.1. **Biochemical failure after RT**

Prostate cancer is usually a slowly progressive disease. In this specific patient population, there are various competing causes of death, and biochemical failure per se is not always associated with clinical symptoms or cancer-specific mortality. Many attempts have been made to define biochemical failure after radical prostatectomy (RP) or radiation therapy (RT). Whilst this approach is a useful aid to clinical decision making, it has proved difficult in practical terms to define treatment failure precisely and universally, particularly in the early stages of prostate cancer progression. The reason for this difficulty lies in the differing effects of surgery and RT on post-treatment PSA levels and the idiosyncratic effects of the PSA after different types of RT, notably the "PSA bounce" effect after brachytherapy and high dose RT.

The old definition of PSA failure followed the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus conference of 1996, in which it was agreed that failure was defined as three consecutive rises in PSA after a nadir, with the date of failure being the point half way between the nadir date and the first rise, or any rise great enough to provoke initiation of salvage therapy. Because of problems with this definition, particularly the non-comparability of survival estimates based on different follow-up periods and a failure to link the criteria to clinical outcomes, a second ASTRO consensus conference re-defined biochemical failure following RT, publishing the "Phoenix definition" [1]. This definition defines failure after external beam RT as "an increase of 2 ng/ml or more above the nadir PSA (ie, the lowest PSA reached following treatment). The data used to arrive at this definition suggest that there is a sensitivity and specificity of 66% and 77%, respectively for predicting clinical failure at 10 yr. Patients who undergo salvage therapies without meeting the PSA failure definition should also be counted as failures at the time of positive biopsy or salvage treatment, whichever is first. A further recommendation is that control rates are quoted 2 yr before the median follow-up to avoid the reporting artefacts. Ongoing research and treatment protocols have now adopted this definition as the standard for post-RT treatment failure after external beam RT.

1.2. **Defining failure after surgery**

The definition of PSA failure after radical prostatectomy differs by virtue of the fact that the prostate is removed; theoretically, there should be no residual PSA in the absence of local residue/recurrence or metastatic disease. In a recent review of the published definitions of biochemical recurrence after surgery and RT by the American Urological Association (AUA) guideline panel [2], recommendations for a standard definition in patients treated with RP were suggested. This review followed the realisation that there was no clearly agreed definition of biochemical recurrence after surgery. Of 436 papers dealing with clinically localised T1–2 disease that were analysed, 145 papers contained 53 different definitions of biochemical recurrence following RP. The AUA panel recommended defining biochemical recurrence as an initial serum PSA ≥ 0.2 ng/ml, with a second confirmatory level of PSA > 0.2 ng/ml. Although this definition has been adopted by the AUA, it is not universally recognised at the present time.

2. **Differentiating local recurrence from metastatic disease**

In the setting of a rising PSA following treatment, it is often difficult to be sure whether the rise in the tumour marker is a consequence of local or distant failure. In the case of RT, it is possible to biopsy the prostate; this approach has proven to be of value in some circumstances, both in directing treatment and in ascertaining prognosis [3]. However, after RP, local biopsy is of limited value. The positivity rate can be as high as >50% in some reports [4], but most practitioners do not find this procedure to be helpful, because a negative biopsy creates uncertainty, usually resulting in treatment and a positive biopsy would trigger a decision to treat in any case. Post-RP treatment with RT is therefore directed to the pelvis on the basis that it is the most likely source of the measured PSA. Long-term follow-up of the Southwest Oncology Group (SWOG) 8794 study bears out this approach to a degree: 10-yr follow-up confirms the relatively high rate of biochemical control in patients with a PSA below 0.2 ng/ml [5].

One of the more helpful predictors of biochemical failure after radical prostatectomy is the interval to biochemical failure after RP. A study of post-RP patients with PSA failure showed that an interval to biochemical failure (IBF) of <18 mo was the only predictor of prostate cancer-specific mortality (PCSM) [6]. In this report, the actuarial 5-yr
disease mortality rate for an IBF of <18 versus >18 mo was 52% versus 20%, and the actuarial PCSM rate was 36% versus 6%, respectively. The authors concluded that the IBF is an important discriminator of PSA kinetics after RT in identifying local versus distant disease.

3. Implications of PSA kinetics and PSA bounce

PSA doubling time (PSADT) has been reported to be an important post-treatment predictor of distant disease [7] and prostate cancer death; this parameter is thought to reflect the biology of the prostate cancer. There is a gathering body of literature on this subject. In a recent review [8] of all articles on PSADT published after 2000 that looked at this situation, six studies with the largest and best-documented cohorts of patients treated with surgery or irradiation were analysed. The results showed that PSADT was the most effective parameter for identifying patients at significant risk for mortality specific to prostate cancer, and that PSADT was a reliable predictor of prognosis. However, it is accepted that prospective validation is needed to optimise its use and to determine specific cut points in determining prognosis.

One effect that can mimic an adverse PSADT or that may be considered PSA relapse according to the current ASTRO criteria is PSA “bounce.” This term refers to the phenomenon whereby the PSA exhibits a transient and often late rise, usually in association with brachytherapy or high dose RT. In a recent study of 295 patients treated with brachytherapy, 49% exhibited a transient PSA rise of >0.2 ng/ml; the mean time to “bounce” was 18 mo [9]. This finding emphasises the need for cautious interpretation of PSA kinetics in this population.

4. The natural history of progression after PSA recurrence

The first important paper studying PSA recurrence [10] showed that men who had PSA relapse after prostatectomy and had no additional intervention had a mean actuarial time of 8 yr to the development of metastasis and, thereafter, a period of 5 yr to death. The natural history of the disease, therefore, is relatively long for many men in this age category. Further study of this phenomenon is facilitated by additional data from this and other US groups looking at the actual outcomes in patients undergoing RP [11–13]. These case series show that not all of the patients undergoing surgery and developing subsequent PSA relapse go on to manifest clinical problems or die from their disease. In the first study [11], the number of men who developed PSA relapse and/or metastasis at 5 yr was 16% and 4%, respectively; only 1% suffered a prostate cancer death. At 10 yr the PSA failure and metastasis rate were 26% and 10%, respectively, with only 4% going on to die specifically of the disease. In the second series [12], which looked at an earlier cohort of patients, the 10-yr PSA, metastasis, and cancer-specific death figures were 48%, 18%, and 10%, respectively. Similar data have also been reported by another large US group [13], who found that in patients undergoing RP the 5-yr PSA failure rate was 41%, but clinical failure was seen in only 16%. It is clear from these data that, in the 10 yr following prostatectomy and PSA relapse, about 35% will develop metastases, but only about 20% will die specifically of their prostate cancer.

The published figures for failure following RT are difficult to compare with those seen with surgery because of the inevitable differences in clinical and pathological staging and the more widespread use of neo- and adjuvant hormonal therapy. The results for RT tend to have the appearance of being slightly worse stage for stage compared with those RP; whether these results are true is uncertain. In a report studying treatment failure in patients treated under the aegis of the Radiation Therapy Oncology Group (RTOG) 86-10 study [14], the overall 5-yr freedom from failure and overall survival rates after RT were 69% and 90%, respectively. In patients with locally advanced disease, results for biochemical failure, development of metastases, and cancer-specific death at 8 yr for RT alone and RT plus 4-mo androgen-deprivation therapy (ADT) were 90% and 76%, 45% and 34%, and 31% and 23%, respectively [15], confirming the facts from the surgical series that PSA relapse does not necessarily equate to metastasis and cancer-specific death in many of the patients. The median time to PSA relapse in this series is between 20 to 24 mo, with death occurring about 5 yr from the time of PSA failure. It is important to be aware that figures quoted from all these series are from an older cohort, and in some cases, from practice carried out in the pre- or early-PSA era. The current day actuality may be even lower in more recent practice when the lead time effects on natural history arising as a consequence of screening and early detection is considered [16].
5. Salvage therapy following primary radiation failure

A full review of the various salvage therapies is beyond the scope of this article; however, there is a worrying lack of level 1 evidence from randomised trials in this field.

Salvage radical prostatectomy is an option for selected patients; the authors of some expert groups consider the morbidity profile to be “acceptable” [17], although scrutiny of the results confirms a relatively high complication rate. Similarly, salvage cryotherapy is successful in establishing biochemical control, especially in recurrent low-risk patients, but success measured as patient survival is very disappointing, being as low as 11% in high-risk groups. The morbidity of the procedure is significant, with 13% incontinence, 4% chronic perineal pain, and a small but significant rectal fistula rate [18].

Whatever salvage therapy considered, the morbidity associated with treatment is considerable. A review of all series of post-RT therapies, including salvage prostatectomy, cryosurgery, and brachytherapy from 1990 onwards [19], confirmed this morbidity unequivocally. Urinary incontinence was greater after salvage prostatectomy (41%) or cryosurgery (36%) than after brachytherapy (6%), but 17% of brachytherapy patients had a risk of grade 3 or 4 genitourinary complications. Furthermore, the rectal fistula risk averaged 3.4% across all series. Rightly, the authors conclude that “prospective randomized studies are needed to determine the relative efficacy of the 3 major local salvage modalities” and that this parameter should be allied to an estimation of the risk–benefit ratio.

6. The case for immediate versus early salvage treatment post-RP

The current management of patients with PSA failure or high-risk features after RP is uncertain, as exemplified by the variation in practice in this clinical scenario. In two separate clinical surveys, there were widespread differences in practice. Amongst urological oncologists, 51% did and 49% did not recommend adjuvant RT for pT3 margin-positive cases [20], whilst a survey of oncologists and urologists showed differences in the use of adjuvant RT as well as the mode, timing, and duration of hormone therapy [21].

The most common scheme of treatment currently used is RT to the prostatic bed when there is evidence of PSA failure. However, it is important to note that only two randomised controlled trials of adjuvant RT are currently in the international literature. The European Organization for Research and Treatment of Cancer (EORTC) 22911 study randomised patients with pT3 disease post-RP between observation and adjuvant RT [22]. A significant advantage for freedom from biochemical and clinical progression was seen for adjuvant RT (hazard ratio, 0.48) at 5 yr. An advantage was also reported for adjuvant RT in terms of clinical progression-free survival (HR, 0.69; 98% confidence interval, 0.43, 0.87; \( p = 0.004 \)) with 87% and 77% PFS event-free at 5 yr, but there was no evidence of a difference in overall survival.

The second randomised controlled trial [23] of 425 men with pT3 disease (SWOG 8794/National Cancer Institute of Canada Clinical Trials Group protocol 2 [NCIC CTG PR-2]) randomised patients with pT3 disease to observation or prostate bed RT. Again, adjuvant RT improved biochemical control (HR, 0.43) and was associated with a trend towards better metastasis-free and overall survival.

Since the design of these studies’ standard practice has changed to the extent that patients with a previously undetectable postoperative PSA level have their static and dynamic PSA changes measured at a much earlier stage with more sensitive PSA assays. It is distinctly possible that these patients will have a lower risk of relapse than in the past, and there is a good rationale for randomised trials in this setting. However, there are few trials addressing this subject. A number of studies, such as EORTC 30094, address the use of adjuvant RT with or without additional treatment (mainly hormones) in high-risk disease, but few deal with the question of treatment combinations and the timing of therapy in the residual or rising PSA setting postsurgery. One trial [24] recently initiated is the UK (NCRI) and Canadian (NCIC) RADICALS trial of early/delayed RT with or without short- or long-term hormones post-RP; this trial will test the timing of treatment and the use of hormones in this setting.

7. PSA failure and adjuvant/early hormone therapy

There are currently a limited number of randomised controlled trials addressing the role of hormone therapy in men receiving postoperative RT or for men failing surgery. Three retrospective nonrandomised studies have compared the outcome of salvage RT alone versus salvage RT plus short-term (4–6 mo) hormone therapy. All of these have observed improved biochemical control rates with
the addition of hormone therapy [25–27]. The RTOG 96-01 trial [28] recruited 840 patients with PSA failure after radical prostatectomy and randomised them to early salvage RT versus early salvage RT plus 2-yr hormone therapy. The first outcome data are not expected until 2008. There is, however, a gathering body of evidence regarding the adverse effects of ADT in early prostate cancer, and timing of ADT in the setting of PSA failure after local treatment is very uncertain. This finding is of particular importance in the setting of PSA failure in screen-detected and low-risk prostate cancer, whose natural history is long and whose overall cancer-specific survival is good. In the large Astra-Zeneca–based Early Prostate Cancer Trial (EPC) using Casodex [29,30], there was a small increase in mortality in patients with relatively early localised disease. There are also increases in the risk of hitherto unrecognised side-effects including weight gain, fatigue, anaemia [31,32], bone loss [30,33,34] cardiovascular disease, insulin resistance, lipid disorders, and loss of cognitive function. The critical issue therefore is when to start ADT in the event of PSA failure. The goal of starting ADT in these patients is the avoidance of distressing symptoms in the long term. There is little point in using ADT if it is associated with a number of side-effects that offset its palliative merit. This issue is to be addressed in two newly planned trials run by the Trans-Tasman Group (the TOAD trial) and the Canadian Urology Oncology group (the Early vs. Late Androgen Ablation Trial [ELAAT]), but there is a need for other groups to join these initiatives to determine more accurately the best form of intervention with the minimum morbidity in this patient group.

8. Conclusions

PSA is critically important as a marker of disease progression in men who have undergone primary treatment for prostate cancer. However, its use can create uncertainty for the clinician when interpreting the significance of a PSA rise, particularly with regard to the necessity and timing of further treatment in individual patients. Although evidence suggests that a number of the existing salvage therapeutic modalities appear to offer significant numbers of men a benefit in terms of prevention of PSA progression, their effect on prostate cancer-specific and overall survival in all cases is less clear. For the future, it is the responsibility of the urological community to examine these important clinical questions in randomised trials when possible and, when it is not, to record and report accurately the results of treatment both in terms of its therapeutic effect and its morbidity. In all of this it is necessary to ensure that the benefit-risk ratio for the patient is on the side of the former, without too great an exposure to the latter.

Conflicts of interest

The author has nothing to disclose.

References


