PSA recurrence: definitions, PSA kinetics, and identifying patients at risk

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Uncertainty exists for clinicians and patients with respect to choosing the optimal therapy for patients with PSA recurrence. There is no consensus as to what the PSA cutpoint should be to define PSA failure after radical prostatectomy (RP) or radiation therapy (XRT). We do, however, have validated nomograms which allow the stratification of patients according to their risk of disease progression and cancer specific death. This is based in large part on PSA kinetics. A short PSA doubling time (PSA-DT) is associated with a marked increase in the risk of prostate cancer death in the 5-10 year time frame. PSA DT can also be used to identify patients most likely to respond to local salvage therapy.

Key Words: PSA kinetics, prostate cancer, biochemical failure

Introduction

Clinicians have been faced with a conundrum when it comes to managing patients with PSA recurrence (PSA failure, biochemical failure), defined as a rising PSA levels after treatment for localized prostate cancer. We face unknowns when selecting treatment strategies for patients with PSA failure. We do not know if survival in these patients is improved by radiation after radical prostatectomy (RP), or by salvage therapies, or early androgen deprivation therapy (ADT). It is not clear whether monitoring PSA after prostate cancer therapy really makes a difference, or if intermittent ADT is equivalent to continuous therapy, or if there is an optimal hormonal therapy — combined androgen blockade (CAB), ADT alone, or luteinizing hormone-releasing hormone (LHRH) monotherapy. There is debate about whether there is a benefit from early chemotherapy for high-risk patients. These are all significant controversies. Every time a clinician has a patient with a rising PSA level, he or she is faced with this.

PSA failure is prevalent in Canada. Last year there were about 180,000 men harboring prostate cancer. This year about 23,200 new cases and 3,000 deaths from prostate cancer are expected. Of these newly diagnosed cases, two-thirds are likely to be

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treated with surgery or radiation. Several studies have shown that up to 40% of treated patients may have a relapse. This translates into roughly 5,000 Canadian men per year who have "PSA-only" early progression.

The management of PSA recurrence incorporates many options. From the most to least aggressive strategies, treatment approaches include local salvage therapies (radiation by external beam or implant, cryosurgery, salvage prostatectomy, and high-intensity focused ultrasound [HIFU]), CAB, ADT alone, nontraditional hormonal therapy, and watchful waiting until objective metastasis.

The natural history of biochemical failure is becoming clarified. We now have validated nomograms that we can use to stratify patients according to their risk of disease progression. We are better able to identify patients who are more likely to respond to salvage radiation. For example, the recently reported results from the Southwest Oncology Group (SWOG) trial showed that there was improved biochemical progression and local recurrence rates in patients treated with adjuvant radiation therapy for positive margins. Studies have shown that salvage therapies can achieve durable PSA responses in selected cases.

Discussion

Identifying patients at risk

Nomograms that stratify post-radical prostatectomy (RP) patients according to risk factors for PSA failure deserve to be more widely used. Stephenson, Kattan, and colleagues recently published a robust, postoperative nomogram that predicts 10-year probability of prostate cancer recurrence after RP.[1] Points are assigned based on a patient's pathologic features (Gleason score), preoperative PSA level, and number of months free of PSA failure after RP. Using the nomogram, the clinician can say to the patient, "Of 100 men exactly like you, X% will remain free of recurrence 10 years following surgery, and after that the likelihood of recurrence is very rare."

Defining PSA failure

PSA failure after RP

There is no consensus yet for the most appropriate PSA cutpoint to define PSA failure after RP. Several studies have aimed to determine the PSA threshold after RP that would indicate that prostate cancer has recurred and something needs to be done. Suggested PSA thresholds vary from a PSA that is detectable, to a PSA of 0.2 ng/mL or higher, to three consecutive increases in PSA, or to a PSA of 0.4 ng/mL.

In a study published 2 years ago, Amling and colleagues concluded that a PSA of 0.4 ng/mL or greater may be the most appropriate cutpoint, since a significant number of patients with lower values did not have a continued increase in PSA levels.[2] They analyzed data from 2,782 men who had undergone RP. A subsequent increase in PSA was found in 49%, 62%, and 72% of patients who had initial post-RP PSA cutpoint levels of 0.2 ng.mL, 0.3 ng/mL, and 0.4 ng/mL or greater, respectively. The main limitation of the study is its 3-year endpoint, which underestimates the likelihood of subsequent PSA progression.

More recently, Freedland et al reported that a PSA value of greater than 0.2 ng/mL is an appropriate cutpoint for defining PSA recurrence after RP. They performed a retrospective survey of 358 men who had undergone RP. For patients with a detectable postoperative PSA value of 0.11 ng/mL to 0.2 ng/mL, the 3-year risk of PSA progression was 93% (95% CI 74% to 99%).

There is a trend towards moving to a more stringent definition of biochemical failure after RP — to a PSA cutpoint of 0.2 ng/mL rather than 0.4 ng/mL. Cutpoint is important in terms of assessing treatment results and making a decision about salvage therapy. Evidence is accumulating that for patients with post-RP biochemical failure, the earlier you intervene with salvage radiation, the better.

PSA failure after radiation

Defining PSA failure after radiation has been very controversial. The American Society for Therapeutic Radiology and Oncology (ASTRO) definition is three consecutive rises in PSA dated back to the midpoint between the nadir (lowest) PSA and the first rise. Other definitions have been proposed: PSA greater than nadir plus 2 (or 3) ng/mL, PSA greater than 0.5 (or 0.2) ng/mL, three consecutive rises in PSA dated from the third PSA increase, or an absolute PSA threshold of 0.5 ng/mL, 1.0 ng/mL, or 2.0 ng/mL.

The ASTRO definition has several inherent problems. It is so sensitive to laboratory variation that even two very slight consecutive rises in PSA levels, which may reflect laboratory variation, would meet the criteria for PSA failure. It may take a long time, dependent on the follow-up interval, to document the three increases in PSA levels. There is bias associated with backdating the failure date. Other definitions that use cutpoints of post-prostatectomy PSA levels of 0.2 ng/mL or 0.3 ng/mL may be more sensitive and specific. There is a large difference between the

ASTRO definition and other definitions of failure for surgery and brachytherapy. Hormone therapy poses a real challenge. In most patients who receive neoadjuvant androgen therapy, testosterone recovery tends to occur before the PSA recovery, and PSA recovery lags behind.[4]

PSA bounce (a fairly minor rise above nadir for one or two PSA values followed by a fall in PSA values) is a complicating factor when trying to determine if a patient has biochemical failure. PSA bounce is a common phenomenon after brachytherapy, likely due to the intervention, and local radiation-induced inflammation. It occurs typically around 2 to 3 years after this procedure, although it may be observed later in some patients.[5]

The rate of PSA bounce depends on the definition. Three definitions for PSA bounce after brachytherapy have been commonly used: a rise in PSA of either $\geq$ 0.1 ng/mL, $\geq$ 0.4 ng/mL, or > 35% above the nadir value. A PSA bounce after external beam three-dimensional conformal radiotherapy has been defined as a PSA level that has risen from a PSA level taken more than 30 days earlier, with a slope of 0.07 or higher when PSA values are plotted over time.[6]

In clinical practice, it is difficult to distinguish between PSA bounce and true PSA failure. The "false call" rate with the ASTRO definition is quite high, about 22%, and this is one reason for interest in abandoning it. A study by Kuban and colleagues concludes that there is a need to revisit how to define PSA recurrence after radiation for prostate cancer.[7]

According to a consensus by radiation oncologists, the best way to define PSA failure after radiation is PSA $\geq$ nadir plus 2 ng/mL. This has the best sensitivity and specificity for predicting subsequent clinical failure. Whether we need to correct for testosterone suppression and if so, how to do this, is unclear.

PSA kinetics

PSA-DT and cancer-specific mortality

There has been tremendous amount of data published in the last couple of years on the subject of PSA kinetics. We know that a short PSA doubling time (PSA-DT) represents bad news for the patient. D'Amico et al reported that this marker is an extremely powerful predictor.[8] They analyzed data from a large population of patients with prostate cancer who were treated with surgery (5,918 men) or radiation (2,751 men), to test whether PSA-DT is a surrogate predictor of prostate cancer-specific death. Among patients treated with RP who had a PSA-defined disease recurrence, those with a PSA-DT of 3 or more months had a 63 times greater likelihood of cancer mortality than patients with a PSA-DT of less than 3 months. No other prognostic parameter even approaches this kind of predictive value. The hazard ratio was less strong but still very robust for patients treated with radiation; patients with the shorter PSA-DT had a 12 times greater risk of prostate cancer-specific death than those who had a longer PSA-DT.

Similarly, Freedland et al reported that PSA-DT is a strong indicator of risk of cancer-specific death.[9] They performed a retrospective study of 379 men who had undergone a RP and had a biochemical recurrence, to define the risk factors for post-RP prostate cancer-specific death. Compared to a PSA-DT of 15 months or more, a PSA-DT of less than 3 months conferred a 27 times greater risk of prostate cancer-specific death, Table 1.[9] Short time to biochemical recurrence only conferred a 3.5-fold increased risk of prostate cancer-specific death, and a high pathologic Gleason score conferred a 2.3-fold increased risk. Even a PSA-DT of 3 to 9 months gave an 8.7 times greater risk of prostate cancer-specific

TABLE 1. **Predictors of prostate cancer-specific death***

Variable	**Hazard ratio for PCSD**	**p value**
Years from RP to biochemical recurrence	HR (≤ 3 Y vs > 3 Y) 3.53	0.002
PSA-DT	HR relative to ≥ 15 mo	
< 3.0 mo	27.48	< .001
3.0-8.9 mo	8.76	< .001
9.0-14.9 mo	2.44	.09
Pathological Gleason score	HR (≥ 8 vs < 8) 2.26	.002

*based on a study of 379 men with biochemical failure after radical prostatectomy
PCSD = prostate cancer-specific death, PSA-DT = PSA doubling time, RP = radical prostatectomy

TABLE 2. **Prostate cancer specific 10-year mortality after biochemical recurrence post-radical prostatectomy***

PSA-DT	Biochemical recurrence > 3 Y After RP		Biochemical recurrence ≤ 3 Y After RP	
	Gleason score < 8	Gleason score ≥ 8	Gleason score < 8	Gleason score ≥ 8
≥ 15 mo	2%	4%	7%	14%
9.0 to 14.9 mo	5%	10%	15%	31%
3.0 to 8.9 mo	16%	32%	45%	74%
< 3.0 mo	41%	70%	85%	99%

*based on a study of 379 men with biochemical failure after radical prostatectomy
PSA-DT = PSA doubling time

mortality, vastly outstripping the increased risk from a high pathologic Gleason score.

The median time to biochemical recurrence in most cohorts is 3 years. These patients have no clinical evidence of metastasis. According to the study by Freedland et al, patients who had a PSA recurrence in less than 3 years and a PSA-DT of less than 3 months had a prostate cancer mortality rate at 10 years of 85%-99%, Table 2.[9] Patients with a PSA-DT of more than 15 months and a long time to PSA progression — whether their Gleason score was low or high — had almost no risk of prostate cancer mortality at 10 years. The message to clinicians is clear. PSA-DT and time to PSA progression should be used to stratify patients according to the risk of prostate cancer mortality. Patients in the high-risk group need aggressive, early therapy. Patients in the low-risk group may not need any treatment, and should be followed. We have been dramatically overtreating these patients with early hormone therapy.

Similarly, another study reported the usefulness of PSA kinetics measurements in predicting survival. The team found that prostate-cancer specific survival of patients treated with surgery or radiation was dramatically different depending on whether their PSA-DT was 3 months or more or shorter than 3 months.[10]

Another group showed that a PSA-DT of less than 6 months was a good predictor of a high rate of disease progression.[11] Among 587 patients who had biochemical failure after RP, those with a PSA-DT of less than 6 months had a 5-year local recurrence/systemic progression-free survival of only 38% and a 5-year systemic progression-free survival of 64%.

PSA kinetics and positive bone scans

A short PSA-DT has been shown to be a significant predictor of a positive bone scan. In a retrospective study of men with biochemical recurrence after RP, the incidence of a positive bone scan in men with a PSA-DT of less than 6 months was 8 of 31 patients (26%).[12] The incidence was only of 2 of 62 patients (3%) in the men with a longer PSA-DT.

In another cohort, PSA slope, PSA velocity, and trigger PSA (the absolute value of PSA) were by far the most powerful predictors of a positive bone scan.[13] A total of 414 bone scans from 239 patients who had biochemical failure after RP were evaluated. A nomogram permits identification of patients with relatively low, but rapidly rising PSA levels who are at high risk of having a positive bone scan. The old rubric that to have a positive bone scan after prostatectomy the PSA has to be greater than 10 or 20 ng/mL falls before this data.

PSA-DT has also been demonstrated to predict the occurrence of metastatic disease, a surrogate for prostate cancer mortality. A study showed that at 7 years, 68% of patients with a PSA-DT of less than 8 months had distant metastases.[14] This was true for only 12% of patients with a PSA-DT of greater than 8 months — a dramatic difference.

Using PSA-DT to select patients for salvage therapy

A large study by Stephenson et al showed that PSA-DT values are very useful to predict which patients with biochemical failure would benefit from salvage radiation.[15] The team performed a retrospective review of 501 patients treated at five US centers with salvage radiation for biochemical recurrence after RP. Predictors of adverse outcome included Gleason score 8 to 10, pre-RT PSA > 2 ng/mL, negative surgical margins, PSA-DT ≤ 10 months, and seminal vesicle invasion. Patients with no adverse features had a 4-year progression-free probability of survival of 77%. Local recurrence of cancer was more common than expected. Patients with a Gleason score of 8 to 10, positive margins, and who received early salvage

radiotherapy had a 4-year PSA progression-free survival probability of 81% if their PSA-DT was longer than 10 months. This probability dropped to only 37% for patients with a PSA-DT of 10 months or less.

The most recent data suggests that salvage therapy is worthwhile for appropriate patients. PSA-DT values identify who is a good candidate for this therapy. The old approach was to go straight to ADT if the patient had PSA recurrence within 18 months with seminal vesicle involvement and a high Gleason grade. The new approach is to treat patients who have a PSA-DT of greater than 10 to 12 months, positive margins, and a PSA of less than 2 ng/mL with salvage radiation therapy. If the patient has a PSA-DT of less than 10 months, negative margins, or PSA > 2 ng/mL, this therapy is unlikely to be of benefit, and androgen deprivation should be considered.

Conclusion

The optimal therapy for PSA recurrence after RP or radiation is uncertain, although we now have more and better data. PSA-DT warrants incorporation into a risk-stratification approach that also looks at Gleason grade and time to biochemical failure. Patients may be selected rationally for salvage radiation based on pathology factors and PSA kinetics. PSA-DT also identifies patients who are candidates for early hormonal therapy. In patients with a slow PSA-DT it is appropriate to wait, often many years, before initiating ADT. ADT should be used conservatively, unless the patient's Gleason score is high, or the PSA-DT is less than 1 year. For those who have enthusiasm for this operation, salvage prostatectomy should be restricted to patients with favorable PSA kinetics. □

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