Management of Asymptomatic Rise in Prostatic-specific Antigen in Patients with Prostate Cancer

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Biochemical failure after curative-intent therapies is an increasingly common dilemma confronting patients and physicians. No definition of biochemical failure exists that can be applied to all forms of treatment and that is not to some degree affected by the follow-up interval, pretreatment prognostic factors, or the frequency of prostatic-specific antigen (PSA) testing. Available imaging techniques lack sensitivity in detection of occult micrometastases. Prognostic factors such as tumor characteristics and PSA kinetics should be considered when recommending second-line therapies. For those patients with suspected localized recurrence, second-line treatment with salvage therapies may provide long-term disease control. Hormonal therapy, although most commonly employed for PSA recurrence, is of palliative benefit only. Currently, the most appropriate therapeutic intervention for asymptomatic patients with evidence of biochemical failure remains undefined.

Introduction

In 2005, one in six men (over 230,000 men) was diagnosed with prostate cancer (PCa) [1]. Routine use of serum prostatic-specific antigen (PSA) for screening and monitoring of PCa has caused a dramatic stage migration, and the rates of curative-intent therapies for presumed localized disease have increased through the 1990s [2•]. An estimated 40% of patients with PCa who have undergone curative-intent therapies, or approximately 50,000 men per year, will eventually relapse [3]. In the PSA era, the overwhelming majority who initially relapse have biochemical failure (ie, a rising PSA without overt clinical or radiologic metastases). Although these patients are initially asymptomatic from their disease, biochemical failure may be a harbinger of other signs of progression. Clearly, not all men with rising PSA after curative-intent therapies carry the same future risk of development of clinical metastatic disease, and knowledge of variables that can help predict who is at highest jeopardy is important. Unfortunately, diagnostic and management approaches for this clinical scenario remain controversial.

Definitions and Natural History of Biochemical Failure

Traditionally, advanced systemic PCa was defined as disease that has spread outside of the prostate or surrounding tissue. More recently, asymptomatic patients with significant risk of progressive disease or death from prostate cancer are included in the definition of advanced disease [4,5]. PSA and PSA changes over time (eg, absolute value, doubling time, or kinetics) are the main criteria for defining high-risk disease after local therapies. The definition of PSA-only relapse differs based on the treatment modality (eg, radical prostatectomy or radiation therapy) previously employed for presumed clinically localized disease.

The goal of radical prostatectomy (RP) is to remove all prostatic tissue. and PSA should subsequently fall to an undetectable level within 2 to 4 weeks after surgery. Therefore, PSA detected postoperatively invariably represents residual cancer [6]. The likelihood of local recurrence is higher if the PSA gradually rises after an initial period of undetectable PSA after surgery as opposed to a still detectable or rapidly rising PSA, commonly signifying the presence of systemic disease [7]. The absolute value of PSA that postoperatively indicates cancer recurrence is controversial. The lower threshold for standard immunoassays is 0.1 ng/mL, and a PSA value lower than this level is considered undetectable. A detectable level of PSA that is associated with cancer recurrence is variably defined as one absolute value (usually 0.4 ng/mL) in some series or as two consecutive PSA levels greater than 0.2 ng/dL [7–9]. The cut-off point of 0.4 ng/mL may be more appropriate than a lower cut-off point, as benign glandular tissue left

at the surgical margins during prostatectomy may account for the presence of a low postoperative PSA level [10]. These levels are usually between 0.1 and 0.3 ng/dL and do not rise significantly. Future research is necessary to help further delineate which men with low postoperative PSA levels after RP ultimately progress to clinical disease.

Biochemical failure after external beam radiation (EBRT) is even more difficult to define because prostatic tissue remains present and the effect of therapy on cancer cells can be prolonged. The median time to PSA nadir after EBRT is 18 months and the nadir value can fluctuate [2•]. For example, elevations of PSA (ie, PSA bounce) can occur for 2 to 3 years after radiation therapy in approximately 10% to 30% of patients [11•,12]. Due to difficulties with developing a standardized definition for PSA recurrence after radiation, the American Society for Therapeutic Radiology and Oncology (ASTRO) organized a consensus panel in 1997 [13]. The consensus panel definition of PSA-only recurrence was three consecutive increases in PSA obtained at 3-month intervals for 2 years after completion of RT or a single rise great enough to warrant initiation of further therapy. The midpoint between the postradiation nadir PSA and the first rise is the date of failure. In addition, the panel agreed that although PSA-only recurrence may be an appropriate endpoint for clinical trials, it may not signify the need for additional therapy and is not equivalent to clinical failure. Alternate definitions of biochemical failure were proposed by Horwitz et al. [14] after they found that the ASTRO definition may significantly overestimate disease-free survival due to its definition of date of failure. In addition, because the median time to PSA nadir is 18 to 36 months after radiation therapy, the ASTRO definition lacks sensitivity, as the vast majority of men have occult systemic disease at the time of recurrence [11•]. A more recent definition of PSA recurrence is a serum PSA level of 2 ng/mL above nadir after radiation [15]. It is unknown whether the ASTRO or alternative definitions correlate to clinical outcomes.

Several studies have suggested a long natural history for men who present with PSA-only progression. Pound et al. [16••] reported the natural history of PCa progression in 1997 persons who received RP at Johns Hopkins Hospital. Of the 15% of patients who developed PSA-only recurrence, approximately one third developed clinical metastasis at a median time of 8 years without further therapy. Early PSA recurrence, rapid PSA doubling time, and high Gleason score were all predictors of PSA recurrence and reduced survival. In another large series of men followed at the Cleveland Clinic, the 10-year survival rate for patients with biochemical recurrence after RP was similar to the rate of those without biochemical recurrence [17]. In the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) prostate cancer research database [2•,18], at a median follow-up of 7 years, 10% of patients after RP (n=611) and 30% of patients after EBRT (n=840) developed biochemical failure. Only 6% and 14% of patients with biochemical failure after RP and EBRT, respectively, died over this time period. Furthermore, close to one third of these patients died of other causes. Although these data may not be completely applicable to the general population due to possible selection bias [2•], patients with PSA-only progression have a long disease course as evidenced by these studies, and a significant proportion will die from other causes even after developing biochemical failure.

Predictors of Biochemical Failure and Poor Outcome

Numerous nomograms and models using pretreatment and/or pathologic factors in an attempt to identify men at a high risk of biochemical recurrence after curative-intent therapies have been developed. These models may help with identifying those men who may benefit from early adjuvant treatment. Pretreatment PSA, Gleason score, presence of extraprostatic extension, and positive surgical margins have all shown significant correlation with PSA recurrence. Other important factors include pathologic stage, tumor volume, race, angiogenesis, and a variety of molecular markers [3]. More recently, preoperative PSA velocity was shown to be a significant clinical factor predicting for relapse in a single-institution study of 202 men who received RP [19].

As clearly not all men with biochemical failure have poor outcomes from PCa, identification of characteristics of those men who will eventually progress to clinical metastasis and ultimately death is necessary. PSA doubling time (PSADT) and time to recurrence have been studied as potential clinical characteristics that could help detect men with more aggressive disease. Patients with a PSADT of more than 6 months after prostatectomy have a better 3-year metastasis-free survival rate than those with a shorter doubling time [20]. Short PSADTs (<12 mo) have also been linked to prostate cancer–specific death after radiation therapy [21]. D'Amico et al. [18] illustrated that PSADT (<3 mo) was a surrogate for prostate cancer–specific death after radiation therapy or surgery. A less than 2-year time to PSA recurrence after RP is associated with worse prostate cancer–specific mortality rates [7]. Although it is clear that the combination of multiple factors can better predict biochemical recurrence and prostate cancer–specific mortality as compared with individual factors, the accuracy of these combinations must be validated in different samples, and it is not known if there is a single best predictive model.

Biochemical Failure and Diagnosis

In the diagnostic evaluation of biochemical failure, determination of locally advanced versus systemic disease should be attempted, as patients with these diagnoses

may still be candidates for cure with additional therapies. However, identification of definite sites of recurrence can be difficult.

Role of bone and CT scans

Most men with a PSA-only recurrence will undergo systemic imaging with radionuclide bone scan or CT. For patients with low absolute PSA values and early PSA progression, the sensitivity of these tests to detect systemic disease is extremely low as occult micrometastatic disease cannot be imaged with current techniques. In one study evaluating 144 bone scans from 93 patients with PSA recurrence after surgery [22], the lowest PSA associated with a positive bone scan in the absence of hormonal therapy was 46 ng/mL. Using the CaPSURE database [23], only 9.4% and 14% of patients with PSA recurrence (n=132) after RP had positive bone scans or positive CT scans, respectively. The average PSA for those who did have evidence of disease by imaging was 60 ng/mL. PSA velocity was found to be the best predictor of positivity of imaging studies for metastatic disease. In a retrospective study of 128 men with biochemical relapse after RP, 11% of bone scans and 7% of CT scans obtained were positive. Men with PSADT of less than 6 months and PSA levels of more than 10 ng/mL were more likely to have positive scans [24]. In summary, imaging studies are rarely positive until PSA levels are greater than 40 ng/mL or rapidly rising (>0.5 ng/mL/mo beyond 20 ng/mL/y) following local therapy. The likelihood of positive bone scan or CT scan is related to the absolute PSA value or the rate of rise. In addition, bone scan and CT scan of the abdomen and pelvis are recommended for patients who may be candidates for salvage local therapy.

Role of the ProstaScint (^{111}In capromab penditide) scan

The ProstaScint scan (Cytogen, Princeton, NJ), a radiolabeled monoclonal antibody imaging test based on prostate-specific membrane antigen (PSMA), has been approved by the US Food and Drug Administration (FDA) for detection of site of recurrence for men with PSA-only recurrence after RP [2•]. The advantage of ProstaScint scanning is its potential ability to improve selection of men who are candidates for further salvage therapy by distinguishing between systemic and local recurrence. In one study of 64 patients with possible recurrent disease after RP, 77% were found to have prostatic fossa activity only. Disease stage was deemed more advanced in 20% of those with recurrent disease based on ProstaScint findings when all other imaging tests were inconclusive [25]. In a multicenter study of the use of the ProstaScint scan in evaluating patients with biochemical recurrence (mean PSA 7.9 mg/dL) after RP [26], the scan revealed disease in 108 of 181 patients, with 34% having disease localized to the prostatic fossa. In another study of 48 patients with generally higher PSA values at recurrence (mean 28.7 ng/mL), 73% had antibody activity systemically, and only 6% of patients had activity localized only to the prostatic bed [27]. ProstaScint scanning has also proven useful in detection of disease in patients with early PSA recurrence. Raj et al. [28] reported the results of 255 men with early PSA recurrence (PSA < 4 ng/mL) following RP; 72% of 184 positive scans revealed distant disease, 31% were limited to the prostatic fossa, and an additional 43% of scans revealed disease in the regional lymph nodes. Of 151 men who underwent additional imaging studies, 16 of 139 men (12%) and 15 of 92 men (16%) showed evidence of recurrent disease by bone scan and CT scans, respectively. Overall, Hinkle et al. [29] reported 75% sensitivity, 86% specificity, and 81% accuracy in detection of distant and local prostatic disease by ProstaScint scan.

The long-term outcomes of men with biochemical failure who have localized disease by ProstaScint scanning have not been well-described. Kahn et al. [30] reported outcomes of 32 men with rising PSA (median value 1.5 ng/mL) after RP who underwent salvage pelvic radiotherapy after ProstaScint scanning. After a median follow-up of 13 months, 70% of men with a normal scan achieved a complete response as compared with 22% of those with uptake systemically. Other studies, however, suggest a lack of correlation between ProstaScint scanning results and outcomes after salvage therapy. For example, in one study, ProstaScint scan did not predict response to salvage radiotherapy in 30 men with rising PSA after RP [31].

Role of other diagnostic procedures

Currently, transrectal ultrasound-guided biopsy is controversial as biopsy outcomes have not been correlated with cancer-specific survival. Although endorectal MRI has also been utilized to evaluate local recurrences after biochemical failure, its utility is limited due to lack of data to support widespread implementation. Because positron emission tomography scanning does not add information to other imaging studies such as CT scanning or radionuclide bone scanning in the detection of systemic disease, and has limited ability to differentiate between cancer, hypertrophy, and scar, it is not advocated for detection of PCa recurrence.

Biochemical Failure and Treatment

Treatment of PCa patients with biochemical failure after local therapy is controversial as there is no evidence to support positive impact on survival. Options should be considered carefully to balance the ultimate goal of cure or extension of life with the risk of treatment side effects in the already asymptomatic patient. Potentially curative options with salvage local therapies should be reserved for those with high likelihood of organ-defined disease. Although the majority of patients who undergo treatment for rising PSA after local therapy receive androgen deprivation, hormonal therapies are of palliative benefit only. Early observation or watchful waiting is also a

valid approach for this asymptomatic patient population. Expectant management is most appropriate for those patients with a limited life expectancy and with a low risk of progression of disease to distant metastases.

Salvage local therapies

Salvage local therapies should be considered in those patients with biochemical recurrence who are otherwise healthy, have long life expectancies, and have cancers that were initially and are still considered potentially curable.

After prostatectomy

Theoretically, salvage radiotherapy should be able to provide long-term disease control in patients with localized disease failure after RP. However, the impact of salvage radiotherapy on survival of patients with PSA-only recurrence is unknown. Current barriers with this approach include difficulty in determining which patients with PSA recurrence after surgery have disease localized to the potential field of radiation, and uncertainty of the most effective radiation dose. Patients with high Gleason scores (>8), high pretreatment PSA levels (>2 ng/mL), fast PSA doubling times, and seminal vesicle invasion have a higher likelihood of having a poor outcome after salvage radiotherapy [32,33•]. Available nonrandomized observational studies yield mixed results. In general, patient populations studied have T3 or T3c disease with median PSA levels between 1 and 2 ng/mL. Several investigators have advocated salvage radiotherapy doses of 66 to 70 Gy and have demonstrated beneficial outcomes of treatment for those patients with PSA levels between 0.5 and 2 ng/mL at time of salvage therapy [34,35]. In contrast, other studies demonstrate poor overall outcomes with salvage radiotherapy. For example, in one large series of 1699 men [36], 57 men with PSA-only recurrence (median PSA 2.2 ng/mL) and 25 men with local recurrence (median PSA 4.1 ng/mL) received salvage radiation. Only 26% of patients with PSA-only recurrence had undetectable PSA levels 2 years after radiotherapy. In summary, the value of salvage radiotherapy for PSA recurrence after radical prostatectomy is still debatable, although low initial PSA and higher administered radiation doses may increase the likelihood of success.

After radiotherapy

Salvage prostatectomy after radiotherapy may provide long-term disease control for carefully selected patients. In multiple series, for those patients who received salvage RP with low preoperative PSA levels (<10 ng/mL), two thirds had organ-confined disease and 70% were progression-free at 5 years [37–39]. Hormonal therapy in conjunction with salvage prostatectomy improved clinical and biochemical disease-free survival rates [40]. Surgical complication rates have improved over time. For example, in one large series, the 5-year recovery rate of urinary continence was 68% for patients treated since 1993 as compared with 57% prior to 1993 [11•]. Impotence rates have also improved due to increased utilization of nerve-sparing techniques. Although the rates of anastomotic stricture and incontinence are higher than with standard RP, in general, only one third of patients will experience these complications [11•]. Nonetheless, salvage prostatectomy should be considered primarily for patients with high likelihood of having organ-defined disease as evidenced by low Gleason score, pretreatment PSA, and tumor volume [2•,38]. Salvage RP should only be performed by surgeons with extensive experience.

Salvage cryotherapy (the use of transperineal cryoprobes placed by transrectal ultrasound) has been proposed as an alternative to salvage prostatectomy for treatment of PSA recurrence after radiotherapy due to its potential for reduced morbidity. However, in one series at the University of Texas M.D. Anderson Center, 4% of patients required surgery after salvage cryoablation due to significant complications such as rectourethral fistula and urethral stricture [41]. Morbidity may be lessened with the development of smaller gas-driven probes [42]. In one multicenter study, 75% of 106 men treated with salvage cryotherapy achieved a biochemical relapse [43]. In this study, although the impotence rate was high, the rates of tissue sloughing, incontinence, and urinary retention were improved from previous series. Although current data suggest that salvage cryotherapy provides inferior cancer control when compared with salvage RP, long-term data are needed for newer approaches [4,11•].

Due to limited experience, salvage brachytherapy is considered largely experimental for men failing EBRT. The largest series available (n=49) reported a 5-year biochemical relapse-free survival rate of 34% [44]. Although urinary continence was largely preserved, two men developed rectal ulcers and transurethral resection of the prostate was necessary in 14% of men due to bladder outlet obstruction. Improved techniques that allow higher radiation doses with reduced complication rates may improve future outcomes of salvage brachytherapy.

Hormonal therapies: traditional approaches

If a patient has a likelihood of having systemic disease based on absolute PSA value, PSADT, and imaging studies, or has a limited life expectancy, androgen deprivation therapy should be considered in lieu of salvage local therapies. Surveys of urologists and radiation oncologists demonstrate that androgen ablation is recommended routinely for patients with biochemical recurrence [45,46]. Among patients with biochemical failure after RP in the CaPSURE database (n=303), 57% were treated with androgen ablation compared with 43% who were given salvage radiotherapy [47].

The most frequently employed mechanisms of androgen ablation include bilateral scrotal orchiectomy and androgen blockage with chemical agonists (eg, luteinizing hormone-releasing hormone agonists). Estrogen

therapy is currently disfavored due to its adverse cardiac toxicity. Complete androgen blockage or maximal androgen blockade (ie, combining an oral antiandrogen with testicular ablation therapy) is a common approach to treatment; however, wide practice variation exists due to conflicting data. The largest experience, from the Prostate Cancer Trialists' Collaborative Group [48••], demonstrated a small (2.9%) but not significant improvement in 5-year survival to maximal androgen ablation as compared with castration alone. In this study, 12% of 8275 patients had no evidence of clinical metastases and no differences were noted by stage of disease. Other groups report a larger benefit, although the value of combination therapy to asymptomatic patients with biochemical recurrence is yet unclear [49–51].

When to initiate therapy in men with advanced PCa is also a matter of debate. The Medical Research Council randomized a large cohort of men with locally advanced or asymptomatic disease to immediate hormonal therapy versus treatment initiation at time of disease progression [52]. Patients with asymptomatic disease who received early hormonal therapy had lower overall death rates (54% compared with 70%) and an improved cancer-specific survival ($P<0.001$). However, caution must be undertaken when interpreting these results as some men in the deferred arm died before receiving therapy, biasing results toward early intervention [4]. In another study reported by Messing et al. and the Eastern Cooperative Oncology Group [53], 98 men with lymph node metastases after RP were randomized to early versus delayed hormonal therapy. Men who received immediate treatment had a 4.3% death rate from cancer at 7 years as compared with 30.8% of men who were initially observed ($P<0.01$). More recently reported data from the Center of Prostate Disease Research Database [54] also demonstrated a benefit of early hormonal intervention to men with biochemical relapse after RP (PSA >0.2 ng/mL) and high-risk disease as defined by a Gleason score of more than 8 and PSADT under 12 months. In this retrospective study, early hormonal therapy was defined as men ($n=355$) receiving treatment prior to PSA level of 10 ng/mL, while delayed therapy was treatment given after PSA reached a level of 10 ng/mL or clinical metastases were identified ($n=997$).

Unfortunately, due to lack of available randomized trials, no current evidence demonstrates treatment impact on survival for men with biochemical recurrence or high-risk disease after local therapy. Extrapolation of data from other sources (large databases or subset analyses) are difficult due to confounding and lack of power to make appropriate conclusions. D'Amico et al. [5] evaluated 7316 men treated with RP or radiation and categorized them into groups at low, intermediate, and high risk of prostate cancer–specific mortality based on Cox multivariate regression analysis of multiple measurable clinical parameters. Low-risk patients were defined as having PSA less than 10 ng/mL, Gleason score less than 6, and clinical stage T1c or T2b, and patients at a high risk of death from PCa had a PSA greater than 20 ng/mL, Gleason score above 8, or clinical stage greater than T2c. Because multiple studies of androgen ablation have demonstrated benefit to patients with clearly defined advanced metastatic disease [50,55,56], the highest-risk patients with biochemical recurrence as defined by D'Amico et al. [5] may be the subset of patients that benefits from castration [2•].

Other hormonal therapy approaches

Although early intervention with traditional androgen ablative therapies may indeed benefit the high-risk patient with biochemical recurrence, these therapies can have significant side effects (eg, sexual dysfunction, osteoporosis, loss of muscle mass and weakness, and cognitive dysfunction). As a result, less toxic interventions, especially for the asymptomatic patient with PSA-relapse only disease, are necessary.

Due to a better side-effect profile (eg, retained sexual interest and physical functioning) antiandrogen monotherapy with bicalutamide has been extensively studied. Antiandrogen therapies work by blocking the cytoplasmic dihydrotestosterone receptor and by blocking androgens produced by the adrenal gland. Bicalutamide, 50 mg daily, was found to be inferior to traditional castration for patients with advanced overtly metastatic disease [57]. However, two large phase III studies evaluating bicalutamide with castration in 1453 patients with locally advanced or overtly metastatic disease found no differences in survival between the two arms. A subset analysis of the 280 patients with PSA-only recurrence also demonstrated no differences in overall survival [58]. A larger study conducted by the Early Prostate Cancer Program ($n=8113$) of bicalutamide, 150 mg daily, versus placebo revealed a significant improvement in overall progression-free survival after a median follow-up of 5.4 years with a reduction of risk of bone scan progression or death of 27% (HR=0.73; $P<0.0002$) [59]. The benefit was observed irrespective of underlying therapy (RP, radiation, or watchful waiting), and the highest-risk patients achieved the best outcomes.

Finasteride, a 5α reductase inhibitor, has also been considered for patients with PSA-relapse only disease both as monotherapy and in combination with antiandrogen therapies. Finasteride works by blocking the conversion of testosterone to dihydrotestosterone within the prostate. Although finasteride alone provides unacceptable cancer control, finasteride in combination with flutamide, an antiandrogen therapy, may prove promising. In one study, 71 men with PSA recurrence previously treated with RP or EBRT received finasteride, 10 mg daily, and flutamide, 250 mg daily [60]. At a mean of 44.4 months of follow-up, 38% continued receiving therapy with no evidence of PSA progression

and six patients maintained a more than 50% reduction in their baseline PSA level. Major side effects were breast tenderness (90%), gynecomastia (72%), gastrointestinal disturbances (22%), fatigue (10%), and decreased libido (4%). Oh et al. [61] demonstrated retained efficacy of castration after therapy with finasteride and flutamide. Because of limited available data, randomized studies with longer follow-up are necessary.

Conclusions

Biochemical recurrence after local therapy to the prostate is estimated to occur in approximately 40% of men after treatment for presumed organ-confined PCa. As most men with PSA-only relapse experience a long survival time, the risks and benefits of further therapies should be carefully considered. Time to recurrence, PSA doubling time, and PSA kinetics, along with pathologic tumor characteristics, may help identify those patients with local versus systemic recurrence and thereby help guide future therapies. Evaluation with other diagnostic procedures such as bone scan, CT scan, ProstaScint scan, or biopsy may be helpful in selected cases, although most lack appropriate sensitivity for differentiating between local and systemic recurrence. For those patients with high likelihood of having organ-confined disease, local salvage therapies can provide a chance for long-term disease control. Recent studies suggest that early treatment with traditional hormonal therapy may provide a survival benefit for patients with nonmetastatic disease; however, the survival benefit for patients with PSA-only relapse has yet to be proven.

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