Management of Biochemically Recurrent Prostate Cancer Following Local Therapy

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Abstract

Localized therapy for prostate cancer is often curative; however, 20% to 30% of patients experience a recurrence. Men with biochemical recurrence (BCR) are typically identified following routine monitoring of prostate-specific antigen after treatment for localized disease. These patients exhibit no signs of prostate cancer. Initial evaluation attempts to determine whether the BCR is due to local recurrence or systemic disease. Depending on the type of initial local therapy, treatment options for local recurrence include salvage radiation therapy or salvage prostatectomy. If systemic recurrence is suspected, other options must balance the onset of metastatic disease with avoidance of overtreatment. The most common treatment is androgen deprivation therapy (ADT) via gonadotropin-releasing hormone agonists or antagonists. Because there are challenges associated with standard ADT, other treatment options are being investigated, including a number of natural products.

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For author information and disclosures, see end of text.

Although local therapy for prostate cancer, such as radical prostatectomy or radiation, is curative for many patients, 20% to 30% experience a recurrence typically detected from a rise in serum prostate-specific antigen (PSA) levels.[1-4] Five years after initial therapy, 15% of men experience this biochemical recurrence (BCR), while 20% to 40% of men exhibit BCR 10 years after radical prostatectomy[1,5,6] and 30% to 50% after undergoing radiation treatment.[7] Although both clinical features as well as pathological findings can predict the likelihood of biochemical relapse, once biochemical relapse occurs the patient is presumed to have recurrent prostate cancer.[8] PSA is a sensitive and specific marker for prostate cancer. Monitoring for PSA levels after treatment of localized prostate cancer leads to the identification of men with a PSA-only (biochemical) recurrence, for which there are no symptoms or signs of locally recurrent or metastatic disease. The definition of PSA recurrence is dependent upon the type of initial local therapy received: radical prostatectomy or radiation therapy. Defining the optimal treatment plan for those who present with BCR represents a clinical challenge, because patients who exhibit a BCR often do not possess any other disease symptoms and may not develop metastatic disease for many years. An important question therefore exists in the medical community: should these men be further treated based solely on their PSA values? This review describes the definition of BCR, current and emerging strategies for the treatment of these patients, and alternative approaches.

Biochemical Recurrence

PSA Recurrence After Surgery

The PSA after radical prostatectomy should be undetectable. The timing for the drop in PSA has been well established,[9] and the half-life of PSA in the serum post prostatectomy is 2 to 3 days.[10,11] In some patients, residual prostatic tissue (for example, residual apical tissue post robotic prostatectomy) can lead to a

measurable PSA after surgery; however, typically this low PSA remains stable over time. A detectable or rising PSA value is defined by the American Urological Association (AUA) as greater than 0.2 ng/mL after surgery with a second confirmatory level of greater than 0.2 ng/mL,[12] although a cut point of 0.4 ng/mL may better predict the risk of metastatic relapse. When BCR is documented in post prostatectomy patients, the critical first patient evaluation step is to determine whether the recurrence is due to local recurrence or disseminated disease. Certain clinical features can help predict this distinction. For example, a PSA failure within 6 months of surgery is highly suggestive of metastatic disease,[13,14] while patients with positive surgical margins are more likely to have locally recurrent disease.[15] Interestingly, capsular involvement is not predictive of local recurrence.[16] Invariably, radiographic evaluation includes CT imaging and bone scan, although these are often negative unless the PSA approximates 20.[17]

Radionuclide Imaging

For post prostatectomy patients suspected to harbor undetected cancer recurrence, radioimmunoscintigraphy (RIS) may help define the extent of disease. In this technique, radiolabeled monoclonal antibodies specifically bind to prostate-specific membrane antigen (PSMA), a protein expressed higher in malignant versus benign prostate cells. Rather than being dependent on a tumor size, RIS depends on the degree of biomarker expression (ie, PSMA).[18] The radiopharmaceutical currently in clinical use is the ^{111}In-capromab pendetide, ProstaScint, approved by the FDA in 1996 to detect distant metastasis in both high-risk patients with newly diagnosed prostate cancer and in patients with increasing PSA levels after radical prostatectomy. This monoclonal antibody specifically binds to the intracellular epitope of PSMA on prostatic epithelial cells, excluding secretory glycoproteins. When used after radical prostatectomy, ProstaScint has a sensitivity of 75% to 86% and a specificity of 47% to 86% in detecting local recurrence.[18] There are conflicting data in the literature concerning the effective use of ProstaScint in determining the need for further therapy in the post prostatectomy setting. For instance, early studies reported that bone metastases cannot be detected by ProstaScint. Importantly, there is no observed difference in PFS in those with a positive scan versus a negative scan.[18,19] Further, any positive predictive value of ProstaScint is low (27% to 50%), perhaps due to false-positive scans from postsurgical inflammation and vascular perturbations.[18,20] Based on the currently published literature, ProstaScint scans should not be used in recommending salvage radiation therapy after radical prostatectomy.[18-21]

For potential improvements in radionuclide approaches to detect PSMA, additional strategies are being explored. These include antibodies binding the extracellular region of PSMA instead of the intracellular, and radiolabeling with various compounds (^{89}Zr and ^{64}Cu have yielded positive results in mouse models).[22-24] Aptamers is another class of radiopharmaceutical that has target specificity and affinity similar to that of antibodies. Aptamers fold into a unique 3-dimensional conformation that is complementary to the surface of the target, and their use has generated specific binding to PSMA-positive cells in vitro.[25] Additionally, low-molecular-weight PSMA inhibitors are showing promise in early clinical studies.[24,26]

The role of other imaging modalities to define the site of recurrent disease is a rapidly evolving field. Initial results with FDG-PET imaging were extremely disappointing. More recent trials using alternative radiolabelled compounds including F18 and C11 Choline suggest improved sensitivity to detect both metastatic disease in lymph nodes and bone. However, the positive predictive value as defined by prolonged PSA-free survival after local salvage is not known. Further, the value in patients with PSA values less than 1 ng/ml seems low.[27] Accordingly, in the setting of biochemical relapse, these modalities are considered investigational.

Salvage Radiation Therapy

The importance of forming a clinical judgment about local versus systemic recurrence lies in the ability to salvage some surgical failures with radiation therapy. Large retrospective studies provide evidence that early salvage radiation therapy, delivered to patients with rapid PSA doubling time (PSADT), or while the PSA levels remain below 2.0 ng/mL, influences survival of patients with BCR.[15,28] In a study carried out at Duke University, 519 patients[29] were examined, and it was determined that salvage radiation therapy significantly ($P = .02$) improved overall survival at a median follow-up of 11.3 years. A study at Johns Hopkins followed 635 patients[28] and determined that salvage radiation therapy was associated with a 3-fold increase in prostate cancer–specific survival after a median follow-up of 6 years after BCR compared with observation alone. However, this improvement was limited to men with a PSADT of less than 6

months. Interestingly, salvage radiation therapy was still associated with significant improvement in prostate-specific survival when administered to patients with a PSA greater than 2 ng/mL, only if those patients also had a PSADT of less than 6 months. No significant increase in prostate cancer–specific survival was observed in patients who were administered salvage radiation therapy more than 2 years after PSA recurrence.[28] It is important to note that the use of salvage radiation post prostatectomy is associated with significantly higher rates of both acute and long-term toxicity, including gastrointestinal and genitourinary complications.[30] In fact, impotence after salvage radiotherapy is almost universal.[31] Given the aforementioned benefits and toxicities, the ultimate decision to proceed with salvage radiotherapy depends on the clinician's judgment that the recurrence is localized to the prostatic fossa. It should be remembered that the studies cited did not employ the most current imaging modalities, and that as these improve the likelihood that disease is localized will also improve the outcomes for patients who are treated with salvage radiotherapy.

PSA Recurrence After Radiation

Following radiation treatment, the PSA levels typically do not fall to zero and the kinetics of PSA decline are different than that post prostatectomy.[9] There have been several definitions offered to define BCR after radiation. One example is the Phoenix definition, which states that an increase in the PSA level by 2 ng/mL or more above the nadir constitutes BCR. The goal of the Phoenix definition is to predict clinical recurrence and progression rather than BCR alone. This approach results in substantially lower estimates of BCR at 5 years, and substantially higher estimates of BCR at 10 years compared with the traditional American Society for Radiation Oncology (ASTRO) definition. As with BCR after surgical relapse, an attempt is made to define probable local recurrence versus probable disseminated disease. In addition to the aforementioned imaging, Doppler ultrasound and ultrasound-guided biopsy of residual prostate tissue is occasionally pursued and can occasionally identify local recurrence; however, it is not a very sensitive or reliable approach.[32]

Surgical Salvage After Radiation

There has been extensive experience with salvage prostatectomy following radiation, but it is typically acknowledged that salvage radical prostatectomy is associated with a higher complication rate than this surgical approach without prior radiotherapy.[33,34] Due to the fibrotic response to potentially curative radiotherapy, surgery is often not curative and is often associated with severe toxicity including bladder and rectal injury that may require urinary or fecal diversion.[35] Further, patients receiving salvage surgery have been shown to have a higher probability of medical and surgical complications, including urinary tract infection, bladder neck contracture, urinary retention, urinary fistula, abscess, and rectal injury. Also, approximately 75% of patients with salvage prostatectomy experience impotence.[34] For these reasons, this surgery should be only performed by highly skilled surgeons operating at centers of excellence with experience managing these patients. Other local modalities to treat local recurrence after radiation therapy, such as cryoablation, should be considered experimental.[36]

Efficacy and Limitations of Available Treatment Modalities

If the clinical decision has been made that local recurrence is unlikely, or that treatment options for managing local recurrence are not appropriate, a different algorithm must be pursued. Treatment decisions for these patients with BCR must balance the attempt to delay the onset of metastatic disease and death while avoiding the over-treatment of a disease that may never affect overall survival or quality of life. Rather than just an increasing PSA value, a more beneficial measure influencing the need to treat BCR may be the PSADT. The PSADT is a mathematical determination of the length of time (in months) needed for the PSA level to double in a given patient and has been shown to be a strong predictor of metastasis. A PSADT of less than 3 months is statistically related to the risk of death from prostate cancer and is proposed to be an indicator for the initiation of systemic treatment.[37] Alternatively, BCR patients with a PSADT greater than 9 months have a high probability of long-term, metastasis-free survival and overall survival. Recent evidence suggests there is no benefit from early intervention with androgen deprivation therapy [ADT] in these low-risk, clinically indolent patients.[38]

The discussion regarding active surveillance versus early intervention is not just of academic interest. Advantages to active surveillance include: 1) avoiding side effects from potentially unnecessary therapy, 2) maintaining normal daily activities and quality of life, 3) preventing small indolent cancers from receiving unnecessary treatment, and 4) decreased cost. There are, however, some downsides to taking the active surveillance approach that patients and caregivers should discuss: 1)

potential for metastasis to occur, 2) treatment of a larger, more complex cancer later may be more challenging, 3) patients may experience enhanced anxiety knowing they have untreated cancer, and 4) frequent medical examinations are required and appropriate timing and true value of imaging remains unclear. The recommendation of active surveillance must be considered individually for each patient and also include considerations of life expectancy, general health status, specific characteristics of their disease, treatment side effects, and patient choice. The National Comprehensive Cancer Care network (NCCN) Guidelines panel supports a strong need for more detailed clinical research addressing the criteria defining "active surveillance," for reclassification on active surveillance, and the patient schedule for those who fall into this category (timing of biopsies, etc).

Androgen Deprivation Therapy

ADT is the standard initial therapy in patients with recurrent, disseminated prostate cancer. ADT can be achieved via bilateral orchiectomy or via gonadotropin-releasing hormone (GnRH) agonists and antagonists. Although ADT is the first-line approach in the treatment of advanced or metastatic prostate cancer, it is often fraught with disadvantages, including both acute and long-term toxicities as well as high cost.

GnRH agonists, such as goserelin and leuprolide, are the standard of care in hormonal therapy for the management of advanced prostate cancer. Their mechanism of action is to bind to GnRH receptors to produce an initial stimulation. This initial activation leads to strong increases in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. Continuous overstimulation of the pituitary gland eventually desensitizes the GnRH receptors followed by a decreased hormone level.[39-41] Although the standard of care, GnRH agonist therapy is often complicated by testosterone surges and microsurges[42] upon subsequent injections. Although the clinical implications of these microsurges are unknown, they often accompany intensified clinical symptoms and delayed therapeutic effects.[39] These "flares" abate after a few months of therapy, and their clinical significance remains unknown.

More recently, GnRH antagonists have been developed as a new class of ADT. Antagonists act faster than agonists by blocking GnRH receptors to immediately inhibit the secretion of LH and rapidly suppress testosterone production, without the initial surge of LH or testosterone.[39,40] The first GnRH antagonist available for treatment of prostate cancer was abarelix, but was pulled from the US market after being associated with systemic anaphylactic-like reactions. Degarelix, a third-generation antagonist and the only one currently available for use in the United States, has a synthetic modification to reduce histamine-releasing activity to avoid systemic anaphylactic reactions.[39,43] Degarelix was as effective as the GnRH agonist leuprolide in the suppression of testosterone to castrate levels in a phase 3 CS21 trial for 1 year.[39] Significantly larger decreases in PSA values were observed at day 14 and 28 for the degarelix group versus the leuprolide group, indicating a more rapid treatment response.[39] Importantly, degarelix is not associated with testosterone microsurges upon repeat injections.

If it is determined that a patient should be given ADT therapy upon BCR, a critical question is whether treatment should be given continuously or on an intermittent basis. This is an important consideration because although treatment has the potential to slow the cancer growth, ADT is also associated with serious side effects, high costs, and quality-of-life issues. Some of these side effects may be lessened by intermittent therapy. Together, the patient and physician need to weigh the advantages and disadvantages of intermittent ADT.

Intermittent ADT treatment (IAD) is a cyclic process whereby treatment induction continues until a maximal PSA response is achieved. On-treatment periods usually last 6 to 9 months or until a PSA nadir is less than 4 ng/mL. Off-treatment periods are more variable, with treatment reinstated if PSA increases. Optimal thresholds for stopping/resuming ADT are empirical, and the best candidates for IAD have not been completely defined. After treatment ceases, there should be a clinical examination every 3 to 6 months (the more advanced the disease, the closer the follow-up), and PSA should be monitored. Treatment is resumed if there is either clinical progression or a PSA value above a predetermined, empirically fixed threshold (usually 4-10 ng/mL in nonmetastatic or 10-15 ng/mL in metastatic patients). Employing the IAD approach can allow testosterone levels to recover during each off-treatment cycle, lessening sexual dysfunction and loss of bone mass often associated with continuous androgen deprivation (CAD). Additional benefits of IAD include an improved quality of life and decreased drug costs.[44] Further, when 8 randomized control trials were evaluated by meta-analysis, there was no difference in overall survival between patients treated with IAD versus CAD (4339 patients; hazard ratio [HR] = 1.01; 95% CI, 0.93-1.10); nor was there any difference in cancer-specific

survival (HR = 1.03; 95% CI, 0.88-1.21).[45] Additionally, most of the 8 studies determined an improvement in quality of life or toxicity profile with IAD. This meta-analysis confirms IAD as a valid standard of care for managing prostate cancer patients.[45]

Given the residual challenges associated with standard ADT, a number of alternatives involving both hormonal manipulations are being investigated. Additional GnRH antagonists currently under investigation for use in prostate cancer[40] include acycline[46,47] and ozarelix.[48] Abiretarone and enzalutamide, novel hormonal therapies currently FDA-approved for castration-resistant disease, are being examined in the BCR setting.

Acyline[46,47] is a GnRH antagonist available in an oral dosage form, in contrast to current injectable therapies. The advantage of an oral agent would eliminate the inconvenience of injections, avoid injection site reactions, and allow individualized dosing regimens.[44] In an initial study of healthy men, oral administration of acyline suppressed testosterone and gonadotropin levels without unwanted side effects, boding well for its potential utility in the management of prostate cancer.[44]

Ozarelix is a fourth-generation LHRH antagonist that has demonstrated an induction of apoptosis in prostate cancer cells that were castration-resistant and androgen-receptor-negative.[48] Further, ozarelix treatment led to a suppression of testosterone levels in a dose-dependent manner with an absence of testosterone surge or clinical flare in early trials of healthy volunteers. It is currently under phase 2 investigation to assess the safety and efficacy of monthly doses compared with goserelin.[49]

The chemotherapeutic agent docetaxel is a well-established treatment option that improves survival for patients with mCRPC. A recently reported study has shown marked survival advantage when docetaxel is added to ADT early in the treatment of men with newly diagnosed hormone-sensitive prostate cancer.[50-53] Although chemotherapy has been proved to improve overall and progression-free survival in men with metastatic prostate cancer, many patients do not receive such therapy due to preexisting conditions or associated side effects. Effective, convenient, and less toxic therapies are greatly needed.

Natural Products

Although there is a lack of quality data supporting the use of natural products for the treatment of prostate cancer, many patients with BCR have found success in lowering their PSA levels without experiencing the negative side effects of ADT. There is little documented evidence that these products alter the clinical course of BCR prostate cancer, and they may not be safe in the quantities or formulations being sold.

One of the most popular natural products thought to be effective in reducing PSA levels is pomegranate juice and extract, based on its antioxidant roles. Two pomegranate trials have been published,[54,55] and both demonstrated improvement in PSADT. Initially, in a single-arm phase 2 trial in 2006, Pantuck and colleagues treated men with rising PSA after initial surgery or radiotherapy (PSA >0.2 and <5 ng/mL and a Gleason score ≤7). Patients were given 8 ounces of pomegranate juice daily until disease progression. PSADT values were significantly increased from a mean of 15 months to 54 months.[55] Paller and colleagues followed up these results with a randomized, multicenter, double-blind phase 2 dose-exploring trial.[54] In this trial, men with a rising PSA, but with no metastases, were given 1 g (45 patients) or 3 g (47 patients) of pomegranate extract in capsule form and treated for up to 18 months. The median PSADT increased from approximately 12 months at baseline to approximately 18 months for either dose. Both of these trials, though, are greatly limited by the lack of a placebo arm. A trial with participants undergoing active surveillance for early-stage prostate cancer that includes a placebo control is currently under way to determine the effect of pomegranate fruit extract (1000 mg), taken daily for 1 year, on the plasma levels of insulin-like growth factor (IGF-1), PSADT, and serum testosterone levels, among other objectives (NCT02095145).[56]

Other natural products that have been studied for their potential in reducing cancer based on antioxidant effects include muscadine grape skin extract,[57] Chinese grass seed oil, acai berries,[58] and Brassica vegetables.[59] Resveratrol, a phytochemical produced by a wide variety of plants (including grapes, peanuts, and mulberries), can inhibit cancer cell growth in response to stress.[57] Through its antioxidant activity, resveratrol in red grapes has been shown to inhibit prostate cancer cell growth in culture conditions; however, muscadine grapes contain unique phytochemicals and are devoid of resveratrol. In an effort to identify novel compounds with antitumor activities, muscadine grape skin extract was tested on primary normal prostate cancer cells.[57] A randomized, double-blind, placebo-controlled phase 1/2 study of Muscadine Plus (MPX) is currently investigating multiple dosage effects on rising PSA levels in men following initial therapy for prostate cancer.[60]

Members of the Brassica family of vegetables (cabbage, radishes, cauliflower, broccoli, and Brussels sprouts) produce indole-3-carbinol (I3C), which has been shown to suppress tumor cell growth in vitro.[59] However, human studies in the Netherlands,[61] United States,[62] and Europe[63] of people who ate a wide variety of daily cruciferous vegetable found little or no association with prostate cancer risk. Nevertheless, some case-controlled studies have demonstrated that people who ate greater amounts of cruciferous vegetables had a lower risk of prostate cancer.[64,65]

Current Guidelines

National Comprehensive Cancer Network (NCCN)[66]

Post prostatectomy radiation therapy should be offered as adjuvant/salvage therapy in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.

- Indications for adjuvant radiation therapy (usually given within 1 year after radical prostatectomy and once any operative side effects have improved/stabilized) include pT3 disease, positive margin(s), Gleason score 8-10, or seminal vesicle involvement. Patients with positive surgical margins and a PSADT greater than 9 months may benefit the most.
- Indications for salvage radiation therapy include an undetectable PSA that becomes detectable and then increases on 2 subsequent measurements. Treatment is most effective when pretreatment PSA is less than 1 ng/mL and PSADT is slow.
- The recommended prescribed doses for adjuvant/salvage post prostatectomy radiation therapy are 64 to 70 Gy in standard fractionation.

If a patient has biochemical relapse after local therapy, it should first be determined if they are a candidate for salvage therapy. If they choose to undergo ADT, healthcare providers should use caution when initiating hormonal therapy for men with asymptomatic prostate cancer in the absence of overt metastases, as there is little evidence that treating these BCR patients improves survival. Treatment at this stage is only a benefit to a subset of patients with adverse tumor characteristics.[67] There is no notable difference in the effectiveness of IAD versus CAD; thus, the US Preventive Services Task Force[66] recommends using IAD in place of CAD in most cases. The timing of ADT initiation should be individualized according to PSA velocity, patient anxiety, and potential side effects. Patients with shorter PSADT or rapid PSA velocity and a long life expectancy should be encouraged to consider early ADT.

American Society for Radiation Oncology/American Urological Association (ASTRO/AUA)[30,68]

This comprehensive review of 324 research articles published from 1990 to 2012 provides the following clinical principles, recommendations, standards, and options:

- Patients who are being considered for treatment of localized prostate cancer with radical prostatectomy should be informed of the potential for adverse pathologic findings that portend a higher risk of cancer recurrence.
- Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiation therapy reduces the risk of biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer when compared with radical prostatectomy only.
- Physicians should offer adjuvant radiation therapy to patients with adverse pathologic findings at the time of prostatectomy, including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression.
- Patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease.
- Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is 0.2 ng/mL or greater with a second confirmatory level of 0.2 ng/mL or greater.
- A restaging evaluation in the patient with a PSA recurrence may be considered.
- Physicians should offer salvage radiation therapy to patients with PSA or local recurrence after radical prostatectomy in whom there is no evidence of distant metastatic disease.
- Patients should be informed that the effectiveness of radiation therapy for PSA recurrence is greatest when given at lower levels of PSA.
- Patients should be informed of the possible short-term and long-term urinary, bowel, and sexual side effects of radiation therapy, as well as of the potential benefits of controlling disease recurrence.

Conclusions

BCR after definitive local therapy is a clinically heterogeneous disorder. The identification of patients with BCR initially treated with surgery or with primary radiotherapy employs different criteria and has distinct treatment options depending on whether the BCR is due to local failure or systemic failure. In all patients, an initial attempt to answer this question will steer the patient toward the appropriate treatment algorithm. In patients with local recurrence, definitive and potentially curative local salvage modalities should be considered. In patients for whom systemic relapse is suspected, the first and most important decision is whether immediate therapy is required or whether active observation is the best approach. Although there are clinical factors to identify a subset of patients who might benefit from early treatment, the decision is often not straightforward. Further, the standard approach of ADT carries significant toxicity and cost considerations. If the decision to proceed with treatment is made, some of these toxicities may be ameliorated with an intermittent treatment approach. Several standard ADTs are available, and new investigative hormonal options may offer better efficacy, greater convenience, or less toxicity. In addition, early chemotherapy, novel immunotherapies, and anti-angiogenic treatments are under investigation as adjuncts to ADT to further improve patient outcomes. Finally, alternative approaches including pomegranate juice, resveratrol, and cruciferous vegetables have shown some in vitro promise and may prolong PSADT, but their clinical benefit remains unclear. As with all other treatment in men with prostate cancer, a thorough assessment of health and comorbidities, as well as patient goals and wishes, plus the best available biological predictors of tumor behavior, need to be considered in formulating an effective treatment plan. Given the frequency of this clinical problem, and the associated financial and human costs of therapy, this remains the best path forward.

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