Natural History of Biochemical Recurrence after Radical Prostatectomy: Risk Assessment for Secondary Therapy

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Abstract

Purpose: A persistently elevated or rising serum level of prostate-specific antigen (PSA) after radical prostatectomy is indicative of recurrent prostate cancer. The natural history of PSA-defined biochemical recurrence (BCR) is highly variable. While a rising PSA level universally antedates metastatic progression and prostate cancer-specific mortality (PCSM), it is not a surrogate for these endpoints. Thus, the management of patients with BCR is controversial.

Methods: A literature review was conducted to determine the incidence and natural history of BCR, prognostic factors for clinical progression (CP), and the available evidence supporting local or systemic salvage therapy for these patients.

Results: BCR is best defined as two successive PSA levels ≥0.4 ng/ml, as this correlates most accurately with CP. PSA doubling time (PSA-DT) and prostatectomy Gleason score are the variables that best predict the development of distant metastasis and PCSM. Prognostic models based on these and other variables are useful for assessing the need for salvage therapy and the anticipated outcome following local salvage therapy. A treatment algorithm for managing patients with post-prostatectomy BCR was devised.

Conclusions: Management of patients with BCR after prostatectomy continues to be a complex and challenging issue. Improved methods for risk stratification allow for identification of patients who require treatment. Furthermore, these methods aid in determination of the pattern of disease recurrence, thereby guiding treatment modality. Randomized trials are essential to determine the value of local or systemic salvage therapy strategies in this patient population.

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1. Introduction

Between 230,000 to 240,000 men are diagnosed annually with prostate cancer in both Europe and the US [1,2]. Approximately 40% who choose definitive therapy will undergo radical prostatectomy (RP). While overall cancer control rates are high for clinically localized disease, 20–30% of patients will experience recurrence manifested initially as a rising serum prostate-specific antigen (PSA) without clinical or radiographic metastases [3]. This biochemical recurrence (BCR) is indicative of the presence of prostatic epithelial tissue, and is assumed to represent cancer.

The clinical course of patients with BCR is highly variable. Some experience rapid clinical progression (CP) to metastases. For others, a rising PSA may pose no threat to longevity. Ten-year survival data has shown that overall survival for men with and without BCR are similar (88% vs. 93%) [4]. Thus, BCR is not a surrogate for CP or prostate cancer-specific mortality (PCSM), and is loosely associated with the development of metastases.

Due to the absence of randomized clinical trials evaluating salvage therapy for patients with BCR, no intervention has been proven definitively to improve survival or prevent the development of progressive disease. As such, treatment paradigms for these patients are mostly derived from retrospective observational studies of local or systemic salvage therapy, or by extrapolating evidence from clinical trials of adjuvant therapy or for metastatic disease. For these reasons, guidelines for treatment of patients with BCR have been difficult to establish.

For patients with BCR, an assessment of the risk that recurrent disease poses to longevity or quality of life should be made. Many patients have indolent disease that grows slowly and requires no treatment, but some will have rapid progression to metastasis. This is illustrated by the findings of Pound, who reported the 5-year risk of CP ranged from 27–60% in untreated men with BCR [5]. A critical issue for patients at risk for CP is determination of whether a rising PSA represents local or systemic disease, as the former may be cured by salvage radiotherapy. Management of patients with a rising PSA is based on the risk of CP, the patient’s life expectancy, and determining whether a rising PSA represents local or systemic disease.

This review focuses primarily on the natural history of BCR, and also on recent advances that have allowed for improved prediction of the clinical behavior. Risk assessment and treatment strategies are discussed. An algorithm is presented to assist in the management of patients with BCR. Finally, treatment options are summarized.

2. BCR defined

BCR is defined as any detectable level of PSA after prostatectomy or a PSA rise after a period of PSA detection absence. The half-life of PSA is 3.1 days, and after RP the PSA level should decrease to an undetectable level after 4 weeks [6]. Periodic PSA testing after RP is the cornerstone of post-operative surveillance strategies for recurrent disease, however there is no data to support a specific recommendation. Our routine is to check the first PSA at 6 weeks to coincide with the patient’s post-operative visit. For most patients it is then checked every 6 months, or more often in patients at high risk of relapse.

There is no consensus regarding standardized PSA criteria that define clinically-significant BCR. Definitions in the literature include single or multiple PSA values between 0.2–0.6 ng/ml. The most commonly cited limit for PSA after RP is ≥0.2 ng/ml, and two sequential PSA values ≥0.2 ng/ml is accepted by the EAU as the basis for treatment initiation [7]. Amling examined the clinical relevance of PSA cut-off values, and found that the progression-free proportion decreased as the limit value increased from 0.2–0.4 ng/ml [8]. Half of men with PSA values from 0.2–0.29 ng/ml tended to stabilize in this range, while the other half showed continued elevation. Of men with a PSA level ≥0.4 ng/ml, 79% demonstrated evidence of CP. Their recommended definition of BCR was PSA ≥0.4 ng/ml. Based on these data the PSA Working Group accepted the definition of BCR as PSA >0.4 at a minimum of 1 month after surgery, followed by a subsequent PSA value equal to or greater than the first measurement [9].

A recent study attempted to identify the BCR definition that best predicts development of metastatic disease among 10 definitions selected on the basis of acceptable sensitivity. PSA ≥0.4 ng/ml followed by another higher value was the best predictor of CP, and was also associated with a high probability of subsequent PSA progression, a rapid PSA-DT, and the need for subsequent secondary therapy [10]. These data indicate that two successive PSAs ≥0.4 is the optimal definition of BCR that predicts clinically significant events.

Patients with low level (i.e., PSA ≤0.29 ng/ml) BCR tend to have a lower incidence of CP [8]. This likely reflects one of two scenarios. The first possibility is recurrence of a low-volume or indolent tumor. The
second possibility is that PSA is being produced by benign prostate tissue that was left behind after RP. The contribution of benign tissue to increasing PSA levels after RP has been debated. Based upon the presence of elevated urinary PSA levels after RP, deVere White demonstrated that up 80% of patients had residual prostate tissue [11]. Djavan reported a 27% incidence of positive benign margins, predominantly located at the posterior midline and lateral regions. Over a 5 year follow-up, 61% of these patients had BCR [12]. In contrast, several studies have shown no significant correlations of benign residual tissue and BCR [13–15].

3. Natural history of BCR

To identify the benefit of treatment in patients with BCR, their clinical course in the absence of treatment (i.e., natural history) must be examined. A summary of results from numerous studies is presented to demonstrate trends in BCR, CP, PCSM, and overall mortality (OM) of RP cohorts (Table 1).

The most comprehensive study of the natural history of BCR was conducted in a cohort of 1997 men who underwent RP between 1982–1997 at Johns Hopkins [5,16]. In this cohort, 25.8% had stage ≥T2b, 40% had a specimen Gleason score ≥7, and 46% had organ-confined disease. BCR occurred in 15% of these men, and time from RP to BCR averaged 3.5 years. Of men with BCR 17% died from prostate cancer. The 5-year risk of CP in men with BCR ranged from 27–60%, and correlated with the time interval from RP to BCR, the prostatectomy Gleason score, and the PSA doubling time (PSA-DT). Median time from BCR to CP was 8 years. The risk of PCSM at 5, 10, and 15 years was 7%, 27%, and 65%. The median time from CP to PCSM was 5 years.

There appears to be an equal risk of PCSM and death from competing causes at the time of BCR. A recent report analyzed survival in a large RP cohort at our institution, and stratified patients into low- and high-risk categories [4]. High risk patients had initial PSA >10 ng/ml (32%), clinical stage ≥T2b (21%), and a specimen Gleason score ≥7 (55%). Overall 10-year survival of patients with PSA ≥10 and stage ≥T2b was decreased by 9% (93% to 84%) and 19% (95% to 76%), respectively. Interestingly, there was no difference in 10-year overall survival between those with and without BCR in both low and high risk groups. Bianco examined the natural history of BCR in a cohort of 1746 men who underwent RP over a 20 year period beginning in 1983 [17]. Of these men 17% experienced BCR, and PCSM at 5, 10, and 15 years was 1%, 5%, and 11% respectively. Of those with BCR, PCSM and non-cancer-related mortality were equivalent at 15 years (33%). Thus a quandary exists regarding the usefulness of BCR for determination of the need for secondary therapy.

Characteristics of the natural history of BCR is variability in disease course and protractedness of CP and PCSM. Overall these studies demonstrate a general trend among men with BCR after RP – for every 100 men treated with RP – for every 100 men treated with RP, approximately 15–30 will develop BCR, and 2–6 of those will die from prostate cancer. These numbers may be even higher in European centers, as selection criteria for RP is

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less stringent. Many European cohorts have higher numbers of T3 disease, Gleason score ≥7, and pre-operative PSA ≥15 ng/ml. Regardless of geographic variations, only 10–15% of patients with BCR are at high risk for progression, and they are most likely to benefit from secondary therapy. Identification of markers for “clinically significant” BCR has been the focus of intense research.

4. **BCR and risk prediction**

Two major distinctions should be made regarding the course of treatment of patients with BCR – severity of disease, and location of recurrence. Indolent cancer will typically be treated more conservatively, while progressive disease may prompt aggressive therapy. Identification of the disease site will determine the type of treatment that is likely to be of greatest benefit.

PSA kinetics have been extensively investigated for their usefulness as predictors of CP and PCSM. PSA-DT after RP correlates strongly with CP and PCSM. Zhou investigated predictors of PCSM in 489 men with BCR [18]. Correlates of CP included PSA-DT, Gleason score, and time from RP to BCR. They found that a PSA-DT of ≤3 months correlated strongly with PCSM. PCSM 5 years after BCR was 31% in men with PSA-DT ≤3 months versus 1% for men with PSA-DT ≥3 months. A subsequent study investigated PSA kinetic patterns associated with metastatic disease [19]. It found that clinically significant BCR was characterized by a post-operative PSA-DT of ≤3 months. This kinetic trend was associated with a pre-operative PSA velocity of ≥2 ng/ml/year, and specimen Gleason grade ≥7. Clinically insignificant BCR was characterized by PSA-DT ≥12 months. Men with this kinetic trend typically had a pre-operative PSA of <10, impalpable disease, and Gleason score of 6 (Fig. 1).

Post-operative PSA-DT appears to be a surrogate for PCSM [18,20]. D’Amico identified patients at high risk for BCR based on PSA-DT and biopsy Gleason score. However, only 10–15% of men with BCR will present with a PSA-DT ≤3 months. Patel found a strong correlation between PSA-DT ≤3 months and CP, but 43% of patients with CP in that cohort had PSA-DT ≥6 months [21]. Additional data supports that the majority of men who die from prostate cancer have PSA-DT ≥3 months [AUA 2006 Abstract #1188], thus it is not advisable to base risk assessment solely on PSA-DT.

Fig. 1 – Cumulative incidence estimates of PCSM and Kaplan and Meier estimate of overall mortality (OM) stratified by the post-operative PSA-DT. Log-rank p value for PCSM = 0.002; log-rank p value for OM = 0.003. (Reprinted with permission from D’Amico AV, et al. Identifying Patients at Risk for Significant Versus Clinically Insignificant Postoperative Prostate-Specific Antigen Failure. J Clin Oncol 23;2005:4975–9.)

It is assumed that rapid PSA-DT reflects a rapidly growing tumor mass. If mitosis and gene expression rates are held constant, then tumor mass and PSA levels should increase exponentially. PSA levels measured at two time points must therefore be mathematically converted to accommodate this non-linear growth. The vast majority of patients exhibit a first-order kinetic rise in PSA. A small subset exhibit a faster rise that reflects second-order kinetic growth. Truskinovsky studied PSA-DT kinetics and found that there was no correlation with first- and second-order growth patterns and PCSM [22]. In this regard, PSA-DT seems to have reached its maximum prognostic potential using the current ≤3 month risk stratification.

4.1. **Nomograms and risk stratification**

Risk assessment must take the variable nature of prostate cancer behavior into account. A multivariable assessment scheme using pathologic, clinical, and biochemical data is required. Pathologic correlates of CP have been extensively characterized, and are used in conjunction with biochemical data to calculate prognosis. Tumor characteristics such as extracapsular extension, seminal vesicle involvement (SVI), lymphovascular invasion, and pre-operative PSA also factor into prognosis prediction.

Contemporary nomograms aid in assessing risk of CP and PCSM for individual patients.
Post-operative nomograms to predict the likelihood of PCSM after RP have been developed. The Pound algorithm is based on outcomes of 1997 men with BCR after RP who were followed from 1982–1997 [5]. The algorithm assigns a likelihood of CP after BCR, and is based on duration of BCR-free interval, Gleason score, and PSA-DT. Freedland reported a system for risk stratification to predict PCSM based on BCR-free interval, Gleason score, and PSA-DT [16]. Significant risk was indicated by a PSA-DT ≤3 months, Gleason ≥7, and time from RP to BCR of ≤3 years. Caution must be taken to prevent over-interpretation of algorithm results, and it should be emphasized that the nomograms have not been internally or externally validated.

Other nomograms have been devised to predict risk of extrapelvic CP. Positive bone scan is a proxy for CP and PCSM. Dotan evaluated 60 men with positive bone scans after BCR, and devised a nomogram to predict the probability of a positive scan [23]. The rate of rise of PSA and the PSA level at the time of the bone scan were the most important predictors. This nomogram may prove useful in identifying both high risk patients that require metastatic evaluation, and also low risk patients in whom bone scans may be deferred.

4.2 Disease recurrence pattern

A key distinction that impacts management is whether the recurrence is local or systemic. Once the risk of CP is assessed using a nomogram, an effort to identify the site of recurrence should be initiated. If tumor is detectable using methods such as TRUS, bone scan, or anastomotic site biopsy, then it is usually too late – cancer has likely disseminated. Because most conventional diagnostic modalities are limited, the decision to administer secondary therapy should be based on PSA.

Older data support that BCR is due predominantly to occult systemic metastasis, and that only 6–19% of patients with BCR have localized recurrence [24–26]. However, recent studies suggest that the incidence of local recurrence has been underestimated. A randomized trial of RP versus watchful waiting demonstrated that the incidence of local recurrence was twice as high as metastatic recurrence in patients who underwent RP [26,27]. Two studies of pelvic fossa biopsy in patients with BCR demonstrated positive biopsy results in 42% of patients [28,29]. These studies were conducted early in the PSA era, and it is not clear whether this data holds true currently. A recent MRI study demonstrated evidence for local tumor recurrence in 81% of men with BCR [30]. However, this study included patients who had surgery as long as 13 years ago, and did not verify MRI lesions with positive biopsy. Outcome studies in patients with BCR after RP treated with salvage EBRT have documented a ≥60% complete response rate [31–33]. This suggests that a large percentage of patients with BCR have localized recurrence that can potentially be treated with EBRT. The limitations of these studies prevent accurate estimation of the true incidence of localized recurrence, but it is likely that it occurs at a rate higher than 19% as reported in the past.

In order to better assess the site of recurrence a predictive nomogram to determine likelihood of response to salvage radiotherapy was created [34]. A cohort of 501 men treated with EBRT for BCR after RP was examined. During a follow-period of 45 months, the 4-year recurrence-free probability was 45%. Multivariate Cox regression analysis revealed that pre-radiotherapy PSA, Gleason score <7, positive surgical margins, lack of SVI, and PSA-DT >11 months correlated with durable response to EBRT. However, subsets of patients with adverse features such as a short PSA-DT and/or poorly differentiated cancer also derived a benefit from salvage radiotherapy if it was administered at low PSA levels.

Bone scans can be used to detect disseminated disease in select patients. One study showed that median PSA in patients with a positive bone scan was 158.0 ng/ml, while a negative scan had a median PSA of 11.3 ng/ml [35]. In another study predictors of a positive bone scan included PSA ≥30 ng/ml and PSA velocity of ≥5 ng/ml/month. In contrast, recent data from our institution has shown that neither absolute value of PSA nor PSA-DT predicts likelihood of positive CT or bone scan [ASCO 2006 Abstract #206].

Nuclear imaging has the theoretical advantage of being able to specifically detect local and disseminated tumor tissue. PET/CT scanning using 111In-Capromab Pendetine Immunoscintigraphy (Prostascint, Cytogen Corp., Princeton, NJ) has shown promise, but its use in routine screening in men with BCR is not validated. PET is limited by low image resolution, and a high-false positive rate due to hypermetabolic conditions such as inflammation [36]. One recent study has shown that only 47% of men with positive scans responded to salvage RT, and of the responders, 30% had a relapse within 9 months after treatment [37]. Thomas examined whether Prostascint positivity correlated with salvage RT outcomes [38]. They found that there was no difference in PSA-free survival after salvage RT in men with extra-pelvic positive versus negative scans. Based on these findings it was concluded that Prostascint scanning was not useful to guide therapy.
Local recurrence can be detected by physical examination and imaging studies. DRE can be used to detect recurrent tumor in the prostatic fossa, however a positive DRE is likely to be associated with disseminated disease [29]. Obek identified an abnormal DRE in only 4 of 72 men with BCR after RP [39]. TRUS and prostatic fossa biopsy have been used to assess tumor status in the resection bed. Scattoni examined the predictive role of TRUS, DRE, and TRUS-guided 6/8 core prostatic fossa biopsy in patients with BCR [40]. In patients with positive biopsy the TRUS and DRE sensitivity and specificity were 75% and 50%, and 66% and 85%, respectively. Of men with PSA ≤0.5 TRUS was positive in 45%, but in men with PSA ≥2 it was positive in 100%. Naya demonstrated a biopsy positive rate of 29% in 100 consecutive patients with BCR [41]. Their recommendation was that biopsy should be avoided in men with negative DRE, TRUS, and with PSA ≤0.5. Koppie examined the correlation of biopsy positivity and PSA-free survival in patients who received salvage EBRT [42]. They found no difference in 3-year recurrence-free survival rates in patients treated for BCR (49%), versus those with biopsy-proven local recurrence (39%). This observation reflects the fact that a positive biopsy does not rule out the presence of metastatic disease, and anastomotic biopsy is no longer recommended to assess for local recurrence.

Another imaging modality that is emerging as a reliable means for prostate imaging is endorectal MRI. Sella examined the sensitivity of MRI in 41 patients with local recurrence verified by positive biopsy [30]. Endorectal MRI detected recurrent tumor in 39 patients. Average tumor size was 1.4 cm (range 0.8–4.5 m), and average PSA was 2.18 (range 0–10). Sensitivity of MRI was 95%, and specificity was 100%.

5. Treatment selection

No prospective randomized placebo-controlled studies of secondary treatment in patients with BCR have been conducted. Currently there is no conclusive evidence that secondary treatment will prolong survival or reduce morbidity. Despite the lack of evidence, salvage local or systemic therapy is advised in selected patients at elevated risk for progression to metastases and PCSM in the hope of decreasing the likelihood of reaching these endpoints. Because of the variability in the clinical behavior of recurrent prostate cancer, no rigid protocol exists to guide treatment. Therapy should be individualized based upon clinical and radiological assessment.

6. Algorithm for BCR management

We have devised an algorithm for treatment of patients with BCR (Fig. 2), with BCR defined as two successive PSAs ≥0.4 ng/ml. An initial metastatic evaluation consisting of chest radiograph and bone scan should be conducted. Patients with evidence of metastasis upon initial diagnosis of BCR should receive hormonal therapy (HT) or be directed to clinical trials.

For patients with BCR without metastasis, an assessment of life expectancy based on comorbidities and age should be conducted. Life expectancy is
typically a subjective assessment based on the patient’s state of health and comorbidities, but a recent nomogram published by Cowen et al can be utilized to predict life expectancy in men with localized prostate cancer with 70% certainty [43]. It is likely that this nomogram is applicable to men with and without BCR, as both groups have been shown to have equivalent PCSM and overall mortality as previously discussed. Men with a life expectancy ≥5–10 years should then have risk of CP calculated with a nomogram [5,16,19]. Patients can then be separated into low and high CP risk categories. Low risk patients with BCR may be observed with annual PSA and imaging studies.

In high risk patients EBRT should be considered. Likelihood of response to EBRT can also be assessed using a nomogram [33,34]. Patients with high likelihood of response should be referred to radiation oncology. Patients with expected low likelihood of response to EBRT or who are unwilling to accept associated morbidity should be monitored or treated with systemic therapy (androgen deprivation, nutritional intervention, or clinical trial enrollment of novel treatment approaches). Patients who receive EBRT who subsequently progress should receive HT therapy or be referred for clinical trials.

7. Secondary therapy

A comprehensive discussion of secondary therapy options would constitute the basis for a separate review. The purpose of this discussion is to focus on pertinent aspects of hormonal therapy (HT) and external beam radiation therapy (EBRT) in patients with BCR after RP. It should be emphasized that both of these therapies can be associated with significant morbidity, and should be administered in a highly selective manner.

7.1. Hormonal therapy

Treatment for patients with evidence of CP has historically consisted of androgen ablation. There is currently no consensus regarding a PSA level that signals the requirement for HT initiation. One option is to delay administration of HT in men with BCR until symptoms or radiological evidence of CP. Another option is to administer HT prior to evidence of CP in high risk patients.

The use of HT in symptomatic men with BCR and no evidence of metastasis is controversial. Some evidence supports that early HT is associated with improvement in both CP-free and overall survival [44]. There have been no randomized controlled clinical trials looking at survival in men with BCR who receive HT. There have been several large trials that examined the effect of HT in a pre-metastatic setting. Two of six trials showed minor survival benefit, while the other four showed none (Table 2). The EPC trial showed a higher risk of death with Casodex in low risk patients [45,46]. While not specifically addressing BCR patients, the data showed no difference in CP-free and overall survival between patients treated with biclutamide and those treated with standard care.

Moul examined early vs. delayed HT for BCR in 1352 men with BCR received HT either prior to or after evidence of metastasis [47]. In the early HT group CP was delayed in patients with Gleason ≥8 or PSA-DT ≤12 months, but HT had no overall impact on PCSM. This study was limited by the selection and detection bias inherent in retrospective analyses.

The administration of HT in men with BCR is associated with significant side effects, including decreased libido, erectile dysfunction, gynecomastia, osteoporosis, and anemia. Hyperlipidemia and insulin resistance caused by HT increase risk for acute cardiovascular events. A recent observational

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OS: overall survival; ACM: all-cause mortality; PCSM: prostate cancer-specific mortality.

Conclusions:
1) No apparent benefit compared to deferred therapy for M0 patients.
2) No evidence that any intervention for BCR improves survival.
study of 73,196 men with prostate cancer demonstrated an elevated risk of incident diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death in those patients who received GnRH agonist treatment [48]. Risk for these events was elevated after as little as 4 months of HT. Men with orchietomy had an elevated risk of developing diabetes, but did not have elevated risk for myocardial infarction or sudden cardiac death, indicating that elevated risk was associated specifically with GnRH agonist treatment. These risks emphasize that use of HT in men at low risk of CP should be done cautiously if at all.

7.2. Salvage radiotherapy

Select patients will benefit from EBRT. Stephenson evaluated the likelihood of response to EBRT in men with BCR [33]. Patients with no adverse features had a 4 year progression-free probability (PFP) of 71%. High risk patients with Gleason score \( \geq 8 \) and positive margins had a 4 year PFP of 81% when the PSA-DT was \( >10 \) months and 37% when the PSA-DT was \( <10 \) months.

Katz examined outcomes of conformal RT in patients with BCR [49]. Predictors of PSA relapse included negative margins, absence of extracapsular extension, and presence of SVI. Adjuvant HT did not improve relapse-free survival. Pazona examined 307 men with salvage RT after BCR [50]. There was a 73% recurrence-free rate, with an average time to post-RT BCR of 23 months. The overall progression-free survival (PFS) rate at 5 and 10 years was 40% and 25%, respectively. In responders the 5- and 10-year PFS was 55% and 35%. Only SVI was associated with progression.

Leventis conducted a study to predict the response of salvage RT. Positive DRE, elevated pre-operative PSA, and post-operative PSA-DT were used to identify patients with local versus metastatic disease as evidenced by biopsy [28]. The response to RT was associated with pre-treatment PSA and post-treatment PSA-DT. Of 95 patients treated with RT the 3- and 5-year relapse-free rates were 43% and 24%, respectively. Overall, most data support that a high percentage of patients with BCR may have localized recurrence, and that these patients may benefit from EBRT. A prospective randomized clinical trial of EBRT in the setting of BCR will allow further assessment of this approach.

At our institution the current recommendation for salvage RT is a total dose 66–70 Gy administered over 6–7 weeks (33–35 treatments). Typically we do not administer ADT during RT because there would be no way to assess response to RT.

8. Conclusions

Management of patients with BCR after RP is complex. Current data supports that BCR defined as two or more PSA levels \( \geq 0.4 \) ng/ml most accurately identifies patients with clinically significant disease. The natural history of recurrent prostate cancer is variable, and we currently have no accurate means of identifying those who will progress. Therefore, administration of secondary therapy to all patients with BCR is unnecessary and potentially harmful. A majority of men with BCR will have a protracted course, and most will die from unrelated causes. In this regard observation and symptomatic treatment may be the best course of management.

In those with high likelihood of CP, early intervention may provide benefit. Several nomograms are available to assess the risk of CP based on a multifactorial approach. PSA-DT, pathologic Gleason score, and tumor stage have proven to be most important in determining prognosis. The treatment algorithm presented in this review provides a decision-making guide for treatment in this unique patient population (Table 3).

Conflicts of interest

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References


