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Management of Biochemical Recurrence After Primary Treatment of Prostate Cancer: A Systematic Review of the Literature

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Abstract

Context: Despite excellent cancer control with the treatment of localized prostate cancer (PCa), some men will experience a recurrence of disease. The optimal management of recurrent disease remains uncertain.
Objective: To systematically review recent literature regarding management of biochemical recurrence after primary treatment for localized PCa.
Evidence acquisition: A comprehensive systematic review of the literature was performed from 2000 to 2012 to identify articles pertaining to management after recurrent PCa. Search terms included *prostate cancer recurrence, salvage therapy, radiorecurrent prostate cancer, post HIFU, post cryoablation, postradiation*, and *postprostatectomy salvage.* Studies were selected according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and required to provide a comprehensive description of primary and secondary treatments along with outcomes.
Evidence synthesis: The data from 32 original publications were reviewed. The most common option for local salvage therapy after radical prostatectomy (RP) was radiation. Options for local salvage therapy after primary radiation included RP, brachytherapy, and cryotherapy. Different definitions of *recurrence* and risk profiles among patients make comparative assessment among salvage treatment modalities difficult. Triggers for intervention and factors predicting response to salvage therapy vary.
Conclusions: Radiation therapy (RT) after RP can provide durable prostate-specific antigen (PSA) responses in a sizeable percentage of men, especially when given early (ie, PSA <1 ng/ml). Though a few studies suggest improvements in mortality, prospective randomized trials are needed and underway. The role of salvage treatment after RT is less clear.

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1. Introduction

Prostate cancer (PCa) accounted for an estimated 899 000 cases and 258 000 deaths worldwide in 2008, with 72% of cases and 53% of deaths occurring in developed countries [1]. Among men in the Surveillance, Epidemiology, and End Results database in the United States, 80% had localized disease, 12% had regional disease, and only 4% had distant

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disease [2]. A recent analysis of 11 892 men in the Cancer of the Prostate Strategic Urologic Research Endeavor registry, a national, largely community-based PCa registry, revealed that 6.8% elected active surveillance, 49.9% chose radical prostatectomy (RP), 11.6% underwent external-beam radiation therapy (EBRT), 13.3% had brachytherapy, 4.0% chose cryoablation, and 11.6% underwent primary androgen-deprivation therapy (ADT) as the primary treatment for PCa [3].

Despite primary treatment of localized PCa, 20–30% of patients experience a recurrence, typically detected by a rise in serum prostate-specific antigen (PSA) levels [4,5]. For these men, options for salvage local therapy are still available. No randomized trials have yet compared different modalities of salvage treatment, and most of the data come from retrospective series, small prospective studies, and extrapolation from clinical trials involving primary management. This review discusses the contemporary management of biochemical recurrence (BCR) after definitive primary therapy.

2. Evidence acquisition

A systematic review of the literature was conducted using the Medline and Embase electronic databases. Search terms included *prostate cancer recurrence, prostate salvage therapy, radiorecurrent prostate cancer, post HIFU, post cryoablation, postradiation*, and *postprostatectomy salvage*. The search was restricted to English-language articles from 2000 to 2012. Citations from original articles and review articles were assessed for important manuscripts not identified in the initial search. One article identified in this manner was outside the study window (1999) but was included because it was the largest series in its area.

Eligibility criteria for selecting studies included original articles with (1) a diagnosis of recurrent PCa after primary therapy, (2) a comprehensive description of primary and secondary treatments received with oncologic outcomes, (3) an adequate sample size, and (4) sufficient follow-up relative to the existing literature in the field. For articles regarding salvage radiation after RP and salvage RP after radiation, a minimum sample size of 100 men and a minimum follow-up of 36 mo were required. One exception to this rule was the largest series on salvage robot-assisted RP (RARP) after radiation failure, which included only 18 men with a median follow-up of 18 mo; this study was included because of the novelty of salvage RARP. For articles assessing salvage brachytherapy after radiation, because of the smaller number of available studies, a minimum sample size of 15 men and a minimum follow-up of 18 mo were required, while studies assessing salvage cryotherapy after radiation required a minimum sample size of 50 men and minimum follow-up of 18 mo. Articles were screened for relevance to the topic and adherence to inclusion criteria. The authors selected 32 articles according to our search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [6]. The authors acknowledge that many studies were not included in this review because of the criteria enforced for selection.

Figure 1 displays a flow diagram of the search strategy and study selection for articles that were included in this review.

3. Evidence synthesis

3.1. Definitions of biochemical recurrence

Several different terminologies have been applied to men with an elevated post-treatment PSA, including *recurrence, progression*, and *persistence*. In theory, for a tumor to "recur," the primary treatment must not have been curative, and some persistence of tumor below biochemical or clinical detection must occur. For those tumors that do have significant declines in PSA levels, for the PSA level to reach the *recurrence* definition, the tumor must have progressed. Therefore, depending on how it is viewed, the terms *persistence, recurrence*, and *progression* are certainly overlapping and often synonymous.

Serum PSA is a valuable tool, used as a surrogate to define recurrence. However, definitions of *BCR* vary by treatment and study because of inherent differences in various treatments on PSA levels [7]. Given that the prostate produces PSA, after complete removal of the prostate (ie, RP), serum PSA should be undetectable, and any measurable PSA may suggest recurrence [4]. The availability of ultrasensitive PSA assays has allowed us to predict PSA relapse at an earlier point than most conventional assays [8]; however, not all patients with a detectable PSA level will manifest clinical progression [9]. For instance, although several studies have suggested that benign prostate glands at the margin are not associated with BCR [10], they may be associated with low levels of PSA that would only be detectable on an ultrasensitive assay. Treatment for such PSA elevations are unlikely to provide any benefit in preventing cancer progression. For this reason, the European Consensus Group recommended that an ultrasensitive assay be used in monitoring for PCa recurrence but not for treatment decision making [11]. In 2007, the American Urological Association Prostate Guideline Update Panel reviewed 53 different definitions of *BCR* after RP and recommended using a serum PSA level >0.2 ng/ml, with a second confirmatory level above 0.2 ng/ml to define recurrence [12]. This recommendation is similar to the definition proposed by a European Consensus committee in 2004 [13].

Defining an ideal cut point for radiation failure is more challenging, because the PSA level does not often drop to undetectable levels after treatment and takes longer to reach its nadir. The American Society for Therapeutic Radiology and Oncology (ASTRO) met in 1997 and suggested three consecutive rises in PSA level above the nadir to define recurrence following radiation [14]. However, the ASTRO definition has been criticized for being poorly linked to clinical progression, being heavily dependent on the length of follow-up, and not performing well in men on concomitant androgen-deprivation therapy (ADT). To address these and other shortcomings of the definition, a second consensus panel suggested an increase in the PSA level by $\geq$2 ng/ml

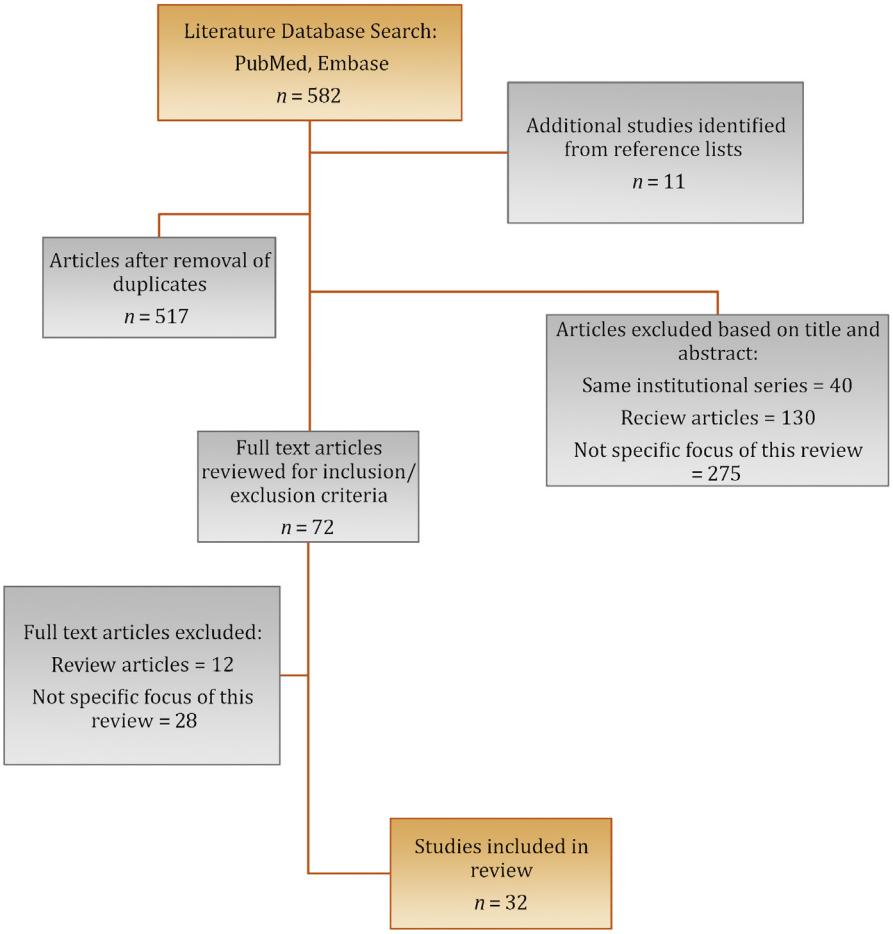

Fig. 1 – Flow diagram: search and selection strategy of included articles.

above the nadir (Phoenix definition) to represent recurrence [15]. Although both definitions have been used to define BCR after radiation therapy (RT) in the past, the Phoenix definition is currently preferred. However, the goal of the Phoenix definition is to predict clinical recurrence and progression rather than BCR alone. Therefore, the threshold for meeting this definition is much higher than it is for surgery, underscoring the point that BCR end points should not be used to compare surgery versus radiation [16]. Current definitions of *BCR* after cryoablation have not been well established, and most studies use radiation-based definitions [17]. Yet, it should be emphasized that some definitions will artificially improve outcomes compared to others.

3.2. *The natural history of prostate cancer after treatment*

As mentioned earlier, the first sign of PCa recurrence is invariably an elevation in the PSA level. Before understanding the potential impact of salvage therapies on PCa, it is important to review the natural history of recurrent PCa. To accomplish this, Freedland and colleagues retrospectively assessed 379 men with BCR after RP who were managed expectantly with ADT for clinical metastasis [18]. Most men lived >15 yr after BCR, and only some men progressed to clinical metastasis or death. The study also found considerable variation in progression depending on various clinical features, with Gleason score (<8 vs >8), time to BCR (<3 vs >3 yr), and PSA doubling time (PSA DT; <3, 3–8.9, 9–14.9, and >15 mo) being sole predictors of PCa-specific survival. For instance, patients with a Gleason score <8, PSA DT >15 mo, and >3 yr from RP to BCR had a 15-yr cancer-specific mortality of only 6%. However, men with a Gleason score >8, PSA DT <3 mo, and <3 yr from surgery to BCR had a cancer-specific mortality of 99% at 10 yr. A more recent study has added to the literature in this field by comparing cancer-specific and all-cause morality in a cohort of 336 men with BCR after RP and adjuvant RT using a competing risk approach [19]. At 10 yr, the authors reported that the cancer-specific mortality was similar to other-cause mortality at 21.5% and 21.7%, respectively. Even among these men with a higher risk of clinical progression after RP, there was a variable clinical course after BCR, with Gleason 8 disease, time to BCR, and two or more positive lymph nodes being the most predictive of PCa death. These studies highlight the point that not all men with BCR after definitive primary treatment will go on to have clinical progression during their lifetime.

3.3. Assessment of prostate cancer recurrence

3.3.1. Risk assessment

Although PCa recurrence is defined by a rise in PSA levels, this elevation could represent either local or distant failure or both. Differentiating between the two, although difficult, is critical, because men with local recurrence only are excellent candidates for salvage local treatment with curative intent, whereas those with distant failure may require systemic therapy and are unlikely to have a durable response to local treatment alone. Numerous risk-prediction models are available to characterize disease risk and determine the probability of recurrence after primary treatment [20]. In a recent update on PCa predictive tools, 17 nomograms that predict the likelihood of metastasis and survival were identified [20]. However, these nomograms displayed a predictive accuracy of 59–93%, suggesting a level of certainty somewhere between a near-perfect score and a coin toss, and only three had been externally validated. Although these tools are helpful in estimating the likelihood of clinical progression after primary treatment, they are unable to predict with perfect accuracy who will need salvage therapy and who will not.

3.3.2. Prostate-specific antigen and prostate-specific antigen kinetics

PSA and its rate of increase can be used to estimate the probability of clinical progression. Although previous studies have shown that longer times to BCR after RP are associated with a greater likelihood of localized disease and decreased PCa mortality [18], more recent studies have failed to find this association between time to BCR and death from PCa [21]. Studies have reported that a longer PSA DT is associated with a decreased likelihood of PCa progression, the development of metastasis, and PCa mortality [22]. In a retrospective analysis of 450 patients with BCR (>0.2 n/ml) after RP, PSA DT was an independent predictor of metastasis-free survival [23]. Men with a PSA DT >15 mo had a 5-yr metastases-free rate of 91%, while those with a PSA DT <3 mo had a metastases-free rate of only 5%. Therefore, although PSA progression is variable, PSA kinetics at the time of recurrence is the strongest factor identified to date to help determine which men are at the greatest risk of progression.

3.3.3. Imaging

The most commonly used imaging modalities for assessing PCa recurrence are axial computed tomography (CT) and bone scan (BS). However, studies have suggested that these modalities are suboptimal and have a low likelihood of being positive in an asymptomatic patient with a PSA <10 ng/ml [22]. In a previous series of 414 BSs performed in 230 patients with BCR after RP, the rates of a positive scan for men with a PSA <10 ng/ml was only 4% [24]. Similarly, a study assessing 71 CT scans in 128 men with a BCR after RP reported zero positive scans in patients with a PSA <10 ng/ml [25]. Therefore, a significant progression of disease must occur before clinical metastasis can be detected by conventional CT and BS. Although not commonly used today, indium In 111 capromab pendetide scanning (ProstaScint; Cytogen, Princeton, NJ, USA) uses an immunoglobulin G monoclonal antibody that binds to prostate-specific membrane antigen (PSMA) on prostatic epithelial cells. Studies have shown variable efficacy in PCa detection using ProstaScint, with average positive and negative predictive values of 60% and 70%, respectively [26]. However, this tracer binds to the intracellular domain of PSMA and thereby detects only necrotic tissue, having limited ability to detect viable cancer, including bone metastasis, giving it a high false-negative rate and limited applicability in the setting of recurrent disease [27]. Promising second- and third-generation humanized PSMA-binding antibodies, such as humanized monoclonal antibody J591, that target the extracellular domain of PSMA hold promise to overcome this limitation.

Other molecular imaging modalities such as positron-emission tomography (PET) CT are gaining popularity in restaging patients with BCR. Choline is a compound used in phospholipid biosynthesis that shows increased uptake in tumor cells [28]; it was recently approved by the US Food and Drug Administration for the detection of recurrent PCa. A recent review article suggested an overall sensitivity of choline PET–CT in detecting sites of PCa relapse between 38% and 98%, with better detection rates at higher PSA levels and shorter PSA DT [29]. Fluoride has high affinity for bone, with increased uptake reflecting osteoblastic activity [28]. Studies have suggested that fluoride PET may have better sensitivity, specificity, and accuracy in detecting skeletal metastasis compared to choline PET [30].

Another modality being increasingly used to assess for local recurrence is multiparametric magnetic resonance imaging (MRI) [31]. The addition of dynamic contrast enhancement allows assessment of neoangiogenesis, while diffusion weighting provides better spatial resolution and more accurate lesion identification compared to conventional T2-weighted MRI [32]. Furthermore, the addition of spectroscopy has also improved the specificity and diagnostic accuracy of MRI by adding a functional assessment through measuring metabolite levels such as choline, which is increased in PCa, and citrate, which is decreased [33]. In addition, with regard to the detection of distant metastasis, whole-body MR can assess nodal regions and appears equivalent to PET–CT in the detection of bone metastasis [34]. However, despite improved accuracy of detection with more contemporary imaging technologies, a negative scan cannot exclude the presence of distant disease. Furthermore, the cost and availability of these technologies may result in varying applicability in different countries where cost differentials are large.

Although contemporary technology and better risk prediction has improved the detection of metastatic disease [35], the current staging of patients with BCR following treatment cannot differentiate between a local recurrence only and microscopic metastasis below the thresholds of detection. Herein lies the largest limitation in the management of men with BCR after treatment. Identifying better markers of metastatic disease is critical to determining which patients are likely to respond to local salvage

treatment versus those with distant disease who are unlikely to respond. However, at least in the postsurgical setting, the fact that approximately 90% of men treated with salvage EBRT have a drop in their PSA levels [36] suggests that most men have at least some local disease. As such, in the absence of documented metastases, which is typically the case early in disease recurrence, men are typically offered a salvage local treatment.

3.4. Management of prostate cancer recurrence

3.4.1. Salvage treatment after radical prostatectomy

The natural history of clinical progression after BCR is variable, and most men live a long time after recurrence. Therefore, life expectancy and comorbidities should be considered when deciding on management. Currently, various clinical and pathologic variables are used to estimate disease progression and guide treatment accordingly. For example, in low-risk patients, we may manage men more expectantly, while in intermediate- to high-risk patients, we may institute more aggressive early salvage RT, often with ADT for the highest-risk patients [19]. However, the variable clinical course of these patients leaves much uncertainty about how and when to appropriately manage these men.

In a retrospective study of 635 patients with BCR after RP, 238 men received salvage RT with or without ADT over a median follow-up of 6 yr [37]. Salvage RT was associated with a significant 3-fold increase in PCa survival compared with observation alone in men with a PSA DT <6 mo only if it was initiated within 2 yr of BCR. This is an important observation in that it suggests that we should not assume that men with a short PSA DT have metastatic disease solely based on a short PSA DT; rather, we should offer them early and aggressive salvage local RT. In a similar study involving 2657 men with BCR after RP, 32% of the cohort received salvage RT [38]. The study found a benefit from radiation on the risk of local recurrence and systemic progression but failed to see a significant impact of salvage radiation on mortality. However, given the reduction in systemic progression in the salvage RT group, one might expect to see a reduction in mortality as well, though this will need to be formally examined in the future as this cohort matures.

Stephenson et al. constructed a nomogram to predict the PSA response to salvage RT for BCR after RP [39]. The authors identified PSA levels before salvage RT, prostatectomy Gleason score, PSA DT, surgical margin status, lymph node involvement, and use of ADT with salvage RT as significant variables in the model. When assessing the PSA progression–free probability by PSA level before salvage RT, the authors noted a better response if salvage RT were initiated before a PSA level of 1 ng/ml. These studies suggest that salvage RT has its best efficacy when initiated early in the course of recurrence. Moreover, although the PSA response rates are best in men with longer PSA DTs, the actual survival benefits may be limited to men with short PSA DTs. If proven true in future studies, it suggests that although we can achieve good PSA control in low-risk men, these men are likely to have excellent outcomes regardless of salvage radiation. On the contrary, men with high-risk disease, in whom obtaining PSA control is most difficult, actually stand to benefit the most and should not be denied the opportunity for a second chance at a cure for their potentially lethal disease. However, uncertainty remains about the optimal timing for instituting salvage RT for BCR after RP, and randomized trials are underway to shed more light on this area (see Radiotherapy and Androgen Deprivation in Combination After Local Surgery [RADICALS]) [40]. Table 1 displays clinical characteristics and oncologic outcomes of selected studies involving salvage RT after primary RP.

With respect to radiation dose for salvage RT, a recent systematic review assessed 41 studies encompassing 5597 patients and found that a dose of 70 Gy resulted in a higher PSA progression–free survival compared to a dose of 60 Gy (54% vs 34%, respectively) [41]. The authors reported a dose response relationship, with a 2% increase in PSA progression–free survival for each additional Gray of radiation dose.

Another debate surrounding salvage RT is the use of concurrent ADT. Most of the literature consists of retrospective studies, which vary in the timing and dosage of RT as well as the duration of ADT. The only randomized study in the salvage setting comes from an abstract presented at the 2011 Genitourinary Cancers Symposium consisting of 771 men with a BCR after RP who were randomized to salvage RT and 2 yr of bicalutamide (150 mg) versus salvage RT alone in a double-blinded placebo-controlled trial [42]. With a median follow-up of 7 yr, the study found no difference in overall survival (OS) but found that patients receiving concurrent ADT and salvage RT had a higher PSA progression–free rate (57% vs 40%; $p < 0.0001$) and lower cumulative incidence of metastatic PCa (7% vs 13%; $p < 0.04$). The study also suggested that the benefit of ADT use with salvage RT was greater in patients with higher-risk disease. Although a significant reduction in mortality was not seen by 7 yr, the difference in rates of metastasis suggests that longer follow-up may result in a divergence of mortality between the arms. However, more evidence from randomized trials is needed to identify which patients truly benefit from the addition of ADT and the duration of ADT that is optimal (see RADICALS) [40].

Although salvage RT may be efficacious in many patients, it comes at some cost to quality of life (QoL). The Southwest Oncology Group compared patients randomized to RP versus RP with adjuvant RT to discern health-related QoL (HRQoL) outcomes [43]. Among the 217 patients with QoL data, more patients reported bowel toxicity in the surgery plus radiation group compared to the surgery only group within the first 2 yr (47% vs 5%). Furthermore, 15% more men reported frequent urination in the surgery plus radiation arm across all time assessments. Baseline levels of erectile dysfunction were high after surgery in both groups, and radiation did not appear to have a significant further detriment. Although these data come from an adjuvant setting and we are extrapolating them to salvage treatment, there is no reason to believe the two would differ significantly in their respective toxicities, especially in the

Table 1 – Studies on salvage radiation therapy after primary surgery

First author, year: LOE	Sample size	Follow-up, mo	Definition of *biochemical recurrence*	PSA at radiation, ng/ml	Radiation dosage, Gy	BCR-free survival	OS	Toxicity
Boorjian, 2009, 3	856	70.8	PSA >0.4 ng/ml	0.8	NR	NR	92% at 5 yr	NR
Trock, 2008, 3	160	72	PSA >0.2 ng/ml	0.7	66.5	NR	81% at last follow-up	NR
Stephenson, 2007, 4	1540	53	PSA nadir + 0.2 ng/ml	1.1	64.8	32% at 6 yr	–	NR
Neuhof, 2007, 4	171	39	3 consecutive rises in PSA	1.1	60–66	35.1% at 5 yr	93.8% at 5 yr	Grade 1–2 rectal bleeding (8.2%)
								Mild to moderate diarrhea (2.3%)
								Cystitis (7%)
								Worsening urinary incontinence (1.8%)
								Urethral stricture (4.7%)
Buskirk, 2006, 4	368	60	PSA >0.4 ng/ml	0.7	64.8	46% at 5 yr	92% at 5 yr	NR
Brooks, 2005, 4	114	75.6	PSA nadir + 0.1 ng/ml	0.9	64	33% at 6 yr	NR	Early genitourinary toxicity:
								grade 2 (11.4%)
								Early gastrointestinal toxicity:
								grade 2 (22.8%)
								Late genitourinary toxicity:
								grade 2 (4%)
								grade 3 (1.7%)
								Late gastrointestinal toxicity:
								grade 2 (8%)
Katz, 2003, 4	115	42	PSA nadir + 0.2 ng/ml	NR	66.6	46% at 4 yr	95% at 4 yr	Early genitourinary toxicity:
								grade 1 (53%)
								grade 2 (21%)
								grade 3 (3%)
								Early Gastrointestinal toxicity:
								grade 1 (47%)
								grade 2 (16%)
								Late genitourinary toxicity:
								grade 2 (9%)
								grade 3 (10%)
								Late genitourinary toxicity:
								grade 2 (12%)
Pazona, 2005, 4	223	56	PSA >0.3 ng/ml	NR	63	40% at 5 yr	NR	NR
Ward, 2004, 4	211	50.4	NR	0.6	64	48% at 5 yr if PSA DT <12 mo, 66% at 5 yr if PSA DT >12 mo	NR	NR
Soto, 2012, 4	441	36	PSA ≥ 0.2 ng/ml with another subsequent increase	NR**	66–68.1	63% with ADT 55% without ADT at 3 yr	NR	NR

LOE = level of evidence; PSA = prostate-specific antigen; BCR = biochemical recurrence; OS = overall survival; NR = not reported; DT = doubling time; ADT = androgen-deprivation therapy.

consideration of early salvage. Therefore, it appears that adjuvant RT and likely salvage RT are associated with some detriment to HRQoL, which can best be minimized by offering them selectively to those who really need them.

3.4.2. Salvage after radiation therapy

Another option for primary treatment of localized PCa is RT, which can be given as brachytherapy or EBRT with or without concomitant ADT [44]. However, the same dilemma and limitations exist regarding the ability to discern between men with local only versus distant disease at the time of BCR. Various options exist for salvage local treatment after failure of RT, including surgery, additional RT, and cryotherapy.

3.4.2.1. Salvage radical prostatectomy after radiation therapy. Salvage RP after RT has the longest history and best likelihood of local control relative to other post-RT salvage treatments

Table 2 – Studies of salvage surgery after primary radiation

First author, year, LOE	Sample size	Follow-up, mo	PSA at time of surgery, ng/ml	Definition of *biochemical recurrence*	BCR-free survival	CSS	Toxicity
Ward, 2005, 4	199	86	8.9	PSA >0.4 ng/ml	58% at 5 yr	79% at 5 yr	RP: <30 d complication (27.5%) Rectal injury (6.5%) Bladder neck contraction (22%) Cystectomy: <30 d complication (50.8%) Rectal injury (19.3%) Ileus (11%)
Bianco, 2005, 4	100	60	7.7	PSA >0.2 ng/ml	55% at 5 yr	73% at 10 yr	NR
Chade, 2011, 4	404	52.8	4.5	PSA >0.1 or 0.2 ng/ml, depending on institution	37% at 10 yr	83% at 10 yr	NR
Eandi, 2010, 4	18	18	6.8	PSA ≥ 0.2 ng/ml	67% at 18 mo	100% at 18 mo	AUS insertion for incontinence (11.1%) Bladder neck contracture (17%) ED (100%)

LOE = level of evidence; PSA = prostate-specific antigen; BCR = biochemical recurrence; CSS = cancer-specific survival; RP = radical prostatectomy; NR = not reported; AUS = artificial urinary sphincter; ED = erectile dysfunction.

[45]. However, it must be weighed against the risk of adverse events from the salvage RP, which are increased from the primary setting because of the fibrosis and poor wound healing induced by the radiation [46]. The best contemporary evidence in this area comes from a retrospective, international, multi-institutional cohort analysis of 404 men with radiation-recurrent PCa [47]. The authors reported a 5-yr BCR-free, metastasis-free, and cancer-specific survival (CSS) of 48%, 83%, and 92%, respectively, following salvage RP. The authors recognized a favorable risk group that they identified as men with a Gleason score <7 and preoperative PSA <4 ng/ml. Among this group of patients ($n = 120$), they reported no deaths from PCa, development of metastasis in only three patients, and a BCR-free survival of 64% at 5 yr. In the era of robotic surgery, a recent review compiled the results of five retrospective series looking at salvage robotic RP after RT [48]. The review found that oncologic outcomes were strongly correlated with positive margin rates. When compiling patients from all the published data, the review reported that 13 of 55 (23.6%) patients had a positive margin after the procedure, and 15 of 51 (29.4%) had a BCR. Although it appears that results from salvage robotic RP are equivalent to those from open surgery, small sample size and short follow-up (4–18 mo) limit these studies' ability to inform us about more meaningful end points (metastases, mortality). Table 2 displays clinical characteristics and oncologic outcomes of select studies involving salvage RP after primary radiation.

To elucidate the morbidity associated with salvage surgery, a recent study compared 3458 men who underwent open RP with 98 who underwent open salvage RP. Patients undergoing salvage surgery had a higher risk of bladder neck contracture (47% vs 5.8%), urinary retention (25.3% vs 3.5%), urinary fistula (4.1% vs 0.06%), abscess (3.2% vs 0.7%), and rectal injury (9.2% vs 0.6%) [49]. A recent review suggested that among reports published before 2000, rates of rectal injury and bladder neck contracture ranged from 0% to 28% and 7% to 27.5%, respectively, while in later series, rates of rectal injury declined to 2–10%, although rates of bladder neck contractures remained high (11–41%) [46]. Furthermore, functional detriments continue to be an issue, with only 0–20% of men displaying erectile function sufficient for sexual intercourse after salvage prostatectomy; however, poor erectile function insufficient for intercourse was seen in as many as 52% of men prior to salvage prostatectomy [46]. Nonetheless, despite improvements in technology and surgical technique, rates of impotence, urinary incontinence, and bladder neck contracture are still high, suggesting that these procedures should be performed primarily at high-volume centers by experienced surgeons.

3.4.2.2. Salvage brachytherapy after radiation therapy. Another alternative for local secondary therapy after failure of primary RT includes salvage brachytherapy. A recent systematic review assessed 18 studies and found marked variation among studies in the patient population, methods of treatment, and outcomes [50]. Rates of biochemical disease-free survival (DSS) at 4–5 yr ranged from 25% to 75%, while OS and DSS ranged from 54% to 94% and 74% to 100%, respectively. Among all studies, the crude rate of grade 3–4 genitourinary toxicity was 13% (0–47), while the crude rate of grade 3–4 gastrointestinal toxicity was 5% (0–20). Most of the literature in this area consists of small, single-institution retrospective studies with short follow-up, limiting our ability to draw reliable conclusions regarding salvage brachytherapy after RT. Although salvage brachytherapy may be an attractive option in select patients with careful dosing, high toxicity rates may likely impair widespread use of this approach. Table 3 displays clinical characteristics and oncologic outcomes of select studies involving salvage brachytherapy after primary radiation.

3.4.2.3. Salvage cryoablation after radiation therapy. Another option for secondary local therapy after primary RT is

cryotherapy. Again, the majority of the literature in this field consists of small retrospective studies. A recent analysis of 156 men undergoing salvage cryoablation after definitive RT in the cryo online data registry found a biochemical disease-free survival of 89%, 73.7%, and 66.7% at 1, 2, and 3 yr, respectively [17]. A recent review identified a pre-RT PSA <10 ng/ml, Gleason score <8, clinical stage T1c or T2 disease, a low presalvage PSA (<5 ng/ml), and a long PSA DT (>16 mo) as factors associated with a favorable response to salvage cryotherapy [51]. This review also suggested a significant decline in complication rates in more contemporary series, with mild to moderate incontinence in 6–13% of patients, severe incontinence in 2–4%, urinary retention in 2–21%, and rectourethral fistula formation in 1–2% of patients [51]. Although cryotherapy appears to be a possible alternative for salvage therapy in select patients, randomized trials are needed to elucidate the relative cancer control and toxicity of various options for local salvage after definitive RT. Table 4 displays clinical characteristics and oncologic outcomes of select studies involving salvage cryotherapy after primary radiation.

3.4.2.4. Salvage after ablative nonradiation treatments (ie, post-cryotherapy and post–high-intensity focused ultrasound). For men who experience local recurrence after primary cryotherapy or high-intensity focused ultrasound (HIFU), options for local salvage include repeat cryotherapy or HIFU, surgery, or radiation. Most of the literature looking at salvage treatment after HIFU or cryotherapy consists of single-institution, small, retrospective studies with short to intermediate follow-up [52–54]. Although short-term outcomes appear favorable, the relative paucity of reliable data limits our ability to draw any dependable conclusions regarding local salvage after cryotherapy or HIFU. Larger studies with longer follow-up and comparable patient populations would enhance the current literature in this area.

Table 3 – Studies on salvage brachytherapy after primary radiation

First author, year, LOE	Sample size	Follow-up, mo	PSA at salvage, ng/ml	Definition of *biochemical recurrence*	Dosage of radiation, Gy	BCR-free survival	CSS	Toxicity
Grado, 1999, 4	49	64	5.6	2 PSA rises above nadir	100–120	34% at 5 yr	89% at 5 yr	TURP 14%
								Incontinent after TURP 6%
								Hematuria 4%
								Penile dysuria 6%
								Rectal ulcer 4%
								Rectal bleeding requiring colostomy 2%
Lee, 2007, 4	21	19	5.9	ASTRO	72	89% at 5 yr	NR	Genitourinary toxicity:
								grade 1–2
								85.7%
								grade 3 14%
								Gastrointestinal toxicity:
								grade 1–2 14%
Lee, 2008, 4	21	36	NR	ASTRO	90	38% at 5 yr	NR	Genitourinary toxicity:
								grade 1 9.5%
								grade 2 19%
								Gastrointestinal toxicity:
								grade 1 4.7%
Wong, 2006, 4	17	44	4.7	ASTRO	127–139	75% at 4yr	94% at 4 yr	Genitourinary toxicity:
								grade 1 12%
								grade 2 41%
								grade 3 41%
								grade 4 6%
								Gastrointestinal toxicity:
								grade 1 29%
								grade 2 35%
								grade 3 6%
Aaronson, 2009, 4	24	30	3.36	Phoenix	144	88% at last follow-up	96% at last follow-up	Genitourinary toxicity:
								grade 2 29%
								Gastrointestinal toxicity:
								grade 1 8%
								grade 3 4%
Nguyen, 2007, 2	25	47	5.5	Phoenix	137	70% at 4 yr	NR	Genitourinary toxicity:
								grade 3 8%
								Gastrointestinal toxicity:
								grade 3 8%
								grade 4 12%

LOE = level of evidence; PSA = prostate-specific antigen; BCR = biochemical recurrence; CSS = cancer-specific survival; TURP = transurethral resection of prostate; ASTRO = American Society for Therapeutic Radiology and Oncology; NR = not reported.

Table 4 – Studies on salvage cryotherapy after primary radiation

First author, year, LOE	Sample size	Follow-up, mo	Definition of *biochemical recurrence*	BCR-free survival	OS	Toxicity
Han, 2003, 4	106	12	PSA >0.4 ng/ml	75% at 1 yr	NR	Tissue sloughing 5%
						Urinary retention 3.3%
						Rectal discomfort 2.6%
Bahn, 2003, 4	59	82	PSA >0.5 ng/ml	59% at 7 yr	NR	NR
Chin, 2001, 4	125	19	PSA >0.5 ng/ml	34% at 5 yr	NR	Rectal fistula 3.3%
						Severe incontinence 6.7%
Izawa, 2002, 4	131	57	Nadir + 2 ng/ml	40% at 5 yr	73% at 5 yr	NR
Williams, 2011, 4	187	89.5	Nadir + 2 ng/ml	39% at 10 yr	82% at 10 yr	NR
Spiess, 2012, 4	156	45.6	Nadir + 2 ng/ml	66.7% at 3 yr	NR	NR

LOE = level of evidence; BCR = biochemical recurrence; OS = overall survival; PSA = prostate-specific survival; NR = not reported.

3.4.2.5. Palliative androgen-deprivation therapy. ADT alone after a recurrence of PCa is primarily reserved for patients with systemic disease, with the goal of delaying progression and reducing morbidity and mortality. Currently, no consensus exists on the ideal timing or PSA cut-point for institution of therapy. Some clinicians advocate for early ADT (ie, treatment prior to the development of clinical metastases), while others prefer to wait until the development of clinical metastasis.

A previous study looking at various PSA thresholds for administration of ADT for BCR after RP reported no difference in systemic progression or cancer-specific survival (CSS) after starting ADT at a PSA of 0.2, 1.0, or 2.0 ng/ml and observed only a small difference in CSS in men who received ADT compared to those who did not [55]. A similar retrospective analysis of 1352 men with BCR after RP found a benefit to early ADT (before clinical metastasis) in delaying clinical metastasis only in higher-risk patients (Gleason >7, PSA DT <12 mo), not the overall cohort [56]. Although ADT is a popular option for management of recurrent PCa displaying progression, uncertainty remains regarding which patients benefit from early ADT and the ideal time for initiation of therapy.

3.5. Limitations

Few randomized trials have been conducted to assess the relative efficacy and toxicity of such treatments as salvage therapy for recurrent PCa. The majority of the available data comes from single- or multi-institutional observational studies and provides level 3 or 4 evidence at best, with short to intermediate follow-up. Evaluating the relative effectiveness of various treatments among these studies is challenging because of differing risk profiles among study cohorts and different treatment-specific definitions of *biochemical progression* that cannot be compared. This should be acknowledged when considering any conclusions based on observational data. Randomized trials are desperately needed to determine the relative benefit and toxicity of various treatment options in the salvage setting. Ongoing RCTs such as the RADICALS trial in the United Kingdom should inform us about the benefit of adjuvant versus early salvage RT as well as the optimum duration of ADT in combination with salvage RT and will be a welcome addition to our current literature.

4. Conclusions

Although the natural history of PCa after treatment is variable, some men will progress and may benefit from salvage local treatment. Salvage RT for BCR after RP appears to have a durable PSA response in a sizeable percentage of men, especially when administered early (PSA <1 ng/ml). Moreover, there is a suggestion it may improve survival among high-risk men. Salvage local therapy after RT is less clear. Although salvage therapies have shown reasonable cancer control in well-selected patients, they can be associated with significant morbidity, compounding the adverse side effects of primary treatment. More randomized trials with longer follow-up are required to adequately compare salvage treatments with regard to relative cancer control and treatment-related morbidity.

Second, our current methods of staging recurrent PCa have a limited ability to accurately discern between men with local recurrence only versus those with distant microscopic disease below the thresholds of detection. Better risk prediction and more efficient markers of progression are desperately needed. They will allow us to be more selective in providing appropriate salvage local treatment to those who may have a second chance of cure while preventing morbidity in those who are unlikely to benefit from it.

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Study concept and design: Punnen, Cooperberg, Freedland.
Acquisition of data: Punnen, Cooperberg, Freedland.
Analysis and interpretation of data: Punnen, Cooperberg, Freedland.
Drafting of the manuscript: Punnen.
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