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Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review

Keywords

Prostate cancer · Biochemical recurrence · Prostatectomy ·
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Abstract

How to manage patients with prostate cancer (PCa) with biochemical recurrence (BCR) following primary curative treatment is a controversial issue. Importantly, this prostate-specific antigen (PSA)-only recurrence is a surrogate neither of PCa-specific survival nor of overall survival. Physicians are therefore challenged with preventing or delaying the onset of clinical progression in those deemed at risk, while avoiding over-treating patients whose disease may never progress beyond PSA-only recurrence. Adjuvant therapy for radical prostatectomy (RP) or local radiotherapy (RT) has a role in certain at-risk patients, although it is not recommended in low-risk PCa owing to the significant side-effects associated with RT and androgen deprivation therapy (ADT). The recommendations for salvage therapy differ depending on whether BCR occurs after RP or primary RT, and in either case, definitive evidence regarding the best strategy is lacking. Options for treatment of BCR after RP are RT at least to the prostatic bed, complete or intermittent ADT, or observation; for BCR after RT, salvage RP, cryotherapy, complete or intermittent ADT, brachytherapy, high-intensity focused ultra-

sound (HIFU), or observation can be considered. Many patient- and cancer-specific factors need to be taken into account when deciding on the best strategy, and optimal management depends on the involvement of a multidisciplinary team, consultation with the patient themselves, and the adoption of an individualised approach. Improvements in imaging techniques may enable earlier detection of metastases, which will hopefully refine future management decisions.

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Introduction

In prostate cancer (PCa) that has not extended beyond the prostate gland, the risk of progression can vary significantly, and thus management approaches range from active surveillance [1–3] to treatment with curative intent, which includes radical prostatectomy (RP) or primary definitive radiotherapy (RT) [1, 4]. Besides RP and RT (external-beam radiation therapy or brachytherapy), other modalities that have emerged as therapeutic options for the treatment of localised PCa include high-intensity focused ultrasound (HIFU) and cryosurgery. A relatively newer development is focal ablative therapy, whereby ablation is undertaken on smaller tumours in a

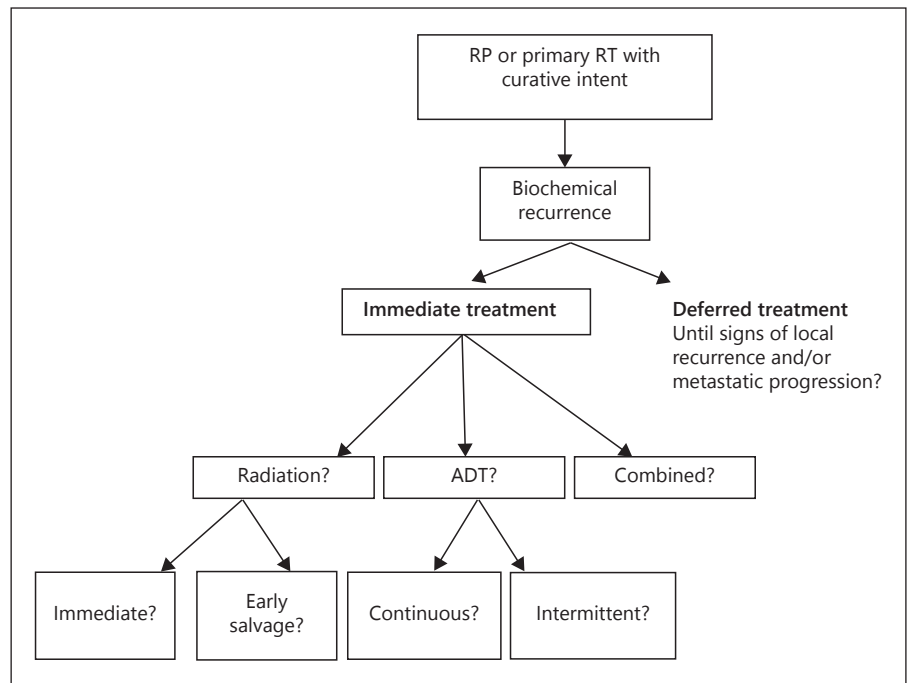


Fig. 1. Decisions faced by physicians upon BCR after primary curative treatment. ADT, androgen deprivation therapy; BCR, biochemical recurrence; RP, radical prostatectomy; RT, radiotherapy.

precise, organ-sparing manner, thereby limiting toxicity [1].

The goal of RP is to eradicate the disease while preserving continence and if possible sexual potency [1, 5]; loss of either or both of these has a significant impact on patients' quality of life (QoL). In low-risk PCa, active surveillance is often the recommended approach [1, 6]. There is stronger evidence of the benefits of RP for intermediate-risk localised PCa than there is for low-risk disease [1, 7, 8]. However, the decision to offer RP to patients with intermediate-risk PCa should be based upon individualised assessment, taking into account the patient's life expectancy and comorbidity, for example. In high-risk PCa, RP may be a reasonable first step in selected patients with a low tumour volume, provided the tumour is not fixed to the pelvic wall or there is no invasion of the urethral sphincter [1]. Several retrospective case series with high-risk PCa have demonstrated good outcomes after RP in the context of a multimodal approach (including adjuvant or salvage androgen deprivation therapy [ADT] and/or RT) [9–12].

RT with dose escalation (range 74–80 Gy) has a positive impact upon biochemical progression in localised PCa, but data is not available for the relative benefits in different risk groups [1]. Results from ProtecT – a large-scale clinical trial, in which 1,643 men with PCa have been randomly assigned to either active surveillance, RP or

RT – may soon provide conclusive data on the value of definitive RT for localised PCa [13].

Local therapy for PCa – RP or definitive RT – is curative in many patients, and remarkable technological advances over the last decade have led to efficacy improvements in both RP and RT. Despite this, biochemical recurrence (BCR) – that is, prostate-specific antigen (PSA) increase – still occurs in 27–53% of patients after definitive local therapy [1]. Within 10 years, 20–40% of post-RP [14, 15] and 30–50% of post-RT [16] patients will experience BCR. Once BCR occurs, the patient is understood to have recurrent PCa, even if there are no signs or symptoms of locally recurrent or metastatic disease. Despite signifying the return of disease, BCR alone may have no impact on either the patient's QoL or their overall survival (OS). The challenge faced by clinicians in managing BCR is to prevent or delay the onset of metastatic disease and the resulting morbidity and mortality, while taking into account the negative impact that treatment may have on patients' QoL, and at the same time avoiding overtreating PCa that is at low risk of clinical progression. Physicians are faced with a number of options for managing patients who experience BCR (Fig. 1), and often the best way forward is unclear. This review therefore discusses the optimal approach to the management of BCR after RP or definitive RT. Adjuvant approaches to reduce the risk of post-RP/RT recurrence are also discussed.

Table 1. Pre- and post-treatment prognostic factors in PSA-recurrent prostate cancer [21, 28, 33, 99]

	Pre-treatment (factors relating to initial tumour)	Post-treatment
Biochemical features	Baseline PSA Tumour stage (T-stage)*	PSA kinetics – PSA-DT – PSA velocity Time to biochemical recurrence** Absolute PSA value at time of testing
Pathologic features	Gleason score	Gleason score Surgical margin status Extracapsular extension Seminal vesicle involvement Lymph node status score

* Based on both biochemical and biopsy findings.
** Studies report conflicting results as to whether time to biochemical recurrence is a prognostic indicator.
PSA, prostate-specific antigen; PSA-DT, PSA doubling time.

Search Strategy

Relevant papers to inform this review were identified through PubMed searches in July 2017 using the terms “prostate cancer” AND “radical prostatectomy” AND “recurrence” AND “management”; and “prostate cancer” AND “radiation therapy” AND “recurrence” AND “management.” Search results were restricted to clinical trials with a start date on or after January 1, 2015. Treatment recommendations provided in this review reflect the latest relevant guidance from the European Association of Urology (EAU; 2016) [1], the National Comprehensive Cancer Network (2016) [17], and the European Society for Medical Oncology (2015) [18]. These guidelines were reviewed for original data sources to supplement the aforementioned literature searches. The guidelines were broadly in accordance with each other.

Defining BCR

The definition of BCR differs depending on whether men have undergone RP or have received primary curative RT. After RP, PSA typically falls to an undetectable level, and BCR is defined as 2 consecutive PSA values higher than 0.2 ng/mL and rising [19]. After RT, PSA levels do not typically fall to zero, and BCR is defined as any PSA increase greater than or equal to 2 ng/mL higher than the PSA nadir [20]. The risk of PCa-specific mortality differs depending on whether the PSA recurrence was after

RP or primary RT, and it is therefore important to interpret BCR endpoints in the context of the initial treatment [1].

The Natural History of BCR

Although a rising PSA level universally precedes metastasis and PCa-specific mortality [1], BCR is not a surrogate for PCa-specific mortality or OS, and may pre-date local recurrence or metastasis by several years. On average, BCR precedes the appearance of clinical metastasis by 8 years after RP [21] and by 7 years after primary definitive RT [22].

The natural history of BCR and the risk of subsequent metastasis may be predicted by pre- and post-treatment clinical features (Table 1). These prognostic indicators are used as a means to assess the patient’s level of risk, and therefore, help physicians to determine whether to initiate early treatment or to adopt a strategy of active surveillance. Treatment decisions following BCR must balance the risk of metastatic disease or death with the impact of treatment, and necessitate involvement of a multi-disciplinary team, as well as informing the patient of the potential for a prolonged natural history of PSA-only recurrence [1].

BCR after RP

As mentioned, not all patients with BCR after RP will develop clinical failure; indeed, published reports suggest that an estimated 24–34% of men who develop

BCR will experience clinically evident recurrence (i.e., metastatic disease) within 15 years of surgery [21, 23]. Furthermore, it has been estimated that 2–6% of men who experience BCR after RP may die from PCa [21, 23].

Several clinical characteristics can help determine those patients most at risk of metastasis and PCa-specific mortality post-RP, and thus help guide treatment decisions. For example, BCR in post-RP men with positive surgical margins is more likely to be a result of local recurrence [24]. If BCR occurs within 6 months of RP, this is a strong indication that metastasis has occurred [25], and a short PSA doubling time (PSA-DT), regardless of the time to BCR, is correlated with early clinical recurrence [26]. The interval to BCR following RP does not affect PCa-specific mortality in men with low-risk PCa; however, in men with high-risk disease, early BCR substantially increases mortality [27].

By amalgamating the available evidence, men who may be at high risk of metastases and PCa-specific mortality have been identified as those with a PSA-DT of <3 months, seminal vesicle invasion (pT3b), specimen Gleason score 8–10, or BCR within 3 years of RP [1, 14, 28–30]. An area of uncertainty regarding whether to classify a patient into this high-risk subgroup or as at low risk exists for when their PSA-DT is between 3 and 12 months [1].

BCR after RT

After definitive RT, factors that signal a high risk of metastases and PCa-specific mortality are similar to those after RP: a PSA-DT of <3 months, clinical stage cT3b–T4, biopsy Gleason score 8–10, or BCR within 3 years of RT [1, 30–32]. An analogous area of uncertainty for risk stratification also exists for recurrence after RT; in this case, when the patient's PSA-DT is between 3 and 15 months [1].

Assessing Metastases and Local Recurrence

Once BCR has been detected, it is important to try to establish whether this represents local recurrence or disseminated (i.e., metastatic) disease, or both, in order to guide subsequent treatment decisions. Importantly, metastatic disease must be acceptably ruled out before subjecting patients to local salvage treatment, owing to the significant morbidity associated with such treatments. Regardless of whether BCR is detected post-RP or post-RT, the same principles of imaging apply.

Detecting Metastases

In case of BCR, the current standard workup for detecting metastases involves a bone scan and abdominopelvic CT. These imaging techniques rarely detect metastases in asymptomatic patients; hence, the need for physicians to rely on the aforementioned pre- and post-treatment metastatic risk factors to predict the likelihood of clinical progression. For example, the probability of a positive bone scan in men with PSA-only relapse after RP is <5% if the PSA level is <7 ng/mL [33, 34]. Likewise, CT scanning has low sensitivity for detecting local recurrence or lymph node metastases after RP [33]; in men experiencing BCR postoperatively, this imaging technique yields a positive result in only 11–14% of cases [35, 36].

Earlier detection of metastases may help drive management decisions, and more sensitive methods are therefore needed. Several imaging techniques and agents are being used to try to detect metastases earlier than is currently possible, including, for example, NaF scintigraphy, PET scans using agents such as choline, acetate or prostate-specific membrane antigen (PSMA), whole body diffusion-weighted MRI, spinal MRI, and lymph node MRI [37, 38].

¹¹C-choline PET/CT may offer better sensitivity and specificity for detecting bone metastases [39–41]. ¹¹C-choline PET/CT has been shown to detect bone metastases in up to 15% of patients who have BCR after RP but negative bone scans [42]. Unfortunately, the high cost of choline PET/CT prevents its recommendation for use in all cases of BCR, and one suggestion is to limit use of this technique to patients fit enough for curative salvage treatment [1]. Alternatively, it may be possible to target the use of this technique to certain individuals after RP (e.g., if the patient's PSA level is >1 or >2 ng/mL); however, the precise cut-off level and the impact of PSA velocity require definition. PSA cut-off levels to target the use of ¹¹C-choline PET/CT following BCR after RT are even harder to define than they are for post-RP BCR [1].

Whole-body diffusion-weighted MRI may also improve detection of bone metastases in patients with high-risk PCa [43–46] but little is known about this technique in the context of BCR after RP or RT. The ⁶⁸Ga-PSMA-ligand is highly specific for PCa, and the use of this radiotracer with PET/CT imaging is emerging as a promising new technique for the detection of lymph node and bone metastases. In a retrospective analysis of 319 patients who underwent this imaging procedure, one or more lesions indicative of PCa were detected in 82.8% of patients. High values were recorded for sensitivity (76.6%), specificity (100%), negative predictive value (91.4%) and positive

Table 2. Current options for improving assessment of local recurrence of prostate cancer after radical prostatectomy or definitive radiotherapy [1, 37]

After radical prostatectomy	After definitive radiotherapy
TRUS is not effective Biopsy is unnecessary Choline PET is promising –But sensitivity is not optimum when PSA <0.5 ng/mL The threshold often used for salvage radiotherapy	Ultrasonography not reliable enough Biopsy is a major predictor of outcome – When performed 18–24 months after treatment mp-MRI can be useful in directing core sampling

mp-MRI, multiparametric-magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

predictive value (100%) [38]. Despite emerging as a superior imaging system to those currently in use, PSMA PET/CT is currently only being implemented in a few centres.

Detecting Local Recurrence

The current options for optimising detection of local recurrence after RP or RT are outlined in Table 2.

Adjuvant Therapy for Radical Prostatectomy

Before addressing the management options for post-RP BCR, it is necessary to examine the question of whether it is possible to reduce post-RP recurrence by targeting men most at risk with adjuvant therapy.

Adjuvant RT for RP

While there is no justification for adjuvant RT (aRT) in all men, evidence suggests that men with positive margins and pT3 disease have a greater than 50% risk of failure 10 years after RP [15, 47, 48] and are therefore considered suitable candidates for aRT. In a Cochrane review of 3 randomised controlled trials (RCTs) involving 1,815 patients with high-risk features found at the time of surgery (e.g., seminal vesicle invasion), aRT improved biochemical progression-free survival (PFS) compared with RP alone at 5 and 10 years (risk difference at 5 years: –0.16; 95% confidence intervals [CI] –0.21 to –0.11 and at 10 years: –0.29; 95% CI –0.39 to –0.19) [49].

Other studies also suggest that the use of aRT may significantly reduce BCR (hazard ratio [HR] 0.48) in the presence of adverse pathology after RP, despite the use of RT doses that are lower than typically used today in routine practice [50–53]. However, the data from these studies may be questioned due to some important contamination biases; for example, 30–34% of patients had detectable

PSA at inclusion and therefore received salvage RT (sRT) rather than aRT. There are questions, therefore, surrounding the quality of the efficacy data, as well as the high numbers needed to treat for preventing cancer-specific death (55.6–66.7 men to prevent one PCa-specific death) [50, 51]. It is also important to consider the potential toxicity and negative impact upon QoL of aRT (including persistent and late occurring adverse events [AEs]) [53].

While aRT may be an option for men who undergo RP, the oncological benefits must be balanced against the negative impact on QoL, and the decision on whether to initiate any treatment must be a shared decision with the patient, after an informed discussion with them.

Neoadjuvant or Adjuvant Androgen Deprivation Therapy for RP

Neoadjuvant or adjuvant ADT with RP may have benefits in some patients with local or locally advanced PCa, where there is evidence that this approach provides a significant survival advantage [54, 55]. The European Association of Urology (EAU) guidelines recommend that adjuvant ADT be offered upon detection of nodal involvement during RP [1].

Management of Post-Radical Prostatectomy Recurrence

The options for treatment of recurrence after RP are, according to the EAU, RT at least to the prostatic bed, complete or intermittent ADT, or observation [1].

Salvage RT

The importance of establishing whether BCR represents local recurrence or metastatic disease lies in the ability or not to salvage the surgical failure with RT. Treat-

ment with sRT is most likely to be effective when the rising PSA level is still low, when the PCa is less likely to have metastasised (i.e., when the disease is more likely to be confined to the prostate bed).

Early sRT delivered to patients with a short PSA-DT, or while the PSA level remains under 2 ng/mL, has been shown to improve survival in patients with BCR after RP. In a retrospective study of men with BCR after RP, at a median follow-up of 6 years after BCR, sRT (alone or with ADT) was associated with a threefold improvement in PCa-specific survival compared with observation, although only in men with a PSA-DT of <6 months (HR 0.32; 95% CI 0.19–0.54; $p < 0.001$) [56]. sRT initiated while the PSA level was 2 ng/mL or lower was associated with a significant increase in PCa-specific survival (HR 0.27; 95% CI 0.15–0.50). However, even in patients with a PSA level greater than 2 ng/mL, there was a significant PCa-specific survival advantage to sRT, so long as they had a PSA-DT of under 6 months (PSA level ≤ 2 ng/mL: HR 0.10; 95% CI 0.03–0.32; PSA level > 2 ng/mL: HR 0.34; 95% CI 0.12–0.95). However, if initiated more than 2 years after BCR, sRT provided no significant increase in PCa-specific survival, regardless of the PSA-DT. In another retrospective study, at a median follow-up of 11.3 years, early (within 1 year of BCR) sRT led to a significant reduction in all-cause mortality both in men with a PSA-DT of <6 months (HR 0.53; 95% CI 0.31–0.90; $p = 0.02$) and in men with a PSA-DT of 6 months or longer (HR 0.52; 95% CI 0.34–0.80; $p = 0.003$) [57].

Currently, there is no definitive recommendation on the relative merits of aRT versus early sRT. One study suggested that early sRT was similar to aRT in improving BCR-free survival in most patients with pT3pN0, R0–R1 PCa previously treated with RP. This study therefore suggests that early sRT, when given at a low PSA level (≤ 0.5 ng/mL), can significantly reduce overtreatment associated with aRT [58]. Another study reported no significant difference in OS between aRT given within 9 months of RP and delayed sRT (≥ 12 months post-RP) [59]. While genito-urinary toxicity was similar with early aRT and sRT, the former may be associated with lower rates of gastrointestinal (GI) events, with HRs of 0.80 and 0.70 for procedure-defined and diagnosis-defined GI events, respectively [59]. This may be an important consideration for patients with comorbidity, and challenges the belief that delaying RT reduces the risk of radiation-related complications.

Following RP with BCR, adding ADT to sRT may provide benefits over sRT alone. For example, the addition of ADT to sRT has shown benefit in terms of biochemical

PFS after 5 years in retrospective series [60, 61] and in PFS for high-risk tumours [62]. In the recently published double-blind, placebo-controlled RTOG trial of 760 patients who underwent sRT with or without 2 years of daily bicalutamide, the 12-year actuarial OS rate was 76.3% in the bicalutamide group and 71.3% in the group receiving daily placebo tablets (HR 0.77; 95% CI 0.59–0.99; $p = 0.04$). The corresponding 12-year incidence of death from PCa was 5.8 and 13.4%, respectively ($p < 0.001$), and the cumulative incidence of metastatic PCa was 14.5 and 23.0%, respectively ($p = 0.005$) [63]. Another RCT – GETUG-AFU 16 – compared standard sRT with or without 6 months of goserelin ADT in patients with a PSA-DT of over 6 months at relapse. Addition of ADT significantly improved biochemical and clinical progression after 5 years compared with sRT alone (80% [95% CI 75–84] vs. 62% [95% CI 57–67] respectively; HR 0.50 [95% CI 0.38–0.66]; $p < 0.0001$), while OS remained high in both study arms [64].

Two ongoing trials may help to guide practice in future: RADICALS aims to recruit approximately 3,000 men with PCa and will study the best way to use RT after RP, as well as the potential merits of additional ADT in this context; and RAVES will compare early sRT with aRT in men with pT3 disease and/or positive margins after RP [65].

Salvage Androgen Deprivation Therapy

Recurrence following RP can potentially be managed with salvage ADT, although data supporting this use is generally obtained from retrospective studies [1]. Not all patients with BCR after primary curative treatment benefit from salvage ADT; however, a favourable effect is observed in a high-risk group, which may be defined as having a short PSA-DT and/or by tumour characteristics [66, 67]. Factors that may favour ADT after RP include a very high risk of clinical recurrence, good recovery of continence, long life expectancy, and the patient being anxious about the future or not being ready to accept the idea of sRT.

The National Cancer Institute of Canada PR-7 trial compared intermittent with continuous ADT in men with BCR and no evidence of metastatic disease after definitive or salvage RT and RP. OS in the intermittent arm was not inferior to that in the continuous arm, and intermittent therapy was associated with beneficial effects on certain domains of QoL. Salvage ADT for BCR may therefore be most appropriately delivered in an intermittent fashion, with the possible exception of patients with a Gleason score of 8 or higher [68].

Limited data is available regarding the optimal timing of salvage ADT. An observational study – in a mixed group of over 2,000 patients experiencing BCR who had either undergone RP (69%) or RT (31%) – compared immediate ADT (patients started on ADT within 3 months of PSA relapse) with deferred ADT (patients started ADT \geq 2 years after PSA relapse or when they presented with metastasis, symptoms or a short PSA-DT) [69]. Interestingly, this study found no differences in either 5- or 10-year OS between the 2 strategies. In this study, the HR for mortality for immediate versus deferred ADT was 0.91 (95% CI 0.52–1.60), which corresponded to an estimated 5-year survival of 85.7% (95% CI 77.7–93.7%) and 87.7% (95% CI 84.8–90.6%), respectively. The 10-year estimated survival in this study was 69.8% (95% CI 54.5–85.1%) and 69.3% (95% CI 60.7–77.9%), respectively [69]. These findings suggest there is no difference in OS regardless of whether ADT is started immediately upon PSA relapse or is deferred until disease progression. Another study compared ultra-early salvage ADT (patients who began salvage ADT before reaching the standardised definition of BCR) with early salvage ADT (patients who started salvage ADT when they met the definition). Fewer patients receiving ultra-early salvage ADT experienced BCR compared with those receiving standard early salvage ADT (one patient [2%] vs. 12 patients [17.1%], respectively). This indicates that salvage ADT could potentially be most effective when administered before patients meet the definition of BCR.

Observation

Observation until the development of clinically evident metastatic disease may be suitable for patients with low-risk features (e.g., PSA-DT >12 months, time to BCR >3 years, Gleason score <7 and stage \leq T3a) or patients who are unsuitable for, or unwilling to receive, salvage therapy [1]. The median time to the development of metastasis from the time of post-RP PSA level elevation is 8 years; upon development of metastatic disease, the median actuarial time to death is 5 years [21]. For patients with BCR following RP and with a PSA-DT of longer than 1 year, a “wait and see” strategy is considered a viable option, rather than proceeding directly to sRT [23].

Summary

Contemporary data concerning improved stratification of high-risk patients, greater knowledge about the impact of aRT on urinary continence, more accurate re-staging, more effective RP and RT techniques, and the potential role of early sRT and salvage ADT needs to be taken into account in order to reach a personalised, shared

decision, balancing quantity of life with QoL. Crucially, the patient must have a strong understanding of the advantages and disadvantages of any treatment before any decision is made.

Neoadjuvant and Adjuvant Hormonal Therapy with RT

A consideration of the role of (neo) adjuvant therapy with RT is useful before examining the treatment choices in the setting of BCR after RT. The combination of RT with gonadotrophin-releasing hormone ADT is proven to be superior to RT alone followed by deferred ADT upon BCR [1]. Use of adjuvant or neoadjuvant ADT with RT in patients with locally advanced PCa is now standard practice.

A meta-analysis showed that for localised and locally advanced PCa, neoadjuvant ADT before RT significantly improved biochemical disease-free survival and clinical disease-free survival [54]. For patients with a Gleason score of 2–6, neoadjuvant ADT before RT significantly improved OS, and a short duration of neoadjuvant ADT should therefore be considered in such patients [54].

While the evidence strongly favours neoadjuvant/adjuvant therapy in patients with locally advanced PCa [1, 70], the value of this approach in intermediate- or high-risk localised PCa is less clear [1, 71, 72]. Rates of BCR may be reduced with adjuvant or neoadjuvant ADT in carefully selected patients with intermediate- or high-risk localised PCa [1, 73], and the decision to use adjuvant or neoadjuvant ADT with RT in such patients should therefore be based upon individualised assessment.

Management of Post-RT Recurrence

In the case of PSA-only recurrence after RT, the timing and mode of treatment remain controversial due to the low quality of the available evidence. Treatment options according to the EAU are salvage RP, cryotherapy, continuous or intermittent ADT, brachytherapy, HIFU, or observation [1].

RP

Of the available salvage therapies, RP provides the greatest likelihood of local control, but is associated with worse functional outcomes and an increased risk of AEs (e.g., urinary retention, urinary fistula, and fistula) compared with primary RP. Salvage RP should therefore be

considered only for patients with low comorbidity, and should be performed by an experienced surgeon. Across several case series of salvage RP following BCR post-RT, the BCR-free probability ranged from 37 to 87% [74–77], with one study reporting a PCa-specific survival rate of 83% [74]. The pre-salvage RP PSA level and prostate biopsy Gleason score were the strongest predictors of PFS and PCa-specific survival [78]. Factors that may indicate salvage RP include: a life expectancy of 10 years or longer, PSA level under 10 ng/mL, Gleason score of 7 or lower, no lymph node involvement, and initial clinical staging of T1 or T2 [78].

Cryotherapy

Salvage cryotherapy may be an alternative to salvage RP; however, despite improvements in complication rates [79–83], studies have shown disappointing results in terms of 5-year biochemical disease-free survival after cryotherapy [80, 82, 84]. For example, no significant difference in PCa-specific survival at 5 years was found between salvage cryotherapy and salvage RP (96 vs. 98%, respectively; $p = 0.283$) [84]. The authors of this study concluded that young, healthy patients with BCR after RT should consider salvage RP as it offers superior biochemical disease-free survival compared with cryotherapy and may offer a better chance of cure.

Androgen Deprivation Therapy

It is as yet unclear under what circumstances ADT should be used in a salvage setting. Salvage ADT (typically for ≥ 2 years for patients with high-risk disease) for post-RT BCR has been associated with significantly better metastases-free survival and disease-specific survival at 7 years' follow-up versus observation but only for patients with a PSA-DT of < 6 months [67]. At 7 years, freedom from distant metastasis for patients with a PSA-DT of < 6 months was 50%, compared with 83% if the PSA-DT was over 6 months ($p = 0.0001$); PCa-specific survival was 61 and 85% respectively ($p = 0.0001$), and OS was 47 and 53%, respectively ($p = 0.04$). PSA-DT may, therefore, be an important factor in determining the efficacy of ADT post-RT. Indeed, in patients with BCR following local therapy, changes in PSA-DT after treatment initiation have been shown to be prognostic for metastasis-free survival [85].

In a large non-inferiority RCT in patients with a PSA level greater than 3 ng/mL 1 year post-RT, intermittent ADT was shown to be non-inferior to continuous ADT in terms of OS (median: 8.8 vs. 9.1 years, respectively; HR for death, 1.02; 95% CI 0.86–1.21) [86]. An intermittent approach to therapy may have a beneficial effect on phys-

ical function, fatigue, urinary problems, hot flashes and sexual function [86], and may be more attractive than continuous ADT in cases where patients respond initially. However, evidence from the use of ADT – albeit in a non-salvage setting – appears to refute the purported benefits of intermittent over continuous therapy. In a recent trial, intermittent ADT was found to be inferior to continuous ADT on survival outcomes [87]. Furthermore, in a secondary analysis of the trial, ischaemic and thrombotic events were more frequent with intermittent ADT compared with continuous ADT (10-year cumulative incidence: 33 vs. 24%, respectively; $p = 0.02$) [88].

As discussed earlier, limited data is available regarding the optimal timing of salvage ADT.

Brachytherapy

The chance of cure using salvage brachytherapy following local recurrence post RT is low, as the total dose is limited [1]. For carefully selected patients, high- or low-dose rate brachytherapy may be an effective treatment option with an acceptable toxicity profile [89–91]. In one study, for example, at 5 years after salvage, OS was an estimated 92% (95% CI 80–97%) and biochemical control was 51% (95% CI 34–66%). The rate of complications in this study was also low, with just 2% acute and 2% late grade 3 genitourinary toxicities, no grade 2 or higher acute GI events and 4% grade 2 GI late events. However, due to lack of robust evidence and the risk of severe AEs with brachytherapy, only experienced centres should offer this treatment [1].

High-Intensity Focused Ultrasound

HIFU is a more recent option for post-radiation recurrent PCa; available data are therefore from shorter-term studies (mostly from a single treatment centre) and are limited [92–96].

Observation

For patients experiencing BCR post-RP, observation is appropriate for those with signs of only local recurrence (e.g., late BCR and a slow PSA rise) who do not wish to undergo second-line curative options [1].

Other Recommendations

Beyond observation, it is prudent to recommend that patients take regular exercise and adopt a healthy diet. Certainly, physical activity has been linked to a lower risk of PCa-specific death [97], and increasing evidence

suggests a complex relationship between obesity, diabetes and PCa [98]. Given this association, it may also be appropriate to assess cardiovascular risk in these patients, and prescribe prophylactic medication where necessary.

Conclusions

How best to treat a rising PSA following treatment of localised PCa with curative intent remains an important clinical question. After RP or primary curative RT, the risk of recurrence and the risk that recurrence will subsequently lead to metastasis need to be assessed in order to optimise management decisions. Current evidence provides clinicians with only general guidance, and it is vital that disease management strategies be individualised, that there is involvement of a multi-disciplinary team, and that every patient be involved in the decision-making process. Management decisions therefore often come

down to patient and provider preferences, taking into account the probability of disease progression and the risks and benefits of treatment. Improved methods for the early detection of early PCa progression and early metastasis will enable treatment to become more refined in the future.

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