Prostate cancer is the second most common solid tumor diagnosed in men in the United States and Western Europe, and the second most common cause of cancer death. \(^1\)\(^2\) The incidence of prostate cancer rose since the introduction of prostate-specific antigen (PSA) screening. \(^3\) Consequently, more men (80% of diagnoses in the United States) present with localized (ie, confined to the prostate capsule)\(^4\) disease, and treatment with radiation or surgery is largely successful at controlling their disease. However with follow-up, approximately one third of these patients may develop biochemical recurrence (BR). BR is detected by rising serum level of PSA.\(^5\)\(^6\) An estimated 20,000–35,000 US men per year experience BR after RP.\(^7\)

A general presumption is that BR will lead to overt progression in patients over subsequent years. Management of these patients is complex and controversial for a number of reasons. First, the definition of BR varies. Second, a transient PSA rise after radiotherapy (ie, a PSA "bounce") may be difficult to differentiate from treatment failure. Third, even after a patient has a confirmed BR, a further dilemma is the determination of the source of detectable PSA (ie, local vs systemic). Moreover, not all patients with a rising PSA go on to develop clinical relapse, and it is difficult to predict which patient will develop relapse and how quickly.

An additional challenge of a rising PSA is the plethora of treatment options available for a patient and the acknowledgment that no single therapy is the appropriate approach for all patients. Salvage options include external-beam radiation therapy (EBRT), brachytherapy (BT), radical prostatectomy (RP), cryotherapy, combinations of these therapies with androgen-deprivation therapy (ADT), and experimental modalities. Finally, the timing of intervention is debated: there is no evidence showing that early intervention improves survival; conversely, early treatment may lead to increased morbidity.

In this article we review the dilemma of a rising PSA post-RP or post-RT. First, we review the use of PSA as a marker of recurrence. We examine the various definitions of BR, both post-RT and post-RP. Next, we

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**Prostate cancer** is the second most common solid tumor diagnosed in men in the United States and Western Europe. Primary treatment with radiation or surgery is largely successful at controlling localized disease. However, a significant number (up to one third of men) may develop biochemical recurrence (BR), defined as a rise in serum prostate-specific antigen (PSA) level. A general presumption is that BR will lead to overt progression in patients over subsequent years. There are a number of factors that a physician must consider when counseling and recommending treatment to a patient with a rising PSA. These include the following (1) various PSA-based definitions of BR; (2) source of PSA (ie, local or distant disease, residual benign prostate); (3) available modalities to treat the disease with the least morbidity; and (4) timing of therapy. In this article we review the current and future factors that clinicians should consider in the diagnosis and treatment of recurrent prostate cancer.

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evaluate the prospective tests that detect failure. Finally, we review the current treatment recommendations and guidelines for patients with BR.

**PSA AS A MARKER OF TREATMENT SUCCESS**

PSA is a soluble protein detected in the peripheral blood that is a surrogate biomarker used in both the initial detection and subsequent post-treatment monitoring for prostate cancer. PSA production is regulated by the androgen receptor, the main proliferative signal for prostate cancer growth. PSA values are typically measured every 3–6 months after RP or RT for the initial 1–2 years after completion of therapy, and then continued yearly.

**Post-Radical Prostatectomy**

Serum PSA should reach undetectable levels by conventional assays in 4–6 weeks in the majority of men undergoing RP given that the half-life of PSA is 2.5–3 days.8,9 A detectable PSA after RP may reflect presence of residual benign prostatic tissue or cancer.10 Studies have shown that 65%–83% of men will have PSA levels that remain stable up to 10 years following RP.11–13

Patients post-RP with BR have an 88% 10-year overall survival (OS) rate in contrast to the 93% 10-year OS rate in men without BR.14 Following RP, Pound et al15 reported the median time from BR to clinical progression was found to be 8 years and that the median time from metastasis to prostate cancer-specific mortality to be 5 years. Thus, they estimated the median time from BR to death to be 13 years. Although recent studies have demonstrated even longer median survival after BR (up to 16 years), a subset of men with aggressive prostate cancer die much sooner after BR.16

**Post-Radiotherapy**

It is more difficult to define treatment success based on PSA values following RT than RP. RT typically induces a slow and unsteady PSA decrease to levels that are typically still detectable. Moreover, 10%–30% of patients exhibit a PSA bounce (ie, a temporary elevation in PSA without disease recurrence) within 3 years after RT, and these bounces may take up to 18 months to normalize.17–19 The etiology of PSA bounce remains unclear; radiation and bacterial prostatitis have been postulated as possible pathophysiological mechanisms.20,21 Nonetheless, the likelihood of metastases in men with PSA stabilization at levels ≥1.0 ng/mL is comparable to outcomes for men with lower or non-rising PSA values.22 Five-year BR rates post-RT have been estimated to be 28%–39% using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition (ie, three consecutive rises in PSA) and 24%–32% using the Phoenix definition (ie, nadir + 2 ng/mL).23,24 For men with a rising PSA, the 10-year metastasis-free survival is estimated to be 90%, while those with stable PSA have a rate of 97%.25 BR has been used as an outcome measure in multiple studies; however, because of variable definitions,24 the difficulty with comparing BR across treatments,26 and post-RT BR not directly translating to mortality, cancer-specific mortality has been the preferred metric for treatment efficacy. For patients treated with RP, EBRT, plus ADT, and EBRT alone, the 10-year cancer-specific survival rates have been estimated to be 92%, 92%, and 88%, respectively.27

**PSA AS A MARKER FOR DISEASE RECURRENCE**

A rising PSA after RT or RP usually signifies local or metastatic recurrence, and it is important to differentiate between these possibilities. The definition of BR varies, and important factors in its definition include the absolute PSA level,28–34 time to recurrence, PSA kinetics,15,16,35,36 nomograms,15,16,37–39 imaging,40 and biopsy of the prostate bed.16,41–44 While a number of guidelines for trending PSA post-therapy have been published, future markers of failure will likely use more sensitive and specific PSA tests and employ other modalities alongside the PSA.

**The Absolute PSA Level**

Often, serial evaluation of PSAs can help evaluate the clinical significance of a detectable PSA. For example, a man with a detectable and low PSA level of 0.05 ng/mL after therapy may have a persistently detectable PSA (ie, 0.05 ng/mL on every visit) without significant change for many years. Such a patient is unlikely to progress and suffer cancer-specific mortality. Thus, a detectable PSA alone may not mandate salvage intervention. In contrast, a patient with a detectable and serially rising PSA of 0.5 ng/mL (ie, from 0.5 ng/mL to 1.0 ng/mL and then to 1.5 ng/mL) is more indicative of residual prostate cancer and may benefit from salvage intervention.

Several studies have evaluated specific PSA cutoffs to define BR after RP.28,29 European Association of Urology (EAU) guidelines define BR with both a post-RP PSA cutoff of 0.2 ng/mL, and two sequential PSA values ≥0.2 ng/mL.30 These cutoffs are based on studies showing that only half of men with a detectable PSA in the 0.2–0.29 ng/mL range had subsequent PSA progression and could be defined as having BR. A PSA level ≥0.4 ng/mL correlated with a 79% risk of PSA progression.28 The PSA Working Group defined BR with a PSA cutoff ≥0.4 ng/mL with a subsequent elevated level.31 A retrospective evaluation of BR criteria showed that PSA cutoff
≥0.4 ng/mL had the highest correlation with the risk of clinical progression.29

Similarly, after RT, elevated PSA is associated with a poorer prognosis. The higher the PSA level, the greater the burden of disease and higher the risk of distant metastasis (DM).15,45 A pretreatment serum PSA level greater than 40 ng/mL is strongly associated with DM.46 Further, a serum PSA level above 1 ng/mL indicates a higher risk of failure of localized salvage therapy.47 However, the definition of BR based on an absolute PSA value post-RT is controversial because PSA levels may remain at detectable levels. A PSA bounce is common in the first 2 years following RT.18,19,48 Meanwhile, the median time to PSA nadir is 18 months.46 Moreover, the concomitant use of ADT either prior to or along with RT complicates the interpretation of the PSA value. Therefore, using an absolute value for PSA to define BR is not recommended.

To define BR after definitive radiotherapy, the ASTRO consensus provided an early common definition for treatment relapse following RT.52 Since the ASTRO criteria did not specify a PSA cutoff, a man whose post-RT PSA rose from a nadir of 0.05 ng/mL to 0.06, 0.07, and 0.08 ng/mL on subsequent evaluations could be classified as having BR. Moreover, the relationship between ASTRO-defined BR and cancer-specific survival or OS has not been clearly demonstrated.49,50 The ASTRO definition incorporates backdating, resulting in an artificial flattening of Kaplan-Meier curves, and therefore falsely provides more favorable estimates of outcomes when follow-up is short.

The PSA nadir + 2 ng/mL (PSAn; Phoenix) definition was introduced in 2005, and it has been shown to reduce these artifacts. It has been shown to be a more significant predictor of DM, cancer-specific survival, and OS after controlling for other significant covariates.33,34 Moreover, it has no apparent length of follow-up bias, provides a BR risk estimate that remains proportional over time with or without ADT,34,51 requires a shorter time to diagnosis,34 and is associated with fewer misclassifications when neoadjuvant and adjuvant ADT is used.17,52 Currently, ASTRO criteria are typically used in RT-only treated patients and Phoenix criteria in both patients treated with RT-only and those treated with RT+ADT.

**PSA Kinetics**

After RP, the time from initial local therapy to BR and shorter PSA doubling time (PSA-DT) have been shown to correlate with the site of recurrence.15 A shorter time to BR after initial local therapy is associated with a higher risk of DM. In contrast, a longer time to BR after initial local therapy is associated with a higher risk of localized recurrence.15,16 While a true cutoff of the time to BR has not been established, a time to BR ≤2 years after RP strongly implicates a distant or metastatic recurrence, while a time period of >2 years suggests a local recurrence.15 Positive surgical margins also are associated with an increased likelihood of BR.53

The main purpose of following PSA after treatment is to predict clinically meaningful outcomes.54 However, there is no current standard interpretation of PSA kinetics after RP or RT. Generally, a shorter PSA-DT indicates a rapidly growing tumor, a higher risk of clinical progression to DM, and a higher risk of cancer-specific mortality.57,55 Trapasso et al55 reported on patients whose PSA-DT was followed post-RP. Patients with a longer PSA-DT (mean, 11.7 months) had a higher risk of localized prostate cancer and a lower risk of clinical progression than patients with a shorter PSA-DT (4.5 months). Patients with PSA-DT of <3 months represent a minority (10%–15%) of men with BR but have the highest risk of systemic recurrence.57

In men post-RP, the use of post-treatment PSAn and PSA-DT have been proposed. For PSAn, it is not clear whether a PSAn during a patient’s lifetime,56 at 12 months,57 or at 24 months58 is most prognostic. Systemic recurrences were associated with higher PSAn and shorter PSA-DT.59 Patients with a PSA-DT <3 months had the greatest risk of cancer-specific mortality, with a median survival of 6 years.55 However, patients with a PSA-DT <3 months represent a small high-risk subgroup60,61 and such a low DT may be miscalculated.52,63 A novel measurement of PSA kinetics is the interval to BR (IBR): an IBR cutoff of 18 months has been shown to predict cancer-specific mortality following RT without ADT.56

**Multivariable Prediction Tools**

Multivariable prediction tools such as nomograms were developed using clinicopathologic and biochemical risk factors such as PSA-DT, time to BR, and Gleason score (GS) to predict clinical progression after RP15,16,42 and RT.39 Parameters that magnify the risk of systemic relapse in these systems include a PSA-DT ≤3 months, time to BR ≤3 years, and GS ≥7.16

**Advanced PSA Detection**

PSA levels are typically undetectable after RP,8,64 and between 65%–83% of men have stable PSA levels after RP.11–13 NADiA ProsVue is an in vitro diagnostic assay approved by the US Food and Drug Administration that uses a reporter monoclonal antibody against PSA attached to a synthetic double-stranded DNA label. After a serum sample is obtained from a patient, a biotin-labeled monoclonal antibody
bound to streptavidin-coated paramagnetic micro-
particles is used to capture and quantify PSA. The
limit of quantitation of the test is 0.65 pg/mL,
significantly lower than the most sensitive commer-
cially available PSA assays. Three samples are col-
clected from patients between 6 weeks and 10
months post-RP, and the three samples are tested
in a single ProsVue run. ProsVue PSA slope results
are calculated using ProsVue software. In a multi-
center, retrospective clinical trial of 304 post-RP
patients with stable and recurring disease, ProsVue
linear slope demonstrated significant and independ-
ent predictive capability for reduced risk of prostate
cancer recurrence and a low false positive rate (Iris
Molecular Diagnostics, Carlsbad, CA).

The characteristics of PSA that are commonly
seen and those that define BR are reviewed in
Table 1. PSA values differ in the post-RP and post-
RT settings; thus, the definitions of BR vary and the
following factors are often considered: the absolute
PSA level, time to recurrence, PSA kinetics, nomo-
grams, imaging, and biopsy of the prostatic bed.
When diagnosing BR, a clinician must discern if the
PSA is produced from local or systemic disease, as
these will drive treatment recommendations.

### SALVAGE THERAPY RISK ASSESSMENT

The initial step in management of BR in either the
post-RP or post-RT patient is determination of the
region of recurrence. Recurrence sites include
(1) locoregional, (2) distant, or (3) a combination
of the two. Only locoregional recurrence is
expected to benefit from additional local therapy.
Patients with distant recurrence may benefit from
systemic therapy. If recurrence occurs both locore-
regionally and distantly, then the patient may benefit
from a combination of the two.

In either case, the benefit of any therapy always
comes with a risk, be it cancer-specific mortality or
treatment morbidity. When considering individual
factors to pursue locoregional versus systemic ther-
apy, there is currently no single marker that can
clearly delineate the two. Moreover, for continuous
variables (eg, initial PSA, time of BR after initial
therapy), overlapping timeframes have been pub-
lished. Nonetheless, the following individual factors
(Table 2) are considered in differentiating local and
systemic recurrence: (1) initial disease risk sta-
tus; (2) pre-primary treatment tumor stage; (3)
data from imaging at the time of BR (ie, computed
tomography [CT], magnetic resonance imaging [MRI],
choline positron emission tomography [PET]); (4)
GS at time of BR; (5) PSA at time of BR; (6) time of BR
after initial therapy; (7) PSA-DT; and (8) PSA velocity.
With the aid of computer algorithms, the use of life expectancy
tables and clinical progression nomograms has been recommended to decide the need for
observation or intervention with salvage therapy.

While a number of factors may influence the
clinician to suspect local versus distant disease at
the time of BR, none is perfect. Advanced imaging
techniques will likely play a large role in determining
the site of BR in the coming decades. In the following
section, we review advances in imaging for BR.

### Table 1. PSA Trajectory After RT or RP, and Definitions of BR

<table>
<thead>
<tr>
<th>PSA trajectory</th>
<th>Post-RP</th>
<th>Post-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA should reach undetectable levels in 4 weeks</td>
<td>PSA falls slowly and unevenly</td>
<td></td>
</tr>
<tr>
<td>65%–83% of men have elevated PSA up to 10 years post-RP</td>
<td>10%–30% of men have PSA bounces in 3 years post-RT</td>
<td></td>
</tr>
<tr>
<td>Absolute</td>
<td>0.2 ng/mL; 2 sequential PSA values ≥ 0.2 ng/mL; ≥ 0.4 ng/mL + subsequent elevated level</td>
<td>Bounces take up to 18 months to normalize</td>
</tr>
<tr>
<td>Kinetics</td>
<td>time to BR ≤ 2 years predicts DM; PSA-DT of &lt; 3 months have highest risk of recurrence</td>
<td>PSA-DT &lt; 3 months predicts PCSS</td>
</tr>
<tr>
<td>Nomograms</td>
<td>Post-RP specific</td>
<td>Post-RT specific</td>
</tr>
</tbody>
</table>

Abbreviations: ASTRO, American Society for Radiation Oncology; BR, biochemical recurrence; DM, diabetes mellitus type 2; DT, doubling time; IBR, interval to biochemical recurrence; PCSS, prostate cancer–specific survival; PSA, prostate-specific antigen; PSAn, PSA nadir; RP, radical prostatectomy; RT, radiation therapy.
Currently, there is no uniformly accepted imaging modality that can distinguish local versus systemic recurrence. Traditional imaging to evaluate BR involves a radionuclide bone scan, CT scan, or MRI.74 These techniques best detect macroscopic disease but have poor sensitivity for microscopic low volume disease, or when PSA levels are below 10 ng/mL.75 A number of imaging modalities are under investigation (Table 3).

**Radiolabeled Imaging**

Immunoscintigraphy is a possible future imaging modality. It uses radiolabeled monoclonal antibodies specific for prostate cancer epitopes. Prostascint (111In–capromab pendetide, the monoclonal antibody to the intracellular epitope of prostate-specific membrane antigen [PSMA]) unfortunately has shown no correlation between response and salvage RT in a postoperative setting.78 J591 is the monoclonal antibody targeting the extracellular domain of PSMA, and it has provided improved imaging of bony metastasis and the prostatic fossa.79

Radiolabeled imaging with 18F-DG PET initially showed promise in detecting recurrent prostate cancer, but has been unsuccessful in practice.80 Recently, investigational PET tracers have shown more promising results. 11C-choline PET was reported to have a sensitivity of 89% and a positive predictive value of 72% for patients with BR and PSA levels <2.5 ng/mL.81 Similarly, 18F-choline PET sensitivity and specificity in detecting bone metastases from prostate cancer were reported to be 79% and 97%, respectively.82 NCT01602783 is an ongoing study that uses 11C-acetate PET screening to detect tumor not seen with conventional imaging for men with post-RP BR. Finally, androgen receptors have been targeted by 18F-DHT, which also has shown metastatic disease.83

18F-NaF was first approved in 1972 but was eclipsed by 99Tc-labeled phosphate agents. It was reapproved for PET use in 2000. NaF has advantages over 99Tc scans, including (1) improved sensitivity and specificity; (2) increased spatial contrast and resolution; (3) superior bone-to-background ratio; (4) faster whole body scanning (up to 60 minutes after injection); and (5) the ability to fuse information with anatomic information from CT or MRI, which may boost sensitivity and specificity to 100%.84 These novel imaging modalities are being explored in advanced prostate cancer patients. They may help discern which patients will benefit from salvage therapy.
Multiparametric MRI

The role of endorectal MRI is limited in evaluation of the patients with BR because of the low signal intensity of T2-weighted images in radiated tissue. Magnetic resonance spectroscopy (MRS), which measures elevation in choline or decrease in citrate in prostate cancer tissue, has a reported sensitivity of 77% compared to the 68% of MRI alone after EBRT. Unfortunately, MRS has poor spatial resolution and a high sensitivity for field inhomogeneities induced by surgical clips; thus, its role after RT is unclear.

Dynamic contrast-enhanced (DCE) MRI, which measures early gadolinium washout in prostate cancer, has improved sensitivity and specificity compared to MRI alone. Detects cancer recurrence, which was later proven by biopsy. Disturbed nodal architecture visible on MRI.

Dynamic contrast-enhanced (DCE) MRI

Modality Comments/References
Immunoscintigraphy 111In-capromab pendetide/ProstaScint MAb targeting the extracellular domain of PSMA 79
\( J591 \) MAb targeting the intracellular domain of PSMA; no correlation between response to salvage RT post-RP 78
MRS Reported sensitivity of 77% compared to the 68% of MRI alone 87
DCE Improved sensitivity and specificity compared to MRI alone 89
DW Detects cancer recurrence, which was later proven by biopsy 91
LTNP Disturbed nodal architecture visible on MRI 92
PET tracers 18F-DG Unsuccessful in practice 80
11C-choline Detects BR 81 and bony metastases 82
11C-acetate NCT01602783, ongoing efficacy study
18F-NaF When combined with CT fusion, sensitivity and specificity approaching 100% 84
18F-DHT Detects bony metastases 83

Abbreviations: BR, biochemical recurrence; DCE, dynamic contrast enhanced; DW, diffusion weighted; 18F-DG, 18-fluorodeoxy glucose; 18F-DHT, 18-fluorohydrotestosterone; CT, computerized tomography; LTNP, lymphotropic nanoparticle; MAb, monoclonal antibody; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.

Table 3. Current and Future Imaging Modalities That May Detect the Source of BR

SALVAGE THERAPY

Once BR is diagnosed and the source of PSA is confirmed, a clinician must choose the optimal treatment modality. In this section, we review the risk–benefit assessment and outcomes when using salvage ADT, RT, RP, and cryotherapy. We then discuss the investigational therapies for recurrent prostate cancer.

SALVAGE RT POST-RP

Risk–Benefit Assessment

Currently, it remains uncertain whether a rising PSA after RP indicates isolated local disease, distant metastases, or both. The best treatment for recurrent prostate cancer in patients with a rising PSA without clinical evidence of disease is controversial, and only RT has been shown to cure patients with localized disease post-RP. However, guidelines for the timing of salvage RT (immediate vs delayed) have not yet been established. Moreover, salvage RT includes risks of bladder irritation, radiation cystitis, and radiation proctitis. If all patients with post-RP BR underwent salvage RT, 44%–88% of patients would benefit, depending on the number of adverse features of the cancer.

Several studies have been published regarding the predicted success of salvage RT in a post-RP setting. The presence of perineural invasion at time of RP, an elevated pre-salvage RT PSA (>1 ng/mL), and a short PSA-DT (<3 months) are independent factors for decreased biochemical relapse-free survival after salvage RT. Conversely, when considering salvage RT, the number of positive surgical margins after initial RP has been shown to have no associated link with a secondary BR. The extension of the
radiation field from prostatic fossa alone to include the full pelvis including obturator nodes may further decrease recurrence rates after salvage RT.97,98

Although not all patients will benefit from whole-pelvis RT, predictors of which patients would benefit most from this are likely those who have a greater burden of disease reflected by radiographic imaging or a higher initial PSA.99 Regarding concomitant ADT during salvage RT, the subset of patients with seminal vesicle invasion on the RP specimen may have the greatest benefit of ADT during RT.100

Outcomes of Salvage RT

In general, salvage RT provides effective long-term biochemical control and freedom from metastasis in selected patients presenting with detectable PSA after prostatectomy.99 High-risk patients receiving both ADT and RT had a 5-year BR-free survival rate of 47% if the whole pelvis was irradiated, compared to 21% for patients with irradiation of the prostate fossa alone. The benefit from total ADT with post-operative RT was only observed when given concurrently with whole-pelvic RT, but not with fossa-alone RT.99 Additionally, the concomitant use of ADT to salvage RT also may decrease biochemical and clinical recurrence rates.94,101 Intensity-modulated RT, with dose escalation to 76 Gy, has been shown to be more effective than three-dimensional conformal RT in a salvage setting after RP.94,102

Bone-Seeking Radio-isotopes Combined With Salvage RT

The majority of men dying of prostate cancer have bone as the only site of metastasis.103 Skeletal metastases are associated with high morbidity, including pain, fractures, spinal compression, bone marrow compression, fatigue, and eventually death. Clinical trials have evaluated the palliative benefits of bone-targeted RT in metastatic prostate cancer. A phase I trial of samarium-153 ethylene-aminetramethylene phosphonate (153SM-EDTMP) for the treatment of clinically non-metastatic high-risk prostate cancer as primary or post-RP therapy showed that 153SM-EDTMP was safe and feasible to use in men.104 A phase II Radiation Therapy Oncology Group (RTOG) trial of consolidation docetaxel and 153SM-EDTMP in 43 men with castration-resistant prostate cancer showed a plateau in rising PSA and eventual PSA relapse in all patients, decreased bony pain in 69% of the cohort, and minimal toxicity.105 Currently, a phase II trial of 153SM-EDTMP followed by salvage RT for high-risk non-metastatic prostate cancer post-RP is underway. The ALSYMPCA trial in metastatic castrate-resistant prostate cancer patients with symptomatic bone metastases showed that the radium-223 arm had improved OS when compared to placebo by 2.8 months.106 Treatments targeting bone metabolism, tumor–bone stromal interactions, and bone metastases themselves are becoming a central element of care in metastatic prostate cancer. Numerous trials of metastasis-seeking RT agents are underway.107

SAVAGE RP POST-RT

Risk–Benefit Determination

Salvage RP may be offered to patients with biopsy-proven prostate-only recurrence after primary RT. Pre-salvage RP PSA value and prostate biopsy GS are the strongest prognostic risk factors for progression-free survival, organ-confined disease, and cancer-specific survival.108 For patients with initially localized cancer, clinically significant post-RT recurrence has been argued to occur at the site of primary tumor.109 Some studies argue for earlier identification (by pre-RT and post-RT MRI) of patients with persistent, viable local cancer post-RP, as these patients will likely benefit most from salvage RP.109,110

Contrarily, recurrent or radio-resistant prostate cancer occurs in about 30% of men receiving primary RT, and they are distributed in regions of the prostate (apical and periurethral), which are at risk for undertreatment using current ablative techniques. Thus, in these men, the efficacy of ablative techniques is adversely affected.111

Outcomes of Salvage RP

In patients who have undergone salvage RP in the post-RP setting, distant metastasis is observed in <25% of men after 10 years,112 disease-free survival is reported to be at 61% at 5 years, and prostate cancer–specific mortality is reported to be between 17%–36% after 5 years.41,113,114 For experienced surgeons, the rate of postoperative complications is low; moreover, open, laparoscopic, and robotic techniques are all effective.108,115 The rate of RP intraoperative morbidity is likely unaffected by prior pelvic RT; however, the rate of postoperative morbidity is increased in men previously treated with RT.116,117 Salvage RP has been shown to be associated with a high rate of erectile dysfunction (80%–100%), incontinence (44%–99%), bladder neck contractures (22%–41%), anastomotic stricture (7%–41%), and rectal injury (2%–28%).108,113,116,118 The use of a nerve-sparing approach helps preserve the erectile function in some patients.119

ADT POST-RP OR POST-RT

The use of ADT for BR when non-metastatic disease is suspected is controversial because it does not affect OS. ADT cannot induce cancer apoptosis, and if it is used alone, it cannot achieve a cure. While
men often do not want ADT for primary therapy, they usually also do not accept delaying ADT in the setting of BR. Lueprolide acetate, for example, is only indicated in the palliative treatment of advanced prostate cancer. Although lueprolide acetate has a number of toxicities, early initiation of ADT is commonly seen in the community setting with BR after definitive local treatments. Currently, the majority of patients with BR are managed by ADT, including 60% of patients who undergo primary RP and 94% of patients who receive primary RT.\textsuperscript{120} ADT has risks of hot flashes, osteoporosis, loss of muscle mass, sexual dysfunction, decreased libido, increase fat deposition, dyslipidemias, and increased risk of cardiovascular events.\textsuperscript{121,122}

Delaying ADT is an option in some men. In a study of 1,352 men treated with early or delayed ADT,\textsuperscript{123} ADT delayed clinical progression only in those with high-risk features, including GS ≥ 7 or PSA-DT ≤ 10 months. To shorten the time of ADT, intermittent schedules also have been investigated. In one phase III study of post-RP BR, patients initially received leuprorelin as a 3-month depot; when PSA values dropped to <0.5, they were randomized to intermittent or continuous leuprorelin and cyproterone. The interim analysis showed progression-free survival rates of 1,233 and 1,009 days, respectively.\textsuperscript{124} Intermittent ADT is currently only recommended for men >70 years of age with GS ≤ 7.\textsuperscript{125}

Thus, there are a number of uncertainties about the use of ADT in the setting of BR, and there is no consensus on who should receive therapy. Medical practitioners should take into consideration their suspicion that the rising PSA is related to metastatic disease, patient comorbidities, the quality of life of the patient with a known rising PSA (ie, "PSA anxiety"), and the quality of life of the patient while on ADT when making recommendations for the therapy.

**SALVAGE CRYOSURGERY**

**Risk-Benefit Determination**

Salvage cryosurgery has been an alternative treatment for patients with BR since the 1990s. The oncologic efficacy of salvage cryotherapy is more pronounced in low-risk patients (freedom from BR = 73%) than in intermediate (45%) or high-risk patients (11%).\textsuperscript{126}

**Outcomes of Salvage Cryosurgery**

The 5-year disease-free survival of cryosurgery has been estimated to be between 23%–74%.\textsuperscript{43,44,127–130} Salvage cryotherapy is associated with significant complications: after about 20 months, the incontinence rate is estimated to be 6%–20%\textsuperscript{43,129,130}; however, in a study with longer follow-up (72 months) this increased to up to 72%.\textsuperscript{44} Moreover, erectile dysfunction may be seen in up to more than two thirds of men.\textsuperscript{131}

**SALVAGE RT WITH REDUCED FRACTIONATION SCHEDULES**

Hypofractionated and stereotactic modalities have shown promising results as well. Hypofractionated salvage RT (65 Gy in 2.5-Gy fractions in about 5 weeks) reduces the length of treatment by from 1.5–3 weeks relative to standard salvage RT. It has been shown to have low rates of BR (33% at 4 years) and of gastrointestinal and genitourinary toxicity.\textsuperscript{132} Stereotactic body radiotherapy trials for local control in BR have not yet been published; NCT00851916 is a phase II single-group assignment trial of efficacy that is currently recruiting patients.

Salvage therapy with ADT, RP, RT, or cryosurgery begins with a risk–benefit determination of a therapy or the individual patient. A number of factors, including PSA-DT and surgical margins status at the time of primary therapy, have been shown to predict the success of salvage therapy. The clinical trials currently investigating these modalities are summarized in Table 4. While these established therapies provide promising results for men with BR, a number of unconventional investigational salvage therapies also exist.

**INVESTIGATIONAL THERAPIES IN THE SETTING OF BR**

Men with an isolated PSA recurrence after local treatment represent an ideal population for the evaluation of novel therapies based on minimal disease state, indolent natural history, and preference to avoid the adverse effects of hormone therapy. However, the evaluation of novel agents in this setting is hampered by the lack of convenient validated end points. Overall or progression-free survival endpoints are impractical because of the long interval between an initial PSA increase and development of metastases. Although PSA-DT has not been adequately evaluated as a clinical trial endpoint, changes in PSA-DT may be more sensitive to detect biologic activity than traditional PSA response criteria and frequently used in the recent clinical trial setting to suggest clinical efficacy of the study drugs.\textsuperscript{133,134} In another randomized controlled trial of men with rising PSA
<table>
<thead>
<tr>
<th>Trial</th>
<th>Identifier</th>
<th>Type</th>
<th>Primary Outcome</th>
<th>Status</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Salvage Cryotherapy in Recurrent Prostate Cancer (SCORE)</td>
<td>NCT00824928</td>
<td>Prospective, multicenter</td>
<td>Biochemical failure</td>
<td>Recruiting</td>
<td>800</td>
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<tr>
<td>Salvage HDR BT</td>
<td>NCT01583920</td>
<td>Phase I, pilot</td>
<td>GI, GU toxicity</td>
<td>Not yet open</td>
<td>4</td>
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<tr>
<td>Salvage MRI-mapped dose-escalated RT v standard RT</td>
<td>NCT01411345</td>
<td>Phase III, randomized, efficacy study</td>
<td>Radiographic</td>
<td>Recruiting</td>
<td>80</td>
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<tr>
<td>Early v late RT</td>
<td>NCT00860652</td>
<td>Phase III, randomized</td>
<td>BR</td>
<td>Recruiting</td>
<td>470</td>
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<tr>
<td>Salvage proton RT v photon/proton/ADT for node negative cancer post-RP</td>
<td>NCT00969111</td>
<td>Phase II, non-randomized, single group assignment</td>
<td>Morbidity</td>
<td>Recruiting</td>
<td>62</td>
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<tr>
<td>Vinflunine in hormone-refractory prostate cancer</td>
<td>NCT00545766</td>
<td>Phase II, non-randomized, single group assignment</td>
<td>PSA</td>
<td>Completed</td>
<td>41</td>
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<td>Salvage RT and docetaxel post-RP</td>
<td>NCT00480857</td>
<td>Phase II, non-randomized efficacy study</td>
<td>Progression-free survival</td>
<td>Recruiting</td>
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<td>153Sm followed by salvage 3D-CRT or IMRT in high-risk clinically non metastatic prostate cancer post-RP</td>
<td>NCT00480857</td>
<td>Phase II, non-randomized efficacy study</td>
<td>PSA</td>
<td>Recruiting</td>
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<td>Everolimus and RT as salvage therapy post-RP</td>
<td>NCT01548807</td>
<td>Phase I</td>
<td>Morbidity</td>
<td>Recruiting</td>
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<tr>
<td>Salvage RP post-RT</td>
<td>NCT00002938</td>
<td>Phase II</td>
<td>survival</td>
<td>Ongoing, not recruiting</td>
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<tr>
<td>MRI-guided HDR BT v RT boost as salvage in locally recurrent prostate cancer</td>
<td>NCT00913939</td>
<td>Efficacy, non-randomized, parallel assignment</td>
<td>Technical measures</td>
<td>Recruiting</td>
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<td>Salvage RT (2 schedules) post-RP for non-metastatic BR</td>
<td>NCT01272050</td>
<td>Phase III, randomized, efficacy study</td>
<td>PSA</td>
<td>Recruiting</td>
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<td>Sm 153 Lexidronam Penta Sodium and RT in BR post-RP</td>
<td>NCT00551525</td>
<td>Phase II</td>
<td>Disease response</td>
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<td>Docetaxel, prednisone, sunitinib and RT for BR after RP</td>
<td>NCT00734851</td>
<td>Phase II, non-randomized, single group assignment</td>
<td>PSA</td>
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<td>Dutasteride v placebo for BR post-RT/ADT/salvage</td>
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<td>Phase II, multicenter, randomized, double-blind, placebo controlled</td>
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<td>CK for local recurrence post-RT</td>
<td>NCT00851916</td>
<td>Phase II, efficacy, single group assignment</td>
<td>PSA</td>
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<td>153SM-EDTMP followed by salvage RT post-RP</td>
<td>NCT01317043</td>
<td>Phase II, efficacy, single group assignment</td>
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Abbreviations: 153SM-EDTMP, samarium-153 ethylenediaminetetramethylenephosphonate; BR, biochemical recurrence; BT, brachytherapy; CK, CyberKnife; CT, computerized tomography; HDR, high dose rate; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; QOL, quality of life.
after RP or RT, 31% of placebo-treated participants had post-treatment PSA-DT of more than 200% of baseline PSA-DT.\textsuperscript{134}

Investigational studies (Table 5) have used PSA kinetics as an outcome measure. Agonists of the peroxisome proliferator-activated receptor (PPAR) $\gamma$ receptor, including troglitazone and rosiglitazone have been shown to inhibit the proliferation on prostate carcinoma cells in vitro. In a phase II study,\textsuperscript{135} troglitazone was associated with stable disease (and only one case of PSA rise) in men with androgen-dependent prostate cancer. Rosiglitazone, unfortunately did not increase PSA-DT or prolong time to disease progression more than placebo in men with a rising PSA after RP and/or RT.\textsuperscript{134} In a single-arm phase II study, granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) decreased PSA levels by > 50% in three of 29 men with BR post-RP or RT.\textsuperscript{136} In another phase II study, high-dose oral calcitriol achieved no PSA decrease > 50% in 22 men who had rising PSA levels after definitive RT or RP, although PSA-DT was increased.\textsuperscript{137} CV706 is a replication-competent, PSA-selective oncolytic adenovirus. In a translational study, it was found to decrease serum PSA values and not be associated with any irreversible toxicities.\textsuperscript{138} Finally, celecoxib has been shown to significantly decrease PSA velocity and increase PSA-DT.\textsuperscript{133}

These investigational salvage therapies are unconventional in that they do not use surgery or radiation for the treatment of recurrent disease. These studies use changes in PSA as an outcome measure, which may correlate with distant metastasis. While their results are promising, none has yet been shown to be effective in a clinical setting, and phase III trials have not been established.

CONCLUSION

PSA screening has resulted in an increase in the overall incidence of prostate cancer diagnosis. While many men can be treated with surgery or radiation, a number of patients experience a rising PSA after primary therapy. A general assumption is that BR will lead to overt progression in patients over subsequent years. Clinicians face a number of dilemmas when encountering a rising PSA, including how to define BR, if the BR comes from localized or systemic disease, the treatment modality that would work best for an individual patient, and the timing of therapy. A number of studies have been published to help guide clinicians through these problems, and more clinical trials are currently ongoing. The future of detecting recurrent prostate cancer will likely use more sensitive PSA assays and advanced imaging; meanwhile, the future of treating recurrent disease will likely use a variety of modalities, including advanced surgical techniques, bone-seeking radiopharmaceuticals, hypofractionated radiation schedules, and pharmacotherapy.

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