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Review Article

A review of salvage treatment options for disease progression after radiation therapy for localized prostate cancer

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Abstract

Recurrence of prostate cancer after initial treatment with radiation therapy (RT) is highly dependent on pretreatment risk group and unfortunately, a proportion of patients fail primary treatment. The treatment of recurrence after primary radiation is rapidly changing with advances in imaging and it is important to distinguish those with a local failure from those with distant failure. If disease remains locally confined, salvage treatment with a variety of techniques can still provide a potential cure. Patients with distant failure are often treated with androgen deprivation, or in those with a shorter life expectancy, conservative management. In patients with a higher burden of metastatic disease, there is emerging evidence that chemotherapy and advanced androgen therapy can improve survival. We review the relevant literature on available salvage treatment options and appropriate patient selection for patients with recurrent prostate cancer after RT. We report on the efficacy and adverse effects of the currently available local salvage modalities including salvage radical prostatectomy, high dose rate and low dose rate brachytherapy, cryotherapy, high intensity focused ultrasound, and stereotactic body RT. We additionally discuss diagnosis of oligometastatic disease on imaging and current approaches to treatment with either radiation or surgery. While a full review of chemotherapy and advanced androgen therapies is beyond the scope of this article we briefly discuss their use in the treatment of newly diagnosed recurrence after radiation. © 2019 Elsevier Inc. All rights reserved.

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1. Introduction

Prostate cancer is the most commonly diagnosed non-dermatologic cancer in men in developed countries and has the second highest incidence to lung cancer among males globally [1]. Definitive treatment of disease confined to the prostate most commonly involves surgery, radiation therapy (RT) or a combination of both and patients over the age of 65 are more likely to receive RT than surgery [2,3].

Failure of primary treatment is separated into biochemical failure and clinical failure. Biochemical failure relates to rising serum prostate specific antigen (PSA) after treatment, and is used to predict future clinical failure. Clinical failure is when a patient presents with symptoms related to local progression or distant metastasis of prostate cancer after treatment. Failure after primary RT is heavily influenced by pretreatment risk grouping, but Nguyen et al. report that between 20% and 50% of patients may experience biochemical failure [4]. Rising PSA often predates clinical metastatic disease by many years and a subset of those with biochemical failure may continue to have organ-confined disease and benefit from additional local treatment [5]. Most patients with biochemical failure are managed with observation or androgen deprivation therapy (ADT) with only a small minority receiving local salvage therapy, though local salvage therapy may be underutilized [6].

In this review we will discuss which patients may benefit from local salvage therapy after failure of primary RT, and the general management of biochemical failure after

primary RT. We will explore the various salvage treatment modalities and compare survival and morbidity outcomes.

2. Patient selection

Failure after primary treatment is most often diagnosed as biochemical recurrence (BCR) due to rising serum PSA. BCR after RT is defined as a rise of ≥2 ng/ml above post-treatment nadir PSA value (Phoenix Definition) [7]. While recurrence is defined based on change in PSA, the absolute PSA value is associated with likelihood of recurrence and is predictive of time to metastatic disease [8,9]. Additionally, the absolute PSA at the time of salvage therapy is associated with biochemical failure free survival (bFFS) [10].

Among patients with BCR in whom the site of recurrence is detected, disease isolated locally in the prostate gland and seminal vesicle is most common. According to a study of patients with clinically detectable recurrence at Memorial Sloan Kettering Cancer Center, the anatomic distribution of recurrence was 41.6% local, 9.7% lymphotropic, 20.3% osteotropic, and 28.5% multiorgan/visceral [11].

Patients with metastatic disease, or distant failure, are not often candidates for curative intent local salvage therapy, and it is therefore of particular importance to attempt to identify these patients to spare them the morbidity of a salvage treatment from which they may not benefit. The standard metastatic workup after biochemical failure has been a bone scan and cross-sectional imaging of pelvis for decades. However, advances in technology including positron-emission tomography with ^{18}F-fluciclovine, choline C-11, or ^{18}F sodium fluoride along with whole body MRI or CT have allowed for earlier detection of metastatic disease, and detection of small volume loco/regional disease recurrence [12,13]. Imaging using radio-labeled prostate specific membrane antigen is an additional promising new technology to help identify disease [14,15]. Despite these more sensitive tests, many patients who undergo local salvage treatment will develop distant failure, some of whom presumably had undetectable micrometastasis at the time of salvage and would have benefited from more restrictive patient selection. Patients with higher T stage and Gleason score at diagnosis as well as PSA doubling time (PSA-DT) after recurrence of less than 6 months are more likely to develop distant metastasis after attempted local salvage and may not benefit from local treatment [16].

The recent advances in imaging have also allowed for identification of "oligometastasis" which describes the state of having limited metastatic spread, often to a single lymph node or distant locus. Patients with oligometastases may still be considered candidates for curative treatment and benefit from focal therapy to the identified lesion(s).

Patients with overt metastatic disease will not benefit from local salvage therapy, but in patients without evidence of metastasis the benefit of local salvage compared to ADT or observation is a controversial topic. Conclusions are based largely on small retrospective studies. The NCCN

suggests that candidates for local salvage therapy are patients with original clinical stage T1-T2, Nx, or N0, with life expectancy greater than 10 years, presalvage serum PSA <10 ng/ml, no evidence of distant metastasis based on imaging and PSA-DT, and a positive prostate biopsy [17]. None of the studies discussed in this article included only those patients meeting all of these criteria and it is therefore important to note the differing inclusion criteria for each study (Table 1).

3. Local salvage modalities

In patients who have radiographic and/or biopsy proven disease confined to the prostate after initial treatment with RT, local salvage treatment provides the possibility of a cure. However, only a small proportion of patients who fail primary RT receive local salvage treatment and there is currently no consensus on a best salvage treatment modality [6]. In evaluating local salvage options it is important to note that there are different definitions of biochemical failure, significant disparity in patient characteristics, and variation in the use of prior, neoadjuvant, and adjuvant ADT across the literature on this subject (Table 1).

3.1. Radical prostatectomy

Salvage radical prostatectomy (SRP) after external beam RT (EBRT) is more technically difficult and is associated with higher potential for morbidity than primary radical prostatectomy (RP) due to effects of primary radiation on normal tissues in the pelvis. For these reasons SRP should be performed by an experienced physician at a high volume center and patients should also be counseled regarding the increased risk of side effects with this procedure. Removal of the prostate gland is achieved by open approach or minimally invasive robotic or laparoscopic technique. Nerve sparing techniques attempt to preserve erectile function by leaving the neurovascular bundles intact but are only appropriate when tumor control will not be compromised. Pelvic lymph node dissection is often performed at the discretion of the surgeon and may be especially appropriate in the setting of oligometastatic disease confined to pelvic lymph nodes.

3.1.1. Oncologic outcomes

In a multi-institutional, international case series, Chade et al. reported on the treatment of 404 patient with SRP after initial RT. The median age was 65 years and median presalvage PSA was 4.5 ng/ml. At a median follow-up of 4.4 years they reported 5-year bFFS of 48%, metastasis free survival (MFS) of 83%, and cancer specific survival (CSS) of 92% [18]. These figures are similar to those reported by 2 smaller single center studies. Mandel et al. reported 5-year bFFS of 48.7% and CSS of 88.7% while Sanderson et al. reported progression free survival , which they define

Table 1
Summary of studies evaluating salvage treatment options for prostate cancer

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
Salvage radical prostatectomy (SRP)					
Chade et al. [18] 2011 N = 404	Retrospective, international case series 1985−2009	Median age 65 Median presalvage PSA 4.5 ng/mL Median FU 4.4 y	SRP	bFFS: 48% at 5 y, 37% at 10 y MFS: 83% at 5 y, 77% at 10 y CSS: 92% at 5 y, 83% at 10 y Pre-SRP PSA and gleason score at SRP predicted BCR and metastasis and positive LNs predicted metastasis	
Mandel et al. [19] 2016 N = 55	Single center, German case series 2007−2012	Radiation OR HIFU recurrent disease 58.2% of patients met Mean presalvage PSA 9.5 ng/mL Median FU 3.0 y	SRP	bFFS: 48.7% at 5 y MFS: 69% at 5 y CSS: 88.7% at 5 y Primary LDR BT and positive nodes correlated with worse bFFS bFFS was 73.9% for patients within EAU guidelines vs. 11.6% outside EAU guidelines	
Sanderson et al. [20] 2006 N = 51, 33 with questionnaire	Single center retrospective case series + questionnaire 1983−2002	Median Age 65 Median pre-SRP PSA 8.0 ng/mL Some patients received neoadjuvant ADT, post op ADT, orchiectomy. Median FU 7.2 y	SRP	PFS: 47% at 5 y overall Median OS was 12.9 y PFS was 100%, 80% and 67% for patients with pT2N0, preop PSA </=5.0 or Gleason </=7 respectively at 5 y. Presalvage PSA predictive of OS	QOL (median age 72 and median 7.5 y after surgery) Total continence or occasional dribbling reported by 82% with and 69% without AUS device Overall, 73% characterized overall urinary function as "small" "very small" or "no" problem. Mean sexual function score was clinically significantly higher for inflatable penile prosthesis (IPP) patients while patients with nerve sparing technique did worse than IPP patients but better than standard SRP patients
Ward et al. [21] 2005 N = 199	Single Center, retrospective case series 1967−2000	Life expectancy >/=10 y, all with positive prostate biopsy, no metastatic disease. Median age: 65 y Mean Preop PSA 8.5 ng/mL Median FU 7.0 y	SRP or salvage cystoprostatectomy (SCP)	PFS: 67%, 58%, and 48% at 3, 5, and 10 y. CSS: 87%, 79%, and 65% at 3, 5, and 10 y Patients undergoing SRP did better than those requiring SCP: Median PFS of 8.7 vs. 4.4 y. Aneuploidy was strongest predictor of PFS Pathological stage was strongest predictor of CSS	Intraop rectal injury in 4% of SRP and 10% SCP. Complete continence maintained in 52% Less overall morbidity in surgeries performed after 1990 as opposed to before

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
Low Dose Rate Brachytherapy (LDR BT)					
Crook et al. [26] 2019 N = 92	Prospective phase II study across 20 sites in the US and Canada 2007−2014	Initial Tx: EBRT alone Median age: 70 y Positive biopsy >30 mo after initial tx. PSA <10 ng/mL Gleason 7 (48%); all others Gleason 2−6 ^{99}Tc bone scan and abdominal/pelvic CT showed no regional/distance disease Median FU: 4.5 y	LDR BT 125-I 140 Gy or 103-Pd 120 Gy		Late grade 3 treatment related GI/GU adverse events experienced by 14% of patients. No late grade 4 or 5 events reported. Only V100 (volume receiving 100% of the prescribed dose) was predictive of late GI/GU adverse events (OR 1.24; $P = 0.03$). Early grade 3 treatment related GI/GU adverse events experienced by 14% of patients. No early grade 4 or 5 events reported. Half of patients with early grade 3 adverse events developed late grade 3 adverse events. The authors conclude that LDR BT after EBRT failure has acceptable tolerance.
Vargas et al. [22] 2014 N = 69	Single institution retrospective case series 1989−2011	Initial Tx: EBRT alone Average Age: 72.5 y Positive biopsy more than 2 y after initial tx PSA >5ng/mL while on HT were considered castration resistant prostate cancer (CRPC) Androgen suppression was used in 89% of cases neoadj and adjuvantly Median FU 5.0 y	LDR BT 103-Pd 100 Gy	bFFS: 73.8% in noncastration resistant disease vs. 20% in castration resistant patients at 5 y MFS: 90% at 5 y OS: 64% at 5 y Excluding CRPC patients (n = 60) 5 y bFFS was 85.6%, 74.8%, and 66% for low, intermediate, and high risk patients respectively. 5 y bFFS was 77.7% and 43.3% without and with treatment delay as defined as receiving 6 mo of ADT prior to salvage BT	
Grado et al. [24] 1999 N = 49	Mayo Clinic Scottsdale retrospective case series 1990−1996	Median age: 73.3 Initial tx: 46 EBRT, 3 BT PreSalvage PSA: 5.6 ng/mL (not including patients with neoadj ADT or prior orchiectomy 11 patients had already failed additional modality and 2 had failed 2 additional modalities. One patient had mets while 48 had no evidence of mets at time of salvage Median FU 5.3 y	LDR BT (37 patients with Pd103 median 120 Gy and 12 with I125 median 160 Gy.) 4 received adjunctive radiation therapy and 8 received neoadj hormone therapy	bFFS: 48% at 3 y, 34% at 5 y CSS: 89% at 5 y, 79% at 5 y OS: 75% at 3 y, 56% at 5 y Post-Salv PSA nadir of < 0.5 ng/mL associated with improved bFFS (RR 4.25 for patients with 0.5 ng/mL or more)	Acute Complications: frequency, urgency, hesitancy, nocturia common during first 3 months but transient and managed with alpha-blocker Sexual Side effects: Only 1 patient reported decreased capacity for sexual activity after salvBT but 60% of patients were not sexually active prior to salvage.

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
Burri et al. [25] 2010 N = 37	Mount Sinai single center retrospective case series 1994−2008	Median age at salvage: 70 Median PSA at salvage: 5.6 ng/mL Initial tx: 32 EBRT, 5 BT Median FU 7.2 y	LDR BT (Pd103 110 Gy, I125 135Gy)	bFFS: 65% at 5 y, 54% at 10 y LRFS: 84% at 5 y, 76% at 10 y DMFS: 94% at 5 y, 79% at 10 y CSS: 96% at 5 y, 96% at 10 y OS: 94% at 5 y, 74% at 10 y	
Moman et al. [27] 2010 N = 31	Single center Retrospective case series 1994−2009	Initial Tx: 20 EBRT and 11 125-I Mean age 69.3 y Mean preSalv PSA 11.4 ng/mL With mean doubling time of 13 mo Median FU 9.0 y	LDR BT 125-I 145 Gy	bFFS: 51% at 1 y, 20% at 5 y CSS: 74% at 5 y, 46% at 10 y OS: 72% at 5 y, 39% at 10 y Gleason >7 had HR 12.4 for BCR compared to Gleason ≤7	GU Toxicity: 87% and 55% of patients had grade 1-2 toxicity in acute (<90 days) and late phase (>90 days) respectively. Grade 3 toxicity occurred in 19% in late phase GI Toxicity: 55% and 51% of patients had grade 1−2 toxicity in acute and late phase respectively. Grade 3 toxicity occurred in 6% in late phase.
Baumann et al. [23] 2017 N = 33	US retrospective case series 1998−2013	Initial Tx: EBRT Median age: 75 y Median presalvage PSA 5.0 ng/mL High risk disease in 55% of patients Median FU: 5.1 y	LDR BT 103-Pd 100 Gy (N = 25) or HDR BT 30 Gy in 6 fractions (N = 8) All received 4−6 mo neoadjuvant plus adjuvant ADT	Relapse free survival: 79% at 5 y, 67% at 7 y DMFS: 93% at 5 y, 86% at 7 y OS: 94% at 5 y, 85% at 7 y Age at diagnosis, PSA nadir after EBRT, age at recurrence, and presalvage PSA were significant predictors of relapse free survival after salvage.	Late grade 3 GU toxicity occurred in 12% of patients with resolution or significant improvement 3 of 4 of these cases. 1 patient experienced late grade 1 GI toxicity but no other cases of GI toxicity were reported. ADT resulted in grade 2 endocrine toxicity in 30% of patients.
High Dose Rate Brachytherapy (HDR BT)					
Chen et al. [28] 2013 N = 52	Single institution retrospective case series 1998−2009	77% patients had increase in Gleason score at recurrence vs. primary tx. Median age: 67.5 Median PSA 5.0 ng/mL Median FU 5.0 y	HDR BT 36 Gy in 6 fractions in 2 separate implants performed 1 wk apart	bFFS: 51% at 5 y OS: 92% at 5 y No significant predictors of biochemical control	GU Toxicity: 2% of patients had grade 3 toxicity. No grade 4 or 5. GI: No grade 3 or higher acute or late GI toxicity. Late grade 2 GI in 4%
Yamada et al. [29] 2014 N = 42	Prospective phase II study 2007−2011	Biopsy proven recurrence after definitive EBRT Median age: 72 Median presalv PSA: 3.5 ng/mL 18 patients had ADT presalvage but all discontinued after HDR BT Excluded: any patient with PSA >10ng/mL at assignment and international prostate symptom score IPSS >15 before salvage therapy. Hx of inflammatory bowel disease, prior rectal surgery. Abnormal coag studies. Median FU 3.0 y	HDR BT 192-Ir 32 Gy in 4 fractions in 1 implant	bFFS: 68.5% at 5 y DMFS: 81.5% at 5 y OS: 79% at 5 y	GU Toxicity: Acute Grade 1 and Grade 2: 38% and 40%. Late Grade 1 and Grade 2: 48% and 48%. 3 total Grade 3 events but no Grade 4 or greater. GI: Late Grade 1 and Grade 2 GI toxicity 43% and 14% without Grade 3 or higher. Most GI complications consisted of transient rectal bleeding.

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
Salvage Cryotherapy (SC)					
Pisters et al. [30] 1997 N = 150	MD Anderson retrospective case series 1992−1995	Median age 68.8 y 91% Caucasian Initial Tx: -Group 1: RT only (98 EBRT only, 4 LDR BT only, 8 EBRT and LDR BT.) -Group 2: Combination of therapies (27 EBRT + HT, 6 EBRT + HT + CT, 1 EBRT + CT, 4 HT only, 2 HT + CT) Mean FU 1.4 y	SC	bFFS: 42% overall Among group 1 patients, BCR was more prevalent in patients who received only 1 freeze-thaw cycle compared to 2. Also the negative biopsy rate after double freeze-thaw cycle was 93% compared to 71% for single cycle.	Urinary incontinence reported in 73%, obstructive symptoms in 67%, impotence in 72%, and severe perineal pain in 8%.
Wenske et al. [32] 2013 N = 328	Columbia University NYC retrospective case series 1994−2011	Median Age 65.8 y Median Presalv PSA 4.0 ng/mL Median time to SC 67.5 mo after primary RT or cryosurgery Initial tx: 259 EBRT, 49 LDR BT, 20 cryosurgery Median FU 4.0 y	SC	bFFS: 63% at 5 y, 35% at 10 y CSS: 91% at 5 y, 79% at 10 y OS: 74% at 5 y, 45% at 10 y PSA nadir after SC was predictive of bFFS and CSS.	Urethral stricture requiring intervention in 4.6%, bladder outlet obstruction requiring intervention in 3.4%. Rectourethral or urethroperineal fistula formation in 1.8%. 55 of the patients underwent focal SC of affected lobe. Overall Survival was better for this cohort but rectourethral fistula formation occurred in 5.5%
Williams et al. [33] 2011 N = 176 of 187	Canadian retrospective case series 1995−2004	Median age: 70.9 y Median presalvage PSA: 4.9 ng/mL 71% had neoadjuvant ADT for 3−6 mo for downsizing Initial tx: 183 EBRT, 3 BT, 1 EBRT + BT. Mean FU 7.5 y	SC	DFS (recurrence including BCR): 47%, 39%, and 39% at 5, 8, 10 y MFS: 87%, 83%, 82% at 5, 8, 10 y OS: 95%, 91% and 87% and 5, 8, and 10 y Post salvage nadir >1 had RR 6.63 for recurrence $P < 0.001$ Presalvage PSA<5ng/mL had DFS 64% at 10 y as opposed to 6.7% with PSA>10 ng/mL Presalvage Gleason and pre-intial tx PSA both also correlated with DFS	
Perrotte et al. [34] 1999 N = 112 of 150	MD Anderson cross sectional study of quality of life 1992−1999	Median age 68.8 y 91% Caucasian Initial Tx: -Group 1: RT only (98 EBRT only, 4 LDR BT only, 8 EBRT and LDR BT.) -Group 2: Combination of therapies (27 EBRT + HT, 6 EBRT + HT +CT, 1 EBRT + CT, 4 HT only, 2 HT + CT) Mean FU 1.4 y	SC		Incontinence: 72% report dribbling or leakage of urine Voiding Symptoms: Medium to severe symptoms in 66% of patients. More cases of voiding symptoms without use of urethral warming catheter (93% vs. 55% of patients) Sexual Function: 41% of patients were potent prior to SC down to 15% after tx. Double freeze-thaw cycle group had significantly worse potency after tx (8% vs. 23%)

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
					Pain: 44% report some degree of chronic perineal pain or discomfort. 70% vs. 34% had pain with vs without urethral warming catheter. 33% overall satisfaction rate with SC
Ng et al. [35] 2007 N = 187	Canadian retrospective case series 1995−2004	Median age: 70.9 y Median presalvage PSA: 4.9 ng/mL 71% had neoadjuvant ADT for 3−6 mo for downsizing Initial tx: 183 EBRT, 3 BT, 1 EBRT + BT. Mean FU 3.3 y	SC	bFFS: 56% in patients with pre-salvage PSA ≤4 ng/mL, 29% with PSA 4−9.99 ng/mL, and 14% with PSA ≥10 ng/mL at 5 y. OS: 97% at 5 y, 92% at 8 y	8% of patients needed additional surgery for complications
High Intensity Focused Ultrasound (HIFU)					
Crouzet et al. [38] 2017 N = 418	International retrospective case seriers 1995−2009	Mean time between initial tx and salvage: 5.1 y Mean age 68.6 y Mean presalvage PSA 6.8 ng/mL 191 patients had hx of ADT but none continued after HIFU. 87.1% of patients had one session of HIFU while 12.2% and 0.7% had 2 and 3 session respectively Median FU 3.3 y	HIFU	bFFS: 49% at 5 y overall. 58%, 51%, and 36% for pre-EBRT low, intermediate, and high risk patients or 67%, 42%, and 22%, for pre-S-HIFU PSA levels of ≤4, 4−10 and ≥10 ng/mL respectively. MFS: 81% at 7 y CSS: 82% at 7 y OS: 72% at 7 y Lower PSA nadir after S-HIFU correlated with decreased need for ADT after salvage.	
Gelet et al. [39] 2004 N = 71	Single center French retrospective case series 1995−2003	No staging pre-HIFU Median presalv PSA 5.7 ng/mL Mean age 67 Mean 1.2 y	HIFU	DFS: 38% at 2.5 y Negative biopsy rate of 73% at 2.5 y Metastasis observed in 12.7% overall	6% developed urethrorectal fistula
Kanthabalan et al. [40] 2017 N = 150	UK retrospective case series 2006−2015	Mean age: 69.8 y Mean presalvage PSA 5.5 45.3% with presalvage ADT Median FU 2.9 y	HIFU	bFFS: 48% at 3 y overall. 100%, 61%, and 32% at 3 y for low intermediate and high risk groups. OS: 92% at 5 y	
Ahmed et al. [41] 2012 N = 84	Two site international retrospective case series 2004−2009	Mean age 68.3 Median Presalv PSA 3.8 ng/mL Initial Tx: all EBRT Gleason 6−7 only Median FU 1.7 y	HIFU	PFS: 59% at 1 y, 43% at 2 y 8% of patients did not respond to therapy and had increased PSA after therapy 25% of whole cohort and 43% of those biopsied had residual disease on biopsy following salvage HIFU	

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
Crouzet et al. [42] 2012 N = 290	French retrospective case series 1995−2009	Mean age 68.7 Mean PSA 6.38 ng/mL D'Amico risk group: 19% low risk, 31.4% intermediate, and 43% high risk and undefined in 6.6% Mean time from Initial tx to salvage was 60 mo 50% received ADT prior to salvage at some point Median FU 2.3 y for PFS and 4.0 y for CSS and MFS	HIFU	PFS: 45%, 31%, and 21% at 5 y for low, intermediate, and high risk groups MFS: 80% at 5 y, 79.5% at 7 y Increased risk of progression with higher presalvage PSA, previous ADT, and Gleason ≥8 vs. Gleason ≤6	6 cases of urethrorectal fistula, 8 cases of pubic bone osteitis. 16% experienced bladder outlet obstruction.
Stereotactic Body Radiation Therapy (SBRT)					
Fuller et al. [44] 2015 N = 29	Prospective single arm study 2009−2014	At least 2 y since prior RT Median age 73 Median presalv PSA 3.1 ng/mL Median interval between initial tx and salvage 88 mo Initial tx: 27 EBRT, 1 BT, 1 SBRT 7 on ADT at time of initial failure but none received neoadj or adjuvant ADT Median FU 2.0 y	SBRT 34 Gy in 5 fractions	bFFS: 82% at 2 y	GU Toxicity: 18% report ≥grade 2 with one case of grade 3 and 1 case of grade 4. GI Toxicity: No acute or late GI toxicity greater than grade 1 Sexual function: Data available on 10 patients who were potent before salvage tx. Three patients had a major decrease in potency while 4 had no significant change. (SHIM scoring)
Leroy et al. [45] 2017 N = 23	Retrospective single institution case series 2011−2014	Median age 70 y Initial tx with EBRT or BT +/- ADT Median presalvage PSA 2.5 ng/mL Recurrence at least 2 y after initial tx Median FU 1.9 y	SBRT 36 Gy in 6 fractions	DFS: 54% at 2 y OS: 100% at 2 y LRFS: 76% at 2 y	Grade 3 toxicity in 9% of patients (cystitis and neuralgia) Grade 1−2 urinary toxicity was common No grade 4 or higher toxicity reported
Oligometastatic Disease					
Ost et al. [46] 2017 N = 62	Multicenter, randomized, phase II study 2012−2015	Median age 64 (surveillance) and 62 (MDT) y Median PSA at inclusion was 3.8 ng/mL for surveillance and 5.3 for MDT One metastasis in 29% of surveillance group vs. 58% of MDT group Median FU 3 y	Metastasis directed therapy (MDT) with SBRT or surgery vs. Surveillance for oligometastasis	Median ADT-free survival was 13 mo for surveillance group and 21 mo for MDT group. Local progression in 6 of surveillance group versus none of the MDT group. PSA decline observed in 35% for surveillance group vs. 75% in MDT group.	Grade 1 toxicity in 17% of the MDT patients without grade 2 or higher events. No difference in quality of life between the 2 groups
Ingrosso et al. [47] 2016 N = 40	Italian retrospective case series 2008−2014	Median age 74 y Median Gleason 7 Primary Tx was surgery, EBRT, or BT Median PSA 4.2 ng/mL Median FU 2.0 y	SBRT for oligometastasis	bFFS: 44% at 2 y OS: 95% at last FU 1 patient with failure within the treatment field	Grade 2 toxicity in 1 case (acute phase diarrhea) Grade 3 toxicity in 1 case (late phase dyspepsia)

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
Porres et al. [48] 2017 N = 87	German prospective study 2009−2016	Mean age 66.7 y Mean pre-salvage PSA 2.63 ng/mL Primary Tx was RP in 87.4% +/- adjuvant or salvage RT. Primary tx of RT in 10.3% of patients. Median FU 1.8 y	Salvage pelvic lymph node dissection (sPLND)	Only 69 patients with complete follow up included in survival analysis bFFS: 35.5% and 27.3% at 1 and 5 y Systemic therapy-free survival: 63.4% and 35.1% at 1 and 5 y. Number of positive lymph nodes and biochemical response 6 wks after surgery were identified as predictors of bFFS and ADT-free survival.	One intraoperative obturator nerve lesion Postoperative lymphocele occurred in 11.5% of cases, half of which required surgical intervention. Two patients with obstructive ileus also required surgery.
Karnes et al. [49] 2015 N = 52	Mayo Clinic retrospective case series 2009−2013	Median age 60 y Median presalvage PSA 2.2 ng/mL Primary Tx was RP in all cases Other therapy after RP in 78.8% of cases before sPLND Median FU 1.7 y	Salvage pelvic lymph node dissection (sPLND) 82.7% received adjuvant hormone therapy	bFFS: 45.5% at 3 y MFS: 46.9% at 3 y CSS: 92.5% at 3 y No further treatment after sPLND in 46.2% of patients at last follow up.	
Androgen Deprivation Therapy (ADT)					
Duchesne et al. [53] 2016 N = 261	Randomized Phase III trial 2004−2012	Group 1: patients with PSA relapse after tx. No more than 12 m adj or neoadj ADT and ADT must have been completed at least 12 m prior to randomization. Group 2: Asymptomatic men unsuitable for curative tx because of age, comorbidity, or locally advanced disease. Excluded if PSA- doubling time <,3 mo Median FU 5.0 y	Immediate vs. delayed ADT Immediate: received tx within 8 wks of randomization Delayed: Treatment was not to begin until at least 2 y after randomization unless symptoms or mets developed, or PSA doubling time decreased to <6 m.	Combined: 5 y OS 86.4% in delayed vs. 91.2% in immediate. Trend toward increased survival in immediate with unadjusted HR of 0.55 (95% CI 0.30−1.00; $P = 0.050$) Group 1 results: 5 y OS 78.2% vs. 84.3% for delayed vs. immediate tx respectively. The adjusted HR for death was 0.54 in favor of immediate tx but not statistically significant ($P = 0.074$). Statistically significant difference in local progression that favored immediate tx but this was not observed with distant progression. 41% of men in delayed arm did not reach a trigger (in other words they made it the full 2 y before starting ADT)	Delayed arm demonstrated fewer treatment associated adverse events than immediate arm. Did not demonstrate relevant difference in quality of life between arms
Crook et al. [54] 2012 N = 1,386	Randomized controlled trial 1999−2005	Definitive RT >12 m before enrollment PSA >3 ng/mL and higher than post-RT nadir No evidence of mets Serum testosterone >5 nmol/L	Intermittent androgen deprivation (IAD) vs. continuous androgen deprivation (CAD) IAD: 8 mo of treatment followed	Median overall survival was 8.8 y in intermittent-therapy group and 9.1 y in the continuous-therapy group. HR for death with IAD vs. CAD was 1.02 (95% CI, 0.86−1.21) which met noninferiority criteria (HR	QOL: -Functional domains non-significant trend in favor of IAD -Symptoms: Hot flashes, desire for sexual activity, and urinary symptoms all significantly better with IAD ($P < 0.05$) in addition to a trend toward improved

Table 1 (***Continued***)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
		Life expectance >5 y Median FU 6.9 y	by surveillance until PSA above 10 ng/mL	<1.25) with a *P* value of 0.009 Significant improved outcomes across groups: age <75 y, >3 y since RT, baseline PSA 3−15 ng/mL, and no prior HT.	fatigue (*P* = 0.07). Potency on IAD: only 29% of those potent at baseline recovered potency during non-treatment interval.
Hussain et al. [55] 2013 N = 1,535	Randomized controlled trial 1995−2008	Prior radiation therapy in 29% and prior radical prostatectomy in about 20% of patients. All patients had metastatic disease Median age 70 y Median pre-ADT PSA: 42 ng/mL Patients were randomized after showing response to ADT	Intermittent androgen deprivation (IAD) vs. continuous androgen deprivation (CAD) Patients received luteinizing hormone-releasing hormone agonist and antiandrogen agent.	They could not demonstrate statistically significant inferiority or non-inferiority of IAD compared to CAD. The IAD group experienced more deaths with HR 1.10 but 90% CI (0.99, 1.23). Median survival after enrollment was 5.7 y for IAD vs 6.4 y for CAD	IAD was associated with better quality of life related to impotence (*P* < 0.001), libido (*P* = 0.04), and mental health (*P* = 0.003) At 15 mo, 78% of the IAD group had resumed hormone therapy.
Chemotherapy James et al. [56] 2016 N = 2962	RCT 2005−2013	Median age 65 y Prior local therapy in 6% of patients. M+ disease in 61%, N+/X M0 in 15%, N0M0 in 24%. Median FU 3.6 y	Four groups: Standard of care (SOC) only (HT), SOC +zoledronic acid (ZA), SOC + docetaxel (Doc), and SOC + ZA + Doc	Survival advantage identified for SOC + Doc (HR 0.78, 95% CI 0.66 −0.93; *P* = 0.006) and SOC + ZA + Doc (HR 0.82, 95% CI 0.69−0.97; *P* = 0.022) groups versus the SOC alone group Failure free survival advantage for SOC + Doc (HR 0.61, 95% CI 0.53 −0.70; *P* = 0.413 × 10^{-13}) and SOC + ZA + Doc (HR 0.62, 95% CI 0.54−0.70; 0.134 × 10^{-12})	Grade 3−5 toxicity occurred in 52% of patients in both the SOC + Doc and SOC + ZA + Doc groups overall. At 6 mo after treatment, Grade 3−5 toxicity occurred in 17% for SOC only, 15% for SOC + ZA, 36% for SOC + Doc, and 39% for SOC + ZA + Doc
James et al. [57] 2017 N = 1917	RCT 2011−2014	Median age 67 y Median PSA 53 ng/mL Median FU 3.3 y Additional RT in 41% Included patients who were newly diagnosed and metastatic, high risk locally advanced, or relapsed after primary surgery or RT.	ADT alone vs. combination therapy (ADT plus abiraterone acetate and prednisolone)	Failure free survival: 75% in combination therapy group vs. 45% in ADT alone group (HR 0.29; 95% CI, 0.25 to 0.34; p<0.001) at 3 y CSS: 76% in combination group vs. 82% in ADT alone group overall	Any grade 3 or higher adverse event in 47% of combination group vs. 33% of ADT alone group. Grade 5: 12 events in combination group vs. 3 events in the ADT along group.
Sweeney et al. [58] 2015 N = 790	RCT 2006−2012	Median age 64 y in ADT + Doc group and 63 y in ADT alone group Median PSA at start of ADT was 50.9 in ADT + Doc group and 52.1 in ADT alone group No local therapy in 72.8% in both groups. Primary tx of RT or RP in others Median FU 2.4 y	ADT alone vs. ADT + Docetaxel (Doc)	Overall survival benefit for ADT + Doc group over ADT alone (HR 0.61; 95% CI 0.47−0.80; *P* < 0.001) Decrease in PSA level to <0.2 ng/mL occurred in 27.7% in the ADT + Doc group and 16.8% in ADT alone group (*P* < 0.001). Median time to castration resistant	Grade 3 toxicity occurred in 16.7% of patients. Grade 4 toxicity occurred in 12.6% of patients. One patient experienced grade 5 toxicity event (sudden death). Most common grade 3−4 events were fatigue, neutropenia, and febrile neutropenia.

Table 1 (*Continued*)

Study	Study type	Patient characteristics	Treatment	Oncologic outcomes	Toxicity outcomes
McKay et al. [59] 2015 N = 41	Single arm phase II study 2008−2010	Median age 58−60 y Previous tx included RP in 36, 29 of whom received salvage RT. The other 5 patients had primary RT. Median FU 2.3 y	Docetaxel, bevacizumab, dexamethasone, and ADT	disease was 20.2 mo for ADT + Doc group vs. 11.7 mo for ADT alone (HR 0.61; 95% CI 0.51 −0.72; $P < 0.001$) 80% developed PSA progression with median time to progression of 27.5 mo	Grade 3 treatment related adverse events in 39% Grade 4 treatment related adverse events in 12%

Abbreviations: SRP = salvage radical prostatectomy; EBRT = external beam radiation therapy; LDR BT = low dose rate brachytherapy; HDR BT = high dose rate brachytherapy; SC = salvage cryotherapy; HIFU = high intensity focused ultrasound; SBRT = stereotactic body radiation therapy; BCR = biochemical recurrence; bFFS = biochemical failure-free survival; CSS = cancer specific survival; PFS = progression free survival; DFS = disease free survival; MFS = metastasis free survival; DMFS = distant metastasis free survival; OS = overall survival; PSA = prostate specific antigen; ADT = androgen deprivation therapy; HT = hormone therapy; CRPC = castration resistant prostate cancer; LN = lymph nodes; FU = follow-up; QOL = quality of life.

as time to ADT initiation or progression, of 47% at 5 years [19,20]. In a case series of 199 patients treated at the Naval Medical Center, bFFS was 58% and 48% at 5 and 10 years respectively [21]. Despite their slightly higher bFFS, they found a slightly lower CSS of 79% and 65% at 5 and 10 years respectively.

Taken as a whole, the literature for SRP suggest that in carefully selected patients with residual disease in the prostate, approximately half can be cured with surgery. However, it is important to note that patient selection for salvage is crucial, and most of the published series of SRP span many decades in which time radiation, surgical, and imaging techniques have changed significantly.

3.1.2. Adverse effects

As previously mentioned the morbidity of SRP can be significant. Ward et al. reported on morbidity after SRP, noting that 4% of SRP patients suffered operative rectal injury which increased to 10% of the patients who had undergone cysto-prostatectomy due to radiation induced adhesions involving the rectal wall, bladder base, or trigone [21]. In a series of patient surveys from 33 patients at a median of 7.5 years from SRP, Sanderson et al. reported that 73% of respondents found their overall urinary function to be "small," "very small," or "no" problem, while continence rates were higher among those who had received an artificial urethral sphincter [20]. Not surprisingly, they found a clinically significant improvement in sexual function in patients with inflatable penile prosthetic implant over patients with nerve sparing SRP, but found no difference in sexual bother between the groups. Bladder neck contractures were a common complication in both studies, occurring in 22%−41% of patients [20,21].

3.2. Brachytherapy

In patients who have previously received EBRT, brachytherapy (BT) can be an appealing option due to the ability to deliver a very conformal high dose to the target lesion while minimizing dose to surrounding healthy tissue. There is also the convenience of as few as a single treatment session. The published literature for salvage BT includes a patient population that was largely treated with ADT prior to salvage BT, and variable rates of neoadjuvant ADT between study populations results in a wide range of biochemical control outcomes. However, in more contemporary and less pretreated populations, low dose rate or high dose rate BT appear to be able to cure about half of all local failures in patients who are candidates for the procedures.

3.2.1. Low dose rate BT

Low dose rate BT (LDR BT) is performed by implanting radioactive seeds directly into and around the target lesion or the entire prostate gland. Seeds remain in the gland permanently and deliver dose slowly over many months as the

isotopes decay. Frequently used radioisotopes include ^{125}I (half-life 59.4 days) and ^{103}Pd (half-life 17.0 days).

3.2.1.1. Oncologic outcomes. The largest reported case series of patients receiving salvage BT was published by Vargas et al. In this study of 69 patients, 89% of the patients received ADT neoadjuvantly and/or adjuvantly and if patients demonstrated serum PSA >5 ng/ml while on ADT their cancer was considered castration resistant. Their 5-year bFFS was 73% for castration sensitive and 20% for castration resistant cancers. MFS and overall survival (OS) were 90% and 64% at 5 years [22]. In a study of largely high-risk patients, Baumann et al. reported on reduced dose BT with concurrent ADT and found relapse free survival to be 79% and 67% at 5 and 7 years respectively and distance MFS was 93% and 86% at 5 and 7 years [23]. Grado et al. reported on a series of 49 patients with median age 73.3 and presalvage PSA 5.6 excluding patients with neoadjuvant ADT or prior orchiectomy. With median follow-up of 5.3 years they report 5-year bFFS, CSS, and OS of 34%, 79%, and 56%, respectively [24]. Of these 49 patients, 11 had already failed 1 additional salvage modality and 2 had failed 2 previous modalities. More recently, Burri et al. reported on 37 patients at Mount Sinai with median age of 70 years and presalvage PSA of 5.6 ng/ml. They reported a bFFS of 54%, CSS of 96%, and OS of 74% at 10 years [25].

3.2.1.2. Adverse effects. In a phase II prospective study of 92 patients previously treated with EBRT, Crook et al. found that LDR BT was well-tolerated, with only 14% of patients experiencing late grade 3 GI or GU adverse events and no reported early or late grade 4 or higher events [26]. Moman et al. reported the toxicity experienced by 31 patients at 9 years median follow-up and they found that 87% of their patients experienced grade 1-2 GU toxicity in the early phase within 90 days of treatment which decreased to 55% after 90 days [27]. The prevalence of grade 3 GU toxicity increased from 3% to 19% from the early to the late phase. Grade 1-2 GI toxicity occurred in 55% and 51% of patients in the early and late phase respectively. Grade 3 GI toxicity was rare and occurred in only 6% of patients in the late phase and no patients experienced grade ≥4 GI or GU toxicity. Grado et al. reported toxicities among their 49 patients which included 2 cases of persistent gross hematuria, 3 patients with significant penile dysuria, and 2 patients with rectal ulcers [24]. They found that acute urinary symptoms were common but typically transitory.

3.2.2. High dose rate BT

Administration of high dose rate BT (HDR BT) involves insertion of catheters into the prostate guided by a perineal template. Highly radioactive isotopes such as ^{192}Ir are inserted and moved through the catheters to distribute dose per the treatment plan. In some cases, patients may have the catheters implanted more than once and often multiple doses are delivered hours apart with a single implant.

3.2.2.1. Oncologic outcomes. Chen et al. published a retrospective series of 52 patients undergoing salvage HDR BT with 36 Gy in 6 fractions across 2 separate implants. Patients had a median age of 67.5 and median presalvage PSA of 5.0 ng/ml. With median follow-up of 59.6 months they found 5-year bFFS of 51% with OS of 92% [28]. In a prospective phase II study of HDR BT in 42 patients treated with 32 Gy in 4 fractions using a single implant, Yamada et al. reported a 5-year bFFS of 68.5% and OS of 79% [29]. This study excluded patients with presalvage PSA >10 ng/ml and any patient with international prostate symptom score greater than 15.

3.2.2.2. Adverse effects. Yamada et al. additionally evaluated treatment toxicity in their 42 patients [29]. They found acute grade 1-2 GU toxicity in 78% of patients, and up to 96% of patients in the late phase. There were 3 total grade 3 GU toxicity events with no grade 4 or greater. GI toxicity was largely transient rectal bleeding without any grade 3 or greater events. Chen et al. reported grade ≥2 acute and late GI toxicity in 38% and 56% of patients respectively with only 4% of patients experiencing any grade 2 GI toxicity [28]. Acute sexual dysfunction was found to be grade ≥2 in 19% of patients, increasing to 35% of patients for late dysfunction.

3.3. Cryotherapy

Cryotherapy, also known as cryosurgery and cryoablation therapy, involves placement of probes within the prostate that undergo extreme cooling using argon gas. Prostate tissue is consumed by an expanding ball of ice that is monitored by transrectal ultrasound often through multiple freeze-thaw cycles [30]. Rapid freezing of the tissue results in ice crystal formation that leads to cell death [31]. A urethral warming catheter is used to prevent urethral tissue damage.

3.3.1. Oncologic outcomes

Wenske et al. published a series of 328 patients who received salvage cryotherapy between 1994 and 2011 at Columbia University and had mostly received EBRT as primary treatment (49 patients had primary LDR BT and 20 patients had primary cryotherapy) [32]. The median age was 65.8 years and median presalvage PSA was 4.0 ng/ml in the study. Their bFFS was 63% and 35% at 5 and 10 years respectively. CSS was 91% and 79% and OS was 74% and 45% at 5 and 10 years respectively. Lu et al. reported their series of 187 patients with mean follow-up of 7.5 years and found disease free survival, which included results of serum PSA and some patients who received biopsies, to be 47% at 5 years and 39% at 10 years while MFS and OS were 87% and 95% respectively at 5 years [33].

3.3.2. Adverse effects

Long-term complications of salvage cryotherapy were assessed with a survey of 112 patients at a median age of

68.8 years and mean follow-up of 16.7 months [30,34]. They found that 72% of patients reported incontinence, 66% reported medium to severe voiding symptoms, 63% lost potency among those who were potent prior to cryotherapy, and 44% reported chronic perineal pain [34]. They additionally found a 33% overall satisfaction rate with cryotherapy. A similar report by Ng et al. fund that among 187 patients treated with salvage cryotherapy 8% required surgery to address complications after treatment [35].

3.4. High intensity focused ultrasound

High-intensity focused ultrasound (HIFU) is used in the treatment of localized prostate cancer through the ablation of tissue by heat generated by a beam of focused ultrasound using a transrectal probe [36]. The US Food and Drug Administration approved HIFU to be marketed for use in prostate tissue ablation only as recently as 2015 due to lack of substantial clinical outcome data [37]. There is limited data on HIFU outcomes relevant to patient decision-making for primary treatment of prostate cancer and with this lack of primary treatment data, it follows that evidence in the context of local salvage therapy is even more sparse.

3.4.1. Oncologic outcomes

Crouzet et al. published the largest series of 418 patients undergoing S-HIFU from 1995 to 2009 in an international, multi-institutional analysis [38]. Mean patient age was 68.6 years, on average 5.1 years after primary treatment. Mean presalvage PSA was 6.8 ng/ml and median follow-up was 3.3 years. Some patients had a history of ADT use but none continued ADT after HIFU. Most patients received 1 HIFU session, with about 13% of patients receiving 2 or 3 sessions. They reported 37% of patients were free from initiation of ADT at 5 years but also report a bFFS of 49% overall at 5 years. Gelet et al. reported 30-month actuarial disease free rate (bFFS or negative biopsy) as 38% in their series of 71 patients with a median presalvage PSA of 5.7 ng/ml, and 13% of patients developed metastases [39]. Kanthabalan et al. reported a bFFS of 48% at 3 years with 92% OS among 150 patients [40]. Interestingly Uddin et al. biopsied a portion of their cohort of 84 patients treated with S-HIFU and found that 43% of those biopsied (25% of the entire cohort) demonstrated a positive biopsy after S-HIFU treatment [41].

3.4.2. Adverse effects

HIFU is less invasive than prostatectomy, but can still lead to significant morbidity. In an earlier study Crouzet et al. reported 16% of patients experienced bladder outlet obstruction. They also reported that 2% and 3% of patients developed a urethrorectal fistula and pubic bone osteitis respectively [42]. Gelet et al. found that 6% of their patients developed urethrorectal fistula [39].

3.5. Stereotactic body RT

Stereotactic body RT (SBRT) is similar to EBRT except that the treatment dose is typically delivered in 2 to 5 total fractions. SBRT is an appealing noninvasive way to approximate the dosimetry achieved by HDR BT [43]. SBRT is a relatively new technique and there are few studies investigating the use of SBRT for local salvage therapy in prostate cancer.

Presenting preliminary results of their prospective study of 29 patients treated with salvage SBRT with 34 Gy in 5 fractions, Fuller et al. reported a bFFS of 82% at 2 years. The median age was 73 and median presalvage PSA was 3.1 ng/ml. They found GU toxicity of grade ≥ 2 in 18% of patients and no patients with GI toxicity above Grade 1. Of 10 patients who were sexually potent prior to SBRT, 4 reported no significant change while 3 experienced a major decrease in potency [44].

In another small series, Leroy et al. reported bFFS of 54% at 2 years among their 23 patients. Patients received 36 Gy in 6 fractions and had a median presalvage PSA of 2.5 ng/ml. They reported 26% of patients with GU toxicity grade ≥ 2 and 2 patients with grade 2 rectal toxicity [45].

4. Treatment of oligometastatic disease

Treatment of oligometastatic disease typically consists of either radiation or surgery. RT usually consists of SBRT while surgery involves salvage pelvic lymph node dissection (sPLND) when disease is confined to the pelvic nodes and metastasectomy for other isolated lesions. While there is growing interest and ongoing research investigating treatment of oligometastatic prostate cancer, published data remains sparse.

Ost et al. published a phase II trial comparing surveillance to metastasis-directed therapy (MDT) with either SBRT or surgery [46]. They found that the MDT group had a significantly longer median time to initiating ADT and no patients in the MDT group experienced grade 2 or greater toxicity. An Italian study of 40 patients evaluated the use of SBRT in patients with isolated lymph node recurrent prostate cancer [47]. They reported a 2-year bFFS of 44%.

Surgery for oligometastatic disease can target distant metastases, but most commonly will target lymphatic disease with salvage pelvic lymph node dissection (sPLND). A German study of sPLND investigated outcomes of surgery in patients with recurrent prostate cancer with lymphatic disease detected on imaging [48]. Most patients had received prostatectomy as primary treatment, but 10% of patients had received RT. Of the 69 patients included in the analysis, 27.3% demonstrated bFFS at 5 years and 35.1% remained free from systemic therapy at 5 years. Postoperative lymphocele occurred in 11.5% of patients, half of whom required surgical intervention. A study of 52 patients with recurrence after RP at Mayo Clinic found that sPLND resulted in bFFS of 45.5%, MFS of 46.9%, and CSS of 92.5% all at 3 years

[49]. This patient population was free from additional treatment in 46.2% of cases at last follow-up. As with these studies, most evidence for sPLND is in patients who underwent RP for primary treatment. Patients with recurrence after primary RT differ from RP patients in that they may have received previous radiation to their lymph nodes, and they retain their prostate gland. However, if imaging identifies disease isolated to the lymph nodes and surgical resection is feasible, it may be reasonable to assume similar outcomes in patients with recurrence after RT.

5. Systemic management options

In recent studies positron-emission tomography/CT is able to identify a lesion(s) in over 70% of patients with a PSA greater than 0.5 [14,15]. However, advanced imaging is not always available, and even with advanced imaging some patients have only biochemical evidence of disease and are presumed to be metastatic. Patients with diffuse metastatic disease on imaging or other complicating factors may not be candidates for metastasis directed therapy, and for these reasons systemic treatment remains a common option for patients who fail RT.

5.1. ADT

ADT is a staple in the treatment of metastatic prostate cancer and has additionally been associated with improved outcomes in localized disease [50,51]. Patients treated with ADT experience side effects including impotence, decreased libido, hot flashes, fatigue, and weight gain among others. There is evidence of an association with incident diabetes, coronary artery disease, myocardial infarction, and sudden cardiac death with ADT [52].

The Timing of Androgen Deprivation trial was a randomized, nonblinded, phase III trial that included patients with biochemical recurrent disease without evidence of metastases (group 1) or who were not eligible for curative treatment (group 2) and evaluated the effect of immediate vs. delayed initiation of ADT. Men assigned to the delayed arm were recommended to start ADT at least 2 years after randomization unless they developed symptoms, metastases, or a PSA-DTs of <6 months. This study found an improvement in OS in favor of immediate ADT, but among the group 1 patients this benefit did not reach statistical significance [53]. The immediate ADT group had more low-grade side effects, but overall quality of life was similar between the groups. Given the lack of an OS benefit for immediate initiation of ADT in patients with biochemical failure, many clinicians will delay initiation of ADT until an arbitrary cut-off (e.g. PSA of 10) or until the PSA-DT is <6 months.

5.1.1. Continuous vs. intermittent ADT

Traditionally, ADT was administered continuously beginning at the time of BCR, but due to the significant side effects of ADT there has been interest in intermittent androgen deprivation (IAD). IAD allows for a treatment-free period, and in theory fewer side effects. In a randomized controlled noninferiority trial of 1,386 patients, Crook et al. compared IAD to continuous androgen deprivation. IAD was given in 8 month treatment cycles followed by nontreatment until PSA was >10. They found that OS was not inferior in the IAD group vs. the continuous androgen deprivation (CAD) group [54]. The median survival was 8.8 vs. 9.1 years in the IAD and CAD groups respectively. Their study additionally found symptom-based quality of life outcomes to favor IAD including hot flashes, desire for sexual activity, and urinary symptoms. In a randomized controlled trial of 1,535 patients with metastatic disease, Hussain et al. similarly found fewer adverse events among the IAD group, however they were unable to conclusively demonstrate noninferiority in regard to survival [55]. This study helps to support the paradigm of IAD, however it is difficult to directly apply the outcomes to our patient population since all of their patients had metastatic disease and a minority had been previously treated with radiation.

5.2. Chemotherapy

Recent studies have evaluated the efficacy of chemotherapy in patients with locally advanced and/or metastatic prostate cancer. The use of systemic therapy in the context of PSA-only recurrence without evidence of metastasis has been investigated, but these patients have made up a small portion of larger randomized trials.

The Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial is evaluating various systemic therapies in local recurrent, locally advanced, and metastatic prostate cancer. The patient population being recruited into the STAMPEDE trial ranges from locally advanced (2 high risk features) to metastatic, with the majority of patients having newly diagnosed metastatic disease without previous treatment.

In a publication evaluating the benefit of adding docetaxel, zoledronic acid, or both to standard of care (ADT +/- radiation) the STAMPEDE authors randomized 2,962 patients between 2005 and 2013 [56]. Standard of care demonstrated a median OS of 71 months while addition of docetaxel resulted in a median OS of 81 months (HR 0.78; 95% CI 0.66−0.93; $P = 0.006$). Addition of zoledronic acid to standard of care and to standard of care plus docetaxel did not demonstrate an advantage compared to standard of care plus docetaxel. Failure free survival favored the docetaxel group over standard of care alone (HR 0.61; 95% CI 0.53−0.70; $P < 0.001$). However, the survival benefit in the setting of biochemical failure only is difficult to ascertain as only 6% of the patients in this study failed primary treatment. In addition the survival benefit of chemotherapy came at the added cost of treatment toxicity with a 20% increase in grade 3-5 toxicity (32% vs. 52%).

In a separate cohort of 1,917 patients, the STAMPEDE authors investigated the effect of ADT alone vs. ADT plus abiraterone and prednisolone. Failure free survival was 75% in the combination therapy group vs. 45% in the ADT alone group (HR 0.29; 95% CI 0.25−0.34; $P < 0.001$). Patients who received combination therapy experienced fewer symptomatic skeletal events than those who received ADT alone (HR 0.46; 95% CI 0.37−0.58; $P < 0.001$), but again patients in the combination group were more likely to experience grade 3 or higher toxicity (47% vs. 33%) [57]. Again in this cohort only 5% of patients had been previously treated.

For patients with clinical or radiographic evidence of metastatic disease the CHAARTED trial randomized 790 patients with metastatic, hormone sensitive prostate cancer to receive ADT alone or ADT plus docetaxel [58]. There was an OS benefit with the addition of docetaxel over ADT alone (HR 0.61; 95% CI 0.47−0.80; $P < 0.001$). Median time to castration resistant disease was 20.2 months for combined therapy compared to 11.7 months with ADT alone (HR 0.61; 95% CI 0.51−0.72; $P < 0.001$). However, again the proportion of patients who had failed previous primary treatment was small (72.8% no prior treatment, 19.5% prostatectomy, and 7.6% radiation) making extrapolation to failure after primary RT difficult.

In a small phase II study of 41 patients, McKay et al. treated patients with docetaxel, bevacizumab, and ADT after BCR following local therapy [59]. At 1 year after completion of therapy, only 44% remained free from BCR and over half of their patients reinitiated ADT within 2 years due to disease progression. Additionally 39% and 12% of patients experienced grade 3 and grade 4 treatment-related adverse events and 22% of patients discontinued treatment due to toxicity.

Chemotherapy and advanced hormonal therapy are moving to the forefront of treatment for metastatic prostate cancer, but their role in treating patients after failure of primary radiation remains controversial. Taken as a whole, the published randomized trials suggest that patients with a higher burden of disease (clinical or radiographic metastasis) are most likely to benefit from chemotherapy or advanced hormonal therapy after failure of primary radiation.

5.3. Watchful waiting

In patients with recurrence who are elderly, have comorbid conditions, or otherwise elect to forego treatment, watchful waiting may be an appropriate strategy. In a retrospective study of men with PSA failure after RP the median time to development of clinical metastatic disease was 8 years from first biochemical failure, and the median time to prostate cancer specific death was 5 years from development of metastatic disease [60]. Clearly biochemical failure does not typically indicate imminent death from disease, and therefore in patients with a life expectancy <10 years aggressive salvage or hormonal treatment is unlikely to prevent clinical disease manifestation or death.

6. Conclusions

Salvage for failure after definitive RT for prostate cancer is a rapidly evolving field as newer imaging technologies are detecting more localized/oligometastatic disease. While there is no high quality comparative data to guide the decision of which local salvage therapy is best, it is reasonable to offer local salvage based on institutional strengths in patients with a presalvage PSA <10, life expectancy >10 years, PSA-DT of >6 months, no evidence of distant disease, and either biopsy proven or imaging evidence of local failure. For patients with biochemical failure and no measurable disease, ADT remains the backbone of treatment, and this can be given continuously or intermittently with no difference in OS. Chemotherapy and advanced hormonal therapy have shown a survival benefit in patients with metastatic disease, but the benefit is likely greatest in those with a higher burden of disease.

Conflicts of Interest

The authors have no conflict of interest.

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J. Global cancer statistics, 2012. 2015;65:87−108. https://doi.org/10.3322/caac.21262.

[2] Burt LM, Shrieve DC, Tward JD. Factors influencing prostate cancer patterns of care : an analysis of treatment variation using the SEER database. Adv Radiat Oncol 2018;3:170–80. https://doi.org/10.1016/j.adro.2017.12.008.

[3] Oglio PD, Valiquette AS, Tian Z, Trudeau V, Larcher A. Treatment trends and medicare reimbursements for localized prostate cancer in elderly patients. Can Urol Assoc J 2018;12:E338–44. https://doi.org/10.5489/cuaj.4865.

[4] Nguyen PL, D'Amico AV, Lee AK, Suh WW. Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure: a systematic review of the literature. Cancer 2007;110:1417–28. https://doi.org/10.1002/cncr.22941.

[5] Zagars GK, Pollack A. Kinetics of serum prostate-specific antigen after external beam radiation for clinically localized prostate cancer. Radiother Oncol 1997;44:213–21.

[6] Tran H, Kwok J, Pickles T, Tyldesley S, Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol Semin Orig Investig 2014;32:701–6. https://doi.org/10.1016/j.urolonc.2013.12.014.

[7] Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO phoenix consensus conference. Int J Radiat Oncol Biol Phys 2006;65:965–74. https://doi.org/10.1016/j.ijrobp.2006.04.029.

[8] Slovin SF, Wilton AS, Heller G, Scher HI. Time to detectable metastatic disease in patients with rising prostate-specific antigen values following surgery or radiation therapy. Clin Cancer Res 2005;11:2576–9. https://doi.org/10.1158/1078-0432.ccr-05-1668.

[9] Freedland SJ, Moul JW. Prostate specific antigen recurrence after definitive therapy. J Urol 2007;177:1985–91. https://doi.org/10.1016/j.juro.2007.01.137.

[10] Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291:1325–32. https://doi.org/10.1001/jama.291.11.1325.

[11] Zumsteg ZS, Spratt DE, Romesser PB, et al. Anatomic patterns of recurrence following biochemical relapse in the dose-escalation era for prostate patients undergoing external beam radiotherapy. J Urol 2015;194:1624–30. https://doi.org/10.1016/j.juro.2015.06.100.

[12] Sartor O, de Bono JS. Metastatic prostate cancer. N Engl J Med 2018;378:645–57. https://doi.org/10.1056/NEJMra1701695.

[13] Glaser ZA, Rais-Bahrami S. Fluciclovine positron emission tomography in the setting of biochemical recurrence following local therapy of prostate cancer. Transl Androl Urol 2018;7:824–30. https://doi.org/10.21037/tau.2018.07.17.

[14] Zacho HD, Nielsen JB, Dettmann K, et al. 68Ga-PSMA PET/CT in patients with biochemical recurrence of prostate cancer. Clin Nucl Med 2018;43:579–85. https://doi.org/10.1097/RLU.0000000000002169.

[15] Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging 2017;44:1258–68. https://doi.org/10.1007/s00259-017-3711-7.

[16] Zelefsky MJ, Ben-Porat L, Scher HI, et al. Outcome predictors for the increasing PSA state after definitive external-beam radiotherapy for prostate cancer. J Clin Oncol 2005;23:826–31. https://doi.org/10.1200/JCO.2005.02.111.

[17] NCCN. Prostate Cancer NCCN Evidence Blocks. 2018.

[18] Chade DC, Shariat SF, Cronin AM, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. Eur Urol 2011;60:205–10. https://doi.org/10.1016/j.eururo.2011.03.011.

[19] Mandel P, Steuber T, Ahyai S, et al. Salvage radical prostatectomy for recurrent prostate cancer: verification of European Association of Urology guideline criteria. BJU Int 2016;117:55–61. https://doi.org/10.1111/bju.13103.

[20] Sanderson KM, Penson DF, Cai J, et al. Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. J Urol 2006;176:2025–32. https://doi.org/10.1016/j.juro.2006.07.075.

[21] Ward JF, Sebo TJ, Blute ML, Zincke H. Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. J Urol 2005;173:1156–60. https://doi.org/10.1097/01.ju.0000155534.54711.60.

[22] Vargas C, Swartz D, Vashi A, et al. Salvage brachytherapy for recurrent prostate cancer. Brachytherapy 2014;13:53–8. https://doi.org/10.1016/j.brachy.2013.10.012.

[23] Baumann BC, Baumann JC, Christodouleas JP, Soffen E. Salvage of locally recurrent prostate cancer after external beam radiation using reduced-dose brachytherapy with neoadjuvant plus adjuvant androgen deprivation. Brachytherapy 2017;16:291–8. https://doi.org/10.1016/j.brachy.2016.12.011.

[24] Grado GL, Collins JM, Kriegshauser JS, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology 1999;53:2–10.

[25] Burri RJ, Stone NN, Unger P, Stock RG. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;77:1338–44. https://doi.org/10.1016/j.ijrobp.2009.06.061.

[26] Crook JM, Zhang P, Pisansky TM, et al. A prospective Phase 2 trial of transperineal ultrasound-guided brachytherapy for locally recurrent prostate cancer after external beam radiation therapy (NRG Oncology/RTOG-0526). Int J Radiat Oncol Biol Phys 2019;103:335–43. https://doi.org/10.1016/j.ijrobp.2018.09.039.

[27] Moman MR, Poel HG Van Der, Battermann JJ, Moerland MA, Vulpen M Van. Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Brachytherapy 2010;9:119–25. https://doi.org/10.1016/j.brachy.2009.06.007.

[28] Chen CP, Weinberg V, Shinohara K, et al. Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy : 5-year outcomes. Int J Radiat Oncol Biol Phys 2013;86:324–9. https://doi.org/10.1016/j.ijrobp.2013.01.027.

[29] Yamada Y, Kollmeier MA, Pei X, et al. A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy 2014;13:111–6. https://doi.org/10.1016/j.brachy.2013.11.005.

[30] Pisters LL, Von Eschenbach A, Scott SM, et al. The efficacy and complications of salvage cryotherapy of the prostate. J Urol 1997;157:921–5.

[31] Mazur P. Cryobiology : the freezing of biological systems. Science (80-). 1970;168:939–49.

[32] Wenske S, Quarrier S, Katz AE. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery : long-term clinical, functional, and oncologic outcomes in a large cohort at a Tertiary Referral Centre. Eur Urol 2013;64:1–7. https://doi.org/10.1016/j.eururo.2012.07.008.

[33] Williams AK, Martinez CH, Lu C, Ng CK, Pautler SE, Chin JL. Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. 2011;60:405–410. doi:10.1016/j.eururo.2010.12.012.

[34] Perrotte P, Litwin MS, McGuire EJ, Scott SM, Von Eschenbach AC, Pisters LL. Quality of life after salvage cryotherapy: the impact of treatment parameters. J Urol 1999;162:398–402.

[35] Ng CK, Moussa M, Downey DB, Chin JL. Salvage cryoablation of the prostate : followup and analysis of predictive factors for outcome. J Urol 2007;178:1253–7. https://doi.org/10.1016/j.juro.2007.05.137.

[36] Lukka H, Waldron T, Chin J, et al. High-intensity focused ultrasound for prostate cancer: a systematic review. Clin Oncol 2011;23:117–27. https://doi.org/10.1016/j.clon.2010.09.002.

[37] Babalola O, Lee T-H(J), Viviano CJ. Prostate ablation using high intensity focused ultrasound: a literature review of the potential role for patient preference information. J Urol 2018;200:512–9. https://doi.org/10.1016/j.juro.2018.04.066.

[38] Crouzet S, Blana A, Murat FJ, et al. Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: multi-institutional analysis of 418 patients. BJU Int 2017;119:896–904. https://doi.org/10.1111/bju.13766.

[39] Gelet A, Chapelon JY, Poissonnier L, et al. Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasonography. Urology 2004;63:625–9. https://doi.org/10.1016/j.urology.2004.01.002.

[40] Kanthabalan A, Peters M, Vulpen M Van, et al. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU Int 2017;120:246–56. https://doi.org/10.1111/bju.13831.

[41] Ahmed HU, Cathcart P, Chalasani V, et al. Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. Cancer 2012;118:3071–8. https://doi.org/10.1002/cncr.26631.

[42] Crouzet S, Murat F, Pommier P, et al. Locally recurrent prostate cancer after initial radiation therapy : early salvage high-intensity focused ultrasound improves oncologic outcomes. Radiother Oncol 2012;105:198–202. https://doi.org/10.1016/j.radonc.2012.09.014.

[43] Fuller DB, Naitoh J, Lee C, Hardy S, Jin H. Virtual HDR cyberknife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. Int J Radiat Oncol Biol Phys 2008;70:1588–97. https://doi.org/10.1016/j.ijrobp.2007.11.067.

[44] Fuller DB, Wurzer J, Shirazi R, Bridge SS, Law J, Mardirossian G. High-dose-rate stereotactic body radiation therapy for postradiation therapy locally recurrent prostatic carcinoma : preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. Pract Radiat Oncol 2015;5:e615–23. https://doi.org/10.1016/j.prro.2015.04.009.

[45] Leroy T, Lacornerie T, Bogart E, Nickers P, Lartigau E, Pasquier D. Salvage robotic SBRT for local prostate cancer recurrence after radiotherapy : preliminary results of the Oscar Lambret Center. Radiat Oncol 2017;12:1–7. https://doi.org/10.1186/s13014-017-0833-9.

[46] Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter Phase II trial. J Clin Oncol 2017;36:446–54. https://doi.org/10.1200/JCO.2017.75.4853.

[47] Ingrosso G, Trippa F, Maranzano E, et al. Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: a two-institution experience. World J Urol 2017;35:45–9. https://doi.org/10.1007/s00345-016-1860-0.

[48] Porres D, Pfister D, Thissen A, et al. The role of salvage extended lymph node dissection in patients with rising PSA and PET/CT scan detected nodal recurrence of prostate cancer. Prostate Cancer Prostatic Dis 2017;20:85–92. https://doi.org/10.1038/pcan.2016.54.

[49] Karnes RJ, Murphy CR, Bergstralh EJ, et al. Salvage lymph node dissection for prostate cancer nodal recurrence detected by 11C-Choline positron emission tomography/computerized tomography. J Urol 2015;193:111–6. https://doi.org/10.1016/j.juro.2014.08.082.

[50] Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300. https://doi.org/10.1056/NEJM199707313370502.

[51] Lu-Yao GL, Albertsen PC, Moore DF, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. JAMA 2008;300:173–81. https://doi.org/10.1001/jama.300.2.173.

[52] Keating NL, Malley AJO, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56. https://doi.org/10.1200/JCO.2006.06.2497.

[53] Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol 2016;17:727–37. https://doi.org/10.1016/S1470-2045(16)00107-8.

[54] Crook JM, O'callaghan Crostopher J, Duncan G, et al. Intermittent androgen suppresion for rising PSA level after radiotherapy. N Engl J Med 2012;367:895–903. https://doi.org/10.1056/NEJMoa1201546.

[55] Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314–25. https://doi.org/10.1056/NEJMoa1212299.

[56] James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163–77. https://doi.org/10.1016/S0140-6736(15)01037-5.

[57] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51. https://doi.org/10.1056/NEJMoa1702900.

[58] Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46. https://doi.org/10.1056/NEJMoa1503747.

[59] McKay RR, Gray KP, Hayes JH, et al. Docetaxel, bevacizumab, and androgen deprivation therapy for biochemical disease recurrence after definitive local therapy for prostate cancer. Cancer 2015;121:2603–11. https://doi.org/10.1002/cncr.29398.

[60] Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591–7. https://doi.org/10.1001/jama.281.17.1591.