Management of Prostate Cancer Recurrences After Radiation Therapy-Brachytherapy as a Salvage Option

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Depending on initial prognostic factors, an estimated 10%–60% of men who undergo definitive radiation therapy for prostate cancer may experience a biochemical recurrence. Even though hormonal therapy is standard for metastatic recurrences, no consensus exists on optimal salvage therapy for those recurrences thought confined to the prostate. Salvage treatment options for these local recurrences have historically been limited to salvage prostatectomy, hormonal therapy, or cryotherapy. Salvage prostate brachytherapy, however, uses a widely available technique and may provide another option for attaining disease control in patients with localized failures, although only about 110 cases have been reported in the literature. In this report, the authors have described their own series of salvage brachytherapy cases as well as presented a review of other such series reported in the literature. In addition, the authors included a comprehensive review of published experiences with surgery and cryotherapy as salvage options. It appears that salvage brachytherapy, when combined with careful patient selection, is at least as effective as other salvage options with comparable or potentially fewer treatment-related side effects. ***Cancer*** **2007;110:1405–16.**

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Prostate cancer is diagnosed in an estimated 230,000 patients annually in the United States, with a rising incidence attributable to early detection programs. Patients undergoing early intervention for prostate cancer are likely to have a better disease-specific prognosis, but a portion of these patients will develop either local failure or metastatic disease. Definitive treatment options for organ-confined prostate cancer include radical prostatectomy and radiation therapy using either external beam radiation therapy (EBRT) or a brachytherapy approach. An estimated 10% of low-risk and up to 60% of high-risk prostate cancer patients, however, will experience a biochemical recurrence after definitive EBRT with a subgroup of these being organ-confined recurrences.[1–4]

Patients who have a rising prostate-specific antigen (PSA) after EBRT are classified as having a biochemical recurrence. Patients experiencing a biochemical recurrence may have either a local (confined to the prostate) recurrence, metastatic disease, or both. Patients thought to have a local-only recurrence after EBRT have historically been offered radical prostatectomy, cryotherapy, androgen ablation therapy, or observation, although no randomized data governing treatment selection have been reported. Furthermore, these therapies involving active intervention are not without significant side effects—complications that can be more pronounced

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TABLE 1
Postradiotherapy Brachytherapy Salvage Series

Year reported	Modality	Institution	Reference	Patients	Median follow-up, mo	DFS
1992	Prostatectomy	UCLA	Stein, et al.[10]	13	65.4	NA
1992	Prostatectomy + AD	City of Hope	Ahlering, et al.[16]	34	53	71% @ 4 y
1998	Prostatectomy	Mayo	Cheng, et al.[18]	86	69.6	CSS 64% @ 10 y
1998	Prostatectomy	Wayne State Univ	Gheiler, et al.[15]	40	36.1	47% @ 3 yrs
1998	Prostatectomy + AA*	Florida	Garzotto, et al.[20]	29	63.6	44–80% @ 5 y
1998	Prostatectomy	USC	Bochner, et al.[11]	18	N/A	NA
2000	Prostatectomy + AD†	Miami	Vaidya, et al.[14]	6	27	83% @ 2 y
2003	Prostatectomy	Paris	Vallancien, et al.[21]	7	11.2	71% @ 1 y
2005	Prostatectomy	MSKCC	Bianco, et al.[22]	100	60	55% @ 5 y
				333		
2000	Cryotherapy	Allegheny Genl Hosp	Benoit et al.[27]	87	60	58% @ 5 y
2001	Cryotherapy + AD‡	Columbia	Ghafar, et al.[31]	38	24	74% @ 2 y
2001	Cryotherapy	Ontario	Chin, et al.[28]	118	18.6	34–68% @ 3 y
2002	Cryotherapy	MDACC	Izawa, et al.[35]	131	57.6	23–57% @ 5 y
2003	Cryotherapy	Ventura	Bahn, et al.[33]	59	84	50–62% @ 7 y
2005	Cryotherapy	Calgary	Donnelly, et al.[34]	46	N/A	51% @ 1 y
				479		
1980	Brachytherapy	Stanford	Goffinet, et al.[36]	14	N/A	57% @ <3 y
1990	Brachytherapy	MSKCC	Wallner, et al.[37]	13	N/A	51% @ 5 y
1993	Brachytherapy	Iowa	Loening, et al.[38]	31	N/A	40% @ <5 y
1999	Brachytherapy	Mayo Scottsdale	Grado, et al.[41]	49	64.1	34% @ 5 y
2003	Brachytherapy	Milan	Losa, et al.[42]	10	20.6	~70% @ 2 y
2004	Brachytherapy	Arizona Oncology	Beyer[40]	30	46	~25% (high risk), ~67% (low risk) @ 3 y
2005	Brachytherapy	Brigham and Women's	Suh, et al.[44]	20	27.6	88% @ 3 y
2005	Brachytherapy	Mount Sinai	Lo, et al.[43]	30	59.3	48% @ 8 y
2005	Brachytherapy + AD‡	Mayo Scottsdale	Wong, et al.[45]	17	30	79% @ 4 y
2006	Brachytherapy + AD‡	Wisconsin	Allen, et al.	12	45	67% @ 4 y
				226		

DFS indicates disease-free survival; NA, not available; AD, androgen deprivation; AA, androgen ablation.

* 24 patients underwent 3 months neoadjuvant androgen ablation or orchiectomy.

† Five patients underwent neoadjuvant androgen ablation for a mean of 6.3 months.

‡ All patients underwent 3 months neoadjuvant androgen ablation.

because of the prior radiation treatment. Salvage brachytherapy may be an appropriate alternative for carefully selected patients because it is less invasive than prostatectomy while still delivering potentially curative therapy, in contrast to androgen ablation or observation. Although several retrospective series describing salvage brachytherapy have been reported in the literature, only about 110 patients in the post-PSA era are represented. In this report, various post-EBRT salvage modalities are reviewed, a salvage brachytherapy cohort from our institution is reported, and a treatment algorithm is outlined.

Review of Salvage Treatment Modalities

Salvage prostatectomy, cryotherapy, and brachytherapy are difficult to compare directly because of heterogeneity in patient characteristics, treatment, and follow-up, but several clinical series representing each modality have been reported and are summarized in Table 1. For ease of comparison, only those studies reporting median follow-up and disease-free survival are included in Table 1.

Salvage prostatectomy

The earliest reports of salvage therapy after EBRT focused primarily on feasibility and surgical morbidity related to the procedure. Salvage surgery was first reported by Mador and colleagues in 1985.[5] In this 7-patient series demonstrating the feasibility of surgical salvage, 4 patients underwent radical prostatectomy, and 3 underwent cystoprostatectomy with urinary diversion (CP). Six of 7 patients were alive at 3 months to 22 months postoperatively, and 1 of these patients developed metastatic disease during this period. Significant surgical morbidity including rectal lacerations and urinary incontinence were described, highlighting the technical challenge of surgical salvation after EBRT. Another small series (n = 5) re-

ported from the Brooke Army Medical Center resulted in complications limited to mild residual stress incontinence and with preservation of sexual function.[6] The Mayo Clinic reported complications of salvage radical prostatectomy at a median of 6.7 years.[7] No perioperative deaths were observed, bladder neck contracture was seen in 17%, lymphedema in 10%, and incontinence in 10%. A series from the Baylor College of Medicine (n = 16) confirmed the feasibility of post-EBRT radical prostatectomy. The surgical margin positivity rate in this study was 37.5%. Surgical sequelae included 3 patients with a major rectal injury, 1 with a urethral transection, and 4 patients with persistent urinary incontinence.

A series from Stanford University (n = 14) quantified the technical challenges of post-EBRT prostatectomy, reporting significant anterior and lateral fibrosis at the time of surgery in 71% of cases and loss of tissue planes between the prostate and rectum in 36%.[8] At a median follow-up of 18 months, 6 patients had no detectable PSA, 4 patients had a detectable PSA but no clinically evident disease, and 4 patients had documented metastases. Complications included impotence and incontinence in 100% and 55% of patients, respectively. The authors concluded that radical prostatectomy after EBRT did not carry greater perioperative complication rates compared with definitive radical prostatectomy but was associated with a significant long-term risk of impotence and incontinence. A series from Duke University of 22 patients with recurrent post-EBRT prostate cancer highlighted differences between salvage radical prostatectomy and CP.[9] Eleven of 12 patients undergoing salvage CP or radical prostatectomy for localized disease were alive at a median follow-up of 49 months, and 4 patients had an undetectable PSA. Nine of 10 patients undergoing either CP or exenteration for more extensive disease were alive at the time of last follow-up. Only 1 of these patients had an undetectable PSA after the procedure. Whereas only 2 of 12 patients who underwent CP were able to retain urinary continence with a Kock pouch, all radical prostatectomy patients were continent. For patients requiring CP because of locally advanced disease, operative morbidity was significant with a 50% major complication rate. A feasibility study from UCLA of 13 patients who underwent either radical prostatectomy or CP (for involvement of bladder neck) reported 10 patients alive without disease, but 7 patients in this cohort were followed for <12 months. One of the 3 patients who experienced disease progression ultimately died of metastatic disease. In the UCLA series, 1 patient experienced minor rectal injury as a result of surgery, and total incontinence was observed in 2 patients.[10] A USC series described 18 patients who underwent salvage CP with 56% of patients able to retain continence after creation of an orthotopic neobladder.[11] A retrospective study of toxicities resulting from salvage radical prostatectomy performed at Memorial Sloan-Kettering Cancer Center (MSKCC) (n = 100) reported an incontinence rate of 33% in patients operated on before 1993, with an improvement to 13% for patients operated on after this period.[12] Similarly, rectal injury rates were initially 15% but improved to 2% after 1993. Of note, the overall rate of potency in the series was 28%, with 45% of those having potency before surgery retaining it afterward.

A Wayne State University series (n = 43) that used either radical prostatectomy or CP reported 10 patients without evidence of disease at a follow-up ranging from 1–10 years. Four patients experienced a significant rectal injury, 1 sustained a urethral injury, and 1 perioperative death was reported.[13] Thirty percent of patients had long-standing urinary incontinence and, significantly, 70% of patients had positive surgical margins. A series from the University of Miami (n = 6) reported a single biochemical failure after salvage radical prostatectomy at a median follow-up of 27 months.[14] Toxicities associated with surgery included 100% impotence, no rectal toxicities, and urinary incontinence in 17%. A second series from Wayne State University (n = 40) with a median follow-up of 36.1 months and a definition of biochemical control as PSA of 0.4 ng/mL or less reported a local control rate of 87.5% after radical prostatectomy, with no evidence of biochemical progression in 47.4%.[15] On multivariate analysis, preradiation clinical stage and organ-confined disease were predictors of disease-free survival. All patients found to have pathologically organ-confined disease were without evidence of biochemical recurrence.

A report from the City of Hope characterized the outcomes of 34 patients who received both androgen deprivation and salvage radical prostatectomy or CP.[16] At a median follow-up of 53 months, only 6% had a detectable PSA, and 9% had radiographic evidence of recurrent disease. Importantly, 21% had died from metastatic disease that was, in retrospect, probably present at the time of surgery. Thirty-six percent of patients retained complete continence, whereas all patients who underwent CP were incontinent. A series from Baylor College of Medicine described salvage radical prostatectomy in 40 patients.[17] At a mean follow-up of 39 months, 2 patients had died of metastatic prostate cancer, 5 had asymptomatic distant metastases, and the 5-year actuarial biochemical control rate was 55%. Rectal injuries were

seen in 15% of patients, serious technical complications were described in 31%, and urinary incontinence persisted in 58% of cases. A Mayo Clinic series of salvage radical prostatectomy (n = 86) with a median follow-up of 5.8 years demonstrated 5-year and 10-year actuarial distant metastasis-free survival of 83% and 69%, respectively.[18] Actuarial cancer-specific survival at 5-years and at 10-years was 91% and 64%, respectively. On multivariate analysis, significant prognostic factors for these 2 endpoints included preoperative PSA and DNA ploidy.[19] A series from the University of Florida examined androgen deprivation combined with radical prostatectomy or CP in 29 patients.[20] At a median follow-up of 5.3 years, cancer-specific survival was 95% or 44%, depending on whether the patient had negative or positive surgical margins, respectively. If patients underwent androgen deprivation only, cancer-specific survival was 20%, whereas the combination of androgen deprivation + surgery yielded a cancer-specific survival rate of 92%. The authors concluded that patients who fail a course of neoadjuvant androgen deprivation as defined by a palpable recurrence on digital rectal examination or a PSA above 4.0 ng/mL are poor candidates for surgical salvage, because surgical margin positivity in these patients is high. In a French series from the Marie Curie Institute of 7 patients who underwent laparoscopic salvage prostatectomy, 5 had an undetectable PSA at a median follow-up of 11.2 months.[21] Incontinence was observed in 29% of patients, and impotence was identified in 100% of cases. In a large series from MSKCC (n = 100) where biochemical progression after radical prostatectomy was defined as PSA of 0.2 ng/mL or higher, the actuarial 5-year biochemical control rate was 55%, and the median progression-free interval was 6.4 years.[22] Significant prognostic factors in this cohort included preoperative serum PSA and involvement of the seminal vesicles or lymph nodes at the time of surgery.

In summary, an average biochemical control rate from 9 published studies (Table 1) of about 50% at 4 to 5 years has been reported with surgical salvage, albeit with significant rates of urinary and gastrointestinal complications possibly augmented by prior EBRT.

Salvage cryotherapy

A prospective phase 2 trial from the University of Chicago (n = 23) was the first report of salvage cryosurgery after EBRT treatment failure.[23] Biochemical control was defined as a PSA value <0.3 ng/mL. After cryosurgical ablation for biopsy-proven recurrent prostate cancer, biopsies performed 3 months after treatment showed no evidence of cancer in 86% of specimens, and PSA values declined in 82%. At 1 year, however, biochemical control was achieved in only 14% of patients. The primary complication was sloughed urethral tissue requiring a transurethral resection in 55% of patients. The authors concluded that salvage cryosurgery offered a low probability of biochemical control with a high complication rate. A phase 1/2 trial performed at M. D. Anderson Cancer Center (MDACC) (n = 150) examined single versus double freeze/thaw cycles.[24] Biochemical control was defined as a PSA that remained within 0.2 ng/mL above the post-treatment nadir. At median follow-up of 13.5 months, 31% of patients had an undetectable PSA. Biochemical control was achieved in 35%, and 56% of patients treated with single versus double freeze/thaw cycles, respectively ($P < .03$). Biopsies obtained at 6 months were negative in 71% and 93% within the same patient groups, respectively ($P < .02$). Treatment complications included urinary incontinence (73%), urinary obstruction (67%), impotence (72%), perineal pain (8%), and fistula (1%). A follow-up report concluded that pretreatment Gleason score and PSA were significant prognostic factors, with 2-year biochemical control rates uniformly higher for a PSA of ≤ 10 and a Gleason score of ≤ 8.[25] Within the same patient cohort, reported urinary incontinence and obstruction rates were higher when a urethral warmer was not used.[26]

Results reported from Allegheny General Hospital in Pittsburgh (n = 87), where 2 freeze/thaw cycles were used, demonstrated biochemical control in 58.3% (PSA <0.4) at 60 months of follow-up.[27] A cryotherapy salvage series reported from Ontario, Canada (n = 118) defined biochemical control as PSA of ≤ 0.5 ng/mL.[28] At a median follow-up of 19 months, biochemical control defined as PSA <2 ng/mL was achieved in 55% of patients, and persistent disease as identified by post-treatment biopsy was found in 6% of patients. If more stringent criteria for failure defined as PSA <0.5 ng/mL were to be used, then only 34% of patients would be defined as biochemically controlled. Poor prognostic factors identified by multivariate analysis included PSA >10, Gleason score ≥ 8, and a classification of T3 or T4 disease. Complications included rectourethral fistula (3.3%), severe incontinence (6.7%), bladder outlet obstruction (8.5%), urethral sloughing (5.1%), and bladder neck contracture (1.6%). A histopathologic analysis was published 2 years later when more biopsies became available.[29] Of 818 biopsy cores analyzed, 23 (2.8%) contained evidence of malignancy for a total of 15 (14.2%) patients with biopsy-proven recurrent disease. A series from Columbia University

(n = 43) that combined 3 months of neoadjuvant androgen deprivation followed by salvage cryosurgery defined biochemical control as PSA <0.1 ng/mL.[30] At a median follow-up of 21.9 months, the actuarial biochemical control rate was 79% and 66% at 6 and 12 months, respectively. Multivariate analysis identified PSA nadir >0.1 as a poor prognostic factor. Complications included incontinence (9%), obstruction (5%), urethral stricture (5%), rectal pain (26%), urinary infection (9%), scrotal edema (12%), and hematuria (5%). A later study that used an updated cryosurgery unit achieved actuarial biochemical control in 86% of patients at 1 year and in 74% at 2 years.[31] Complications were similar to the prior report, including rectal pain (39.5%), urinary tract infection (2.6%), incontinence (7.9%), hematuria (7.9%), and scrotal edema (10.5%). A UCLA series (n = 106) was reported with biochemical control defined as an inability to reach a PSA of ≤0.4 ng/mL.[32] At 12 months of follow-up, 77% of patients achieved biochemical control. Complications included tissue sloughing (5%), incontinence requiring pads (3%), incontinence not requiring pads (5%), transient urinary retention (3.3%), and rectal discomfort (2.6%).

A series reported from the Prostate Institute of America (Ventura, Calif; n = 59) used a PSA cutoff value of ≤0.5 ng/mL for biochemical control.[33] The 7-year actuarial biochemical control rates, stratified by PSA, were 61%, 62%, and 50% for PSA <4, 4–10, and >10, respectively. Results reported from the University of Calgary (n = 46) used a PSA of ≤0.3 ng/mL to define biochemical control.[34] Actuarial biochemical control at 1 and 2 years was 51% and 44%, respectively. With a PSA cutoff of 1.0 ng/mL, the 1-year and 2-year control rates were 72% and 58%, respectively. When a less stringent PSA cutoff of 2.0 ng/mL above the post-treatment nadir was used in a MDACC series (n = 131), 5-year actuarial biochemical control was 57% for patients with a PSA of ≤10 and 23% for patients with a PSA >10[35]. When stratified by tumor stage, 5-year actuarial biochemical control was 90% and 69% for T1-2 and T3-4 disease, respectively.

Although it demonstrates significant inter-reporter variability likely influenced by patient selection, various definitions of biochemical control, and evolving technology and experience, 5-year biochemical control after cryotherapy salvage also appears to be on the order of 50%, similar to outcomes seen after salvage radical prostatectomy (Table 1). As with surgical salvage, however, this procedure entails significant treatment-related risks, although some risks have been reduced with the evolution of improved technology.

Salvage brachytherapy

The earliest report of prostate brachytherapy used in the post-EBRT salvage setting derives from Stanford University, where 14 patients were treated with I-125 brachytherapy via a retropubic approach between 1975 and 1979.[36] Clinical local control was achieved in 79% of patients over a follow-up period of 6 months to 36 months, and 57% were clinically disease-free. Four of 14 patients experienced significant urinary toxicities including cystoproctitis, urinary incontinence, and vesicorectal fistula. Because this study was performed in the pre-PSA era, outcomes are difficult to compare with modern treatment. A series of 13 patients from MSKCC, where salvage I-125 brachytherapy was used for patients originally treated with definitive prostate brachytherapy, was also performed in the pre-PSA era.[37] Clinical failure was defined as palpable recurrence confirmed by biopsy. Actuarial local control at 5 years was 51%, but the actuarial distant metastatic rate at 6 years was 100%. As such, these patients likely had metastatic disease at presentation, further illustrating the importance of careful patient selection to rule out patients with high risk of extraprostatic disease, a selection process more readily accomplished in the PSA era. Toxicities from this series included 4 cases of mild to moderate urinary incontinence and 2 severe rectal complications. The first study describing ultrasound-guided transperineal seed placement was performed at the University of Iowa (n = 31) and evaluated disease response by measuring prostate volume and performing biopsies.[38] On average, the prostate volume decreased from 17.7 mL to 10 mL within 24 months of seed implantation, although 9 of 15 (60%) patients who underwent biopsy at 1 year had evidence of persistent disease. Patients treated in the PSA era uniformly experienced a decline in PSA up to 6 months after salvage therapy, with no subsequent further decline.

Multiple studies have been reported in the post-PSA era, although the published reports comprise fewer than 100 patients. A series initially consisting of 17 patients and later expanded to 30 where either I-125 or Pd-103 was used after EBRT failures was reported from Arizona Oncology Associates.[4,39,40] Failure was defined according to the 1997 American Society for Therapeutic Radiology and Oncology (ASTRO) consensus statement, which requires 3 consecutive PSA increases. At a median follow-up of 62 months, actuarial biochemical control at 5 years was 53%, and 5-year overall survival was 93%. Prostate cancer-specific survival at 10 years was 60%, and no prostate cancer-specific deaths were observed in patients with Gleason scores <7 at recurrence. Acute complications were qualitatively described, including

urinary frequency, urgency, and dysuria. The major long-term complication was a 24% risk of urinary incontinence at 5 years. Importantly, potential prognostic factors emerged from this series, although none reached statistical significance. For patients with a PSA >10 ng/mL at the time of recurrence, biochemical control at 5 years was 25% compared with 63% for those with a PSA of ≤10. Furthermore, only 30% of patients with high-grade tumors achieved biochemical control by 5 years compared with 83% of patients with low-grade or intermediate-grade tumors. Several important factors governing patient selection emerged from this study, including histologically confirmed local recurrence, no clinical or radiographic evidence of distant disease, international prostate gland urinary symptom scores (IPSS) <20, >5–10 year life expectancy, >2 year disease-free interval after primary EBRT, Gleason score ≤6, PSA less than 10 ng/mL, and PSA doubling time >6 months to 9 months before salvage therapy.

A 49-patient series from the Mayo Clinic Scottsdale is the largest clinical experience in the post-PSA era reported to date.[41] Biochemical failure in this study was defined as 2 serial rises in the serum PSA, a more stringent definition of recurrence than the 1997 ASTRO consensus definition. At a median follow-up of 64 months, the 3-year and 5-year biochemical control rates were 48% and 34%, respectively. Significantly, 13 patients included in this series had already failed at least 1 prior salvage therapy. On multivariate analysis, a post-treatment PSA nadir of ≤0.5 ng/mL was found to be a significant prognostic factor for subsequent biochemical control. Acute complications included urinary frequency, urgency, hesitancy, and nocturia, although these were not quantified. Chronic complications included gross hematuria (4%), dysuria (6%), rectal ulcers (4%), hematochezia requiring surgical intervention (2%), and urinary incontinence requiring a transurethral resection of the prostate (6%).

A series reported from Italy (n = 18) that examined postprostatectomy and post-EBRT salvage brachytherapy clarified the urinary toxicities associated with this therapy.[42] In all patients, the IPSS scores normalized by 3 months after the procedure, with only 1 patient experiencing a worsening of urinary incontinence, which subsequently improved to pretreatment baseline. The median IPSS score was highest at 1 month postimplantation; it was 10.5 relative to the median preprocedure IPSS score of 8.3. At 3 months, the median IPSS score returned to 8.6, indicating that prostate seed implantation in this series did not significantly impact longer term urinary function.

More recently, 3 series have been reported in abstract form describing 67 additional patients treated with post-EBRT salvage brachytherapy.[43–45] The median follow-up for these studies ranged from 27 months to 59 months, and all used the 1997 ASTRO consensus definition of biochemical failure. In the Brigham and Women's Hospital series (n = 20), actuarial 3-year biochemical control was achieved in 88% of patients.[44] 50% of patients required an α-1a blocker for urinary obstructive symptoms, but 80% of patients were free of grade 3 or 4 urinary and gastrointestinal complications at 3 years. To treat rectal bleeding, argon plasma coagulation was required by 15% of patients. In the Mount Sinai Hospital series (n = 30), the 8-year actuarial biochemical control rate was 47.8%, which improved to 61.5% when patients treated after definitive brachytherapy were excluded.[43] Complications included grades 1–2 hematochezia (17%), grade 3 urinary obstruction requiring transurethral resection of the prostate (10%), and 1 patient had a rectourethral fistula that required a colostomy. A recently updated series from Mayo Clinic Scottsdale (n = 17) that used neoadjuvant hormonal therapy followed by salvage brachytherapy demonstrated 2-year and 4-year actuarial biochemical control rates of 88% and 79%, respectively.[45] Grade 3 genitourinary toxicities requiring minor procedures were experienced by 35% of patients, and 1 patient had a grade 4 genitourinary complication requiring creation of an ileal conduit. Grade 2 gastrointestinal complications were seen in 35% of patients, and there were no grade 3 gastrointestinal toxicities. A recent report from the University of California at San Francisco (n = 21) evaluated high-dose-rate salvage brachytherapy.[46] Estimated biochemical control at 2 years was 89%, with 18 patients reported to have had grade 1 or 2 complications and 3 patients who developed grade 3 genitourinary complications.

University of Wisconsin experience

Twelve patients treated in the PSA era have undergone salvage brachytherapy at the University of Wisconsin. Patient characteristics before definitive EBRT are summarized in Table 2. Patients originally presented with a median PSA of 9.6 ng/mL (range, 3.3–26.9), clinical classification T1c-T3a, and median Gleason score of 6 (4–7). The median EBRT dose for the initial treatment was 70 Gy (range, 59.4–70.2), delivered by a 3-dimensional conformal technique in an era before image-guided localization or intensity-modulated radiation therapy were routinely used.

Patient characteristics at the time of biochemical recurrence are summarized in Table 3. Biochemical recurrence was defined according to the initial Amer-

ican Society of Therapeutic Radiology and Oncology (ASTRO) consensus statement definition of 3 serial PSA rises.[47] At the time of recurrence, the median PSA was 3.8 ng/mL (range, 2–11.5), median PSA velocity was 3.6 ng/mL/y (range, 1.4–10.8), median PSA nadir was 0.6 ng/mL (range, 0.1–1.38), and median Gleason score on repeat biopsy was 7 (6–9). The median time from initial therapy to implant was 5.76 years (range, 3.33–9.1 years), and the median brachytherapy dose delivered was 97 Gy (90–113). Before undergoing salvage brachytherapy, all patients received 3 months of hormonal ablation with a luteinizing hormone-releasing hormone (LHRH) antagonist.

TABLE 2
Patient Characteristics at Original Diagnosis

Patient	PSA (ng/mL)	Stage	Gleason score	EBRT Dose, Gy	Year Dx
1	5.2	T3a	2 + 3 = 5	59.4	1992
2	26.9	T2c		70	1994
3	5.7	T2a	2 + 2 = 4	68	1992
4	9.2	T1c		68.4	1996
5	10.6	T1b		70.2	1992
6	12.4	T1c	3 + 4 = 7	68	1995
7	9.5	T1c	3 + 3 = 6	68.4	1995
8	22	T2b	3 + 4 = 7	70	1995
9	9.6	T1c	3 + 4 = 7	70.2	1998
10	9.2	T1c	3 + 3 = 6	70.2	1999
11	11.7	T2a	3 + 3 = 6	70	1997
12	3.3	T2a	3 + 3 = 6	70.2	1994
Median	9.55		6	70	
Range	3.3–26.9		4–7	59.4–70.2	
SD	6.79		1.00	3.04	

PSA indicates prostate-specific antigen; EBRT, external beam radiation therapy; Dx, diagnosis; SD, standard deviation (standard error of the mean).

At a median follow-up of 45 months (range, 11–64 months) postsalvage treatment, the 4-year actuarial biochemical disease-free survival was 63%, and overall survival was 54% (Fig. 1). Four deaths from intercurrent illness were observed, indicating that the prostate cancer-specific survival for the group was 100%. Patient numbers preclude a formal analysis of the prognostic factors for biochemical control with brachytherapy at the time of first recurrence, but it is noted that the only patient with a Gleason score of 9 at first recurrence experienced a biochemical recurrence after brachytherapy. Three patients in the population had a Gleason score of 8 at the time of initial recurrence, 2 of whom continued to be biochemically controlled after salvage brachytherapy at 40 and 65 months of follow-up.

Both prebrachytherapy and postbrachytherapy IPSS scores quantifying urinary function were available for 7 patients and are summarized in Table 4. IPSS is a validated, objective, urinary-symptom scale ranging from 0–35, where higher scores indicate poorer urinary function. Assessed symptoms include urinary frequency, urgency, hesitancy, force of stream, nocturia, and incomplete bladder emptying. In the study population, the median preprocedure IPSS was 10 (0–21). One month after implantation, the median IPSS rose to 25 (4–35) and subsequently declined to 10 (1–22) at last follow-up, with only 1 patient experiencing a prolonged, significant increase in urinary symptoms (Fig. 2). These results indicate that prostate brachytherapy causes transient

TABLE 3
Patient Characteristics at First Recurrence

Patient	PSA (ng/mL)	Velocity, ng/mL/y	PSA nadir	Gleason	Time to implant, y	Source	Dose
1	5	10.8	0.1		6.65	I-125 + EBRT	75 + 27 Gy
2	8.3	1.44	1.2		5.22	I-125	109 Gy
3*	8.83	6.84	0.4	3 + 5 = 8	6.67	I-125	108.75 Gy
4	2.7				3.27	Pd-103	90 Gy
5	11.5		0.7	4 + 4 = 8	7.78	I-125	112.5 Gy
6	5.28	5.76	1.38	3 + 3 = 6	5.26	Pd-103	90 Gy
7*	4.3	1.44	0.7	3 + 4 = 7	5.77	Pd-103	90 Gy
8*	2.6	3.6	0.2	3 + 4 = 7	6.5	Pd-103	97 Gy
9	2.5	6.24	0.93	4 + 4 = 8	4.35	Pd-103	90 Gy
10	2	3	0.6	3 + 4 = 7	3.5	Pd-103	97 Gy
11	3.4	2.76	0.3	3 + 4 = 7	5.75	Pd-103	97 Gy
12*	2		0.1	4 + 5 = 9	9.08	Pd-103	97 Gy
Median	3.85	3.6	0.6	7	5.76		97
Range	2–11.5	1.44–10.8	0.1–1.38	7–9	3.27–9.08		90–112.5
SD	3.10	3.05	0.43	0.88	1.68		8.10

PSA indicates prostate-specific antigen; EBRT, external beam radiation therapy; SD, standard deviation (standard error of the mean).

* These patients (3, 7, 8, and 12) experienced a second recurrence after brachytherapy.

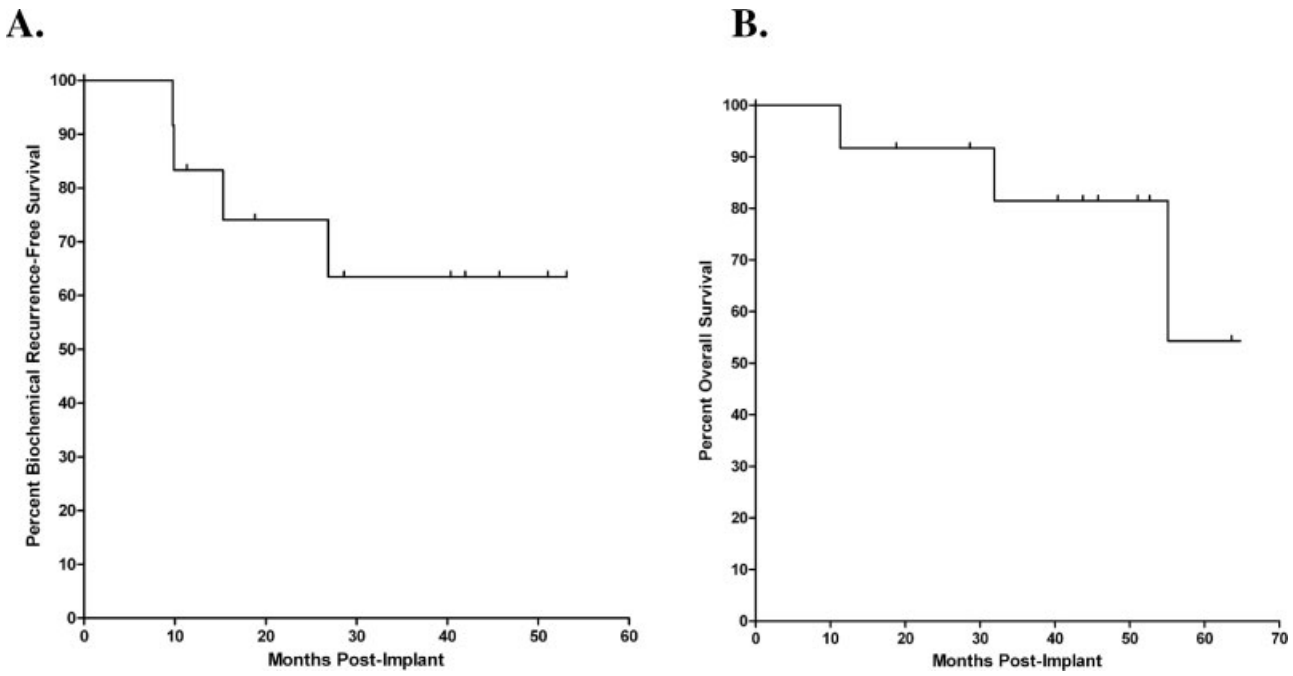

FIGURE 1. Postimplant biochemical recurrence-free survival and overall survival.

TABLE 4
Preimplant and Postimplant Urinary Function

Patient	Preimplant IPSS, max 35	Initial postimplant IPSS	Last IPSS	Follow-up, mo
1			1	45.8
2			NA	43.7
3			10	51.5
4			NA	45.8
5			23	10
6	4	29	9	11.1
7	10	35	13	33.7
8	21	25	20	18
9	0	10	7	19.7
10	7	4	NA	11.3
11	11	27	22	20.4
12	10	21	9	6.7
Median	10	25	10	19.7
Range	0–21	4–35	1–22	6.7–51.5
SD	6.58	10.95	7.50	16.53

IPSS indicates international prostate gland urinary symptom scores; SD, standard deviation (standard error of the mean).

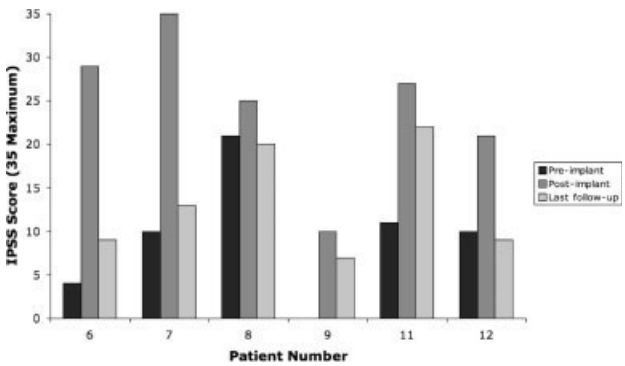

FIGURE 2. Preimplant and postimplant urinary function.

increases in urinary symptoms in the immediate postprocedure period that generally normalize on longer follow-up. Three patients in the population developed grade 2 urinary incontinence, and 2 patients developed grade 1 hematuria that had not resolved at the last follow-up visit. No rectal toxicities were identified above the preprocedure baseline. Toxicity data from this patient cohort and the earlier surgical, cryotherapy, and brachytherapy salvage series is summarized in Table 5.

The results from this series and the few previously reported brachytherapy salvage series from the post-PSA era indicate that in carefully selected patients with likely local-only recurrences, effective salvage therapy can be achieved with a minimum of procedure-related morbidity and favorable long-term side effect profiles. Genitourinary toxicities predominate in the short term after salvage brachytherapy, but these effects may be expected to normalize over time. Of particular note, no significant gastrointestinal toxicities were seen. A treatment algorithm outlining the preprocedure assessment used in the

TABLE 5
Salvage Therapy Complications

Modality	Institution	References	No. pts	% Retention, stricture	% Tissue sloughing	% Incontinence	% Impotence	% Pelvic pain	% Rectal injury
Radical Prostatectomy (Chen 2003)	Wayne State	Mador, et al.[5]	7	0		29			0
	Brooke Army Med Ctr	Thompson, et al.[6]	5	20		20			20
	Baylor	Neerhut, et al.[51]	16	25		25			25
	Stanford	Link and Freiha[8]	14	7		55			7
	Duke	Moul and Paulson[9]	12	NR		0			NR
	City of Hope	Ahlering, et al.[16]	34	0		64			0
	UCLA	Stein, et al.[10]	13	15		18			15
	Wayne State	Pontes, et al.[13]	43	9		29			9
	MSKCC	Brenner, et al.[52]	10	20		20			20
	Baylor	Rogers, et al.[17]	40	28		58			28
	Univ Florida	Garzotto and Wajsman[20]	29	7		67			7
	Wayne State	Gheiler, et al.[15]	40	13		50			13
	Mayo	Amling, et al.[19]	108	21		50			21
	Univ Miami	Vaidya and Soloway[14]	6	0		17			0
Cryotherapy (Touma 2005)	Allegheny Genl Hosp	Miller, et al.[53]	33	7.2	15.4	10.3	NR	NR	
	Univ Chicago	Bales, et al.[23]	23	55	40.9	73	100	77.3	
	MDACC	Pisters, et al.[24,25]	150	44	22	73	72	18	
	Tufts	Long, et al.[54]	18	55	27	83	89	37	
	Columbia	de la Taille, et al.[30]	43	10	5	9	NR	26	
	Ontario	Chin, et al.[28]	118	8.5	5.1	20.3	NR	NR	
	UCLA	Han, et al.[32]	18	3.3	11	11	86	5.6	
Brachytherapy	Wisconsin	Allen, et al.*	12			23	NR		0
	Arizona Oncology	Beyer, et al.[4,39,40]	30			24	NR		0
	Milan	Losa, et al.[42]	10			10	NR		
	Mayo Scottsdale	Grado, et al.[41]	49			6	NR	6	2
	Iowa	Loening, et al.[38]	31	3		NR	NR		
	MSKCC	Wallner, et al.[37]	13			31	NR		15
	Stanford	Goffinet, et al.[31]	14			29	NR		

NR indicates not reported.
* Current study.

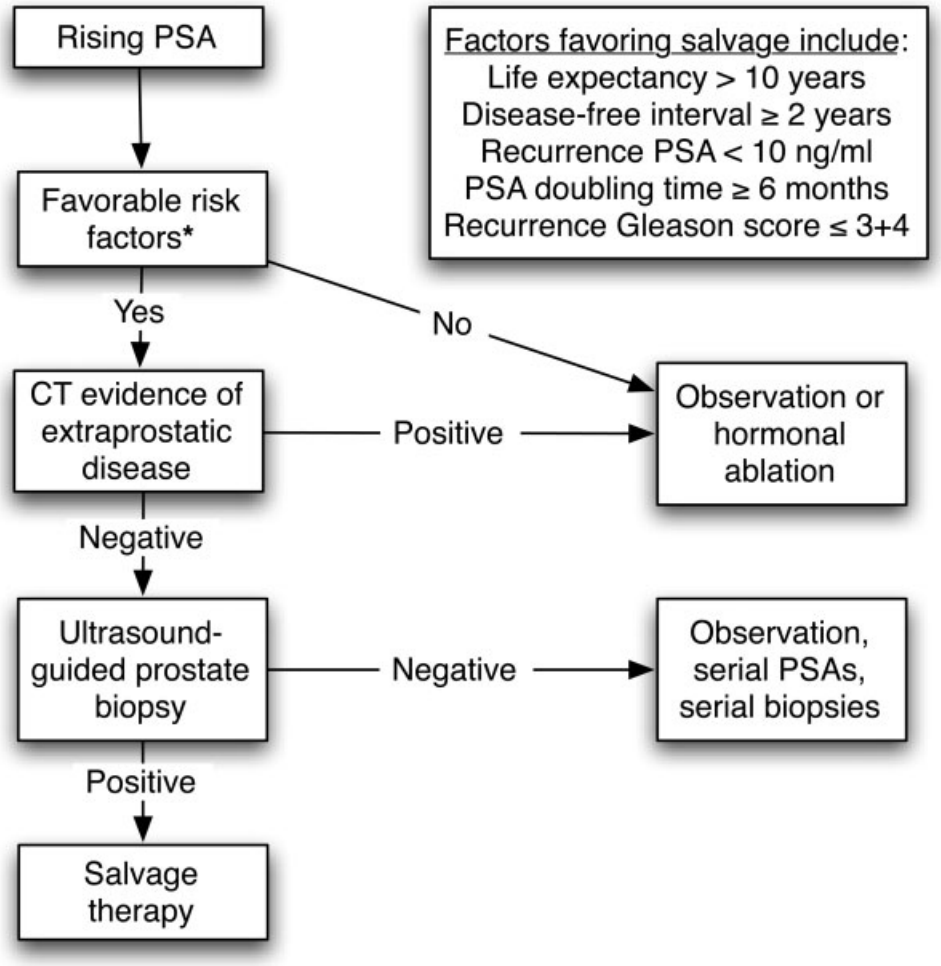

FIGURE 3. Diagnostic and treatment schema. Risk factors and schema are a modification of those described by Beyer.[40]

present study and incorporating risk factors from a previous report[40] is outlined in Figure 3.

Observation and hormonal ablation

Observation or hormonal ablation therapy are also reasonable options for patients with recurrent prostate cancer, especially if the probability of distant disease is great, life expectancy is limited, or the PSA doubling time is long. Patients experiencing PSA failures after definitive EBRT who have a doubling time <3–6 months are at particularly high risk for developing distant metastases and experiencing prostate cancer-specific mortality, so a greater emphasis on androgen deprivation rather than local treatment is warranted.[48–50] Furthermore, patients desiring to avoid the complications associated with aggressive salvage therapy may also reasonably choose to pursue a course of observation or hormonal therapy.

Conclusions

Comparisons of outcomes after modern, primary radiation therapy or radical prostatectomy suggest similar biochemical and local control rates. Although presumed local failures after surgery are readily treated with radiotherapy with low toxicity and an average success rate of about 50%, suitable salvage options for local failure after radiation therapy have never been as clearly apparent or as readily accepted. Although salvage prostatectomy and, more recently, cryotherapy, have attracted some interest as salvage options, salvage brachytherapy has been less often considered. A review of the salvage brachytherapy literature and our retrospective results, however, although difficult to comparatively analyze because of patient heterogeneity, suggest salvage success rates that are likely to be equivalent for these 3 salvage modalities of surgery, cryotherapy, and brachytherapy.

Patient selection for salvage therapy should be tempered by consideration of multiple prognostic factors in addition to patient preference for aggressive intervention. Patients with a short life expectancy from either advanced age or medical comorbidities may not derive significant benefit from salvage therapy, regardless of modality. A more conservative approach of either hormonal ablation therapy or observation may be warranted for this patient population. In addition, patients with poor prognostic features at the time of failure, such as high grade, a short disease-free interval after initial definitive treatment, or a short PSA doubling time, all factors indicating a more aggressive disease process, may be better served by initiation of hormonal therapy or by enrollment in a clinical trial that is testing systemic therapy, as the likelihood of systemic disease is relatively high. For patients with a reasonable life expectancy in the absence of poor prognostic factors, aggressive salvage therapy remains an important option. Any prospective patient must, however, be fully informed of the potential for toxicities and the remaining uncertainties over success rates given the lack of prospective trials. Given the published retrospective series and including our own experience, a treatment algorithm incorporating several clinically relevant factors is presented in Figure 3.

As in the case with definitive therapy for prostate cancer, decisions regarding which salvage modality to use can be heavily influenced by treatment-related side effect profiles. The long-term toxicities of brachytherapy compare favorably with other salvage modalities, although this conclusion is tempered by nonuniform reporting of toxicities that is typical of single-institution retrospective series. In our series of carefully selected patients, salvage brachytherapy was clinically effective, and treatment-related side effects were limited to obstructive and irritative voiding symptoms that generally resolved to pretreatment baseline. In contrast to radical prostatectomy, which by all accounts is more challenging in irradiated patients, or cryotherapy, which requires training and equipment not routinely available in most urologic care settings, salvage brachytherapy uses readily available equipment and a treatment technique familiar to many practitioners. Thus, with its seemingly equivalent effectiveness, technical availability to most practices, and likely lower complication rates, prostate brachytherapy should be considered a viable salvage option in appropriately selected patients with local failure after radiation therapy. Before any salvage procedure is performed, however, prospective patients must be fully informed of the potential risks and the remaining uncertainties regarding efficacy.

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