Brachytherapy for prostate cancer
Follow-up and management of treatment failures

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A number of competing treatment options are available for men with localized prostate cancer. Among these, prostate brachytherapy has been used increasingly for early-stage, low-volume disease. Principal reasons for its growing popularity include its “less-invasive” approach compared with prostatectomy and its convenience compared with external beam radiation therapy (EBRT), with a comparatively short treatment course and convalescent time. Despite these perceptions and the fact that brachytherapy has been used in various forms for decades, the long-term efficacy compared with other forms of therapy is not well established and urinary symptoms following brachytherapy remain a potentially troubling consequence [1–3]. Even with many unanswered questions, the number of American men choosing brachytherapy for treatment of localized prostate cancer continues to rise. Although most men receiving brachytherapy tend to be older and have low-risk disease, prostate brachytherapy also has been offered by some clinicians to younger men with favorable tumor profiles. Given the prolonged natural history of early-stage, low-grade prostate cancer, treatment failures following brachytherapy may take years or even decades before becoming clinically evident. It is therefore likely that as the brachytherapy data mature, clinicians will be asked to help manage a potentially large cohort of men who have failed this local therapy—a scenario that will provide a number of unique challenges for the treatment of the disease and the management of the lower urinary tract.

Permanent implants have been part of the prostate cancer treatment armamentarium since the early 1920s, when radium needles were inserted transurethrally into men with clinically localized prostate cancer [4]. However, the modern era of prostate brachytherapy began with the introduction of the transrectal ultrasound–guided transperineal approach by Holm et al [5–8] in 1983. These techniques have since been refined and improved using computer-assisted pretreatment planning, such that brachytherapy now is considered a viable treatment option in appropriately selected men [9–15]. Currently, two primary isotopes are used for permanent low-dose rate (LDR) prostate brachytherapy. Their physical properties and radiobiologic impact are pertinent in determining the principles of follow-up and...
understanding the implications for treatment failure following failed brachytherapy.

Isotopes

The two most common isotopes used for LDR permanent prostate brachytherapy are iodine 125 (I-125) and palladium 103 (Pd-103). LDR implants deliver dose at less than 1 Gy/h, whereas high-dose rate (HDR) implants deliver dose at greater than 1 to 2 Gy/min. I-125 emits low-energy \( \gamma \) rays at an average 28 KeV and has a half-life of 59.4 days. Pd-103 is similar to I-125 in that it emits low-energy \( \gamma \) rays at an average 21 KeV; however, its half-life is considerably shorter at 17 days [16]. These isotopes are considered “LDR” sources with initial dose rates of 7 cGy/h and 18 to 20 cGy/h, respectively. The standard prescription dose for I-125 and Pd-103 implants are 145 Gy and 115 to 120 Gy, respectively. In contrast, iridium 192 (Ir-192) is a higher-activity isotope (380 KeV; half-life, 74 days), which is used as an LDR or HDR temporary implant depending on the activity of the source. Ir-192 is not implanted permanently in patients because of the high average photon energy, making radiation protection difficult.

A number of important clinical considerations exist when determining which isotope to use. Ling [17] first compared isotope dose rate and cell doubling times for I-125, Pd-103, and Au-198 based on in vitro radiobiologic data. This study suggested that Pd-103 might be more beneficial for tumors with cell doubling times of 10 days [17]. Based on this laboratory data, there has been a tendency to use Pd-103 for patients with higher Gleason scores (≥7) [18]. However, several authors [9,19–22] have demonstrated comparable clinical results for I-125 and Pd-103 LDR permanent implants. Cha et al [23] reported the outcome of patients treated with I-125 or Pd-103 permanent prostate implants and three-dimensional conformal radiation therapy (3DCRT) in a matched-pair analysis for pretreatment prostate-specific antigen (PSA), Gleason score, and T stage at Memorial Sloan-Kettering Cancer Center (MSKCC) treated during the same time period. The authors [23] did not demonstrate any difference between the two isotopes and 3DCRT in biochemical no evidence of disease (bNED) control and concluded that there were no observed advantages for either I-125 and Pd-103 based on Gleason score or pretreatment PSA level.

Results with brachytherapy monotherapy or as a boost following EBRT

With longer follow-up, more data are available that demonstrate the efficacy of bNED control rates for prostate brachytherapy using I-125 and Pd-103 in well-selected individuals [9,22,24]. Ragde et al [22] treated 147 patients with T1–T2 prostate adenocarcinoma using I-125 monotherapy [22]. The overall 10-year bNED control rate was 66%. Multiple other studies [9,20,25,26] have demonstrated that brachytherapy alone is a viable option for treatment of localized prostate cancer in appropriately selected individuals. The most troubling side effects include urethral and bladder symptoms such as irritative voiding (urgency, frequency, and dysuria) and obstructive patterns (hesitancy, decreased force of stream, straining, and urinary retention). Grade 2 acute urinary morbidity occurs in 20% to 40% of patients, many of who may be found to have some degree of baseline urinary dysfunction, whereas more serious grade 3 urinary morbidity occurs in less than 10% of patients [3,27,28]. Although rectal symptoms tend to be more mild following brachytherapy, impotence remains a potential long-term complication [29–33]. As with most forms of local radiation therapy (RT), the risk of these side effects is related to factors that predict urinary morbidity and sexual dysfunction including prostate volume, baseline urinary function measured by a validated toxicity scale, number of seeds or needles, baseline sexual function measured by a validated toxicity scale, and radiation dose to the penile bulb or corporeal bodies.

Significant controversy exists with regard to the appropriate use of LDR monotherapy for the treatment of patients with high-risk or locally advanced disease. The role of androgen suppression and EBRT in combination with prostate brachytherapy also is not fully defined. The rationale behind the use of neoadjuvant and adjuvant androgen suppression is twofold. First, the short-term use of neoadjuvant androgen suppression may reduce local tumor burden in preparation for definitive radiotherapy [34] and may radiosensitize the cells to the effects of radiotherapy [35], although there is significant debate on this latter point. Additionally, the prolonged use of adjuvant androgen suppression may control systemic disease outside of the radiation field, although radiobiologic data supporting this have not been demonstrated in brachytherapy patients.
In the 1980s, the Radiation Therapy Oncology Group (RTOG) developed adjuvant hormone trials, based on information from earlier studies, which incorporated new hormonal agents with less cardiovascular toxicity. RTOG 85-31 examined the role of long-term hormones (LTH) in combination with EBRT. This study randomized 945 analyzable patients with T1–2 N0 M0, T3 N0–1 M0, or pt3 N0–1 M0 disease between EBRT and long-term monthly hormones (H) with goserelin acetate or RT alone with goserelin given at the time of relapse. Lawton et al [36] reported the 8-year update of this trial, and significant differences between the two treatment arms for bNED control (RT + H versus RT alone, \( P < 0.0001 \)), distant failure (RT + H versus RT alone, \( P < 0.0001 \)), and local failure (RT + H versus RT alone, \( P < 0.0001 \)) were observed. Eight-year distant failure rates were 27% and 37% and 8-year local failure rates were 23% and 37%, respectively. A subset analysis revealed significant differences in overall and cancer-specific survival for patients with centrally reviewed Gleason score 8–10 tumors [36]. Bolla et al [37] reported data from the second trial involving LTH and EBRT. The European Organization for the Research and Treatment of Cancer (EORTC) trial included 415 patients randomized between EBRT alone (70 Gy) and EBRT with goserelin starting the first day of treatment and continuing for 3 years posttreatment. The authors reported a statistically significant improvement in overall survival (\( P < 0.001 \)). Five-year overall survival rates were 79% and 67%, respectively, for the two groups (\( P < 0.001 \)) [37].

The RTOG addressed the issue of short-term hormonal ablation in the companion study to 85-31. RTOG 86-10 randomized patients with locally advanced T2b–4 N0–1 M0 prostate cancer between goserelin and flutamide 2 months before and during EBRT versus RT alone. Patients in this study had to have tumors greater than or equal to 25 cm². Pilepich et al [38] reported the 8-year update and, as with the previous RTOG study, a significant difference in local failure continued between the two arms (RT + H versus RT alone, \( P = 0.004 \)). Eight-year local failure rates were 32% and 43%, respectively, between the two groups. An improvement in progression-free survival for the RT + H patients (\( P = 0.0019 \)) and distant failure (RT + H versus RT alone, \( P = 0.04 \)) was observed [38].

The apparent benefit of combined androgen suppression and EBRT has led several investigators to examine whether androgen suppression when combined with prostate brachytherapy confers a disease-free survival benefit. D'Amico et al [39] evaluated 1872 men treated with radical prostatectomy or brachytherapy with or without neoadjuvant androgen deprivation or conformal EBRT; 216 were treated with prostate brachytherapy [39]. Of these, 66 had an implant alone and 152 had an implant with androgen suppression. The androgen suppression was 3 months of neoadjuvant luteinizing hormone-releasing hormone agonist preceded by 7 to 10 days of a nonsteroidal antiandrogen. The patients were stratified according to risk groups and Gleason scores. No differences between the two groups of patients were seen except in those patients with Gleason 7. Stone and Stock [18] evaluated 152 men with moderate-risk disease treated with prostate brachytherapy. Seventy of the one hundred and fifty-two men received 5 months of neoadjuvant and adjuvant hormonal deprivation beginning 3 months before the implant. The 4-year, disease-free survival was improved in the androgen-treated group; however, the follow-up was relatively short. Based on a review of the literature, Lee [40] concluded that little evidence exists to support improved disease-free survival in men treated with a combination of androgen suppression and prostate brachytherapy. He has speculated that the possible reasons for this lack of effect may be related to the fact that most men treated with prostate brachytherapy do not have clinical evidence of extracapsular disease, and therefore represent a different population of men than those evaluated in the combination EBRT and androgen suppression trials. Furthermore, the androgen suppression administered in the prostate brachytherapy trials is substantially shorter than the duration of androgen deprivation in trials showing a benefit.

Brachytherapy has been given in combination with EBRT [21,22,41,42]. This generally has been reserved for patients with higher stage or grade disease. Radje et al [22] evaluated 229 patients who received I-125 permanent prostate brachytherapy, and divided them into two treatment groups. The first group was treated with an implant alone, whereas the second group was treated with combined EBRT of 45 Gy to the prostate and pelvis followed by an implant 2 weeks after the completion of the EBRT. The 82 patients in this group had higher-risk disease based on clinical stage and Gleason grade. bNED control at 10 years was 79% [22].
Grado et al [41] evaluated 490 patients with T1–T3 prostate cancer treated with I-125 and Pd-103 brachytherapy. Seventy-two patients with T2b or greater disease received adjuvant EBRT. The authors [41] found no evidence of incremental benefit with the addition of EBRT. Rates of disease-free survival in the implant alone and the combination groups were not significantly different, even in multivariate models taking into account differences in disease stage. However, the authors [41] did note that a 72% actuarial, 5-year, disease-free survival was achieved in the combined group, despite the more advanced stage of these patients. The American Brachytherapy Society (ABS) currently recommends adjuvant EBRT for those patients who are felt to be at significant risk for extraprostatic extension [43].

Some authors have advocated trimodality therapy including implant, EBRT, and neoadjuvant hormonal deprivation. Stock and Stone [44] treated 301 patients with T1–T3 prostate cancer with brachytherapy alone or combined with hormonal therapy or EBRT. Forty of these patients were deemed high risk based on a PSA level greater than 15 ng/mL, Gleason score greater than or equal to 8, clinical stage T2c–T3, or positive seminal vesicle biopsy. This group was given combination brachytherapy, EBRT, and 9 months of hormonal therapy. The 3-year biochemical freedom from failure rate in this group was 71%. The authors [41] concluded that the favorable 3-year freedom from PSA failure in this group of high-risk patients suggested that trimodal therapy offered a significant improvement over standard monotherapy with radiation or radical prostatectomy alone. These results were supported by data on 72 men with high-risk disease (PSA level ≥ 10 ng/mL or Gleason score ≥ 7 or clinical stage ≥ T2c) who underwent EBRT followed by palladium-103 brachytherapy boosts. All patients in this study underwent 8 months of combined androgen ablation with leuprolide and an oral antiandrogen beginning 3 months before initiation of EBRT. To allow for comparisons to contemporary literature, Kaplan-Meier survival curves were generated using three alternate definitions of biochemical recurrence: PSA level greater than 0.2 ng/mL, PSA level greater than 1.0 ng/mL, and three consecutive rising PSAs. Results indicate that when a PSA level greater than 0.2 ng/mL was used to define biochemical progression, 88% (95% confidence interval [CI] = 80–97) of patients remained disease free at 24 months. When a PSA level greater than 1.0 ng/mL was used, 97% (CI = 92–100) of patients remained disease free at 24 months. The three consecutive rise criteria yielded 90% (CI = 82–98) recurrence-free survival at 24 months.

Follow-up

Postimplant dosimetry

Adequate dose and coverage of the prostate is critical in reducing the incidence of local recurrence and minimizing acute and chronic toxicity. In 1999 and 2000, the ABS [43,45] published guidelines in an effort to standardize the recommended follow-up for patients treated with permanent I-125 or Pd-103 prostate implants. These guidelines covered all aspects of a patient’s care, including postimplant dosimetry analysis as well as timing of follow-up. All patients should undergo postimplant dosimetry to assess implant quality and to create a permanent record of the implant and the actual radiation dose delivered. Postimplant dosimetry should be CT based and the scan should be done 3 to 4 weeks after the surgery to allow for the resolution of postoperative edema. Standard implant quality indicators include D90, defined as the dose that covers 90% of the prostate volume, and V100, which is the fractional volume of the prostate that receives 100% of the prescribed dose. For example, D100 is the dose that covers 100% of the prostate volume and V100 is the fractional volume of the prostate that receives 100% of the prescribed dose. The three values that should be reported are D90, D100, and V100 [46]. Parameters that should be obtained postimplant include examination of the isodose distribution, generation of the dose–volume histogram (DVH), and determination of dose uniformity and dose conformity indices. The isodose distribution plots offer the best assessment of prostate coverage and are generated from multiple CT slices through the prostate and adjacent structures (Fig. 1).

Methods for obtaining postimplant dosimetry include plain films, CT, and MRI. Plain films were the first method used to perform a geometric reconstruction. The problem with this method was that it could not visualize the prostate and adjacent structures [47]. No information about the spatial relationship of the dose distribution to the prostate and surrounding tissues is available with this technique. The advantage of CT-based dosimetry was readily apparent based on the ability to determine seed location in relation to...
prostate and adjacent tissues. A potential limitation of CT-based dosimetry is the difficulty in reliably imaging the border of the prostate due to poor soft tissue contrast [48]. Despite this potential disadvantage, CT-based imaging is the most common technique for postimplant dosimetry. Contiguous axial slices at 3 to 5 mm are obtained, including the prostate and, at minimum, a 2-cm margin superior and inferior to the prostate. It is particularly important to adequately image the urethra and anterior rectal wall. Because it is possible for a single seed to appear on multiple CT slices, a seed-sorting program is used to eliminate any duplication. A single plain film is used to determine the exact number of seeds implanted, because this number is necessary to use the seed-sorting program [49]. MRI was introduced as a method for postimplant dosimetry based on the ability to clearly delineate soft tissue anatomy in several different planes [50,51] (Fig. 2). This may be particularly important in evaluating the borders of the prostate at the apex and base (Fig. 3). Some authors [52,53] have advocated the combination of imaging modalities for postimplant dosimetry.

The timing of postimplant dosimetry remains controversial. Edema develops in the prostate following seed placement, and it is thought that this affects immediate postimplant dosimetry [54–58]. Waterman et al [55] reported a 10% underestimate of calculated prostate coverage when CT was performed immediately following the implant procedure [55]. The optimal time for postimplant dosimetry also may differ by isotope.

Yue et al [59] performed an image-based dose evaluation for I-125 and Pd-103 prostate brachytherapy implants. Based on the model used, they recommended that postimplant dosimetry be performed at 7 weeks postimplant for I-125 and at 3 weeks postimplant for Pd-103 [59]. Because there still remains a lack of consensus with regard to the ideal time for postimplant dosimetry, the ABS recommends that each center perform dosimetric evaluation at a consistent interval [45].

Physical examination, serum PSA, and prostate biopsy

The intervals in which patients are seen in the clinic following brachytherapy are dependent on several factors that pertain to the biology of the tumor, treatment algorithm, and side-effect profile experienced by the patient. Patients are seen initially 2 to 3 weeks after brachytherapy for postimplant dosimetry as described above. The next office visit is at 6 to 8 weeks, at which point an evaluation of the patients voiding function is performed. This consists of the application of a voiding questionnaire to quantify a symptom score, combined with evaluation of the postvoid residual, preferably by ultrasonography. The
latter examination is particularly important because a significant minority of patients develop acute urinary retention [11,60]. Therefore, in patients who are not managed with alpha-receptor antagonists in the pre- and postoperative period, initiation of such agents is advisable in the presence of significant postvoid residual. In addition, patients who develop sexual dysfunction [13–15]—due to androgen deprivation or secondary to the brachytherapy procedure—are offered management options at this time.

Patients with low-risk disease [12] usually are followed every 6 months with a digital rectal examination and PSA. This examination protocol is continued for the first 5 years, after which the frequency is reduced to yearly visits. A similar protocol can be used for patients with high-risk disease, although in many cases such patients have examinations and PSA analysis performed every 3 to 4 months in the first 3 years, followed by a reduction to every 6 months for the next 2 or 3 years, with yearly follow-up thereafter. Recently, nomograms have been developed for patients treated with brachytherapy that can help to guide the intensity of follow-up based on the risk of recurrence [61].

The added benefit of routine prostate biopsies in following brachytherapy in the absence of biochemical failure is unclear. In the setting of EBRT, Crook et al [62] reported prospectively on 226 patients and showed that for those patients with PSA levels near nadir after radiation, there is little value in performing biopsy. Most recently, the American Society for Therapeutic Radiology and Oncology (ASTRO) reported a consensus panel recommendation that routine prostate biopsy should not be performed for evaluation of PSA recurrence after EBRT unless salvage prostatectomy or other salvage procedures were being considered [63]. In addition, if a new nodule is palpated at the follow-up examination, a biopsy should be performed only if the patient is a candidate for potentially curative approaches (discussed below).

Detection of recurrent disease

Assessment of success following treatment with an implant is based on biochemical or PSA (bNED) control as well as clinical control. Defining bNED control following prostatectomy is more straightforward in cases in which the prostate is removed and PSA is undetectable. Assessing bNED control following treatment with either EBRT or implants is more complicated in cases in which the prostate is not removed and the normal tissue makes some PSA, even if the cancer is eradicated. Before 1997, various institutions across the United States and Europe defined bNED control differently, and comparing results was difficult [64]. In an effort to standardize reporting, the ASTRO convened a panel to develop a standardized definition of PSA success or failure. The consensus statement on PSA after radiation therapy (RT) [65] was published in 1997 and quickly adopted within the radiation oncology community, allowing for uniformed reporting of bNED control. This definition defined the point of biochemical failure as the time midway between the posttreatment PSA nadir and the first of the three consecutive rises in PSA level. This definition was to be applicable in clinical practice and in research trials; avoid the issue of the amount of baseline serum PSA that might be produced in the prostate gland following RT; be valid for comparing different methods of radiation delivery; and avoid requiring a specific single value for posttreatment nadir PSA, which can be fraught with statistical peril. However, this definition also has significant drawbacks. First, many of the articles that publish biochemical-free survival in patients treated with brachytherapy have used alternative methods for evaluating treatment failure. Most commonly, absolute PSA cutoffs have been used in the studies [22,66], making future comparisons with studies using the ASTRO criteria difficult. In a recent study from Fox Chase Cancer Center evaluating 1017 men treated with radiotherapy for localized prostate cancer, the ASTRO definition of biochemical failure was noted to artificially improve bNED rates. Several alternative definitions have been proposed [67]. Another study from the University of Virginia, Coblentz et al [10] showed that when a PSA level greater than 0.2 ng/mL was used to define biochemical progression, 88% (95% CI = 80–97) of patients remained free of disease at 24 months compared with 97% (CI = 92–100) and 90% (CI = 82–98) when a PSA level greater than 1.0 ng/mL and ASTRO criteria were used, respectively, demonstrating how different methods of defining bNED can lead to slightly different outcomes.

This definition also is difficult to apply to patients treated with neoadjuvant hormonal manipulation in view of the fact that their PSA nadir is related to the duration of hormonal manipulation.
Although there are recognized limits to the definition—including those described above and the fact that the definition was designed originally for EBRT patients only—the use of this definition has been valuable for reporting and comparing most results [67].

Recently, the phenomena known as the PSA bounce has been recognized as occurring in at least 30% of patients postimplant. Critz et al [66] first reported on this event in 2000 where 273 of 779 men experienced a transient increase in PSA a median 18-months postimplant. The median bounce was 0.4 ng/mL and 92% of bounces occurred within 36 months [66]. The group from the Seattle Prostate Institute [68] made similar observations later that year in 591 patients treated between 1988 and 1993. Thirty-five percent of their patients also experienced a temporary increase of at least 0.2 ng/mL. Seventy-five percent of these patients experienced a PSA rise between 0.3 and 3.4 ng/mL. In this study [68], the mean time to rise was 24.8 months. Both of these studies and unpublished data from Fox Chase Cancer Center (E.M. Horwitz, personal communication, 2003) suggested that there was no clinical significance in the PSA bounce.

Predictors of failure following treatment with an implant include both clinical and dosimetric parameters [61]. Clinical parameters include pretreatment PSA level, Gleason score, and T stage, where the ideal patient for treatment with an implant alone is one with a pretreatment PSA level of less than or equal to 10 ng/mL, Gleason score of less than or equal to 6, and stage T1c/T2a. Multiple authors [9,22] have reported that patients experience increased rates of biochemical failure when intermediate- or high-risk patients are treated with implant alone.

In addition to these known clinical parameters, several predictors of failure are based on the quality of the implant itself. Stock et al [69] demonstrated that bNED control rates varied depending on the $D_{90}$. Sixty-five patients with a $D_{90}$ less than 140 Gy had 68% 4-year bNED control rates compared with 92% 4-year bNED control rates for the 69 patients with a $D_{90}$ greater than or equal to 140 Gy ($P = 0.02$). Two-year posttreatment biopsies were negative in 70% of patients with a $D_{90}$ less than 140 Gy versus 83% for patients with $D_{90}$ greater than or equal to 140 Gy. Dose remained the most significant predictor of bNED control on multivariate analysis [69].

Management of recurrence following brachytherapy

Restaging and risk stratification of the patient with recurrent disease

Despite improvements in clinical staging, patient selection, and implant technique, the management of disease recurrence following brachytherapy remains a clinical challenge. Considerable debate exists over the definition of failure following radiation treatment and the significance of the postbrachytherapy prostate biopsy [70,71]. In practical terms, the diagnosis of recurrence poses a number of difficult clinical issues. Clinicians must rely on clues supporting tumor recurrence—such as pretreatment PSA level, Gleason score, and clinical stage—and the definitions (and limitations) of biochemical failure, and must be aware of the “PSA bounce” phenomenon. [66,68]. Furthermore, they must have a good understanding of the adequacy of the initial implant as it relates to $D_{90}$ and $V_{100}$, because this may influence the probability of treatment failure [9].

Once a patient is determined to have failed primary therapy, the pressing issue then becomes distinguishing local from systemic recurrences. Local failure has been defined as histologically proven active adenocarcinoma on repeat prostate biopsy in the absence of radiographic evidence of disease. Unfortunately, multiple studies have demonstrated the relative lack of sensitivity and specificity of most radiographic tests including CT, MRI, bone scan, and more recently monoclonal antibody–labeled nuclear scans (Prosta-Scint, Cytogen Corp, Princeton, NJ) for the diagnosis of systemic disease in biochemically recurrent prostate cancer [72]. Despite these shortcomings, these modalities should be applied if recurrence is suspected, because the presence of overt metastatic disease may obviate the patient being exposed to unnecessary local therapies. In this setting, pathologic confirmation via prostate biopsy of locally recurrent disease is warranted before consideration of invasive salvage therapies.

The PSA doubling time following external RT also appears to aid in predicting the eventual development of metastatic compared with local disease [73]. In one study [73], faster doubling times were significantly associated with higher T stage, higher Gleason grade, and higher pretreatment PSA levels. Thus, in patients with initially adverse disease, PSA values began to rise
faster after treatment than did patients with less adverse disease. The most striking correlation was between rapid doubling time and the likelihood of metastatic relapse. Patients who developed metastases had a median PSA doubling time of 4.2 months compared with a median doubling time of 11.7 months in patients who developed local recurrence. Overall, patients with a PSA doubling time of less than 8 months had a 7-year actuarial metastatic rate of 54%, whereas patients with a PSA doubling time exceeding 8 months had only a 7% metastatic rate. Particularly ominous was the combination of a doubling time shorter than 8 months, which began to rise within the first year; by 3 years, 50% of these men had metastases and all were actuarially projected to develop such relapse by 6.5 years [73].

In addition, a recent study [74] has shown that the risk of prostate cancer–specific death after EBRT was predicted by PSA doubling time and delayed use of hormonal therapy. Nearly identical estimates of prostate cancer–specific death and all-cause death after PSA failure were noted for patients with a short PSA doubling time (ie, ≤12 months), suggesting that the cause of death for patients with a short PSA doubling time after RT was nearly always prostate cancer. These data also suggest that a short posttreatment PSA doubling time may serve as a possible surrogate for prostate cancer–specific death.

Although similar analyses have not been performed for patients treated with brachytherapy, it is reasonable to expect that similar guidelines also may apply in this setting, because the treatment modality in both cases is radiation. Clearly, prospective validation of these concepts is needed in the brachytherapy population.

Salvage therapies for the patient with locally recurrent disease

Once prostatic recurrence following brachytherapy is confirmed and the risk of systemic disease if considered low (ie, good risk prebrachytherapy tumor features [61], negative restaging imaging, and greater than 12-months PSA doubling time), a number of potentially curative therapeutic options can be considered for patients with a greater than 10-year life expectancy, including salvage prostatectomy, re-irradiation, and salvage cryosurgery. Hormonal deprivation and observation can be reserved for patients with a less than 10-year life expectancy or those who desire less invasive management options. Hormonal management and observation will not be discussed here. The patient must be fully informed and an active participant in the decision process, because complication from local salvage techniques may be substantial. It is important to mention that in the discussion of the salvage modalities outlined below, the information presented is primarily from series reporting the results from patients that have failed EBRT. There currently is a paucity of data on salvage treatment of brachytherapy failures.

Salvage radical prostatectomy following brachytherapy failure

Salvage radical prostatectomy for patients who have failed local RT remains a feasible option, yet one associated with potentially significant complications. Although there are no widely agreed on selection criteria, most surgeons who perform salvage prostate surgery choose patients carefully and fully inform them of the potential associated risks. Candidates for salvage prostatectomy must have a good performance status; the absence of significant medical comorbidities; a life expectancy exceeding 10 years; organ-confined disease by digital rectal examination, TRUS, or endorectal MRI; a low postimplant PSA level (< 10 ng/mL); and favorable preimplant tumor parameters. Additionally, the patient should be relatively free of urinary or bowel symptoms, and, if not, an endoscopic evaluation to rule out radiation cystitis or proctitis should be considered. The patient also must be willing to accept the potential for postprostatectomy incontinence and impotence in the setting of prior radiation and the possibility of rectal injury, which may necessitate fecal diversion (colostomy) to allow the irradiated tissues to heal. It is therefore imperative that the patient be highly motivated and willing to accept the potential risks of salvage surgery in an effort to affect a cure.

Although some authors [75] have recommended an antegrade or combined abdominoperineal approach to salvage prostatectomy, most employ a standard radical retropubic prostatectomy technique with modest modifications. Pelvic lymph node dissection during radical prostatectomy for initial treatment of patients with low-risk disease often is omitted, whereas several large studies have demonstrated a low risk of nodal disease and no additional therapeutic benefit in this population [76]. However, during salvage prostatectomy, a full pelvic lymph node dissection should be performed and frozen sections must be strongly
considered, whereas positive nodes would signify extraprostatic disease. This possibility should be discussed with the patient preoperatively, since further attempts at salvage prostatectomy may be abandoned in the setting of node-positive disease. As with standard prostatectomy, the apical dissection must proceed in a meticulous fashion. Patients who have had brachytherapy may have adherence of the anterior surface of the prostate to the pubis or the posterior surface to the rectum, making dissection more tedious. If this is the case, sharp dissection is most appropriate and blunt dissection is to be avoided. In cases of salvage prostatectomy, nerve preservation is not advocated or feasible. Postoperative management should proceed in much the same manner as after a standard prostatectomy, yet with a more judicious concern with regard to the higher risk of bladder neck contractures following salvage surgery [77].

Despite the willingness of most surgeons to consider postradiation salvage surgery, the collective published experience is relatively small and relates more specifically to failures of EBRT than to brachytherapy. The rate of pathologically organ-confined disease in most series is low and ranges from 5% to 36%, whereas the risks of rectal injuries (15%), bladder neck contractures, and urethral strictures (7%–28%) and severe urinary incontinence (23%–64%) are relatively high. [78] In a contemporary series from Baylor Medical Center reporting on salvage prostatectomy [79], 40 patients with a mean radiation dose of 7194 cGy underwent salvage surgery an average of 58.9 months after radiation treatments. Thirty-one patients (78%) were found to have extracapsular or locally advanced disease, whereas only eight patients (20%) had tumor still confined within the prostate. Preoperative PSA level correlated best with pathologic diagnosis and cancer-specific outcomes [79]. In another recent series reported from the Mayo Clinic [80], 108 patients undergoing salvage prostatectomy over a 20-year period were reviewed; of these, only two had received brachytherapy. The authors [80] reported a relatively favorable 10-year bNED rate of 43% in this highly selected group of individuals. One of the larger experiences to date of patients undergoing salvage surgery following the placement of interstitial radioactive seeds comes from MSKCC, where 10 men with locally recurrent prostate cancer underwent secondary prostatectomy at a median of 77 months following I-125 implantation. After a mean fol-

low-up of 35 months, three men had an undetectable PSA level [81].

Salvage radiotherapy (re-irradiation) following brachytherapy failure

Salvage radiation or re-irradiation is a relatively new concept in clinical radiation oncology. Before the advent of effective means to accurately target the prostate, radiation dose was limited by the adverse effects on the adjacent normal tissues. Following the development of more sophisticated targeting techniques such as 3DCRT and, more recently, intensity-modulated RT (IMRT) with the ability to develop inverse treatment plans, investigators have successfully escalated the planned treatment dose and demonstrated an important relationship between dose and biochemical response in prostate cancer [82,83]. This subsequently has allowed clinicians to dose escalate to a maximum effective target dose above 80 Gy. Lessons from dose escalation studies have given some justification to the concept of re-irradiation. It is important to recognize that the term re-irradiation differs significantly from planned combination radiotherapy. In men undergoing multimodal RT, the derived treatment plan includes interstitial radiation in the form of HDR radiation with Ir-192 or LDR radiotherapy (ie, I-125 or Pd-103) followed by external radiation with 3DCRT or IMRT. Under such a treatment plan, the total dose administered by brachytherapy is modified to permit subsequent or concurrent EBRT. In the case of re-irradiation, a full prescribed course of a single modality (brachytherapy or EBRT) is administered, followed at some distant time in the future by a second modified course that takes into account the prior treatment. Re-irradiation may be administered in combination with radiosensitizing agents such as chemotherapy to decrease the delivered dose, although such approaches currently are experimental.

Although there are no widely agreed on selection criteria for re-irradiation, most radiation oncologists are guided by the same principles as those used to choose candidates for salvage prostatectomy. Specifically, patients must have a good performance status, a reasonable life expectancy, and favorable pretreatment tumor characteristics. As the experience with re-irradiation following brachytherapy grows, two specific indications appear most relevant: men with an inadequate initial implant and men with a long disease-free interval who underwent implant in the relatively distant past. Another issue relevant
when considering re-irradiation, is the tolerance of the normal surrounding tissue to radiation. Normal tissue can tolerate only a certain dose, even after many years. This is known as radiation recall and this phenomenon guides considerations of re-irradiation and planning.

One of the largest series to examine the role of re-irradiation evaluated 49 men with a median pretreatment PSA level of 5.6 ng/mL (range = 1.5–79.1) who failed prior RT and subsequently went on to salvage brachytherapy [84,85]. Among these men, 46 (94%) had undergone prior EBRT with a median primary treatment dose of 66.2 Gy (range = 20–70.2) administered in a median of 35 fractions (range = 5–39) over a median of 50 days (range = 7–74). In this study, only three men had received I-125 radioactive seed implants as primary therapy. The median time elapsed between primary radiotherapy and salvage brachytherapy was 41.7 months (range = 21.8–185.2). All patients underwent prostate biopsy before re-irradiation, confirming poorly differentiated disease in 27 (55%). Thirty-seven patients (76%) were implanted with Pd-103, whereas 12 patients (24%) were implanted with I-125. Although a minority of patients received additional therapies before (11 patients (22%) received an orchiectomy or antiandrogens) or after re-implantation (four patients received adjuvant RT, eight received adjuvant hormones), salvage brachytherapy was associated with a 34% actuarial rate of biochemical disease-free survival at 5 years. Physician-reported complication rates were slightly better than with other forms of salvage therapy and included rectal ulcers or bleeding requiring colostomy in 6%, significant dysuria in 6%, and the need for a channel TURP in 14%. However, equally importantly, these data provide proof of principle that re-irradiation is a technically feasible alternative to radiation failures.

Salvage cryosurgery following brachytherapy failure

Initial enthusiasm for cryoablation of the prostate as a curative treatment for localized prostate cancer waned with multiple reports of poor biochemical control rates and unacceptable complications [86]. However, several groups have continued to improve cryoablative techniques in both the primary and salvage settings [87,88]. Although salvage cryosurgery has been reported to be more technically challenging than primary therapy, multiple authors have noted acceptable response rates, with morbilities roughly equivalent to other modes of salvage therapy [89-91]. Chin et al [90] recently reported their results of salvage cryotherapy in 118 patients with biopsy-proven local recurrence following RT [90]. Nearly all patients underwent posttreatment prostate biopsy, which identified persistent disease in only 3.1%. The posttreatment PSA nadir reached less than 0.5 ng/mL in 114 patients (96.6%) with 34% bNED at last follow-up. Complications included rectourethral fistula in 5 patients (4.2%), moderate to severe incontinence in 24 patients (20.3%), and bladder outlet obstruction in 10 patients (8.5%). Similar results have been published by de la Taille et al [91] who showed a 66% bNED rate at 12 months following salvage cryosurgery [91]. Despite these data demonstrating a therapeutic effect of salvage cryoablation following prostate radiation, to our knowledge there are no known reports specifically evaluating this technique following brachytherapy. Ultimately, the role of salvage cryosurgery following brachytherapy theoretically may be limited by the cumulative effects of each modality on the urethra.

References


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