REVIEW

Salvage therapy for locally recurrent prostate cancer after radiation

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Introduction: *External beam radiotherapy (EBRT) is widely utilized as primary therapy for clinically localized prostate cancer. For patients who develop locally recurrent disease after EBRT, local salvage therapy may be indicated. The primary modalities for local salvage treatment in this setting include radical prostatectomy, cryotherapy, and brachytherapy. To date, there is little data describing outcomes and toxicity associated with each of these salvage modalities.*

Materials and methods: *A review of the literature was performed to identify studies of local salvage therapy for patients who had failed primary EBRT for localized prostate cancer. We focused on prospective trials and multi-institutional retrospective series in order to identify the highest level of evidence describing these therapies.*

Results: *The majority of reports describing the use of local salvage treatment for recurrent prostate cancer after EBRT are single-institution, retrospective reports, although small prospective studies are available for salvage cryotherapy and salvage brachytherapy. Clinical outcomes and toxicity for each modality vary widely across studies, which is likely due to the heterogeneity of patient populations, treatment techniques, and definitions of failure. In general, most studies demonstrate that local salvage therapy after EBRT may provide long-term local control in appropriately selected patients, although toxicity is often significant.*

Conclusions: *As there are no randomized trials comparing salvage treatment modalities for localized prostate cancer recurrence after EBRT, the selection of a local treatment modality should be made on a patient-by-patient basis, with careful consideration of each patient's disease characteristics and tolerance for the risks of treatment. Additional data, ideally from prospective randomized trials, is needed to guide decision making for patients with local recurrence after EBRT failure.*

Key Words: prostatic neoplasms, radiotherapy, prostatectomy, cryotherapy, brachytherapy, salvage therapy

Introduction

Prostate cancer is the most common noncutaneous cancer and the second leading cause of cancer death among men in the United States and Canada. Based on estimates by the American Cancer Society, approximately 240,890 cases of prostate cancer were diagnosed in 2011 with approximately 33,720 prostate cancer deaths.[1] The majority of prostate cancer patients present with low or intermediate risk disease, according to the risk classification scheme proposed by D'Amico et al.[2] According to National Comprehensive Cancer Network (NCCN) guidelines, the primary treatment options for low or intermediate risk disease prostate cancer include active surveillance, radical prostatectomy (RP) with or without pelvic lymph node dissection, brachytherapy, and external beam radiation therapy (EBRT) alone or with brachytherapy boost.[3]

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In patients with low or intermediate risk prostate cancer, reported outcomes associated with the use of primary EBRT are generally excellent. Several studies demonstrate outcomes for EBRT that are equivalent to those reported in the largest surgical studies. A randomized controlled trial by Zietman et al including patients with stage T1b through T2b prostate cancer and PSA < 15 ng/mL reported a 5 year biochemical relapse free survival (BRFS) rate of 91.3% in patients receiving high dose EBRT.[4] Additionally, a randomized controlled trial from M.D. Anderson Cancer Center (MDACC) including 301 patients with stage T1b to T3 prostate cancer demonstrated a BRFS rate of 78% for patients treated with high dose EBRT with a median follow up of 8.7 years.[5,6]

Following primary EBRT, patients are typically monitored for evidence of disease recurrence by serial prostate specific antigen (PSA) testing and digital rectal exams.[3] With the widespread use of PSA monitoring for patients after primary therapy for prostate cancer, disease recurrences are most often detected by a rising PSA, which is referred to as biochemical failure. For patients who are treated with EBRT or brachytherapy, the most widely accepted definitions of biochemical failure are the ASTRO definition (three consecutive rises of PSA after reaching a nadir) and the Phoenix definition (PSA rising to 2 ng/mL above the nadir).[7-10]

A number of factors have been found to predict for biochemical failure in patients undergoing EBRT for primary treatment of prostate cancer. In a study of 1650 patients treated with EBRT at Memorial Sloan Kettering Cancer Center (MSKCC), PSA doubling time (PSADT), clinical T stage, and Gleason score were independently associated with biochemical failure.[11] Several other studies have corroborated these results, particularly with regard to PSADT.[12-14]

Although it is well established that biochemical failure correlates with clinical outcomes, clinical progression after biochemical failure typically occurs over a relatively long period of time. In a study involving 1997 patients with biochemical failure following RP who received no salvage treatment, the median time from biochemical failure to distant metastasis was 8 years, and the median actuarial time to death after the development of metastasis was 5 years.[15] Moreover, in a recently published randomized controlled trial by the Radiation Therapy Oncology Group (RTOG), the 10 year rate of biochemical failure was 26% in patients receiving EBRT with concurrent ADT, with a corresponding 10 year rate of distant metastasis of only 6%.[16] Accordingly, in the majority of patients with biochemically recurrent prostate cancer, there is a substantial window of opportunity after initial recurrence during which disease may be presumed to be locally confined. Local salvage therapy, therefore, is indicated in appropriately selected patients in this setting.

The choice of a salvage modality depends largely on the primary therapy, along with clinical and patient factors that may influence the outcome of salvage treatment. In general, there is a lack of high level evidence supporting the use of local salvage therapies after primary radiation, and the majority of the reports are retrospective single-institution studies. For this reason, there is no established standard of care for local salvage treatment in this setting; nonetheless, several treatment modalities are currently utilized for this purpose. This article will comprehensively review indications, outcomes, quality of life implications, and potential complications of salvage options for biochemically recurrent prostate cancer following EBRT.

Work-up

While a significant percentage of patients with biochemical failure of prostate cancer after EBRT will harbor occult micrometastases, there remains a subset of patients who will present with a truly localized recurrence (i.e. within the prostate only).[17] Prior to consideration of local salvage treatment, a comprehensive work-up focused on excluding the presence of metastatic disease should be performed. The PSA trend should be noted, including calculating the PSADT. A bone scan should be performed to rule out bony metastasis, although this test is considered to be fairly insensitive if the PSA level is less than 20 ng/mL.[18] Magnetic resonance imaging (MRI) with or without endorectal coil has high sensitivity (up to 97%) for identifying disease within the prostate gland, although its specificity is limited.[19] MRI and/or computed tomography may also be used to evaluate the status of pelvic lymph nodes. Finally, prior to any local salvage therapy, prostate biopsy should be performed.[3] While pathologic details such as Gleason score may provide prognostic information, the primary purpose of the prostate biopsy is to confirm the presence of locally recurrent disease.

In addition to the standard imaging modalities listed above, there are several emerging technologies that may play a role in the work up of patients with biochemical recurrence. The use of ^{18}F sodium fluoride in bone scans may be associated with higher sensitivity and specificity compared to technetium-99 for the detection of bone metastases, although further study is needed to directly compare the use of these agents for this purpose.[20] Another modality that is often employed

is ^{111}Indium-capromab-pendetide (ProstaScint) (EUSA Pharma, Langhorne, PA, USA), which may help localize active disease but to date has not been associated with optimal diagnostic performance.[18,19,21-27] Several studies have reported overall low efficacy of ^{111}Indium-capromab-pendetide,[26,28,29] and in practice, the scan is difficult to interpret and cumbersome to perform. Alternatively, another modality that may be used is positron emission tomography (PET). While fluorodeoxyglucose(^{18}F)-PET is not of sufficient diagnostic accuracy for routine clinical use for prostate cancer,[22,26,30-34] other PET radiotracers are being studied for the staging and restaging of prostate cancer. One radiotracer which has shown promise is anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (anti-3-[^{18}F]FACBC), which is a synthetic amino acid analog.[35-37] In a recent study, anti-3-[^{18}F]FACBC demonstrated higher accuracy compared with ^{111}Indium-capromab-pendetide in the restaging of patients with suspected prostate cancer recurrence.[29] Nevertheless, more research is needed before this technology is widely adapted as part of the standard work-up of patients with biochemical recurrence of prostate cancer.

Local salvage treatment options

In patients who qualify for local therapy, local salvage treatment options may include radical prostatectomy, cryosurgery, or brachytherapy.[3] The choice of local therapy should be determined on a patient-by-patient basis, depending on each patient's risk of further progression, the risks and toxicities of each treatment, and the patient's preferences. Furthermore, in patients with short life expectancy, long PSA doubling time, or significant comorbidity burden, observation may be the most appropriate course of action.

Salvage prostatectomy

At the present time, the role for surgical intervention for recurrent prostate cancer after radiotherapy remains limited.[38] To date, although presently approximately 100,000 prostatectomies are performed annually as initial therapy for men with prostate cancer, a recent review of the world's literature reveals that there are only a reported 1511 cases of salvage radical prostatectomy (SRP).[39] This number continues to increase, especially as more experience emerges with salvage robot-assisted laparoscopic prostatectomy (SRALP).[40]

While there are no prospective trials evaluating the use of SRP in the post-EBRT setting, there are a number of retrospective studies that describe associated outcomes and toxicity. There is significant heterogeneity across studies, with varying definitions of biochemical failure, variable follow up times, and inconsistent reporting of the use of androgen deprivation therapy (ADT). Furthermore, surgical methods are inconsistent across studies, with varying rates of nerve-sparing and robot-assisted laparoscopic techniques.

The most robust experience published in the literature to date is an international multi-institutional cohort study that reported outcomes on 404 men who underwent SRP after PSA failure following primary EBRT. In this study, the 10 year BRFS, metastasis free survival, and cancer specific survival estimates were 37%, 77%, and 83%, respectively. Multivariate analysis identified pre-salvage PSA, pre-salvage Gleason score, and prostatectomy Gleason score as significant predictors of biochemical recurrence and distant metastasis.[38] Similarly, a study from Memorial Sloan Kettering Cancer Center (MSKCC) reported on 146 patients who underwent SRP after primary EBRT failure for localized prostate cancer. With a median follow up of 3.8 years, the 5 year recurrence free survival estimate in this study was 54%, and only one patient had a clinical local recurrence. Finally, a series from Mayo Clinic reported outcomes of 199 patients undergoing salvage surgery (including 138 patients undergoing SRP and 61 patients undergoing cystoprostatectomy) after primary EBRT. In patients undergoing SRP, median progression free survival was 8.7 years, and 10 year cause specific survival was 77%.[41] While there are other series reporting on outcomes associated with SRP in this setting, most of these studies have significant limitations including short median follow up times and small patient numbers.

It is generally accepted that the perioperative morbidity of SRP is greater than that of primary RP; however, there is a lack of data describing the true toxicity rates for this treatment. The majority of SRP reports do not evaluate toxicity, and reported data on the morbidity of SRP are largely derived from a relatively small set of studies. In a study from MSKCC, SRP after primary EBRT failure was associated with a 53% surgical complication rate, compared to 19% in patients undergoing primary RP ($p < 0.001$).[42] Acute morbidities of SRP in this study included urinary tract infection, bladder neck contracture, urinary retention, urinary leak, pelvic abscess, and rectal injury. These results are similar to those of other published reports that report rectal injury and bladder neck contracture rates as high as 19% and 41%, respectively.[39]

Similar to surgical complication rates, functional outcomes — erectile function and urinary continence — have been measured in this subset of patients with sobering results. Although not all studies report

rates of pre-SRP erectile function, it is clear that SRP is associated with worsening ability to obtain and maintain erections. Masterson et al reported a 5 year erectile function recovery rate of 16% in a cohort of 100 patients treated with SRP at MSKCC, with 45% of previously potent patients maintaining potency after surgery.[43] With regards to urinary incontinence, a separate MSKCC study reported that 39% of patients were dry at 5 years, and 68% of patients required one pad or less daily.[44]

Finally, in a similar manner to the evolution of robot-assisted laparoscopic radical prostatectomy for the primary treatment of localized prostate cancer, the use of minimally-invasive approaches has been extended to the salvage setting for men with recurrent prostate cancer after EBRT. Data on SRALP is sparse, and early series have contained small cohorts of men (n = 6 to 15) with follow up measured in months.[40] Nevertheless, the choice of an open or robotic approach for a salvage prostatectomy is ultimately up to the surgeon and his comfort level with either modality.

Salvage cryotherapy

When approaching patients for consideration of salvage cryotherapy (SCT), many of the same issues that arise for SRP are applicable. There is a great deal of overlap in the oncologic and functional outcomes between SRP and SCT; however, patients undergoing surgery tend to be younger (median age = 65), and due to the less invasive nature of SCT, it is not associated with many of the medical and surgical complications seen in patients undergoing SRP.[38,45] However, in contrast to patients undergoing SRP, patients treated with SCT after biochemical failure cannot be assessed pathologically, and oncologic success is therefore defined by a patient's PSA response.

With the exception of a single prospective series, the available literature on SCT primarily consists of retrospective studies with small patient numbers and short median follow up times. Among the published retrospective studies, there is significant heterogeneity in patient characteristics, the definition of treatment failure, and cryotherapy techniques. Not surprisingly, outcomes among these studies are highly variable.

The only prospective study to evaluate outcomes of SCT after primary EBRT is a series from the United Kingdom that reported on 100 patients treated with SCT between 2000 and 2005. With a mean follow up time of 33.5 months, the overall BRFS rate in this cohort was 83% at 12 months, 72% at 24 months, and 59% at 36 months. Post-hoc subset analysis demonstrated that patients who achieved an undetectable PSA nadir after SCT had better outcomes compared to patients with a PSA nadir of > 0.1 ng/mL. Furthermore, post-SCT PSA nadir > 0.1 ng/mL and pre-radiation Gleason score were significantly associated with eventual biochemical recurrence after SCT on multivariate analysis.[46]

In addition to the aforementioned prospective analysis, there are several retrospective studies that provide prognostic guidance for patients undergoing SCT in this setting. The largest of these is a multicenter cohort study that included 797 patients and reported a biochemical failure rate of 66% after a median follow up of 3.4 years. The data from this study was used to develop and validate a nomogram to predict the likelihood of biochemical failure after SCT based on the initial PSA, initial clinical T stage, and initial biopsy Gleason score.[47] Similarly, in an analysis of 49 patients treated with SCT at MDACC after primary radiotherapy failure, pre-salvage PSA and PSADT were both found to be predictors of biochemical failure after SCT.[48]

Although SCT spares the patient an operative intervention, the risks associated with the procedure are not insignificant. Recto-urethral fistula, urethral stricture formation, urinary tract infection, urinary retention, hematuria, lower urinary tract discomfort/symptoms, chronic perineal pain, and proctitis are all acute procedure-specific complications that can occur with varying frequencies. Fortunately, the introduction of more precise machines with temperature sensors and urethral warmers has resulted in a markedly improved complication rate profile.[49]

Finally, similarly to SRP, SCT is associated with deleterious effects on functional outcomes. In fact, rates of erectile dysfunction with SCT may be even worse than those associated with SRP, since the ice ball created to ablate the prostate gland will extend beyond the prostatic capsule to the neurovascular bundles.[49] In the aforementioned prospective study from the United Kingdom, 57% of patients who reported adequate erectile function prior to SCT experienced reduced erectile function after treatment. With regards to urinary outcomes, 13% of patients developed persistent urinary incontinence after SCT requiring at least one pad per day, and 16% of patients experienced lower urinary tract symptoms such as frequency and urgency.[46]

Salvage brachytherapy

The same characteristics that make brachytherapy a useful primary treatment modality for localized prostate cancer also contribute to its significant potential as an effective salvage treatment after EBRT. Given the dose distribution characteristics of the radioactive seeds used for the implant (typically iodine-125 or palladium-103),

brachytherapy allows for the delivery of high radiation doses to the target volume while avoiding significant radiation dose delivery to adjacent structures. There have been a number of high quality studies that have described the use of permanent low dose-rate (LDR) brachytherapy implantation for local salvage treatment after EBRT.

One prospective study evaluating salvage brachytherapy in this setting is a phase II trial by Nguyen et al that reported on 25 patients treated with MRI-guided salvage brachytherapy after primary EBRT or brachytherapy in men who initially presented with favorable features (GS ≤ 7, PSA < 10 ng/mL, negative metastatic imaging work up). With a median follow up of 47 months, the 4 year actuarial BRFS in this cohort was 70%. Seven patients developed grade 3 or 4 gastrointestinal (GI) and/or genitourinary (GU) toxicity, corresponding to a 4 year actuarial rate of 30%.[50] A separate quality of life analysis of the same cohort used a patient-reported questionnaire filled out at baseline and at various time points thereafter. There was a significant decline in sexual function scores over time. Urinary and bowel scores were worse at 3 or 15 months post-treatment compared to baseline; however, these symptoms improved to the point that there were no significant differences between urinary and bowel scores at baseline and 27 months post-treatment.[51]

The largest retrospective series, by Grado et al, describes outcomes and toxicity for 49 patients treated at Mayo Clinic with biopsy-proven localized prostate cancer after EBRT failure. In this study, the actuarial BRFS was 48% at 3 years and 34% at 5 years. While acute urinary symptoms were common in the acute period after treatment, the frequency of late complications in this cohort were generally low. Overall, 14% of patients required transurethral resection of the prostate (TURP) for management of urinary symptoms after treatment, and late rectal toxicity was found in 4% of patients.[52] Similarly, a study by Burri et al reported 10 year BRFS and cancer-specific survival rates of 54% and 96%, respectively, with a median follow up of 86 months. In this study, pre-salvage PSA < 6 ng/mL was significantly associated with improved BRFS.[53]

In addition to low dose-rate brachytherapy, there is emerging data regarding the use of high dose-rate (HDR) brachytherapy as salvage treatment after EBRT. Lee et al retrospectively analyzed 21 patients who underwent salvage HDR brachytherapy at the University of California-San Francisco with a median follow up of 18.7 months and a 2 year BRFS of 89%. While almost all patients (18/21) experienced grade 1 or 2 GU toxicity, only three patients developed grade 3 GU toxicity, and GI toxicity was rare.[54]

Currently, the RTOG is accruing patients on a phase II multi-institutional, prospective study (RTOG 0526) evaluating the use of brachytherapy for locally recurrent prostate adenocarcinoma following EBRT. The primary endpoint of this study is to evaluate the incidence of late treatment-related GI or GU toxicity related to salvage brachytherapy in this patient population. Secondary endpoints include BRFS, overall survival, and disease-free survival. The results of this study will provide the most robust data to date regarding salvage brachytherapy for prostate cancer and will have the potential to further validate this modality for salvage treatment.

Experimental treatments

Other treatments that may be employed for salvage treatment of biochemically recurrent prostate cancer after EBRT include high intensity focused ultrasound therapy (HIFU) and thermal ablation. Both treatments are currently considered experimental, and there is very little data to support their use in the salvage setting at the present time. Notably, neither treatment is currently approved by the Federal Drug Administration for routine use in the United States.

HIFU involves the use of a transrectal ultrasound probe to ablate prostate tissue by delivery of high intensity sonographic waves. Ahmed et al reported on 84 men treated with salvage HIFU for biopsy-proven localized prostate cancer recurrence after EBRT. Following salvage therapy, the 1 year and 2 year progression free survival rates were 49% and 43%, respectively. The treatment was associated with significant risks of urinary incontinence (38%) and erectile dysfunction, and 20% of patients required intervention for bladder outlet obstruction.[55] Additionally, Gelet et al reported on 71 patients treated with salvage HIFU after EBRT failure and found 44% progression free survival with median follow up of 30 months. Treatment related toxicity in this study included bladder neck stenosis (17%), grade 3 urinary incontinence (7%) and rectourethral fistula (6%).[56]

Ferromagnetic thermal ablation is an experimental therapy in which permanent cobalt-palladium rods are implanted into the prostate and are subsequently passed through an oscillating magnetic field in order to generate enough heat to ablate prostate cancer tissue. In a review of 14 patients receiving this treatment for salvage therapy after EBRT failure, Master et al reported that 57% of patients had PSA decrease to less than 0.1 ng/mL 6 months after the procedure. Long term complications included urinary retention (21%) and incontinence (7%), and 36% of patients required a secondary procedure for management of treatment-related toxicities.[57]

At this point in time, the literature on HIFU and thermal ablation for salvage treatment of biochemically recurrent prostate cancer is not robust, and the available studies demonstrate significant risk of chronic grade 3 or above toxicity with either option. Further studies with higher patient numbers and longer follow-up are needed to more completely evaluate the potential risks and benefits of these therapies. At this time, HIFU and thermal ablation are not considered standard treatment options for salvage treatment of prostate cancer after EBRT.

Systemic therapy

The first-line systemic treatment for patients with recurrent prostate cancer consists of ADT. Options for ADT include surgical castration or medical castration with luteinizing hormone releasing hormone (LHRH) agonists or antagonists. The optimal timing of ADT for a patient with biochemically recurrent prostate cancer is not established, and the decision to initiate ADT may depend on individual patient and disease factors, including the absolute PSA level, the PSADT, patient comorbidities, and life expectancy. Moreover, ADT likely contributes to multiple undesirable effects on the body, including cardiovascular disease and diabetes.[58] In a recently published survey of Canadian radiation oncologists, the majority of respondents did not routinely advocate ADT delivered concurrently with local salvage therapy after prostatectomy, and there was no consistent PSA threshold for initiation of ADT.[59] A recent study by Crook et al demonstrated that intermittent ADT was noninferior to continuous ADT in patients with PSA recurrence after radiation, and some quality-of-life factors were improved with intermittent therapy.[60] Accordingly, this regimen will likely be widely adopted in the setting of PSA recurrence after radiotherapy. Nonetheless, further study is needed to optimize patient selection and treatment delivery in this population.

Systemic options for men who develop resistance to ADT have expanded greatly over recent years. Antiandrogens such as bicalutamide and adrenal inhibitors such as ketoconazole have shown effect in delaying rise in PSA but have not shown an overall survival benefit in men with castrate resistant prostate cancer (CRPC).[61,62] Docetaxel and prednisone was the initial therapy to demonstrate a survival benefit in CRPC.[63] Sipuleucel-T is an immune based infusion 'vaccine' of patients' cells that have been pulsed with a prostatic acid phosphatase conjugate and has shown a survival benefit in asymptomatic CRPC patients.[64] Abiraterone is a Cyp -17 inhibitor that has shown an overall survival benefit and has been approved for use after docetaxel[65] but has recently been shown to be effective in the pre-chemotherapy CRPC setting as well.[66] Cabazitaxel is a second post docetaxel approved agent and has been shown to also improve OS in that setting.[67] Lastly, Denosumab is a RANK ligand inhibitor that decreases the rate of events and prolongs time to skeletal related events in CRPC patients.[68,69]

In addition to the aforementioned therapies that are currently available for clinical use, a phase III study recently demonstrated improved overall survival with the use of alpharadin (radium-223 chloride), which is an alpha-emitting radioisotope delivered by intravenous injection.[70] Novel androgen axis/Cyp 17 based inhibitors such as MDV-3100 have also shown an OS benefit.[71]

Lifestyle modifications

All patients with recurrent prostate cancer should be counseled on lifestyle modifications that may help prevent further disease progression. At the present time, there are no dietary modifications that have been shown to definitively impact the clinical course of prostate cancer. However, there is some evidence to suggest a clinical benefit associated with intake of lycopene and soy phytoestrogens.[72] Furthermore, as obesity is a risk factor for prostate cancer development, patients should be counseled on the importance of limiting fat intake along with participating in regular exercise.

Conclusions/recommendations

At the present time, the primary local salvage options for locally recurrent prostate cancer after EBRT include SRP, SCT, and salvage brachytherapy. As demonstrated above, rates of BRFS for each of these modalities vary between studies, and each modality is associated with significant risks of both acute and late toxicities. As there is currently no randomized prospective data comparing the use of SRP, SCT, and brachytherapy for salvage local treatment of biochemically recurrent prostate cancer, the selection of the most appropriate treatment modality should be performed on a patient-by-patient basis, with careful attention paid to each individual patient's pre-treatment comorbidities and ability to tolerate both the acute and long-term side effects of salvage therapy. We recommend multidisciplinary evaluation for all such patients, including consultation with urology, medical oncology, and radiation oncology, along with discussion at a multidisciplinary tumor board. Finally, if available, enrollment of these patients on clinical trials may provide an opportunity for novel and potentially more effective treatment. □

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