Salvage Therapy for Prostate Cancer

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Abstract

Biochemical recurrence after treatment of prostate cancer occurs in 30–50 % of patients. Confirming that recurrence is localized to the pelvis is challenging as PSA is nonspecific and imaging modalities are imperfect in identifying location of recurrent disease. Salvage therapy after radical prostatectomy is limited to external beam radiotherapy and androgen-deprivation therapy. After radiotherapy, local salvage therapy consists of salvage radical prostatectomy, salvage brachytherapy, and salvage high-intensity ultrasound. Each treatment modality provides various rates of cure but with its own side-effect profile, prompting discussion between patient and clinician to determine appropriate treatment course. Local salvage therapy has the potential to be curative and disease control has been reported in a substantial number of select patients. However, the survival benefit of these therapies has yet to be definitively proved.

Keywords

Prostate cancer, biochemical recurrence, external beam radiotherapy, prostatectomy, brachytherapy, cryosurgery, high-intensity ultrasound, androgen-deprivation therapy

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Prostate cancer is the most common nonskin cancer in men—217,000 men were diagnosed in 2010.[1] Approximately 55 % will undergo external beam radiotherapy (EBRT) and 40 % will undergo radical prostatectomy.[2] Of the patients treated with prostatectomy, up to 35 % will have rising prostate-specific antigen (PSA) as evidence of biochemical recurrence (BCR) within 10 years of treatment[3] and 30–50 % of patients will have BCR after EBRT.[4] The interval between BCR and overt recurrent disease or distant metastases is prolonged but cis variable among patients. Observational studies suggest an average of 5 to 8 years.[5] Evaluation and long-term follow up of patients have determined that several risk factors increase the likelihood of prostate cancer specific mortality (PCSM). The most significant factors are pretreatment PSA, pathologic stage and Gleason score 8–10. Post treatment, the shorter the interval between treatment and evidence of BCR, the higher the likelihood of prostate-cancer specific mortality.[5] Furthermore, a short PSA doubling time (PDT) is associated with an increased likelihood of PCSM, irrespective of Gleason score,[6] likely due to the PDT more accurately reflecting the true tumor biology. A PDT of 11.7 months predicts local failure with a low potential for systemic progression and PDT of <4.3 months is associated with a high probability of developing systemic recurrence or existing systemic recurrence.[7] Advanced pathologic features after prostatectomy, such as seminal vesicle invasion, lymph node invasion, poorly differentiated cancer, and positive surgical margins (PSMs)[6] also increase the risk for PCSM.

Interpreting PSA after EBRT is challenging. In 10–30 % of patients, PSA levels will increase—'PSA bounce'—even up to 2 to 3 years after treatment. Although likely due to benign prostate cells left behind, the rise may initially be indistinguishable from a true recurrence.[8] Prostate biopsy is not recommended by the American Society for Therapeutic Radiology and Oncology (ASTRO) as a positive result has minimal impact on outcome up to 2 years after radiation;[9] however, in a review by Pollack, there was a 50 % progression of PSA at 7 years after EBRT in patients with a positive biopsy.[10] Intervention at the earliest stage after recurrence provides the best chance for cure, and as such any patient with BCR and a positive biopsy 2 or more years after treatment, should undergo salvage therapy especially if no treatment effect is seen on pathology.[11] Once recurrent disease is present the critical matter remains to determine location, local or systemic. Imaging is unreliable to determine location of recurrent disease. Trans-rectal ultrasound and biopsy is difficult to interpret due to sampling errors and unknown time required for cancer cells to become nonviable after radiation. The sensitivity and specificity of trans-rectal ultrasound was not superior to digital rectal exam in predicating a positive biopsy.[12] Useful in pretreatment prostate, magnetic resonance imaging may also helpful in a radiated prostate. Experienced radiologists can distinguish benign prostate tissue from suspicious nodules, to help in biopsy planning and step-section postradiation prostatectomy.[13]

After initial treatment, evidence of BCR prompts discussions between the patient and clinician. Systemic therapy, such as androgen-deprivation therapy (ADT), can provide long-term disease control for both local and systemic disease. However, there remains debate about whether conventional ADT offers cure for patients with relapsed disease. Likewise, concerns about long-term toxicity limit its appeal. Local salvage therapy may be curative though the morbidity may not be trivial and may represent unnecessary treatment for those with occult systemic

disease. While no salvage therapy is proved to reduce risk for developing metastases or decrease mortality and most have significant treatment related morbidity, the decision to proceed with salvage therapy must take all factors into account.

Local Salvage Radiotherapy

For BCR postradical prostatectomy, salvage radiotherapy is the most frequently employed option. The rationale for salvage radiotherapy, opposed to adjuvant radiotherapy, is that waiting for PSA recurrence is unlikely to compromise curability and the risk for PCSM is far outweighed by risk for death from competing causes. Furthermore, deferring radiotherapy will delay the development of treatment-related side effects and only patients with demonstrated recurrent disease receive treatment. There is no evidence from prospective randomized trials supporting salvage radiotherapy to reduce distant metastases, cancer-specific or overall survival (OS). Clinical trials are ongoing in hopes of proving salvage radiotherapy noninferior to adjuvant EBRT. Data from retrospective and observational studies suggest that salvage radiotherapy can be used to control local recurrence, thus reducing distant metastases and PCSM.

In retrospective analyses, lack of progression after salvage radiotherapy has been reported in 10–50 %, with increased progression seen in patients with adverse pathologic features.[14,15] In a multi-institutional observational study, 1540 patients received salvage radiotherapy with a response rate of 32 %, 14 % of whom received neoadjuvant ADT. However, 48 % of those who underwent salvage radiotherapy when PSA was <0.5 ng/mL had no evidence of disease at 6 years, compared with 18 % of patients who started salvage radiotherapy at a PSA level of 1.5 ng/ mL.[15] In Southwest Oncology Group (SWOG) 8794 and European Organisation for Research and Treatment of Cancer (EORTC) 22911, an approximately 50 % response rate was seen in patients receiving adjuvant radiotherapy. Further retrospective studies have shown a benefit similar to adjuvant radiotherapy in patients with several risk factors for developing distant metastases and PCSM. In 501 patients who underwent salvage radiotherapy, 38 % with PDT <10 months were disease free at 4 years as were 70 % of men with BCR within 12 months of prostatectomy. Follow-up studies showed that in high-risk patients who received salvage radiotherapy when PSA levels were 0.5 ng/mL, 41 % were disease free at 6 years, whereas this group of patients have a 60–70 % chance of developing metastases at 6 years if untreated.[5] In practice now, patients with long life expectancy with BCR postprostatectomy are advised salvage radiotherapy based on 2–3 rising PSA levels and radiotherapy started at PSA levels 0.1–0.2 ng/mL, recognizing the risk that the increasing PSA level may be residual benign prostatic glands.

Of the significant risk factors (Gleason score, PDT <10 months and short interval to developing BCR), patients with a short PDT seem to benefit the most from salvage radiotherapy. In a study of 635 patients with BCR after prostatectomy, 238 had salvage radiotherapy and 397 received ADT. The patients who had salvage radiotherapy had a statistically significantly improved PCSM compared with ADT alone. Subgroup analysis showed that benefit was greatest for patients who had a PDT of <6 months.[16]

Complications after salvage radiation are not common but can have significant morbidity. In the SWOG 8794 trial, which albeit studied adjuvant radiotherapy, not salvage radiotherapy, there were significantly more complications in the adjuvant radiotherapy group (23.8 % versus 11.9 %) and certain complications (proctitis and rectal bleeding) were unique to the radiotherapy group. Urethral stricture and total urinary incontinence rates were significantly higher in the radiotherapy group. Overall assessment of quality of life was similar at 2 years and superior at 3 years in the radiotherapy group.[17] Although radiation of any kind has the potential for causing a secondary malignancy, this may be reduced with improved image-guided techniques, utilizing operative and pathologic reports and guidelines to optimize target volume and margins.[18]

Salvage radiotherapy is delivered either to the whole pelvis or to the prostatic fossa. When delivered to the pelvis, the pelvic lymph nodes are included. In the Radiation Therapy Oncology Group (RTOG) 9413,[19] high-risk patients who received whole pelvic radiation had a longer biochemical-free period. Spiotto et. al[20] found that patients who received whole pelvic salvage radiation had a longer biochemical relapse-free survival, with 47 % with undetectable PSA levels at 5 years compared with 21 % who received radiotherapy to the prostatic fossa only. This improvement was seen only in high-risk patients.

The question remains whether the combination of ADT and adjuvant or salvage radiotherapy is superior to radiotherapy alone. It is well established that adjuvant ADT in intermediate to high-risk patients is superior to radiotherapy when used for primary treatment. In RTOG 9601, high-dose bicalutamide was combined with salvage radiotherapy in patients with BCR and extraprostatic extension (EPE) or PSM. At follow up, there was no significant difference in OS. However, patients who did receive ADT had lower risk for PSA progression and fewer distant metastases but, as expected, higher rates of gynecomastia.[21] In SWOG 8794, it was suggested that lack of local control may diminish response and effectiveness of ADT.[22]

Salvage Therapy after Radiotherapy

Salvage Radical Prostatectomy

Salvage radical prostatectomy represents a local salvage therapy for presumed isolated local recurrence of prostate cancer with curative potential. Only salvage prostatectomy has been shown to provide cancer control for 10 years or more in a substantial proportion of patients.[23,24] The 10-year PSA progression-free probability after salvage prostatectomy alone is 30 % to 43 % and 10-year cancer-specific survival rates of 70 % and 77 % have been reported.[23,24] Rates are dependent on pathologic findings postsalvage prostatectomy. The 5-year PSA progression-free probability is 77 %, 71 %, and 24 % for patients with organ-confined disease, isolated extra-capsular extension, and seminal vesicle invasion and/or regional lymph node metastases, respectively.[11] However, salvage prostatectomy complications after are higher. In a review of 100 patients undergoing salvage prostatectomy after either EBRT and interstitial radiotherapy,[25] the rate of rectal injury was 13 %, reoperation was 3 %, and one patient required cystectomy due to a urinary fistula. Complication rates are noted to be higher after retropubic radiotherapy compared with EBRT. Anatomic stricture rate was 30 % with a somewhat higher rate seen in patients receiving EBRT. In terms of urinary incontinence, 68 % of patients required one pad per day and 38 % were completely dry. Compared with primary radical prostatectomy, these rates are significantly higher but are decreasing.[25,26] Based on a review by Pisters et al.,[27] salvage radical

prostatectomy, compared with cryosurgery, offers higher biochemical-free rates with 61 % of patients having PSA <0.4 ng/mL at five years, compared with 21 % in the cryosurgery group. OS was improved: 95 % versus 85 %. Because of the morbidity and complication rate of salvage prostatectomy, but the greatest chance of cure, the ideal candidate should be highly motivated, have a life expectancy >10 years, lack severe medical comorbidities, and have a pre-treatment PSA of <10 ng/mL.

Cryosurgery

When initially used as salvage therapy after radiation, cryosurgery using liquid nitrogen probes, there was significant hesitation due to high rates of incontinence and fistulas. Now with use of gas probes with smaller diameters, urethral warming devices, and thermocouplers to prevent freezing of the sphincter, these rates are decreasing and cryosurgery is more accepted as an option for recurrent prostate disease. In the Cryo On-Line Data (COLD) patients, 279 underwent salvage cryosurgery after radiation for BCR.[28] After a median follow up of 21 months, 58 % remained BCR-free and 83 % had a detectable PSA, expected as cryosurgery does leave benign prostate tissue in situ. Postoperative biopsy rate was positive in 15 patients of the 46 biopsied (32 %) and the MD Anderson series[29] noted a similar rate (23 %). Chin et al.,[30] in a review of 118 patients, of which 15 % had a pretreatment PSA >15 ng/mL and 59 % were clinical stage T3 or greater, 7 % had positive biopsy but 60 % received pretreatment ADT, 34 % had a PSA level <0.5 ng/mL at 5 years. Izawa et al. showed that a pretreatment PSA <10 ng/mL, Gleason grade <9, and clinically T1 or T2 disease were predictors of success with salvage cryosurgery.[31] Complication rate is higher after salvage cryosurgery compared with primary cryosurgery, with erectile dysfunction and pelvic pain being the most common. In the MD Anderson series, 28 % were completely dry postoperatively and moderate to severe voiding symptoms were seen in 66 % of patients; this improved to 8–20 % with the use of modern probes and a urethral warming device.[32] Rectal fistula rate was 1.2 % but reported as high as 11 % in some series;[33] however, decreased rates were seen with the use of urethral warming devices and intraoperative use of ultrasound. Other series reported similar rates, majority within 1 year after cryosurgery.[31,34] Based on the series and lack of long-term survival data, it appears that salvage cryosurgery is inferior to salvage prostatectomy in terms of cancer control but a more favorable morbidity profile.

Salvage Brachytherapy

The benefit of brachytherapy used in the salvage setting is not as well established.[35,36] The largest consists of 49 patients[36] with BCR defined as a PSA rise over two measurements. The 3-year BCR-free rate was 48 %, which fell to 34 % at 5 years; of note, 28 of these patients received neoadjuvant hormonal therapy. Thirteen of the 46 patients had already failed another salvage procedure. Complications were not uncommon: 29 % had bladder outlet obstruction requiring trans-urethral resection. More chronic complications, including gross hematuria, dysuria, and rectal ulcers were seen in approximately 5 %. Hematochezia requiring surgical intervention was seen in 2 %. Further series[37,38] showed similar complications rates. Rectal bleeding was seen in 15–35 % and grades 3–4 genitourinary complications in 10–35 % of patients. Because of poor PSA response and significant risk for complications and morbidity, the use of salvage brachytherapy is not recommended; it may in fact reflect inherent radiobiologic resistance. In a series reviewed by Huang et al.[39] salvage prostatectomy specimens were analyzed in terms of anatomic location of residual cancers. Of the 46 prostates examined, 93 % had foci of cancer at the apex and 65 % had foci <5 mm from the urethra, 7 % had urethral involvement. These areas, the apex, periurethral, and urethra, are difficult and problematic areas to treat with both brachytherapy and cryosurgery. Because of this, in the salvage setting, these therapies may not provide the greatest chance for cure.

Salvage High-intensity Ultrasound

Salvage high-intensity ultrasound (HIFU), similar to cryosurgery, is still somewhat experimental, even in the primary treatment setting. Because of rapid dissipation of energy, treatment is more targeted. In the reported series, disease-free rates ranges from 25–54 %.[40] Murat et al. reviewed 167 patients with BCR defined by ASTRO guidelines with positive biopsies after EBRT who underwent salvage HIFU.[41] After mean follow-up time of 18 months, 41 had positive biopsies prompted by rising PSA and 52 had evidence of BCR but a negative biopsy; 17 patients developed metastatic disease, 11 of whom died. Five-year OS was 84 % with a progression-free survival (PFS) rate of 25 % in the high-risk patient group. Series report urethral stricture or bladder neck contracture rate of 10–20 % and recto-urethral fistula late of 3 to 12.5 %.[40] Similar to cryosurgery, salvage HIFU provides only minimal improvement in PFS with significant morbidity and, as such, is not recommended as salvage therapy.

Systemic Therapy

To date, there is no role for systemic chemotherapy in the salvage setting for localized recurrent disease. However, with the advent of abiraterone acetate and enzalutamide as novel forms of ADT, there is optimism that this may change in the future. As more is learned of their long-term side effects, these agents may be used in the hormone-naïve, nonmetastatic setting in addition to the metastatic, castrate-resistant setting. Although not evaluated as salvage therapy, ADT has been shown to improve PFS but has no impact on OS. In the Messing trial,[42] men with localized disease and positive nodes on pathology were randomized to immediate ADT after prostatectomy or delayed ADT to start after signs of disease progression, 80 % of the patients had an undetectable PSA postoperatively. After a median of 7 years follow up, OS as well as recurrent-free survival was significantly improved in the immediate ADT group. Thirty-six of 51 patients in the observation group went on to start ADT. One patient in the immediate ADT group suffered a myocardial infarction and one had severe thrombocytopenia; these did not prompt cessation of ADT. The immediate ADT group had a higher rate of ADT-related side effects such as gynecomastia and hot flashes. As this trial was in the pre-PSA era, it remains unclear at what time ADT should be optimally initiated.

As the majority of men receiving ADT will die of something other than prostate cancer, long-term effects are essential to prevent and treat as needed. ADT is associated with increased obesity and specifically the lack of androgens result in a fall in lean body mass and accumulation of subcutaneous abdominal fat, both of which has been shown to increase mortality. Despite exercise, body composition does not change. Furthermore, ADT increase insulin resistance, in combination with obesity, can contribute to developing diabetes, another risk factor for cardiovascular mortality. ADT increases triglycerides and high-density lipoprotein. The exact effect on cardiovascular health is unknown but increased lipids in the general population are associated with mortality due to cardiovascular disease. Prospective trials demonstrate that ADT

increases bone turnover, decrease bone mineral density and increase fracture risk the longer ADT is maintained. Bisphosphonates and denosumab increase bone mineral density and can decrease the number of fractures.[43]

To reduce frequency of side effects and decrease risk for adverse ADT-related events, but prevent patients from becoming symptomatic and decreasing OS, Klotz et al.[44] randomized 1,386 patients to intermittent androgen suppression and continuous androgen suppression. In a median follow up of 6.9 years, mean OS was 8.8 years and 9.1 years for intermittent and continuous respectively (confidence interval [CI] 0.86–1.21) although the intermittent group had more deaths due to prostate cancer and fewer due to competing causes. Of side effects, only the numbers of hot flashes were reduced in the intermittent arm; cardiovascular and orthopedic events were the same.

Bicalutimide was evaluated as an adjuvant therapy in men with T1b–T4 without lymph node involvement or distant metastases.[45] PFS was improved in all patients, but the greatest improvement was seen in patients with locally advanced disease, regardless of initial therapy modality. OS was unchanged. Common side effects including gynecomastia and breast pain were present in 68 % and 73 % of patients, respectively, resulting in withdrawal in 28 % of the bicalutimide group. In a randomized, double-blind, placebo-controlled study of 8113 patients,[46] the benefit of bicalutimide in the adjuvant setting was confirmed. Over a follow up of 9.7 years, 36 % of the treatment group progressed and 38 % in the placebo group. PFS was improved by reducing the risk by 15 %, regardless of initial treatment modality, but the improvement was greatest in the group managed with watchful waiting. No difference in OS was observed. As mentioned above, combination of bicalutimide with radiation improved time to BCR and reduced incidence of metastatic disease without adding additional radiation toxicity. OS was improved from 85 % to 91 % with the addition of peripheral androgen blockage.[21]

5α-reductase inhibitors are being studied in terms of a possible role in salvage therapy. Andriole et al.[47] found that addition of finasteride delayed PSA rise by 14 months. There were fewer local and distal recurrences in the finasteride group. In vitro models showed that dutasteride has anti-tumor properties against human prostate cancer and—confirmed in a mice model. Perrotti et al.[48] studied 35 men with BCR after definitive treatment, 46 % had a PSA decrease >10 % and 25 % had PSA decrease >50 %. After 6 months, PSA levels decreased in 24 patients (68 %). In 19 of these 24 patients with a durable decrease, PSA levels have remained down. Mean follow up is only 24 months so definitive conclusions cannot be drawn yet. The Avodart after Radical Therapy for prostate cancer Study (ARTS) trial, a multicenter trial to evaluate use of dutasteride in patients with BCR is under way.[49]

Conclusion

Recurrent disease after prostate cancer treatment is more common than expected. Salvage therapy for local control can provide a possibility of cure in proportion of patients with certain adverse clinical features such as rapid PDT and high-grade cancer. To date, no salvage therapy has been proved to prolong OS and salvage therapy is associated with significant morbidity. Further studies and randomized clinical trials are required to determine effectiveness of salvage therapies. ■

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