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Review Article

Salvage Radiotherapy for Patients with PSA Relapse Following Radical Prostatectomy: Issues and Challenges

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A progressively rising level of serum prostate specific antigen (PSA) after radical prostatectomy (RP) invariably indicates the recurrence of prostate cancer. The optimal management of patients with post-RP PSA relapse has remained uncertain due to a wide variability in the natural course of post-RP PSA relapse and the inability to separate a recurrent disease confined to the prostate bed from that with occult distant metastasis. Management uncertainty is further compounded by the lack of phase III clinical studies demonstrating which therapeutic approach, if any, would prolong life with no significant morbidity. Radiotherapy has been the main therapeutic modality with a curative potential for patients with post-RP PSA relapse. This review article depicts issues and challenges in the management of patients with post-RP PSA relapse, presents the literature data for the efficacy of salvage radiotherapy, either alone or in combination of androgen ablation therapy, and discusses future directions that can optimize treatment strategies.

Key words
Salvage radiotherapy, PSA relapse, Post radical prostatectomy

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Introduction

Radical prostatectomy (RP) is one of standard treatment options for clinically localized prostate cancer. In the U.S.A., about 40% of patients with newly diagnosed prostate cancer undergo RP as their primary treatment (1). In recent years, the proportion of patients diagnosed with low risk prostate cancer has significantly increased due to widely employed prostate specific antigen (PSA) screening, and the utilization of RP for low risk prostate cancer has correspondingly increased (2).

Although RP is performed with curative intent, a significant proportion of surgically treated patients face with the risk of prostate cancer recurrence. The recurrence of prostate cancer following RP is invariably heralded by a progressively rising PSA before there is any clinical or radiological manifestation - the so - called 'PSA relapse' or 'biochemical failure'. PSA relapse after RP can be due to a local tumor recurrence at the prostate bed, occult nodal or distant metastasis, or the combination of both.

The optimal management for patients with post-RP PSA relapse has remained unclear. This stems from the inability to separate patients whose recurrent disease is confined to the prostate bed from those that have already developed occult metastasis. Furthermore, the clinical course of patients with post-RP PSA relapse is highly variable. Some experience rapid clinical progression to metastasis, while others have a very indolent natural course. As a result, management options are diverse, ranging from salvage RT, either alone or in combination of androgen ablation therapy, as a definitive therapy to expectant management or androgen ablation therapy alone as a palliative therapy. Up to now, there have been no published outcomes from randomized clinical trials addressing the efficacy of salvage therapeutic modalities. As such, treatment strategies for patients with PSA relapse have been mostly derived from retrospective series and small prospective studies, or by extrapolating evidences from clinical trials of primary

cancer setting.

Radiotherapy (RT) has been the main salvage therapeutic modality with a curative potential for patients with post-RP PSA relapse. The aim of this review article is to discuss the issues and challenges in the management of patients with post-RP PSA relapse and to evaluate the role of salvage RT, either alone or in combination of androgen ablation therapy. It also discusses future directions that can assist a risk assessment and optimize management approach.

Definition and Prevalence of PSA Relapse after Radical Prostatectomy

Monitoring PSA level after RP is the cornerstone of post-operative surveillance strategies to detect the recurrence of prostate cancer. Given that the half-life of PSA is 3.15 days (3), PSA usually declines to an undetectable level within 30 days after RP (4). Thus, persistently detectable or subsequent rising PSA levels after RP indicate either residual or recurrent prostate cancer.

Various PSA cut-off points, ranging from >0.1 ng/mL to >0.5 ng/mL, have been used for the definition of PSA relapse after RP (5-12). One of commonly used definitions has been PSA ≥ 0.2 ng/mL with one subsequent rise. The American Urological Association and the European Association of Urology put forward a guideline that recommended PSA ≥ 0.2 ng/mL with a second confirmatory level of >0.2 ng/mL as the definition of PSA relapse (13-15). Freeland suggested PSA >0.2 ng/mL as an appropriate cut-off for PSA relapse, and reported that the likelihood of further PSA progression was 86% at 1 year and 100% at 3 years, when a post-operative PSA was >0.2 ng/mL (12). Another commonly used PSA cut-off point for the definition of PSA relapse has been ≥ 0.4 ng/mL. Stephenson examined a PSA relapse definition that would best predict the development of metastatic disease among 10 definitions selected on the basis of acceptable sensitivity. PSA ≥ 0.4 ng/mL with one subsequent rise was the best predictor for clinical progression, and was associated with a high probability of subsequent PSA progression and the need for subsequent secondary therapy (16). Amling reported that the probability of subsequent PSA progression increased as a PSA cut-off value increased from 0.2 to 0.4 ng/mL, and recommended PSA ≥ 0.4 ng/mL for the definition of PSA relapse (10). The PSA Working Group recommended PSA ≥ 0.4 ng/mL at a minimum of 1 month after surgery followed by a subsequent PSA value equal to or greater than the first measurement to be used for clinical trials that target patients with post-RP PSA relapse (17).

The availability of an ultrasensitive PSA assay in recent years has enabled a clinician to predict PSA relapse earlier, but at the same time has further complicated how it should be incorporated into a clinical practice. Ellis compared a PSA cut-off point >0.008 ng/mL using an ultrasensitive assay with a PSA cut-off point >0.1 ng/mL on a conventional assay for the definition of PSA relapse. He reported that the ultrasensitive PSA assay could detect PSA relapse much earlier with a lead time of 12.7～22.5 months (18). Doherty reported that the likelihood of PSA relapse, defined as three consecutive PSA rises above 0.01 ng/mL on an ultrasensitive assay, was 75% for patients who failed to achieve PSA <0.01 ng/mL, compared with only 3% for those attaining PSA <0.01 ng/mL (19). The dilemma is, however, that not all patients who appear to have PSA relapse on ultrasensitive assays develop clinical progression and subsequent PSA rise (18, 20). Such a low PSA level may be due to non-malignant tissues such as benign prostatic glands or periurethral glands (18,20,21). Thus, when treatment is initiated at such a low PSA level, there is concern for over-treatment. In addition, there has been no study yet supporting that therapeutic intervention at such a low PSA level using an ultrasensitive assay would provide any therapeutic gain, compared with that triggered by PSA levels via a conventional PSA assay. The European Consensus Group advised that an ultrasensitive PSA assay could be used for monitoring patients, but not for management decision-making (14).

The risk of PSA relapse after RP depends on several, well-defined, clinical and pathologic factors such as pre-operative PSA level, Gleason score, pathologic stage, and surgical margin status. In the pooled data of RP among 8 institutions (22), the risk of PSA relapse was 19% at 10 years for pathologically organ-confined disease with negative surgical margins. The risk of PSA relapse increased substantially with the presence of extracapsular tumor extension, positive surgical margins, or the combination of both. The risk of PSA relapse at 10 years was 39% for positive surgical margins with no extracapsular extension, 54% for extracapsular extension with negative surgical margins, and 75% for extracapsular extension with positive surgical margins. Kahn constructed a modelling of four prognostic groups based on Gleason score, pathologic stage, and surgical margin status for the likelihood of being free from PSA relapse after RP (23). In recent years, the outcomes of three randomized studies (24-27), comparing observation with post-operative adjuvant radiotherapy for pathologic T3 (pT3) and/or positive surgical margins, have confirmed that extracapsular tumor extension and/or positive surgical margins are associated with a high risk of PSA relapse. In the Southwest Oncology Group 8794 clinical trial, the rate of PSA relapse was 72% at 10 years in 122 patients with pT3 and/or positive surgical resection margins who had initially achieved an undetectable post-operative PSA (≤ 0.2 ng/mL) (25). Similarly, in the European Organization for Research and Treatment of Cancer 22911 clinical trial (26) and the German study (27), the risk of PSA relapse was high, 40% and 46% at 5 years, respectively, in those with pT3 and/or positive surgical resection margins even if they had initially attained an undetectable post-operative PSA.

Radiological Investigations for PSA Relapse

Radiological investigations are usually considered for patients with post-RP PSA relapse in order to evaluate the site of tumor recurrence and to rule out any distant metastasis. Radiological studies can complement clinical and pathologic information to guide management approach. However, there has been no reliable radiological tool up to now to accurately identify the site of tumor recurrence for patients with post-RP PSA relapse.

The yield of conventional investigations such as bone scan and computed tomography (CT) of the abdomen and pelvis has been very low for patients with post-RP PSA relapse. Nevertheless, these tests are commonly performed, as the detection of any distant metastasis obviates the need for local salvage treatment. Cher reported in a series of 93 patients with PSA relapse that the probability of a positive bone scan was < 5%, unless a PSA level was above 40 ng/mL (28). In the Dotan's series of 414 bone scans, the rate of a positive scan was 4%, 36%, 50%, and 79% for PSA < 10, 10.1～20, 20.1～50, and >50 ng/mL, respectively (29). Gomez described a very low probability of a positive bone scan with PSA < 7 ng/mL (30). Similarly, the sensitivity of abdominopelvic CT scan has been limited, when PSA levels are low. Okotie reported that when PSA was < 10 ng/mL, the probability of a positive CT scan was non-existent (31). Given this very limited sensitivity and an additional risk of false positive, the routine application of bone scan and abdominopelvic CT scan has been questioned in the setting of low PSA levels. It has been suggested that the incorporation of other PSA parameters such as PSA velocity and PSA doubling time, in conjunction with PSA level, could augment the judicious use of these tests (29,31,32). Kane suggested that low PSA velocities of < 0.5 ng/mL/month and < 0.7 ng/mL/month were associated with negative bone scan and abdominopelvic CT scan, respectively (32). In another series, a short PSA doubling time of < 6 months was associated with a higher likelihood of a positive bone scan and abdominopelvic CT scan (31).

The usefulness of routine transrectal ultrasonography (TRUS) of the prostatic fossa is unclear. Several studies have suggested a poor sensitivity of TRUS for patients with low PSA levels (33-38). In addition, Koppie questioned a predictive value of TRUS-guided biopsy of the prostatic fossa, since a positive anastomotic biopsy was not associated with an improved outcome after salvage RT (39).

Magnetic resonance imaging (MRI) has gained increasing favor in recent years for the evaluation of patients with post-RP PSA relapse for several reasons (40-42). First, MRI has enabled a clinician to assess local recurrence in the prostate bed more accurately. Sella reported that endorectal coil MRI demonstrated at least one soft tissue mass in the prostatic bed in 39 of 41 patients with clinical evidence of local recurrence (40). In a series by Miralbell, MRI was capable of documenting a recurrent or residual disease in the setting of PSA levels ranging from 0.05 to 13.3 ng/mL (median: 0.87), typically in the inferior and posterior region of the vesicourethral anastomosis (41). Sciarra suggested that the sensitivity and specificity of MRI could be further improved by the combined use of dynamic contrast-enhanced MRI and MR spectroscopic imaging (42). This combined approach yielded a sensitivity of 87% and a specificity of 94% for local recurrence in a series of 50 patients with PSA relapse (PSA range: 0.9～1.9 ng/mL). Second, MRI can assist to evaluate pelvic lymph nodes and bone metastasis in visualized bones. Third, another potential benefit of MRI is to enable a clinician to treat areas of identified local recurrence with an escalated radiation dose, which can, in turn, potentially enhance the efficacy of salvage RT.

^{111}In-capromab pendetide scan (ProstaScint®) has shown some promise in a primary cancer setting, but its utility for patients with post-RP PSA relapse has not been validated. In a primary prostate cancer setting, a multi-center study reported that ProstaScint had a sensitivity of 75%, a specificity of 86%, and an overall accuracy of 81% in detecting extraprostatic lymph node metastasis, when it was tested for patients with a high risk prostate cancer (43). However, in the setting of post-RP PSA relapse, ProstaScint has been reported with a wide range of specificity, sensitivity, and predictive values (44-47). Raj estimated in a subset of 95 patients with post-RP PSA relapse that the sensitivity, specificity, and positive predictive value of ProstaScint were 73%, 53%, and 89%, respectively (44). Nagda reported, on the other hand, that the positive predictive value of ProstaScint in detecting recurrent disease outside the prostatic bed was only 27% (47). Furthermore, in his study of 58 patients who underwent salvage RT for PSA relapse, PSA relapse-free survival rates at 4 years were not different among patients with negative scan (53%) vs. those with positive uptake in the prostate bed alone (45%) vs. those with positive uptake outside the prostate bed (74%). Koontz and Thomas similarly reported that a positive vs. negative result of ProstaScint did not predict the treatment outcome after salvage RT (48,49).

The use of conventional positron emission tomography (PET) tracers such as ^{18}F-fluorodeoxyglucose (FDG) is limited for prostate cancer due to a low glycolysis rate in most prostate cancer and the renal excretion of the isotope into the bladder, thus obscuring any local uptake. ^{11}C-choline has been studied as a PET tracer for prostate cancer and has shown some promise. Rinnab reported that ^{11}C-choline PET/CT had a sensitivity of 89% and specificity of 40% for patients with post-RP PSA levels < 2.5 ng/mL (50). Castelluci reported that PSA level, PSA velocity and PSA doubling time were predictive factors for the outcome of ^{11}C-choline PET/CT for patients with post-RP PSA relapse (51). Scattoni, in a series of 21 patients with post-RP PSA relapse (median PSA: 1.98 ng/mL), correlated the outcome of ^{11}C-choline PET/CT for the detection of lymph node metastases with pelvic +/− retroperitoneal lymph node dissection (52). Nineteen of 21 patients (90%) with positive ^{11}C-choline PET/CT had histologically confirmed nodal metastases. On a nodal site-based analysis, it was estimated that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{11}C-choline PET/CT was 64%, 90%, 86%, 72%, and 77%, respectively. However, Schilling cautioned a limited positive predictive value of ^{11}C-choline PET/CT, as 3 of 10 patients deemed to have pelvic nodal metastases on ^{11}C-

choline PET/CT turned out no malignancy on pathology (53). Also, a recent study raised some doubt over the sensitivity of PET in the clinical setting of low PSA levels. Vees reported, in a series of 20 patients with post-RP PSA levels < 1 ng/mL, that only 11 were found to have a positive PET/CT using either ^{18}F-choline or ^{11}C-acetate, while 15 of 18 who also underwent endorectal MRI examinations had an evidence of local recurrence (54).

In summary, the ultimate aim of radiological investigations is to differentiate the tumor recurrence confined locally to the prostate bed from that with regional or distant metastasis; thereby, identifying patients who are likely to benefit from a definitive local salvage treatment, while sparing those least likely to respond. Currently, there is no reliable radiological tool to accurately identify the site of tumor recurrence for patients with post-RP PSA relapse. The sensitivity of current imaging techniques in detecting the site of tumor recurrence falls short of the sensitivity of PSA detection. Further study is warranted to examine the utility of various radiological modalities including functional imaging techniques.

Management Options for Patients with PSA Relapse

The optimal management for patients with post-RP PSA relapse has remained unclear. This uncertainty is due to the inability to separate patients who have the recurrent disease confined to the prostate bed from those that have already developed occult metastasis. Another factor complicating the management decision is a wide variation in the natural course of post-RP PSA relapse. Furthermore, there has been no published phase III study addressing the efficacy of salvage therapeutic modalities. As such, management options are diverse, ranging from salvage RT, either alone or in combination with androgen ablation therapy, as a definitive therapeutic intervention to expectant management or androgen ablation therapy alone as a palliative treatment.

Management decision must be based on not only tumor factors but also patient factors. Predictive tumor factors for prognosis include Gleason grade of malignancy, initial pathologic stage, surgical margin status, pre-operative PSA level, the time from RP to the first sign of PSA relapse, PSA level prior to salvage radiotherapy, and PSA doubling time. In addition, patient factors associated with life expectancy, such as age, medical co-morbidity, and family history of longevity, must be taken into consideration for management decision, given that the natural course of post-RP PSA relapse is quite heterogeneous and that a patient with PSA relapse is often old and has other medical illness. The heterogeneity of the natural course of post-RP PSA relapse has been reported by Freeland (55). In his study of 379 patients with post-RP PSA relapse who were managed expectantly or androgen ablation therapy only at the time of distant metastasis, significant prognostic factors for prostate cancer-specific mortality were Gleason score, time from surgery to PSA relapse and PSA doubling time. When PSA doubling time was ≥15 months along with Gleason score < 8 and time from surgery to PSA relapse > 3 years, the estimated risk of prostate cancer death at 15 years was only 6%. In contrast, when PSA doubling time was < 3 months in conjunction with Gleason score ≥8 and time from surgery to PSA relapse < 3 years, a median survival was only 3 years and the estimated risk of prostate cancer death at 10 years was 99%. This wide variation in the natural course of post-RP PSA relapse indicates that the management decision for patients with post-RP PSA relapse should be based on not only clinicopathologic features of malignancy but also an individual patient's life expectancy. For example, a conservative management of observation alone with delayed androgen ablation therapy at the of time of distant metastasis or symptomatic local progression can be a reasonable option for a patient with a short life expectancy < 5 years and favorable clinicopathologic features such as a long PSA doubling time. On the other hand, an aggressive salvage therapeutic intervention should be considered for a patient with a life expectancy > 10 years and/or adverse clinicopathologic features such as a short PSA doubling time and a high Gleason score.

There has been no published data of phase III clinical studies demonstrating which therapeutic approach, if any, would prolong life with no significant morbidity for patients with post-RP PSA relapse. Androgen ablation therapy alone is considered palliative, since castration-refractory disease invariably develops in almost all patients. There has been no randomized study that can guide the optimal timing to introduce androgen ablation therapy for patients with post-RP PSA relapse. While there are some retrospective studies suggesting the benefit of early androgen ablation therapy vs. delayed implementation for patients with PSA relapse after primary therapy (56,57), the early institution of androgen ablation therapy should be carefully weighed in due to its potential long-term adverse effects such as lethargy, metabolic syndrome, potential cardiovascular effect, and osteoporosis. There has been no published data from phase III studies to address the effectiveness of salvage RT. It remains uncertain whether salvage RT confers a survival benefit compared with observation or androgen ablation therapy. However, RT is considered the only therapeutic modality that offers a potential of cure for patients with post-RP PSA relapse. Recently, the benefit of salvage RT, compared with expectant management, is suggested by two retrospective studies (58,59). Trock reported, in a series of 635 patients with post-RP PSA relapse, that salvage RT was associated with a statistically significant improvement in both prostate cancer-specific survival and overall survival, in comparison with observation alone. Among 511 patients with no pelvic node metastases, the hazard ratio for prostate cancer-specific death was 0.34 for salvage RT vs. observation alone, and 0.35 for salvage RT plus androgen ablation therapy vs. observation alone (58). Similarly, in a retrospective series of 2,657 patients with post-RP PSA relapse, Boorjian reported that salvage RT was associated with 90% reduction in the risk of local recurrence, 20% reduction in the need of androgen ablation therapy, and 75% decrease in the risk of distant metastasis, in comparison with no salvage RT (59).

Salvage Radiotherapy for PSA Relapse

RT remains the only therapeutic intervention that offers a potential of cure for patients with post-RP PSA relapse. A PSA response rate of salvage RT, defined as any incremental decrease of PSA in response to RT, has been reported up to 90% (60). A high PSA response rate to RT suggests that a majority of patients with post-RP PSA relapse have at least an element of local tumor recurrence at the prostate bed, although they may also have occult distant metastasis simultaneously. A complete PSA response rate, defined as a decline of PSA to an undetectable level, has been reported 57% by Choo (PSA cut-off: $<$ 0.2 ng/mL) (60), and 55% by Stephenson (PSA cut-off: $\leq$0.1 ng/mL) (61). Choo reported that up to 10% of patients did not show any PSA response to RT (60). The most plausible explanation for the lack of PSA response to RT would be the presence of occult nodal or distant metastasis that is beyond the radiotherapy field.

The ability to provide an excellent local tumor control is one of the important factors when salvage RT is considered for patients with post-RP PSA relapse, although it may not be as critical as other end points such as relapse-free and overall survival benefit. Almost all the published studies reported that salvage RT could provide excellent local tumor control at the prostate bed for patients with post-RP PSA relapse including those presenting with clinically palpable local recurrence (60,62,63). Whether equally good local control can be achieved with androgen ablation therapy alone remains unknown. It is worthwhile to note that a few studies reported that RT was effective in controlling local recurrence which had progressed on androgen ablation therapy (64,65).

The ultimate goal of salvage RT is to keep a PSA level undetectable in post-RT follow-up, in which case a claim that salvage RT has been curative can be made. The vast majority of published series evaluating the efficacy of salvage RT have been retrospective studies, and limited by a relatively small sample size, a short follow-up, and inherent shortcomings associated with a retrospective study. Table 1 shows selected studies published in the last 10 years. The outcomes of salvage RT have been variable among published series. The difference in outcomes is, in part, due to the variation in PSA cut-off levels used to define freedom from PSA relapse, and the heterogeneity of patient and tumor characteristics among studies. For example, in the series by Loeb (66), De Meerleer (67), and Stephenson (61), PSA $\geq$0.2 ng/mL followed by another higher value was used for the definition of PSA relapse after salvage RT. On the other hand, Buskirk (68) and Pisansky (69) used a PSA cut-off of $\geq$0.4 and $\geq$0.3 ng/mL for the definition of PSA relapse, respectively. Neuhof (70), and Wiegel (71) used yet another definition for PSA relapse after salvage RT - three consecutive PSA increases. Another significant variation is patient and tumor characteristics among studies. Some series, compared with others, had a higher PSA level prior to salvage RT and a higher proportion of patient with poor prognostic factors such as a high Gleason score, and seminal vesicle invasion. For instance, Leventis reported in a series of 49 patients that a 5-year PSA relapse-free probability after salvage RT was 24%. In his series, median PSA prior to salvage RT was 2.1 ng/mL (72). In contrast, in the Pisansky's series, which reported a 5-year PSA relapse-free probability of 46%, median PSA prior to salvage RT was 0.9 ng/mL (69).

The efficacy of salvage RT for patients with post-RP PSA relapse has been suboptimal, as shown in Table 1. In the pooled data of 17 North American tertiary referral centers, Stephenson examined the efficacy of salvage RT for a retrospective cohort of 1,540 patients with post-RP PSA relapse. With a median follow-up of 53 months, the overall progression-free probability (defined as PSA $<$0.2 ng/mL) at 6 years was 32% (61). In the Buskirk series, the estimated PSA relapse-free rate (defined as PSA $<$0.4 ng/mL) at 8 years was 35% (68). Pazona reported that only 25% remained free of PSA relapse (defined as PSA $<$0.3 ng/mL) at 10 years (73).

Why the efficacy of salvage RT has been mediocre? The main reason stems most likely from the underlying adverse pathologic and/or clinical features that patients with post-RP PSA relapse often possess. In the Stephenson's series (61), 65%, 24%, and 74% of the pooled cohort of 1,540 patients had extracapsular tumor extension, seminal vesicle invasion, and Gleason score $\geq$7, respectively, on RP specimens. In addition, 29% of the patients had persistently detectable PSA after RP. In another salvage RT series by Buskirk (68), 62% and 53% of the patients displayed pT3-T4 disease and Gleason score $\geq$7, respectively, on RP specimens. These underlying adverse pathological features predict inherently aggressive biological disposition with a high probability of developing distant metastasis and locoregional relapse. Thus, it is not a surprise, to some extent, that a significant proportion of patients undergoing salvage RT exhibit a second wave of PSA relapse on a follow-up, even if they initially show a very favorable PSA response to RT.

Many series evaluated prognostic factors for PSA relapse-free outcome following salvage RT. Reported prognostic variables include pathologic stage, seminal vesicle involvement, Gleason score, surgical margin status, the interval between RP and the first sign of PSA relapse, PSA level prior to salvage RT, radiation dose, the use of neoadjuvant and/or concurrent androgen ablation therapy, and PSA doubling time. However, these variables were not consistently reported or correlated with treatment outcomes among published series. One of consistent variables associated with PSA relapse-free outcome has been PSA levels prior to salvage RT. Multiple studies examined various PSA cut-off levels and showed that the lower the PSA level at the time of salvage RT, the better the treatment outcome (61,68-70,72,74-84). No specific PSA cut-off level has been identified as being superior to others at predicting treatment outcome. In the Stephenson's series of the pooled cohort of 1,540 patients, a nomogram was constructed to predict treatment outcomes following salvage RT (61). Significant predictive factors associated with progression-free outcome were PSA levels prior to salvage RT, Gleason grade, PSA doubling time, surgical margin status, androgen ablation therapy before or during RT, and lymph node metastasis. The predictive accuracy of the nomogram as measured by c-index was 0.69 in internal validation. Recently, Moreira reported, using the outcome of

Table 1. Selected series of salvage radiotherapy for PSA relapse after radical prostatectomy

Study	Year	Number of patients	Median radiation dose, Gy	Median follow-up	PSA¶¶ relapse-free rate, %
Stephenson et al (61)	2007	1,540*,†	64.8	53.0 mo	32.0 at 6 yr§§
Stephenson et al (74)	2004	541*,†	64.8	45.0 mo	45.0 at 4 yr
Buskirk et al (68)	2006	368*	64.8	5.0 yr	46.0 at 5 yr
					35.0 at 8 yr
Pazona et al (73)	2005	223*	63.0	56.0 mo	40.0 at 5 yr
					25.0 at 10 yr
Ward et al (96)	2004	211	64.0	4.2 yr	48.0 at 5.0 yr for PSADT*** < 12.0 mo‖‖
					66.0 at 5.0 yr for PSADT > 12.0 mo
Loeb et al (66)	2008	192*	63.0	53.0 mo	56.0 at 5 yr for PSM††† or ECE†††
					26.0 at 5 yr for SVI§§§
Neuhof et al (70)	2007	171*	60.0～66.0 (range)	39.0 mo	42.3 at 3 yr
					35.1 at 5 yr
Maier et al (75)	2004	170*,†	68.0‡	49.0 mo	44.0 at 7 yr
			78.0‖		
Pisansky et al (69)	2000	166*	64.0	52.0 mo	46.0 at 5 yr
Wiegel et al (71)	2009	162	66.6	41.5 mo	54.0 at 3.5 yr
King and Spiotto (76)	2008	122*	67.8	5.0 yr	58.0 at 5 yr for 70 Gy
					25.0 at 5 yr for 60 Gy
Katz et al (91)	2003	115*	66.6	42.0 mo	46.0 at 4 yr
Brooks et al (97)	2005	114*	64.0	6.3 yr	50.0 at 4 yr
					33.0 at 6 yr
Moreira et al (77)	2009	102†	66.0	50.0 mo	57.0 at 6 yr
MacDonald et al (78)	2004	102	66.0	4.2 yr	38.0 at 5 yr
Choo et al (60)	2002	98*,¶	60.0～66.0 (range)	4.2 yr**	26.0 at 4 yr**
				3.3 yr††	39.0 at 4 yr††
				4.0 yr††	14.0 at 4 yr††
Anscher et al (98)	2000	89*	66.0	48.0 mo	50.0 at 4 yr
De Meerleer et al (67)	2008	87*	74.8	30.0 mo	67.0 at 3 yr
					67.0 at 5 yr
Peyromature et al (99)	2003	62	65.0	44.0 mo	42.0 at 5 yr
Song et al (79)	2002	61*	66.6	36.0 mo	39.0 at 4 yr
MacDonald et al (80)	2003	60	64.8	51.0 mo	45.0 at 5 yr
Catton et al (81)	2001	59	60.0	43.0 mo	30.0 at 5 yr for PSA < 2.0
					5.0 at 5 yr for PSA > 2.0
Quero et al (82)	2008	59*	66.0	38.0 mo	56.1 at 3 yr
					41.2 at 5 yr
Sasaki et al (83)	2006	55*	60.0	21.0 mo	60.0 at 3 yr
Chawla et al (100)	2002	54	64.8	45.0 mo	35.0 at 5 yr
De la Taille et al (101)	2002	52*	68.0	27.7 mo	51.0 at 3 yr
Liauw et al (102)	2003	51	65.7	3.8 yr	56.0 at 3 yr
					16.0 at 5 yr
Tomita et al (103)	2009	51*	60.0	36.0 mo	55.1 at 3 yr
Symon et al (84)	2006	50	66.6	39.6 mo	54.0 at 3 yr
Leventis et al (72)	2001	49	66.0	29.2 mo	43.0 at 3 yr
					24.0 at 5 yr
Delongchamps et al (104)	2009	46	72.0	23.0 mo	66.0 at 30 mo
Jacinto et al (105)	2007	43	70.0	26.0 mo	70.7 at 3 yr

*included patients receiving androgen ablation therapy for variable duration in addition to RT, †pooled data from multi-institutions, ‡149 patients with photon irradiation, 21 with a combination of photon and neutron irradiation, §photons, ‖photons plus neutrons, ¶subgroups analyzed separately,**persistently detectable PSA, ††delayed PSA rise, ‡‡local recurrence, §§year, ‖‖month, ¶¶prostate specific antigen, ***prostate specific antigen doubling time, †††positive surgical margin, ‡‡‡extracapsular extension, §§§seminal vesicles invasion.

102 patients treated with salvage RT in other institutions, that the concordance index of the nomogram was 0.65 (77).

Optimal radiation dose required for patients with post-RP PSA relapse remains unknown. Most published studies used a radiation dose <70 Gy for salvage RT, due to the concern for radiation morbidity. It is plausible that a higher radiation dose may yield better treatment outcome. King suggested a dose-response relationship in salvage RT setting (85). He estimated that 66.8 Gy would give a 50% chance of achieving PSA relapse-free rate at 5 years and that the proportional gain in PSA relapse-free rate would be 3.8% per additional Gray within the steep part of the tumor control probability curve. Bernard (86) and King (76) described in their retrospective series that a higher radiation dose was associated with improved PSA relapse-free rates. In recent years, the adaptation of more sophisticated techniques in radiation delivery such as intensity-modulated radiotherapy has allowed escalating radiation dose to the target, while minimizing toxicity to the surrounding normal tissues. De Meerleer recently reported, using intensity-modulated radiotherapy, that a dose of 75 Gy could be delivered with a low risk of serious acute and late radiation toxicity in a salvage RT setting (67).

Toxicity of Salvage RT

Salvage RT to the prostate bed is generally well tolerated with a low risk of severe acute and late gastrointestinal (GI) and genitourinary (GU) toxicity. Most of toxicity information in the literature has been, however, hampered by a retrospective nature of analysis, a small sample size, and the lack of baseline evaluation prior to salvage RT. In the retrospective database of 959 patients who were treated at 11 academic centers with either adjuvant RT or salvage RT (81% treated with salvage RT), 4% and 0.4% had Grade 2 and Grade 3 late GI toxicity at 5 years, respectively, using the Radiation Therapy Oncology Group (RTOG) toxicity scoring system (87). 10% and 1% had Grade 2 and Grade 3 late GU toxicity at 5 years, respectively. Peterson estimated in a retrospective study of 308 patients that the cumulative rate of Grade 3 or 4 late GI or GU complication was 0.7% at 5 years, using the RTOG toxicity scoring system (88).

The comprehensive information on the toxicity of salvage RT has been recently reported by Pearse (89). In this study, which was a phase I/II clinical trial evaluating the efficacy of salvage RT plus 2-year adjuvant androgen ablation therapy for patients with post-RP PSA relapse, acute and late GI and GU toxicity was prospectively assessed using the National Cancer Institute (NCI) Expanded Common Toxicity Criteria version 2 (http://ctep.info.nih.gov). Toxicity assessment was administered prior to salvage RT (baseline), 3 and 6 weeks into RT, 10 weeks after the completion of RT, then four monthly for the first two years, and then six monthly. The study comprised of a cohort of 75 patients treated with radiation doses ranging from 60 Gy to 66 Gy (median: 66 Gy; 2 Gy per fraction). The clinical target volume of radiotherapy was limited to the prostate bed. It noted that 30 patients (40%) had pre-existing GU dysfunction prior to RT, mainly due to urinary incontinence (28/30 patients). Four patients (5%) experienced Grade 3 acute GI or GU toxicity. With the median follow-up of 45.1 months, cumulative incidences of Grade 3 late GI and GU toxicity at 36 months were 1.6% and 2.6%, respectively; 8.7% and 22.6% for Grade ≥ 2 late GI and GU toxicity, respectively. None had Grade 4 late toxicity. The severity of acute GU toxicity (Grade <2 vs. ≥ 2) was a significant predictor factor for Grade ≥ 2 late GU toxicity after adjusting for pre-existing GU dysfunction. Five patients (7%) reported Grade 3 late GI or GU toxicity. One patient had Grade 3 radiation proctitis requiring argon plasma coagulation. Two patients developed self-limiting gross hematuria. One patient had Grade 3 incontinence at baseline, which persisted throughout the follow-up. The remaining one patient developed Grade 3 urinary frequency and Grade 3 urethral stricture requiring dilatation.

Compromising urinary continence and exacerbating urethral stricture by RT are major concerns to both patients and clinicians, given that patients may have already suffered some degree of urinary incontinence and/or urethral stricture after surgery. The prevalence of pre-existing urinary incontinence prior to salvage RT was illustrated by the Pearse's series (89), in which 28/75 patients (37%) reported Grade 1 to 3 incontinence before salvage RT. The study reported that the cumulative incidence of urinary incontinence at 36 months was 16.8% for Grade ≥ 2 incontinence, and that pre-existing urinary incontinence was associated with a higher incidence of Grade ≥ 2 incontinence at 36 months (35.0% for patients with pre-existing incontinence vs. 9.6% for patients with complete continence at baseline) (89). Pearse also examined the prevalence of urinary incontinence at one specific time point of follow-up. At 30-month post-RT, 71 patients were available for this analysis. Of these patients, 45 were fully continent at baseline, and 26 had some degree of underlying urinary incontinence (23 with Grade 1, 2 with Grade 2, and 1 with Grade 3) prior to salvage RT. Of the 45 patients with complete continence at baseline, 31 remained totally continent, while 13 had Grade 1 and 1 had Grade 2 incontinence at 30 months. None had Grade 3 incontinence. Of the 26 patients with pre-existing incontinence prior to salvage RT, incontinence was unchanged in 11, worsened in 2, and improved in 13 at 30 months (89).

Salvage Radiotherapy Plus Androgen Ablation Therapy for PSA Relapse

There has been a paucity of data in the literature examining the efficacy of a combined approach of salvage RT plus androgen ablation therapy. Furthermore, there has been no published phase III study demonstrating the benefit of adding androgen ablation therapy to salvage RT for patients with post-RP PSA relapse.

Choo recently reported the outcome of a phase I/II study evaluating the combined approach of salvage RT plus 2-year androgen ablation

therapy (90). In the study, a total of 75 patients with post-RP PSA relapse were treated with salvage RT followed by 2-year androgen ablation therapy. Androgen ablation therapy started within 1 month after the completion of salvage RT, and consisted of nilutamide for 4 weeks and buserelin acetate depot for 2 years. All completed RT. Sixty-five patients completed the planned 2-year of androgen ablation therapy, while 10 terminated it prematurely. The median duration of androgen ablation therapy for these 10 patients was 19 months. The median age of the cohort was 63 years at the time of salvage RT. The study used a PSA rise above 0.2 ng/mL with two consecutive increases over a minimum of three months as the definition of PSA relapse post-therapy. All achieved initially complete PSA response (< 0.2 ng/mL) with the protocol treatment. With the median follow-up of 6.4 years (range: 2.0～9.8) from salvage RT, the study reported that a relapse-free rate including the freedom from PSA relapse was 91.5% at 5 years and 78.6% at 7 years, and overall survival rate was 93.2% at both 5 and 7 years. These study outcomes were encouraging and more favorable than those of published series of salvage RT alone. A confirmatory phase III or another large prospective study is, however, needed to demonstrate the benefit of adding androgen ablation therapy to salvage RT.

There have been a few retrospective studies, which suggested a possible benefit of adding androgen ablation therapy to salvage RT. Katz reported in a retrospective series of 115 patients that a PSA relapse-free rate at 4 years appeared better for 45 patients receiving a median duration of 3 months of neoadjuvant androgen ablation therapy prior to salvage RT, compared with 70 patients treated with salvage RT alone (59% vs. 39%) (91). In another retrospective study with a median follow-up of 38 months, Tiguert reported that a 5-year PSA relapse-free rate was 50% at 5 years for 81 patients treated with 3 months of neoadjuvant androgen ablation therapy followed by salvage RT (92). King compared treatment outcomes between salvage RT plus 4-month androgen ablation therapy (2-month before and 2-month during RT) and salvage RT alone in a retrospective study of 122 patients (93). A 5-year PSA relapse-free rate was better for those treated with salvage RT plus 4-month androgen ablation therapy than for those receiving salvage RT alone (57% vs. 31%). In a retrospective series of 71 patients undergoing salvage RT, Taylor explored a potential benefit of adding adjuvant androgen ablation therapy to salvage RT (94). In his series, 35/71 received adjuvant androgen ablation therapy for a median duration of 24 months. The study reported, with a median follow-up of 39 months, that a 5-year PSA relapse-free rate was 81% for patients receiving adjuvant androgen ablation therapy, compared with 54% for those treated with salvage RT alone.

Past and Current Phase III Studies for PSA Relapse

The Radiation Therapy Oncology Group completed a phase III clinical trial (RTOG 9601) comparing salvage RT with salvage RT plus 2 years of a high dose bicalutamide (150 mg per day) for patients with post-RP PSA relapse. The study closed in 2003 after accruing a total of 840 patients. Its outcome is pending at present. Currently, the RTOG is conducting another phase III, 3-arm, study (RTOG 0534) to examine the potential benefit of adding 4～6 months of androgen ablation therapy to salvage RT and to address a potential role of treating pelvic lymph nodes. The United Kingdom is conducing a phase III study called RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery), and part of this study is to assess the benefit of adding 6-month or 24-month androgen ablation therapy to salvage RT. The Japan Clinical Oncology Group is conducting a phase III study comparing androgen ablation therapy alone with salvage RT+/− androgen ablation therapy (androgen ablation therapy limited to patients with PSA relapse after salvage RT) (95). A French group is conducting a phase III study comparing salvage RT with salvage RT plus 6-month androgen ablation therapy (Clinical Trials Gov. Identifier: NCT00423475).

Future Directions

There is a need to further study radiological means and molecular markers that can separate local tumor recurrence from regional or distant metastasis for patients with PSA relapse. These tools will assist clinicians to identify patients who are likely to benefit from definitive local salvage treatment such as radiotherapy, while sparing those least likely to benefit. In addition, molecular markers, along with clinicopathologic features, which can separate indolent disease from biologically aggressive disease that is likely destined to progress need to be explored to facilitate an individualized management decision.

For salvage RT, further study is needed to address optimal radiation dose required for patients with PSA relapse. In parallel, more advanced techniques in radiation simulation and delivery need to be explored in order to minimize radiation toxicity to the surrounding normal tissues, while escalating radiation dose to the target. Another unresolved question is whether regional pelvic nodes should be irradiated along with the prostate bed, and the current RTOG 0534 study is addressing this question.

Strategies that optimize the control of systemic disease and the local prostate bed need to be explored, particularly for patients with adverse clinicopathologic features such as a high Gleason score, a short PSA doubling time, and a high PSA level at the time of salvage RT. The efficacy of salvage RT alone for patients with adverse clinicopathologic features has been suboptimal in spite of a high initial PSA response rate and an excellent local control achieved by RT. The limited efficacy of salvage RT is likely, in part, due to occult distant metastasis at the time of referral for salvage RT and/or radio-resistant clones. Thus, therapeutic approaches that target occult systemic disease as well as the local prostate bed need to be examined. Such approaches include combining androgen ablation therapy and/or chemotherapy with salvage RT.

Conclusion

PSA relapse after RP presents a difficult clinical dilemma for both patients and clinicians. For the patient, it is a sign that the initial surgery was not successful and brings a sense of anxiety and burden to consider a second-line therapy. For the clinician, it presents management challenges that do not have definitive answers to many unresolved questions. In particular, management decision has been complicated by a wide variation in the natural course of post-RP PSA relapse and the lack of clear evidences demonstrating which therapeutic approach, if any, prolongs life with no significant morbidity.

RT has been the main therapeutic modality with a curative potential for patients with post-RP PSA relapse. Its efficacy has been, however, adversely affected by the underlying adverse pathological and/or clinical features that patients with post-RP PSA relapse often present with. Clinical studies are in progress to evaluate various therapeutic approaches including a combined approach of salvage RT plus androgen ablation therapy.

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