Review Article

Salvage radiotherapy following radical prostatectomy

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Abstract: Recurrent disease following radical prostatectomy will occur in approximately 20% of patients, for whom the therapeutic options include surveillance, salvage radiotherapy, or hormonal therapy. This review will focus on the evidence for salvage radiotherapy. Efficacy results of 30–50% have been reported from multiple retrospective series, with minimal morbidity. Unfortunately there are no randomized or prospective studies in this area. Results of salvage radiotherapy improve when given earlier, ideally with the serum prostate-specific antigen < 1 ng/mL. Other positive prognosticators are positive margins at radical prostatectomy, longer prostate-specific antigen doubling times, lower radical prostatectomy Gleason scores, and the absence of lymph node metastases. Current standard dosage is 64 Gy or slightly higher, although the optimal dosage has yet to be defined with prospective randomized trials. Salvage radiotherapy can provide a durable response when given early, and patients with recurrent disease should be considered for treatment or enrolment in clinical trials.

Key words: prostate-specific antigen failure, prostatectomy, prostatic neoplasms, radiotherapy, recurrence, salvage therapy.

Introduction

Radical prostatectomy is one of the most common procedures for the treatment of localized prostate cancer.¹ In modern series, the long term recurrence rates following radical prostatectomy are in the range of 17–29%,²⁻⁵ with most recurrences being detected by prostate-specific antigen (PSA) failure. The current treatment options available for patients with PSA recurrence following radical prostatectomy are salvage radiotherapy, immediate or delayed androgen deprivation therapy, or finally surveillance. Newer, experimental therapies such as salvage high intensity focused ultrasound (HIFU) have also been reported,⁶ but require further study before being offered widely. For patients with a good life expectancy, salvage radiotherapy (SRT) is the only option which is potentially curative. The difficulty for the clinician, however, is in trying to judge whether the patient has local or distant failure, as this will influence the outcome of SRT for presumed local failure.

The goal of salvage radiotherapy is to obtain local control and to prevent or delay distant failure with the subsequent risk of death. There are no randomized or prospective studies on the use of SRT, therefore management decisions have to be based on the available retrospective published reports. Not surprisingly, there is little agreement on the optimal management of patients with PSA failure following radical prostatectomy among radiation oncologists and urologists.⁷,⁸

Recent large retrospective studies have added to the existing published reports and provide guidance using nomograms to predict the outcome of SRT.⁹ This article will review the available evidence for SRT, the current guidelines for the management of PSA failure and ongoing clinical trials that may provide more definitive data on the long-term outcomes following SRT.

Methods

A literature search was conducted in MEDLINE including Pre-MEDLINE (1950 to April 2008), EMBASE (1980 to April 2008), the Cochrane Central Register of Controlled Trials (1st Quarter, 2008) and included a combination of exploded and non-exploded subject headings and free text words, such as but not limited to: prostatic neoplasms; prostatic intraepithelial neoplasia; prostatectomy; radiotherapy; salvage therapy; combined modality therapy; prostate cancer; prostatic carcinoma; prostate tumor; prostatic neoplasm; metastatic prostate; prostate adenocarcinoma; prostate adenoma; prostate malignancy; prostatectomy; prostate surgery; beam radiotherapy; external beam irradiation; external beam radiation; external beam therapy; salvage radiotherapy. The searches were restricted to studies published in the English language. Case reports, letters and editorials were excluded. The search strategy was modified for each database using suitable terms and fields for a particular database. The bibliographies of relevant retrieved articles and reviews were also examined for additional studies. A total of 2627 records were identified, of which 1025 were duplicate studies; 89 studies were included in the final analysis.

Natural history of biochemical failure following radical prostatectomy: Is there a need to treat patients?

The landmark paper from Pound et al. showed that the median time from PSA relapse to the development of metastasis, without any additional therapy, was 8 years; and then a further 5 years from metastasis to death.¹⁰ Thus, it is clear that the natural history of PSA relapse following radical prostatectomy is that of a protracted course. Several large series have made it clearer that at the 10-year mark after PSA relapse, the majority of patients will not have metastases.⁴,¹¹

In a recent update¹² of the original work by Pound et al., the median time to death had not been achieved at 16 years of follow up and the 15-year cause specific survival from the time of biochemical recurrence was 55%. However, not all patients will follow a protracted course. In patients with Gleason 8–10 disease and a short PSA doubling time (PSADT), the median metastasis free survival is reduced to 3 years.
Patient selection for SRT: Who is the ideal patient?

In general, increasing levels of PSA above 0.2 ng/mL are considered to represent evidence of biochemical failure.\textsuperscript{13,14} The utility of restaging investigations when serum PSA values are below 5 ng/mL is low.\textsuperscript{15,16} For most patients with PSA failure that is detected when the PSA initially rises (i.e. less than 2 ng/mL), it is likely that digital rectal examination (DRE), computerized tomography (CT), and bone scan will be normal, unless there is a rapid rise or clinical findings.\textsuperscript{17} Recently there has been increasing interest in the use of indium-capromab pendetide (ProstaScint) scanning prior to salvage therapy.\textsuperscript{18,19} However, a recent study from Nagda \textit{et al.} with long term follow up showed the low positive predictive value of the capromab pendetide scan.\textsuperscript{20}

There is currently no evidence to recommend a threshold PSA level at which point restaging investigations should be carried out in the context of PSA failure following radical prostatectomy.

Numerous studies have shown that the best outcome for SRT is when it is given at low PSA values, preferably under 1 ng/mL.\textsuperscript{21–25} Presumably this is when the tumor burden is the lowest, and is before metastatic spread has occurred. The most recent paper from Stephenson \textit{et al.} showed that a durable 6-year response is achieved in approximately 50% of patients if treatment was commenced at PSA levels \(\leq 0.5\) ng/mL.\textsuperscript{9} Other important determinants of SRT results are Gleason grade, PSA doubling time, surgical margins, and seminal vesicle invasion.\textsuperscript{9,21,24,26}

In summary, the ideal patient would have evidence of local failure with biochemical recurrence occurring >3 years after radical prostatectomy, Gleason score <8, positive surgical margins, a PSA doubling time of over 1 year, no seminal vesicle involvement, no lymph node involvement, and SRT to be initiated before the PSA is over 1 ng/mL.\textsuperscript{27} However, Stephenson \textit{et al.} have shown favorable response rates in high risk patients (e.g. short PSA doubling time and high Gleason grade) when SRT was given at PSA levels <0.5 ng/mL.\textsuperscript{9}

Efficacy of salvage radiotherapy

There have been no prospective studies of SRT and there are only six studies with more than 100 patients (Table 1).

The 5-year actuarial biochemical control rates range from 10–66\%,\textsuperscript{10–36} although methodologically, it is difficult to compare studies as evidenced by the disparity in the published results. The studies have different patient populations (e.g. rapid PSADT vs. slow PSADT), treatment methods (e.g. radiotherapy dosage) and definitions of treatment failure.

The largest study is a multi-institutional, retrospective cohort of 1540 patients who were treated with SRT between 1987 and 2005 at 17 North American tertiary referral centers,\textsuperscript{9} with a median follow up of 53 months. This cohort was created for the purpose of developing a nomogram to predict outcomes following SRT. Patients who received adjuvant hormonal therapy were excluded from the original dataset. Disease progression after SRT was defined as a serum PSA of <0.2 ng/mL or more above the post radiotherapy nadir followed by another higher value, a rising PSA, or the initiation of additional treatment. The overall 6-year progression free probability (PFP) was 32%; however, when treated at PSA levels \(\leq 0.5\) ng/mL, the PFP was 48%, as compared to 18% if treated when the PSA was >1.5 ng/mL. Other factors that favored longer progression free probability were positive margins at radical prostatectomy, lower Gleason scores, and longer PSADT. The main limitation of this study is the fact that it was

<table>
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a retrospective cohort spanning an 18-year period with no standardized treatment fields, dosages and follow up.

Numerous smaller studies, not listed in Table 1, have found similar results.47–59

**Toxicity of SRT**

The toxicity of SRT can be subdivided into genitourinary (GU) toxicity and gastrointestinal (GI) toxicity primarily, but the rare but potentially lethal possibility of secondary pelvic malignancies needs to also be remembered. Most published series have reported low rates of toxicity, which has been attributed to the low dosage usually used when compared with radiotherapy on the intact prostate.

Two recent publications have focused on the toxicity of SRT. Jung et al. have reported on the toxicity of high dose salvage radiotherapy, using dosages of 70.2 Gy60 in 30 patients with a median follow up of 21 months. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and the AUA Symptom Index (AUASI). The CTCAE grades run from grade 1 (mild) to grade 5 (death). They found the median change in AUASI was 3, while GI toxicity was noted to be mainly mild, with nine patients developing diarrhea (31%) and 12 patients (41%) developing grade 1 or 2 proctitis. No grade 3 or higher toxicity was noted.

The largest study focusing on the toxicity of SRT was a multi-institutional retrospective database of 959 patients who were treated at 11 academic centers with either adjuvant radiotherapy (ART) or salvage radiotherapy,61 which was created in order to try to find predictive factors for GI or GU toxicity. The majority of patients in this database (81%) were treated with SRT. Toxicity was graded using standard criteria from the Radiation Therapy Oncology Group (RTOG). Unfortunately, these grading systems do not include urinary incontinence, and so this was dependant on the practice at each individual institution. Overall, they found that 11% of SRT patients had grade 2 or higher late GU toxicity at 5 years, and 4.7% of patients (both SRT and ART) had grade 2 or higher late GI toxicity. On multivariate analysis, they found that adjuvant radiotherapy, androgen deprivation, and prostate bed-only RT were significant predictors of GU toxicity. There were no factors predictive of GI toxicity. These toxicity results, as they are pooled from multiple institutions, are likely to be as representative a sample as can be obtained in a retrospective fashion; the main limitation of this study is its retrospective nature and the fact that the scoring of urinary incontinence was not consistent.

Previously published reviews62–66 have found long term rates of GU toxicity (≥ grade 2) to be in the range of 0–10%,61,62,65–78 and GI toxicity rates (≥ grade 2) in the range of 0–10%.54,65,66,77,78

Several studies have looked at health related quality of life outcomes following SRT. Namiki et al. did a prospective study using the Medical Outcomes Study 36-Item Short Form version (SF-36) and the University of California, Los Angeles Prostate Cancer Index (UCLA PCI), given prior to radical prostatectomy and 24 months after radical prostatectomy.79 They found no difference in the urinary and bowel domains between those patients treated with salvage therapy versus those who had no recurrence after radical prostatectomy. The SRT group, however, did worse in mental health, sexual function and social function. Several other studies have reported similarly minor health related quality of life changes after SRT.80–82

In summary, as there have been no prospectively collected datasets, the toxicity reports of SRT series need to be viewed carefully, as it is likely to be under reported; no cases of severe acute toxicity are reported, and, in general, the late toxicity results appear to be mild.

**Nomograms**

Stephenson et al. have developed a nomogram to predict the outcome of SRT using a multi-institutional cohort of 1540 patients, with a concordance index of 0.69.83 Statistically significant variables in the model were PSA level before SRT, prostatectomy Gleason grade, PSADT, surgical margins, androgen deprivation therapy given before or during SRT and lymph node metastasis. There is no absolute level at which SRT should be denied to a patient, but rather the results from the nomogram can be used as part of the clinical decision-making process when counseling the patient about the likely outcome of SRT. Furthermore, patients with a poor probability of response may be considered for entry into clinical trials.

**Randomized trials with adjuvant radiotherapy**

The Southwest Oncology Group (SWOG) study 8794 was a randomized trial involving 425 post-radical prostatectomy patients with pT3 who were randomized to either adjuvant radiotherapy or observation plus usual care, which included SRT.84 This study was designed to show a reduction in metastasis free survival. Ultimately, it was a negative study, as no difference in survival was found. There was, however, an improvement in biochemical relapse rates.

The European Organization for Research and Treatment of Cancer (EORTC) study 22 911 also involved post-radical prostatectomy patients with pT3 disease. A total of 1005 patients were randomized between adjuvant RT and ‘wait and see’ policy. They found benefits in terms of biochemical control,84 but not in terms of overall survival, for which longer follow up is required. SRT was used in the ‘wait and see’ arm; however, it was for local recurrence rather than PSA recurrence. As such, this study did not truly represent a comparison between adjuvant RT and ‘wait and see’ approach, as current ‘wait and see’ strategies would involve early salvage RT for PSA recurrence.

**Dosage of salvage radiotherapy**

King et al. compared the outcomes of 38 patients treated with 60 Gy to 84 patients treated with 70 Gy. They found a significantly higher 5-year biochemical control rate of 25–58% with the higher dose of 70 Gy.85 A recent review of the published reports on dose escalation for SRT concluded that there was sufficient evidence to justify a trial comparing 64 Gy to 70 Gy.86

Nevertheless, the current American Society for Therapeutic Radiology and Oncology (ASTRO) guidelines recommend a dose of 64 Gy or slightly higher.87

**Current recommendations from major consensus panels**

The European Association of Urology (EAU) 2007 guidelines recommend SRT when there is evidence of local recurrence, with a dose of 64–66 Gy at a serum PSA level of ≤1.5 ng/mL (http://www.uroweb.org/fileadmin/user_upload/Guidelines/07_Prostate_Cancer_2007.pdf). (grade B recommendation) The American Urological Association has recently updated its prostate cancer guidelines (http://www.auanet.org/guidelines/main_reports/proscan07/content.pdf); however, the new guidelines do not give any recommendations on the role of SRT. The National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf) suggest that SRT be considered in patients with biochemical failure who meet...
the suggestions from Stephenson et al.26 The NCCN are cautious, however, as previous randomized trials of adjuvant RT have not shown a survival benefit.

**Current trials and future directions**

The University of Michigan Comprehensive Cancer Center is running a phase II trial looking at SRT and docetaxel (weekly during radiation therapy) for PSA failure after radical prostatectomy (http://clinicaltrials.gov/show/NCT00480857). The primary outcome for this trial is the progression free proportion of patients with an estimated completion in 2014.

The Japan Clinical Oncology Group is running a trial comparing radiation therapy followed by endocrine therapy versus endocrine therapy alone for PSA failure after radical prostatectomy.27 RADICALS is a large scale randomized trial aiming to recruit over 4000 patients.27 This study commenced in 2007 and aims to address two separate issues: the timing of post-radical prostatectomy RT (adjuvant versus early salvage) and the use of concomitant androgen deprivation therapy (none versus short-term versus long-term).

‘Radiation Therapy With or Without Goserelin in Treating Patients Who Have Undergone Surgery for Recurrent or Refractory Prostate Cancer’ is a phase III randomized trial that started in October 2006 (ClinicalTrials.gov Identifier: NCT00423475), aiming to recruit 466 patients. Inclusion criteria for this trial are patients who have had a previous radical prostatectomy with a postoperative undetectable PSA and then a subsequent PSA failure. Patients must have a PSA ≥0.2 ng/mL and <2 ng/mL at study entry. This study aims to answer the question of whether or not to give systemic hormonal therapy at the time of SRT.

**Conclusions**

There is currently a lack of good quality data on SRT; however, based on the available retrospective series, all patients with PSA failure following radical prostatectomy should be considered for SRT when the serum PSA levels are <1.0 ng/mL. Gleason score, PSADT, and time to relapse are helpful to predict the outcome of SRT, which is in general well tolerated.

**References**

Salvage radiotherapy


