Salvage radiotherapy after radical prostatectomy

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Introduction

In modern series, the long-term recurrence rates after radical prostatectomy are in the range of 17%–29%,[1–4] with most recurrences detected by prostate-specific antigen (PSA) failure. For patients with adverse pathological features, the risk of recurrence is about 40%. The goal of salvage radiotherapy is to obtain local control and to prevent or delay metastases with the subsequent risk of death. There are no randomized or prospective studies on the use of salvage radiotherapy; therefore management decisions have to be based on the available retrospective literature. Not surprisingly, there is little agreement among radiation oncologists and urologists on the optimal management of patients with PSA failure after radical prostatectomy.[5–7] Furthermore, there is controversy regarding whether adjuvant or salvage radiotherapy is the optimal curative strategy for patients with adverse pathological features after radical prostatectomy.

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

The landmark paper from Pound and colleagues[8] showed that the median time from PSA relapse to the development of metastasis, without any additional therapy, was 8 years, with a further 5 years from metastasis to death. Thus it is clear that the natural history of PSA relapse after radical prostatectomy is that of a protracted course. Several large series have made it clearer that at the 10-year mark after PSA relapse, most patients will not have metastases.[3,9]

In a recent update[10] of the original work by Pound and colleagues, 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 grade 8–10 disease and a short PSA doubling time (PSADT), the median metastasis-free survival is reduced to 3 years.

Patient selection for salvage radiotherapy: Who is the ideal patient?

In general, increasing levels of serum PSA above 0.2 μg/L are considered to represent evidence of biochemical failure.[11] The utility of restaging investigations when serum PSA values are below 5 μg/L is low.[12,13] For most patients with PSA failure that is detected when the serum PSA level initially rises, it is likely that the results of digital rectal examination, computed tomography and bone scan will be normal. Recently there has been increasing interest in the use of indium-capromab pendetide (ProstaScint) scanning before salvage therapy.[14,15] However, a recent study from Nagda and colleagues[16] with long-term follow-up showed the low positive predictive value of the indium-capromab pendetide scan.

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

Numerous studies have shown that the best outcome for salvage radiotherapy occurs when it is administered at low serum PSA values, preferably under 1 μg/L.[17–21] Presumably this is when the tumour burden is the lowest, and is before metastatic spread has occurred. The most recent paper from Stephenson and colleagues[5] showed that a durable 6-year response was achieved in about 50% of patients if treatment was commenced at serum PSA levels of 0.5 μg/L or less. Other important determinants of salvage radiotherapy results are Gleason grade, PSADT, surgical margins and seminal vesicle invasion.[7,17,20–22]

In summary, the ideal patient would have evidence of local failure with biochemical recurrence occurring more than 3 years after radical prostatectomy, a Gleason grade of less than 8, positive surgical margins, a PSADT of more than 1 year, no seminal vesicle involvement, no lymph node involvement and salvage radiotherapy to be initiated before the serum PSA level was greater than 1 μg/L.[23] However, Stephenson and colleagues[5] have shown favourable response rates in high-risk patients (e.g., short PSADT and high Gleason grade) when salvage radiotherapy was administered at serum PSA levels of less than 0.5 μg/L.

Efficacy of salvage radiotherapy

There have been no prospective studies of salvage radiotherapy and there are only 6 studies with more than

100 patients.[5,17,21,22,24,25] The 5-year actuarial biochemical control rates range from 10% to 66%,[26,27] 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 v. 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 salvage radiotherapy between 1987 and 2005 at 17 North American tertiary referral centres with a median follow-up of 53 months.[5] Patients who received adjuvant hormonal therapy were excluded from the original data set. Disease progression after salvage radiotherapy was defined as a serum PSA level of 0.2 μg/L or greater above the postradiotherapy nadir followed by another higher value, a rising serum PSA level or the initiation of additional treatment. The overall 6-year progression-free probability was 32%; however, when treated at serum PSA levels of less than 0.5 μg/L, the progression-free probability was 48%, as compared with 18% if treated when the serum PSA level was greater than 1.5 μg/L. Other factors that favoured longer progression-free probability were positive margins at radical prostatectomy, lower Gleason grades and longer PSADTs. The main limitation of this study is the fact that it was a retrospective cohort spanning an 18-year period with no standardized treatment fields, dosages and follow-up. Numerous smaller studies have found similar results.[28–40]

Toxicity of salvage radiotherapy

The toxicity of salvage radiotherapy can be subdivided primarily into genitourinary (GU) toxicity and gastrointestinal (GI) toxicity. However, the rare but potentially lethal possibility of secondary pelvic malignancies must 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 salvage radiotherapy. Jung and colleagues[41] have reported on the toxicity of high-dose salvage radiotherapy, using dosages of 70.2 Gy 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 American Urology Association Symptom Index (AUASI). The CTCAE grades run from grade 1 (mild) to grade 5 (death). The authors found the median change in AUASI was 3, and GI toxicity was noted to be mainly mild, with 9 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 salvage radiotherapy was a multi-institutional retrospective database of 959 patients who were treated at 11 academic centres with either adjuvant radiotherapy or salvage radiotherapy,[42] which was created to try to find predictive factors for GI or GU toxicity. The majority of patients in this database (81%) were treated with salvage radiotherapy. Toxicity was graded using standard criteria from the Radiation Therapy Oncology Group. Unfortunately, these grading systems do not include urinary incontinence, and so this was dependent on the practice at each individual institution. Overall, the authors found that 11% of salvage radiotherapy patients had grade 2 or higher late GU toxicity at 5 years, and 4.7% of patients (both salvage and adjuvant radiotherapy) had grade 2 or higher late GI toxicity. On multivariate analysis, the authors found that adjuvant radiotherapy, androgen deprivation and prostate bed–only radiotherapy 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 was its retrospective nature and the fact that the scoring of urinary incontinence was not consistent.

Previously published reviews[43–45] have found long-term rates of GU toxicity (≥ grade 2) to be in the range of 0%–10%,[32,33,46–58] and GI toxicity rates (≥ grade 2) in the range of 0%–10%.[46,47,58–60]

Several studies have looked at health-related quality of life outcomes after salvage radiotherapy. Namiki and colleagues[61] did a prospective study using the Medical Outcomes Study 36-Item Short Form Health Survey and the University of California, Los Angeles Prostate Cancer Index, administered before radical prostatectomy and 24 months after. They found no difference in the urinary and bowel domains between those patients treated with salvage radiotherapy versus those who had no recurrence after radical prostatectomy. The salvage radiotherapy group did worse, however, in mental health, sexual function and social function. Several other studies have reported similarly minor health-related quality of life changes after salvage radiotherapy.[62–64]

In summary, as there have been no prospectively collected data sets, the toxicity reports of salvage radiotherapy series need to be viewed carefully, as toxicity is likely to be underreported. No cases of severe acute toxicity are reported, and, in general, the late toxicity results appear to be mild.

Nomograms

Stephenson and colleagues[5] have developed a nomogram to predict the outcome of salvage radiotherapy using a multi-institutional cohort of 1540 patients, with a concordance index of 0.69. Statistically significant variables in the model were serum PSA level before salvage radiotherapy, prostatectomy Gleason grade, PSADT, surgical margins, androgen deprivation therapy administered before or during salvage radiotherapy, and lymph node metastasis. There is no absolute level at which salvage radiotherapy 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 counselling the patient about the likely outcome of salvage radiotherapy. 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 pT3N0M0 who were randomly assigned to either adjuvant radiotherapy or observation plus usual care, which included salvage radiotherapy.[65] This study was designed to show a reduction in metastasis-free survival. Extracapsular extension or positive surgical margins, seminal vesicle invasion and all 3 adverse histological features were present in 67%, 33% and 22% of patients, respectively. Ultimately, it was a negative study, as no difference in survival was found. Total urinary incontinence was more frequent in the adjuvant radiotherapy group (6.5% v. 2.8%), but this was not statistically significant ($p = 0.11$). However, the incidence of urethral stricture was significantly more in the adjuvant radiotherapy group (17.8% v. 9.5%, $p = 0.02$).

With extended follow-up of patients in the SWOG study 8794, Thompson and colleagues[66] have recently reported that adjuvant radiotherapy significantly reduces the risk of metastases and increases survival. It is important to note that about 33% of patients had a detectable serum PSA level of 0.2 μg/L or greater after surgery; a significant number of patients did not undergo central pathological review; of the 211 men randomly asssigned to observation, only 70 ultimately received salvage radiotherapy; and more patients in the observation arm had higher Gleason grades of 7 to 10. Also, of the men who received salvage radiotherapy, 37% of the treatments were for objective recurrences other than a detectable serum PSA level. The serum PSA level for men receiving salvage radiotherapy for PSA failures alone was not reported. Therefore, there were many factors that may have biased the study results in favour of adjuvant radiotherapy. Furthermore, the study did not contribute any reliable data that can be used to compare adjuvant radiotherapy with the current recommended salvage radiotherapy, whereby patients should initiate salvage radiotherapy when the serum PSA level is less than 0.5–1.0 μg/L and there is no other clinical evidence of disease recurrence.

The European Organization for Research and Treatment of Cancer (EORTC) study 22911 also involved post–radical prostatectomy patients with pT3 disease.[67] Capsular perforation, seminal vesical invasion and positive surgical margins were present in 77%, 25.5% and 63% of patients, respectively. The postoperative serum PSA level remained greater than 0.2 μg/L in 10.7% of patients. A total of 1005 patients were randomly assigned between adjuvant radiotherapy and a "wait and see" policy. The investigators found adjuvant radiotherapy benefited patients in terms of biochemical control, but not in terms of overall survival, for which longer follow-up is required. Salvage radiotherapy 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 radiotherapy and a "wait and see" approach, as current "wait and see" strategies would involve early salvage radiotherapy for PSA recurrence. Further criticism for either the SWOG[65,66] or EORTC[67] trials to add to our understanding of the superiority of adjuvant or salvage radiotherapy is hampered by the fact that these trials were initiated in the pre-PSA era and conducted without the contemporary PSA follow-up patients undergo today.

In both the EORTC[67] and SWOG[65] trials, low-grade, nonurinary morbidity was significantly more frequent in the adjuvant radiotherapy group. In both trials, grades 1–3 late effects were more frequent in the adjuvant radiotherapy group (e.g., SWOG trial 23.8% v. 11.9%) with rectal complications, such as proctitis and bleeding, occurring in 3.3% of the adjuvant radiotherapy group.

Dosage of salvage radiotherapy

King and Spiotto[68] compared the outcomes of 38 patients treated with 60 Gy to the outcomes of 84 patients treated with 70 Gy. They found a significantly higher 5-year biochemical control rate of 25% to 58% with the higher dose of 70 Gy. A recent review of the literature on dose escalation for salvage radiotherapy concluded that there was sufficient evidence to justify a trial comparing 64 Gy with 70 Gy.[69]

Nevertheless, the current American Society for Therapeutic Radiology and Oncology guidelines recommend a dose of 64 Gy or slightly higher.[70]

Adjuvant versus salvage radiotherapy

Adjuvant and salvage radiotherapy have not been compared in a well-designed, prospective, controlled trial. Retrospective data are available;[27,37,44,70–72] however, no definitive conclusions can be made. A recent study by Trabulsi and colleagues[73] attempted to provide data on this question with a retrospective case-matched study from a multi-institutional database. Unfortunately because of its retrospective design, it did little to provide data to further answer this question. In the absence of level I evidence showing the superiority of a salvage or adjuvant radiotherapy strategy, arguments can be made for either.

Based on the presented data there are arguments in favour of a salvage radiotherapy strategy. The efficacy of salvage radiotherapy appears to be equivalent to that of adjuvant radiotherapy when applied for biochemical failure after surgery, especially when serum PSA levels are 0.5 μg/L or less. In the current PSA era, patients are followed up at intervals that will allow detection of a serum PSA level of 0.5 μg/L or less after radical prostatectomy. Salvage radiotherapy strategies also avoid the administration of radiotherapy to those that are not destined to have disease recurrence. Furthermore, there is level I evidence indicating that morbidity is greater with adjuvant radiotherapy, in particular the high rate of urethral stricture development, and a salvage radiotherapy strategy will minimize this postradiotherapy morbidity. In addition, a salvage radiotherapy approach will maximize erectile function in men who have undergone nerve-sparing radical prostatectomy. A salvage radiotherapy strategy may also be more cost-effective. Lastly, for men with a positive margin as their only adverse pathological finding, the survival is outstanding with surgery alone and we should not be too aggressive with therapy without definitive evidence showing a survival benefit with adjuvant radiotherapy.

Current recommendations from major consensus panels

The European Association of Urology 2007 guidelines recommend salvage radiotherapy when there is evidence of local recurrence, with a dose of 64–66 Gy at a serum PSA level of 1.5 μg/L or less[74] (grade B recommendation). The American Urological Association has recently updated its prostate cancer guidelines;[75] however, the new guidelines do not give any recommendations on the role of salvage radiotherapy. The National Comprehensive Cancer Network guidelines[76] suggest that salvage radiotherapy be considered in patients with biochemical failure who meet the criteria from Stephenson and colleagues.[22] The Genito-Urinary Radiation Oncologists of Canada consensus meeting resulted in recommendations that all patients with biochemical relapse or a persistent detectable PSA after radical prostatectomy should be assessed by a radiation oncologist.[77]

Current trials and future directions

The University of Michigan Comprehensive Cancer Center is running a phase II trial looking at salvage radiotherapy and docetaxel (weekly during radiotherapy) for PSA failure after radical prostatectomy.[78] 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 radiotherapy followed by endocrine therapy versus endocrine therapy alone for PSA failure after radical prostatectomy.[79]

Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) is a large-scale randomized trial aiming to recruit more than 4000 patients.[80] This study commenced in 2007 and aims to address 2 separate issues: the timing of post–radical prostatectomy radiotherapy (adjuvant v. early salvage radiotherapy) and the use of concomitant androgen deprivation therapy (none v. short term v. 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 which 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 serum PSA level of 0.2 μg/L or greater and less than 2 μg/L at study entry. This study aims to answer the question of whether or not to give systemic hormonal therapy at the time of salvage radiotherapy.

Conclusion

There is currently a lack of level I evidence on salvage radiotherapy; however, based on the available retrospective series, all patients with PSA failure post–radical prostatectomy should be considered for salvage radiotherapy when the serum PSA levels are less than 1.0 μg/L. Gleason grade, PSADT and time to relapse are helpful to predict the outcome of salvage radiotherapy, which is in general well tolerated. It is unknown whether salvage radiotherapy is superior to adjuvant radiotherapy.

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