Salvage Prostatic Fossa Radiation Therapy for Biochemical Failure after Radical Prostatectomy: the Sheba Experience

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Abstract

Background: The role of prostatic fossa radiation as salvage therapy in the setting of a rising prostate-specific antigen following radical prostatectomy is not well defined.

Objectives: To study the efficacy and safety of pelvic and prostatic fossa radiation therapy following radical prostatectomy for adenocarcinoma.

Methods: A retrospective review of the charts of 1,050 patients treated at the Sheba Medical Center for prostate cancer between 1990 and 2002 identified 48 patients who received post-prostatectomy pelvic and prostatic fossa radiotherapy for biochemical failure. Two patients were classified as T1, T2A-9, T2B-19, T3A-7 and T3B-11. Gleason score was 2–4 in 9 patients, 5–6 in 22 patients, 7 in 10 patients and 8–10 in 7 patients. Positive surgical margins were noted in 28 patients (58%) of whom 18 had single and 10 had multiple positive margins. Radiation was delivered with 6 mV photons using a four-field box to the pelvis followed by two lateral arcs to the prostatic fossa.

Results: At a median follow-up of 34.3 months (25th, 75th) (14.7, 51.3) since radiation therapy, 32 patients (66%) are free of disease or biochemical failure. Exploratory analysis revealed that a pre-radiation PSA less than 2 ng/ml was associated with a failure rate of 24% compared with 66% in patients with a pre-radiation PSA greater than 2 ng/ml (chi-square $P < 0.006$).

Conclusions: For patients with biochemical failure following radical prostatectomy early salvage radiation therapy is an effective and safe treatment option.

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Following radical prostatectomy, patients with adverse pathologic features such as extracapsular extension, positive surgical margins and seminal vesicle involvement are at risk for biochemical failure representing local and/or distant recurrence. Therapy for biochemical failure following prostatectomy is controversial: the two main issues are local vs. systemic therapy, and early systemic therapy versus observation with delayed therapy [1–3]. A recent study from the Mayo Clinic identified prostate-specific antigen doubling time as the most important prognosticator of local and systemic progression in 879 of 2,809 men (31%) who had biochemical failure after radical prostatectomy. Patients with PSA doubling times greater than 6 months have primarily local recurrence and therefore may benefit from local therapy. Patients with more rapid PSA doubling times of less than 6 months are more likely to have systemic progression and require systemic therapy.

The median time to clinical failure with positive surgical margins is approximately 7 years, however PSA progression may be detected as early as 3–4 years after surgery in 50–70% of these patients [2–4]. There are data suggesting that early salvage radiation therapy may eliminate subclinical recurrence, induce PSA control and possibly alter the clinical course. Several small series have reported a PSA response rate after radiotherapy of 48–68% with much heterogeneity in adverse pathologic features [5–7]. Some reports suggest that only 25–33% of these men will remain free of a second biochemical progression at 5 years post-radiation [8]. Until the results of randomized studies are available, it is important to carefully report retrospective clinical experience. Thus we studied the characteristics and outcome of all patients referred for pelvic and prostatic fossa radiation therapy following radical prostatectomy for prostatic adenocarcinoma in our institution.

PSA = prostate-specific antigen

Patients and Methods

All patient charts (n=1,050) extracted from the Sheba Oncology database with an ICD-9 diagnosis of prostate cancer from 1990 to 2003 were systematically reviewed. Fifty patients who received prostatic fossa or pelvic radiotherapy following radical prostatectomy were identified. Biochemical failure after radical prostatectomy was defined as either the persistence of a detectable PSA postoperatively, or the elevation of PSA to a detectable from a previously undetectable postoperative level. Two patients receiving adjuvant radiation without evidence of biochemical failure were excluded, thus 48 eligible patients were evaluated. Patient characteristics are given in Table 1. Two patients were classified as T1, T2A-9, T2B-19, T3A-7 and T3B-11. All patients had negative lymph nodes. Gleason score was 2–4 in 9 patients, 5–6 in 22 patients, 7 in 10 patients and 8–10 in 7 patients. Perineural invasion was reported in 14 patients. Pathologic examination revealed positive margins in 28 patients (58%) of whom 18 had a single positive margin and 10 had multiple positive margins. Eleven patients had tumors invading the seminal vesicles. The median pre-radiation PSA was 1.2 ng/ml (25th, 75th) (0.66, 2). Biopsies were performed in 24 patients, 14 of which showed local recurrence. The median time between radical prostatectomy and radiotherapy was 24.4 months (25th, 75th) (7, 49.2). Only six patients received androgen ablation concomitantly with radiation. Failure following salvage radiotherapy was defined as three consecutive rises in PSA therapy or evidence of metastasis.

Radiation technique

Radiation was delivered with 6 mV photons initially using a four-field box to a standard pelvic field with the upper border at the L5-S1 interface and inferior border at the ischial spine. For planning of

Table 1. Patient characteristics (n = 48)

	No. of patients
Pre-RP PSA	
⩽ 10 ng/ml	22
10–20 ng/ml	4
>20 ng/ml	4
Unknown	18
Pathologic T stage	
T1	2
T2A	9
T2B	19
T3A	7
T3B	11
Gleason score	
2–4	9
5–6	22
7	10
8–10	7
Margin status	
Negative margins	21
Single positive margin	18
Multiple positive margins	10
Perineural invasion	
Present	14
Absent	36

Table 2. Characteristics of patients failing salvage radiotherapy

	No. of patients (n=48)	Failure of salvage radiotherapy (n=16) No. of patients (%)
Gleason score		
2–6	31	8 (26%)
7	10	5 (50%)
8–10	7	4 (57%)
Pathologic stage		
2A	9	2 (22%)
2B	19	8 (42%)
3A	7	1 (14%)
3B	11	6 (56%)
Pre-radiation PSA		
<1 ng/ml	21	3 (14%)
1–2 ng/ml	15	5 (33%)
>2 ng/ml	12	8 (66%)
Positive margins	29	10 (36%)

the boost, computed tomography-based delineation of the clinical target volume included the prostatic fossa, relevant surgical clips and the bladder base with a planning treatment volume margin of 1 cm. Prior to 2000 the boost was delivered using two lateral arcs, but in latter years six fields are employed to achieve a homogenous dose to the clinical target volume while limiting the dose to the anterior rectal wall. The median dose of radiation was 66.6 Gy with a (25th, 75th) percentile of 63 and 70.2 Gy.

Results

At a median follow-up of 34.3 months (25th, 75th) (14.7, 51.3) since radiation therapy, 32 patients (66%) are free of disease or biochemical failure. To date 16 patients have failed salvage therapy: 5 patients had rising PSA immediately following radiotherapy, and 11 enjoyed a protracted disease-free interval with a median time to progression of 19 months (25th, 75th) (13.3, 33). The pre-treatment characteristics of patients failing salvage radiation in our series are shown in Table 2. Of the six patients who received concomitant hormonal therapy, four have failed with bone metastases, one has succumbed to gastric cancer and one remains disease free.

In this series, neither Gleason score nor T stage were predicative of response to salvage radiation therapy. However a pre-radiation PSA greater than 2 ng/ml was associated with a failure rate of 66% as compared to 24% in patients with a pre-radiation PSA less than 2 ng/ml (chi-square $P < 0.006$).

Toxicity

Overall, radiation therapy was well tolerated: 11 patients experienced mild transient bowel toxicity during radiotherapy and 15 had mild transient irritative urinary symptoms. Two patients developed chronic proctitis with late rectal bleeding. Eight patients reported some degree of urinary incontinence.

Discussion

Prostatic fossa radiation therapy is an effective treatment for biochemical failure after radical prostatectomy. In our experience two-thirds of the treated patients remain disease free with a median follow-up of almost 3 years. This compares favorably with reported biochemical control rates in the literature, which range from 10 to 64% [9,10].

In our study, at a median follow-up of 34 months a pre-radiation PSA under 2 ng/ml was associated with a freedom-from-failure rate of 78%. This finding concurs with data of Forman et al. [11] from the Wayne State group, who reported an 83% disease-free survival in patients with a pre-radiation PSA less than 2 ng/ml. However, pre-radiation PSA was not an important predictor of response to salvage radiation therapy in all other series: Katz et al. [12] found that patients most likely to benefit from salvage radiotherapy were those with positive margins without other adverse prognostic factors and a biochemical control rate of 77%. It is important to note that although pre-radiation PSA was not a significant predictor of response to radiation in the Memorial Sloan-Kettering series, the mean pre-radiation PSA of the patients in this cohort was 0.87 ng/ml. In an attempt to validate a nomogram to predict successful salvage radiotherapy, multi-institutional data were pooled and presented at ASCO 2003 by Dr. A.J. Stephenson of Sloan-Kettering [13]: 375 patients received salvage radiation therapy with an overall 2 and 5 year progression-free probability of 57% and 31% respectively. Patients with a pre-radiation PSA of <2ng/ml, PSA doubling time >10 months, Gleason score ⩽ 7 and T3A had a 65–95% chance of 2 year progression-free survival.

Better imaging techniques and further clinical studies are currently under investigation to refine the selection of patients for salvage radiotherapy and to avoid unnecessary radiation to those patients harboring distant micrometastases [14].

Conclusions

We have demonstrated that salvage radiotherapy is reasonably well tolerated, and the majority of our patients experienced grade 2 toxicity or less and a low risk of late complications. In patients with a high risk of metastatic disease such as those with seminal vesicle or lymph node involvement, rapid PSA doubling times are less likely to benefit from local salvage therapy [15]. For patients with local failure, salvage radiation therapy using conformal radiotherapy to reduce toxicity is an increasingly popular treatment option [16]. The results of our series support the recommendations of the ASTRO consensus panel, which recommend that patients receive salvage radiotherapy at doses of at least 6,400 cGy before the PSA rises above 1.5 ng/ml [17].

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