Salvage Radiation Therapy for Biochemical Failure Following Radical Prostatectomy

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ABSTRACT: **Background:** Radiotherapy to the prostate bed is used to eradicate residual microscopic disease following radical prostatectomy for prostate cancer. Recommendations are based on historical series.

Objectives: To determine outcomes and toxicity of contemporary salvage radiation therapy (SRT) to the prostate bed.

Methods: We reviewed a prospective ethics committee approved-database of 229 patients referred for SRT. Median pre-radiation prostate-specific antigen (PSA) was 0.5 ng/ml and median follow-up was 50.4 months (range 13.7–128). Treatment was planned and delivered using modern three-dimensional radiation techniques. Mean bioequivalent dose was 71 Gy (range 64–83 Gy). Progression was defined as two consecutive increases in PSA level › 0.2 ng/ml, metastases on follow-up imaging, commencement of anti-androgen treatment for any reason, or death from prostate cancer. Kaplan-Meier survival estimates and multivariate analysis were performed using STATA.

Results: Five year progression-free survival was 68% (95%CI 59.8–74.8%), and stratified by PSA the rates were 87%, 70% and 47% for PSA ‹ 0.3, 0.3–0.7 and › 0.7 ng/ml (P ‹ 0.001). Metastasis-free survival was 92.5%, prostate cancer-specific survival 96.4%, and overall survival 94.9%. Low pre-radiation PSA value was the most important predictor of progression-free survival (HR 2.76, P ‹ 0.001). Daily image guidance was associated with reduced risk of gastrointestinal and genitourinary toxicity (P ‹ 0.005).

Conclusions: Contemporary SRT is associated with favorable outcomes. Early initiation of SRT at PSA ‹ 0.3 ng/ml improves progression-free survival. Daily image guidance with online correction is associated with a decreased incidence of late toxicity.

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KEY WORDS: prostate fossa, prostate-specific antigen (PSA), salvage radiation therapy (SRT), image-guided radiation therapy (IGRT)

Salvage radiation therapy (SRT) to the prostate bed for a rising prostate-specific antigen (PSA) level following radical prostatectomy is an effective therapy that can restore biochemical control in a large number of patients on treatment [1-4]. Recent reports have shown that SRT to the prostate fossa is most effective when PSA levels are very low [5]. In recognition of this finding, the 2013 Adjuvant and Salvage Radiotherapy after Prostatectomy ASTRO/AUA Guidelines recommend that SRT be administered to post-radical prostatectomy patients "at the earliest sign of PSA recurrence and ideally before PSA rises to 1.0 ng/ml" [6,7]. Furthermore, the 2013 ASTRO/AUA guidelines stated that most of the available outcome data are from older studies that use older techniques and suggest that additional reports of patient outcomes using current treatment techniques are needed [7].

Several large prospective randomized studies reported improved progression-free survival in high risk patients receiving adjuvant prostatic fossa radiation [3,4,7]. However, since not all patients with reported positive margins will experience biochemical failure or recurrence, it is possible to avoid routine adjuvant therapy for all patients with adverse pathology and monitor them closely for rising PSA. Early salvage radiation in the case of biochemical failure in these patients is associated with excellent outcomes [8]. Two current clinical trials are addressing this controversy by evaluating adjuvant vs. salvage prostate fossa radiation in high risk patients [9,10].

Although improved outcomes from early salvage treatment are apparent, there are substantial variations in treatment techniques and radiation doses in current use and these can affect reported outcomes. Institutions and even cooperative groups differ on selection of clinical target volume (CTV), selection of treatment dose, use of planning and image-guided techniques, and even the role of adjuvant pelvic nodal radiation

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or androgen-deprivation therapy. For example, increasing the radiation dose to the prostatic fossa has also been shown to improve results [1,11]. In separate reviews, King [1] and Ohri et al. [11] report 2% and 2.5% improvements in relapse-free survival with each additional Gy given over 60 Gy. However, increasing the dose to the prostate fossa places patients at risk for increased complications from treatment. Ohri et al. [11] also state that the risk of late gastrointestinal and genitourinary toxicity increases by 1.2% and 0.7% respectively with each additional Gy given over 60 Gy.

Image-guided radiation therapy (IGRT) techniques described for treating the prostatic fossa include invasive techniques that require implantation of electromagnetic transponders, and non-invasive techniques such as cone beam computed tomography (CT) scanning or KV/KV imaging which use surgical clips as fiducial markers [12]. These techniques improve targeting of the prostatic fossa and may reduce toxicity to normal tissues [13].

We evaluated the 2013 ASTRO/AUA guidelines to confirm if initiation of salvage radiation to the prostate fossa would be most beneficial if treatment was offered at the earliest sign of PSA recurrence. Furthermore, we hypothesized that the use of IGRT would reduce genitourinary and gastrointestinal toxicity rates in patients receiving SRT after radical prostatectomy. We conducted a retrospective review of our database and report treatment outcomes for a series of patients given salvage prostate fossa radiation using dose escalation and modern radiation techniques at a single center.

PATIENTS AND METHODS

This retrospective review of a prospective database was approved by the institutional ethics committee. Between November 2002 and July 2013, 229 patients were treated with SRT to the prostate fossa for persistent or rising PSA after prostatectomy. Biochemical recurrence after radical prostatectomy was defined as PSA ≥ 0.2 ng/ml with a second confirmatory level ≥ 0.2 ng/ml. Patients who received adjuvant radiation without biochemical recurrence were not considered in this analysis. Patient and treatment characteristics are shown in Table I. Median pre-radiation PSA was 0.5 ng/ml (range 0.21–10.42 ng/ml). Mean bioequivalent radiation dose (ED2Gy) was 71 Gy (range 64–83 Gy). Median follow-up time was 50.4 months (range 13.7–127.7 months). All patients had a pretreatment history and physical examination including a pretreatment PSA. Metastatic evaluation included bone scan and pelvic CT scan. Selected patients underwent MRI or choline PET/CT (positron-emission tomography/CT) imaging when macroscopic disease was suspected. Patients with evidence of macroscopic recurrence were offered dose escalation. Patients with radiographic evidence of lymph node involvement or metastatic disease were not included in this study.

Patients were scanned on a Phillips Big Bore CT simulator (Phillips Healthcare, The Netherlands). The prostatic fossa was contoured according to an in-house analysis of patterns of recurrence which proved to be in agreement with the EORTC guidelines published in 2008 [14]. Treatment planning was performed using an Eclipse treatment planning system (Varian, Palo Alto, CA, USA). Dose was prescribed to the 95% isodose line of the planning target volume (PTV). All prostate doses were converted to a bioequivalent radiation dose using the linear quadratic model (α/β ration of 1.5) and reported as 2 Gy equivalents (ED2Gy). Dose escalation for macroscopic recurrence was delivered using sequential or simultaneous integrated boost technique. Treatment included 3D conformal and intensity-modulated radiation therapy with stationary or arc techniques. Prior to the introduction of IGRT, the planning target volume with a bioequivalent dose of 56 Gy was a 1 cm expansion of the CTV followed by a 20–24 Gy cone down with a reduced posterior margin of 0.5 cm. After the introduction of IMRT, the planning target volume was expanded 1 cm from the CTV except posteriorly where the margin was reduced to 7 mm for the entire treatment.

Between 2002 and 2008 the accuracy of the radiation portal was verified with daily portal imaging for the first five fractions followed by a weekly image if within tolerance. Daily image guidance with cone beam CT or KV/KV imaging was introduced in May 2008 after instillation of a Varian Trilogy. The symphysis pubis was contoured for field matching, and surgical clips in the prostatic fossa were used as fiducial markers. Patients had cone beam CT on the first 3–5 days of treatment and then daily KV/KV imaging with online correction. Additional cone beam CTs were performed if the marker match was unsatisfactory.

Androgen-deprivation therapy was offered to patients by the referring surgeon or at the time of consultation based on physical findings, Gleason score, margin status and PSA level. Surgeon preference and patient willingness to accept androgen-deprivation therapy often determined if patients received treatment. Adjuvant pelvic lymph node radiation was given based on the estimated risk of lymph node involvement, pre-surgery PSA, Gleason score, the extent of nodal dissection at the time of surgery, patient's co-morbidities and age.

Patients were seen during therapy by the treating physician and for follow-up examination at 6 weeks, 4 months, and thereafter every 6 months for the first 3 years, and then once a year. To determine progression-free survival (PFS) after SRT, progression was defined as two consecutive increases in PSA level > 0.2 ng/ml, metastases on follow-up imaging, commencement of anti-androgen treatment for any reason,or death from prostate cancer. Toxicity and side effects were recorded using the CTCAE version 4.0 [15].

Statistical analysis was performed using STATA. Continuous variables were compared using the two-tailed Student *t*-test, and

categorical variables were compared using chi-square test. The Kaplan-Meier method was used to calculate PFS. Cox univariate and multivariate proportional hazards model were used to identify predictors of gastrointestinal or gastrourinary toxicity and PFS.

RESULTS

Of 229 patients, 61 suffered biochemical failure, 16 developed metastasis and 7 died of metastatic prostate cancer. Four patients died of unrelated causes. Five year progression-free survival was 68% [95% confidence interval (95%CI) 59.8–74.8%], metastasis-free survival was 92.5%, prostate cancer-specific survival was 96.4% and overall survival was 94.9%.

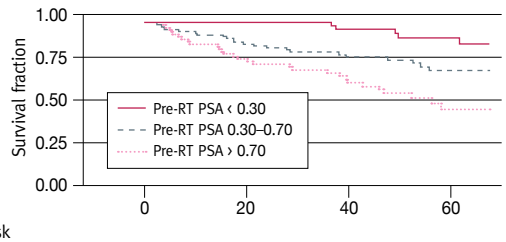
In Figure I, Kaplan-Meier estimates show that patients who began radiotherapy treatment at PSA levels < 0.3 ng/ml had the best 5 year biochemical control of 86.9% [95%CI 70.8–94.5%, hazard ratio (HR) 1, n=66], patients who began at PSA values of 0.3–0.7 ng/ml had intermediate control at 70.4% (95%CI 57.7–80%, HR 3.57, $P = 0.01$, n=94), and patients with PSA values > 0.7 ng/ml had the least favorable control at 46.6% (95%CI 31.2–50.6%, HR 7.29, $P = 0.001$, n=69). Kaplan-Meier estimates show that the three pre-treatment PSA subgroups (PSA < 0.3 ng/ml, 0.3–0.7 ng/ml, > 0.7 ng/ml) continued to predict PFS for patients when stratified by Gleason score (Gleason score < 7: progression-free survival 100%/83%/54%, HR 3.1, 95%CI 1.17–8.21%, $P = 0.023$; Gleason score = 7: progression-free survival 94%/64%/58%, HR 2.72, 95%CI 1.48–5.0, $P = 0.001$; Gleason score 8–10: progression-free survival 75%/63%/12%, HR 2.88, 95%CI 1.61–5.18, $P = 0.001$). Progression-free survival was distinct for PSA subgroups also according to margin status. (Positive margins: survival 88%/77%/60%, HR 1.87, 95%CI 1.01–3.47, $P = 0.047$; negative margins: survival 83%/62%/45%, HR 2.27, 95%CI 1.30–3.96, $P = 0.004$).

Table 2 lists the results of univariate and multivariate Cox regression analysis. Low pre-radiation PSA value was the most important predictor of progression-free survival (HR 2.76, $P < 0.001$). Low Gleason score and positive margin status were also associated with favorable 60 month survival estimates. The interval between radical prostatectomy and salvage radiotherapy had no impact on outcome. There was no benefit seen with use of pelvic nodal radiation or androgen-deprivation therapy.

There was no acute grade IV or V gastrointestinal or gastrourinary toxicity. Late gastrointestinal toxicity grade was I-67 (28.3%), II-6 (2.5%) and III-1 (0.4%), IV/V-1 (0.4%) (one patient died of small bowel necrosis possibly related to an adhered loop of bowel in the prostatic fossa that was unrecognized at the time of planning). Late gastrourinary toxicity grade was I-61 (25.7%), II-18 (7.5%) and III-5 (2.1%)

Prior to starting radiation therapy, 46 patients (19.5%) reported significant urinary incontinence (two pads). After completion of the radiation treatment, 58 patients reported some degree of urinary incontinence as grade I-46 (19.5%), II-12 (5%), III-2 (0.8%). Most patients (80%) experiencing

Figure 1. Kaplan-Meier survival estimate: progression-free survival by pre-treatment PSA levels



Number at risk

Pre-RT PSA < 0.30	66	59	39	20
Pre-RT PSA 0.30–0.70	94	73	45	20
Pre-RT PSA > 0.70	69	47	28	8

Table 1. Patient characteristics

	SRT patients (n=229)
Median age in years (range)	67 (53–84)
Median months between surgery and SRT (range)	22.4 (3.1–212.5)
Pathological T-stage	
T1-T2A	24
T2B, T2C	86
T3A	80
T3B-T4	38
Gleason sum	
4–6	74
7	100
8–10	55
Post-RP, Pre-SRT PSA (ng/ml)	
PSA < 0.3	66
0.3 ≤ PSA < 0.7	94
0.7 ≤ PSA	69
Median PSA ng/ml (range)	0.5 (0.01–10.42)
Surgical margins	
Negative	74
Positive	140
Not assessable	15
Androgen-deprivation therapy	
No	134
Yes	95
Biological equivalent dose (Gray)	
< 70	40
70	131
> 70	48
Treatment extent	
Prostate fossa	183
Prostate fossa and pelvic lymph node	46
Treatment modality	
Conformal radiation therapy	97
Intensity modulated RT	100
Volumetric modulated arc therapy	32
Daily image guidance	
Yes	146
No	83

RP = radical prostatectomy, PSA = prostate-specific antigen, SRT = salvage radiotherapy

Table 2. Progression-free survival (PFS) probabilities, univariate and multivariate hazard ratios of pre-treatment and treatment variables

Variables	(n)	60 month survival %	Univariate		Multivariate	
Overall	229	68%	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Pre-SRT PSA group			2.45 (1.67–3.59)	‹ 0.001	2.76 (1.76–4.32)	‹ 0.001
PSA ‹ 0.3 0.3 ≤ PSA ≤0.7 PSA › 0.7	66 94 69	87% 70% 47%				
Gleason group			1.49 (1.05–2.11)	‹ 0.026	2.33 (1.42–3.83)	0.001
4–6 7 8–10	72 102 55	75% 72% 54%				
Margin status			0.39 (0.23–0.7)	0.001	0.46 (0.25–0.85)	0.01
Negative Positive	74 140	59% 78%				
Age (yrs)			1.08 (0.79–1.49)	0.602	0.975 (0.68–1.41)	0.89
Age ‹ 65 65 ≤ age ‹ 70 Age ≥ 70	71 62 96	74% 69% 64%				
Endorectal MRI			1.68 (1.11–2.53)	0.013	0.99 (0.56–1.74)	0.96
Not done Yes, clear Yes, suspicious	198 19 12	71% 51% 45%				
Bioequivalent dosage			1.32 (0.74–2.36)	0.348	0.73 (0.36–1.52)	0.403
BEQD ≤ 70 BEQD > 70	171 58	70% 59%				
Pelvic nodal radiation			1.85 (1.06–3.25)	0.031	0.79 (0.38–1.68)	0.55
No Yes	183 46	74% 50%				
Concurrent hormones			1.67 (0.99–2.81)	0.057	0.96 (0.49–1.85)	0.89
No Yes	147 82	74% 59%				
Radiation modality			1.18 (0.77–1.8)	0.456	1 (0.64–1.56)	0.99
3D conformal IMRT Rapid arc	97 100 32	68% 75% 28%				

P values and hazard ratios are derived by univariate and multivariate Cox regression

SRT = salvage radiotherapy, PSA = prostate-specific antigen, IMRT = intensity-modulated radiation therapy, BEQD = bioequivalent dosage

urinary incontinence of any degree were symptomatic prior to receiving SRT.

Table 3 shows the univariate and multivariate logistical regression of factors associated with gastrointestinal and gastrourinary toxicity-free outcomes. The use of daily image guidance was associated with a significantly reduced risk of gastrointestinal and gastrourinary toxicity (odds ratio 0.25 and 0.44, $P < 0.005$).

Table 3. Factors associated with toxicity-free outcomes. Univariate and multivariate logistic regression

	Genitourinary		Gastrointestinal	
Factor	Odds ratio 95%CI	*P* value	Odds ratio 95%CI	*P* value
Gleason score	0.81 (1.6, 1.2)	0.24	0.73 (0.4, 1.4)	0.32
Pre-XRT PSA	0.94 (0.7, 1.3)	0.7	1.40 (0.8, 2.5)	0.27
Androgen Deprivation	0.84. (0.6, 1.4)	0.52	1.06 (0.4, 2.6)	0.9
Bioequivalent dosage	0.9 (.6, 1.4)	0.67	1.34 (0.7, .71)	0.41
Treatment extent	1.2 (0.7, 2.4)	0.52	2.17 (0.8, 5.72)	0.12
Treatment modality	0.69 (0.5, 1]	0.07	0.4 (0.2, 0.9)	0.03
Follow-up since treatment	1.21 (1, 1.4)	0.02	1.24 (0.9, 1.7)	0.14
Image guidance	0.44 (0.3, 0.8)	0.004	0.25 (0.1, 0.6)	0.002
Multivariate logistic regression				
Image guidance	0.44 [0.3, 0.8]	0.004	0.25 (0.10, 0.6)	0.003

DISCUSSION

Initiating salvage prostate fossa radiation early, when PSA values are low, has been shown to offer patients the best chance of achieving progression-free survival [1,11,16]. Although some previous studies have used PSA levels of 1 ng/dl to initiate SRT [7], more recent reports show that initiation of salvage radiation at lower PSA values such as 0.5 ng/ml, 0.4 ng/ml or 0.28 ng/ml is associated with better patient outcomes [1,11]. We found that initiating SRT when PSA levels are < 0.3 ng/ml is associated with better progression-free survival than patients with PSA between 0.3 ng/ml and 0.7 ng/ml or > 0.7 ng/ml. These findings are consistent with tumor control probability modeling by King [16], who showed progressively improved biochemical control with lower PSA levels at the time of postoperative RT. King [1,16] estimated that each 0.1 ng/ml increase in PSA at the time of salvage radiation therapy would result in a 4% loss of biochemical control at 5 years. The decrease in biochemical control with increasing PSA reported in this study conforms well to the outcomes predicted by King [16]. Furthermore, when stratifying our results by PSA, higher Gleason score was associated with a worse prognosis, and positive margin status was associated with more favorable progression-free survival, consistent with other studies [7].

Three prospective studies have shown benefit for adjuvant radiation therapy in patients with T3 disease or positive margins [2-4]. However, because of toxicity concerns, acceptance of adjuvant radiation is not uniform, and currently, several large prospective trials are underway comparing adjuvant radiation therapy to early SRT [9,10]. Our treatment policy has been to defer adjuvant therapy for patients with T3 disease or positive margins and offer salvage radiation at the time of biochemical failure. Our findings are consistent with other retrospective studies of patients who are closely monitored and referred early to SRT, supporting our policy of close observation and early SRT rather than use of adjuvant radiation therapy [8]. Results from ongoing prospective randomized studies are needed to verify our approach. The mean PTV dose in our series was 71 Gy (64–81 Gy), which is higher than doses reported from other series [7]. Other Investigators have shown that biochemical control improves when the radiation dose increases from 60 Gy to 70 Gy; however, dose was not a predictor of response in our study [1,11]. This may be due to our use of dose escalation only in patients with evidence of macroscopic recurrence found either on physical exam or by radiographic imaging, or with surgical or pathologic findings suggesting areas at risk for recurrence. We believe these patients may have benefited from dose escalation and therefore had biochemical control rates similar to those in patients without macroscopic recurrence and who were treated with a lower dose.

We could not demonstrate a benefit of adjuvant pelvic nodal radiation or androgen-deprivation therapy. Our small sample size and patient selection may explain the lack of observed benefit. Our evolved treatment policy had been to offer treatment to the prostate fossa alone to patients with favorable risk factors, and additional treatment with pelvic nodal radiation, androgen-deprivation therapy or both to patients with adverse risk factors. Several large clinical trials to evaluate the role of androgen-deprivation therapy and pelvic radiation in patients receiving SRT to the prostatic fossa are currently underway [9,10,17].

Improvements in radiation techniques may have contributed to the improved outcomes in our series when compared to older observational studies [18,19]. We used a consistent approach to contouring the prostate fossa, dose escalation for margin involvement and macroscopic disease, conformal radiation therapy planning, and daily IGRT to improve treatment accuracy [18,19]. We were able to demonstrate on multivariate analysis a substantial decrease in gastrointestinal toxicity and a lesser reduction in gastrourinary toxicity with the introduction of image guidance techniques into the daily treatment routine. Concomitantly with the introduction of image guidance, a policy of patient education encouraging bowel emptying and bladder filling was commenced. Patients are routinely coached by therapists during treatment regarding adequacy of bowel emptying and bladder filling based on cone beam CT. Tissue redistribution following radical prostatectomy including caudal mobilization of the bladder to the anastomosis and increased anterior rectal wall motion has been described [20]. Thus, daily image guidance assures not only that radiation is on target but is a powerful tool to optimize patient preparation and reduce bowel and bladder exposure to radiation.

Further improvements in outcome are anticipated with the use of new techniques such as anisotropic margins for creation of more conformal planning target volumes, better standardization of bladder filling, use of a rectal balloon, and additional use of imaging studies to better locate macroscopic tumor in the prostate fossa for dose escalation as well as to identify patients with involved lymph nodes and distant metastatic disease who are unlikely to benefit from prostate fossa radiation alone [20-22].

We found that the vast majority of patients who reported urinary incontinence after radiation had previously reported persistent incontinence after surgery. Risk factors for urinary dysfunction after adjuvant or salvage radiation include age, stage, Gleason score, and prior androgen-deprivation therapy [23]. The use of adjuvant or salvage RT has been reported as a significant risk factor for urinary incontinence after radical prostatectomy [24]. Suardi and co-authors [24] recently reported that patients who received adjuvant radiation therapy had a lower rate of recovery from urinary incontinence than patients who did not receive adjuvant radiation. These results are consistent with our findings that patients who were incontinent at the start of salvage therapy were likely to report incontinence after salvage radiation was completed. While further investigation of this issue is warranted, for now patients who have incontinence prior to adjuvant or salvage radiation should be counseled about the increased risks of persistent or worsening incontinence after radiotherapy.

Limitations of this retrospective study include the absence of central pathology evaluation. Since PSA values from the time of initial biochemical failure were not available for most patients, we were unable to calculate PSA doubling times which have been shown to be an important prognostic variable [25]. A standardized quality of life survey was introduced in 2010 so data on erectile function were not available for the majority of patients.

CONCLUSIONS

Our results show that contemporary salvage radiation therapy to the prostatic fossa is most effective when delivered as soon as biochemical failure becomes evident following radical prostatectomy. Treatment is well tolerated and causes few significant acute or late complications. We noted a significant decrease in gastrointestinal and gastrourinary toxicity when image guidance techniques were introduced into patients' daily treatment course.

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