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Early Hypofractionated Salvage Radiotherapy for Post-Prostatectomy Biochemical Recurrence

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Abstract

Background—Post-prostatectomy adjuvant or salvage radiotherapy, when using standard fractionation, requires 6.5–8 weeks of treatment. We report on the safety and efficacy of an expedited radiotherapy course for salvage prostate radiotherapy.

Methods—A total of 108 consecutive patients were treated with salvage radiation therapy to 65 Gy in 26 fractions of 2.5 Gy. Median follow-up was 32.4 months. Median pre-salvage PSA was 0.44 (0.05–9.50). Eighteen patients (17%) received androgen deprivation following surgery or concurrently with radiation.

Results—The actuarial freedom from biochemical failure for the entire group at 4 years was 67% +/− 5.3%. An identical 67% control rate was seen at 5 years for the first 50 enrolled patients whose median followup was longer at 43 months. One acute grade 3 GU toxicity occurred, with no acute grade 3 GI and no late grade 3 toxicities observed. On univariate analysis, higher Gleason score (p=0.006), PSA doubling time ≤ 12 months (p=0.03), perineural invasion (p=0.06), and negative margins (p=0.06) showed association with unsuccessful salvage. On multivariate analysis, higher Gleason score (p=0.057) and negative margins (p=0.088) retained an association with biochemical failure.

Conclusions—Hypofractionated radiotherapy (65 Gy in 2.5 Gy fractions in about 5 weeks) reduces the length of treatment by from 1–1/2 to 3 weeks relative to other treatment schedules commonly employed, produces low rates of loxicity, and demonstrates encouraging efficacy at 4 – 5 years. Hypofractionation may provide a convenient, resource efficient and well-tolerated salvage approach for the estimated 20–35,000 US men per year experiencing biochemical recurrence after prostatectomy.

Keywords

Salvage radiotherapy; hypofractionation; prostate cancer; prognostic factors; post-prostatectomy

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Introduction

Recent analyses of practice patterns utilizing the Surveillance, Epidemiology, and End Results (SEER) and Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) registries have demonstrated that while the use of radiotherapy (EBRT or brachytherapy) for definitive management of organ-confined prostate cancer has increased, radical prostatectomy still accounted for 41–74% of all patients who underwent definitive management as of 2004 [1, 2]. Roughly 25% of these patients will develop biochemical recurrence following radical prostatectomy [3]. Therefore, with nearly 200,000 cases of prostate cancer diagnosed per year in the US [4], approximately 20–35,000 men suffer post-prostatectomy biochemical recurrence.

The optimal management of these patients is the topic of much current debate. Recently, three large prospective randomized clinical trials comparing adjuvant radiotherapy to observation [5–7] have demonstrated a significantly improved biochemical control and, in one study, a survival benefit for adjuvant radiation to the prostatic fossa in patients with extraprostatic tumor extension, seminal vesicle invasion, and/or positive surgical margins. While these trials have established a clinical benefit of postprostatectomy radiotherapy for patients with high-risk pathologic features, there remain questions regarding the optimal timing of the radiotherapy; whether it should be delivered adjuvantly for patients with high-risk pathologic features or as early salvage at the first sign of a PSA recurrence has not been definitely determined.

Numerous retrospective series have demonstrated that salvage RT after biochemical recurrence following radical prostatectomy is well tolerated [8–13], can be effective in reestablishing biochemical control, and could potentially be a viable alternative to adjuvant therapy [12]. However, whether postprostatectomy radiation is delivered adjuvantly or in the salvage setting, the required doses of 65–70 Gy takes 6.5–8 weeks to deliver the 33–39 fractions required when standard fraction sizes of 1.8–2 Gy are used. Hypofractionation (fewer, larger fractions) is an approach that has been increasingly explored in primary radiotherapy for prostate cancer, and may provide a method for achieving a safe but shorter, more convenient and resource efficient course of treatment while still delivering effective doses [14–17]. The purpose of this present study was to determine whether hypofractionation can be safely applied in a postprostatectomy, salvage setting.

In this study, we employed a 26 fraction, hypofractionated salvage radiotherapy regimen, and we report toxicities and early biochemical control rates in 108 patients who were treated for post-prostatectomy biochemical failure.

Methods

Patient demographics and clinical characteristics

One hundred eight consecutive patients with biochemical recurrence after radical prostatectomy were treated between May 2003 and November 2008 with hypofractionated radiotherapy. An institutional review board-approved retrospective analysis was performed. The patient characteristics are given (Table 1). Surgical Gleason score was <7 in 38 patients (36%), =7 in 54 patients (51%), and >7 in 14 patients (13%). Data on extracapsular extension was available in 102 patients, and was noted in 25 patients. Pathologic stage was pT2 in 77 patients (73%), pT3a in 19 (18%), pT3b in 8 (7%), and TxN1 in 2 (2%). Margins were positive in 72 patients (69%) and perineural invasion noted in 43 patients (40%). The median pre-salvage PSA was 0.44 ng/ml (0.05–9.50); median pre-salvage PSA doubling (PSA-DT) time was 6.97 months (1.4–38.2).

Planning and treatment

All patients underwent planning computed tomography scans, and the prostatic fossa was contoured in a fashion that closely corresponds to the recent RTOG consensus guidelines for prostate fossa clinical target volume (CTV) definition [18]. The CTV included the region superior to the urogenital diaphragm, anterior to the rectum, and posterior to the pubic symphisis, including the vesicourethral anastamosis. The superior contours included the posterior bladder and proximal residual seminal vesicles in most patients, and the entire residual seminal vesicle was included in patients with pathologic evidence of seminal vesicle involvement. Intensity-modulated RT (IMRT) was used for each treatment plan, with ≥95% of the PTV receiving 2.5 Gy per fraction. Normal tissue IMRT planning constraints specified that <20% of the rectal wall should receive 60 Gy, the residual bladder maximal dose should be <59.5 Gy, and the femoral heads should be limited to a maximal dose of 39 Gy.

All patients were treated with IMRT with daily image localization, an endorectal balloon in place, and a comfortably full bladder. For all patients, the bladder base was used as the imaging localization landmark. Of the 108 patients, 49 underwent linear-accelerator based IMRT with daily ultrasound localization (Varian, Sonarray) [19]. In these patients the CTV was expanded 5 mm posteriorly and 7 mm in all other directions to create planning target volume (PTV) [20]. Helical tomotherapy with daily megavoltage computed tomography scan imaging was used for 59 patients. CTV expansion in these patients was 3 mm posteriorly and 5 mm in all other directions to create the PTV [21].

All but 7 patients were treated to a dose of 65 Gy, with six patients treated instead to 67.5 Gy and one to 70 Gy in 2.5 Gy fractions due to palpable abnormalities in the prostatic fossa and/or magnetic resonance imaging (MRI) abnormalities suggestive of gross local recurrence. These areas were contoured in the CTV with PTV expansions as above. Fourteen patients were treated concurrently to the pelvic nodal volumes to 52–56 Gy in 2 Gy fractions for high-risk features or known nodal involvement. Nodal PTVs consisted of the external, internal, and common iliac vessels with a 7 mm radial expansion. The majority of these pelvic nodal patients were treated in the prone position with a bowel displacement board to minimize the irradiated volume of small bowel.

Eighteen patients (17%) received androgen deprivation therapy (ADT) before or during salvage RT. Ten of these patients received ADT from outside providers before radiation oncology consultation and did not continue ADT during or after RT. Eight patients received 6 months of ADT starting 2–3 months prior to salvage radiation. No patient received ADT following salvage RT beyond that needed to finish a 6-month course of neoadjuvant and concurrent ADT as above.

Follow-up and Toxicity scoring

Median follow-up for the entire group of patients was 32.4 months (range 5.8–70.5) and was 43 months for the first 50 patients treated. Acute toxicities were defined as including all events during and within 90 days after RT completion. A modified Radiation Therapy Oncology Group grading system was used for acute gastrointestinal, acute genitourinary, and late genitourinary toxicity [22]. The Fox Chase modification of Late Effects Normal Tissue scale was used to evaluate late gastrointestinal toxicity [22] due to its detailed incorporation of rectal bleeding as a toxicity endpoint.

Biochemical control and statistical analysis

Similar to Stephenson *et al* [10], biochemical progression was defined as and recorded at a serum PSA value of 0.1 ng/mL or more above the post radiotherapy nadir followed by

another higher value, a continued rise in the serum PSA despite salvage RT, initiation of systemic therapy after completion of salvage RT, or clinical progression. Freedom from biochemical progression was calculated using the Kaplan-Meier method for the entire cohort and with respect to prognostic variables. Univariate analysis examining relationships between prognostic variables and biochemical progression after salvage RT was performed using pairwise log-rank associations. The Cox proportional hazards model with stepwise variable selection was used to assess the impact of multiple factors. All statistical tests were 2-tailed, and *P* was considered statistically significant when <0.05.

Results

Survival and Biochemical Control

With a median overall follow-up of 32.4 months (range 5.8–70.5), only one patient, with hormone refractory disease at the time of salvage RT, had died. The actuarial freedom from biochemical progression at 4 years was 67.0% (+/− 5.3%) (Figure 1). In a subset analysis of the first 50 patients, with a longer median followup of 43 months, actuarial freedom from biochemical progression at 5 years was also 67.0% (+/− 7%). Of the 108 patients, 78 demonstrated continuous biochemical control after salvage RT. With 48 patients still at risk for biochemical failure beyond 24 months, only 2 additional failures occurred. Of the 30 patients with biochemical progression, 14 patients showed persistent PSA progression despite salvage RT, suggesting the presence of occult metastatic disease at the time of salvage. An additional 2 high-risk patients had PSA response to ADT administered around the time of radiation, with rapid PSA progression once ADT ended, suggesting the presence of previously ADT-suppressed metastatic disease. The remaining 14 patients had initial response to salvage RT with subsequent PSA progression, at a median time of 16.3 months (range 3–42.1mo).

Prognostic Variables

On univariate log-rank analysis, higher Gleason score (p=0.014), PSA doubling time ≤12 months (p=0.037), presence of perineural invasion (p=0.066), and negative margins (p=0.067) showed association with biochemical progression after salvage RT (Table 2). Pathologic stage (T3 vs. T2), initial postoperative PSA (detectable vs. undetectable), and presalvage PSA (>0.4 vs. ≤0.4) were not significantly associated with biochemical progression following salvage RT. To further analyze the impact of Gleason score, log-rank pairwise comparisons were performed, demonstrating no significant difference between Gleason scores ≦6 vs. Gleason =7 (p=0.46) but significant differences between Gleason ≤6 vs. Gleason 8–10 tumors (p=0.01) and Gleason =7 vs. Gleason 8–10 tumors (p=0.012) (Figure 2). When grouped, Gleason scores 8–10 vs. ≤7 were associated with biochemical failure (p=0.004).

On multivariate Cox regression analysis, Gleason score 8–10 [hazard ratio (HR) 2.42 (0.97–6.00 95% confidence interval, p=0.057) and negative margins [HR 1.95 (0.91–4.21; p=0.088)] maintained trends toward association with biochemical progression. PSA doubling time (p=0.16) and perineural invasion (p=0.14) were not significant prognostic factors in the multivariate model.

Toxicities

Acute grade 2 or greater GU toxicities were noted in 8 patients (7%). Acute grade 3 GU toxicity (obstruction) was noted in a patient with previous bladder neck contracture. Acute grade 2 toxicities consisted of dysuria (n=4) or frequency (n=2) requiring medications, and macroscopic hematuria (n=1). Late grade 2 GU toxicities were noted in 16 patients (15%), consisting of macroscopic hematuria (n=10), bladder neck contracture requiring dilatation

(n=5), urinary frequency or urgency requiring medication (n=3) and worsened incontinence (n=1) (some patients experienced more than 1 type of late grade 2 GU toxicity). At last follow-up, however, only 3 patients (3%) had grade 2 late GU toxicity. No acute grade 4 or late grade ≥3 urinary toxicities were documented.

Acute grade 2 GI toxicities occurred in 15 patients (14%), consisting of rectal pain requiring medication (n=4), diarrhea requiring medication (n=6), and/or bleeding or hemorrhoid exacerbation (n=6). No acute grade ≥3 GI toxicities were noted. Late grade 2 GI toxicities were noted in 4 patients (4%), all consisting of radiation proctitis. Two of these patients had endoscopic cautery to treat rectal bleeding. At the time of last follow-up, 1 patient had grade 2 late GI toxicity. No late grade ≥3 GI toxicities were documented.

Treatment of salvage failures

Thirty patients had biochemical progression following salvage RT. One patient with hormone refractory disease before salvage RT died 6 months after treatment as described above. Sixteen patients were observed without active intervention at the time of last follow-up, with a median PSA of 0.9 (range 0.26–16.9) and a median follow-up after salvage RT of 28 months (range 8–65). Thirteen patients received androgen deprivation therapy after salvage RT at a median time of 21 months (range 5–50) following RT. These patients had a median PSA of 2.2 (range 0.15–39.3) at a median length of follow-up of 53 months (range 9–71) after radiation therapy. Two of these patients had developed radiographic evidence of lymph node metastases, and one patient had bony metastases documented. Three patients (3%) ultimately developed castrate-resistant disease following salvage RT.

Discussion

The optimization of management of post-prostatectomy patients at higher risk of biochemical progression is an area of ongoing investigation. Prospective randomized trials [5–7] of adjuvant therapy for patients at risk of local recurrence have provided definitive evidence of the clinical benefit of post-prostatectomy radiotherapy in terms of biochemical control [11, 12, 23], metastasis-free survival and cause-specific and overall survival, but have arguably left unresolved the issue of optimal timing of the radiation. The fact that a number of non-randomized salvage trials have demonstrated the importance of early intervention, a practice not routinely followed in the observation arms of the randomized adjuvant trials, leaves incompletely answered the question of whether patients are best managed by an adjuvant versus an early salvage approach [24].

Our institutional practice has been one of early salvage therapy [13]. This present report includes 108 patients and demonstrates that a hypofractionated schedule of 65 Gy in 26 fractions of 2.5 Gy each is well tolerated and yields excellent 4-year biochemical control (67.0 +/− 5.3%), with only an infrequent use of concurrent, short-term androgen deprivation. Multivariate analysis demonstrated higher Gleason score (p=0.057) and lack of positive margins (p=0.088) to be the only factors to maintain association with biochemical progression following salvage RT.

Several studies of radiation therapy alone for prostate cancer have suggested that delivering larger daily radiation fraction sizes may be radiobiologically advantageous. Such a hypofractionated approach is now being extensively investigated in the nonsurgical setting [25, 26]. While it is less clear whether such a radiobiological advantage applies in the post-prostatectomy setting where microscopic rather than macroscopic cancer would be expected, a hypofractionated approach to salvage therapy still clearly offers advantages in terms of cost and of coveniences to the patient.

Based upon a reasonable range of standard radiobiological modeling parameters, the fractionation regimen used in this study (65 Gy in 2.5 Gy fractions) would be expected to be equivalent to a dose in 2 Gy fractions (EQD_2) of between 68 and 74.4 Gy, a dose range found to be more effective than lower doses in other studies [27–29]. Retrospective studies have demonstrated salvage RT after biochemical recurrence using standard 1.8–2 Gy fractions to total doses of 60–70 Gy to be variably effective, with 5-year biochemical recurrence-free rates ranging from 10–66% at 5 years (as summarized in [23]). The largest, multi-institutional reports have come from Stephenson *et al*, who have reported actuarial biochemical control rates of 45% at 4-years [10] and 32% at 6 years [9]. Furthermore, that group highlighted the importance of pre-salvage PSA as a prognostic marker for control after salvage radiotherapy, with the lowest-risk patients (pre-salvage PSA ≤0.5) achieving biochemical control of 48% at 6-years. We demonstrate actuarial biochemical control at 4 years (67.0%, +/− 5.3%) and 5 years (67.0% +/− 7%) in a patient cohort with a median pre-salvage PSA of 0.44 (range 0.05–9.50).

On the other hand, the fraction size response of the pertinent surrounding normal organs such as rectum and bladder is arguably somewhat better defined. The fraction size and dose we used would be equivalent, in terms of normal tissue toxicity, to about 71.5 Gy delivered instead in 2 Gy fractions, a total dose within the upper range used in most retrospective salvage studies. Our regimen, as reported here, has been very well tolerated. While possible differences in volumes of bladder and rectum included in the clinical target volumes in this present and other studies cannot easily be accounted for, the low late toxicities observed here compare favorably with a recent salvage series of 68 patients who received 74 Gy in 2 Gy fractions, in which late grade ≥2 GU side effects were reported in 31% (with 6% strictures), and late grade ≥2 GI toxicities were noted in 13% [30]. Similar low late toxicity rates were noted in a prospective evaluation of toxicities in patients receiving 60–66 Gy salvage RT in standard fractions [31]. Of note, no late grade 3 or 4 toxicities were seen in this present study, and late grade 2 side effects were usually easily treated or resolved spontaneously, with only a 3% and 1% prevalence of late grade 2 GU and GI toxicities, respectively, at last follow-up.

Limitations of our study stem from its retrospective nature, and from the heterogeneity that exists with regard to treatment parameters and pathologic factors in this patient cohort. While the utility of concurrent hormone ablation has not been prospectively evaluated in the salvage setting, 8 patients in our series (7.4%) received concurrent hormone ablation, and this may have augmented the biochemical control rates presented. Furthermore, 14 patients (13%) received radiation to high doses (52–56 Gy) to the pelvic lymph nodes, with unknown impact on overall biochemical control for this patient cohort. Additionally, while most patients (73%) had pT2 tumors with a relatively low pre-salvage PSA (median 0.44), a few patients were included with very high-risk disease, including 2 patients with node positivity, patients with bulky recurrence, and 2 patients with markedly high PSAs (8.95 & 9.50 ng/ml). These heterogeneous pretreatment and treatment factors, in addition to the inability to completely account for the differences in clinical and pathologic variables between studies, preclude definitive comparison of biochemical outcomes. Nonetheless, our outcomes utilizing a hypofractionated approach appear at least comparable to, if not more favorable than those from series using standard fractionation.

The prospective randomized trials investigating adjuvant radiotherapy after radical prostatectomy have demonstrated that 36–54% of patients in their observation arms do not develop biochemically recurrent disease in the timeframe of the studies' followup [5–7], indicating, as with any adjuvant treatment, that some patients do not derive benefit. Additionally, analysis of these three trials demonstrated ultimate biochemical progressions in the adjuvant arms of 26–35%, suggesting that the use of adjuvant RT doses of 60–64 Gy

to the prostatic fossa ultimately prevents recurrence in less than half of the patients destined to have biochemical progression, numbers not too dissimilar to the biochemical control rates seen in many studies of salvage radiotherapy. Thus, while the clinical benefits of postprostatectomy radiation therapy in high risk patients have been clearly established in randomized trials, the optimal timing of such treatment remains an investigational question, one that is currently being re-explored in three large randomized trials: GETUG-17 (ClinicalTrials.gov identi er NCT00667069), RAVES (Radiotherapy Adjuvant Versus Early Salvage; ClinicalTrials.gov identi er NCT00860652), and RADICALS (Radiotherapy and Androgen Deprivation In Combination After Local Surgery) [32]. These trials will ultimately determine whether close postoperative observation of patients with positive margins, extracapsular extension, or seminal vesicle invasion and early initiation of salvage RT after biochemical progression will provide an effective, perhaps optimal postoperative management approach. With an overall goal of maximizing benefit versus risk and cost, there certainly is likely to also exist a middle ground, where patients deemed to be at very high risk for local failure are offered adjuvant therapy, whereas others at lower but still significant risk are followed closely and, if necessary, salvaged early.

In summary, hypofractionated radiotherapy (65 Gy in 2.5 Gy fractions in 5+ weeks) is a convenient, resource efficient and safe approach for salvage after radical prostatectomy. It reduces the length of treatment by from 1–1/2 to 3 weeks relative to other treatment schedules commonly employed. Biochemical control rates at 4 – 5 years are encouraging and await further confirmation with longer followup. The low toxicities and early favorable biochemical control outcomes found, if confirmed, may warrant future testing of similarly expedited courses of radiation therapy in an adjuvant setting as well.

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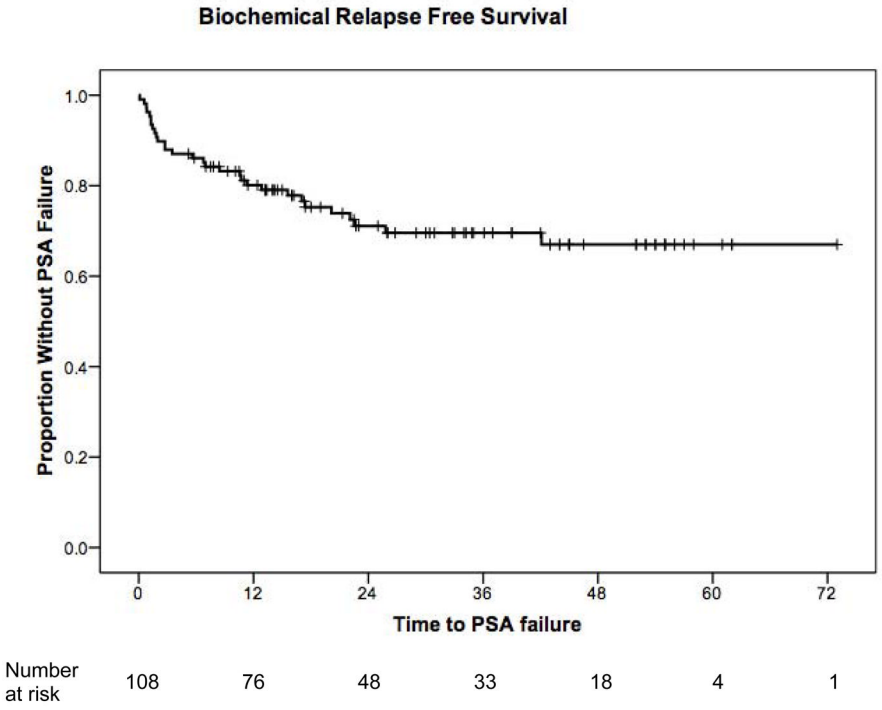

Figure 1.

Actuarial biochemical control of 108 patients undergoing hypofractionated salvage radiotherapy for biochemical failure after radical prostatectomy. Median follow-up was 32.4 months. The actuarial freedom from biochemical failure at 4 years was 67% (+/− 5.3%).

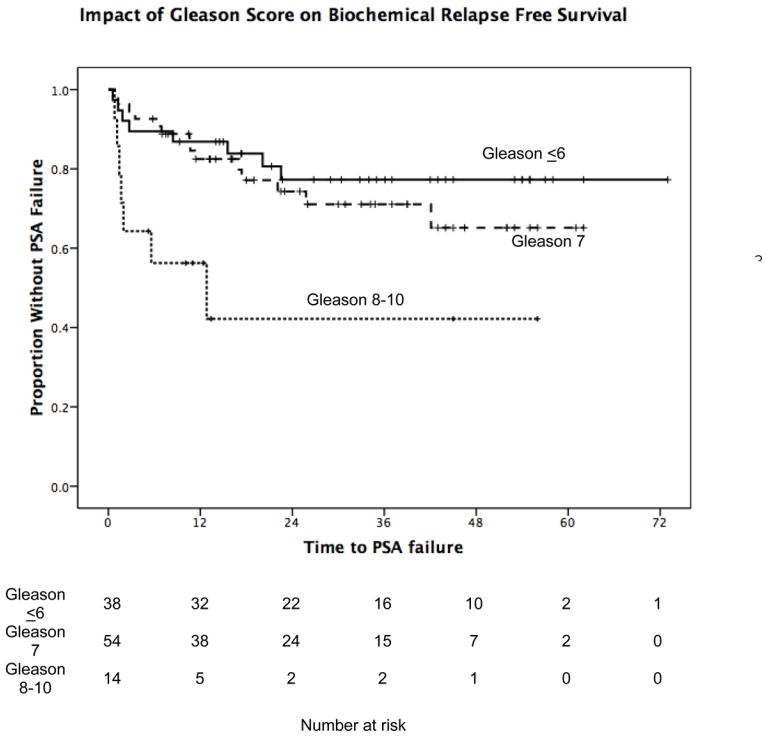

Figure 2.

Actuarial biochemical control, stratified by Gleason score, of 106 patients undergoing hypofractionated salvage radiotherapy for biochemical failure after radical prostatectomy.

Table 1

Clinical and Pathologic Characteristics

Age	n=108
Median	63
Range	45–78
Preoperative PSA (ng/ml)	n=103
Median	6.79
Range	2.2–38.46
Gleason Score	n=106
≤6	38 (36%)
7	54 (51%)
3+4	34 (32%)
4+3	20 (19%)
8–10	14 (13%)
Pathologic Stage	n=106
pT2	77 (73%)
pT3a	19 (18%)
pT3b	8 (8%)
TxN1	2 (2%)
Margins	n=105
Positive	72 (69%)
Negative	33 (31%)
Perineural invasion	n=108
Positive	43 (40%)
Negative or not specified	65 (60%)
Type of prostatectomy	n=94
Open retropubic	68 (72%)
Perineal	29 (31%)
Robotic-assisted	7 (7%)
Lymph node sampling	n=99
No	26 (26%)
Yes	73 (73%)
Median LNs (range)	3 (1–17)
Postoperative PSA nadir	n=107
Undetectable	70 (65%)
Detectable	37 (35%)
Range	0.05–2.3 ng/ml
Post-prostatectomy PSA doubling time (months)	n=100

Median (range)	6.97
≤12 mo	66 (66%)
>12 mo	34 (34%)
Pre-radiotherapy PSA (ng/ml)	n=108
Median (range)	0.44 (0.05–9.5)
≤0.4	51 (47%)
>0.4	57 (53%)

Table 2

Prognostic Variables

Univariate Analysis			
Variable	**Hazard Ratio**	**95% confidence interval**	**P value**
Gleason Score (Global)			0.014
7 vs. ≤6	1.38	0.58–3.31	0.46
8–10 vs. ≤6	2.00	1.18–3.38	0.010
8–10 vs. 7	3.26	1.29–8.20	0.012
7 (4+3) vs. 7 (3+4)	1.44	0.50–4.15	0.51
8–10 vs. ≤7	3.62	1.50–8.73	0.004
Perineural invasion; present vs. absent/unknown	1.97	0.96–4.06	0.066
Margin status; negative vs. positive	1.98	0.95–4.13	0.067
Pathologic stage; T3 vs. T2	1.77	0.82–3.81	0.14
Postoperative PSA nadir; Detectable vs. undetectable	1.21	0.55–2.63	0.64
Post-prostatectomy PSA doubling time; ≤12 mo vs. >12 mo	2.80	1.06–7.36	0.037
Pre-radiotherapy PSA (ng/ml); >0.4 vs. ≤0.4	1.44	0.69–2.99	0.33
Multivariate Analysis			
Variable	***Hazard Ratio***	***95% confidence interval***	***P value***
Gleason Score; 8–10 vs. ≤7	2.42	0.97–6.00	0.057
Margin status; negative vs. positive	1.95	0.91–4.21	0.088
Perineural invasion; present vs. absent/unknown	1.82	0.83–4.00	0.14
Post-prostatectomy PSA doubling time; ≤12 mo vs. >12 mo	2.05	0.75–5.63	0.16