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Can High-Grade Prostate Cancer (Gleason 8-10) be Cured with Definitive Local Therapy without Hormone Suppression? Disease Control and Survival Outcomes after Up-Front Radical Prostatectomy in Patients with High-Grade Clinically Localized Disease

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Abstract

Background: High-grade prostate cancer (HGPC) is associated with an aggressive clinical course and poor outcomes, thus testosterone-suppressive hormone therapy (HT) frequently accompanies definitive local therapy. Selected HGPC patients who undergo radical prostatectomy (RP) without HT enjoy long-term disease control; however, the prognostic factor selection for this approach remains to be identified.

Methods: A retrospective study of men diagnosed with biopsy-proven, clinically localized Gleason (GS) 8-10 adenocarcinoma managed with primary RP from 2003 through 2010 was undertaken. Patient-, tumor-, and treatment-related factors were analyzed for association with biochemical (PSA) relapse-free surviva (bRFS), employing Cox proportional hazard regression.

Results: Among the 96 patients with HGPC who underwent RP, 69 met eligibility criteria. Median age was 62 years (range, 48-75) and median pre-RP PSA was 7.1 ng/mL (3.5-64.9) with highest GS at biopsy of 8, 9 and 10 for 41, 26 and 2 patients respectively. Highest GS at RP was <7, 8, and >9 for 23, 17, and 29 patients, respectively. Extraprostatic extension, involved surgical margin, seminal vesicle invasion, and lymph node involvement were identified in 32, 33, 18, and 6 patients, respectively, with adjuvant radiotherapy delivered to 5 patients immediately post-RP. At median follow-up of 67.3 months (2.7-141.2), 40 patients had disease recurrence and 8 patients died (6 cancer-specific). Five-year bRFS and overall survivals were 39% (95% CI, 27-51%) and 87% (75-93%), respectively.

Primary grade and overall GS at RP, involved surgical margin, seminal vesicle involvement, nodal involvement, and elevated initial post-prostatectomy PSA were significantly associated with bRFS at univariate analysis, with primary grade at RP (HR=1.80; p<0.01) and post-RP PSA (HR=4.64; p<0.01) significant at multivariable analysis.

Conclusions: HGPC is associated with high rates of early disease recurrence. Following RP without systemic therapy, high primary grade and detectable initial post-RP PSA (>0.1 ng/mL) were independently associated with worse bRFS.

Keywords: Prostate cancer; Radical prostatectomy; Survival analysis; Radiotherapy; Systemic therapy

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Introduction

Clinically localized high-grade prostate cancer (HGPC) is characterized by higher rates of cancer-specific death relative to low or intermediate grade [1,2]. This is primarily a result of subsequent manifestation of metastatic disease [1-3]. As a result of this, multidisciplinary consensus guidelines[4] advocate for radiation therapy with long-term androgen deprivation therapy as curative-intent interventions for HGPC, with local therapies (including brachytherapy and radical prostatectomy,

Table 1: Patient Demographics and Staging Studies.

Variable	RP (n=69)	
		N (%)
Age		
Median	64 yrs	
(Range)	(50-75)	
≥70 years		14 (20)
Race		
Caucasian		67 (97)
Other		2 (3)
Clinical Stage		
cT1c		48 (70)
cT2a		12 (17)
cT2b		6 (9)
cT2c		3 (4)
Biopsy Gleason Score		
8		41(59)
9		26 (38)
10		2 (3)
PSA		
Median	7.1 ng/mL	
(Range)	(3.5-64.9)	
≥10 ng/mL		21 (30)
≥20 ng/mL		10 (14)
Staging Studies		
Bone Scan		48 (70)
CT Scan		17 (25)

Table 2: Pathology Characteristics.

Variable	RP (n=69)	
		N (%)
Interval Biopsy to RP		
Median	42 days	
(Range)	(15-123)	
Prostatectomy Techniques		
Nerve-Sparing		34 (49)
Robot-Assisted Laparoscopic		11 (16)
Open (Retropubic)		58 (84)
Prostate Specimen Volume		
Median	49.9cc	
(Range)	(22.0 – 90.7)	
Pathologic T-stage		
pT2a		2 (3)
pT2b		1 (1)
pT2c		27 (39)
pT3a		22 (32)
pT3b		17 (25)
Gleason Score at RP		
≤7		22 (32)
8		17 (25)
≥9		29 (43)
GS Concordance with Biopsy		
RP Lower than Biopsy		27 (39)
Concordant		34 (49)
RP Higher than Biopsy		8 (12)
Pathology Findings		
Extraprostatic Extension		32 (46)
Involved Seminal Vesicle(s)		18 (26)
Involved Margin(s)		33 (48)
Involved LN(s)		6 (9)
Perineural Invasion		
Yes		53 (77)
No		9 (13)
Not Recorded		7 (10)
Initial Post-RP PSA*		
Median Interval	10 wks	
Range	(2.9-39.1)	
>16 weeks		8 (12)
<0.1 ng/ml		44 (65)
0.1 ng/ml		6 (9)
>0.1 ng/ml		18 (26)
Adjuvant RT#		5 (7)

* Includes only patients with first post-RP PSA drawn ≤40 wks post-RP; denominator excludes one patient with post-RP mortality.

Radiation Therapy (6300-7200 cGy, at 180-200 cGy per once-daily fraction)

RP) considered alternative options [4]. These recommendations are due, in part, to evidence from randomized trials demonstrating an overall survival benefit for the addition androgen deprivation therapy ("hormone therapy," HT) to radiation therapy (RT) over RT alone [5-7]. Despite this, several series have demonstrated long-term disease control and survival after primary RP (with or without RT) or primary RT (particularly with brachytherapy boost) in selected populations of patients with HGPC [8-12]. Such approaches may permit avoidance of the adverse metabolic effects of prolonged HT [13]; however, identification of which HGPC patient subset(s) may be safely managed with such an approach remains to be determined.

The objectives of the current investigation are to describe mature disease control and survival outcomes for a population of patients diagnosed with Gleason score (GS) ≥8 prostate cancer at biopsy who were managed with local therapy alone. Secondary aims include analysis for factors associated with disease control and survival, in order to identify subset(s) who may potentially be cured by this approach.

Patients and Methods

Following Institutional Review Board (IRB) approval at the study institutions, a research database was created from existing medical records and quality assurance databases. Data collected included demographic, tumor staging, treatment and outcome variables. The study population included males with prostate adenocarcinoma whose highest GS at biopsy was ≥8, without clinical or radiographic evidence of suspicious regional lymph nodes or any distant metastases. Patients with pre- or immediate post-operative (non-salvage) HT, biopsy GS ≤7, or insufficient follow-up (defined as PSA follow-up <12 months post-RP) were excluded. Follow-up consisted of PSA at least every 3-6 months for 5 years, and annually thereafter. If patients had PSA failure or clinical symptoms suggestive of relapse, re-staging imaging was performed at the discretion of the primary urologist. Decisions regarding salvage or intervention were also determined by the managing urologist and oncologist.

The primary outcome for this retrospective analysis was PSA (biochemical) relapse-free survival (bRFS); defined as PSA >0.1 ng/mL and rising, clinical or radiographic evidence of recurrence, or upon initiation of salvage therapy. Stable or oscillating PSA ≤0.1 were identified but not considered events for bRFS. Overall survival (OS) was measured from date of prostatectomy to date of death or last clinical follow-up.

Statistical analysis

Survival probabilities were estimated and plotted using the Kaplan-Meier method. Estimates, along with 95% pointwise confidence intervals, were reported. Cox proportional hazards regression was used to assess the effects of clinicopathologic variables. Using a stepwise selection procedure, variables significantly associated with bRFS at the univariate level were considered for inclusion in the multivariable model. Estimated effects of predictors are reported as hazard ratios (HR) along with 95% confidence intervals (C.I.). All statistical testing was two-sided and assessed for significance at the 5% level using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Between 2003 and 2010, 96 patients with GS ≥8 prostate cancer underwent RP, of whom 69 were eligible for the present analysis.

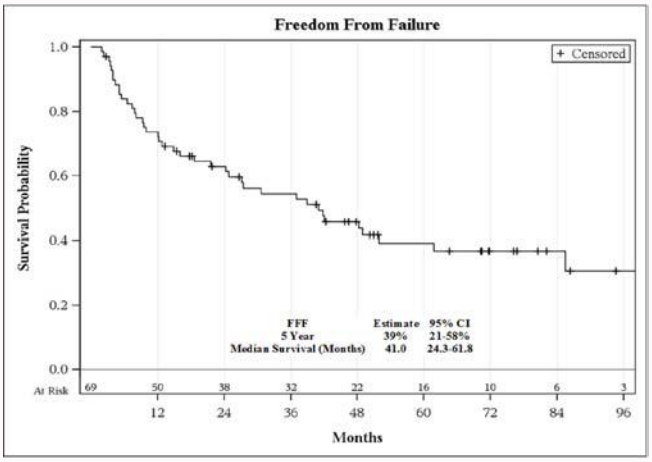

Figure 1: Biochemical (PSA) Relapse-Free Survival.

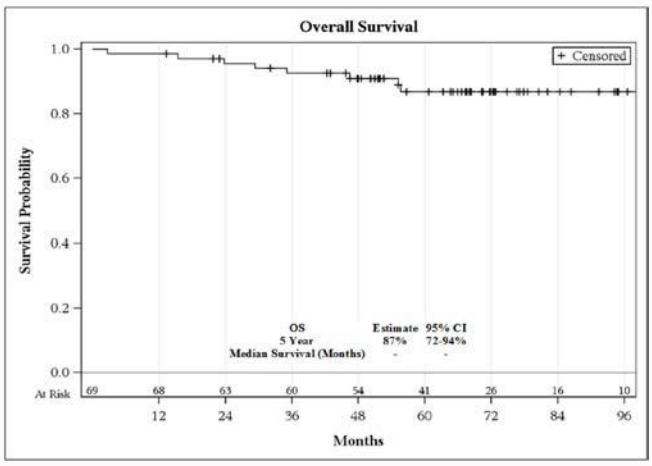

Figure 2: Overall Survival.

Reasons for ineligibility were pre and/or post-RP hormone therapy (n=11), non-curative or aborted prostatectomy (7), insufficient follow-up (6), pre-RP chemotherapy (1), absence of cancer in biopsy specimen at review (1), and metastatic disease at diagnosis (1). The median age at diagnosis was 62 years (range, 48-75) and average PSA at biopsy was 7.1 ng/mL (3.5-64.9). Detailed patient demographics, pre-operative staging and tumor characteristics are outlined in Table 1. At RP, GS was <7, 8, and >9 for 23, 17, and 29 patients, respectively. Extraprostatic extension, involved surgical margin, seminal vesicle invasion, and lymph node involvement were identified in 32, 33, 18, and 6 patients, respectively, with adjuvant radiotherapy delivered to 5 patients immediately following RP (Table 2).

At a median follow-up of 67.3 months (2.7-141.2), 40 patients (58%) experienced disease recurrence (all initially detected by rising PSA) and 8 patients had died (6 cancer-specific). The estimated 5-year bRFS was 39% (95% C.I., 21-58%; Figure 1), and the 5-year OS was 87% (72-94%; Figure 2). On univariate analysis, primary Gleason grade (GG) and overall GS at RP, involved surgical margin(s), seminal vesicle involvement, nodal involvement, and elevated initial post-RP PSA (>0.1 ng/mL, within 6 months of RP) were significantly associated with bRFS (Table 3). Multivariable analysis identified primary GG at RP (HR=1.80; p<0.01) and post-RP PSA (HR=4.64; p<0.01) as independently associated with bRFS (Table 3).

Table 3: Univariate and Multivariable Analyses of Factor Association with PSA (Biochemical) Relapse-Free Survival for High-Grade Prostate Cancers at Biopsy, Managed with Local Therapy Only.

Variable	RP (n=69)		*P*
	HR	(95% C.I.)	
Univariate Analysis (bRFS):			
Primary Gleason Grade at RP*	**1.91**	(1.23-2.96)	**<0.01**
Overall Gleason Score at RP*	**1.46**	(1.02-2.10)	**0.04**
Involved Surgical Margin	**3.33**	(1.72-6.45)	**<0.01**
Seminal Vesicle Involvement	**2.61**	(1.36-5.02)	**<0.01**
Pathological Positive Lymph Nodes	**4.60**	(1.75-12.12)	**<0.01**
PSA Velocity*	1.07	(0.88-1.31)	0.324
Initial Post-RP PSA	**4.85**	(2.57-9.16)	**<0.01**
Perineural Invasion	1.91	(0.58-6.24)	0.29
Adjuvant Radiotherapy	1.58	(0.38-6.58)	0.53
Multivariable Analysis (bRFS):			
Primary Gleason Grade at RP*	**1.80**	(1.14-2.84)	**<0.01**
Post-RP PSA	**4.64**	(2.42-8.91)	**<0.01**

*Units=1. PSA velocity data available for 23 patients. Within the univariate analysis, Cox regression for Gleason Grade and Score were scored as continuous variables; however, in the multivariable analysis, these were scored as categorical variables for subsequent risk subgroup stratification.

Table 4: Five-Year Estimates of Biochemical (PSA) Relapse-Free Survival, by Subset Populations.

Subgroup*	N	5 Year FFF Estimate	95% CI
GG3, PSA <0.1	14	61%	(30-82%)
GG3, PSA ≥0.1	3	-	-
GG4-5, PSA <0.1	30	49%	(27-69%)
GG4-5, PSA ≥0.1	21	10%	(2-26%)

GG = primary Gleason grade at prostatectomy; PSA = initial post-prostatectomy prostate specific antigen, performed within 6 months post-prostatectomy, expressed in ng/mL.

*Excludes one patient who did not have an initial post-operative PSA, owing to death related to peritonitis following prostatectomy. No estimates provided for GG3/PSA≥0.1 ng/mL owing to low number of patients within this subset (2 of the 3 did experience recurrence).

In combining these factors, three discrete subsets were identified, with 5-year estimates of disease control described in Table 4.

Discussion

Gleason 8-10 prostate cancer is characterized by an aggressive clinical course, including high rates of PSA relapse and poor disease-specific survival [1-3]. Two major randomized trials have demonstrated superior disease control and survival outcomes with the addition of long-course hormone therapy to radiotherapy [5-7], though such has not been demonstrated for hormone therapy addition to RP [14,15]. Despite this, several small series have suggested that a subset of HGPC patients may achieve favorable disease control and survival with local therapy alone, whether RP or RT (with or without brachytherapy) [8-12].

Consistent with prior investigations [16-18], the present study demonstrates high rates of early PSA relapse after primary RP for HGPC. The 5-year bRFS was only 39%, reflecting both the high rate of locally invasive features and the elevated risk of lymph node and distant metastasis. We elected to include patients with HGPC at biopsy (rather than RP specimen only) in order to consider the data available at the time of primary intervention decision-making, at which point either RP or RT are being considered as definitive local therapy options. The rate of GS concordance between biopsy and RP specimen was 61% (with 39% downgraded), which aligns with previous reports specific to high-risk presentation of disease [19,20]. For patients treated with RP, confirmation of Gleason >9 disease

or more advanced pathologic stage (pT3b or pN1) portends worse outcomes, including biochemical recurrence, metastasis, and death [9,10]; however, specific subsets of patients with favorable long-term disease control have been described [25]. Our own findings align with these data, as primary GG of 4-5 was independently associated with PSA relapse, yet overall survival remained high (87% at 5 years). Further, all recurrences initially manifest as PSA relapse, which alone does not necessarily portend death from prostate cancer. In fact, in the era of PSA screening and surveillance, over 80% of patients with PSA failure die of an alternate etiology [3].

Specific to radiotherapy alone, while historical rates of HGPC control using external-beam RT alone are suboptimal [5-7], patients enrolled in these trials had more locally advanced tumors and higher pre-treatment PSA than is seen in the contemporary setting. Recent evidence suggests impressive PSA control rates employing combined RT and brachytherapy in selected HGPC cases [11,12]. These outcomes approach those seen with primary RP (when adjuvant RT is given in the setting of high-risk features) [16-18].

Detectable initial post-RP PSA (>0.1 ng/mL) was identified as independently associated with bRFS. Other investigators have noted this as well [21,22], with worse prognosis associated with earlier time to PSA failure [22]. While trials of post-operative radiotherapy improved bRFS irrespective of detectable initial post-op PSA [16,17], there remains some debate as to whether early salvage radiotherapy may produce comparable symptom-free and survival outcomes [23,24].

Given the present study findings, no true "low-risk" group could be identified, for whom definitive local therapy without systemic therapy would be appropriate. One major confounding factor was the low utilization of adjuvant RT in the setting of high-risk pathologic features, such as involvement of pelvic lymph nodes, seminal vesicles, extraprostatic tissue, or surgical margin(s). Randomized trials have demonstrated superior bRFS, [16,17] as well as improved distant metastasis-free survival benefit [17], for adjuvant RT over RP alone, reinforcing the importance of local control on systemic involvement. These differences remained significant for HGPC cases as well [16,17].

Conclusion

High-Gleason grade prostate cancer has a high rate of recurrence after RP alone as demonstrated in the present study by the low rate of freedom from failure after 5 years. However, 5-year OS remains high, suggesting that identification of patients who will recur early versus late is important. Higher primary GG at RP and detectable post-RP PSA (>0.1 ng/mL) are high-risk features that were associated with worse bRFS and warrant investigation along with other prognostic markers to determine the timing of adjuvant therapy for HGPC patients who undergo RP.

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