

# High-grade prostate adenocarcinoma: survival and disease control after radical prostatectomy

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**Background and objective** The optimal primary intervention for treatment of clinically localized high-grade prostate adenocarcinoma remains to be identified. The present investigation reports disease control and survival outcomes in patients treated with primary radical prostatectomy.

**Methods** Eligible patients were diagnosed with Gleason score 8-10 at diagnostic biopsy and prostate-specific antigen (PSA) < 30 ng/mL, treated with primary radical prostatectomy, without clinical evidence of distant metastatic disease, seminal vesicle invasion, or lymph node involvement. Demographic, treatment, and outcome data were retrospectively collected and analyzed from a clinical database. Survival analysis methods were employed to assess disease control and survival rates, as well as association of patient-, tumor-, and treatment-specific factors for endpoints.

**Results** Fifty patients were eligible for the present analysis, with Gleason 8 and 9 in 32 (64%) and 18 (36%) patients, respectively. Surgical margin, seminal vesicle, and lymph node involvement were noted 32 (64%), 18 (36%), and 6 (12%) patients, respectively; only 4 (8%) received adjuvant radiotherapy. At a median follow-up of 44.9 months (range, 4.2-104.6), 33 patients (66%) had experienced PSA relapse, of whom 7 have been successfully salvaged. Four patients died, all with uncontrolled disease. The estimated 5-year freedom from failure was 17%. Interval from biopsy to prostatectomy, surgical margin status, and seminal vesicle involvement were associated with decreased overall survival.

**Conclusions** High-risk Gleason score at biopsy is associated with suboptimal PSA control at 5 years following prostatectomy alone; however, in the setting of uninvolved seminal vesicles and lymph nodes, the dominant pattern of failure appears to be local, and early postoperative radiotherapy should be considered.

High-grade localized prostate cancer is associated with suboptimal prostate-specific antigen (PSA) control and survival,<sup>1</sup> and optimal management remains to be defined.<sup>2</sup> While radical prostatectomy is not precluded, high-risk pathologic features are often identified for which postoperative radiotherapy is presently recommended, based upon the results of 2 large multicenter phase 3 trials.<sup>3,4</sup> Thus, many patients are treated upfront with radiation therapy-based applications, coupled with long-term hormone therapy, which has been established as a standard of care.<sup>2,5</sup> As such, there are few contemporary studies evaluating the disease control outcomes specifically for patients with high-grade disease

(Gleason score  $\geq$  8, per AJCC, low risk defined as score  $\leq$  6, intermediate risk 7, and high-risk  $\geq$  8), treated with radical prostatectomy, and followed post-operatively without hormone manipulation. The present investigation reports on disease control and survival outcomes for this population, including pre- and postoperative factors associated with these endpoints.

## Patients and methods

Following Institutional Review Board approval at Sanford Medical Center and St. Alexius Medical Center (Bismarck, ND), a research database was created with study-specific patient, treatment, and outcome data fields. Eligible cases were identified by review of medical records and quality assurance database. After selection for prostate adenocarcinoma cases, a review of patient records was performed to eliminate patients with advanced or metastatic dis-

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ease at diagnosis (including preprostatectomy evidence of seminal vesicle or pelvic lymph node involvement) or Gleason score < 7 at biopsy. All of the patients had undergone radical prostatectomy with pathologic evaluation of surgical margins, seminal vesicles, and regional lymph nodes. Postoperative evaluations included physical examination and PSA measurement every 3-6 months for the first 2 years postprostatectomy, and every 6-12 months thereafter. In the setting of PSA or clinical relapse, re-staging imaging and subsequent intervention or interventions were performed at the discretion of the managing urologist.

The principal outcome measure of this retrospective study was freedom from failure, specifically postprostatectomy PSA, measured from date of prostatectomy to date of first rising PSA > 0.1 ng/mL, or last follow-up or death if no PSA rise occurred. Secondary outcome measures included overall survival and analysis of factors associated with freedom from failure and survival. Patient status at last follow-up was recorded as “alive, no evidence of disease,” “alive with disease,” “died of or with disease,” or “died of other cause.”

### Statistical analysis

Kaplan-Meier survival curves were constructed to describe freedom from failure and overall survival for the entire cohort. Cox proportional hazards model were used to identify continuous and dichotomous variable association with disease control; categorical variables were analyzed by log-rank analysis. Analyses were performed using SPSS Version 10 (SPSS Inc; Chicago, IL).

### Results

Between January 2002 and December 2010, 533 patients diagnosed with prostate cancer underwent radical prostatectomy using the retropubic approach. Of these, 50 patients with Gleason score > 8 at biopsy were identified and included in the present investigation. Patient demographics and pre-operative tumor characteristics are shown in Table 1, and pathologic tumor characteristics, treatment specifics, and postoperative data are described in Table 2.

At a median survivor follow-up of 46.6 months (range, 4.2-104.6 months), 33 patients had experienced disease recurrence, and 4 had died with uncontrolled disease. Estimated 5-year freedom from failure was 16.6% (95% CI, 14.5%-18.7%; Figure 1), and overall survival was 87.6% (95% CI, 85.7%-89.5%; Figure 2). Only 1 patient was demonstrated to have had distant failure at the time of recurrence. Characteristics of recurrence and salvage therapy are shown in Table 3. Specific to success of salvage therapies, 11 of 33 patients underwent curative-intent salvage radiotherapy, of whom 7 (60%) demonstrated PSA control at a

**TABLE 1** Patient demographics

Demographic	n	%
Age, y		
Median (range)	65 (50-75)	–
Race		
White	50	100
PSA, ng/mL		
Median (range)	7.1 (3.7-64.9)	–
Gleason score		
3+5	5	10
4+4	21	42
5+3	6	12
4+5	12	24
5+4	6	12
Clinical tumor stage <sup>a</sup>		
T1c	29	58
T2a	12	24
T2b	5	10
T2c	4	8
Bone scan	27	54

<sup>a</sup>American Joint Committee on Cancer, TNM Staging Manual, version 7.0.

median of 38.5 months post salvage (range, 7.0-63.0; 3 with concurrent hormone therapy).

Analysis of factors associated with freedom from failure demonstrated statistically significant associations with pathologic AJCC stage, Gleason score at biopsy and prostatectomy, capsule invasion, involved surgical margin, seminal vesicle involvement, percent lymph nodes involved, and postoperative PSA (Table 4).

Analysis of factors associated with overall survival demonstrated statistically significant associations with interval from biopsy to prostatectomy, surgical margin status, and seminal vesicle involvement (Table 4).

### Discussion

High-grade prostate adenocarcinoma is associated with poor disease control and survival outcomes; the findings of the present investigation mirror those of other investigators,<sup>1,6-11</sup> with disease control rates below 50% at 5 years. For Gleason 8-10 patients treated with a primary surgical approach, locoregionally advanced disease is a common finding,<sup>6,12</sup> which was corroborated within the present study. In these cases, postoperative radiotherapy (RT) is strongly recommended,<sup>2</sup> particularly when there is seminal vesicle invasion, penetration of the prostate capsule, and/or involvement of the surgical margins. Several randomized phase III trials have demonstrated superior PSA control with

**TABLE 2** Surgical pathology, treatment, and postoperative data

	n	%
Interval biopsy to RP, <sup>a</sup> days		
Median (range)	45 (15-123)	
Nerve-sparing RP?		
Yes	34	68
Prostate volume, cc		
Median (range)	45.5 (22-131)	
Perineural invasion?		
Yes	40	80
No	2	4
Not recorded	8	16
Pathologic Gleason score		
3+3	1	2
3+4	6	12
4+3	9	18
3+5	6	12
4+4	2	4
5+3	6	12
4+5	10	20
5+4	10	20
Change from biopsy score		
Decreased	19	38
Unchanged	24	48
Increased	7	14
Surgical margin		
Negative	21	42
Positive/through	29	58
Capsular invasion <sup>#</sup>		
Negative	16	32
Positive	24	48
Unable to determine <sup>#</sup>	10	20
Seminal vesicle involvement		
None	32	64
Unilateral	6	12
Bilateral	12	24
Pathologic tumor stage <sup>§</sup>		
T2b	1	2
T2c	20	40
T3a	11	22
T3b	17	36
T4	1	2

**TABLE 2** (continued)

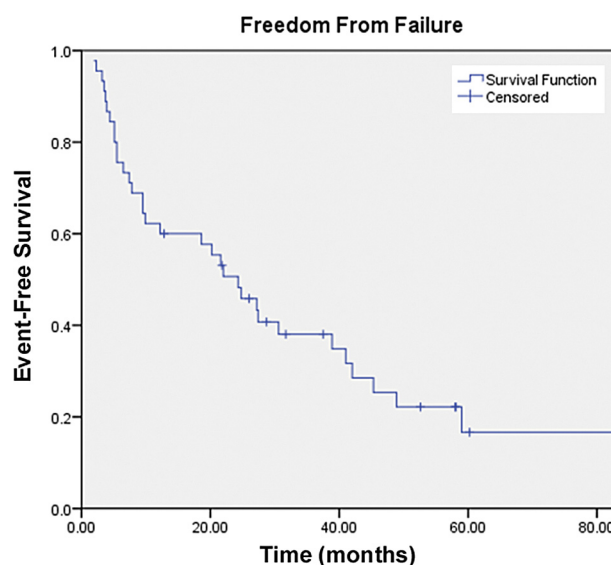
	n	%
Lymph node evaluation		
Median number removed (range)	5 (2-17)	
Uninvolved	44	88
1	1	2
2	3	6
3	2	4
Hormone therapy <sup>^</sup>		
Yes	7	14
Adjuvant RT <sup>*</sup>		
Yes	4	8
Median dose, cGy (range)	6,840 (6,840-7,020)	
Median interval RP to RT, d (range)	59 (54-112)	

<sup>a</sup>RP = radical prostatectomy; <sup>\*</sup>RT = radiotherapy.

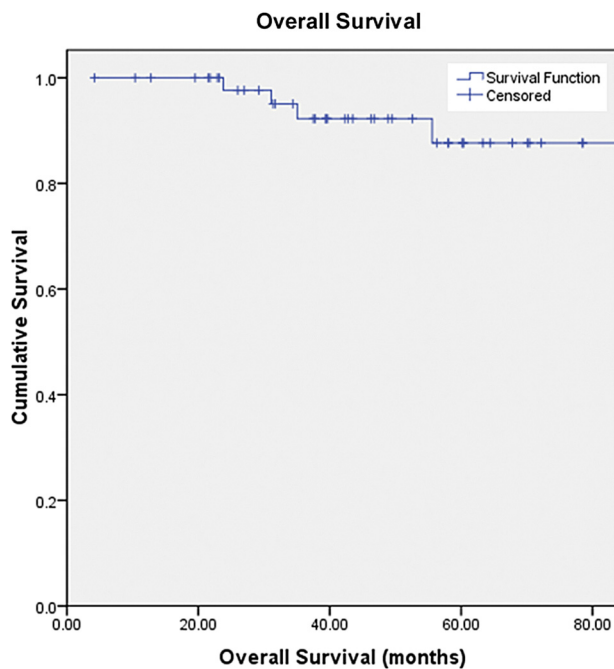
<sup>#</sup>Excludes 10 patients with involved margin in area of capsular disruption, as capsular invasion could not be excluded.

<sup>§</sup>American Joint Committee on Cancer, TNM Staging Manual, version 7.0.

<sup>^</sup>Prior to PSA failure.

**FIGURE 1** Freedom from failure for study population.

early postoperative RT,<sup>3,4,13</sup> which has translated into superior distant metastasis-free and prostate cancer-specific survival.<sup>3</sup> The contemporary magnitude of benefit may be higher, as subsequent evidence has demonstrated superior efficacy of higher doses of RT than was employed in the trials.<sup>14</sup> While the randomized trials were not limited to patients with high-grade pathology, several



**FIGURE 2** Overall survival for the study population.

**TABLE 3** Recurrence and salvage therapy characteristics

	n	%
Any Post-RP PSA Rise		
Yes	37	74
Median Interval to Rise	12.2 months	
(Range)	(1.9-59.0)	
Only to 0.1, without further rise	4	8
PSA Doubling Time*		
Median	6.0 months	
(Range)	(1.0-44.4)	
Salvage Therapy		
None	8	16
RT <sup>#</sup>	5	10
Hormone	14	28
RT + Hormone	6	10
Chemotherapy + Hormone	1	2

\*For 26 patients with PSA > 0.1 and rising, for whom doubling time could be calculated.

<sup>#</sup>RT = radiotherapy.

studies have confirmed improved outcomes for node-negative patients treated with postoperative RT.<sup>6,7</sup> This benefit holds in the setting of undetectable PSA following prostatectomy.<sup>12,15</sup> For those patients with radiographi-

cally nonmetastatic but pathologically node-positive disease, androgen deprivation therapy is recommended, due to high likelihood of subclinical metastatic disease.<sup>2</sup>

Within the present study population, 11 patients underwent salvage radiotherapy after PSA failure, of whom 7 have sustained PSA control at a median of 28.4 months post salvage. While many of these patients had indication(s) for early postoperative (adjuvant) radiotherapy, the response rates would suggest that local failure remains a predominant pattern of recurrence or progression. This finding has been demonstrated in other series of high-risk patients,<sup>6,16,17</sup> particularly in the setting of an involved surgical margin<sup>16,17</sup> and when salvage radiotherapy is initiated early.<sup>17</sup> Subset analysis from the landmark Southwest Oncology Group (SWOG) randomized trial demonstrate superior PSA control and decreased risk of distant metastases when radiotherapy is initiated within 4 months of prostatectomy rather than at salvage,<sup>3</sup> likely owing to reduced tumor burden and less opportunity for metastasis.

Given the likelihood of recommendation for post-operative radiation and/or hormone therapy following prostatectomy for high-grade prostate cancer, the use of definitive RT plus long-course hormone therapy is a standard recommendation,<sup>2</sup> as evidenced by long-term data from phase 3 trials.<sup>5,18</sup> While prospective head-to-head comparisons have not been performed, retrospective analyses suggest at least equivalent outcomes for RT plus hormone therapy,<sup>8</sup> sparing patients the morbidity of upfront surgical intervention. The present investigation confirms the high likelihood of advanced disease, with 32 of 44 (73%) node-negative patients having an indication for postoperative radiotherapy with or without hormone therapy.

Further confounding the optimal therapy recommendation for Gleason 8-10 disease are the limitations of pre-intervention staging. While pelvic CT is considered standard, the diagnostic yield is considered low, with accuracy of about 65%.<sup>19</sup> For distant metastatic disease staging, bone scans are recommended;<sup>2</sup> however, the specificity of scintigraphy at PSA < 20 ng/mL is low,<sup>19</sup> and bony relapse following a negative staging scintigraphy is common in the setting of high-grade prostate cancer.<sup>5</sup>

Within the univariate analysis, several factors were identified as correlated with disease control and survival outcomes. Of these, seminal vesicle invasion was the only factor associated with both PSA relapse and overall survival, a finding reported by other investigators.<sup>6</sup> Our findings also align with factors described by others, including pre-operative PSA<sup>6,8,9</sup> and margin status.<sup>9</sup> An interesting finding of this study is the inverse association between interval between biopsy to prostatectomy and overall survival. Adverse outcomes for delayed initiation of therapy have been described with other aggressive tumor types,<sup>20</sup> but such an association has not been previously described

**TABLE 4** Univariate analysis of factors associated with disease control and survival

	Freedom from failure		Overall survival	
	exp(b)*	p-value	exp(b)*	p-value
Age	1.002	0.94	0.993	0.927
Pre-operative PSA	1.021	0.054	1.012	0.669
Gleason Score at Biopsy	2.424	0.012	113.247	0.272
Interval from Biopsy to RP	1.009	0.262	1.03	0.037
Gleason Score at RP	1.547	0.072	20.969	0.255
Margin Involvement	8.102	0.088	16.087	0.003
Capsule Penetration	4.386	0.008	45.611	0.435
SV Involvement	4.441	<0.0001	11.259	0.004
# LNs Involved	1.582	0.06	1.893	0.148
Post-RP PSA	1.066	0.01	1.003	0.964

\*Exp(b) = exponentiation of the beta-coefficient, representing change in the Odds Ratio for each one unit change of the variable measured.

in the literature specific to high-grade prostate cancer. At present, no specific recommendation can be made, as this finding should be validated on a larger pool of high-grade prostate cancer patients.

## Conclusions

Biopsy-proven high-risk Gleason score prostate adenocarcinoma is associated with suboptimal PSA control at 5 years post prostatectomy; however, in the setting of negative seminal vesicles and lymph nodes, the pattern of failure appears to be local. Further investigation of the association between survival and the biopsy-prostatectomy interval is warranted. Early postoperative RT should be considered, particularly when the surgical margin involvement, extraprostatic extension, and/or seminal vesicle invasion is noted.

## References

- Walsh PC, DeWeese T, Eisenberger MA. Localized prostate cancer. *N Engl J Med.* 2007;357:2696-2705.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): *Prostate Cancer*, version 4.2011.
- Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* 2009;181:956-962.
- Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet.* 2005;366:572-578.
- Horwitz EM, Bac K, Hanks GE, et al. Ten-year follow-up of Radiation Therapy Oncology Group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol.* 2008;26:2497-2504.
- Do TM, Parker RG, Smith RB, et al. High-grade carcinoma of the prostate: a comparison of current local therapies. *Urology.* 2001;57:1121-1127.
- Oefelein MG, Grayhack JT, McVary KT. Survival after radical retropubic prostatectomy of men with clinically localized high grade carcinoma of the prostate. *Cancer.* 1995;76:2535-2542.
- Arcangeli G, Strigari L, Arcangeli S, et al. Retrospective comparison of external beam radiotherapy and radical prostatectomy in high-risk, clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2009;75:975-982.
- Lau WK, Bergstralh EJ, Blute ML, et al. Radical prostatectomy for pathologic Gleason 8 or greater prostate cancer: influence of concomitant pathological variables. *J Urol.* 2002;167:117-122.
- Lu-Yao GL, Siu-Long Y. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet.* 1997;349:906-910.
- Tewari A, Divine G, Chang P, et al. Long-term survival in men with high grade prostate cancer: a comparison between conservative treatment, radiation therapy, and radical prostatectomy – a propensity scoring approach. *J Urol.* 2007;177:911-915.
- Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol.* 2009;27:2924-2930.
- Hull GW, Rabbani F, Abbas F, et al. Cancer control with radical prostatectomy alone in 1000 consecutive patients. *J Urol.* 2002;167:528-534.
- Bernard JR, Buskirk SJ, Heckman MG, et al. Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. *Int J Radiat Oncol Biol Phys.* 2010;76:735-740.
- Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol.* 2007;25:2225-2229.
- Trock BJ, Han M, Freedland, SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA.* 2008;299:2760-2769.
- tephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA.* 2004;291:1325-1332.
- Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomized study. *Lancet Oncol.* 2010;11:1066-1073.
- Akin O, Hricak H. Imaging of prostate cancer. *Rad Clin N Amer.* 2007;454:207-222.
- Jensen AR, Nellesmann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. *Radiother Oncol.* 2007;84:5-10.