Long-Term Prognostic Significance of Primary Gleason Pattern in Patients With Gleason Score 7 Prostate Cancer: Impact on Prostate Cancer Specific Survival

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Purpose: We determined the long-term clinical significance of primary Gleason pattern in patients with Gleason score 7 prostate cancer.

Materials and Methods: We reviewed the records of all patients who underwent bilateral pelvic lymph node dissection and radical retropubic prostatectomy for Gleason score 7 prostate cancer at our institution. All patients who underwent adjuvant hormonal or radiation therapy were excluded from analysis. Patients were monitored for biochemical failure, that is PSA progression, systemic recurrence and cancer specific survival.

Results: We identified 1,688 patients who met admission criteria, of whom 1,256 (74.4%) had primary Gleason pattern 3 and 432 (25.6%) had primary Gleason pattern 4. Median followup was 6.9 years. At 10 years primary Gleason pattern 3 was associated with increased biochemical recurrence-free survival (48% vs 38%, $p < 0.001$), lower systemic recurrence (8% vs 15%, $p < 0.001$) and higher cancer specific survival (97% vs 93%, $p = 0.013$) for Gleason primary grades 3 and 4, respectively. All of these end points remained significant on multivariate analysis when controlling for preoperative PSA, seminal vesicle involvement, margin status, DNA ploidy and TNM staging. PSA doubling time was shorter in patients with primary Gleason pattern 4 (1.64 vs 1.01 years). Systemic recurrence and cancer specific survival were associated with a PSA doubling time of less than 1 year.

Conclusions: Gleason score 7 prostate cancer is a heterogeneous entity. We should continue to stratify patients according to primary Gleason pattern. Patients with Gleason score 4 + 3 prostate cancer have more aggressive disease and experience higher rates of biochemical failure, systemic recurrence and cancer specific death.

Key Words: prostate, prostatic neoplasms, prostatectomy, mortality, disease progression

Accurate determination of patient prognosis is important when treating patients with adenocarcinoma of the prostate. GS has been shown to be an important prognostic factor for predicting biochemical failure, systemic recurrence and overall patient survival.[1] Patients with well differentiated tumors (GS 2 to 6) generally have a favorable prognosis. Those with high grade tumors (GS 7 to 10) experience higher rates of progression.[2]

GS 7 tumors are heterogeneous in histological appearance, combining elements of Gleason pattern 3 and 4. Several studies have demonstrated that Gleason pattern 4 is associated with seminal vesical invasion, lymph node involvement, DNA ploidy, extraprostatic extension and surgical margin status. However, primary Gleason pattern was not independently associated with disease progression.[3–5] Other studies have shown that Gleason pattern 4 or percent of high grade tumor (Gleason pattern 4 to 5) is an independently significant factor for biochemical recurrence.[6–9] To our knowledge no studies have demonstrated an impact on systemic progression or cancer specific survival. We assessed the long-term clinical significance of stratifying patients following RRP with GS 7 PC by primary Gleason pattern, ie 3 + 4 vs 4 + 3.

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Study received institutional approval from the Mayo Foundation Institutional Review Board.

METHODS

Institutional approval from the Mayo Foundation Institutional Review Board was received on November 25, 2003.

From 1987 to 2000, 9,199 patients underwent radical prostatectomy and bilateral pelvic lymphadenectomy with a reported Gleason score at our institution. A total of 6,810 patients received no adjuvant therapy preoperative or postoperatively, of whom 1,688 (25%) were found to have a pathological Gleason 7 tumor. All clinical and pathological information (using the 1992 TNM system) was collected prospectively.

Surgical procedure. All men were evaluated preoperatively with serum PSA and digital rectal examination. RRP was performed using an anatomical approach and bilateral lymphadenectomy was performed in all patients, as previously described.[2]

Pathological evaluation. Radical prostatectomy specimens were graded histologically according to the Gleason system and the TNM staging system was used for clinical and pathological staging. Clinical stage was determined by digital rectal examination. Frozen and subsequent paraffin embedded sections of all lymph nodes removed during bilateral pelvic lymph node dissection were examined. Immediately after resection pathologists examined the radical

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TABLE 1. *Clinical and pathological features by primary Gleason pattern*

	Pattern			
	3+4	4+3	Totals	p Value
No. pts	1,256	432	1,688	0.0104
Rounded age at surgery:				0.0104
SD ± Mean	64.5 ± 6.78	65.5 ± 6.39	64.8 ± 6.69	
Median	65.0	67.0	66.0	
Range	43.0–82.0	47.0–80.0	43.0–82.0	
Preop PSA (ng/ml):				<0.0001
Median	7.5	8.8	7.8	
Quartile 1, 3	5.2, 11.7	5.7, 15.3	5.3, 12.3	
Range	0.5–219.0	0.8–201.0	0.5–219.0	
No. 1997 TNM revision clinical stage (%):				0.0394
Missing	5	0	5	
T1ab	12 (1)	6 (1.4)	18 (1.1)	
T1c	340 (27.2)	89 (20.6)	429 (25.5)	
T2a	633 (50.6)	236 (54.6)	869 (51.6)	
T2b	164 (13.1)	64 (14.8)	228 (13.5)	
T34	102 (8.2)	37 (8.6)	139 (8.3)	
No. biopsy Gleason (%):				<0.0001
Missing	313	94	407	
2–5	177 (18.8)	55 (16.3)	232 (18.1)	
6	351 (37.2)	80 (23.7)	431 (33.6)	
7	386 (40.9)	166 (49.1)	552 (43.1)	
8+	29 (3.1)	37 (10.9)	66 (5.2)	
No. seminal vesicle involvement (%)	191 (15.2)	98 (22.7)	289 (17.1)	0.0004
No. margin positive (%)	438 (34.9)	174 (40.3)	612 (36.3)	0.0439
No. ploidy (%):				0.0141
Missing	36	16	52	
Diploid	817 (67)	256 (61.5)	1,073 (65.6)	
Tetraploid	333 (27.3)	116 (27.9)	449 (27.4)	
Aneuploid	70 (5.7)	44 (10.6)	114 (7)	
No. pathological stage (%):				<0.0001
T2abN0	246 (19.6)	48 (11.1)	294 (17.4)	
T2cN0	529 (42.1)	176 (40.7)	705 (41.8)	
T34N0	467 (37.2)	196 (45.4)	663 (39.3)	
TxN+	14 (1.1)	12 (2.8)	26 (1.5)	
Gleason pattern surgical margin score:				<0.0001
Mean ± SD	9.3 ± 1.65	9.7 ± 1.83	9.4 ± 1.71	
Median	9.0	10.0	9.0	
Quartile 1, 3	8.0, 10.0	8.0, 11.0	8.0, 10.0	
Range	7.0–14.0	7.0–14.0	7.0–14.0	

prostatectomy specimen by gross inspection as well as by analysis of multiple frozen sections. All surgical margins, including the prostate base, apex, urethra, bladder neck, capsule, periprostatic soft tissues and seminal vesicles, were evaluated. Multiple routine fixed paraffin sections from the prostate were examined later. Primary Gleason pattern was defined as the predominant portion identified (51% or greater). Tumor DNA histograms were created using the technique of Nativ et al for prostate cancer[10] and classified as diploid, tetraploid or aneuploid.

Followup. Followup visits were generally scheduled at 3 to 4-month intervals for 2 years, semiannually for 2 to 3 years and annually thereafter. All visits included digital rectal examination and serum PSA measurement. When clinically indicated, other studies, including abdominal or pelvic computerized tomography and radionuclide bone scan, were performed. PSA progression was defined as a single serum PSA of greater than 0.4 ng/ml. Systemic progression was defined as a positive bone scan or other lesion identifying metastatic prostate cancer. Prostate cancer death was defined as a death primarily caused by metastatic prostate adenocarcinoma.

PSA-DT. PSA-DT was calculated from the first detectable PSA (greater than 0.2 ng/ml) to the last contact or to the initiation of additional therapy. PSA-DT was determined using a standard formula of the slope from the linear regression of log-e of PSA (y) vs the time of PSA measurement (x).[11]

RESULTS

Patient characteristics. Median age of the 1,688 men at surgery was 66 years (range 43 to 82). Patients with GS 4 + 3 were slightly older than those with GS 3 + 4 (65.6 vs 64.5 years, $p = 0.01$). GS 3 + 4 and 4 + 3 were identified in 1,256 (74.4%) and 432 men (25.6%), respectively. Median preoperative PSA was 7.5 and 8.8 ng/ml for GS 3 + 4 and 4 + 3, respectively ($p < 0.0001$). Patients with GS 3 + 4 were more likely to have nonpalpable T1 clinical stage vs those with GS 4 + 3. Biopsy derived Gleason score was also more likely to be 6 or less in patients with GS 3 + 4 disease on radical prostatectomy pathological findings. Consistent with previous reports, cases were more likely to be up graded on final pathological evaluation rather than down graded (table 1).

Tumor characteristics. Patients with primary Gleason pattern 3 cancer were less likely to have seminal vesicle involvement (15.2% vs 22.7%, $p = 0.0004$) and positive surgical margins (34.9% vs 40.3%, $p = 0.04$) relative to those with primary Gleason pattern 4. Patients with GS 4 + 3 were more likely to have nondiploid tumors (38.5% vs 33.0%, $p = 0.01$). Those with GS 4 + 3 tumors were also more likely to have advanced pathological stage, T3 to 4 and/or positive lymph nodes (2.8% vs 1.1%).