Correlation of the primary Gleason pattern on prostate needle biopsy with clinico-pathological factors in Gleason 7 tumors

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Objectives: *To correlate the primary Gleason pattern among patients with biopsy-derived Gleason 7 tumors with the radical prostatectomy specimen Gleason grading and other clinical and pathologic outcomes.*

Methods and materials: *Among 474 patients who underwent radical prostatectomy for clinically localized prostate cancer between 1997-2001, 205 (43%) had Gleason 7/10 tumors on pre-operative needle biopsy. Among theses patients, 148 (72.2%) were assigned a primary Gleason 3 pattern (3+4 = 7) and 57 (27.8%) were assigned a primary Gleason 4 pattern (4+3 = 7). The two groups were compared with respect to age, serum PSA levels, Gleason grade in the radical prostatectomy specimen, pathological stage and surgical margin status.*

Results: *Among patients with 3+4 tumors on needle biopsy, 64% remained primary Gleason grade 3 while 35% were up-graded to a primary pattern 4 following analysis of the radical prostatectomy specimen. Patients with 4+3 tumors on needle biopsy remained primary Gleason grade 4 in 51% of patients, while 49% of patients had their tumors down-graded to a primary 3 pattern (p = 0.09). There were no differences between patients with needle biopsy 3+4 and 4+3 patterns with respect to total Gleason score in the radical prostatectomy specimen (p = 0.42), pTNM stage (p = 0.36), extra-prostatic extension (p = 0.88), surgical margin involvement (p = 0.16), and seminal vesicle invasion (p = 0.19). In contrast, the primary Gleason pattern in the radical prostatectomy specimen correlated significantly with pTNM stage (p = 0.02) and seminal vesicle invasion (p= 0.003), but not with extra-prostatic extension (p = 0.32) and surgical margin involvement (p = 0.17).*

Conclusions: *Among patients with Gleason 7 adenocarcinoma of the prostate, the biopsy-derived primary Gleason pattern does not appear to correlate with important clinical and pathologic outcomes. The utility of distinguishing a primary Gleason pattern on needle biopsy among patients with Gleason 7 tumors remains unclear given the limited and conflicting literature addressing this issue.*

Key Words: prostatic neoplasms, neoplasm staging, biopsy, prognosis

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Introduction

Histologic tumor grade is an important prognostic factor for clinically localized prostate cancer.[1-3] The Gleason scoring system has been the established

method for reporting histologic tumor grade.[1,4] Despite its value, the correlation of Gleason grade between the prostate needle biopsy and the radical prostatectomy specimen is low. The exact concordance rates range from 31% to 68%, with 29% to 43% differing by one Gleason score.[5-9] Reports suggest that between 36% to 54% of needle biopsy samples are under-graded and 15% to 22% are over-graded, when compared to the radical prostatectomy specimen.[5-9]

Recently, there has been specific interest in the prognostic significance of Gleason 7 prostate cancer.[10-13] Approximately 25% to 40% of patients diagnosed with prostate cancer on needle biopsy have tumors with a Gleason score of 7.[10,14] This increases to 40% to 50% following analysis of the radical prostatectomy specimen because of the tendency to under-score the Gleason grade on needle biopsy.[11,15,16] Data suggests that Gleason 7 prostate cancer represents a unique histological category.[10,11,17] The basis for this unique distinction rests on the fact that Gleason 7 tumors can either have a predominant Gleason grade 3 pattern (3+4 = 7) or a predominant Gleason grade 4 pattern (4+3 = 7).

The prognostic significance of the primary Gleason pattern among patients with Gleason 7 tumors in the radical prostatectomy specimen is well established.[14,17,18] Patients who have a predominant primary grade 4 pattern (4+3 = 7) have higher mean serum PSA levels, more advanced clinical and pathological stage, larger tumor volumes, higher biochemical failure and local recurrence rates, more evidence of distant metastasis and a shorter disease-free survival rate compared to patients who have a primary grade 3 pattern (3+4 = 7).[14,17,18]

The relationship between the primary Gleason pattern on prostate needle biopsy and radical prostatectomy specimen has yet to be firmly established among patients with Gleason 7 tumors.[12,13] An understanding of the predictive power of the biopsy-derived primary Gleason pattern would enhance the physician's ability to counsel patients regarding disease prognosis and treatment.

Given the significant discordance rates between biopsy-derived Gleason scores and Gleason scores derived from the radical prostatectomy specimen, coupled with the tendency for the primary Gleason pattern to influence prognostic and treatment decisions, it would be important to establish the significance of the biopsy-derived primary Gleason pattern among patients with Gleason 7 tumors.

We conducted a historical cohort study with the goal of correlating the primary Gleason pattern on prostate needle biopsy with important clinical and pathological factors among patients with Gleason 7 tumors.

Materials and methods

Between January 1997 and February 2001, we identified 481 patients who underwent radical retropubic prostatectomy (with or without pelvic lymph node dissection) for clinically localized prostate cancer at the University Health Network – Toronto General Hospital. Patients who underwent treatment prior to radical prostatectomy, including androgen deprivation and radiation therapy were excluded from our analysis (seven patients). Of the remaining 474 patients, 205 (43%) were assigned a Gleason score of 7/10 on the pre-operative needle biopsy. Among these patients, 148 (72%) had a primary 3 Gleason pattern (3+4=7), and 57 (28%) had a primary 4 Gleason pattern (4+3=7) on the pre-operative needle biopsy.

The two groups were compared with respect to patient age, serum prostate-specific antigen (PSA) levels, Gleason score in the radical prostatectomy specimen, pathological stage,[19] and surgical margin status. Gleason scores on the prostate needle biopsy and prostatectomy specimens were defined as the sum of the Gleason grades (1 to 5) assigned to the primary and secondary most predominant histological patterns of the tumor.[4] All pathology was examined and reported by one of three genitourinary pathologists at our institution according to standardized protocol.[20]

Statistical analysis was performed using SPSS 10.0 (Chicago, IL). Un-paired T-tests were used to analyze mean differences in patient age according to the primary Gleason pattern (3 versus 4) on prostate needle biopsy. Median differences in serum PSA were analyzed using non-parametric tests. We examined the correlation between the needle biopsy primary pattern (3 versus 4) and: i) primary Gleason pattern in the radical prostatectomy specimen; ii) total Gleason score in the radical prostatectomy specimen; iii) pTNM stage; iv) extra-prostatic extension; v) seminal vesicle invasion; and vi) surgical margin status.

Results

Among the 205 patients with Gleason 7 tumors on pre-operative needle biopsy, the mean age was 61.9 years and the median serum PSA was 7.45 mg/ml. The majority of patients (60%) were pathologic stage T3 and 10% of patients had their tumors up-graded (7%) and down-graded (3%) from a Gleason score of 7 following analysis of the radical prostatectomy specimen Table 1. Our positive margin rate for this

TABLE 1. **Clinical and pathological characteristics amongpatients with Gleason 7 tumors on pre-operative prostate needle biopsy**

Mean age		61.9 years
Median serum PSA		7.45 ng/ml
PTMN		
	T2	81 (40%)
	T3a	98 (48%)
	T3b	26 (12%)
Gleason score in radical prostatectomy specimen		
	6	6 (3%)
	7	184 (90%)
	8	9 (4%)
	9	6 (3%)
Extra-capsular extension		
	Negative	81 (40%)
	Positive	124 (60%)
Seminal vesicles		
	Negative	179 (87%)
	Positive	26 (13%)
Surgical margins		
	Negative	155 (76%)
	Positive	50 (24%)

subset of patients was 24% Table 1.

Among patients with biopsy derived Gleason 7 tumors, 148 (72%) were assigned a primary 3 Gleason pattern (3+4 = 7) and 57 (28%) were assigned a primary 4 Gleason pattern (4+3 = 7). There was no significant difference in the mean age among patients with a primary 3 Gleason pattern (61.4 years) and a primary 4 Gleason pattern (62.3 years) on pre-operative needle biopsy (p = 0.39). Median serum PSA levels between patients with a primary 3 Gleason pattern (7.6 ng/ml) and a primary 4 Gleason pattern (7.0 ng/ml) were not significantly different (p = 0.63).

We compared patients who had 3+4 =7 and 4+3 =7 patterns on the prostate needle biopsy specifically, with pathologic variables from the radical prostatectomy specimen. There were no significant differences between patients with needle biopsy Gleason patterns 3+4 and 4+3 with respect to total Gleason score in the radical prostatectomy specimen (p = 0.42), pTNM stage (p = 0.36), extra-prostatic extension (p = 0.88), surgical margin involvement (p = 0.16), and seminal vesicle invasion (p = 0.19) Table 2. Among patients who had 3+4 tumors on needle biopsy, 64% remained primary Gleason grade 3, while 35% were up-graded to a primary pattern 4, and 1% were up-graded to a primary 5 pattern following analysis of the radical prostatectomy specimen Table 2. In contrast, patients who had 4+3 tumors on needle biopsy remained primary Gleason grade 4 in 51% of patients, while 49% of patients had their tumors down-graded to a primary 3 pattern Table 2. The odds ratio for having a discordant grade between the biopsy and the radical prostatectomy specimen for patients with 3+4 prostate cancer on needle biopsy was 1.8 (95% CI: 0.9-3.5), compared to patients with 4+3 on needle biopsy.

Total Gleason score in the radical prostatectomy specimen was greater than 7 in 7% (n = 15) of cases. Seventy three percent (11/15) of these tumors were pre-operatively 3+4 and were up-graded to 3+5=8 (n = 8) and 4+5=9 (n = 3). Twenty three percent (4/15) of these tumors were 4+3 pre-operatively and were up-graded to 3+5=8 (n = 1) and 4+5=9 (n = 3). Total Gleason score in the radical prostatectomy specimen was less than 7 in 3% (n = 6) of cases. Sixty seven percent (4/6) and 33% (2/6) of these tumors were pre-operatively 3+4 and 4+3, respectively and were down-graded to a total Gleason score of 6 (3+3).

We also compared patients who had 3+4 and 4+3 Gleason patterns in the radical prostatectomy specimen with pathologic stage parameters. In contrast, to the biopsy derived primary Gleason pattern, the primary pattern in the radical prostatectomy specimen correlated significantly with pTNM stage (p = 0.02) and seminal vesicle invasion (p = 0.003), but not with extra-prostatic extension (p = 0.32) and surgical margin involvement (p = 0.17) Table 3.

Discussion

Our results suggests that among patients with Gleason 7 prostate cancer and a primary 3 pattern on needle biopsy, over one third of these patients will have their tumors up-graded to a primary pattern 4 or 5 upon analysis of the final surgical specimen. Patients with a primary 4 pattern pre-operatively are approximately equally like to have their tumors remain a primary 4 pattern or be down-graded to a primary 3 pattern post-operatively (odds ratio 1.8). Overall, this study failed to identify any clinical or pathological significance of the primary Gleason pattern (3 versus 4) in the pre-operative needle biopsy among patients with Gleason 7 tumors. Consistent with previous reports, our analysis demonstrated that a primary 4 pattern in the radical prostatectomy specimen is a predictor of adverse outcome among patients with these tumors.[12,14,17]

Several factors may explain the disparity between the significance of the primary Gleason pattern in the

TABLE 2. **Correlation of primary Gleason pattern on prostate needle biopsy (3 versus 4) with i) primary Gleason pattern in the radical prostatectomy specimen, ii) total Gleason score in the radical prostatectomy specimen, iii) pTNM stage, iv) extra-prostatic extension, v) seminal vesicle invasion, and vi) surgical margin status**

	Biopsy 3 + 4	Biopsy 4 + 3	P value
Primary Gleason pattern in the radical prostatectomy specimen*			0.09
(3 + 4)	94 (64%)	28 (49%)	
(4 + 3)	52 (35%)	29 (51%)	
Total Gleason score in radical prostatectomy specimen			0.42
6	4 (3%)	2 (4%)	
7	133 (90%)	51 (89%)	
8	8 (5%)	1 (2%)	
9	3 (2%)	3 (5%)	
PTMN			0.36
T2	58 (39%)	23 (40%)	
T3a	74 (50%)	24 (42%)	
T3b	16 (11%)	10 (18%)	
Extra-capsular extension			0.88
Negative	58 (39%)	23 (40%)	
Positive	90 (61%)	34 (60%)	
Seminal vesicles			0.19
Negative	132 (89%)	47 (82%)	
Positive	16 (11%)	10 (18%)	
Surgical margins			0.16
Negative	108 (73%)	47 (82%)	
Positive	40 (27%)	10 (18%)	

*2 (1%) of patients with biopsy (3 + 4) had (5 + 3) in the radical prostatectomy specimen

prostate needle biopsy and radical prostatectomy specimen. Since prostate cancer is known to be multi-focal, with a heterogeneous population of tumor cells, the potential for sampling errors exists.[1] Given that prostate needle biopsies sample only a small amount of tissue, the true histologic phenotype of the cancer may be missed. Moreover, the significant discordance between pathologist's interpretations of both prostate biopsy and surgical specimens only adds to the disparity.[5-9]

Previous studies investigating the relationship of the biopsy derived primary Gleason pattern (3 versus 4) with the radical prostatectomy specimen Gleason grading and pathologic outcomes are limited and have yielded conflicting results. Groll et al[13] studied 108 surgically treated prostate cancer patients with biopsy derived Gleason 7 tumors. They found that the pathologic features at radical prostatectomy were not associated with the assigned primary Gleason pattern (3 versus 4) on prostate needle biopsy.[13] Makarov et al[12] examined a group of 537 patients with Gleason 7 tumors on pre-operative needle biopsy. They found a significant correlation between the biopsy-derived Gleason primary pattern (3 versus 4) and radical prostatectomy specimen Gleason grading.[12] Among patients with biopsy-derived 3+4 = 7 prostate cancer, over 73% of their tumors remained primary Gleason grade 3 following analysis of the radical prostatectomy specimen. Patients with 4+3 = 7 tumors on needle biopsy were equally likely to have their tumors remain a primary 4 (52%) or be down graded to a primary 3 Gleason pattern (48%) upon examination of the entire prostatectomy specimen. Moreover, these researchers demonstrated that patients with biopsy-derived Gleason score 4+3 = 7 prostate cancer were at increased risk of advanced pathological stage

TABLE 3. **Correlation of the primary Gleason pattern in the radical prostatectomy specimen (3 versus 4) with i) PTNM stage, ii) extra-prostatic extension, iii) seminal vesicle invasion, and iv) surgical margin status**

	RP specimen 3 + 4	RP specimen 4 + 3	P value
PTMN			0.02*
T2	52 (43%)	29 (36%)	
T3a	62 (51%)	35 (43%)	
T3b	8 (6%)	17 (21%)	
Extra-capsular extension			0.32
Negative	52 (43%)	29 (36%)	
Positive	70 (57%)	52 (64%)	
Seminal vesicles			0.003*
Negative	114 (93%)	64 (79%)	
Positive	8 (7%)	17 (21%)	
Surgical margins			0.17
Negative	97 (80%)	56 (69%)	
Positive	25 (20%)	25 (31%)	

compared to patients with 3+4 = 7 tumors on needle biopsy.[12]

The results of the current investigation, coupled with the findings of Groll et al[13] suggest that care providers must recognize the limitations of the predictive value of the biopsy derived primary Gleason pattern with regards to prognosis and treatment decisions (i.e. the decision to perform pelvic lymph node dissection or perform a non-nerve sparing prostatectomy) among patients with Gleason 7 tumors.

A limitation of this study was that pathologists were not blinded to pre-operative biopsy reports or slides. Nonetheless, experienced genitourinary-oncology pathologists examined all pathology specimens. This may account for the high concordance rate (90%) between pre and post-operative Gleason scores among this group of patients. Secondly, the current investigation did not specifically measure tumor volume or the number of positive biopsy cores and therefore cannot correlate the predictive value of these parameters with Gleason grade assignment. This information may prove valuable as larger tumors with relatively greater proportion of aggressive histological features (i.e. primary 4 Gleason pattern) may demonstrate more aggressive behavior patterns.[17,18] Specific to this issue, Stamey et al[18] have shown that the percentage of Gleason pattern 4 (determined from radical prostatectomy specimens) is the most the most significant factor in predicting biochemical failure among men with early-stage prostate cancer.[18] By contrast, Makarov et al[12] demonstrated that the biological behavior of biopsy-derived Gleason score (3+4 or 4+3) is independent of the number of positive biopsy cores. Finally, this study relied on relatively short-term end points. Long-term follow up data, stratifying for primary Gleason pattern with respect to biochemical failures, local recurrences, distant metastasis and disease free survival is essential.

Conclusions

Among patients with Gleason 7 adenocarcinoma of the prostate, the biopsy-derived primary Gleason pattern does not appear to correlate with important clinical and pathologic outcomes. The utility of distinguishing a primary Gleason pattern on needle biopsy among patients with Gleason 7 tumors remains unclear given the limited and conflicting literature addressing this issue. □

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