Comparison of histologic grade between initial and follow-up biopsy in untreated, low to intermediate grade, localized prostate cancer

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Objective: *To examine the change of histologic grade of untreated, low to intermediate grade, clinically localized prostate cancer over time on repeat prostate biopsy.*
Methods and materials: *In a prospective single-arm cohort study, patients were managed with observation alone unless they met pre-defined criteria of disease progression (PSA, clinical or histologic progression). Sixty-seven (54%) of a total of 123 eligible patients underwent follow-up prostate biopsy. Median time to the follow-up biopsy was 22 months (range: 7-60).*
Results: *On the follow-up biopsy, Gleason score was unchanged in 20 patients (30%), upgraded in 19 (28%), and downgraded in 27 (40%). Twenty-one (31%) had no malignancy on the follow-up biopsy. Sixteen (37%) of 43 patients with $\leq$ 2 positive cores on the initial biopsy had negative follow-up biopsy, while only 2 (11%) out of 18 with $\geq$ 3 positive cores on the initial biopsy did. Five (7%) patients were upgraded to Gleason score 8. There was no correlation between the extent of grade change and baseline variables (age, clinical stage, and initial PSA) as well as PSA doubling time.*
Conclusions: *There was no consistent histologic upgrade on the follow-up biopsy at a median of 22 months in untreated, low to intermediate grade, clinically localized prostate cancer.*

Key Words: histologic grade change, repeat biopsy, watchful observation, prostate cancer

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Introduction

The heterogeneity of the natural history of prostate cancer has led to a significant diversity of management approach for clinically localized prostate cancer (CLPC). Management options for CLPC vary from a conservative approach (expectant management) to definitive treatment (radical prostatectomy or radiotherapy). The major challenge in managing CLPC is how to differentiate patients with biologically

aggressive disease for which curative therapy is indicated from those with indolent malignancy for which conservative management is sufficient. A blanket policy of either observation for all, or radical therapy for all likely results in either under-treatment for some or over-treatment for others. We have been conducting a clinical study to evaluate a novel approach in which the choice between definitive therapy and conservative policy is determined by the rate of PSA increase over time and the development of clinical and/or histologic progression.

In our current prospective study of watchful observation with selective delayed intervention, patients are to undergo repeat prostate biopsy in their follow-up to assess any histologic progression over time. Histologic progression is one of the disease progression criteria that stipulate the termination of surveillance and the implementation of definitive therapy in the study. Thus the study has provided a unique opportunity to evaluate the extent of histologic change over time. The objectives of this report are to examine the histologic findings of follow-up prostate biopsy in men with untreated, low to intermediate grade, prostate cancer and to assess any correlation between the change in histologic grade and various pathological and clinical parameters including PSA doubling time.

Methods and materials

A prospective, single-arm, cohort study has been in progress since November 1995 to assess the feasibility of an observation protocol with selective delayed intervention using clinical, histologic, and/or PSA progression as treatment indicators. In this study, a subject is conservatively managed with watchful observation alone as long as he does not meet the criteria of disease progression. The criteria of disease progression are empirically defined with three parameters: a PSA doubling time of less than 2 years, clinical progression, and histologic upgrade on repeat prostate biopsy. The interim analysis of this study including the details of disease progression criteria was described in our previous report.[1] When a patient meets any of the pre-defined criteria of disease progression during follow-up, he comes off watchful observation, and treatment is implemented according to his age, extent of disease, co-morbidity, and personal preference. Patients are closely monitored to enhance the likelihood, in those identified as progressors, of intervening within the therapeutic window of curability.

Study patients, evaluations and follow-ups

Each patient was screened according to well-defined inclusion and exclusion criteria and enrolled into the study if all of the following eligibility criteria were met: 1) histological diagnosis of adenocarcinoma of prostate within 12 months prior to entry, 2) no previous treatment for prostate carcinoma, 3) clinical stage T1b-T2b N0M0 (1997 TNM Classification), 4) prostate specific antigen (PSA) $\leq$ 15 ng/ml (Hybritech), 5) Gleason score (GS) $\leq$ 7, 6) signing of an informed consent.

As baseline, all patients had histopathological review of the prostate biopsy specimen to confirm low to intermediate grade of malignancy. Medical history, physical examination, chest x-ray, trans-rectal ultrasound (TRUS) of the prostate and blood tests including serum creatinine, PSA, prostate acid phosphatase (PAP) were performed. Radioisotope bone scan and CT scan of abdomen and pelvis were optional and performed on an individual basis. Patients were followed every 3 months for the first 2 years and every 6 months thereafter as long as they remained on the study.

At each visit, a medical history, physical examination including digital rectal examination, and blood tests for PSA, PAP, and serum creatinine were obtained. Bone scan was performed every 12 months for the first 2 years and then every 24 months as long as the patient remained on surveillance. When PSA exceeded 15 ng/ml, bone scan was done every 12 months. Patients underwent TRUS of the prostate every 6 months. TRUS guided re-biopsy of the prostate at 12 to 18 months after enrolment was stipulated in the protocol. Histologic progression calling for therapeutic intervention was defined in the study as the upgrade of GS to 8 or greater in the re-biopsy of the prostate.

Prostate biopsies and pathological evaluation

Except for the five patients who had transurethral resection of the prostate (TURP) leading to the diagnosis of prostate cancer, all prostate biopsies at both initial and follow-up biopsy were performed transrectally with TRUS guidance. The initial and follow-up biopsies of the prostate were centrally reviewed by the two expert genitourinary pathologists. The changes in overall GS from the initial biopsy to follow-up biopsy were examined. When several Gleason scores were available in a patient (as a result of the presence of malignancy in multiple biopsy cores), the highest GS was chosen for the tumor. Additional analyses included the changes in primary and secondary Gleason grade. Also any change in the number of cores involved with malignancy from initial biopsy to follow-up biopsy was assessed.

TABLE 1. **The number of biopsy cores taken at the initial and follow-up biopsy**

Timing	Number of biopsy cores taken												
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**M***	**TURP**	**Median**	**Mean**
Initial biopsy	4	1	3	30	8	7	5	2	1	1	5	6	6.5
Follow-up biopsy	1	3	0	36	15	8	3	1	0	0	0	6	6.5

* M: multiple cores taken (≥ 3 cores, not specified)

Statistical analyses

Calculations were performed using SAS (release 6.12; SAS Institute Inc., Cary, NC). The relationship of the change in GS with baseline variables and PSA doubling time was examined with correlation analysis.

PSA doubling time was calculated with the assumption that PSA changed over time in a simple exponential fashion, as described in detail in our previous report.[2] All PSA measurements available since the date of enrolment were used for the calculation of PSA doubling time.

Results

As of April 2001, 67 patients (54%) of a total of 123 eligible patients underwent a follow-up prostate biopsy. Patient's preference was the primary reason for not undertaking follow-up prostate biopsy in the rest. There was no significant difference with respect to median age, median PSA at study enrolment, clinical stage, and initial Gleason score between those that had a follow-up biopsy and those that did not. As the focus of this manuscript is the evaluation of the change in histologic grade over time, the following analyses pertain to those 67 patients who underwent the follow-up biopsy. The median age was 70 years (range: 58 - 81). The median follow-up from study enrolment was 40 months (range: 13 - 67). Forty and 27 patients had clinical stage T1 and T2, respectively. The distribution of PSA at study enrolment was as follows: < 5: 5-9.9: 10-14.9 = 23: 34: 10. The median PSA at study enrolment was 6.2 ng/ml. On the initial prostate biopsy, two patients had GS 4, 9 with GS 5, 42 with GS 6, and 13 with GS 7. In one patient, the focus of malignancy was too small to allow proper histologic grading and scored as Gx. The interval from the initial biopsy to the follow-up biopsy was 7 months in 1, 12-24 months in 44, 24-36 months in 17, 36-48 months in 3 and 48-60 months in 2 (median: 22 months, range: 7-60 months).

Table 1 shows the numbers of biopsy cores taken at the time of initial and follow-up biopsy. For the initial biopsy, this information was unavailable in six patients. Five had transurethral resection of the prostate (TURP). In one patient, the TRUS or pathology report did not specify the exact number of biopsy cores taken, although the TRUS report clearly stated multiple core samplings (≥ 3 cores). For the remaining 61 patients, the number of biopsy cores taken at the time of initial biopsy ranged from 3 to 11 (mean: 6.5, median: 6). The follow-up biopsy had the same mean and median with a similar range (3 to 10).

Table 2 shows the change in GS from the initial biopsy to the follow-up biopsy. GS was unchanged in

TABLE 2. **Changes of Gleason score from the initial biopsy to the follow-up biopsy**

Follow-up GS	Initial GS					
	GX*	**GS 4**	**GS 5**	**GS 6**	**GS 7**	**Total**
No malignancy	0	1	4	13	3	21
GX*	0	0	0	0	0	0
GS 4	0	0	0	0	0	0
GS 5	0	0	1	3	0	4
GS 6	0	0	2	12	3	17
GS 7	1	1	1	10	7	20
GS 8	0	0	1	4	0	5
Total	1	2	9	42	13	67

* Gx: the focus of malignancy too small to assign GS

TABLE 3. **Changes of primary Gleason grade from the initial biopsy to the follow-up biopsy**

Follow-up primary GG	Initial primary GG				
	GX	**GG 2**	**GG 3**	**GG 4**	**Total**
No malignancy	0	3	18	0	21
GG 2	0	0	4	0	4
GG 3	1	1	27	1	30
GG 4	0	1	11	0	12
Total	1	5	60	1	67

20 patients (30%). In 19 patients (28%), GS was upgraded by 1 or greater. Only seven patients (10%) had GS increase of 2 or greater. Five patients (7%) had the upgrade of GS to 8. GS was decreased by 1 or greater in 27 patients (40%) including 21 who had no malignancy on the follow-up biopsy. One patient with Gx on the initial biopsy was considered inevaluable with respect to the change in histologic grade (1%). In this patient, the follow-up prostate biopsy showed GS 7.

Table 3 represents the change in the primary Gleason grade (GG) from the initial biopsy to the follow-up biopsy. Primary GG was unchanged in 27 patients (40%), up-graded in 13 (19%), and down-graded in 26 (39%).

Table 4 shows the change in the secondary Gleason grade from the initial biopsy to the follow-up biopsy. Secondary GG was unchanged in 24 patients (36%), up-graded in 17 (25%), and down-graded in 25 (37%).

Among the 61 patients in whom the information with regards to the number of biopsy cores taken was available, the relationship between the number of positive cores on the initial biopsy and the probability of no malignancy on the follow-up biopsy was examined. In those patients with one or two positive biopsy cores on the initial biopsy (n=43), 16 (37%) had no malignancy on the follow-up biopsy. On the other hand, when three or more biopsy cores were involved with malignancy on the initial biopsy (n=18), the probability of no malignancy on the follow-up biopsy was much lower, occurring in only two patients (11%). Six patients were excluded from this analysis, and consisted of five TURP patients at initial diagnosis and one patient in whom the pathology report described the extent of malignancy as "multiple cores involved". In the five TURP patients, three had no malignancy on the subsequent prostate biopsy. The one who had had "multiple cores involved" on the initial biopsy had positive follow-up biopsy. Table 5 depicts the change in the number of positive biopsy cores from the initial biopsy to the follow-up biopsy. Table 6 describes the number of positive biopsy cores and percent volume of tissue involved with malignancy in the initial biopsy for those 21 patients that had negative follow-up biopsy.

There was no statistically significant correlation between the change in GS and PSA doubling time as well as baseline variables including age, clinical T stage, and PSA level at study enrolment Table 7. Similarly, there was no association between the absence of malignancy on the follow-up biopsy and PSA doubling time and the baseline variables.

Discussion

GS has been a useful parameter in predicting the clinical course of prostate cancer. Chodak reported in

TABLE 4. **Changes of secondary Gleason grade from the initial biopsy to the follow-up biopsy**

Follow-up secondary GG	Initial secondary GG				
	GX	**GG 2**	**GG 3**	**GG 4**	**Total**
No malignancy	0	3	15	3	21
GG 2	0	0	0	0	0
GG 3	0	3	19	4	26
GG 4	1	1	13	5	20
Total	1	7	47	12	67

TABLE 5. **Changes in the number of positive cores from the initial biopsy to the follow-up biopsy**

# of +ve cores on follow-up biopsy	# of +ve cores on initial biopsy									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**TURP**	**M+**	**Total**
No malignancy	11	5	2	0	0	0	0	3	0	21
1	6	4	0	2	0	0	0	1	0	13
2	4	4	1	0	0	0	0	0	0	9
3	4	1	0	1	0	0	0	1	0	7
4	0	1	2	0	0	0	0	0	1	4
5	0	2	2	2	0	1	1	0	0	8
6	0	1	0	1	0	0	0	0	0	2
7	0	0	1	0	1	1	0	0	0	3
Total	25	18	8	6	1	2	1	5	1	67

M+: multiple cores involved with malignancy ($\geq$ 2 cores, not specified)

the pooled data of watchful observation series that the probabilities of metastasis-free survival in 10 years were 81%, 58% and 26% for low, intermediate, and high grade malignancy, respectively.[3] However, a single GS at the time of diagnosis, representing the biological characteristics of malignancy at a single point in time in its long natural history, lacks specific information with respect to potential histologic progression of malignancy occurring over much longer period of time. Does low grade malignancy maintain its indolent biological characteristics throughout its natural course? Or can it de-differentiate to more malignant phenotype over its long natural history? Also a single GS at the time of diagnosis does not predict which group of patients within a given GS will develop clinical progression. Why does some low grade malignancy manifest clinical progression, while others do not?

The change in histologic grade based on serial prostate biopsies over a period of time would be potentially useful predictor of the inherent biological behavior of a given malignancy, as it may better reflect tumor kinetics and biological evolution. No change in histologic grade may imply relatively indolent cancer, while significant histologic upgrade may suggest biologically more aggressive phenotype. Our study

TABLE 6. **Percent tissue volume and number of cores involved with malignancy in the initial biopsy for those 21 patients that had negative follow-up biopsy**

Case #	Percent volume involved	Positive core/ number of biopsy cores
20	< 5%	1/8
46	< 5%	3/6
77	< 2%	1/8
84	< 5%	1/7
88	< 5%	1/10
89	< 5%	1/6
93	< 5%	1/6
94	5%	2/7
96	< 5%	2/9
112	10%	1/6
117	< 5%	2/6
119	< 5%	TURP
122	< 5%	1/6
133	< 5%	TURP
136	5%	3/10
152	< 5%	2/6
153	< 5%	1/7
163	< 5%	1/7
165	< 5%	1/7
168	10%	TURP
174	10%	2/11

TABLE 7. **Correlation of the change in GS versus PSA doubling time and baseline variables**

Variables	Spearman correlation coefficients (versus the change in GS)	P value
Age	0.128	0.31
Initial PSA	0.184	0.14
Clinical T stage	0.196	0.12
PSA doubling time	0.098	0.44

attempted to examine the change in histologic grade in patients managed with expectant management by comparing the initial biopsy to the follow-up biopsy and its usefulness in monitoring prostate cancer patients opting for expectant management.

There are several limitations in our study that demand cautious approach for the interpretation of our data. Firstly, one may argue that the interval between the two biopsies in our series is too short to truly reflect the biological evolution of malignancy. Much longer time interval between the two biopsies, or several sequential biopsies (not just two biopsies as in our study) may be needed to accurately assess the change in histologic grade of prostate cancer which has a very long natural history. Secondly, pathological interpretation of histologic grade is subject to the adequacy of biopsy sampling as well as intra- and inter-observer variability. Thirdly, our study finding is limited by the fact that a significant proportion of eligible patients did not undergo the follow-up biopsy as stipulated in the study protocol. This limited participation of eligible patients makes the generalization of the study finding more difficult. Fourthly, some patients came off the surveillance protocol before their scheduled follow-up biopsy, as they met the empirically defined disease progression definition based on PSA doubling time or clinical progression. In this subgroup, the information regarding the histologic grade change was not available. Thus there is a possibility that our study may under-estimate the proportion of patients with histologic upgrade. Fifthly, the lack of a systematic biopsy strategy in the cohort introduces difficulty in assessing the extent of tumor burden present in these patients and makes the interpretation of data more difficult. Another weakness is that the median of six biopsy cores in this cohort may not be adequate to characterize the distribution and extent of malignancy present in the prostate. More extensive biopsy may reduce a false negative biopsy rate and yield more accurate information for the extent of malignancy. Another criticism is variability in the timing of repeat biopsy in this cohort. This heterogeneity of the timing of follow-up biopsy also makes the interpretation of data more difficult. Despite all these limitations, our study provides some insight into the extent of grade change in untreated, clinically localized, prostate cancer and potential usefulness of serial prostate biopsies.

In our series, there was no consistent upgrade of GS on the follow-up biopsy. Instead, downgrade or no change of GS on the subsequent biopsy was more prevalent. Furthermore, 21 patients (31%) had no malignancy on the follow-up biopsy. There are several possible reasons to explain these findings either as a sole factor or more likely as one of several contributing factors. One possible explanation is that a significant proportion of our study cohort may indeed have biologically indolent malignancy. Thus it is not a surprise to find that only a small proportion of patients show the upgrade of GS on the follow-up biopsy. Another possible reason for the lack of up-grade on the follow-up biopsy is a relatively short time interval between the two biopsies in comparison to a very long natural history of CLPC. Another factor is related to the adequacy of biopsy sampling. One can argue that the absence of malignancy on the follow-up biopsy in our series is due to sampling error (i.e. false negative). However, considering the fact that the median number of biopsy cores taken for the follow-up biopsy was 6, the inadequacy of biopsy sampling may not be sufficient explanation for the above finding. Alternatively, the observation that 31% of the cohort had no malignancy on the follow-up biopsy may imply that they indeed had a minimal volume of cancer to begin with and were more likely to have negative follow-up biopsy. This reasoning is supported by the interesting inverse relationship between the number of positive biopsy cores in the initial biopsy and the probability of being negative on the follow-up biopsy in our series. A smaller number of positive biopsy cores in the initial biopsy in our cohort was associated with a higher likelihood of having negative follow-up biopsy. This observation is consistent with Epstein's study of radical prostatectomy specimens, which reported that low tumor volume was one of independent predictors of negative repeat biopsy.[4] Furthermore, as depicted in Table 6, the 21 patients with negative follow-up biopsy had a low percent volume of tissue involved with malignancy in the initial biopsy specimen (all with $\leq$ 10% tissue involvement). These findings suggest that a significant proportion of our cohort might indeed have a minimal volume of disease to begin with. This may have, in turn, contributed to a high incidence of negative follow-up biopsy and a low likelihood of histologic or clinical progression in our cohort.

The above findings can be explained entirely differently on the basis of the multi-focal nature of prostate cancer bearing various histologic phenotypes. While a biopsy core from one area of the prostate gland shows low grade malignancy, another focus from other part of the prostate may contain high grade phenotype. It can be argued that the change in histologic grade on the follow-up biopsy observed in this study may be simply the reflection of sampling different parts of the prostate which resulted in

different distribution of histogic grades on the subsequent biopsy. In this scenario, one can argue that histologic progression over time is unlikely, and that the reason why some low grade malignancy shows clinical progression is that it harbors a focus of high grade malignancy to begin with which then leads to clinically evident tumor progression.

There is very limited literature examining the change in histologic grade in CLPC managed with watchful observation. Cumming examined GS change in 34 prostate cancer patients who underwent two transurethral prostatic resections (mean interval between resections: 2.4 years) while being managed with watchful observation alone.[5] There was a trend toward a higher GS on the second resection specimens (GS increased in 23, unchanged in 5 and decreased in 5). Another study by Epstein reported no significant grade change in 70 men with clinical stage T1c prostate cancer who underwent repeat needle biopsy 1.5 to 2 years after the initial biopsy while being managed with watchful waiting.[6] The difference between these series is likely, in part, due to patient heterogeneity and selection bias.

It remains to be proven whether or not histologic up-grade is a useful predictor of disease progression requiring therapeutic intervention in patients managed with watchful observation. This study was not designed to address that question. In fact, the rationale underlying our study protocol assumes that histologic progression identifies aggressive phenotype and calls for a definitive therapy to be offered to the patient as soon as the criterion of histologic progression is met. Treating patients at the time of histologic progression eliminates the opportunity to observe whether they would progress clinically if left untreated.

Conclusion

There was no consistent histologic upgrade on the follow-up biopsy at a median of 22 months in untreated, low to intermediate grade, CLPC. The absence of malignancy in the follow-up biopsy was more prevalent in patients with only one or two positive biopsy cores in the initial biopsy and associated with initial, low volume of malignancy. □

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