Published in final edited form as:

J Urol. 2008 March ; 179(3): 901–905. doi:10.1016/j.juro.2007.10.062.

Change in Prostate Cancer Grade Over Time in Men Followed Expectantly for Stage T1c Disease

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Abstract

Purpose—We assessed whether the Gleason grade changes in men followed expectantly with nonpalpable prostate cancer diagnosed on needle biopsy (stage T1c).

Materials and Methods—We studied 241 men with stage T1c prostate cancer who were treated expectantly with repeat yearly needle biopsy sampling to assess for cancer progression. Following the initial cancer diagnosis all men had at least 1 other biopsy demonstrating cancer.

Results—Median patient age was 66 years. The number of biopsies showing cancer over time was 2 in 119 (49.4%), 3 in 74 (30.7%), 4 in 33 (13.7%) and 5 or greater in 15 (6.2%). The average followup for those without progression was 32.3 months. Of 241 cases 45 (18.7%) showed a significant change in grade from Gleason score 6 or less to Gleason score 7 or greater (Gleason score 7 in 41 cases, Gleason score 8 in 4 cases). Of 45 (53.5%) cases 24 that showed progression did so within 24 months of diagnosis.

Conclusions—Within the first 3 years after diagnosis of Gleason score 6 prostate cancer, there is a relatively low risk of grade progression. Within the first 3 years, our data suggest that in most cases tumor grade did not evolve but rather that the higher grade component was not initially sampled since most grade changes occurred relatively soon after biopsy. Grade progression does appear to occur in some men with long-term followup who had multiple biopsies showing Gleason score 6 followed by higher grade cancer.

Keywords

prostatic neoplasms; disease progression

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Study received institutional review board approval.

Nothing to disclose.

Editor's Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1208 and 1209.

We have been expectantly following a cohort of men with stage T1c prostate cancer who met the criteria for and opted into an active surveillance protocol based on predicted extent of limited (less than 0.5 cc) tumor involvement with a Gleason score of 6 or less on needle biopsy of the prostate. Patients undergo yearly prostate biopsy as part of the followup. We previously reported our findings in 70 patients in this cohort with emphasis on tumor dedifferentiation over time.¹ The current study represents a larger cohort of patients followed under the expectant management protocol, including those from the previous study, with assessment of Gleason scores on sequential biopsies to determine the risk of tumor progression over time.

MATERIALS AND METHODS

A total of 407 men are currently being followed expectantly with stage T1c prostate cancer, all of whom met the criteria for an institutional review board approved expectant management program and signed informed consent,^{2,3} and chose expectant management when presented with treatment alternatives. Of these patients 241 have had at least 1 subsequent biopsy demonstrating cancer over a followup period of 12 months or more. The cohort includes extended followup on patients reported in a previous study.¹

Men were candidates for surveillance if the biopsy contained a tumor with a Gleason score of 6 or less, and there were less than 3 positive cores with no core occupied by greater than 50% of cancer and PSA density was less than 0.15 ng/ml/cm³. All men in this program agreed to undergo an annual surveillance biopsy and the mean time between biopsies was 1.0 (SD 0.49) year.

RESULTS

The mean age of the 241 patients was 66 years (median 66, range 48–79). The number of biopsies showing cancer over time was 2 in 119 (49.4%), 3 in 74 (30.7%), 4 in 33 (13.7%), and 5 or more in 15 (6.2%). The average followup for those without progression was 32.3 months (median 26, range 12 to 120). Of the 241 patients 45 (18.7%) had a significant change in grade from Gleason score 6 or less to Gleason score 7 or greater, increasing to Gleason score 7 in 41 and to Gleason score 8 in 4 (table 1). Of the cases showing progression 24 of 45 (53.3%) did so within 24 months of diagnosis. Of the 4 cases with a change to Gleason score 8, 3 occurred within 24 months, and 1 occurred at 25 months. The remaining 20 cases showed a grade change within 72 months. The actuarial risk of grade progression at various years from diagnosis is shown (table 2).

DISCUSSION

The proportion of patients presenting with nonpalpable (stage T1c) disease has increased significantly, while the proportions presenting with extracapsular extension and metastases have decreased.⁴ At our institution, 29% of radical prostatectomies show minimal or insignificant disease (less than 0.5 cm³ tumor volume with a Gleason score of 6 or less),³ which is similar to other groups.⁵ Since the presence of insignificant or minimal disease can

be fairly accurately predicted using PSA values and needle biopsy results,^{2,3,6} many patients can be followed and managed expectantly until evidence of tumor progression is identified.

In the current study, an increase in grade occurred 18.7% of 241 patients, compared to 12.9% in our prior study of 70 men.¹ Whereas almost all the grade changes occurred within 24 months in our prior study, 53.3% of grade changes were seen within 24 months of the initial diagnosis in the current report. As in our prior study, our updated series suggests that in many cases the higher grade component was not initially sampled given the short interval between biopsy showing higher tumor. The potential for missing higher grade tumor exists, as evidenced by 20% of radical prostatectomy specimens removed within a few months of needle biopsy showing a grade change from Gleason score 6 or less to Gleason score 7 or greater.⁷ However, one cannot directly compare the upgrading seen in the current study to that seen between needle biopsy and subsequent radical prostatectomy. Given the complete tumor sampling at radical prostatectomy, one would expect higher upgrading of the biopsy compared to the prostatectomy as opposed to the grade change between 2 biopsies over time. In addition, there are several factors in our study that could have affected the risk of grade change over time. Most men entering the program before 1998 had been diagnosed with cancer on a 6-core biopsy because at that time a sextant biopsy was standard of care. After 1998, we began performing 12 core confirmation biopsies on men diagnosed with cancer to better predict disease extent prior to their entry into the expectant management program. Approximately 40% of our patients underwent this confirmatory biopsy. The relatively poor sampling prior to 1998 increased the likelihood during the early part of the study of a grade change due to unsampled cancer rather than dedifferentiation. Conversely, the increased sampling with confirmatory biopsies more recently within our study decreases sampling as an explanation for the increased grade changes we observed.

With longer followup and more cases, the current study demonstrates that grade change seems to occur in some cases. Eleven cases showed an increase in grade after 3 years or more. Although 4 of these cases had only 2 biopsies containing cancer, they all had intervening benign biopsies. These may represent cases of true dedifferentiation, as it is less likely the higher grade component would be missed, given an inherently higher proliferation rate in the grade 4 component. There was a tendency for grade increase in patients older than 60 years at the time of initial diagnosis (data not shown), but 2 patients younger than 60 years also showed grade increases. However, most of the patients older than 60 years showed no grade change, including 1 patient followed out to 120 months.

Dedifferentiation is a well-recognized occurrence in both epithelial and stromal malignancies,⁸ but its occurrence in prostatic carcinoma has not been well studied. The multifocal nature of prostate cancer⁹ and the presence of small volume, high grade foci in some radical prostatectomy specimens resected for nonpalpable disease¹⁰ create difficulties in its definition. Most previous studies suffer from the inclusion of advanced disease and selection bias. To our knowledge, this is the first prospective evaluation of grade changes over time in men followed expectantly with nonpalpable prostate cancer with an initial Gleason score of 6 or less.

Brawn was the first to look at dedifferentiation in prostate carcinoma.¹¹ Using the M.D. Anderson grading system, he evaluated transurethral resection of the prostate procedures in 54 patients separated by 3 to 11 years. In 35 of 54 patients (64.8%) the second TURP specimen showed an increase to the next highest grade. However, most of the patients in the study received intervening therapy (hormones, radiation, chemotherapy) that may have altered the histological appearance. In a similar study by Cumming et al, paired TURP specimens from 74 patients were evaluated.¹² They found an increase in the Gleason score of the second TURP in 49 of 68 evaluable patients (72%). In this study, also, many patients received additional therapy. Both studies also included only those patients requiring a second TURP for obstruction or hematuria, which may have selected for more aggressive tumors.

Studies have also assessed differentiation in metastatic disease. Brawn and Speights compared the histology of carcinoma in the prostate with that of metastases to lymph nodes and distant sites in 200 lymphadenectomies and 100 autopsy cases using the M.D. Anderson grading system.¹³ The metastases from 41% of the lymphadenectomies were entirely differentiated (gland-forming) and 43% were predominantly (50% or more) differentiated, while the distant metastases from the autopsies were entirely undifferentiated in 70% of the cases and predominantly undifferentiated in 18% of the cases. Comparison of the surgical specimen and the lymph node metastases showed equivalent M.D. Anderson grades in 73.5% of cases, and the same histological pattern was noted in both the prostate and metastases in 96% of the autopsy cases. Greater sampling of the autopsy cases relative to the surgical specimens may explain the greater concordance of differentiation patterns between the primary tumor and the metastases at autopsy. Many patients also underwent hormone therapy. Overall, the cases represent patients with advanced disease, and the presence of dedifferentiation and the time-course involved is uncertain.

Cheng et al conducted a similar study assessing 242 patients with lymph node metastases and radical prostatectomies.¹⁴ The Gleason score in the lymph node metastases was higher in 45% of patients, matched in 43% of patients, and was lower in 12% of patients when compared with the Gleason score of the tumor in the prostate. They also noted that patients with dedifferentiation in the lymph node metastases had a higher rate of systemic disease progression. The authors concluded that there is a trend toward dedifferentiation in metastases, and its presence portends a worse prognosis. Although adequately sampled for staging purposes, only part of the prostate was submitted in each case, so the presence of high grade areas in the unsampled prostate cannot be excluded. All of the cases comparing primaries and metastases also are selected cases that are by definition more aggressive and have higher grade primaries that do not necessarily reflect the behavior of an unselected group of low volume Gleason score 6 or less cancer, as in our study.

Wheeler et al studied specimens of 49 patients both before and after local radiation therapy, determining tumor grade using the M.D. Anderson grading system.¹⁵ The recurrence had a higher grade in 35 (71.4%) of the patients. They noted that tumors that recurred later had a higher likelihood to be dedifferentiated than those that recurred earlier, and they concluded that the progression was due to time dependent tumor progression. While providing solid arguments for the possibility of dedifferentiation in some prostate cancer, the selection bias

in assessing only 49 of 1,249 patients receiving definitive radiation therapy, all 49 of whom were symptomatic, precludes assessment of the risk of dedifferentiation over time.

Adolfsson and Tribukait assessed cytologic progression and modal DNA value in serial prostatic FNA biopsies from 167 patients.¹⁶ Of the 78 patients with at least 24 months separating repeat biopsies and evaluable cytologic material, 18 (23%) of the patients showed a change to a higher grade in the second specimen. Of the 72 patients followed by flow cytometry for DNA analysis, a change in ploidy occurred in 17 (24%) cases, though the majority of the tumors were nondiploid initially. This represents the only other study assessing dedifferentiation in an unselected population with sampling of all patients. Although the findings support the occurrence of dedifferentiation in some prostate cancers, most of the cases involved aggressive tumors which were stage T2 or above and as with our study, the initial FNA may have missed a higher grade component.

In a novel study by Whittemore et al, autopsy data of low grade, latent prostate cancers was compared with annual incidence rates of clinically detected prostate cancer, of which at least 70% are high grade, compiled by the SEER program.¹⁷ The authors generated separate curves comparing latent tumor volume stratified by age and clinical cancers yearly per man stratified by age. Their hypothesis predicted that, when the curve of the latent tumor volume is shifted to the right by the number of years required for the high grade cancers to become detectable, the curve will overlay the SEER data curve. The downward shift to overlay the curves would therefore determine a proportionality constant determining the rate of high grade cancers arising from low grade, clinically silent cancers. They concluded that each cubic cm of latent cancer volume at any age evolves into 0.024 high grade cancers yearly approximately 7 years later. The authors attest to the amount of inference involved and recommend analysis of additional data, but the findings suggest a time course of tumor progression beyond the course of our study. This is supported by the findings of Wheeler et al,¹⁵ who reported more cases of dedifferentiation as the time to recurrence increased.

The most recent study of dedifferentiation in prostate cancer applied MISCAN simulation models to data collected from 2,204 cancers diagnosed in the Rotterdam center of the European Randomized study of Screening for Prostate Cancer (ERSPC).¹⁸ The MISCAN program simulates the development of prostate cancer in individuals as a sequence of tumor states characterized by T-stage and differentiation grades (Gleason scores 2–6, 7 and 8–10). They constructed 2 models: Model I in which the differentiation grade is determined before entering the preclinical screen detectable phase and does not change afterward; and Model II in which dedifferentiation may occur in the screen detectable phase. The ERSPC data showed more favorable Gleason grades in screen detected cancers (70% grades 2 to 6, 6% grades 8 to 10) than in the control arm (46% grades 2 to 6, 24% grades 8 to 10, detected on TURP or prostatectomy specimens treated for bladder cancer or benign prostatic hyperplasia). Comparing this data with the MISCAN models, they determined that Model II, allowing dedifferentiation in the screen detectable phase, fits the observed data more closely. They also noted that a higher percentage of low grade tumors in the second round of screening, performed 4 years after the first screening, suggests that few tumors progress to a higher grade within a 4-year interval.

The results of our current study suggest that if dedifferentiation does occur, the risk is low in the short-term. The cases showing an increase in grade after 3 years may represent true dedifferentiation, but the emergence of a separate focus of high grade carcinoma is also possible. Despite obtaining 12 needle biopsies on each patient, many patients had intervening benign biopsies, occasionally spanning 3 years of followup. This suggests extremely low volumes of tumor in these patients, and long doubling times. It is likely the biology of such tumors is inherently different from those showing early grade changes. Molecular studies are ongoing and will hopefully begin to address this issue.^{19,20} It would be interesting to see if the radical prostatectomy specimens of the cases demonstrating tumor progression showed multiple tumor foci or regions of isolated Gleason pattern 4. Additional followup will also further clarify the issue of dedifferentiation, especially in those cases with followup out to 10 years with no evidence of dedifferentiation.

CONCLUSIONS

Our data show that the risk of grade progression within the first 3 years of diagnosis is relatively low. In most of the cases that did show progression, the short period between the initial diagnosis and the grade change suggests the higher grade component was not initially sampled. The results should be reassuring to patients suspected of harboring small volume, low grade cancer, and they further support the concept of active surveillance as a reasonable alternative to immediate curative intervention.

Abbreviations and Acronyms

ERSPC	European Randomized study of Screening for Prostate Cancer
FNA	fine needle aspiration
PSA	prostate specific antigen
SEER	Surveillance, Epidemiology, and End Results
TURP	transurethral resection of the prostate

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Table 1

Gleason scores of sequential followup biopsies

Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4	Biopsy 5	Biopsy 6	Biopsy 7	Biopsy 8	No. Cases
6	6							94
6	6	6						61
6	6	6	6					27
6	6	6	6	6				6
6	6	6	6	6	6			6
6	6	6	6	6	6	6		2
6	7							22
6	6	7						13
6	6	6	7					6
6	6	6	6	7				1
6	8							3
6	6	8						1

Table 2

Actuarial risk of grade progression during 5 years

Yrs Followup	Risk of Grade Progression (%)	No. Men at Risk
1	3	240
2	11	145
3	20	75
4	31	38
5	35	24