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Gleason grade remains an important prognostic predictor in men diagnosed with prostate cancer while on finasteride therapy

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Abstract

OBJECTIVE—To evaluate men treated with finasteride for lower urinary tract symptoms, who subsequently were diagnosed with prostate cancer and had a radical prostatectomy (RP) at our institution, to determine if finasteride therapy prevented accurate Gleason grade assignment and prediction of biochemical recurrence.

PATIENTS AND METHODS—Between May 1996 and July 2003, 45 men were identified who had RP and had previously been treated with finasteride for ≥ 6 months before the diagnosis of prostate cancer. Clinical and pathological information was gathered from a RP database. Serum prostate-specific antigen (PSA) level, duration of finasteride therapy, biopsy Gleason grade, clinical stage, RP Gleason grade and pathological stage were reviewed. Freedom from recurrence was predicted using validated nomograms before and after RP, and compared against actuarial 5-year freedom from recurrence using the Kaplan-Meier method.

RESULTS—The mean duration of finasteride therapy before diagnosis was 23.6 months, the mean serum PSA (doubled to account for finasteride use) 11.02 ng/mL and mean biopsy Gleason score 6. When comparing the biopsy and RP specimen Gleason score, it was downgraded by 1 point in six men, upgraded by 1 point in eight, and upgraded by 2 points in one. The Gleason score was constant in 30 patients. The nomograms predicted freedom from recurrence in 83% and 85%, respectively; the 5-year actuarial freedom from recurrence was 86%.

CONCLUSION—Finasteride does not appear to compromise the assignment of Gleason grade for use in prediction tools before or after RP in men undergoing prostate biopsy or RP. The actuarial 5-year freedom from recurrence was similar to that predicted by the validated nomograms. Gleason grade remains an important prognostic predictor in men treated with finasteride and undergoing RP for clinically localized prostate cancer.

Keywords

prostate cancer; finasteride; Gleason grade

The controversial topic of the effect of finasteride therapy on Gleason grade, raised by the Prostate Cancer Prevention Trial, is discussed by authors from New York. They assessed a series of patients who had been treated with finasteride, and who subsequently had a radical

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CONFLICT OF INTEREST

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prostatectomy, to see if this pharmaceutical agent prevented accurate Gleason grade assignment and prediction of biochemical recurrence. They found that Gleason grade remains an important prognostic predictor in men diagnosed with prostate cancer while on finasteride therapy.

Authors from Amsterdam assessed the accuracy of ultrasonography- guided fine-needle aspiration cytology as a method of detecting occult lymph node metastases in patients with penile cancer, and found that it can be used as an initial investigation in such patients, with helpful clinical outcomes.

INTRODUCTION

With the recent reports on the influence of finasteride on the development of prostate cancer, debate has surfaced as to whether pathologists are able to assign an accurate Gleason grade to prostate cancer in men currently taking finasteride. Thompson *et al.* [1] reported a 24.8% reduction in the prevalence of prostate cancer in men treated with finasteride compared with placebo; in the latter, 24.4% (1147/4692) were subsequently found to have prostate cancer on TRUS-guided prostate biopsy, compared with 18.4% (803/4368) in the finasteride group. Despite the reduction in the prevalence of prostate cancer in the finasteride group, there was a significantly higher proportion of tumours with Gleason scores of ≥ 7 than in the placebo group (37.0% vs 22.2%, respectively). One possible explanation for this was attributed to a grading bias, i.e. histological changes that mimic high-grade disease caused by androgen-deprivation therapy (ADT).

ADT with either LHRH agonist-antagonists or antiandrogens has been well documented to cause distinct histological effects on prostate adenocarcinoma [2-7]. Architecturally, most treated cancers have a variety of patterns of high-grade disease, including compressed glands, sheets of tumour cells, small cell clusters and single ribbons of cells [7]. Many pathologists will not assign a Gleason grade in the setting of ADT because of the histological changes associated with this treatment.

However, there are a few reports addressing the effects of finasteride on prostate cancer histology [7-9]. Civantos *et al.* [8] evaluated five prostatectomy specimens from patients with prostate cancer who were previously treated with finasteride, and compared the findings with those after ADT. The finasteride group had mild histological changes, e.g. vacuolated epithelial cells, prominent basal cells, acinar atrophy and small tumour glands. Most of these features were less common, heterogeneous and milder than in the group treated with ADT. In contrast, Yang *et al.* [9] reported no significant histological differences when reviewing 103 prostate biopsies with and without prostate cancer from men treated with finasteride or placebo, as part of a large trial. They concluded that prostate cancer in needle biopsies from men treated with finasteride is unaltered and readily identified as cancer. These studies suggest that the impact of finasteride therapy on prostate cancer histology is less than that seen with ADT.

To further evaluate whether a Gleason grade could accurately be assigned to prostate cancer in men treated with finasteride, we assessed men at our institution undergoing radical prostatectomy (RP) for clinically localized disease and who were treated concomitantly with finasteride for LUTS. We determined the predictive accuracy of nomograms before and after RP, both of which rely on Gleason grading to determine the risk of cancer recurrence, in men treated with finasteride undergoing RP [10,11].

PATIENTS AND METHODS

Between May 1996 and July 2003, 45 men were identified who had RP at our institution and had previously been treated with finasteride for ≥ 6 months before the diagnosis of prostate cancer. Clinical and pathological information was gathered using a RP database. Serum PSA, duration of finasteride therapy, biopsy Gleason grade, clinical stage, RP Gleason grade and pathological stage were reviewed. The down- or up-grading of Gleason scores were evaluated from prostate biopsy and RP pathology. RP specimens were reviewed with the pathologist unaware of the patients' history of finasteride therapy. Biochemical recurrence was defined as one serum PSA value of >0.2 ng/mL after RP. Freedom from recurrence was predicted using our validated nomograms before and after RP, and compared against actuarial 5-year freedom from recurrence using the Kaplan-Meier method.

RESULTS

The mean (range) duration of finasteride therapy before prostate cancer was diagnosed was 23.6 (10-35) months, the mean serum PSA (doubled for finasteride use) 11.02 (0.92-36.48) ng/mL and the mean biopsy Gleason score 6 (6-8). The clinicopathological information before and after RP is reported in Table 1. When comparing the biopsy and RP specimen Gleason score, it was downgraded by 1 point in six men (13%), upgraded by 1 point in eight (18%) and upgraded by 2 points in one (2%); the Gleason score remained constant in 30 men (67%).

During the mean follow-up of 33.5 (6.6-91.4) months, six (13%) patients had a biochemical recurrence (Table 2), the mean time to which was 5.8 (3.3-11.8) months. The nomograms predicted a mean 5-year freedom from recurrence of 0.83 and 0.85 before and after RP, respectively, and the 5-year actuarial freedom from recurrence was 0.86 (Fig. 1).

DISCUSSION

In the trial reported by Thompson *et al.* [1], while treatment with finasteride reduced the prevalence of prostate cancer compared with placebo, a higher proportion of high-grade tumours were detected in men treated with finasteride. In the finasteride group, 37% of the diagnosed cancers were Gleason score ≥ 7 , compared to 22% of those diagnosed in the placebo group. A possible explanation for this was over-grading by pathologists secondary to the histological effects of finasteride on prostate cancer cells. If finasteride therapy systematically increases Gleason grading, predictive tools (including the present nomograms) using Gleason grade will overestimate the risk of cancer recurrence.

Previous reports show that the assignment of Gleason grade in prostate cancer is hindered during ADT [2-5]. These reports evaluated the effect of LHRH agonist-antagonists with or without an antiandrogen on the Gleason grading system, but did not specifically address 5 α -reductase inhibitors. Several investigators reported that finasteride has less histological effect on prostate cancer cells than do LHRH analogues or antiandrogens [7,8,12], but these studies do not address whether or not these histological changes from finasteride therapy make Gleason grading unreliable.

In the present study we evaluated whether an accurate Gleason score could be assigned in men treated with finasteride; the Gleason score is a predictor of pathological stage, lymph node invasion, and ultimately disease recurrence [10,11,13]. Using our RP nomograms, which consider Gleason score as a predictive variable, we were able to compare predictive models of freedom from biochemical recurrence with actuarial recurrence during the follow-up [10,11]. We hypothesized that if an accurate Gleason score could not be assigned and biopsies were upgraded secondary to potential histological effects of finasteride, patients would actually have a higher freedom from recurrence than predicted by our nomogram. However, the nomograms

predicted a freedom from biochemical recurrence of 0.83 and 0.85, vs an actuarial 5-year freedom from recurrence of 0.86. Thus in the present patients the predictive nomograms compared favourably with the actual rate of cancer recurrence. Therefore, Gleason grade appears to remain a valid predictor of disease recurrence in men with prostate cancer on finasteride therapy.

Although this series of men undergoing RP after treatment with finasteride represents the largest reported thus far, there are several limitations. One is the duration of treatment with finasteride before the prostate cancer diagnosis (23.6 months). Whether longer therapy with finasteride, as in the trial cited above [1], is associated with more treatment-related histological changes has not been evaluated. Another limitation of the present study is that relatively few men were included, as most men undergoing RP do not have LUTS requiring therapy, and the follow-up was relatively short (33.5 months).

While the present study suggests that the Gleason score assigned in men with prostate cancer and treated with finasteride can be used in predictive tools, a follow-up of the cohort of men from the earlier trial of men with high-grade prostate cancer [1] is needed to determine if their assigned Gleason score accurately reflects their outcome.

In conclusion, finasteride does not appear to compromise the use of the Gleason grade in men undergoing prostate biopsy or RP for use in prediction tools before or after surgery. The actuarial 5-year freedom from recurrence was similar to that predicted by validated nomograms. The Gleason grade remains an important prognostic predictor in men treated with finasteride undergoing RP for clinically localized prostate cancer.

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Abbreviations

ADT, androgen deprivation therapy; RP, radical prostatectomy.

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FIG 1. Kaplan-Meier analysis of 5-year freedom from biochemical recurrence (45 men; the numbers above the axis indicate the number at each time).

TABLE 1

Clinical and pathological information for 45 men treated with finasteride who were diagnosed with prostate cancer and underwent RP

Clinicopathological variable	n (%)
Mean (range) PSA, ng/mL (doubled for finasteride)	11.02 (0.92-36.48)
Biopsy Gleason score	
6	29 (64)
7	10 (22)
8	6 (13)
Clinical stage (TNM 1992)	
T1c	24 (53)
T2a	12 (27)
T2b	6 (13)
T2c	3 (7)
RP Gleason score	
6	19 (42)
7	24 (53)
8	1 (2)
9	1 (2)
Pathological stage (TNM 1992)	
T2a	10 (22)
T2b	16 (36)
T2c	6 (13)
T3a	7 (16)
T3b	3 (7)
T3c	2 (4)
T4a	1 (2)
N0	42 (93)
N1	3 (7)

Clinical and pathological data on six patients with evidence of biochemical recurrence

Variable	Patient 1	2	3	4	5	6
PSA, ng/mL [*]	16.08	2.32	13.62	11.78	1.60	7.18
Biopsy GS	8	6	8	7	7	8
Clinical stage	T2b	T1c	T2a	T2b	T2a	T2c
RP GS	8	7	7	7	9	7
Pathological stage	T3aN0	T3cN1	T2aN0	T2bN0	T3bN1	T2bN1
Nomogram prediction [†]						
pre-RP	0.54	0.92	0.76	0.62	0.86	0.64
post-RP	0.56	0.24	0.95	0.87	0.49	0.48

No patient had a positive surgical margin; GS, Gleason score;

^{*} serum PSA doubled for finasteride therapy before RP;

[†] Probability of freedom from biochemical recurrence.