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Original article

Prognostic influence of the third Gleason grade in prostatectomy specimens

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Abstract

Background: Gleason grading of prostatic specimens remains as one of the most powerful factors predicting prognosis in patients with prostate cancer. This grading system was created by Donald Gleason about 49 years ago and it takes into account the 2 most prevalent grades in the tumor sample, but it does not consider the presence of a third high grade pattern when it represents less than 5% of the whole radical prostatectomy specimen.

Objective: The objective of the present study is to determine whether the existence of a third pattern of growth in the radical prostatectomy samples correlates with a shorter recurrence free survival.

Material and methods: We have reviewed 85 consecutive specimens of radical prostatectomy from patients with clinical localized disease. Those who received previous hormonal or radiation therapy were excluded. We have determined the Gleason grade and also the presence of a third higher grade pattern, surgical margins status, capsular, vascular, and lymphatic invasion. We have analyzed whether the existence of this high grade third pattern areas influences prognosis. Recurrence was defined with PSA levels (biochemical recurrence).

Results: We have shown that the presence of a Gleason's grade 5 pattern of growth worsens prognosis in patients with tumors grade 7 (both 3 + 4 and 4 + 3), with a shorter time to recurrence. The latter group of patients behaves more like patients with Gleason 8 tumors. This worse prognosis should be taken into account for patient surveillance and future adjuvant therapies. We feel this information is relevant and should be reported in the pathology reports.

Keywords: Prostatectomy; Prostatic carcinoma; Gleason grading system; High grade pattern; Tertiary Gleason pattern

1. Introduction

Prostatic adenocarcinoma is the most frequent tumor and the second leading cancer-related cause of death in men in Western countries [1]. Four decades ago, Donald Gleason [2] developed a grading system for this tumor mainly based on the architectural pattern of growth under low power view. This system has been honored by time and remains one of the most important factors determining prognosis in these patients. As it is well known, the grading considers the 2 most prevalent patterns in the tumor and adds the 2 figures to give only one global number. The score value can range between 2 and 10; the higher the figure, the higher the aggressiveness of the tumor. In the original grading system, there is no consideration to the existence of a higher less prevalent area in the tumor samples. In 2005, the International Society of Urologic Pathology [3] held the consensus about the grading system in both radical prostatectomy specimens and needle biopsy.

A study by Patel el al. [4] reviewed 2,370 radical prostatectomy (RP) specimens and found a shorter time to biochemical recurrence in patients with Gleason 7 tumors with a tertiary pattern 5 ($P = 0.04$). A significant difference was not observed when these group were compared with patients with Gleason score 8 to 10 ($P = 0.90$).

Similar results were found by Trock el al [5], who analyzed 3,230 RP and found that tumors Gleason 7 with a tertiary grade 5 behave like tumors grade 8 ($P = 0,409$). Biochemical recurrence was observed more frequently in Gleason 7 when a third high grade was present, than when

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it was not ($P = 0.0001$) and recurrence time was always shorter in patients with Gleason grade 5 areas, independently of the associated Gleason score. Unfortunately, very few studies have addressed this issue, but in the 2 aforementioned studies and in others [6–12], a correlation has been confirmed between the presence of this third higher grade pattern and an earlier biochemical recurrence; this should be considered relevant for the management of the patients. The goal of the present report is to analyze the prognostic significance of the third pattern of growth in prostatic adenocarcinomas Gleason 7.

2. Materials and methods

We have reviewed 85 consecutive prostatectomy specimens from men with prostatic adenocarcinoma. These cases were operated in a single tertiary hospital (Hospital Gregorio Marañon in Madrid, Spain) between 1995 and 1997 with clinical localized disease, with a follow-up period of approximately 13 years (mean 114 months) and ended in June of 2009. The inclusion criteria for the study were localized prostatic adenocarcinomas with no previous hormonal or radiation therapy for their tumors [13,14]. The patients underwent radical open prostatectomy with curative intention. During follow-up serial measurements of prostatic specific antigen (PSA) were obtained, first at 6 months interval for 2 years and thereafter once a year. Biochemical recurrence was defined as an increase of PSA levels that had normalized following surgery over 0.2 ng/ml in 2 consecutive controls.

The whole material from prostatectomy was embedded in whole-mount paraffin blocks and serially sectioned. All the margins of the specimen were ink-stained before inclusion. Two independent pathologists reviewed the tumor slides to estimate the Gleason grade. In discordant cases, they achieved a consensus after slide revision in a two-headed microscope.

The data collected were age, clinical stage, Gleason grade, capsular invasion, extraprostatic invasion, lymphatic, vascular and perineural invasion, presence of high grade intraepithelial neoplasia, and time to biochemical recurrence (months).

The base data was analyzed with the statistical computer package SPSS 13.0 for Windows (SPSS Inc., Chicago, IL). The quantitative variables were estimated with mean (range or standard deviation) and the qualitative ones with percentages and absolute number. Statistical analysis included Student's *t*-test or analysis of variance (ANOVA) for comparison of quantitative variables and χ^2 test for qualitative ones and the survival analysis was performed with Kaplan-Meier curves and log-rank test for the differences in survival between groups. We have also performed Cox's multivariate model of survival to show independent predictive value of the different prognostic factors. The significance cut-off was established at $P < 0.05$ for all the statistical analysis in this study.

Table 1
Main features of our series

Age (year)	63.3 (5.7)
PSA level (ng/ml) prior to surgery	17.8 (1–430)
Gleason grade	
6	31 (36.5%)
7 (4 +3 or 3 +4)	33 (48.8%)
8 or higher	21 (24.7%)
Biochemical recurrence	
No	49 (57.6%)
Yes	36 (42.4%)
PIN	
No	12 (14.1%)
Yes	73 (85.9%)
Bilateral tumor	
No	15 (17.6%)
Yes	70 (82.3%)
Capsular invasion	
No	5 (5.8%)
Yes	80 (94.1%)
Extraprostatic invasion (F = focal; E = extensive)	
No	32 (37.6%)
Yes	53 (62.4%); 42 (79.2%) E; 11 (20.8%) F

3. Results

We have included 85 consecutive radical prostatectomy specimens. Table 1 summarizes the characteristics of our patients. We analyzed the existence of a third higher grade pattern of growth (either 5 grade foci for tumors with a Gleason grade 7 and 4 or 5 foci for tumors grade 6). Table 2 summarizes our results regarding the existence of a third higher grade pattern of growth. We found a statistically significant association between PSA presurgical levels and Gleason grade ($P = 0.03$), but we found no association between age and grade ($P = 0.15$).

We have performed a survival analysis in our series. Table 3 summarizes the rate of recurrences in the different groups. It can be noted that the recurrence rate tends to be higher with increasing Gleason grades. The comparison of the Kaplan-Meier survival curves between the groups found no statistically significant differences between patients with grade 6 tumors with and without third pattern of growth (long rank $P = 0.23$) with median times to recurrence of 105 and 67 months, respectively. However, when we compared the survival curves between grade 7 tumors with and without higher grade areas, we found statistically significant differences ($P = 0.03$) (Fig. 1). There were no significant differences in the survival between grade 7 with higher grade areas and tumors grades 8 or higher ($P = 0.9$). Our study also showed significant differences between grade 7 tumors without higher grade areas and grade 8 lesions ($P = 0.01$) (Table 4).