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Can microfocal prostate cancer be regarded as low-risk prostate cancer?

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Purpose: Prostate specific antigen (PSA) screening for prostate cancer has become widespread, the prostate biopsy technique has evolved, and the occurrence of low-risk prostate cancer has been increasing. Even low-risk patients may demonstrate disease upgrading or upstaging. We aimed to evaluate the clinical importance of a single microfocal prostate cancer at biopsy in patients subsequently treated with radical prostatectomy.

Methods: A total of 337 cases of patients who underwent radical prostatectomy after prostate biopsies were retrospectively reviewed. Microfocal prostate cancer was defined as Gleason score 6 and a single positive core with ≤5% cancer involvement after the standard 12-core extended biopsy.

Results: Of the 337 prostatectomy specimens, 22 (6.5%) were microfocal prostate cancer based on prostate biopsy. On final pathology, microfocal patients were found to have significant 45% Gleason score upgrading ($P=0.02$) and 27% positive surgical margins ($P=0.04$) despite low PSA, compared with the nonmicrofocal prostate cancer group. Gleason upgrading was significantly higher in the microfocal prostate cancer group ($P=0.02$), whereas Gleason downgrading was significantly higher in the nonmicrofocal prostate cancer group ($P<0.01$). Furthermore, biochemical recurrence rate was no different between microfocal and nonmicrofocal prostate cancer at mean 31 months ($P=0.18$). Overall, 13 of 22 cases (53.1%) in the microfocal prostate cancer group showed Gleason upgrading or stage upgrading.

Conclusions: Based on higher rates of Gleason score upgrading or stage upgrading cases in microfocal prostate cancer group, compared with nonmicrofocal prostate cancer group, active surveillance should be cautiously applied to these patients.

Keywords: Prostate neoplasms, Biopsy, Low-risk prostate cancer, Prostatectomy

INTRODUCTION

Prostate specific antigen (PSA) screening for prostate cancer has become widespread, the prostate biopsy technique has evolved, and the detection of low-risk prostate cancer has been increasing [1]. Concerns have been expressed that the increased detection of indolent prostate cancer leads to patients receiving unnecessary treatment and dealing with unnecessary side effects [2].

Patients diagnosed with Gleason score (GS) 6 microfocal prostate cancer are often considered to have low-risk disease during initial counseling [3]. However, according to the Epstein criteria [4], the preoperative diagnosis of low-risk prostate cancer is a difficult decision to make since prostate cancer is a multifocal, heterogeneous disease. Some studies have reported that even low-risk patients may demonstrate disease upgrading or upstaging [5].

A strong connection between microfocal prostate cancer at biopsy and clinically insignificant disease would be a strong argument against treating these patients [6]. We aimed to evaluate the clinical importance of single microfocal prostate cancer (GS ≤ 6) at biopsy in patients subsequently treated with

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radical prostatectomy (RP). We characterized pathological stage, surgical margin, tumor volume, and PSA density in men with low-risk cancer and identified pretreatment clinical parameters that may predict pathological outcomes.

MATERIALS AND METHODS

1. Patients and procedure

The study was approved by the Institutional Review Board of our institution. From January 2002 to September 2012, 337 cases that underwent RP after 12-core extended prostate biopsies were retrospectively reviewed. Microfocal prostate cancer was defined as GS 6 and a single positive core with ≤5% cancer involvement after the 12-core biopsy. We excluded patients who had undergone prostate biopsy at another institution, hormone therapy, or radiation therapy before the RP.

In all patients, serum PSA levels were obtained before digital rectal examination and transrectal ultrasonography. Clinical staging was performed according to the TNM staging system, and the ellipsoid formula was used to derive prostate volume via transrectal ultrasonography. All biopsy and RP specimens were reviewed by a single genitourinary pathologist. All biopsy cores were individually labeled. For each biopsy protocol, the number of cores involved by cancer, total length of tissue sampled, total length of cancer detected, and GS were determined.

Patient age, preoperative PSA level, and clinical stage were recorded in all patients. The RP was performed by a single surgeon (B.H.C.). Lymph node dissection was selectively performed in patients with clinical stage T3 or greater. Pathological grade and stage were defined, and surgical margin status was noted following light microscopy examination of the specimen slides. The prostatectomy specimens were fixed overnight in 10% neutral buffered formaldehyde and coated with India ink. Transverse whole mount step section specimens were obtained with 4-mm intervals on a plane parallel to that in which transverse T2-weighted sequences were performed. Upstaging was defined as pathological stage T3a, T3b, and T4. Patients were followed postoperatively at every 3 months for the first year and every 6 months afterward with serum PSA measurement. We define biochemical recurrence as PSA greater than 0.2 ng/mL.

2. Statistical analysis

Statistical analyses were performed using Student *t*-test to evaluate the demographic and clinical differences between microfocal prostate cancer and nonmicrofocal prostate cancer groups. The Mann-Whitney *U* test was used to compare the microfocal tumor characteristics, including biopsy location, as well as pathologic findings between the disease upgrading or upstaging group and the other group. All *P*-values less than 0.05 were considered statistically significant. The Kaplan-Meier method was used to compare biochemical recurrence-free survival between microfocal prostate cancer and nonmicrofocal prostate cancer. All statistical analyses were performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

Of the total 337 RP cases, 22 patients were diagnosed with microfocal prostate cancer upon biopsy. Mean age was comparable between both groups, and mean PSA and GS were 5.6 ng/mL and 5.8, respectively, in the microfocal prostate cancer group and 13.2 ng/mL and 7.1, respectively (Table 1). PSA density in the microfocal prostate cancer group was significantly lower than in nonmicrofocal prostate cancer group

Table 1. Patient characteristics and pathological outcome

Characteristic	Microfocal PCa	Nonmicrofocal PCa	*P*-value
Number	22	315	
Age (yr)	63.6±7.0 (49–71)	63.5±5.8 (48–74)	0.49
PSA (ng/mL)	5.6±2.6 (2.5–11.3)	13.2±3.8 (3.2–21.7)	0.02
PSA density (ng/mL)	0.18±0.09 (0.07–0.37)	0.36±0.07 (0.10–0.78)	0.01
Prostate volume (mL)	30.2±10.5 (16.4–64.5)	36.7±11.4 (14.8–121.3)	0.48
Gleason score, mean (range)	5.8 (4–6)	7.1 (5–9)	<0.01
Pathology, n (%)			
PSM	6 (27.2)	45 (14.3)	0.04
GS upgrading	10 (45.4)	69 (21.9)	0.02
GS downgrading	1 (4.5)	101 (32.1)	<0.01
Stage upgrading	11 (50.0)	152 (48.3)	0.55
Biochemical recurrence	3 (13.6)	56 (17.6)	0.18

Values are presented as mean±standard deviation (range) unless otherwise indicated.
PCa, prostate cancer; PSA, prostate specific antigen; PSM, positive surgical margin; GS, Gleason score.

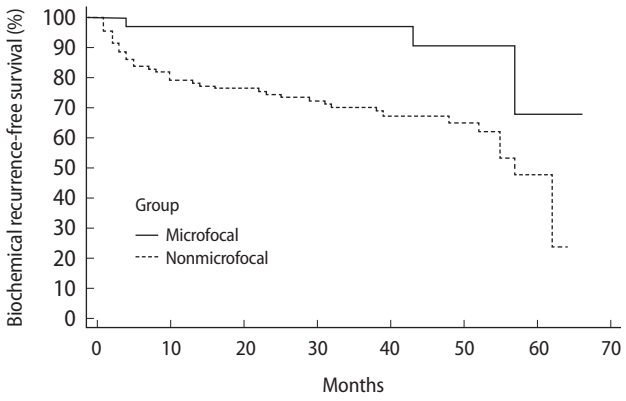

Fig. 1. Comparison of Kaplan-Meier biochemical recurrence-free survival curves between two groups.

Table 2. Microfocal tumor characteristics

Characteristic	GS or stage upgrading	Nonupgrading	*P*-value
Number	13	9	
Biopsy findings (location)			
Apex	7 (53.8)	1 (11.1)	<0.01
Lateral	5 (38.5)	6 (66.7)	<0.01
Others	1 (7.7)	2 (22.2)	0.02
Pathologic findings (location)			
Apex	6 (46.2)	1 (11.1)	<0.01
Lateral	6 (46.2)	7 (77.8)	<0.01
Others	1 (7.7)	1 (11.1)	0.12
Biochemical recurrence	3	0	

Values are presented as number (%).
GS, Gleason score.

(*P*=0.01) (Table 1). Among RP specimens, there were higher margin positive rates in the microfocal prostate cancer group (27.2%) than in the nonmicrofocal prostate cancer group (14.3%, *P*=0.03). On the final pathology, microfocal patients were found to have 45% Gleason upgrading, 50% staging upgrading, and 27% positive surgical margins despite low PSA. In addition, the rate of GS upgrading in the microfocal prostate group (45.4%) was significantly higher than in the nonmicrofocal prostate cancer group (21.9%, *P*=0.02), whereas Gleason downgrading was significantly higher in the nonmicrofocal prostate cancer group (*P*<0.01). The biochemical recurrence rate was no different between microfocal and non microfocal prostate cancer (Table 1). However, after a mean postoperative follow-up of 31 months, a log-rank test of the Kaplan-Meier survival curves demonstrated that overall biochemical recurrence-free survival rate is significant higher in the microfocal group compared with non microfocal group (Fig. 1) (*P*=0.004).

Of the 22 cases of microfocal prostate cancer upon biopsy, 13 cases (59.09%) showed GS upgrading or staging upgrading. Seven out of 13 patients with prostate cancer (53.8%) were detected at the foci of the apex lesion upon biopsy. Six out of 13 GS (46.2%) or stage upgrading cases were detected with prostate cancer located at the apex portion of the prostate. However, only one case out of 9 nonupgrading cases (11.1%) was detected at the apex (Table 2).

DISCUSSION

PSA screening for prostate cancer has become widespread, and the occurrence of low-risk prostate cancer has been dramatically increasing [5]. Using definite therapy such as RP, clinically localized prostate cancer might be curatively treated, especially in low-risk prostate cancer patients. However, for low-risk prostate cancer patients with insignificant prostate cancer, RP is obviously an overtreatment considering the morbidities, postoperative complications, and oncologic features of these cases [7]. Despite the variation of the terminology and definitions used for insignificant prostate cancer in the literature, the intellectual concept of insignificant prostate cancer is well established: a low-grade, small-volume, and organ-confined prostate cancer that is unlikely to be clinically or biologically significant without treatment [8]. There have been many attempts to establish criteria to predict insignificant prostate cancer before surgery, using biopsy results, PSA density, and PSA/free PSA ratio [9].

The high rates of GS or staging upgrading (59.1%) in microfocal prostate cancer in this study might result from cancer foci (apical portion of the prostate) which were hard to detect lesions at taking biopsies. At the apex portion of the prostate gland, the peripheral zone extends anteriorly to the distal prostatic urethra. It may be difficult to palpate by digital rectal examination cancers that arise in this apico-anterior peripheral zone [10]. Furthermore, an apical biopsy may not be performed in the initial biopsy because it is widely recognized as being more painful than a biopsy of the remainder of the prostate and difficulty in palpating by digital rectal examination [11]. The zonal origin of prostate cancer affects the pathological findings and biochemical recurrence rate after RP [12]. Anterior prostate cancer including apical lesion were not only of lower clinical stage, but they also had lower GS on preoperative prostate biopsy compared with peripheral zone tumor [12]. However, data from whole mount specimens showed that anterior tumors are not insignificant cancers [13]. Patients with anterior prostate cancers had a higher tumor volume and a higher rate of positive surgical margins than patients with peripheral prostate cancers [12].

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Furthermore, extraprostatic extension was more likely to be associated with positive surgical margins for anterior prostate cancers than peripheral prostate cancers, suggesting that anterior positive margins might be clinically significant, and at greater risk of biochemical recurrence [14].

In our previous study [15], insignificant prostate cancer based on an Epstein criteria from a prostate biopsy underestimated the true nature of prostate cancer in as many as 42.1% of Koreans. This high inaccuracy rate of the Epstein criteria might result from more aggressive and poorly differentiated prostate cancer in Korean men, despite a low clinical stage or low serum PSA level [16]. Prostate cancer arising in Korean men that is of a predominantly high grade may be attributed to reduced testosterone metabolism. Hoffman et al. [17] demonstrated that patients with a low serum-free testosterone level have an increased mean percentage of biopsies revealing cancer with a GS of 8 or higher, suggesting that a low serum-free testosterone level may be a marker of more aggressive disease. However, in our study we do not know the exact reason why the high incidence of stage migration from insignificant disease at biopsy to significant disease at final pathology was occurred. Additional studies from a large data would be needed to confirm our results.

When counseling patients with low grade, microfocal prostate cancer on biopsy, final decision making regarding management should be guided by the sampling technique, the potential risk of upgrading or upstaging, and contextual considerations, such as patient age and comorbidity [15]. Further improved biopsy sampling technique and imaging in patients who choose active surveillance may help minimize the risk of understaging and/or undergrading [18].

There are several limitations to our study. First, the present study consists of a relatively small number of patients; therefore, statistical results should be cautiously interpreted. Another limitation is a retrospective study design. Future prospective, large cohort study should be needed to confirm our current results.

In our study, microfocal prostate cancer showed higher rate of Gleason upgrading compared to nonmicrofocal prostate cancer. In GS or stage upgrading cases, prostate cancer was usually located at the apical portion. Based on higher rates of GS upgrading or stage upgrading cases in microfocal prostate cancer group, compared with nonmicrofocal prostate cancer group, active surveillance should be cautiously applied to these patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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