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Original Article

Clinical significance of single microscopic focus of adenocarcinoma at prostate biopsy

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ABSTRACT

Objective: Prostate cancer (PC) is one of the most common cancer and an important reason of cancer specific death. The incidence of patients who diagnosed at low stage increased because of widespread using Prostate Specific Antigen (PSA) testing. We evaluated the patients who were diagnosed single microscopic focus of adenocarcinoma and treated radical prostatectomy at final pathology.

Methods: The patients who underwent transrectal ultrasound guided prostate biopsy between January 2004 and January 2012 were enrolled retrospectively. We extracted the patients who were diagnosed single microscopic focus of adenocarcinoma and treated with RP. Single microscopic adenocarcinoma was defined as one single focus measuring 3 mm or less, well differentiated (Gleason ≤6) adenocarcinoma. 37 patients were included at the study. Clinical data; including age, serum PSA levels, PSA density and prior biopsy and prostatectomy specimen results were recorded. In pathological examination; high molecular weight cytokeratin (HMW-CK), p63, and alpha-methylacyl-CoA racemase (AMACR) were used for differential diagnosis.

Results: The patients' ages were between 42 and 77 with a mean age of 64.9 ± 7.57 years. Mean PSA levels and prostate volumes were 8.03 ± 5.21 ng/ml and 54 ± 25.51 cc. T0, T2a, T2c and T3a were reported in 2 patients, 17 patients, 17 patients and 1 patient after pathological evaluation. According to the Gleason grading system; 6 patients were 7 (3 + 4), one patient was 7 (4 + 3), one patient was 5 (3 + 2) and 27 patients were 6 (3 + 3).

Conclusion: Small volume of cancer at prostate biopsy is not necessarily small cancer in radical prostatectomy. The treatment choice may be over or under treatment for some patients, so the patients must be informed when choosing the treatment.

1. Introduction

The widespread use of prostate specific antigen (PSA) screening and aggressive prostate biopsy protocols have increased the incidence of small volume organ confined prostate tumors.[1] Although 30–40% of men older than 50 years have prostate cancer, only 8% of the cancers are clinically significant.[2] The Epstein criteria are the most frequently used criteria for defining whether prostate cancer is clinically significant or not.[3] Epstein criteria consists of: (1) a Gleason score ≤ 6; (2) fewer than three positive cores; (3) PSA density ≤ 0.15 ng/mL; and (4) < 50% of cancer involvement in any core.[4] However, there is no clear consensus for managing single microscopic focus of adenocarcinoma at prostate biopsy. This is because small volume of cancer at biopsy is not necessarily small cancer in radical prostatectomy (RP) specimens.[1]

We evaluated patients who were diagnosed with single microscopic focus of adenocarcinoma at prostate biopsy and who were treated with RP at our department.

2. Materials and methods

The patients (2,425 cases) who underwent transrectal ultrasound guided prostate biopsy between January 2004 and January 2012 were enrolled retrospectively. We extracted the data on patients who were diagnosed with single microscopic focus of adenocarcinoma and who were treated with RP. Single microscopic adenocarcinoma was defined as one single focus measuring ≤ 3 mm and well differentiated (Gleason ≤ 6). Clinical data including age, serum PSA levels, PSA density, (dividing PSA by the weight of

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Table 1
Clinical data of the patients treated with radical prostatectomy.

	Mean ± SD	Range
Age (y)	64.9 ± 7.57	42–77
PSA (ng/mL)	8.03 ± 5.21	1.4–38.6
PSA density	0.15 ± 0.09	0.04–0.51
Prostate volume (cc)	54 ± 25.51	20–140
Tumor volume (cm^3)	2.11 ± 2.33	0–10

PSA, prostate specific antigen; SD, standard deviation.

Table 3
Analysis of the radical prostatectomy specimens for staging.

No.	37 (100)
T0	2 (5.4)
T2a	17 (45.9)
T2c	17 (45.9)
T3a	1 (2.7)

Data are presented as *n* (%).

prostate at RP), and prior biopsies were noted. In pathological examination, immunohistochemical studies were performed with high molecular weight cytokeratin, p63, and alpha-methylacyl-CoA racemase (AMACR). The RP specimens were sectioned and entirely embedded using 5 mm thick blocks. The tumors were graded according to the Gleason system and staged using TNM classification. The tumor volume in the RP specimens was calculated. Criteria for diagnosing insignificant prostate cancer (IPCa) were a tumor volume < 0.5 cm^3, Gleason score < 7, and organ confined disease at RP specimen defined by Epstein criteria.[4]

3. Results

Sixty patients had microscopic adenocarcinoma on needle prostate biopsy, accounting for 2.4% of 2,425 cases. The incidence of prostate cancer diagnosed with prostate biopsy is 7.1% in our study. The patients who were diagnosed with microscopic prostate cancer and treated with RP were included in the study (37 patients). Patients were aged 42–77 years with a mean age of 64.9 ± 7.57 years. The number of prostate cores was between six and 18, with a median number of 8.3 ± 2.26. Table 1 lists the patient characteristics and clinical data of the patients. Prior prostate biopsies were present in seven patients, four patients had atypical acinar proliferation, and the others were benign prostate hyperplasia (BPH). Immunohistochemical studies with high molecular weight cytokeratin, p63, and AMACR were performed in 24 of the 60 patients (Table 2). Localization of cancers were reported: 20 from apex, 15 from base, 20 from mid zone, and five from transition zone of the prostate.

Treatments used on these patients were active surveillance, radiotherapy, RP, orchiectomy, and maximal androgen deprivation therapy. Active surveillance was used for 15 patients and three patients were treated with radiotherapy. Surgical orchiectomy was performed in one patient and 37 patients were treated with RP. In the active surveillance group, three patients had undergone prostate biopsy, two of these patients were reported BPH, and one patient was reported ASAP. In the second biopsy, after six months, BPH was reported.

At RP, six patients had a Gleason score of 7 (3 + 4), one patient had a Gleason score of 7 (4 + 3), and one patient had a Gleason score of 5 (3 + 2). The other 27 patients had a Gleason score of 6 (3 + 3). The pathological stage of the patients are shown in Table 3. IPCa was present in seven (18.9%) patients at final pathology. A tumor was not found in two patients' (5.4%) RP specimens. One patient had local advanced prostate cancer that was reported as T3a. Clinically significant prostate cancer was determined in 75.6% of the patients at final pathology.

Table 2
Immunohistochemical studies of the patients for differential diagnosis.

	AMACR	p63	HMW-CK	34BE12
Positive	14	–	–	–
Negative	–	19	16	2

AMACR, alpha-methylacyl-CoA racemase; HMW-CK, high-molecular weight cytokeratin.

4. Discussion

The widespread use of PSA testing with extensive transrectal ultrasound prostate biopsy protocols with lower PSA thresholds have resulted in an increase of low volume (< 0.2–0.5 mL) prostate cancers.[5] Single microscopic focus of low grade prostate cancer at prostate biopsy is not associated with patients that have clinically insignificant disease on final RP specimens.[6] These cancers cause little harm during the patient's lifetime, but overdiagnosis can potentially lead to overtreatment, which accounts for 40–50% on the European Screening Program.[7]

Several authors have compared specimen and biopsy tumor characteristics for determining the indolent prostate cancer.[5] Terris et al[8] considered that one single positive biopsy containing a focus of ≤ 3 mm well differentiated prostate cancer (Gleason score ≤ 6) is predictive of IPCa. Epstein criteria consists of less than three positive cores containing < 50% of well differentiated prostate cancer and PSA density lower than 0.15.[4] Bocon-Gibod et al[5] reported that 29% of patients had IPCa of 56 patients with one single focus of < 3 mm. On the contrary, Allan et al[9] analyzed 54 patients with one single neoplastic focus of 0.5 mm in length of biopsy, and 67% of the patients were IPCa at RP specimens. Thorsan et al[10] reported that patients with minimal adenocarcinoma on needle biopsy was defined as less than 1 mm linear extent, but only 18% of had IPCa at RP specimens. In another study, patients with a minute focus of carcinoma of ≤ 5 mm on needle biopsy, 13.85% of the patients had Stage 3 carcinoma and only 17.25% of patients had clinically insignificant cancer at RP specimens.[11] In our study, 18.9% of the patients had IPCa at final pathology.

Gleason score concordance range in the biopsy and RP specimens is between 28% when using sextant biopsy and 72% with more extended biopsy protocols.[1] Sheridan et al[12] reported that men who were undergoing active surveillance were at 19% risk for upgrading on subsequent biopsies. Most of the tumors were upgraded within 2 years of the initial diagnosis because the higher grade tumor was not sampled in the biopsy. The presence of a Gleason score of 7 on biopsy is significant cancer and warrants active therapy such as surgery or radiotherapy.[9] In this study, Gleason scores of 6 and 7 accounts for 72.9% and 18.91% of the patients, respectively.

T0 means an absent primitive tumor in a specimen according to the 2002 TNM classification for prostate cancer.[13] T0 has been noted after prostate surgery, biopsy, and hormonal treatment. The prevalence is 2.25–15% of RP specimens after neoadjuvant hormonal therapy. Di Giusseppe et al[14] reported that tumors < 0.1 cc as minute and 0.03 cc tumors as difficult to find, Goldstein et al[15] defined a mean 0.0199 cc tumor volume. The incidence of T0 is 5.4% of present study.

Treatment of limited adenocarcinoma of a Gleason score of ≤ 6 at prostate biopsy is a dilemma of whether to subject patients to definitive therapy such as RP.[11] RP is a very aggressive

treatment for these patients.[1] PSA screening has resulted in overdiagnosis and overtreatment of prostate cancer, with the majority of prostate cancer likely to be clinically insignificant.[16] To reduce overtreatment and overdiagnosis, active surveillance was introduced. Active surveillance includes closely monitoring a patient with regular follow-up PSA, prostate biopsy, and digital rectal examination. If progression of the disease is detected by any of these monitoring measures, curative therapy should be considered.

There is no consensus about a predictive model for IPCa.[1] Epstein criteria was defined in 1994 and is the most common used for determining IPCa.[16] The overall predictability for IPCa fell from 84% to 37–76% after 2005. A microfocus adenocarcinoma Gleason score 6 has a risk of upgrading and upstaging to pT3 in 18% and 8% of patients at final pathology.[6]

The underdiagnosis of limited prostate adenocarcinoma on needle biopsy is a frequent problem in prostate pathology.[17] Immunohistochemistry may be useful for diagnosis of limited adenocarcinoma of the prostate. Basal cell markers, such as high molecular weight and p63, are found in benign glands and absent in adenocarcinoma of the prostate. AMACR is a cytoplasmis protein, is known as P504S, and has been recognized as a tumor marker. The majority of the prostate cancers (80–100%) have positive staining for AMACR.

Our study has several limitations. This study includes a small number of patients and is retrospective. The patients were not treated by a single surgeon and evaluated by a single pathologist. Further studies are needed for defining the clinical importance of microscopic adenocarcinoma of the prostate.

In conclusion, the presence of microscopic prostate adenocarcinoma at prostate biopsy corresponds to clinically significant in 75.6% of patients. While two patients had no tumor, one patient had advanced stage at final pathology.

Clinicians should consider that RP can be overtreatment for some patients. The patients who were diagnosed with single microscopic prostate cancer must be evaluated carefully and all of the treatment modalities must be discussed with the patients.

Conflicts of interest

All authors have no conflict of interest to declare.

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