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Single Positive Core Prostate Cancer in a 12-Core Transrectal Biopsy Scheme: Clinicopathological Implications Compared with Multifocal Counterpart

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Purpose: The incidence of single positive core prostate cancer at the time of biopsy appears to be increasing in the prostate-specific antigen (PSA) era. To determine the clinical implication of this disease, we analyzed surgical and pathological characteristics in comparison with multiple positive core disease.

Materials and Methods: Among 108 consecutive patients who underwent robotic radical prostatectomy following a diagnosis of prostate cancer based on a 12-core transrectal biopsy performed by the same method in a single institute, outcomes from 26 patients (Group 1) diagnosed on the basis of a single positive biopsy core and from 82 patients (Group 2) with multiple positive biopsy cores were analyzed.

Results: The preoperative PSA value, Gleason score, prostate volume, and D'Amico's risk classification of each group were similar. The proportion of intermediate+high-risk patients was 69.2% in Group 1 and 77.9% in Group 2 (p=0.22). Total operative time and blood loss were similar. Based on prostatectomy specimens, only 3 patients (11.5%) in Group 1 met the criteria for an indolent tumor (7.31% in Group 2). Although similarities were observed during preoperative clinical staging (p=0.13), the final pathologic stage was significantly higher in Group 2 (p=0.001). The positive-margin rate was also higher in Group 2 (11.5% vs. 31.7%, p=0.043). Despite similarity in upstaging after prostatectomy in each group (p=0.86), upgrading occurred more frequently in Group 1 (p=0.014, 42.5% vs. 19.5%). No clinical parameters were valuable in predicting upgrading.

Conclusions: Most single positive core prostate cancer diagnoses in 12-core biopsy were clinically significant with similar risk stratification to multiple positive core prostate cancers. Although the positive-margin rate was lower than in multiple positive core disease, an increase in Gleason score after radical prostatectomy occurred more frequently.

Key Words: *Biopsy; Prostatectomy; Prostatic neoplasms*

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INTRODUCTION

The widespread use of serum prostate-specific antigen (PSA) screening associated with transrectal ultrasonography (TRUS) prostate biopsy has led to an increase in the proportion of patients with low-stage, low-volume disease [1]. As with stage migration, the prevalence of single positive core disease appears to have shown a recent increase. Because tumor volume in single positive core disease may be relatively small, these tumors are expected to be clinically insignificant, indolent tumors with a lower positive surgical margin. However, the clinical implication of such disease compared with that of multiple positive core disease has not yet been established. In an earlier study, a le-

sion with a single positive biopsy containing a focus of 3 mm or less of moderately differentiated adenocarcinoma was suggested as indolent cancer [2]. In contrast, additional studies on a single microscopic focus of low-grade prostate cancer in preoperative biopsy have warned that not all of these patients have clinically insignificant disease in the final prostatectomy specimen [3,4]. However, most of the studies were based on a heterogeneous biopsy scheme, predominantly with sextant biopsy, or were especially focused on low-volume disease with low to intermediate Gleason grades as an attempt at preoperative identification of insignificant disease.

Studies have shown that the use of more biopsy cores may minimize discrepancy with prostatectomy specimens owing to the sampling effect [5]. Currently, a 12-core scheme is recommended as a reasonable biopsy approach, providing an acceptable sampling of the prostate gland [6,7] without increasing the complication rate [8]. Here then, to determine the clinical implications of a single positive core in a 12-core scheme, we analyzed characteristics of single positive core prostate adenocarcinoma compared with multiple positive core disease in patients undergoing radical prostatectomy.

MATERIALS AND METHODS

1. Patient population

We performed robotic assisted radical prostatectomy (RARP) for a total of 144 patients from November 2008 through December 2009. Because of possible effects on final pathologic outcomes, patients who underwent prior hormone treatment, radiotherapy, or any ablative technique were excluded in this series. Patients who underwent transrectal biopsy conducted by other institutions were also excluded in this series. A total of 108 consecutive patients who underwent systemic 12-core biopsy at the Department of Urology of our hospital and subsequent RARP for clinically localized or locally advanced prostate cancer (clinical stage T1c to T3b) from November 2008 through December 2009 were enrolled in this study. Clinical stage was assigned according to the 1992 TNM staging system on the basis of digital rectal examination or transrectal ultrasound findings. All RARP procedures were performed by a single full-faculty surgeon with robotic experience. RARP was performed by the standard transperitoneal approach with an interfacial technique by use of the da Vinci-S robot (Intuitive Surgical, Inc., Sunnyvale, CA, USA), as reported by Patel et al [9].

2. Prostate biopsy technique and histologic evaluation

The 12-core biopsy scheme used in our institution includes a standard sextant, which was originally described by Hodge et al [10], as well as a lateral sextant scheme (lateral apex, lateral mid-gland, lateral base) [11]. The biopsy policy of our institution consists of an additional two more core biopsies in cases of palpable nodule or suspicious lesions in TRUS, and two more transitional zone biopsies in cases of repeat biopsy [6]. In this series, for standardization of the number of biopsy cores, patients with hypoechoic lesions on transitional zones, patients with finger-directed nodules, or patients diagnosed by repeat biopsy were excluded. Patients received appropriate antibiotic coverage, and selected patients underwent bowel preparation. All procedures were performed by three dedicated urologists, each of whom has experience with over 300 cases of transrectal prostate biopsy by use of the 12-core scheme. Biopsies were performed under ultrasound guidance by 18-gauge, 2 cm long, Trucut core needle biopsy. Each biopsy core was separately labeled to identify the location. TRUS-measured total prostate gland and transitional zone volumes were determined by using the prostate ellipsoid formula. Cores from needle biopsy were interpreted by a single experienced full-faculty uropathologist before radical prostatectomy, without consensus interpretations. Prostate specimens from RARP were also interpreted by the same full-faculty uropathologist. All radical prostatectomy specimens, including the seminal vesicles and distal vas deferens, were weighed, and the external surfaces were inked and submitted for pathological evaluation according to a modified Stanford protocol [12]. They were then fixed overnight in 10% formalin. Following fixation, the apex and base were amputated and serially sectioned at 3 mm intervals in the vertical, parasagittal plane. The seminal vesicles were sectioned parallel to their junction with the prostate and were entirely submitted for examination. The remaining prostate was sectioned serially, perpendicular to the long axis from the apex of the prostate to the base, and whole-mount sections were prepared. The greatest diameter of the largest single focus of tumor was obtained by marking both ends of the tumor on the glass slide and measuring this distance with a ruler marked in millimeters. The volume of carcinoma in the entire prostate was determined by using the grid method [13]. In this method, the sum of each area was multiplied by the thickness of the average slice. The level of capsular invasion, presence of seminal vesicle invasion, surgical margin status, and Gleason grade of the cancer were inspected.

3. Data collection and analysis

For enrolled patients, preoperative data, including biopsy results, clinical stage, initial serum PSA, operative outcomes, and final pathological results, including margin positivity and pathologic stage, were collected prospectively. Results from patients diagnosed by a single positive biopsy core (Group 1) were compared with those of patients diagnosed by multiple positive cores (Group 2). On the basis of preoperative Gleason score, serum PSA, and clinical stage, patients were classified according to D'Amico's risk stratification scheme. Age, body mass index, PSA level, operation time, Gleason score, and estimated blood loss (EBL) were analyzed by independent t-test, and D'Amico's risk classification was analyzed by Pearson's chi-square test. The relation of pathologic stage and positive margin were calculated by chi-square test (linear by linear association).

Correlation analysis was used to predict the relationship of the number of positive cores and the positive-margin rate. Statistical significance in this study was set at $p < 0.05$. All reported p-values are 2-sided. All analyses were performed with SPSS, ver. 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Among the patients enrolled, 26 patients had a single positive core in the 12-core biopsy (Group 1), and 82 patients had multiple positive cores (Group 2). The perioperative characteristics of each group are summarized in Table 1. Serum PSA (7.7±3.9 vs. 8.7±5.6 ng/ml), Gleason score (6.3±0.7 vs. 6.8±0.8), and prostate volume (29.9±9.9 vs. 29.2±10.0) were similar in each group. A total of 94 patients had clinically localized disease, and 14 had locally advanced disease. Classification of patients by D'Amico's classification showed that the proportion of patients in each risk group was similar (Pearson's chi-square test, p=0.17). In Group 1, only 30.8% of patients were stratified as low risk. The proportion of intermediate+high risk patients was 69.2% in Group 1 and 77.9% in Group 2 (p=0.22) (Table 1).

Surgical results showed no significant difference between the two groups in total operative time (205.3±101 vs. 211.9±71.6 minutes), estimated blood loss (372.3±127.7 vs. 344.6±73.7 ml), or hospitalization duration (8.0±0.7 vs. 7.9±0.6 days).

On the basis of prostatectomy specimens, only 3 patients (11.5%) in Group 1 met the criteria for an indolent tumor (7.31% in Group 2), which was defined by a tumor volume below 0.5 cc and Gleason score below 7 [14]. Although similarity in preoperative clinical stage was observed (p=0.13), pathologic stage based on prostatectomy specimens was significantly higher in Group 2 (p=0.001) (Table 2). Changes in stage after prostatectomy were similar in each group

TABLE 1. Preoperative clinicopathologic characteristics and surgical results of each group

	Group 1 (n=26)	Group 2 (n=82)	p-value
Age (yr)	63±5.8	62.8±6.5	0.898[a]
Body mass index (kg/m^2)	24.7±2.3	23.8±2.4	0.101[a]
ASA status	1.80±0.4	1.84±0.4	0.691[a]
Prostate volume	29.9±9.9	29.2±10.0	0.818[a]
Preoperative PSA (ng/ml)	7.7±3.9	8.7±5.6	0.418[a]
Preoperative Gleason score	6.3±0.7	6.8±0.8	0.607[a]
Total operative time (minutes)	205.3±101.1	211.9±71.6	0.232[a]
Estimated blood loss (ml)	372.3±127.7	344.6±73.7	0.348[a]
Duration of admission (d)	8.0±0.7	7.9±0.6	0.235[a]
D'Amico's risk stratification (%)	Low: 30.8	Low: 22.1	0.17[b]
	Intermediate: 50.0	Intermediate: 42.7	
	High: 19.2	High: 35.2	
	Intermediate+high: 69.2	Intermediate+high: 77.9	0.22[b]
Positive-margin rate (%)	11.5	31.7	0.043[b]

ASA: The American Society of Anesthesiologists Physical Status Classification System, PSA: prostate-specific antigen, Group 1: single positive core, Group 2: multiple positive cores, [a]: Student's t-test, [b]: Pearson's chi-square test

TABLE 2. Preoperative clinical stage and postoperative pathologic stage in each group

Stage	Group 1 (n=26)		Group 2 (n=82)	
	Preoperative clinical stage (%)	Preoperative pathologic stage (PSM)	Postoperative clinical stage (%)[a]	Postoperative pathologic stage (PSM)[b]
T1c	11 (43.4)		22 (23.4)	
T2a	4 (13.1)	11 (0)	6 (6.5)	8 (0)
T2b	2 (4.3)	5 (0)	12 (12.9)	9 (2)
T2c	6 (26.1)	8 (1)	31 (33.8)	29 (5)
T3a	2 (8.7)	1 (1)	10 (11.7)	26 (12)
T3b	1 (4.3)	1 (1)	1 (1.3)	5 (3)
T3c	0	0 (0)	0	4 (3)
T4	0	0 (0)	0	1 (1)
Total	26	26 (3)	82	82 (26)

PSM : positive surgical margin, [a]: comparison of preoperative clinical stage in each group. p=0.126, [b]: comparison of postoperative pathologic stage in each group. p=0.001

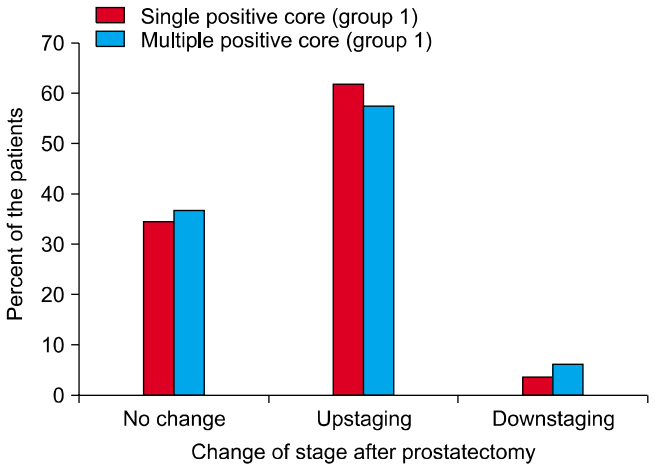

FIG. 1. (A) Change in stage after prostatectomy. Changes in stage after prostatectomy were similar in each group (p=0.86); 61.5% of Group 1 and 57.3% of Group 2 experienced upstaging after prostatectomy. Change in Gleason score after prostatectomy showed a significant difference between each group (p=0.014). (B) Changes in Gleason grade after prostatectomy. Upgrading after prostatectomy occurred more frequently in Group 1 (42.5%), than in Group 2 (19.5%).

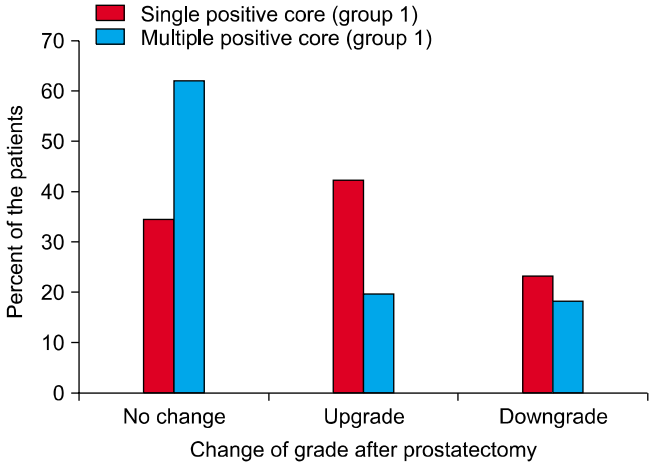

FIG. 2. Relationship of margin positivity with number of positive cores in a 12-core systematic transrectal biopsy scheme. A significant positive correlation between the number of positive cores and the positive-margin rate was found in Group 2 (correlation analysis, Spearman's correlation coefficient=0.918, p=0.001).

(p=0.86); 61.5% in Group 1 and 57.3% in Group 2 experienced upstaging (Fig. 1A). However, change in Gleason score showed a significant difference (p=0.014). Upgrading was higher in Group 1 (42.5%) than in Group 2 (19.5%) (Fig. 1B). According to both the univariate and the multivariate analysis, this change had no correlation with preoperative clinical parameters, including serum PSA, prostate volume, clinical stage, biopsy Gleason score, and tumor volume in biopsy specimens.

The positive-margin rate was significantly higher in Group 2 (11.5% vs. 31.7%, p=0.043). In Group 1, whereas only one patient (4.2%) among 24 with pathologically localized disease had positive margins, there were 7 patients (15.2%) among 46 with localized disease in Group 2. There was a significant positive correlation between the number of positive cores and the positive-margin rate in Group 2 (correlation analysis, Spearman's correlation coefficient= 0.918, p=0.001) (Fig. 2).

DISCUSSION

Although the clinical implication has not been clearly determined, the incidence of single positive core prostate cancer appears to be increasing in the PSA screening era. In a population-based screening study conducted by the Rotterdam section of the European randomized study on screening of prostate cancer, the proportion of focal cancers, defined as those involving less than 3 mm in a single core without Gleason grade 4 or 5 during the second screening after 4 years, increased from 16% to 29% of all detected cancer [14].

If physicians are to recommend a specific management to patients with prostate cancer, an accurate estimation of risk is essential. Because tumor volume in single positive core prostate cancer may be relatively small, the disease is expected to be curable, toward low-risk patient groups in risk stratification, as shown in a 6-core scheme. Active surveillance with delayed intervention appears to be a viable option for carefully selected men with low-risk prostate cancer. Good-risk prostate cancer, defined as a Gleason score of 6 or less, PSA of 10, and T1c to T2a, now constitutes 50% of newly diagnosed prostate cancer [15]. In most of these patients, the disease is indolent and slow growing. The challenge is to identify those patients who are unlikely to experience significant progression while offering radical therapy to those who are at risk. Currently, the best means of selecting such patients for definitive therapy is an approach based on the interpretation of PSA kinetics and repeat biopsy during a period of surveillance [16]. The approach of active surveillance with selective delayed intervention based on PSA doubling time represents a practical compromise between radical therapy for all (which results in overtreatment of patients with indolent disease) and watchful waiting with palliative therapy only (which results in undertreatment of those with aggressive disease). Clinical judgement incorporating patient comorbidity, life expectancy, and attitude towards quality versus quantity of life is required in making this recommendation. However, our study and many other published studies have reported that upstaging in pathology and Gleason score upgrading occurs after radical prostectomy [17]. D'Amico et al mentioned that it is not appropriate to do active surveillance for prostate cancer over a Gleason score of 7, because of the high biochemical and pathological progression rate [18]. Thus, it is hard to define the group of active surveillance.

However, several series that focused on a single focus as a potential variable in the prediction of insignificant prostate cancer reported outcomes in contrast with these

assumptions. Analysis of the final pathologic outcome for 27 patients who had only an identifiable Gleason grade or a tumor confined to only one core of the sextant biopsy specimen by Bruce et al found that 26% of patients had extracapsular disease [19]. Thong et al reported on a total of 192 patients with Gleason score 6 prostate cancer involving 5% or less of one biopsy core: overall, 42 patients (22%) were upgraded or upstaged after surgery [20]. In a microfocus (5% or less of cancer in a single core) series, D'Amico et al and Boccon-Gibod et al failed to identify preoperative clinical factors for prediction of unfavorable final pathological findings [3,21]. Recently, Pepe et al analyzed prostatectomy specimens from 55 patients with a single neoplastic microfocus in saturation biopsies with a median of 30 cores [22]. Histological examination showed that 87.3% of patients had significant cancer, with the presence of extracapsular extension in 27.3% and positive surgical margins in 14.5%.

As an explicit extension of these findings, our series provides additional evidence to support the clinical significance of single positive core disease in preoperative biopsy. Risk stratification for the single positive core group was comparable with that of the multiple positive core group; many of them were clinically moderate or high risk in this series. Among 26 patients in the single positive core group, only three patients had pathologically indolent tumors. There are several plausible explanations for our findings. The inherent sampling error in prostate needle biopsies contributes to this, due to the fact that prostate cancer is usually associated with multifocal lesions [23]. Additionally, when the cancer is misinterpreted as being single positive core disease on the basis of a biopsy specimen, this would be secondary to a small volume of cancer that was not adequately sampled and missed by the needle. In a study of whole mount, serial sectioned radical prostatectomy specimens, Cupp et al found significant variability in actual prostate cancer volume for a given percent of biopsy core involvement [24]. Moreover, there is evidence to show that compared with multifocal disease, single-focus prostate cancer differs in its clinicopathological behavior. In a comparison of 1,056 radical prostatectomy specimens with multifocal disease and 103 specimens with single focus disease.

One of the advantages of the present series is the use of an identical process in the conduct of the prostate biopsy. All biopsies were taken from the same 12-core scheme by experienced urologists in a single institution. As expected, when a smaller volume of prostate tissue is sampled, the correlation between biopsy findings and prostatectomy pathology shows more variability, depending on the number of biopsy cores [3]. Thus, studies based on a heterogeneous biopsy scheme may have potential inherited bias. Since the introduction of a systematic sextant biopsy scheme, with the aim of increasing cancer detection, several modifications in biopsy techniques and number and localization of biopsy cores have been described. However, although more biopsy cores ensure higher sensitivity, higher complication rates and poorer patient comfort are major well-known drawbacks. Twelve-core biopsy is a commonly used scheme and is recommend by currently established guidelines [6,7]. This scheme has been validated in a large study of 2,299 patients involving 167 community-based urologists; results from a randomized trial found that increasing the number of cores taken from 6 to 12 did not substantially increase complications or delay return to normal activities [8]. Moreover, to avoid the overall risk of understaging or undergrading, at least a 12-core scheme should be performed [25].

Considering that the Gleason scoring system is one of the most important prognostic factors in prostate cancer, the increase in the rate of upgrading in the single positive core group is noteworthy. Studies have shown that biopsy grading, when compared with matched surgical grades, suffers from a significant rate of upgrading, ranging from 27% to 57% [26]. However, according to our analysis, there was no preoperative parameter for prediction of upgrading of Gleason score.

Taken together, our findings suggest that it might be clinically beneficial to treat single positive core disease at the time of biopsy in the same manner as multiple core disease. Single positive core disease tends to be clinically significant cancer with a similar risk stratification, with a high potential for upgrading after prostatectomy, without clinical factors for prediction of upgrading. Because treatment decisions for prostate cancer are based on our ability to evaluate the prognosis of individual patients, gaining a better understanding of the basis of pretreatment biopsy is of the utmost importance. Considering the significantly lower margin positivity, our data imply the potential benefits of radical resection in patients diagnosed by a single positive core, because these patients may have a higher possibility of curative resection than their multiple positive core counterparts. However, these data were obtained from a single center by a single surgeon. Further large-scale, prospective, multi-institutional trials are necessary for verification of the clinical and pathological characteristics of patients diagnosed with single positive core prostate cancer.

CONCLUSIONS

In summary, most single positive core prostate cancers that were diagnosed by using 12-core transrectal biopsy were shown to be clinically significant cancers in the radical prostatectomy specimens with similar preoperative risk stratification compared to multiple positive core disease. At the time of the prostatectomy, the positive-margin rate was lower; however, an increase in Gleason score occurred more frequently. These characteristics imply that it might be clinically beneficial to treat this disease in the same manner as multiple positive core disease, including radical resection, rather than watchful waiting.

Conflicts of Interest
The authors have nothing to disclose.

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