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Does the Presence of Hypoechoic Lesions on Transrectal Ultrasound Suggest a Poor Prognosis for Patients With Localized Prostate Cancer?

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Purpose: The purpose of this study was to investigate the value of hypoechoic lesions on transrectal ultrasound (TRUS) as a prognostic factor for patients with localized prostate cancer.

Materials and Methods: The patients consisted of 71 patients with pT2N0M0 disease following radical prostatectomy between 2002 and 2008. The group with hypoechoic lesions was labeled group 1, whereas the group without hypoechoic lesions was labeled group 2. The presence of hypoechoic lesions on preoperative TRUS was analyzed as a prognostic factor along with several parameters, including preoperative factors and pathologic factors. The biochemical progression-free survival (BPFS) rate was compared between the two groups according to the presence of hypoechoic lesions on TRUS.

Results: A total of 35 patients had hypoechoic lesions on TRUS, whereas 36 had no hypoechoic lesions. Preoperative baseline characteristics were not significantly different between the two groups. In the univariate analysis, BPFS showed significant differences according to the presence of hypoechoic lesions on TRUS and the preoperative prostate-specific antigen level. The BPFS rates over the first 24 months were 97.0% in group 1 and 97.1% in group 2; however, the difference in the BPFS rate over 48 months significantly widened to 75.3% compared with 91.7%, respectively. Despite this finding, no significant independent prognostic factor for BPFS was found on multivariate analysis in this patient cohort.

Conclusions: The presence of hypoechoic lesions on TRUS may suggest worse prognostic characteristics in pT2 prostate cancer. Further studies involving larger subject populations are needed to corroborate the significance of the presence of hypoechoic lesions as a prognostic factor.

Keywords: Prognosis; Prostate neoplasms; Ultrasonography

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INTRODUCTION

Many urologists routinely use transrectal ultrasound (TRUS) for the diagnosis and staging of localized prostate cancer. However, with the widespread use of prostate-specific antigen (PSA) screening, there has been a shift to earlier stages and smaller volumes at the time of diagnosis. Furthermore, TRUS is limited in the detection of hypoechoic lesions and therefore shows a low predictive value

[1]. The probability that a hypoechoic lesion contains prostate cancer varies from 3% to 52% [2]. Most research to date has focused on the diagnostic value of hypoechoic lesions on TRUS, and little is known about the biological significance of hypoechoic lesions in prostate cancer. There are reports that the presence of hypoechoic lesions is associated with a higher stage on presentation, such as extracapsular invasion. However, no study currently exists on the use of hypoechoic lesion status as an independent

prognostic factor [3,4]. In this study, therefore, we investigated the prognostic value of the presence of hypoechoic findings on TRUS in patients with localized prostate cancer and evaluated biochemical progression-free survival (BPFS) rates according to the presence of hypoechoic lesions.

MATERIALS AND METHODS

A total of 71 patients diagnosed with pT2N0M0 disease following radical prostatectomy (RP) between January 2002 and December 2008 were enrolled in the study. Of the 71 patients, 59 underwent open RP and 12 underwent laparoscopic RP. The preoperative magnetic resonance imaging showed no signs of locally advanced prostate cancer. The enrollment was confined to patients with pT2 disease to eliminate the impact of pathologic stage on different outcomes. Patients who had undergone other treatments such as radiation therapy or hormonal therapy before or after surgery were also excluded from the subject population. Patients with positive surgical margins were excluded to eliminate the confounding effects of a positive surgical margin and to identify the prognostic effects of other factors being considered. Patients were divided into two groups according to the presence of hypoechoic lesions on preoperative TRUS as interpreted by a single experienced radiologist. The group with hypoechoic lesions was labeled group 1, whereas the group without hypoechoic lesions was labeled group 2. Preoperative and postoperative characteristics including pathologic T2 substage, preoperative serum PSA levels, Gleason scores on biopsy, and prostatectomy specimens were compared between the two groups. Microscopic extension of malignant cells, tumor involvement percentage, and perineural invasion were also examined. The pathological stage was recorded on the basis of American Joint Committee on Cancer Prostate Cancer Staging, 7th edition. Patients were followed up and the PSA level was assessed at regular intervals of about 3 months after RP during the first 2 years. Subsequent follow-up was done every 6 months for 1 year. Biochemical failure was defined as the first occurrence of two consecutive rises in the PSA level of more than 0.2 ng/mL [5]. Each variable was compared by using Student's t-test for continuous data and the chi-square test for categorical data. Univariate and multivariate Cox proportional hazard analyses were used to determine relevant prognostic indicators of biochemical progression. In these analyses, patients were stratified according to the PSA level (≥ 9 or < 9 mL). Cutoff points for the variable PSA level were chosen to separate the patient populations by a median value. The BPFS rate was estimated by using the Kaplan–Meier curve, which compared each potential prognostic factor by using the log-rank test. The level of statistical significance was set at a $p < 0.05$. All analyses were done by using the statistical software SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Among the 71 enrolled patients, 35 had hypoechoic lesions and 36 had nonhypoechoic lesions on TRUS. Nonhypoechoic lesions consisted of either isoechoic regions or unidentifiable lesions, and hyperechoic lesions were excluded. Preoperative baseline characteristics were identical between the two groups (Table 1). When group 2 was divided according to clinical stage, 14 of the 36 patients had clinical T2 disease (38.88%), and the others had clinical T1 disease. As for postoperative parameters such as the Gleason score of the prostatectomy specimen, the percentage of tumor involvement, and the presence of perineural invasion, there were no significant differences between the two groups (Table 2). The median follow-up period was 44.49 months in group 1 and 38.81 months in group 2. The

TABLE 1. Comparision of preoperative characteristics between patients with hypoechoic lesions (group 1) and those with nonhypoechoic lesions (group 2) on TRUS

Characteristic	Group 1 (n=35)	Group 2 (n=36)	p-value
Age (y)	64.63±7.04	65.61±5.28	0.50
PSA (ng/mL)	6.93±3.55	7.83±4.14	0.32
Total prostate volume (cm^3)	27.24±9.47	34.08±19.09	0.06
Biopsy Gleason score			0.47
≤ 7	20/35 (57.15)	23/36 (63.88)	
> 7	15/35 (42.85)	13/36 (36.12)	
BMI (kg/m^2)	23.71±1.79	24.34±2.96	0.28
% positive core	34.37±1.94	37.33±2.39	0.57

Values are presented as mean±standard deviation or number (%). TRUS, transrectal ultrasound; PSA, prostate-specific antigen; BMI, body mass index.

TABLE 2. Comparison of postoperative characteristics between patients with hypoechoic lesions (group 1) and those with nonhypoechoic lesions (group 2) on TRUS

Characteristic	Group 1 (n=35)	Group 2 (n=36)	p-value
Postprostatectomy Gleason score			0.23
≤ 7	13/35 (37.14)	19/36 (52.77)	
> 7	22/35 (62.86)	17/36 (47.23)	
Stage			0.76
2a	9/35 (25.71)	11/36 (30.56)	
2b	7/35 (20.00)	5/36 (13.88)	
2c	19/35 (54.29)	20/36 (55.56)	
Tumor involvement percentage	14.53±17.82	19.56±19.053	0.25
Perineural invasion			0.45
Positive	4/35 (10.71)	6/36 (18.18)	
Negative	31/35 (89.29)	30/36 (81.82)	

Values are presented as number (%) or mean±standard deviation. TRUS, transrectal ultrasound.
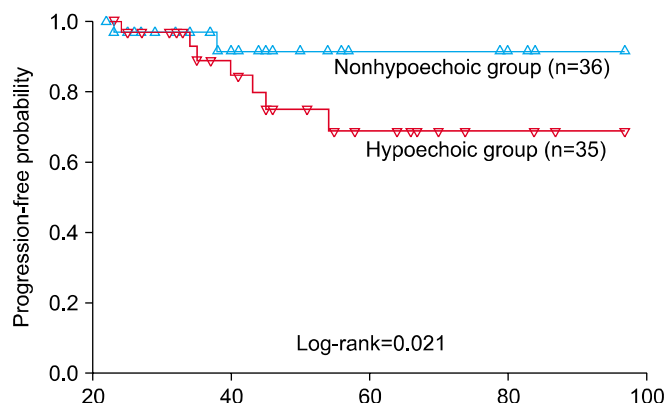
FIG. 1. The hypoechoic group had an overall shorter progression-free survival period than did the nonhypoechoic group.

TABLE 3. Clinical parameters for predicting prognostic factors

Prognostic factor	RR (95% CI)	p-value
Univariate analysis		
Age (>65 y vs. ≤65 y)	1.74 (0.36–3.34)	0.089
Hypoechoic lesion (yes vs. no)	2.38 (1.12–5.38)	0.025
Body mass index (≥25 kg/m^2 vs. <25 kg/m^2)	0.69 (0.12–1.58)	0.121
Preoperative PSA (≥9 ng/mL vs. <9 ng/mL)	2.86 (1.86–4.09)	0.038
Prostate volume (<35 mL vs. ≥35 mL)	2.63 (0.26–2.85)	0.095
Gleason score (>7 vs. ≤7)	5.84 (0.38–9.69)	0.265
Stage (2c vs. 2a, b)	7.92 (0.31–5.66)	0.132
Tumor percentage involvement ($\geq20\%$ vs. $<20\%$)	1.66 (0.31–8.76)	0.293
Percentage of positive result in core biopsy ($\geq33\%$ vs. $<33\%$)	3.48 (0.15–7.50)	0.385
Perineural invasion (positive vs. negative)	1.67 (0.32–6.02)	0.405
Multivariate analysis		
Hypoechoic lesion (yes vs. no)	2.44 (0.25–4.80)	0.312
Preoperative PSA (≥9 ng/mL vs. <9 ng/mL)	3.67 (0.65–1.14)	0.078

RR, relative risk; CI, confidence interval; PSA, prostate-specific antigen.

BPFS rate over the first 24 months was 97.0% in group 1 and 97.1% in group 2. However, divergence after 48 months significantly widened, to 75.3% vs. 91.7%, respectively. Group 1 had an overall shorter progression-free survival period than did group 2 (Fig. 1). During the follow-up period, clinical failure was observed in 4 cases. In group 1, L-spine metastasis was observed in two cases at 45 and 54 months after the operation and urethrovesical anastomosis site recurrence was observed in one case at 35 months after RP. One case of L-spine metastasis was observed at 38 months after the operation in group 2. To assess the prognostic value of each variable, univariate and multivariate analyses were carried out with the Cox proportional hazard model. In the univariate analysis, preoperative PSA level and the presence of hypoechoic lesions had prognostic significance (Table 3). Age, body mass index, prostate volume, pathologic Gleason score, and pT2 substage did not have prognostic significance. As shown in Table 3, however, preoperative PSA level and presence of hypoechoic lesions, which were shown to be significant in the univariate analysis, were not of statistical significance in the multivariate analysis.

DISCUSSION

Few studies have examined the potential utility of hypoechogenicity, a TRUS-related indicator of potentially cancerous lesions in the prostate, as a prognostic factor. We chose to focus on the prognostic value of hypoechoic lesions because, considering that only 3% to 52% of prostate cancers show hypoechoic lesions, its value as a diagnostic marker is limited, and we thought it appropriate to focus instead on its value for evaluation of disease progression. Furthermore, Ohori et al. [3,4] noted that hypoechoic cancers were more likely to show extraprostatic extension, to have a poorly differentiated component, and to be nondiploid compared with isoechoic cancers. However, these studies showed only that hypoechoic lesions were related to more advanced stage disease and did not focus on its value as a prognostic factor. We restricted the subject pop-

ulation to patients with stage pT2N0M0 disease; furthermore, to control the effects of BPFS, patients with positive postsurgical margins were excluded. Ohori et al. [6] showed no significant difference in BPFC for T1c tumors that were visible on sonography. However, they included all hypoechoic, isoechoic, and hyperechoic lesions that were visible on sonography as cases and thus did not exclusively examine hypoechoic lesions, as was done in the present study.

Preoperative PSA, Gleason score, and tumor-node-metastasis stage are well-known prognostic parameters [7-9]. Caso et al. [10], in their study on postprostatectomy biochemical recurrence in each of the substages in pathologically confirmed T2 lesions, stated that the substages of T2 were of significance only on univariate analysis and that the most important factors were PSA and the status of the surgical margins. However, in our study, the univariate analysis differed in that only preoperative PSA and the presence of hypoechoic lesions were correlated with the prognosis of prostate cancer. As shown in Fig. 1, no significant difference in BPFS was observed 30 months after the operation, but a subsequent divergence in BPFS became evident later. Considering that Gleason's score and other parameters such as perineural invasion and the percentage of tumor involvement did not differ significantly between the two groups during this period, it is possible that there are other factors yet to be isolated.

We assume the reason prostate cancer with hypoechoic lesions has a worse prognosis than other prostate cancers may be because hypoechoic prostate cancers have molec-

ular markers related to prognosis and nondiploid DNA. A recent study showed that cases positive for the antibodies S0456, EP1972-1, S0725M, and S5073, which are directed against the protein products of the genes *Hey2, STMN1, CYP4Z1,* and *CDH1*, had poorer prognosis than did those that were negative for these antibodies [11,12]. Although the study did not deal with hypoechoic lesions on TRUS, the authors speculated that such molecular markers may be detected in prostate cancer with hypoechoic lesions. In addition, the absolute volume of the tumor can influence the detection rate of hypoechoic lesions, and the volume itself may be a prognostic factor on TRUS [13]. Also, because it has already been shown that digital rectal examination (DRE) palpation is a prognostic factor, we think it will be relevant to study its relationship with hypoechoic lesions on TRUS [14]. Regrettably, this study did not examine the tumor volume or DRE palpation findings.

In the current study, univariate analysis and Kaplan-Meier curves showed that hypoechoic lesions were of prognostic significance for prostate cancer. However, on multivariate analysis, such lesions did not possess prognostic value. Nevertheless, the statistical significance observed in the univariate analysis and Kaplan-Meier curves suggest that the presence of hypoechoic lesions on TRUS images may hold at least some importance as a prognostic factor for prostate cancer.

The present study had several limitations. First, the study was retrospective. Second, we did not review the DNA findings through DNA analysis and molecular marker analysis to support our hypothesis on the biochemical significance of hypoechoic lesions. Further studies on this issue are needed. Third, our study population was very small. To what extent our results can be generalized remains unanswered. Further studies involving larger subject populations appear to be necessary to fully evaluate the significance of the presence of hypoechoic lesions as a prognostic factor.

CONCLUSIONS

Localized prostate cancers that present preoperatively with hypoechoic lesions on TRUS were associated with worse prognostic characteristics than were prostate cancers with no hypoechoic lesions. However, such sonographic findings were shown to have no value as a prognostic factor. To further certify the results of this study and to investigate the associated underlying biological mechanisms, a larger-scale study on this subject is needed.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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