Evaluation of Resistance Index in Patients with Prostate Cancer

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Abstract. Background: The purpose of this study was to evaluate the relationship of the resistance index (RI) of the prostate measured by transrectal ultrasonography (TRUS) in Taiwanese prostate cancer patients to Gleason score, staging and prostate volume. Patients and Methods: Forty-five patients (mean age, 73.3 years; range 56 to 97) diagnosed to have prostate cancer via prostate biopsy and/or transurethral prostatectomy were recruited for our study. The patients were divided into 3 groups according to Gleason score, low grade (2-4, LG n=14), intermediate grade (5-7, IG n=14) and high grade (8-10, HG n=17) groups. The blood flow pattern and mean RI of the prostate vessels were recorded and compared with age, prostate volume, serum prostate specific antigen (PSA) and oncological stage. A follow-up color Doppler ultrasonography was also performed in 17 patients after 3-6 months of hormone therapy and the changes of RI were recorded. Results: The mean age, serum PSA and prostate volume were comparative among the three groups, but the differences of RI were statistically significant (p=0.029). Advanced prostate cancer (HG group) tended to have higher RI. There was a close correlation between RI and Gleason score (Spearman R=0.452, p=0.002). The high RI phenomenon could be reversed after 3-6 months of hormone therapy (paired t-test, p<0.05). Conclusion: High grade prostate cancer tends to have higher RI. RI measurement during color Doppler TRUS may be helpful in the evaluation of the vascularity of prostate cancer and its vascular changes to hormone treatment.

The conventional gray-scaled transrectal ultrasonography (TRUS) of the prostate has been used extensively in clinical practice for the diagnosis of prostate cancer, but its use alone is limited to morphological diagnosis and guidance for prostate needle biopsy (1). While the combination of digital rectal examination (DRE), prostate specific antigen (PSA) and TRUS has increased the diagnostic rate of prostate cancer, but their sensitivity and specificity are still not good enough for early detection (2, 3). Most prostate cancers have been characterized by hypoechoic density, but benign prostate hyperplasia may also appear as a hypoechoic nodule, similar to the appearance of prostate cancer (4). Systemic echo-guidance needle biopsy of the prostate is still the major diagnostic tool for the early detection of prostate cancer (1, 5).

The presence of aberrant tumor vessels and turbulent blood flows is common in prostate cancer. The introduction of color Doppler ultrasonography has provided more vascular information of the prostate. But these findings are not specific and diagnostic for the diagnosis of this disease (3). The resistance index (RI) had been used as a quantitative measurement of hemodynamic changes for many years. Kojima et al. (6) have found that patients with benign prostate hyperplasia (BPH) had higher RI than healthy volunteers. To evaluate the possibility of using RI in the study of hemodynamic change within prostate cancer, transrectal color Doppler ultrasonography was performed in 45 patients with prostate cancer. The color Doppler ultrasonography findings were compared to the clinical and pathological characteristics, including age, PSA, clinical stage, prostate volume and tumor grade.

Patients and Methods

A total of 1,070 patients with lower urinary tract symptoms (LUTS), abnormal DRE or high PSA (>4 ng/dl) were referred to the Urologic Clinic of Chang Gung Memorial Hospital at Taoyuan, Taiwan, ROC, for TRUS study of the prostate. All color Doppler ultrasonography studies were performed by the same urologist (STH) using an Acuson (Mountain View, CA, USA), 128XP machine and an EC7 endo-caval, biplane probe. Subsequently, only 173 patients underwent transrectal prostate sextant needle biopsy and/or transurethral resection of the prostate (TUR-P).

The indications for prostate needle biopsy and/or TUR-P included urine retention, persistent high PSA, suspected prostate malignancy or symptoms of bladder outlet obstruction unrelated

Abbreviations: BPH, benign prostate hyperplasia; DRE, digital rectal examination; PSA, prostate specific antigen; RI, resistance index; TRUS, transrectal ultrasonography.

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by medication. There were 45 cases of adenocarcinoma of the prostate according to pathological assessment. The patients’ ages ranged from 56 to 97 years (mean 73). They were divided into low grade (2–4, LG), intermediate grade (5–7, IG) and high grade (8–10, HG) groups according to their Gleason score.

The patients were examined in the true left lateral position with the knee and hip flexed to the abdomen. Sagittal and coronal ultrasound views of the prostate were taken and the largest width, height and length were measured and recorded. The contour, capsular margin and echogenicity within the prostate were also recorded. After the grayscale study, color Doppler studies (using the same machine, Acuson 128XP/10) were made using the same probe (EC7) to determine the blood flow pattern of the prostate. The RI (peak systolic velocity – end diastolic velocity/peak systolic velocity) was measured using a cursor angle of 55˚ and 0.05 m/sec threshold. Three to five measurements were made in each patient with each vessel measured only once. Since there were vascular variations within the prostate, these measurements were made only in areas of visible vascular flow. The mean RI value without consideration of transitional or peripheral zones was used for comparison. The volume of the prostate was calculated using the following formula: volume (cm$^3$) = width × width × length × 0.5236 (7). The age, mean RI, prostate volume and PSA were compared among the HG, IG and LG groups. The one-way ANOVA test was used to calculate the statistical significance of data among these three groups. A $p$-value of less than 0.05 was considered statistically significant.

In order to investigate the effect of androgen blockade on RI and prostate volume changes, 17 patients with advanced prostate cancer from these 3 groups (LG n=2, IG n=6, HG n=9), who underwent color Doppler ultrasonography of the prostate before and 3 to 6 months after hormone therapy were also monitored. Hormone therapy included anti-androgen agents (cyproterone or flutamide) plus bilateral orchiectomy or LH-RH analogues (goserelin or leuprorelin). The mean RI, prostate volume and PSA before and after hormone treatment were assessed. Paired Student's t-tests were used to calculate the statistical significance, which was defined as a $p$-value less than 0.05.

### Results

Among the 45 cases of established prostate cancer, there were 14 LG, 14 IG and 17 HG cases. Detailed information of age, prostate volume, RI and PSA in each group is listed in Table I.

The age, serum PSA and prostate volume were not statistically different among these 3 groups ($p>0.05$). Around 80% of the patients were in the advanced stage (stage C or D). More patients with higher and intermediate total Gleason scores (>4) also tended to be in the advanced stages ($p<0.05$). There was a close correlation between RI and total Gleason score (Spearman R=0.452, $p=0.002$), but not correlated with age, prostate volume or serum PSA.

In the 17 patients with advanced prostate cancer who had received hormone therapy, the prostate volume, PSA and mean RI were compared before and after hormone treatment (Table II). Smaller prostate volume (32.9 vs. 19.7, $p<0.05$), decreased PSA (126.4 vs. 3.0, $p<0.05$) and lower mean RI (0.72 vs. 0.63, $p<0.05$) were found 3 to 6 months after hormone therapy.

### Discussion

The role of color Doppler ultrasonography in the diagnosis of prostatic cancer had been questioned in the recent past because of individual vessel variations and lack of specific parameters. Neumaier et al. (8) classified the vascularity pattern of normal prostate into urethral and capsular groups. Patel et al. (9) showed that grading of the signals of color flow with Doppler ultrasound was of limited diagnostic discrimination for prostate cancer and prostatitis. Rifkin et al. (10) found no statistical difference in the mean resistance

### Table I. Summary of patient data, mean (95% CI).

<table>
<thead>
<tr>
<th>Group</th>
<th>LG (n=14)</th>
<th>IG (n=14)</th>
<th>HG (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.6 (68.4, 80.9)</td>
<td>73.9 (67.5, 80.4)</td>
<td>71.7 (68.1, 75.2)</td>
</tr>
<tr>
<td>Prostate volume (cm$^3$)</td>
<td>39.3 (26.9, 51.7)</td>
<td>42.5 (26.4, 58.6)</td>
<td>48.9 (35.4, 62.3)</td>
</tr>
<tr>
<td>PSA (ng/dl)</td>
<td>71.18 (6.28, 136.08)</td>
<td>169.30 (51.42, 287.17)</td>
<td>473.8 (27.39, 920.27)</td>
</tr>
<tr>
<td>RI</td>
<td>0.70 (0.64, 0.75)</td>
<td>0.72 (0.69, 0.74)</td>
<td>0.77 (0.73, 0.82)</td>
</tr>
<tr>
<td>Stage</td>
<td>D2: 7</td>
<td>D2: 9</td>
<td>D2: 14</td>
</tr>
<tr>
<td></td>
<td>C2: 1</td>
<td>D1: 1</td>
<td>C2: 1</td>
</tr>
<tr>
<td></td>
<td>B2: 3</td>
<td>C2: 1</td>
<td></td>
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<tr>
<td></td>
<td>B1: 1</td>
<td>C1: 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2: 2</td>
<td>B2: 1</td>
<td></td>
</tr>
</tbody>
</table>

*One-way ANOVA; $^a$Chi-square.
indices between cancer and benign prostate disease, but Miller et al. (11) found higher RI’s in both prostate cancer and BPH patients and a high pulsatility index (peak systolic velocity – end diastolic velocity/end diastolic velocity) in prostate cancer patients.

In the present study, higher grade prostate cancer tended to have higher RI, which was not related to age, prostate volume or serum PSA level. Louvar et al. (12) had also noted that a greater Gleason score in malignant prostate tissue was associated with increased tissue micro-vascularity. Angiogenesis with increased microvascular density (MVD) has been a common finding in prostate cancer and increased MVD has been found in prostate cancer than in BPH (13). It has been suggested that quantitative MVD may provide important staging and prognostic information in patients with prostate carcinoma (14).

Increased flow signals on color or power Doppler sonography are common signs of prostate cancer with diffuse prostatic lesions (15). Interestingly PC patients with increased blood flow have been noted to have a higher Gleason grade and higher incidence of seminal vesicle involvement (16). However Doppler sonography vascularity imaging in prostate cancer did not correlate with the likelihood of prostate cancer (17).

The RI measurement by color Doppler sonography of the prostate can afford a simple, quantitative parameter of tumor blood flow in prostate cancer. Additionally the use of RI simplifies the descriptive issue in color Doppler ultrasonography studies of prostate cancer. Okihara et al. (18) found decreased RI in eleven prostate cancer patients who underwent castration and the reduction of RI even preceded the reduction of prostate volume. In this study this kinetic change of tumor flow was confirmed in our 17 prostate cancer patients where dramatic reductions in both RI and prostate volume were found after 3-6 months of hormone therapy.

RI measurement has also been used as an indicator of intra-prostatic pressure in BPH patients with infravesical obstruction (19). Ozdemir et al. (20) further confirmed the correlation of mean RI with maximum uroflow rate in BPH patients. Whether RI measurement by color Doppler ultrasonography can be used for the early diagnosis of prostate cancer is still questionable, but the present data confirmed that increased RI had a close relationship to Gleason score. Tang et al. (21) reported similar findings with increased blood flow in higher tumor grade prostate cancer patients using pixel ratios as a parameter. The present results differed from a previous study by Rifkin et al. in 1993 (10), where the mean RI in cancer group (n=46) was 0.579 (±0.105), which was much lower than in our patients (0.74±0.08). No difference in RI between the cancer group and benign disease was noted in their study. The possible explanation for this discrepancy may be due to more cases with advanced tumor stage found in our prostate cancer patients (80% stage C or D).

We hypothesized that high grade prostate cancer with overt proliferation and angiogenesis may result in rapid tissue growth within the prostate capsule, which in turn, might manifest as higher intra-prostatic tissue pressure and a higher RI in prostatic arterial flow. Similar phenomenon has been observed inside the corpus cavernosum during cavernosal artery velocity measurement after pharmacologically-induced erection (22). A high vascular RI can be found during full corporeal rigidity when the intracorporeal pressure is higher than the arterial pressure. Neoplastic tissue growth within the prostate gland may result in neovascularity and intra-prostatic pressure elevation. Additional direct intracapsular tissue pressure and MVD measurement may be helpful to verify whether the mean RI can be used as an indirect parameter of tissue pressure and vascularity within the prostate.

In conclusion, prostate cancer patients with higher Gleason score tend to have a higher mean RI, which can be reversed after androgen blockade therapy. In addition to traditional DRE, PSA and TRUS, color Doppler ultrasonography study could also provide vascular information of the prostate. RI measurement may be helpful in the evaluation of the vascularity of prostate cancer and its vascular changes to hormone treatment.

### References


