Wash-In Rate on the Basis of Dynamic Contrast-Enhanced MRI: Usefulness for Prostate Cancer Detection and Localization

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Purpose: To evaluate the usefulness of the wash-in rate based on dynamic contrast-enhanced (DCE) MRI for the detection and localization of prostate cancer.

Materials and Methods: In 53 patients, the wash-in rate was measured in the cancer area and in three normal areas (the peripheral zone, inner portion of the transitional zone, and outer portion of the transitional zone). On the basis of these data, parametric imaging was generated and then its accuracy for cancer detection and location was evaluated compared to that of T2-weighted imaging without the use of an endorectal coil. For that purpose the entire prostate was divided into 18 segments.

Results: The wash-in rate value was greater in cancer tissue (9.2/second) than in three normal tissues (3.3/second, 6.7/second, and 3.2/second, respectively; \( P < 0.001 \)). The sensitivity and specificity were greater on parametric imaging of the wash-in rate compared to T2-weighted imaging in the entire prostate (96% and 82% vs. 65% and 60%, respectively; \( P < 0.001 \) ) and the peripheral zone (96% and 97% vs. 75% and 53%; \( P < 0.05 \) ). In the transitional zone, the sensitivity was greater on parametric imaging (96%) than on T2-weighted imaging (45%; \( P = 0.016 \)), but the specificity was similar (51% vs. 73%; \( P = 0.102 \)).

Conclusion: The wash-in rate based on DCE-MRI is a useful parameter for prostate cancer detection and localization.

Key Words: prostate cancer; wash-in rate; dynamic contrast-enhanced MRI; tumor perfusion; contrast enhancement

of the wash-in rate with DCE-MRI for prostate cancer detection and localization.

**MATERIALS AND METHODS**

This study was approved by our institutional review board for human investigations, and informed consent was obtained from all of the patients.

**Patients**

Between May 2003 and June 2004, a total of 79 patients underwent radical retropubic prostatectomy for biopsy-proven prostate cancer. Of those patients, 59 who underwent DCE-MR examinations at our institution were the primary candidates for this study. Of the 59 patients, six were excluded from the study because histologic maps of their prostate cancer were not available \((N = 4)\) or neoadjuvant hormonal therapy was performed \((N = 2)\). Finally, 53 patients who underwent both DCE-MRI and histologic mapping of prostate cancer were enrolled in this study. Their mean age was 64.9 years \((\text{age range } 49–75 \text{ years}; \text{SD } 5.8)\) and the mean value \(\pm \text{SD}\) of the prostate-specific antigen was \(13.7 \pm 10.6 \text{ ng/mL}\) \((\text{range } 2.6–43.5 \text{ ng/mL})\). The time interval between biopsy and MRI was 15–28 days. The pathologic Gleason score of a radical prostatectomy specimen was \(7 \pm 2\) \((\text{range } 6–10)\), and the time interval between the MR examination and radical retropubic prostatectomy was \(9 \pm 4\) days \((\text{range } 1–17\) days).

**MRI Technique**

MRI was performed on a 1.5 T MRI unit (Gyrosan Intera; Philips Medical Systems, Best, The Netherlands) using a commercially available surface coil (SENSE Flex-M; Philips Medical Systems). This system had a maximal gradient strength of 30 mT/m and a slew rate of 150 mT/m/msec.

First, transverse, coronal, and sagittal T2-weighted fast spin-echo images without an endorectal coil were acquired from the bladder dome to the anus using the following parameters: repetition time \((\text{TR})/\text{echo time } (\text{TE}) = 4000/90 \text{ msec}, \text{echo-train length } = 16,\text{ three signals acquired, flip angle } = 90^\circ,\text{ slice thickness } = 4 \text{ mm, interslice gap } = 0.1 \text{ mm, field of view } (\text{FOV}) = 150 \text{ mm, matrix size } = 256 \times 512,\text{ and number of sections } = 20).\)

Thereafter, transverse DCE images were obtained using a three-dimensional fast-field echo sequence \((\text{TR/TE} = 17/2.9 \text{ msec, flip angle } = 20^\circ, \text{slice thickness } = 4 \text{ mm, no interslice gap, FOV } = 225 \text{ mm, matrix size } = 256 \times 192; 25 \text{slices})\). The time resolution of each dynamic set was 30 seconds, and 15–18 sequences were obtained in each patient. After the initial two image sets were obtained, a rapid bolus intravenous injection of gadopentetate dimeglumine (Magnavist; Schering, Berlin, Germany) was performed with the use of a mechanical injector and was followed by a 20-ML saline flush (also by mechanical injection). Contrast injection began concurrently with the start of the third imaging session. The dosage of injected contrast material per patient was 15 mL, and the injection rate was 3 mL/second. Therefore, contrast material was injected for five seconds.

**Histologic Examination**

Following radical prostatectomy, various staff pathologists at our institution, who were unaware of the MRI findings, obtained a histologic map of the prostate cancer. The specimens were fixed in 5% buffered formalin for 24 hours before slicing. The entire prostate was then cut by hand at 4-mm intervals perpendicular to the long axis of the prostate. Each slice was halved or quartered according to its size for further processing. Macrotome slices \((7– 8 \mu\text{m thick})\) were then obtained from each section and stained with hematoxylin-eosin. Slides of the halved or quartered slices at the same section level were collected to simulate the whole-mount section slice, and then a schematic map marking both the cancer and normal tissues was generated on the superimposed transparent films over the slices.

**Measurement of the Wash-in Rate**

The wash-in rate is a parameter defined as the maximum slope between the time of onset of contrast inflow and the time of peak enhancement on the time intensity curve. This parameter in each voxel was automatically calculated on the basis of the DCE-MR data sets. A radiologist measured the wash-in rate value in four different regions of interest \((\text{ROIs})\) that were placed over cancer tissue, normal tissue in the peripheral zone, normal tissue in the inner two-thirds of the transitional zone, and normal tissue in the outer third of the transitional zone.

A round or elliptical ROI was placed over each of four locations chosen with reference to the histological maps. When the area of cancer tissue or normal tissue was less than 40 mm², the measurement of the wash-in rate value was not performed. The observer attempted to cover as much cancer or normal tissue as possible within the ROIs and to avoid including the prostate capsule, urethra, and periprostatic tissue within the ROIs. The ROI area varied from 40 mm² to 70 mm² by patient, but all ROIs were the same size within each patient.

**Generation of Parametric Imaging of the Wash-In Rate**

All of the DCE images were transferred to a workstation (Advantage Windows 4.0; General Electric Medical System, Milwaukee, WI, USA) to measure the wash-in rate and generate parametric imaging of the wash-in rate. On parametric imaging, the value of the wash-in rate in each pixel was displayed with a color scale. From statistical analysis, the radiologist extracted a threshold value of the wash-in rate that was optimal for differentiating cancer from normal tissue. Then the radiologist generated parametric imaging using the same threshold for all patients. In parametric imaging, pixels with a wash-in rate value greater than the threshold value were color-coded over the unenhanced fast-field echo images. Consequently, the color-coded areas were considered as cancer tissue.
Cancer Detection
To systematize the cancer detection and localization, each prostate was divided into a total of 18 segments. The prostate was divided into three levels including the base, midgland, and apex in either the right or left lobe. At each level the gland was further subdivided into the transitional zone, lateral portion of the peripheral zone, and medial portion of the peripheral zone.

A second radiologist, who was unaware of the T2-weighted imaging and histologic map findings, recorded the presence or absence of color-coded lesions in each segment on parametric imaging. A third radiologist, who was blinded to the parametric imaging and histologic map findings, documented the presence or absence of a hypointense lesion in each segment on T2-weighted imaging. A fourth radiologist, who was unaware of the T2-weighted and parametric image findings recorded the presence or absence of cancer tissue in each segment with reference to the histologic map provided by the pathologists.

Statistical Analysis
A repeated-measures analysis of variance (ANOVA) with pairwise multiple comparisons using the Tukey method was applied to compare the wash-in rate value in the four ROIs.

To evaluate the diagnostic performance of the wash-in rate for differentiating cancer and normal tissue, a receiver operating characteristics (ROC) analysis was performed for comparative pairs consisting of cancer tissue and three normal tissues. From an ROC analysis that was additionally performed with a comparative data set consisting of the wash-in rate of cancer tissue and the greatest wash-in rate from the three normal tissues, the optimum cutoff point was extracted, which showed the best separation (i.e., minimal false-negative and false-positive results) between the two groups. The cutoff value was then used as a threshold for generating parametric imaging.

Using a paired t-test, the number of segments in which the MRI findings agreed with the histologic results was compared for parametric imaging of the wash-in rate and T2-weighted imaging in the entire prostate, transitional zone, and peripheral zone.

In the entire prostate, transitional zone, and peripheral zone, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for cancer detection were evaluated by segment on both parametric imaging of the wash-in rate and T2-weighted imaging. The sensitivity and specificity of these two imaging methods were compared using a Z-test for the paired proportion after the effect of clustering was adjusted according to literature references (21,22). In addition, the sensitivity and specificity of parametric imaging of the wash-in rate were compared between the transitional zone and the peripheral zone by means of the same method.

In every statistical analysis, significance was considered to be present when the $P$ value was less than .05.

RESULTS

Wash-In Rate
We were able to measure the wash-in rate value in 39 of 53 patients (74%). In the other 14 patients, this measurement was not performed because cancer tissue involved the entire peripheral zone ($N = 10$) or because the volume of the normal peripheral zone was too small due to severe benign prostatic hyperplasia ($N = 4$). The measured wash-in rate values are shown in Table 1. The wash-in rate value was greater in cancer tissue than in the three normal tissues ($P < 0.0001$; Fig. 1). The normal tissue in the inner portion of the transitional zone showed a greater wash-in rate value than did the other two normal tissues ($P < 0.0001$). The wash-in rate value of normal tissue was similar in the peripheral zone and in the outer portion of the transitional zone ($P > 0.05$). The wash-in rate of cancer tissue was greater than that of any of the normal tissues in 31 of 39 patients (79%). In the other eight patients (21%), the wash-in rate was greater in normal tissue in the inner portion of the transitional zone than in cancer tissue. In those patients the wash-in rate of cancer tissue was also greater than that of normal tissue in the outer portion of the transitional zone and in the peripheral zone.

The area under the receiver operating curve for tissue differentiation according to the wash-in rate was $0.95 \pm 0.05$ (95% CI, 0.929–0.983) for cancer tissue vs. normal peripheral zone tissue, $0.96 \pm 0.02$ (95% CI, 0.949–0.984) for cancer tissue vs. normal tissue in the outer one-third of the transitional zone, and $0.68 \pm 0.06$ (95% CI, 0.558–0.791) for cancer tissue vs. normal tissue in the inner two-thirds of the transitional zone (Fig. 2). From the ROC analysis with a comparative data set consisting of the wash-in rate of cancer tissue and the greatest wash-in rate from the three normal tissues, the wash-in rate value of 5.7/second was determined as an optimal threshold value for differentiating cancer from normal tissue. A pixel with a wash-in rate value greater than 5.7/second was then color-coded and considered to have cancer tissue on parametric imaging.

Location of Cancer on Histologic Examination
From the histological maps, cancer tissues were found in 434 of 954 segments (45%). The distribution of cancer tissue according to the segment is shown in Table 2.

Table 1
The Wash-In Rate Value of Cancer Tissue and Normal Tissue

<table>
<thead>
<tr>
<th>Wash-in rate</th>
<th>Cancer tissue</th>
<th>Normal tissue in peripheral zone</th>
<th>Normal tissue in transitional zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>9.2 ± 4.5</td>
<td>3.3 ± 1.8</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>Range</td>
<td>2.1–26.5</td>
<td>1.1–9.4</td>
<td>1.4–8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.7 ± 3.0</td>
<td>1.5–15.1</td>
</tr>
</tbody>
</table>
Cancer tissue was identified in the peripheral zone in 51 patients (96%) and in the transitional zone in 46 patients (87%). In seven of 53 patients (13%), prostate cancer was noted only in the peripheral zone, whereas two patients (4%) had prostate cancer only in the transitional zone. Therefore, 44 patients (83%) had cancer in both the peripheral and transitional zones. Prostate cancer was noted in the apex in 46 patients (87%), in the midgland in 51 patients (96%), and in the base in 41 patients (77%).

Figure 1. MRI data and histologic section from a 65-year-old patient. 

- **a**: The histologic step section at the level of the apex shows cancer tissue (outlines). According to the histologic findings, the lateral and medial portions of the peripheral zone in the left lobe, and the transitional zone in the right lobe contain prostate cancer. 
- **b**: According to the histologic findings, four ROIs were placed over 1) cancer tissue, 2) normal tissue in the peripheral zone, 3) normal tissue in the inner two-thirds of the transitional zone, and 4) normal tissue in the outer one-third of the transitional zone, as well as an unenhanced fast-field echo image. 
- **c**: Time-intensity curves of four ROIs based on the DCE-MRI. The wash-in rate was 1) 9.7/second for cancer tissue, 2) 2.1/second for normal tissue in the peripheral zone, 3) 4.3/second for normal tissue in the inner two-thirds of the transitional zone, and 4) 1.3 s for normal tissue in the outer one-third of the transitional zone. 
- **d**: On parametric imaging of the wash-in rate at the corresponding level to image a, color-coded areas represent the wash-in rate value greater than 5.7/second. Parametric imaging of the wash-in rate and histologic mapping are concordant for cancer detection and localization. 
- **e**: On T2-weighted imaging at the corresponding level to image a, a hypointense lesion (arrow) is noted only in the medial portion of the peripheral zone in the right lobe. However, this lesion was false-positive according to the histologic map. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
Cancer Detection on MRI

The agreement between the MRI findings and the histologic results is shown in Table 2, and the comparison of the diagnostic accuracy for cancer detection and localization is demonstrated in Table 3.

Entire Prostate

The number of segments in which the MRI findings agreed with the histologic results in each patient was 15.9 ± 1.9 (95% CI, 15.4–16.4) for parametric imaging of the wash-in rate, and 11.1 ± 3.2 (95% CI, 10.3–12.1) for T2-weighted imaging. The paired t-test showed a significant difference between the two MRI methods ($P < 0.0001$; Fig. 1).

Both the sensitivity and specificity for cancer detection were significantly greater on parametric imaging of the wash-in rate (96% and 82%) than on T2-weighted imaging (65% and 60%; $P = .036$ for sensitivity, $P = .039$ for specificity).

Peripheral Zone

The number of segments with concordance between the MRI findings and the histologic results in each patient was 11.6 ± 1.0 (95% CI, 11.3–11.9) for parametric imaging of the wash-in rate, and 7.6 ± 2.6 (95% CI, 6.9–8.3) for T2-weighted imaging. The paired t-test showed a significant difference between the two MRI methods ($P < 0.0001$).

Table 2
Agreement of MR Imaging Findings to Histologic Results

<table>
<thead>
<tr>
<th></th>
<th>Entire prostate</th>
<th>Peripheral zone</th>
<th>Transitional zone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>All</td>
</tr>
<tr>
<td>Parametric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2WI</td>
<td>+</td>
<td>270</td>
<td>244</td>
</tr>
<tr>
<td>Parametric</td>
<td>+</td>
<td>145</td>
<td>183</td>
</tr>
<tr>
<td>T2WI</td>
<td>−</td>
<td>13</td>
<td>66</td>
</tr>
<tr>
<td>Parametric</td>
<td>−</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Parametric</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2WI</td>
<td>−</td>
<td></td>
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</tr>
</tbody>
</table>

Parametric = parametric imaging of the wash-in rate. T2WI = T2-weighted imaging, + = agree with the histologic results, − = disagree with the histologic results.
Both the sensitivity and specificity for cancer detection were significantly greater on parametric imaging of the wash-in rate than on T2-weighted imaging ($P = 0.032$ for sensitivity, $P = 0.008$ for specificity; Table 3).

**Transitional Zone**

The number of segments with concordance between the MRI findings and the histologic results was $4.3 \pm 1.6$ (95% CI, 3.8–4.7) for parametric imaging of the wash-in rate, and $3.6 \pm 1.4$ (95% CI, 3.2–4.0) for T2-weighted imaging. The paired t-test showed a significant difference between the two MRI methods ($P = 0.031$).

The sensitivity for cancer detection was significantly greater on parametric imaging of the wash-in rate than on T2-weighted imaging ($P = 0.016$), whereas there was no significant difference in the specificity between the two MR methods ($P = 0.102$; Table 3, Fig. 3).

**Peripheral Zone vs. Transitional Zone**

The specificity of parametric imaging of the wash-in rate for cancer detection was greater in the peripheral zone than in the transitional zone (97% vs. 51%, $P = 0.043$), although the sensitivity was similar between the two zones (96% vs. 96%, $P = 0.742$).

**DISCUSSION**

In an attempt to overcome the limitation of T2-weighted imaging for prostate cancer detection and localization, the enhancement characteristics of prostate cancer have been evaluated in several studies (19,20,23–25). All of those studies postulated that prostate cancer showed earlier and stronger enhancement than normal tissue. However, those studies performed only quantitative measurement of some parameters on the time-enhancement curves, and did not obtain the anatomic detail required for cancer detection and localization. Therefore, the real utility of this method has not yet been completely proven in clinical practice (24).

According to our results, the wash-in rate differs significantly between cancer and normal tissue in the prostate. Our data also show that parametric imaging of the wash-in rate is more sensitive for cancer detection than T2-weighted imaging without the endorectal coil in both the transitional and peripheral zones, and more specific than T2-weighted imaging without the endorectal coil in the peripheral zone. Consequently, we assume that the use of the wash-in rate can improve the performance of MRI for prostate cancer detection and localization.

In this study the wash-in rate showed a wide range and variety in both cancer and normal tissue. However, our data showed that 79% of the study patients had the greatest wash-in rate in cancer tissue, and all patients had a greater wash-in rate in cancer tissue than normal tissue in the peripheral zone and in the inner portion of the transitional zone. These data show that the wash-in rate can be used to differentiate cancer and normal tissue despite the variable absolute value by patient. In addition, the estimates of the sensitivity of parametric imaging were optimistic because the optimum threshold value was derived from the same data set as that used to evaluate the utility of that threshold.

Despite our promising results, the wash-in rate still appears to be less reliable for discriminating cancer from normal tissue in the transitional zone than in the peripheral zone. Although in our study the mean wash-in rate value was significantly higher for cancer tissue compared to normal tissue in the transitional

![Figure 3. MRI data and histologic section from a 72-year-old patient. a: A histologic step section at the level of the midgland shows no cancer tissue. b: A parametric image of the wash-in rate at the corresponding level to image a shows multifocal color-coded areas with the wash-in rate greater than 5.7/second, which are false-positive lesions. c: A T2-weighted image at the level corresponding to image a also shows multifocal hypoechoic areas, which are false-positive lesions.](image)
zone, 21% of our patients (8/39) showed a greater wash-in rate value in normal tissue in the inner portion of the transitional zone than in cancer tissue. Consequently, in our study the specificity of the parametric imaging for cancer detection was only 51% in the transitional zone.

As a possible explanation for this problem, we believe that benign prostatic hyperplasia may be the main culprit behind the unsatisfactory performance of parametric imaging of the wash-in rate in the transitional zone. Oyen (24) also documented a significant overlap of the microvessel density between benign prostatic hyperplasia and prostatic cancer, and the enhancement patterns of prostate cancer and benign prostatic hyperplasia may therefore be similar. He concluded that it was not yet appropriate to use DCE-MRI to detect prostate cancer originating in the transitional zone in patients with benign prostatic hyperplasia.

It is already known that the peripheral zone is more vulnerable to prostate cancer than the transitional zone. In a previous study, 65% of cancers were noted in the peripheral zone, while 30% of cancers were identified in the transitional zone (26). In addition, other studies have documented that transitional zone cancer tends to be organ-confined, with lower Gleason scores and better cure rates than peripheral zone cancer (27–30). However, our data show that the frequency of prostate cancer did not vary significantly according to location, since most patients (83%) had cancer tissues in both the transitional and peripheral zones. Since disease-targeted treatments such as interstitial brachytherapy, intensity-modulated radiation therapy, high-intensity focused ultrasound, and cryosurgery are increasingly being used, adequate tumor detection in both the transitional and peripheral zones is becoming more important for monitoring treatment efficacy and surveying tumor recurrence after treatment (31). Therefore, future studies should concentrate on improving cancer detection and localization in the transitional zone as well as the peripheral zone.

A recent study documented that it may be possible to diagnose prostate cancer in the transitional zone using $^1$H MRS (32). However, as in the current study, there was an overlap in the metabolic parameters between cancer and noncancer tissue.

In this study we did not apply an endorectal coil for T2-weighted imaging, and therefore the accuracy of our T2-weighted imaging for cancer detection was less than that in previous studies that used a combination of phase-array and endorectal coils (33–35). Since our study focused on DCE-MRI, we believed that improvement of spatial resolution using an endorectal coil would not be required in order to evaluate the wash-in rate. The parametric imaging in the present study appears to have better sensitivity and specificity (96% and 97%, respectively) for detecting peripheral zone cancer compared to the endorectal coil imaging of previous studies (73% and 80%, respectively) (34,35). However, it seems worthwhile to evaluate the accuracy of combining parametric imaging with T2-weighted endorectal coil imaging.

One question concerning the usefulness of parametric imaging of the wash-in rate is whether it can differentiate prostatectomy from prostate cancer. To our knowledge, there are no findings regarding prostatitis on parametric imaging of the wash-in rate in the literature. We believe it is possible that hypervascular prostatitis mimics prostate cancer on parametric imaging of the wash-in rate.

Another question concerns the variability of vascularity in prostate cancer tissue. The degree of tumor vascularity can vary according to the various degrees of differentiation of prostate cancer (24). Therefore, some well-differentiated cancers or intraepithelial neoplasms without a significantly increased vessel count may not be found on parametric imaging of the wash-in rate within the threshold of this study.

The wash-in rate is basically a parameter to display the enhancement rate and is therefore dependent on various physical and physiological factors, including the MR acquisition sequence and parameters chosen, contrast dosage, microvessel density, flow through the vessels, vascular resistance, capillary wall permeability, composition of the extracellular space, and venous outflow. Therefore, further research should be performed to standardize the protocol for MR acquisition and generation of parametric imaging.

Several parameters can be used to determine the enhancement characteristics based on the time-intensity curve, including the wash-in rate, maximal enhancement, area under the time-intensity curve, and wash-out rate. We used the wash-in rate because we assumed that this parameter would adequately demonstrate the degree of early and strong enhancement. However, it seems worthwhile to evaluate the usefulness of other parameters for prostate cancer imaging.

In conclusion, the wash-in rate on the basis of DCE-MRI may be a useful parameter for prostate cancer detection and localization. Given the merits of this method, the performance of MRI may be improved. However, further studies will be necessary to achieve accurate detection of transitional zone cancer.

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