Usefulness of a Pharmacokinetic Model Based on Dynamic Contrast-enhanced MRI for the Detection and Localization of Prostate Cancer

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Purpose: To investigate the usefulness of a pharmacokinetic model based on dynamic contrast-enhanced (DCE) MR imaging for the detection and localization of prostate cancer.

Materials and Methods: Forty-four patients that had undergone radical prostatectomy for prostate cancer and dynamic contrast enhanced (DCE) MR imaging (slice thickness, 4 mm; time resolution of each set, 5 seconds), were enrolled in the study. From the pharmacokinetic model, the time of arrival, and the parameters Ah, Kep, and Kel were extracted and were compared for cancerous tissue and non-cancerous tissue in the central gland and peripheral zone. The diagnostic performance of each parameter for differentiating cancerous tissue from non-cancerous tissue was evaluated using receiver-operating-characteristics analysis.

Results: The Kep and Kel values were significantly greater in cancerous tissue (0.13 sec⁻¹ ± 0.14 and 1.59 × 10⁻³ sec⁻¹ ± 1.35 × 10⁻³) than in non-cancerous tissue from the central gland (0.03 sec⁻¹ ± 0.02 and 0.26 × 10⁻³ sec⁻¹ ± 1.24 × 10⁻³) and peripheral zone (0.04 sec⁻¹ ± 0.07 and 0.58 × 10⁻³ sec⁻¹ ± 1.98 × 10⁻³) (p < 0.05). The area under the ROC curve for differentiating cancerous from non-cancerous tissue was 0.850 (95% CI, 0.778 - 0.876) for Kep and 0.814 (95% CI, 0.737 - 0.876) for Kel.

Conclusion: Kep and Kel are useful perfusion parameters for the differentiation of prostate cancerous tissue from non-cancerous tissue.

Index words: Prostate
Magnetic resonance imaging (MRI)
Pharmacokinetics
Prostatic neoplasms
Neoplasm staging
The incidence of prostate cancer has been increasing since the measurement of the level of prostate specific antigen was introduced for cancer screening [1]. For adequate local staging, a biopsy plan and follow-up guidance following local treatment, accurate cancer detection and localization are important. Although magnetic resonance (MR) imaging is widely used for the evaluation of prostate cancer, several studies has shown that the use of conventional spin-echo imaging, T2-weighted imaging is limited in differentiating prostate cancer from normal prostate tissue [2-9]. Therefore, the addition of other MR techniques to T2-weighted imaging, such as spectroscopy, diffusion weighted imaging, and dynamic contrast-enhanced imaging have been evaluated for improving the diagnostic performance of MR imaging.

Over the past few years, several studies have demonstrated that analysis of contrast enhancement characteristics on the basis of a pharmacokinetic model is useful for depicting the enhancement pattern of hypervascular tumors and for investigating neoangiogenesis [10-18]. Preliminary studies have showed that prostate cancer tissue is enhanced earlier and more intensively than normal tissue on dynamic contrast-enhanced (DCE) MR imaging [19, 20].

The present study was performed to evaluate the feasibility of a pharmacokinetic two compartment model and to investigate which perfusion parameters are useful for prostate cancer detection and localization.

**Materials and Methods**

The institutional review board for human investigation approved this study and informed consent was signed by and obtained from all patients.

**Patients**

This study was retrospectively designed. The inclusion criteria for patient enrollment in this study was as follows: 1) patients underwent dynamic contrast MR imaging in our institution; 2) patients underwent a radical retropubic prostatectomy for biopsy-proven prostate cancer; 3) a pathological map of the prostate cancer was available; 4) a patient did not undergo chemotherapy or radiation prior to surgery; 5) the area of the cancer tissue and normal tissue in the central gland and peripheral zone was equal to or greater than 40 mm², thereby providing an adequate condition for drawing regions-of-interest (ROI). A computerized search of the medical records and review of the histological maps between May 2005 and June 2006 generated a list of 44 patients that met the inclusion criteria. The mean patient age was 64.9 years (range, 49-75 years; SD, 5.8 years) and the mean value± SD of prostate-specific antigen was 13.7±9.6 ng/mL (range, 2.6-2.5 ng/mL). The time interval between the time of biopsy and MR imaging was 15-23 days. The TNM stages of the patients were T2a-T3b, No and Mo and the pathological Gleason score of the radical prostatectomy specimens was 7±2 (range, 6-10). Forty-two of the 44 patients showed multiple cancer foci and the remaining two patients had prostate cancer in the peripheral zone. In the 42 patients with multiple cancer foci, cancer tissue was noted only at the peripheral zone in eight patients, only at the central gland in seven patients, and at both the central gland and peripheral zone in 27 patients. The greatest diameter of cancer tissue was equal to or greater than 3 cm in 32 patients and less than 3 cm in 12 patients. The time interval between the MR examination and radical retropubic prostatectomy was 9±4 days (range, 1-16 days).

**MR Imaging Technique**

MR imaging was performed with a 1.5-T MR imaging unit (Gyroscope Intera; Philips Medical Systems, Best, the Netherlands) by 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/ms.

First, transverse, coronal and sagittal T2-weighted fast spin-echo images without an endorectal coil were acquired; flip angle, 90°; slice thickness, 4 mm; interslice gap, 0.1 mm; field of view, 150 mm; matrix size, 224×513; and number of sections, 20.

Thereafter, transverse dynamic contrast-enhanced images were obtained by use of a three-dimensional fast-field echo sequence [repetition time msec/echo time msec, 4000/90; echo-train length, 16; three signals acquired; flip angle, 90°; slice thickness, 4 mm; interslice gap, 0.1 mm; field of view, 225 mm; matrix size, 256×192; 25 slices]. The time resolution of each dynamic set was 5 seconds and 100-120 sequences were obtained for each patient. After an initial five image sets were obtained, a rapid bolus intravenous injection of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was administered by using a MR-compatible power injector (Spectris; Medrad, Indianola, PA...
U.S.A.), which was followed by a 20 mL saline flush. The dosage of the injected contrast material per patient was 0.1 mmole per kilogram of body weight, and the injection rate was 3 mL/sec.

**Histological Examination**

Following the radical prostatectomy, various staff pathologists in our institution who were unaware of the MR image findings obtained a histological map of the prostate cancers. 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 of 7-8 μm thickness were then obtained from each section and were stained with hematoxylin-eosin. Slides of halved or quartered slices at the same level of section were collected to simulate a whole mount section slice, and then a schematic map marking both the cancer and normal tissues was generated on superimposed transparent films over the slices.

**Postprocessing of the MR images and the measurement of perfusion parameters**

According to the two compartment model proposed by Brix [21], the time of arrival, Ah, Kep (sec⁻¹) and Kel (sec⁻¹) can be calculated according to the following formula: \( f(t) = S_0 + Ah \times Kep \times \left[ \exp\left( Kep \times \frac{t}{TA} \right) - \exp\left( Kel \times \frac{t}{TA} \right) \right] / (Kel - Kep) \), where \( S_0 \) is the base line signal intensity, \( TA \) is the time of arrival, Ah is the constant that corresponds to the size of interstitial space, Kel is the elimination rate constant from the plasma by renal excretion, and Kep is the elimination rate constant from the extracellular space back to the plasma. Each perfusion parameter was measured by using an in-house software (4D analyzer, Seoul, South Korea).

One radiologist measured the perfusion parameters in three different ROIs, which were placed over cancer tissue, normal tissue in the peripheral zone and normal tissue in the central gland. A round or elliptical ROI was placed over each of the three locations chosen by referring to the histological maps and T2-weighted images. When the area of the cancer tissue or normal tissue was less than 40 mm², a measurement was not performed. The observer attempted to cover as much cancer or normal tissue as possible within the ROIs while attempting to avoid the prostate capsule, urethra and periprostatic tissue within the ROIs. The area of the four ROIs was kept constant in each patient, but varied from 40 mm² to 70 mm² for each patient.

**Statistical Analysis**

The repeated measures of analysis of variance with pair-wise multiple comparisons by using Tukey’s method were applied for the comparison of the perfusion parameters in the three ROIs.

In order to evaluate the diagnostic performance of the wash-in rate for differentiating cancer and normal tissue, a receiver operating characteristics (ROC) analysis was performed. From the ROC analysis, the optimal cut-off point was extracted, which showed the best separation [minimal false negative and false positive results] between the prostate cancer and non-cancerous tissue. Thereafter, the sensitivity and specificity of the perfusion parameters were calculated. For every statistical analysis, significance was considered to be present when the \( P \) value was less than 0.05.

**Results**

The perfusion parameters for prostate cancer tissue and non-cancerous tissue of the central gland and peripheral zone are summarized in Table 1. In cancer tissue, all of the perfusion parameters were not significantly different, and the location; the time of arrival, Ah, Kep and Kel were 50.34 ± 20.35 sec, 2.03 ± 0.87, 0.12 ± 0.10 sec⁻¹ and 1.49 ± 1.01 sec⁻¹ in the cancer tissue of the central gland, respectively, and 52.10 ± 19.56

<table>
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<th>Table 1. Various Perfusion Parameters for Prostate Cancer Tissue and Non-cancerous Tissue of the Central gland and Peripheral Zone</th>
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<td><strong>Cancer tissue</strong></td>
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<td><strong>Central Gland</strong></td>
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<tr>
<td>Ah</td>
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<td>Kep [sec⁻¹]</td>
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<td>Kel [× 10⁻³] [sec⁻¹]</td>
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Note. = Kep and Kel were significantly greater in cancer tissue than in non-cancerous tissue in the central gland and peripheral zone \( p < 0.05 \).
sec, $1.88 \pm 0.62$, $0.14 \pm 0.14$ sec$^{-1}$ and $1.62 \pm 1.40$ sec$^{-1}$ in the cancer tissue of the peripheral zone, respectively ($p > 0.05$). Therefore, the location of the cancer tissue was not considered in the comparison of parameters between the cancer tissue and normal tissue and the mean value of all cancer tissues represented each parameter. Kep and Kel were significantly greater in prostate cancer tissue than in non-cancerous tissue-range, $0.02 - 0.50$ sec$^{-1}$ for Kep and $- 0.00196 - 0.00634$ sec$^{-1}$ for Kel for prostate cancer tissue; range, $0.00 - 0.09$ sec$^{-1}$ for Kep and $- 0.00424 - 0.00634$ sec$^{-1}$ for Kel in the central gland; range, $0.00 - 0.50$ sec$^{-1}$ for Kep and $- 0.00203 - 0.008710$ sec$^{-1}$ for Kel in the peripheral zone ($p < 0.05$) (Fig. 1).

The time of arrival and Ah were similar between prostate cancer tissue and non-cancerous tissue ($p > 0.05$). All perfusion parameters showed no significant difference between the non-cancerous tissues of the central gland and the peripheral zone ($p > 0.05$).

Kep for cancerous tissue was greater than Kep of non-cancerous tissue in 37 (84%) of 44 patients and Kel for cancerous tissue was greater than Kel for non-cancerous tissue in 34 (77%) patients. In 28 (64%) patients, both Kep and Kel were greater in cancerous tissue than in non-cancerous tissue. In 43 (98%) patients, either Kep or Kel was greater in the cancerous tissue than in the non-cancerous tissue.

The ROC curves analysis to determine the diagnostic performance of Kep and Kel in differentiating prostate cancer from each of the non-cancerous tissues is demonstrated in Figure 2. The area under the ROC curve for differentiating prostate cancer from non-cancerous tissue was 0.850 (95% CI, 0.778 - 0.906) for Kep and 0.814 (95% CI, 0.737 - 0.876) for Kel. The area under the

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**Fig. 1.** A 63-year-old male patient with prostate cancer. Histological step sections at the level of mid-gland (A) shows prostate cancer (dotted lines, arrows). (B) By referring to the histological map and transverse T2-weighted fast spin echo images (TR/TE, 4310 msec/90msec; echo train length, 15) at the same levels, ROIs were drawn in the prostate cancer tissue (PCa) and non-cancerous tissue of the peripheral zone (Pz) and central gland (Tz) using an in-house software. Kep was $0.18$ sec$^{-1}$ in the cancer tissue, $0.06$ sec$^{-1}$ in the non-cancerous tissue of the central gland, and $0.03$ sec$^{-1}$ in the non-cancerous tissue of the peripheral zone. Kel was $1.36 \times 10^{-3}$ sec$^{-1}$ in the cancer tissue, $0.42 \times 10^{-5}$ sec$^{-1}$ in the non-cancerous tissue of the central gland, and $0.19 \times 10^{-7}$ sec$^{-1}$ in the non-cancerous tissue of the peripheral zone.

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**Fig. 2.** Receiver operating characteristics curve for differentiating prostate cancer tissue from non-cancerous tissue. The area under the curve is 0.850 for Kep and 0.814 for Kel, respectively.
The area under the ROC curve for Kep was 0.830 (95% CI, 0.735-0.902) for differentiating prostate cancer from non-cancerous tissue, central gland-zone tissue and 0.870 (95% CI, 0.780-0.932) for differentiating cancerous from non-cancerous, peripheral-zone tissue. The area under the curve for Kel was 0.830 (95% CI, 0.733-0.903) for differentiating prostate cancer from non-cancerous, central gland-zone tissue and 0.768 (95% CI, 0.663-0.854) for differentiating cancerous from non-cancerous, peripheral-zone tissue.

The corresponding sensitivity and specificity were 86% and 71% for Kep and 84% and 76% for Kel, respectively. The sensitivity and specificity were not significantly different between Kep and Kel (p = 0.455).

With these thresholds, the sensitivity and specificity for differentiating cancerous tissue from non-cancerous, central gland tissue were 86% and 66% for Kep and 82% and 82% for Kel, respectively. The sensitivity and specificity for differentiating cancerous tissue from non-cancerous, peripheral zone tissue were 86% and 75% for Kep and 84% and 73% for Kel, respectively.

Discussion

The two compartment model was introduced in the late 1990s and has been widely used for the evaluation of perfusion characteristics in various organs. This method is based on the concept that intravenous contrast material transfers between the two compartments in the body, i.e. intravascular and extravascular/extracellular compartments, according to the concentration gradient of the contrast material [10-13]. Based on this concept, various perfusion parameters can be extracted, such as velocity of contrast transfer (Kep and Kel in this study), the area of extravascular/extracellular space, and the time of arrival. Therefore, this method seems to be adequate in evaluating a disease that alters tissue perfusion.

This study applied the two compartment model proposed by Brix. In comparison with other two compartment models, i.e. the Toft model and Larsson model, the Brix model does not require the acquisition of arterial input function, which is accompanied with a complex process and longer scan times [10-13]. Furthermore, in comparison with a simple analysis of the time intensity curve on DCE MR, the Brix model provides more detailed information on the transfer route of contrast material, using parameters such as Kep and Kel.

In this study, the Kep and Kel were significantly greater in prostate cancer tissue than in non-cancerous tissue, and the diagnostic performance of these two perfusion parameters were satisfactory as the area under the ROC curve was 0.814-0.850. Therefore, our results suggest that Kep and Kel may be useful parameters for prostate cancer detection and localization.

The theoretical background of the pharmacokinetic model utilizing DCE MR imaging is based on tumor angiogenesis. In cancer tissue, gene mutation leads to production and release of angiogenic factors, such as the vascular permeability factor or vascular endothelial growth factor. Under these circumstances, the number of vessels increases in the cancer tissue; the tumor vessels have greater permeability relative to normal vessels due to weak integrity of the vessel wall [22-24].

Kep is the elimination rate of contrast material from the interstitial space to the plasma, thereby representing permeability in a tissue. Therefore, our results that showed a greater value for Kep in cancerous tissue than in non-cancerous tissue correspond well to the fact that permeability is increased in the cancerous tissue [25-27].

Kel is the elimination rate of contrast material from the plasma to renal excretion, thereby being related to the circulation rate of plasma in the tissue. Due to increased microvessel density, there is an increased circulation rate through the plasma in the cancer tissue. Therefore, our results that showed a greater value for Kel in cancerous tissue than in non-cancerous tissue reflects the circulation environment of the cancer tissue.

Our results correspond to those of previous experimental studies, in which the mean transit time, blood flow, permeability surface area and interstitial volume were significantly greater in cancer tissue than in normal tissue [25-27]. Engelbrecht et al. [26] showed the usefulness of relative peak enhancement and the washout rate for prostate cancer detection and localization. From an ROC analysis in their study, the relative peak enhancement was the most accurate parameter for cancer detection in the peripheral zone and central gland. Kim et al. [27] demonstrated that parametric imaging of the wash-in rate was more accurate than T2WI alone for peripheral zone cancer detection. In their study, the sensitivity and specificity of peripheral zone cancer detection were 96% and 97% by parametric imaging of the
wash-in rate but 75% and 53% on T2WI (P < 0.05).

According to the results of previous and current studies, it is obvious that the enhancement characteristics are different between the cancerous and non-cancerous tissue. There are many perfusion parameters that are useful for differentiating prostate cancer from non-cancerous tissue, and furthermore, various pharmacokinetic models have been introduced. However, these various parameters and pharmacokinetic models have been separately evaluated in each study. Therefore, it is necessary to perform a comprehensive evaluation of the many perfusion parameters and to determine the advantages and disadvantages of each pharmacokinetic model.

There are several limitations in this study. First, this study measured perfusion parameters in ROIs of cancerous and non-cancerous tissue in a retrospective fashion. However, an ROI study has an inherent weakness in that the value from the ROI is not representative of the entire tissue in any zone. Therefore, in order to evaluate the actual usefulness of the perfusion parameters in prostate cancer detection and localization, a prospective systematized study with a pixel-by-pixel analysis should be conducted.

Second, there has been no agreement concerning the MR acquisition protocol and the optimal perfusion parameters for differentiating cancer tissue from normal tissue. Because the value of the perfusion parameters may be influenced by various factors, such as the temporal resolution of the DCE MR imaging and the dose and injection rate of contrast material, it is necessary to standardize the protocol for MR imaging acquisition.

Third, this study divided the prostate into only cancerous and non-cancerous tissue and compared the perfusion parameters between the types. However, there may be various non-cancerous conditions that could alter the perfusion environment, such as benign prostate hyperplasia, prostatitis, or atrophy. As Kep and Kel are not cancer-specific parameters and just reflect the transfer velocity of contrast material in a certain tissue, various conditions that can alter the perfusion environment can also change these parameters. Therefore, the diagnostic performance based simply on the ROI measurement may be exaggerated, and the actual diagnostic accuracy may vary according to the presence or absence of benign prostatic disease.

Lastly, this study included only patients with prostate cancer tissue large enough to allow drawing of a ROI. Therefore, our results for differentiating prostate cancer from non-cancerous tissue cannot suggest the successful diagnostic performance in detecting small prostate cancers.

In conclusion, determination of Kep and Kel based on DCE MR imaging may be useful parameters for prostate cancer detection and localization. Given the merits of this method, the performance of MR imaging may be improved.

Acknowledgements

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