Blood flow change quantification in cervical cancer before and after radiotherapy using perfusion CT

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Purpose

Cervical cancer is one of the most common female cancers in the world. Radiation therapy is an essential element of the cervical cancer treatment, and tumor oxygenation status has been implicated as a critical factor contributing to tumor control and the curability of cervical cancer (1-5). The local blood flow (BF) influences the oxygenation status of the tumor cells and might affect treatment outcome, so some noninvasive methods to evaluate the tumor perfusion in clinical practice have been proposed (6, 7).

Due to the recent progress in imaging technique, computed tomography (CT) has applications not only for anatomical information, but also for functional information such as the BF. In reported studies, MRI was been used for evaluating tumor perfusion, but quantitative evaluation with this technique was difficult. Tumor perfusion analysis with dynamic CT can quantify tumor BF, since the concentration of the contrast medium has a linear correlation with the increase in CT number.

Several analytical methods have been proposed to demonstrate the BF using perfusion CT, but the standard analytical methods of perfusion CT have not been applied to cervical cancer. The maximum-slope (MS) method of deriving perfusion measurement has been proposed by Miles et al. (8-11). The principle of the MS method is very simple. However, in this method, venous outflow is not taken into account, and high-dose rate bolus injection of contrast material is essential for accurately quantifying the perfusion.

The single-input one-compartment model (SOCM) method have been derived from the classical pharmacokinetic model (12). Materne et al. extended this model to the dual-input one-compartment model (DOCM) method for quantification of liver perfusion (13). With the DOCM method, two inflow vessels are assumed, i.e. hepatic artery and portal vein, while the SOCM method is based on one inflow model. The outstanding characteristic of the SOCM and DOCM methods are consideration of venous outflow and not requiring high-dose rate bolus injection.

The purpose of this study is to quantify the changes of tumor BF in cervical cancer after radiation therapy by using perfusion CT, and to examine the difference between the MS and SOCM methods.
Methods and Materials

Patients

Institutional review board of our hospital approved for this observational study, and written informed consent was obtained from each patient. Between October 2009 and April 2010, fourteen consecutive patients who met the inclusion criteria and agreed to participate in the study were enrolled. Inclusion criteria and exclusion criteria are shown in Fig. 1. Histological conformation was required in all patients that were clinically staged as The International Federation of Gynecology and Obstetrics (FIGO) classification IB to IVA. All patients underwent baseline perfusion CT within 1 week before the beginning of therapy, and follow up with a second perfusion CT study within 1 week after 20 Gy irradiation.

Imaging protocol

All CT images obtained using a 64 multidetector-row CT (Aquillion 64; Toshiba Medical Systems Co., Tochigi, Japan). The CT parameters and scanning protocol are summarized in Fig. 2. In perfusion CT, 370mgI/kg of iopamidol (Iopamiron 370 Inj. Syringe, Bayer Yakuhin, Ltd. Tokyo, Japan) was injected via an 18G needle inserted in the medial cubital vein at the rate of 5.0 ml/s by using the automatic injector (Dual shot; Nemoto Kyorindo co., Ltd. Tokyo, Japan). Static dynamic CT scanning was initiated simultaneous to contrast medium injection. Image data were obtained every 2 s from the beginning of contrast material administration up to 50 s and then every 7 s from 50 to 120 s. The patients were freely breathing during the scan time. CT images were transferred to the prototype workstation (Toshiba Medical Systems Co.) by DICOM protocol.

Maximum-slope method

The maximum slope method hypothesizes that there is no venous outflow. Under this condition, the CT value of the target tissue increases in proportion to the volume of the transferred contrast medium. On the basis of the Fick's principle, tissue concentration of the contrast medium: Ct(t) corresponds to the value of tissue BF multiplied by the arterial concentration of the contrast medium: Ca(t). Time attenuation curve (TAC) of artery and tissue are shown in Fig. 3. Thus, tissue BF is calculated as follows: Tissue BF = maximum Ct(t) increments per unit time / maximum Ca(t) increments.

Single-input one-compartment model method

The tissue compartment model is shown in Fig. 4. The CM method is summarized by the following equation: \[ \frac{dC_t(t)}{dt} = k_aC_a(t-a) - k_vC_t(t). \]
Ct and Ca represent the concentrations of contrast medium at time t within the tissue and the artery, respectively. The concentrations of contrast medium reflect the CT value derived from TAC of the tissue and artery. The ka and kv indicate arterial inflow and venous outflow constant, respectively. The delay parameter represent the transit time from the artery to the tissue. The value of is defined the delay time between the beginning of artery and tissue enhancement. The value of ka was calculated using the least squares method. The values of ka and kv converted to the perfusion units by multiplying by 60 s/min and by 100 ml (of blood) / ml (of tissue). As shown in this equation, SOCM method does not need to assume no venous outflow.

**Blood flow measurement**

In both analytical methods, external iliac artery was selected as the input function Ca(t). The mean CT value over the maximum section of the tumor was shown as the function Ct(t). Both parameters were shown as artery and tissue TAC. BF was calculated by both methods based on these TACs. In the MS method, the peak gradients of the artery TAC were selected manually. In the SOCM method, the value of is defined the delay time between the beginning of artery and tumor enhancement on both TACs.

The CT images were compressed to 256 × 256 matrices, and the BFs were calculated pixel by pixel using the two analytical methods (the MS and SOCM). After generation of color maps, the BFs were measured in the slice containing the maximum transverse section of the tumor in the uterine cervix (Fig. 5). The regions of interest (ROIs) were contoured including as much tumor as possible, without including regions directly adjacent to vessels and other organs.

The same ROIs were used for both the MS and SOCM methods. We calculated mean BFs within the ROIs and investigated the correlation. All measurement were done by one radiologist (K. S.).

**Statistical analyses**

All the statistical analyses were performed using SPSS statistics software (Version 17.0; SPSS Inc., Chicago, IL). Numerical variables are expressed as median (inter-quartile range: IQR). Shapiro-Wilk test was used to test the hypothesis that a given sample was from a normally distributed population. The Wilcoxon signed rank test was used as a non-parametric test for assessing the significance between two analytical methods. P was considered statistically significant. The correlation coefficient (R) was calculated using the Spearman's coefficient correlation method and linear regression.
Fig. 0: Flowchart of the study population

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## CT Acquisition

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan parameter</td>
<td>Non-helical</td>
</tr>
<tr>
<td>Scanning</td>
<td>0.5 sec</td>
</tr>
<tr>
<td>Rotation time</td>
<td>AEC: Automatic exposure control (S.D. 12.5)</td>
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<tr>
<td>Effective exposure</td>
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</tr>
<tr>
<td>Reconstruction</td>
<td></td>
</tr>
<tr>
<td>Matrix size</td>
<td>$512 \times 512$ axial images</td>
</tr>
<tr>
<td>Intersection distance</td>
<td>8 mm</td>
</tr>
<tr>
<td>Section width</td>
<td>8 mm</td>
</tr>
<tr>
<td>Multiphase CT acquisition</td>
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</tr>
<tr>
<td>0 - 50 sec</td>
<td>Every 2 sec</td>
</tr>
<tr>
<td>50 - 120 sec</td>
<td>Every 7 sec</td>
</tr>
</tbody>
</table>

* S.D.: Standard deviation

**Fig. 0:** CT acquisition

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Fig. 0: The external iliac artery was selected as the input function $Ca(t)$. The mean CT value over the maximum section of the tumor was shown as the function $Ct(t)$. Both parameters were shown as artery and tissue TAC: the green and red line, respectively.

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**Single-Input One-Compartment model (SOCM)**

![Diagram of SOCM model](image)

$$\frac{dC_t(t)}{dt} = k_a C_a(t - \tau_a) - k_v C_t(t)$$

- $k_a$: arterial inflow constant
- $k_v$: venous outflow constant
- $\tau_a$: the transit time from artery to tissue

**Fig. 0:** In this model, $k_a$ is the arterial inflow constant, $k_v$ is the venous outflow constant, and $C_a(t)$ and $C_t(t)$ represent the concentration of contrast medium from the artery and tissue, respectively.

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**Fig. 0:** A 48-year-old female with FIGO Ib2 uterine cervical cancer. Images in each row are from each evaluation point. (a,b,c: before radiation therapy d,e,f: after 20 Gy irradiation). (a, h) Contrast enhanced CT (CECT) images show the mass in the uterine cervix. The BFs were measured in the slice containing the maximum transverse section of the tumor. The regions of interest (ROIs) were contoured to include as much tumor as possible, without including regions directly adjacent to vessels and other organs. (b, e) The mean BFs calculated by the MS method before and after 20 Gy irradiation are 38.4 and 152.1 ml/min/100ml, respectively. (c, d) The mean BFs calculated by the SOCM method before and after 20 Gy irradiation are 57.7 and 240.5 ml/min/100ml, respectively. The same ROIs were used for both the MS and SOCM methods.

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Results

Perfusion CT analyses were performed in eleven of the 14 patients. Three cases were excluded from the analyses because of a technical error in contrast media injection, an error in the imaging position, or a tumor size insufficient for selecting a ROI. Perfusion color maps were successfully created by two analytical methods from dynamic CT data in remaining 11 patients. Patient's characteristics were shown in Fig. 1. Baseline BFs were 72.2 (median; IQR 46.7 - 132.2) ml/min/100 ml by the MS method and 103.0 (median; IQR 50.9 - 129.5) ml/min/100 ml by the SOCM method.

Blood flow changes of cervical cancer before and after radiation therapy

The BF of the tumors after 20 Gy of radiation therapy calculated by the MS method was significantly larger than that before treatment (126.9 vs. 72.2 ml/min/100 ml, median; p=0.016). However, the difference between tumor BFs before and after 20 Gy of radiation therapy calculated by the SOCM method was borderline significance (141.5 vs. 103.0 ml/min/100 ml, median; p=0.075) (Fig. 2).

Comparison of the maximum slope method and single-input one-compartment model method

The results of the BF of the tumor evaluated by the two analytical methods were summarized in Fig. 3. In 22 analyses of 11 patients, the BFs calculated by the MS method was lower than that obtained by the SOCM method (103.7 vs. 115.1 ml/min/100 ml, median; p=0.002) (Table 3). BFs calculated by the MS and SOCM methods showed a positive linear correlation (p<0.001, R=0.981) (Fig. 4).
**Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
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<td></td>
</tr>
<tr>
<td>FIGO Stage</td>
<td></td>
<td></td>
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<tr>
<td>IB</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>IIA</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>IIB</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>IIIB</td>
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<td>7</td>
</tr>
<tr>
<td>IVA</td>
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<td>7</td>
</tr>
<tr>
<td>Treatment</td>
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</tr>
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</tr>
<tr>
<td>RT alone</td>
<td>9</td>
<td>64</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>71</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>4</td>
<td>29</td>
</tr>
</tbody>
</table>

**Fig. 0:** Patient characteristics

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Fig. 0: Comparison between the BFs of the tumor before and after 20 Gy radiation therapy. The BF after 20 Gy of radiation therapy calculated by the MS method was significantly greater than that before treatment (126.9 vs. 72.2 ml/min/100 ml, median; p=0.016). The difference between the BFs before and after 20 Gy of radiation therapy calculated by the SOCM method was of borderline significance (141.5 vs. 103.0 ml/min/100 ml, median; p=0.075)

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Results of the BF of the tumor evaluated by the two analytical methods

<table>
<thead>
<tr>
<th></th>
<th>MS method</th>
<th>SOCM method</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RTx</td>
<td>72.2 (46.7 – 132.2)</td>
<td>103.0 (58.8 – 142.9)</td>
<td>0.021</td>
</tr>
<tr>
<td>Post-20 Gy</td>
<td>126.9 (65.2 – 301.2)</td>
<td>141.5 (98.7 – 421.0)</td>
<td>0.033</td>
</tr>
<tr>
<td>Total</td>
<td>103.7 (59.0 – 163.9)</td>
<td>115.1 (65.9 – 167.6)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Fig. 0:** Results of the BFs of the tumor evaluated by the two analytical methods. Data are shown as median (inter-quartile range: IQR).

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**Fig. 0**: Correlation between the BF calculated by the MS and CM methods. The BFs by two the analytical methods showed a highly significant positive linear correlation (p

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Conclusion

In the present study, BFs were successfully measured by perfusion CT using both analytical methods, and could be expressed as numerical values. Our results demonstrated that there is individual variation in tumor BF and changes in BF in response to radiation therapy. It is well known that intratumoral oxygenation is improved by fractionated irradiation, since treatment decreases intratumoral cell density, which in turn increases BF (14, 15). In our study, perfusion CT successfully confirmed the increase in BF after 20 Gy of radiation therapy.

To the best of our knowledge, this was the first report comparing different analytical methods in perfusion CT of cervical cancer. In our present study, the BFs calculated by the MS and SOCM methods showed a highly significant positive linear correlation. The SOCM method has the advantage of being less influenced by the bolus infusion rate, since it takes venous outflow into account. The BFs calculated by the SOCM method correlates well with those by the MS method, and may replace the MS method.

Furthermore, our results suggest that the BF values were lower with the MS method than with the SOCM method. Our results were not correlated with any gold standards, since there were no other practical methods to evaluate tissue perfusion in vivo. Recently, various analytical models for perfusion CT have been developed, such as some non-compartmental analysis: the deconvolution method or the Patlak plot model (16-19). These new methods may also help to obtain the information about the reliability of these perfusion analytical methods in cervical cancer.

In conclusion, the changes of tumor BF in cervical cancer before and after radiation therapy could be monitored using perfusion CT by conducting blood flow analysis. BF by the MS method was lower than that by the SOCM method, but the two analytical methods correlated well. It is hoped that the perfusion study protocol could be helpful in providing valuable information for monitoring vascular-modulation by radiation therapy or anti-angiogenesis drug in the future.
References


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