Noninvasive Monitoring of Radiation-Induced Early Therapeutic Response Using High-resolution MR Imaging and Proton MR Spectroscopy in VX2 Carcinoma

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The purpose of this study was to evaluate the usefulness of high-resolution MRI (HR-MRI) and proton MR spectroscopy (1H-MRS) for monitoring the early therapeutic response to radiotherapy. Twenty rabbits with VX2 carcinoma were divided into control (n = 8) and irradiation (n = 12) groups. The irradiation group underwent HR-MRI and 1H-MRS using a microscopy coil at 1, 3, 7 or 14 days after irradiation. Rabbits in the control group were subjected to HR-MRI and 1H-MRS at the same time intervals. All rabbits were killed after imaging and subjected to histopathologic examinations. The diameter of necrosis by HR-MRI was then compared to that on the gross specimens. The ratios of choline/creatine (Cho/Cr) and lactate/creatine (Lac/Cr) on the tumor and necrotic area detected by in vivo 1H-MRS were compared between the control and irradiation groups, respectively. In addition, the ratios of Cho/Cr and Lac/Cr were compared between the tumor and necrotic area in each irradiation group. A significant correlation was found between the diameter of necrosis in each sequence of HR-MRI and that in the gross specimens (r = 0.84–0.91, p = 0.03–< 0.003). The ratios of Lac/Cr in the tumors of the irradiation groups were significantly higher than those in the control groups after 1 day and 3 days of irradiation (p = 0.04, and p = 0.02). Histological analysis showed necrosis and swelling of the endothelia of capillaries and arterioles at 1 day and 3 days after irradiation. It was suggested that HR-MRI and 1H-MRS are useful methods for monitoring the early therapeutic response to radiotherapy.

INTRODUCTION

An evaluation of the therapeutic response at an early stage after radiotherapy using imaging modalities would provide useful information regarding the effectiveness of the therapy. However, at an early stage after radiotherapy, accurate evaluation of therapeutic response can be difficult, due to differentiate between post-therapeutic change and residual tumor is limited in imaging modalities based on lesion morphology. In addition, tumor volume regression is documented as a sign of response, but a number of months are usually required to confirm a change in the tumor size. However, if prediction or early detection of the therapeutic response to radiotherapy area is possible, it has great clinical significance.

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MRI allows the characterization of tumors on the basis of signal intensity characteristics and/or morphologic features. Recent developments in MR technology allow the use of a combination of a microscopy surface coil with a small field of view and a high-field clinical MR imager system with customized pulse sequence, which together provide high-resolution images. There have been several reports in which high-resolution MRI (HR-MRI) using a microscopy coil is a useful technique for the diagnosis of carcinoma in situ and for the evaluation of tumor extension in surrounding tissue because of the good correlation between HR-MRI and histopathology.1,2

Magnetic resonance spectroscopy (MRS) is a non-invasive technique which can be performed using a conventional MRI machine with additional hardware tuned for frequency of the chosen nucleus, e.g. 1H, 13C, 14N, 19F, 23Na, and 31P. In particular, proton-MRS (1H-MRS), because of its much greater sensitivity than other spectroscopic nucleus, allows in vivo detection with substantially higher spatial resolution. Therefore, 1H-MRS is much applicable to clinical investigation. The most common metabolites of 1H-MRS that have been studied and validated are choline and creatine. The
ratio of choline/creatine has been shown to be helpful in discriminating among regions of normal tissue, tumor, and necrosis in several solid tumors, specifically gliomas and prostate cancer. In addition, several studies have evaluated the correlation of tumor lactate in vivo 1H-MRS with therapeutic response and outcomes; however, the potential role of 1H-MRS in predicting therapeutic response after radiotherapy has not yet been determined.

The purpose of this study was to correlate HR-MRI findings and the serial changes of choline and lactate detected using in vivo 1H-MRS with the histopathologic changes after irradiation in VX2 rabbit carcinoma, and to evaluate the usefulness of HR-MRI and 1H-MRS for monitoring of radiation-induced early therapeutic response.

MATERIALS AND METHODS

Animals and experimental model

 Animals were handled according to the Biomedical Research compiled by the Committee on Safety Handling Regulations for Laboratory Animal Experiments at our institution. The experiments were performed with 20 Japanese white rabbits that ranged in weight from 2 to 3 kg. All rabbits were anesthetized intramuscularly using a combination of xylazine (5 mg/kg of body weight) and ketamine hydrochloride (50 mg/kg). Anesthesia was maintained with 15 mg/kg intravenous sodium pentobarbital, with additional supplements via a marginal ear vein.

VX2 carcinoma was serially implanted in the thighs of carrier Japanese white rabbits. After 14–21 days, the tumor was surgically removed. The tumor was then minced with scissors, subjected to forceful pipetting, and filtered through a stainless steel mesh to obtain a suspension of single tumor cells. The tumor suspension (0.5 ml, approximately $1 \times 10^7$ tumor cells) was injected in the bilateral thighs of each animal using an 18-gauge needle. The tumors, when they had grown to about 2 cm in diameter, were used in the experiments.

The twenty rabbits, which were implanted VX2 carcinoma in the bilateral thighs, were divided into 2 groups: a control group ($n = 8$, and number of tumors = 16) and an irradiation group ($n = 12$, and number of tumors = 24). In addition, the irradiation group was divided into four sub-groups for the purpose of examinations of HR-MRI and 1H-MRS at different time intervals as follows: group A ($n = 3$, and number of tumors = 6) underwent HR-MRI and 1H-MRS after 1 day of irradiation; group B ($n = 3$, and number of tumors = 6) after 3 days; group C ($n = 3$, and number of tumors = 6) after 7 days; and group D ($n = 3$, and number of tumors = 6) after 14 days. In the control group also, the rabbits were divided into four sub-groups (group E, F, G, and H. each sub-group: $n = 2$, and number of tumors = 4), and HR-MRI and 1H-MRS were performed at the same time intervals of the irradiation group.

Irradiation

Each rabbit of the irradiation group received irradiation at a single fraction of 30 Gy, delivered focally to the tumor in the rabbit’s bilateral thigh using a 9-MeV electron beam from a linear accelerator (Clinac ix, Varian Medical Systems, Palo Alto, CA USA). The rabbits were placed in a prone position and shielded using a whole-body lead cover except for their thighs. A dose rate of 3 Gy/min, a source-to-surface distance of 100 cm, and a field size of 6 cm x 6 cm were used.

MR imaging

HR-MRI was performed using a 1.5 T MR system (Magnetom Vision; Siemens AG, Erlangen, Germany) with a microscopy surface coil of 4.5 cm in diameter. The construction of the coil enabled local acquisition of the signal with a high signal-to-noise ratio. The rabbits anesthetized using the same anesthetic regimen used for tumor implantation were fixed in a supine position on a board made of rigid paper. The coil was positioned on the thigh surface and centered on the area of interest.

T1-weighted MR images (T1WI) were obtained by the spin-echo technique at $TR/TE = 500/20$ and 3 excitations. T2-weighted MR images (T2WI) were obtained by the spin-echo technique at $TR/TE = 2000/70$ and 2 excitations. After unenhanced spin-echo T1- and T2WI, contrast-enhanced MRI (CE-MRI) was performed by the same methods as T1WI after three minutes of injection of gadopentetate dimeglumine (0.1 mmol/kg). In all sequences, images were obtained in the axial plane with a $256 \times 256$ matrix and a 5-mm field of view. This resulted in a 0.20-mm plane resolution. The section thickness was 3 mm, and there was no intersection gap.

For analysis of MRI, visual estimate of the necrotic area were made by consensus by two radiologists who were blinded to the results of the histopathological examinations, and on each sequence of HR-MRI, the diameters of the necrosis of the tumor were measured using an MR analysis system. The lesion measurements were obtained on the slice with the largest transverse diameter. Then comparisons of the diameter of necrosis were performed between each sequence of HR-MRI and gross specimens.

MR spectroscopy

Proton MRS examinations were performed using the same 1.5 T MR system and the same microscopy surface coil. Proton MRS data acquisitions of implanted VX2 carcinoma in the bilateral thighs were performed in each thigh separately. Placement of the surface coil was based on the initial MR image to minimize surface tissue intervention between the coil and tumor. T1-weighted images were used to guide volume-selected long echo spectroscopic examinations, and the parameters were: $TR/TE = 1500/135$ msec and $128 \times 256$ acquisitions. Sixteen separate rectangular 1H-MRS voxels of the multivoxel examination were used in all rab-
Monitoring of HR-MRI and \(^1\)H-MRS

The volumes of each voxel constituted 0.8 cc. Before spectroscopic acquisition, global and localized shimming on the water proton and optimization of water suppression was done. Metabolic data of \(^1\)H-MRS were analyzed separately in each voxel of the multivoxel MRS examination. For each case, the MR spectra were obtained from at least two regions of interest. One was obtained from the voxel coinciding with the necrosis, and the other was obtained from the viable tumor evaluated by histopathological examinations. Proton MRS data were interactively evaluated using an MR scanner using commercially available software (Siemens). The signal intensities of choline-containing compounds (Cho, \(\delta = 3.2\) ppm), creatine-phosphocreatine (Cr, \(\delta = 3.0\) ppm), and lactate (Lac, \(\delta = 1.3\) ppm) were calculated by fit and integration of the resonance lines in post-processed Fourier spectra. Choline-containing compounds reflects membrane synthesis and turnover, and lactate reflects anaerobic metabolism. Creatine-phosphocreatine is important in cellular energetic.

In several previous studies with regard to the metabolic changes of tumor after radiotherapy, the changes of the Cho/Cr ratio, or lactate peak have been reported.\(^5\)–\(^7\),\(^9\),\(^10\) Therefore, in this study, we took notice of the changes of the choline and the lactate peaks in vivo \(^1\)H-MRS after radiotherapy, and the metabolite ratios of Cho/Cr and Lac/Cr were used for monitoring of radiation-induced early therapeutic response. A difficulty of using ratios to quantify the metabolic abnormality is that ratios with very small denominators are very sensitive to the noise in the spectrum. In this xenograft, the creatine peak was used for the denominator of metabolite ratios because its peak was usually detected clearly.

The serial changes of the ratios of Cho/Cr and Lac/Cr on the viable tumor and necrosis were compared between the control and irradiation groups. In addition, in the irradiation group, the serial changes of the ratios of Cho/Cr and Lac/Cr were compared between the viable tumor and necrosis.

Pathologic examination

After HR-MRI and \(^1\)H-MRS were obtained for each group, all rabbits were killed with an intravenous overdose of pentobarbital. The tumor was removed surgically, and a central cross-sectional incision was made. The diameter of the central necrotic region was measured in each specimen based upon the consensus of 2 observers. The specimens were fixed in 10% phosphate-buffered neutral formalin for 7 days. Five-mm axial sections were cut along the same plane of HR-MRI studies and embedded in paraffin for sectioning. All materials were stained with hematoxylin-eosin.

Statistical analysis

The relationships between each sequence of HR-MRI and the gross specimens with regard to the diameters of areas of necrosis in the tumors were analyzed using Spearman rank correlation coefficients. The comparisons of \(^1\)H-MRS data between the viable tumor and necrosis and between the control and irradiation groups were performed using Mann-Whitney U test. A P value of .05 or less was considered to indicate a significant difference.

RESULTS

Tumor growth and necrosis

Mean changes in diameters of tumor and necrosis of control and irradiation groups are shown in Fig. 1. In irradiation groups, tumor growth was significantly slowed compared with control groups. In addition, tumor necrosis in irradiation groups was significantly larger than that in control groups.

MR findings with histopathologic correlation

The comparisons of the mean maximum diameters (mean ± SD) of necrosis between each sequence of HR-MRI and gross specimens in irradiation and control groups were shown in Table 1. A significant correlation was found between the diameter of necrosis in each sequence of HR-MRI and that in the gross specimens (Fig. 2A, B, and C. r = 0.84–0.91, p = 0.03– < 0.003).

MR spectroscopy findings

The comparisons of the Cho/Cr ratios of the tumors and necrosis between the control and irradiation groups were shown in Table 2. There was no statistically significant difference in the Cho/Cr ratios of the tumors and necrosis between the control and irradiation groups. The comparisons of the Lac/Cr ratios of the tumors and necrosis between the control and irradiation groups were shown in Table 3. The Lac/Cr ratios of the tumors in the irradiation group tended
to be higher than those in the control group, particularly after 1 day and 3 days of irradiation, when the Lac/Cr ratios of the tumors in the irradiation group were significantly higher than those in the control group (p = 0.04, and 0.02). There was no statistically significant difference in the Lac/Cr ratios of the necrosis between the irradiation and control groups. In addition, there was no statistically significant difference in the Cho/Cr and the Lac/Cr ratios between the tumors and necrosis in the irradiation groups.

**Histological features**

In group A, the residual viable tumor cells showed nuclear condensation and nuclear collapse, as well as swelling and vacuolization of the cytoplasm. The necrosis showed mosaic patterns encountered by admixture of small areas of necrotic portion and viable neoplastic cell nests. In group B, the residual viable cells showed swelling of the nucleus and cytoplasm, vacuolization of the nucleus and chromatin condensation. There was capillary dilatation in the peripheral portion of the tumor, and swelling of endothelia was noted in capillaries and arterioles (Fig. 3E). The necrosis showed sheets and nests of degenerated tumor cells with sparse content of stroma. In groups C and D, necrosis, which revealed liquefaction change with scattered degenerating neoplastic cells together with marked degree of neutrophilic infiltration, was seen in the central portion, and the mantle of viable

<table>
<thead>
<tr>
<th>Table 1. Comparisons of the diameter of necrosis between the each sequences of high-resolution MRI and gross specimens</th>
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<td>Group</td>
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<tr>
<td>T1 WI</td>
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<td>T2 WI</td>
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<td>CE-MRI</td>
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<td>Specimens</td>
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Parenthesis is number of tumors. Values reported area mean ± standard deviation. N/A: not available for measurement.

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**Fig. 2.** Correlation of each sequence of high-resolution MRI and gross specimens. Graphs show that a significant correlation is found between each sequence of high-resolution MRI and gross specimens. (A) T1-weighted MR images vs. gross specimen. (B) T2-weighted MR images vs. gross specimen. (C) Contrast-enhanced MR images vs. gross specimen.
Table 2. Comparisons of the choline/creatine ratios in viable tumor and necrosis between control and irradiation groups

<table>
<thead>
<tr>
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<th>Viable tumor</th>
<th>Necrosis</th>
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<td>1 day</td>
<td>3 day</td>
<td>7 day</td>
<td>14 day</td>
<td>1 day</td>
<td>3 day</td>
<td>7 day</td>
<td>14 day</td>
</tr>
<tr>
<td>Control</td>
<td>1.89 ± 1.26</td>
<td>1.48 ± 1.47</td>
<td>1.22 ± 0.72</td>
<td>1.62 ± 0.59</td>
<td>N/A</td>
<td>1.22 ± 0.97</td>
<td>1.17 ± 0.77</td>
<td>1.18 ± 0.77</td>
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<tr>
<td>Irradiation</td>
<td>1.54 ± 1.23</td>
<td>1.41 ± 0.90</td>
<td>1.61 ± 0.45</td>
<td>1.48 ± 0.75</td>
<td>1.40 ± 1.10</td>
<td>1.27 ± 0.84</td>
<td>1.20 ± 0.54</td>
<td>1.21 ± 0.59</td>
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Values reported area mean ± standard deviation. N/A: not available for measurement.

Table 3. Comparisons of the lactate/creatine ratios in viable tumor and necrosis between control and irradiation groups

<table>
<thead>
<tr>
<th></th>
<th>Viable tumor</th>
<th>Necrosis</th>
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<td>14 day</td>
<td>1 day</td>
<td>3 day</td>
<td>7 day</td>
<td>14 day</td>
</tr>
<tr>
<td>Control</td>
<td>0.63 ± 0.45</td>
<td>0.52 ± 0.79</td>
<td>0.88 ± 0.82</td>
<td>0.92 ± 0.27</td>
<td>N/A</td>
<td>1.46 ± 0.67</td>
<td>1.83 ± 0.89</td>
<td>1.93 ± 0.94</td>
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<tr>
<td>Irradiation</td>
<td>2.12 ± 1.10</td>
<td>2.06 ± 0.85</td>
<td>1.35 ± 0.86</td>
<td>1.79 ± 1.29</td>
<td>1.76 ± 0.77</td>
<td>1.44 ± 0.73</td>
<td>1.73 ± 0.94</td>
<td>1.62 ± 0.65</td>
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</table>

Values reported area mean ± standard deviation. N/A: not available for measurement. *: p < .05.

Fig. 3. High-resolution MR images, proton MR spectroscopy, and photomicrography of VX2 carcinoma at 3 days after irradiation. (A) Axial T1-weighted image shows slightly hyperintense tumor containing a central hypointense area coinciding with necrosis. (B) Axial T2-weighted image shows hyperintense tumor containing a central strong hyperintense area coinciding with necrosis. (C) Axial T1-weighted contrast-enhanced image shows mild enhanced tumor containing a hypointense area coinciding with a central strong hyperintense area on T2-weighted image. (D) The choline (a), creatine (b), and lactate (c) signals of residual tumor are detected by in vivo 1H-MRS. The elevation of lactate signal is shown. (E) Photomicrography of residual tumor shows swelling of the nucleus and cytoplasm. There are capillary dilatation and swelling of the endothelia of capillaries in peripheral portion of the tumor (arrows).
tumor cells was located in the peripheral portion. The necrotic area was surrounded by marked inflammatory cell infiltration and an increase in the amount of fibrosis tissue. The endothelia of capillaries and arterioles were normal, and mild thickening was noted in arterioles.

Figure 3 presents typical images of HR-MRI, ¹H-MRS, and histopathology of a VX2 carcinoma after 3 days of irradiation.

**DISCUSSION**

Some investigators who studied conventional MRI reported that CE-MRI is the most sensitive for detecting necrosis, and that strongly enhanced areas corresponded to viable tumor tissue and richly vascularized connective tissue, whereas non-enhanced areas corresponded to necrotic tissue histologically. In addition, Choi et al. reported that on T2WI, the areas of late-phase necrosis showed very high intensity due to liquefaction and high water content, whereas the area of early-phase necrosis showed low intensity due to low water content. Therefore, T2WI may be useful in characterizing different stages of necrosis. Regarding the evaluation of tumor response to radiotherapy on HR-MRI in this study, HR-MRI was sensitive for detecting and monitoring tumor necrosis at an early stage after radiotherapy, and correlated well with histologic findings. On a subjective visual basis, a comparison of diameters of necrosis between HR-MRI and specimens revealed good correlation. In particular, CE-MRI was the most sensitive for detecting tumor necrosis, and the early necrosis involving an admixture of the necrosis portion and viable neoplastic cell nests after 1 day or 3 days irradiation, which was detected insufficiently on T1WI and T2WI, could be detected in non-enhanced areas.

In this study, the Lac/Cr ratios of viable tumors in irradiation groups tended to be higher than those in control groups. Particularly, after 1 day and 3 days irradiation, the Lac/Cr ratios of viable tumors in the irradiation group were significantly higher than those in control group. In addition, after 1 day and 3 days irradiation, the Lac/Cr ratios of viable tumors tended to be higher than those of necrosis. The pathophysiological status of solid malignant tumors is characterized by pronounced tissue hypoxia and results in high levels of lactate. The lack of intracellular oxygen shifts the balance of cellular energy production from oxidative phosphorylation to glycolysis, whose end product is lactate. Some investigators reported that the elevated tumor lactate level detected by ex vivo ¹H-MRS correlated with malignant progression of the disease and prognosis in squamous cell carcinomas of the head and neck, of cervical cancers, and non-small cell lung carcinoma. However, there have been a few studies analyzing the correlation between therapeutic response and prognostic significance and tumor lactate level after radiotherapy using in vivo ¹H-MRS. In the study by Tarnawski et al. evaluating in vivo ¹H-MRS of lactate in gliomas, a high correlation between lactate signal intensity and prognosis was shown; however, in the study by Le et al. analyzing in vivo ¹H-MRS of lactate in head and neck squamous cell carcinoma after radiotherapy, the lactate level did not correlate with tumor response or locoregional control. Therefore, the usefulness of determining tumor lactate level by in vivo ¹H-MRS for predicting tumor response and prognosis has not yet been determined.

A key objective of ¹H-MRS studies is the identification of metabolic or physiological indices for predicting or detecting tumor response to radiotherapy. In the study evaluating the feasibility and accuracy of monitoring ¹H-MRS of glioma for response to radiotherapy and relapse by Laprie et al., loss of lactate peak after radiotherapy correlated with response, and its presence and stability with relapse. In addition, in the study evaluating in vivo ¹H-MRS of a tumor model using a RIF-1 tumor after irradiation of 2, 4, and 20 Gy by Bhujwalla et al., significant decreases of lactate levels were revealed at all doses at 48 hours after irradiation. Bhujwalla et al. supposed that the decline in lactate might be caused by reoxygenation of the tumor due to improvement of blood flow. Therefore, Lactate may reflect the hypoxia or impediment of blood flow of tumor before radiation; decrease in level of this metabolite may reflect reoxygenation or improvement of blood flow following radiation. Consequently, it was thought that monitoring lactate peak of in vivo ¹H-MRS may be useful for predicting tumor response at early stage of after irradiation.

In the study evaluating in vivo ³¹P-MRS of the NU-82 mammary tumor in the first 48 hours following 10 or 20 Gy irradiation by Sijens et al., an overall decrease in ATP/Pi was found. They described the reason of results as the decrease in ATP/Pi might be caused by hypoxia of the tumor due to accumulation of necrotic tissue. In this study, after 1 day and 3 days irradiation, admixture of necrotic portion and viable neoplastic cell was observed in histological analysis, therefore, it was thought that hypoxic status of the tumor contributed to the increase in lactate at early stage after irradiation. In addition, in the study evaluating the quantitative and morphologic changes of microvasculature of CH3/Bi mouse mammary tumors after irradiation by Hilmas et al., they reported that a transient capability for improved oxygen status conceivably existed for cell of the carcinoma at various times after single-dose irradiation of 5 or 15 Gy, however, very large single-doses of 30 or 45 Gy, appear to damage tumor vascular endothelial cells severely, causing decrease in capability for exchange of essential nutrients and for improvement of oxygen status. Histological analysis in this study showed changes of the nucleus and cytoplasm of viable tumor cells and capillary dilatation and swelling of the endothelia of capillaries and arterioles at 1 day and 3 days after irradiation. Therefore, it was supposed that either a decrease in the clearance of lactate due to an impediment of the blood flow or an impediment of the
aerobic glycolytic pathway due to hypoxia, or both, might occur in the viable cells of a tumor in the early stage after irradiation, which might cause the elevation of the lactate level in the viable tumor in this study. This would result in the elevation of the Lac/Cr ratio in the viable tumor. Therefore, the Lac/Cr ratio might be sensitive to the tumor response induced by irradiation. However, our result was the reverse of that described in the study by Bhujwalla et al who reported significant decreases of lactate levels were revealed at early stage after irradiation. It might be for this reason that our xenograft model and irradiation dose were different from their study model. A VX2 carcinoma which we used in our study was prone to necrosis, and a single fraction of 30 Gy was delivered focally to the tumor in our study.

The choline signal, which includes contributions from choline, phosphocholine, glycerol-phosphocholine, and trimethylamines, reflects cell membrane synthesis and breakdown and is characteristically elevated in tumors, that is, the choline level increases with increased tumor proliferation and tumor cell density. In addition, the breakdown of tumor membrane turnover due to the development of tumor necrosis resulted in a continuous decrease of the Cho/Cr ratio, and the Cho/Cr ratio is an important marker of tumor activity. However, in this study, there was no statistically significant difference in the Cho/Cr ratio between the irradiation and control groups. A VX2 carcinoma is characterized by fast tumor growth and the occurrence of central necrosis. In this study, central necrosis was recognized in 3, 7, and 14 days control groups. Although necrosis of irradiation groups was significantly larger than that of control groups, it was thought that in control groups, the breakdown of tumor membrane turnover due to the development of necrosis was happened same as the irradiation groups. Therefore, in this study, the Cho/Cr ratio might be not useful to predict the primary effects of radiotherapy in comparison with the control groups.

In conclusion, HR-MRI, which correlated with the histopathological findings and enabled us to detect even small areas and early stages of tumor necrosis, was a suitable method to determine the therapeutic response at the early stage after radiotherapy. In addition, the Lac/Cr ratio obtained from viable tumors by in vivo 1H-MRS might be a sensitive marker of the tumor damage induced by radiotherapy, and might be useful for predicting therapeutic response at the early stage after radiotherapy. Therefore, it was suggested that HR-MRI and 1H-MRS are useful methods for monitoring of early therapeutic response of radiotherapy.

REFERENCES