MAJOR PAPER

MR Imaging of Brain Injury Induced by Carbon Ion Radiotherapy for Head and Neck Tumors

Riwa KISHIMOTO1*, Jun-etsu MIZOE1, Shuhei KOMATSU1, Susumu KANDATSU1, Takayuki OBATA2, and Hirohiko TSUJI1

1Center Hospital, 2Department of Medical Imaging, National Institute of Radiological Sciences
4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan
(Received September 13, 2005; Accepted November 2, 2005)

To clarify the characteristics of magnetic resonance (MR) imaging of radiation-induced brain injury following carbon ion radiotherapy and to observe the changes in lesions over time, we evaluated 40 patients with radiation-induced brain injury from carbon ion radiotherapy for head and neck tumors. Their primary lesions received a radiation dose of 48 to 70.4 Gray equivalent (GyE) in 16 to 18 fractions. MR imaging of radiation-induced brain injury was graded as follows: Grade 1: change in focal white matter; focal contrast enhancement and surrounding edema; Grade 2: nonenhanced area or cystic lesion in enhanced lesion; Grade 3: focal necrosis with mass effect; and Grade 4: mass effect requiring surgical intervention. Radiation-induced brain injury appeared as early as 2 months and as late as 57 months after carbon ion therapy (mean interval, 22.2 months). MR findings of initial lesion were Grade 1 in 26 cases (65.0%), Grade 2 in 13 (32.5%), and Grade 3 in 1 (2.5%). Brain injury was always found in the radiation field initially, but cystic lesion and edema later extended outside the field in 10 cases (25.0%). In follow-up MR studies, size of edema or enhanced lesion was reduced in 17 patients (42.5%) without treatment. Two cases with large cystic lesions required surgery. Improvement of radiation-induced brain injury was observed more often than had been previously described. Because edema and cystic lesion can occasionally extend outside the radiation field, such findings do not exclude the possibility of radiation-induced brain injury. Careful observation is recommended because cystic lesions can enlarge enough to require surgical treatment in some cases.

Keywords: MR imaging, radiation brain injury, carbon ion therapy

Introduction

The Heavy Ion Medical Accelerator in Chiba (HIMAC) is the world’s first heavy ion accelerator complex dedicated to medical use in a hospital environment.1 We have performed carbon ion radiotherapy for head and neck tumors since 1994 with this equipment.2 Carbon ion beams containing high-linear energy transfer (high-LET) components have the advantage of favorable dose localization, providing increasing biological effect with depth. Thus, an isodose can be distributed to conform closely to the target volume, allowing a high dose to the tumor while minimizing irradiation to surrounding normal tissue.3

Radiation-induced brain injury is classified as acute, early delayed, or late reaction according to its timing after radiotherapy. Acute injury occurs during or just after completion of radiation therapy; early delayed injury develops a few weeks (up to about 12 weeks) after radiation therapy; and late injury develops a few months to several years after irradiation.4,5 Late radiation injury is one of the most serious complications of radiation therapy of head and neck tumors. The spectrum of late radiation injury ranges from faint damage to white matter to complete ischemic necrosis. Radiation necrosis is thought generally to be progressive and irreversible.4,5

In general, the diagnosis of radiation brain injury is not confirmed by biopsy; evidence is usually obtained by follow-up observation and image findings such as those from computed
tomography (CT) and magnetic resonance (MR). Because brain necrosis from radiation may appear as an aggressive lesion on imaging studies, recurrence of brain tumor may not be reliably differentiated from radiation necrosis. Because head and neck tumor rarely metastasize to the brain after radiation therapy, the diagnosis of radiation necrosis is relatively reliable unless there is direct invasion from a primary tumor. Patients with head and neck tumors are therefore prime candidates for the evaluation of brain injury from radiation.

The purpose of our study was to clarify the characteristics of MR imaging of radiation brain injury following carbon ion radiotherapy for head and neck tumors by comparing them with findings of brain injury following conventional photon radiotherapy. We also examined changes in lesions over time.

**Materials and Methods**

This was a retrospective study of 40 patients (19 men, 21 women; age range: 21 to 76 years; mean age: 52.8 years) with radiation brain injury following carbon ion radiotherapy for head and neck tumors. Our institutional review board did not require the patients’ informed consent for this study. During this period, we administered carbon ion radiotherapy to 281 patients with head and neck tumors. We excluded from study patients with invasion of the brain because of the difficulty in differentiating between radiation necrosis and tumor in these patients. Consequently, none of the patients had parenchymal brain lesions before carbon ion radiotherapy, although in some cases, tumor had invaded to the skull or meninges. The sites and histopathology of the primary lesions are summarized in Tables 1 and 2. The primary lesions received a radiation dose of 48 to 70.4 Gray equivalent (GyE) in 16 to 18 fractions. Patients with malignant melanoma received systemic chemotherapy per a DAV protocol consisting of dacarbazine (DTIC, 120 mg/m², Days 1, 2, 5), nimustine hydrochloride (ACNU, 70 mg/m², Day 1) and vincristine (VCR, 0.7 mg/m², Day 1) in combination with carbon ion radiotherapy.

Follow-up after the occurrence of radiation injury was 6 to 46 months (average, 24 months). Patients usually underwent MR examination monthly the first 3 months after carbon ion radiotherapy, then every 2 to 4 months until 2 years after radiotherapy, and every 3 to 6 months thereafter, according to the patient’s condition.

The diagnosis of radiation brain injury was based on MR findings of an area of high intensity on T2-weighted images and an area of enhancement in post-contrast images without direct continuity from the primary lesion and appearing after carbon ion radiotherapy within the irradiation field and that 1) either decreased or showed no change in size for at least 6 months or 2) showed no evidence of malignancy or abscess during follow-up observation after 12 months or more, even though the lesion itself might be progressive. 11C-Methionine positron emission tomography (MET-PET) was also referred in questionable cases. MR imaging of radiation brain injury was graded according to the LENT SOMA scoring system as follows: Grade 1: change in focal white matter; focal contrast enhancement and surrounding edema; Grade 2: non-enhanced area or cystic lesion in the enhanced lesion; Grade 3: focal necrosis with mass effect; and Grade 4: mass effect requiring surgical intervention.

MR study was performed with a 1.5T MR imaging unit (Magnetom Vision; Siemens Medical Systems, Eriangen, Germany) with a standard head coil. The following imaging sequences were performed: axial T1-weighted spin echo (SE) image (repetition time ms/echo time ms = 735/14); axial T2-weighted fast SE image (4000/96); axial T1-weighted post contrast SE image (735/14); and coronal T1-weighted post contrast fat suppressed SE image (988/14). These MR images were obtained with a 4-mm (axial section) or 5-mm (coronal section) slice thickness and 2-mm inter-

### Table 1. Site of primary lesion

<table>
<thead>
<tr>
<th>Site of primary lesion</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Nasal cavity/Paranasal sinus</td>
<td>16</td>
</tr>
<tr>
<td>Skull base/Temporal bone</td>
<td>12</td>
</tr>
<tr>
<td>Nasopharynx, Parapharyngeal space</td>
<td>4</td>
</tr>
<tr>
<td>External/Middle ear</td>
<td>3</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>3</td>
</tr>
<tr>
<td>Orbital fossa</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 2. Histopathology of the primary lesion

<table>
<thead>
<tr>
<th>Histopathology of the primary lesion</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>8</td>
</tr>
<tr>
<td>Chordoma</td>
<td>6</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Meningioma</td>
<td>4</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>1</td>
</tr>
</tbody>
</table>
Fig. 1. Interval between completion of irradiation and detection of radiation brain injury on magnetic resonance (MR) imaging. Twenty-seven point five percent of radiation injury cases appeared within 12 months, 62.5% within 24 months, and 85% within 36 months.

Results

The interval between completion of irradiation and recognition of radiation injury in the MR study varied from 2 to 57 months (mean interval, 22.2 months) (Fig. 1). The average dose of irradiation at the initially detected site was 50 GyE, more than 90% of isodose in 30 cases (75%) and 50 to 90% of isodose in 10 cases (25%).

MR findings of the initial lesions were Grade 1 in 26 cases (65.0%), Grade 2 in 13 (32.5%), and Grade 3 in 1 (2.5%). These lesions were found in both white and gray matter. Multiple lesions, including bilateral lesions or lesions in different lobes, were found in 21 cases (52.5%). These did occasionally fuse afterward.

In 11 of the 26 Grade 1 cases, a nonenhanced area developed afterward and became Grade 2 and more. Only 15 cases remained Grade 1, and 25 (62.5%) of 40 cases became Grade 2 and more (Fig. 2). Cysts formed in 5 cases (12.5%). Although surrounding edema and cyst formation extended outside the radiation field in 10 cases (25%), the contrast-enhanced lesion was always in the radiation field. Mass effect, indicative of Grade 3, was seen in 9 cases (22.5%) in follow-up examination. Two cases (5%) progressed to Grade 4 and received surgery (Fig. 2). No malignancy was found on biopsy during surgery in these 2 cases.

MR findings in 17 cases (42.5%) showed some improvement at least once in the observation period (Fig. 3). In these cases, radiation injury was found 3 to 31 months after irradiation. Ten of these 17 cases received no treatment for radiation brain injury. There was no definite relation between the clinical course of radiation injury and the radiation dose or the time interval from irradiation to onset.

Eleven cases (27.5%) showed some clinical symptoms, such as vertigo, headache, and convulsion, and 14 cases (35%) were treated with steroids. The other 29 patients had no symptoms, and 26 patients required no treatment for cerebral radiation injury.

Discussion

Little evidence is available in the literature on the exact rate of improvement of radiation brain injury. Many earlier reports claim that late radiation injury is generally irreversible, but one-third of our cases showed some improvement of areas of contrast enhancement or surrounding edema in follow-up MR studies. More than half of the cases that showed improvement had received no treatment for radiation brain injury. Because radiation injury in these cases appeared 3 to 31 months after radiation therapy, these lesions were not considered early or early-delayed radiation-induced changes.

Radiation therapy induces fibrinoid necrosis of the vascular walls followed by thrombosis, infarction, and coagulation necrosis of the surrounding parenchyma. The contrast enhancement associated with radiation necrosis results from radiation-induced endothelial damage, which leads to the breakdown of the blood-brain barrier. The improvement in our MR findings suggest that these lesions are reversible vascular changes or parenchymal abnormalities that do not lead to complete necrosis.

We have no evidence why recovery from radiation injury is better after carbon ion radiotherapy than after conventional photon therapy. We think one reason is that the irradiated volume of normal brain is relatively small in our patients because of the excellent dose-localizing properties of carbon ion therapy. If the volume of damaged brain is small, the blood supply from surrounding tissue,
Fig. 2. A 47-year-old man treated with carbon ion radiotherapy for undifferentiated carcinoma of the ethmoid sinus. (a) Dose distribution on planning computed tomography (CT). (b) Axial T₂-weighted and (c) contrast-enhanced T₁-weighted magnetic resonance (MR) images 26 months after radiation therapy show small spots of enhancement (arrow) in the left frontal lobe and surrounding edema (long arrow) (Grade 1), which is in the area of 50% isodose. (d) Coronal contrast-enhanced T₁-weighted MR image 36 months after radiation therapy shows nonenhanced area (asterisk) in the enlarged enhancement (Grade 2). (e) Coronal contrast-enhanced T₁-weighted MR image 56 months after radiation therapy shows a cystic lesion (arrow) with minimal mass effect (Grade 2 to 3). (f) Coronal contrast-enhanced T₁-weighted MR image 62 months after radiation therapy shows a large cystic lesion with mass effect requiring decompression surgery (Grade 4). Cystic lesion has extended outside the radiation field.

which is presumed to help damaged tissue to recover, is preserved.

Our study included 40 patients with radiation brain injury of 281 patients with head and neck tumors who received carbon ion radiotherapy. It is difficult to estimate the incidence of radiation injury because not all of the head and neck cases received irradiation to the brain, and we excluded cases in which tumors had invaded the brain parenchyma. The manifestation of radiation cerebral injury in these 40 cases was acceptable because, as noted, most tumors invaded the skull or meninges and irradiation to the brain parenchyma could not be avoided to accomplish treatment despite the excellent dose distribution of the carbon ion beam.

The interval between carbon ion radiotherapy and the detection of radiation injury was relatively longer than in conventional photon beam therapy. In a published review, 74% of cases of cerebral radiation injury from photon radiotherapy appeared within 24 months. In our study, 60% of the cases appeared in the same period.

The average dose of irradiation at which radiation injury initially developed was 50 GyE. Necrosis following photon radiotherapy has been reported with conventionally fractionated total doses of 50 to 60 Gy. This is almost the same as our results, although our cases included faint changes in white matter.

Even though radiation brain injury always developed in the irradiation field first, edema and cystic lesions occasionally extended outside the radiation field. When such lesions are detected outside the radiation field in imaging studies, a
Fig. 3. A 52-year-old man treated with carbon ion radiotherapy for adenoidcystic carcinoma of the nasal cavity. (a) Axial T2-weighted and (b) contrast-enhanced T1-weighted axial magnetic resonance (MR) images 20 months after radiation therapy show marginal enhancement (arrow) and surrounding edema (long arrow) in the inferior-medial part of the bilateral frontal lobe. On (c) T2-weighted and (d) contrast-enhanced T1-weighted MR images 24 months after radiation therapy, enhancement and edema in the left frontal lobe became small. This patient received no treatment for cerebral radiation injury.

diagnosis of radiation injury cannot be ruled out.

In 2 cases, which required surgery, the cystic lesion enlarged and caused a strong mass effect. Because cystic lesions can become large and may occasionally require surgical decompression, careful observation is needed. These cystic lesions have a thin, faintly enhanced rim after administration of contrast material. They can be differentiated from abscesses because the latter have thick and strongly enhanced walls.

It has been suggested that neurons are relatively insensitive to radiation and, so, gray matter is less damaged by radiation.\textsuperscript{9,11} In the present study, gray matter was also involved, and this was considered to result from the topographically high doses received by the surface of the brain in our study.

In a previous report of radiation brain injury induced by photon radiation therapy,\textsuperscript{9} foci with heterogeneous signal intensity consistent with necrosis were detected in 37 (65\%) of 57 lobes. This finding is thought to be consistent with Grade 2 in our study and constituted 62.5\% of our cases, almost identical results. In the same article, cystic changes were present in nine (26.4\%) and a mass effect in 12 (35.3\%) of 34 patients. Although direct comparison cannot be made because Chan’s group
counted the number of lesions, and not cases, with regard to cystic change, it does appear that these percentages are relatively higher than our results of 12.5% and 22.5%, respectively.

About three-fourths of our patients had no symptoms, and two-thirds required no treatment for radiation brain injury. Most patients of our study were considered to have tumor invasion adjacent to the brain, a condition for which there was no other effective local treatment. In view of these dire conditions, this incidence of complications as a result of carbon ion radiotherapy is considered acceptable.

A major problem in the diagnosis of radiation injury is differentiating it from recurrent tumor. Some investigators reported the usefulness of MET-PET, magnetic resonance spectroscopy (MRS), and DWI. MET-PET and MRS are not widely available yet. With regard to DWI, it should be noted that a precise evaluation of the apparent diffusion coefficient (ADC) is sometimes difficult because of the strong artifact around the skull base in echo planar imaging. It is important to know the characteristic MR findings of radiation brain injury. Radiation cerebral injury should be considered a possibility in the differential diagnosis of enhancing lesions in the radiation field.

The major limiting factor in this study was the lack of pathologic evidence. We confirmed the absence of tumor pathologically in only 2 cases of Grade 4. However, we continued our follow-up for at least 6 months in cases whose lesions were reduced in size or remained without changes and for more than 12 months in cases whose lesions increased in size. It is therefore reasonable to claim that our diagnosis of radiation injury is reliable.

Conclusion

Radiation brain injury associated with carbon ion radiotherapy always occurred in the radiation field initially, but cystic lesions and edema could extend outside the radiation field later. Careful observation is recommended because in some rare cases, cystic lesions will increase in size so that surgery will be required. On the other hand, the size of edema or enhanced lesion can occasionally reduce without treatment. For the diagnosis and treatment of radiation brain injury, it is important to be familiar with the MR characteristics of such lesions.

References