Cerebral Metastasis in Patients with Uterine Cervical Cancer

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We report on eight patients who developed brain metastases following uterine cervical cancer. The mean interval between diagnosis of the primary cancer and diagnosis of the brain metastasis was 28.4 months (range: 6.1–61.8 months). Nausea and vomiting due to increased intracranial pressure were the most frequent symptoms. Surgical excision of the brain lesions, followed by postoperative radiotherapy, was performed in three patients. The other five patients received only cranial radiotherapy. When the metastatic brain lesions were detected, other distant metastatic lesions were confirmed at the same time in five patients. The median survival time after diagnosis of the brain metastases was only 3.0 months.

Key words: uterine cervical cancer – brain metastasis – survival

INTRODUCTION

Uterine cervical cancer is a common malignancy among Japanese women. It is reported to be the 11th most frequent cause of cancer death in women, with 1911 deaths in 1993 (1). This disease frequently metastasizes to the retroperitoneal lymph nodes because of the rich lymphatic network of the cervix. However, brain metastasis from cervical cancer is extremely rare. There have been few reports clarifying prognosis and the effects of therapy on brain metastases due to cervical cancer.

This report describes symptoms and signs, metastasic sites in the brain, treatment modalities, survival time and other factors in eight patients with brain metastases from cervical cancer.

PATIENTS AND METHODS

We reviewed the records, covering the 20 year period from 1974 to 1994, of patients who had invasive uterine cervical cancer and who were treated at the National Cancer Center Hospital in Japan. The following data were retrieved from the medical records: method of initial treatment, stage of disease, histopathological findings, treatment modality at the time of relapse, site of the brain metastasis, neurologic complications and results of the follow-up. Prior to 1978, diagnosis was made by means of isotope brain scan and angiography. Thereafter, brain CT and MRI scanning have been used to establish the presence of brain metastases. Mean survival time was calculated using the Kaplan–Meier method and estimated from the initial dates of therapy.

RESULTS

PATIENT CHARACTERISTICS

Eight cases of brain metastasis have been found among the 1961 patients. Patient characteristics are listed in Table 1. The mean age at initial therapy was 61.4 years (range: 41–73 years). Two patients with stage IB1, one patient with stage IB2, four patients with IIB and one patient with IIIB were studied. Initial treatment for the eight patients consisted of: surgery alone (two patients), radiotherapy (two patients), radiotherapy and surgery (four patients). The histological findings were: poorly differentiated squamous cell carcinoma (four patients), moderately differentiated squamous cell carcinoma (one patient), poorly differentiated adenocarcinoma (two patients) and undifferentiated carcinoma (one patient). All these patients were treated initially with radiotherapy and/or craniotomy. The median interval between diagnosis of the primary cancer and that of brain metastasis was 28.4 months (range: 6.1–61.8 months).

SYMPTOMS AND SIGNS OF BRAIN METASTASIS

The presenting symptoms are summarized in Table 1. Nausea and vomiting due to increased intracranial pressure were the most frequent symptoms (four patients). Headache was the second most frequent symptom (three patients). Convulsion was present in two patients. Two patients had hemiplegia. Three out of the eight patients suffered from two symptoms.
Table 1. Features of patients with uterine cervical carcinoma metastatic to the brain

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Clinical staging</th>
<th>Initial therapy</th>
<th>Histology</th>
<th>Interval</th>
<th>Symptoms and signs</th>
<th>Diagnostic method</th>
<th>Distribution of brain mets</th>
<th>Nos of mets</th>
<th>Craniot.</th>
<th>Radiation approach</th>
<th>Other distant mets</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>IIIB RT P/D SCC 6.1</td>
<td>Hemiparesis headache</td>
<td>Isotope</td>
<td>Rt. parietal lobe</td>
<td>1</td>
<td>Done</td>
<td>WB (30Gy)</td>
<td>Peritoneum, pleura, lt. subclavicular LN</td>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>IIB OP+RT U/D C 61.8</td>
<td>Hemiparesis</td>
<td>Isotope</td>
<td>Lt. frontal lobe, temporal lobe</td>
<td>3</td>
<td>Done</td>
<td>WB (35Gy)</td>
<td>Lt. cervical LN</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>IIIB RT P/D AD 28.7</td>
<td>Nausea, vomiting headache</td>
<td>CT</td>
<td>Lt. temporal lobe, Lt. parietal lobe</td>
<td>2</td>
<td>Done</td>
<td>WB (30Gy)</td>
<td>Lung</td>
<td>10.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>54</td>
<td>IIB OP P/D AD 8.9</td>
<td>Nausea, vomiting headache</td>
<td>CT</td>
<td>Rt. occipital lobe</td>
<td>2</td>
<td>None</td>
<td>WB (40Gy)</td>
<td>Pelvis, 7th rib, diaphragm</td>
<td>1.9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>60</td>
<td>IIB OP+RT P/D SCC 53.5</td>
<td>Nausea, vomiting</td>
<td>CT</td>
<td>Lt. Rt. frontal lobe, Lt. parietal lobe</td>
<td>4</td>
<td>None</td>
<td>WB (40Gy)</td>
<td>Long, 3rd lumbar</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>IIB OP M/D SCC 14.3</td>
<td>Nausea, vomiting</td>
<td>CT</td>
<td>Lt. occipital lobe</td>
<td>1</td>
<td>None</td>
<td>WB (40Gy)</td>
<td>Pelvis</td>
<td>12.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>36</td>
<td>IIB OP+RT P/D SCC 20.5</td>
<td>Convulsion</td>
<td>CT</td>
<td>Lt. frontal lobe</td>
<td>1</td>
<td>None</td>
<td>WB (35Gy)</td>
<td>Skin</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>59</td>
<td>IIB2 OP+RT P/D SCC 33.8</td>
<td>Convulsion</td>
<td>CT</td>
<td>Rt. temporal lobe</td>
<td>1</td>
<td>None</td>
<td>WB (40Gy)</td>
<td>Lt. cervical LN</td>
<td>22.6</td>
<td></td>
<td></td>
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</table>

Age, age at the time of initial therapy; interval, interval between diagnosis of primary tumor and CNS symptoms; diagnostic method, diagnostic method for brain metastases; mets, metastases; survival, survival time from the beginning of treatment for brain metastasis; isotope, isotope brain scan and angiography; RT, radiotherapy; OP, operation; P/D, poorly differentiated; M/D, moderately differentiated; U/D, undifferentiated; SCC, squamous cell carcinoma; C, carcinoma; AD, adenocarcinoma; WB, whole brain; Lt, left; Rt, right; LN, lymph node

**NUMBERS AND SITES OF BRAIN METASTASES**

As to the numbers of brain lesions, a single lesion was found in each of four patients, two lesions were found in two further patients, three lesions were found in one patient and four lesions were found in the remaining patient. In Patient 2, brain metastasis was diagnosed by isotope brain scan and angiography, and, at first, only one lesion was found. As a result of craniotomy, we found two other unexpected lesions. Patient 3 had two lesions. These were resected at the same time because of their close proximity. The site of brain metastasis in all eight patients was the supratentorial region.

**TREATMENT OF BRAIN METASTASIS**

Surgical excision of the brain metastasis followed by postoperative radiotherapy was performed in three patients. The other five patients received only cranial radiotherapy. Radiation doses were 30 Gy in 10 fractions over 2 weeks or 40 Gy in 20 fractions over 4 weeks, to the whole brain area.

**METASTASIS IN OTHER DISTANT ORGANS**

The extent of the disease was evaluated for all patients. Those with brain metastases had metastases in other distant organs: bone, lung, skin, pleura, peritoneum and lymph nodes. Three patients who had undergone craniotomy were found to have distant metastases just after craniotomy.

**SURVIVAL**

The median survival time after diagnosis of brain metastasis was 3.0 months, ranging from 1.8 months to 22.6 months; two patients survived more than 12 months after treatment for brain metastases in spite of the fact that they had distant metastases. The survival curve is given in Fig. 1.

**DISCUSSION**

Brain metastasis is common in patients with leukemia, lymphoma, lung and breast cancers (2). However, gynecologic malignancies comprise a small percentage of central nervous system metastases, but 0.52% of patients reported as having uterine cervical cancer also had brain metastases (3).
In general, headache and hemiplegia are the most commonly reported symptoms of brain metastasis (4). However, nausea and vomiting were the most frequently encountered symptoms in our study; the next most frequent were convulsions and hemiplegia. These symptoms were severe and occurred suddenly. For this reason, it is very important to suspect brain metastasis and examine precisely, even if patients show signs and symptoms of cerebrovascular disease.

In clinical studies covering all cancers, 80% of brain metastases were located in supratentorial regions (5). The preference for this location has been reported as being related to the regional brain weight and blood flow. In all our cases, too, tumors were located in the supratentorial area. Their symptoms and signs were caused mainly by the focus of metastasis and by the extended edema in the surrounding tissue.

The treatment of brain metastases was either radiation only or surgery combined with adjunctive postoperative radiation therapy. At the time covered by this study, it was thought that only selected patients should undergo surgery. Surgical indications (5) were as follows: 1, diagnostic uncertainty; 2, solitary or adjacent multiple metastases; 3, life-threatening or critically located multiple metastases; 4, recurrent or persistent symptoms after nonsurgical therapy; 5, treatment of metastatic complications (hemorrhagic, infectious, CSF obstruction) and 6, placement of devices for intrathecal access.

Subsequent to the reviewing of past research papers, there have been three randomized trials on the role of surgery in the treatment of solitary brain metastases (6–8). Two of these controlled studies confirmed that total resection of the solitary metastatic lesion, combined with adjunctive postoperative radiation therapy, improved survival as against the use of radiation only (6,7). However, one randomized trial showed no difference between these two approaches (8).

In our cases, three patients underwent craniotomy and two of them were diagnosed with isotope brain scan and angiography. These two patients had multiple lesions, which in one case was discovered only after craniotomy. Total resection was achieved in these three patients. Survival time in the three patients who underwent craniotomy combined with postoperative radiation were 7.5, 4.1 and 10.3 months. In patients treated with radiation only, median survival time was 2 months. Although the number of cases was too few, and several other limitations need to be considered, we did find a difference between the effects of the two therapeutic approaches.

It was very encouraging to us that a reduction in or disappearance of metastatic lesions was evident in all patients who showed either remission or disappearance of symptoms and signs. The overall median survival time was only 3.0 months and the prognosis was consistently very poor.

For this reason, it is essential to use other more efficient modes of treatment, including radiation surgery (γ-knife) and stereotactic radiotherapy, which have been developed to control metastatic brain tumors.

After July 1991, stereotactic radiotherapy came into service to treat brain tumors in our hospital. When the MRI technique reveals solitary metastasis in the brain but does not indicate metastasis transfer to other distant organs, the use of stereotactic radiotherapy prolongs survival.

When considering treatment strategy for metastatic brain lesions, other distant metastatic lesions should always be considered. Five out of our eight patients with brain metastases also showed distant metastases.

Metastatic brain lesions are only partial signs of systemic cancer, so efficient treatments are vitally needed to control both these and other metastatic tumors and to prolong survival.

References