Intracranial Metastases from Carcinoma of the Cervix: Report of 4 Cases and Review of the Literature

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ABSTRACT
Although the brain is a common site of blood-borne metastases in many cancers, a tumour in the brain secondary to cervical cancer is very rare. This report describes 4 patients with brain metastases from cancer of the cervix who were identified from 674 patients with invasive cervical cancer at one institution in Delhi, India, between January 2001 and December 2003. This report presents and discusses these 4 cases and reviews the literature for the optimal management of such cases.

Key Words: Brain neoplasms; Cervix neoplasms; Neoplasm metastasis; Radiotherapy; Surgery

INTRODUCTION
Cancer of the uterine cervix is the second most common cancer among women worldwide. In developing countries such as India, it is the most common cancer among women. It is also a major cause of cancer-related morbidity and mortality. Owing to early detection and improved therapeutic strategies (i.e., improved radiation techniques, radiation dose fractionation schedules, chemotherapy regimens, and surgical skills), there has been improved tumour control as well as prolonged survival among patients with carcinoma of the cervix. As the survival time is becoming more prolonged, however, the incidence of distant metastases is increasing.

Cervical cancer characteristically spreads to adjacent structures by contiguous dissemination, to pelvic and para-aortic nodes through the lymphatic system and to distant organs by the haematogenous route. Studies have suggested that advanced-stage disease, bulky disease, endometrial extension, and lymph node metastasis are poor prognostic indicators that are associated with an increased rate of distant metastasis.1-3 The sites that are most commonly affected are the lungs, liver, and bones, in decreasing order of frequency.4 Metastases to the brain are rare; only a few cases have been reported in the literature.1,2,4,5 From January 2001 to December 2003, the Department of Radiation Oncology, Lok Nayak Hospital, Delhi, India, has encountered 4 patients with brain metastases originating from cancer of the cervix among 674 patients with invasive cervical cancer. The patients developed brain metastases 37, 19, 13, and 15 months after the primary diagnosis was made. All patients had multiple brain metastases.

CASE REPORTS
Case 1
A 32-year-old woman, a mother of 3 children, presented in December 2001 complaining of a white discharge and bleeding from the vagina for the previous 8 months. Routine blood investigations and the chest X-ray yielded normal results. Ultrasonography of the abdomen and pelvis was suggestive of a 5- x 6-cm mass in the cervix and right-sided gross hydronephrosis. Biopsy of the cervical mass revealed poorly differentiated squamous cell carcinoma. After thorough investigations, a diagnosis of cancer of the cervix of International Federation of Gynecology and Obstetrics (FIGO) stage IIIb was made.

The patient was treated with radiation therapy from February 2002 to March 2002. She received 50 Gy by conventional fractionation to the whole pelvis by the anteroposterior technique using a cobalt-60 machine. This treatment was followed by intracavitary radiation therapy at 30 Gy by a low–dose rate (LDR) machine in...
a single fraction. She was followed up regularly and found to be locally disease-free.

In December 2004, however, the patient developed severe headache in the frontal region, as well as nausea. Her chest X-ray was normal but computed tomography (CT) of the brain revealed multiple brain metastases. Neurological examination results were normal. The patient was given palliative radiotherapy to 30 Gy in 10 fractions. Ten weeks after radiotherapy, she experienced complete relief of headache but complained of 1 episode of haemoptysis, chest pain, and anorexia. Chest X-ray and CT of the thorax revealed metastasis in the upper zone of the left lung for which she received palliative radiotherapy in March 2005. She is asymptomatic and is being regularly followed up.

**Case 2**

A 60-year-old woman, a mother of 6 children, presented in November 2002 complaining of a foul-smelling watery discharge and bleeding from the vagina. She gave a history of weakness, anorexia, and weight loss. At examination, she was pale-looking and had a growth that involved the cervix and upper third of the vagina, as well as thickening of the bilateral parametrium up to the lateral pelvic wall. Routine blood and urine examinations yielded normal results. The chest X-ray was normal. Ultrasonography of the abdomen and pelvis revealed 5- x 4-cm mass in the region of the cervix and bilateral mild hydronephrosis. Biopsy examination revealed squamous cell carcinoma that was moderately differentiated.

A diagnosis of cancer of the cervix of FIGO stage IIIb was made. She received external radiation therapy of 50 Gy by conventional fractionation to the whole pelvis by the anteroposterior technique on a cobalt-60 machine, followed by intracavitary radiation at 30 Gy using an LDR machine. She was followed up for 6 months after radiotherapy. She was locally disease-free thereafter but was temporarily lost to follow-up.

The patient presented again in June 2004 (15 months after treatment) complaining of headache and vomiting. Neurological examination results were normal. A vaginal examination revealed recurrent cervical disease. Blood test results and the chest X-ray were normal. Fundus examination showed disc oedema. CT of the brain revealed multiple hypodense space-occupying lesions that were suggestive of brain metastases. The patient was given palliative radiotherapy to 30 Gy in 10 fractions, but died suddenly after receiving the third fraction.

**Case 3**

A 56-year-old woman received a diagnosis of moderately differentiated squamous-cell carcinoma of the cervix of grade III, FIGO stage IIB in December 2002. She received 50 Gy of radiation by conventional fractionation to the whole pelvis by the anteroposterior technique with a cobalt-60 machine, followed by intracavitary radiation therapy at 30 Gy using an LDR machine. During follow-up, she had residual disease in the pelvis, for which she received 6 courses of chemotherapy using bleomycin, ifosfamide, and cisplatin, but this treatment achieved little response. She was regularly followed up.

The patient presented again in January 2004 (4 months after treatment) complaining of headache and weakness in the left side of the body. Neurological examination revealed left-sided hemiparesis. A vaginal examination revealed residual disease. Blood investigations yielded normal results but CT of the brain suggested multiple brain metastases. The patient received palliative radiotherapy to 30 Gy in 10 fractions and was also given symptomatic treatment. She died 2 months later.

**Case 4**

A 38-year-old woman, a mother of 3 children, presented in December 2003 with complaints of post-coital bleeding, a foul-smelling watery discharge, and bleeding from the vagina for 3 months. At examination, she was pale-looking and had a growth involving the cervix and upper third of the vagina and bilateral parametrium up to the lateral pelvic wall. Routine blood and urine examinations yielded normal results. The chest X-ray was normal. Ultrasonography revealed a 6.0- x 4.5-cm mass in the region of the cervix, bilateral mild hydronephrosis, and 2- x 2-cm left iliac lymph nodes. Biopsy examination revealed adenocarcinoma grade 4. A diagnosis of cancer of the cervix of FIGO stage IIIb was made.

The patient received external radiation therapy to 40 Gy by conventional fractionation to the whole pelvis and an additional 10 Gy with midline shielding by the anteroposterior technique using a cobalt-60 machine, followed by intracavitary radiation to 30 Gy using an LDR machine, with weekly administration of cisplatin 30 mg. She showed good response to treatment but had persistent local cervical induration at the end of radiation therapy. Contrast-enhanced CT of the abdomen after
5 months of treatment was suggestive of enlarged para-aortic, periaortic, and aortocaval lymph nodes with right-sided hydronephrosis. She was then given radiotherapy to the para-aortic region by the 4-field technique using 45 Gy to the para-aortic region, followed by an 8-Gy boost.

Repeat ultrasonography after 2 months showed persistent abdominal lymph nodes. She received chemotherapy of cisplatin 80 mg every 21 days for 3 cycles. Response in terms of lymph node size was minimal, and local disease also persisted. She developed convulsion and weakness in the right half of the body in March 2005 (15 months after diagnosis). Neurological examination revealed decreased power in the right limbs. Vaginal examination revealed persistent cervical disease. Blood test results and the chest X-ray were normal. CT of the brain showed 2 metastatic deposits in the left temporal and occipital lobes. Symptomatic treatment was started and whole-brain irradiation was given. After 3 fractions of irradiation, the patient’s condition deteriorated, with a loss of speech and memory loss. She did not complete the radiation schedule and was taken home by her family against medical advice. At the time of writing, the patient is alive with disease and is taking steroids.

DISCUSSION

Distant metastases in patients with cervical carcinoma usually occur by the haematogenous route. In unselected series of patients with invasive cervical carcinoma, 5% to 15% had distant metastasis. In studies based on postmortem examinations, the incidence was much higher, ranging from 25% to 75%. Central nervous system metastases from cervical carcinoma are unusual. Metastases to the brain from female genital tumours comprise less than 3% of all brain metastases. Conversely, carcinoma of the cervix represents only a small fraction of total metastatic deposits in the brain. Once again, the highest reported rates of brain involvement in patients of cervical carcinoma — 1.9%, 3.2%, and 5% — come from autopsy series. Virtually all other studies cite frequencies between 0% and 1%. Among 674 patients with cervical carcinoma who were registered over a period of 3 years in the Department of Radiation Oncology, Lok Nayak Hospital, Delhi, India, from January 2001 to December 2003, the incidence of brain metastases was 0.59%. The follow-up duration in this study ranged from 1.5 years to 4.0 years (median, 2.0 years). All patients had multiple brain metastases. Dissemination to the central nervous system was thought to have occurred by the retrograde flow of tumour cells through Batson’s plexus.

A review of the available literature found only a few similar cases. In 1949, Henriksen described brain metastases in 1 (0.8%) patient after an autopsy study of patients with cervical cancer. In a study by Cormio et al, only 1.18% (14/1184) of patients with cervical carcinoma developed cerebral metastases. Kumar et al found only 0.4% (2/481) of such patients. Carlson et al reported that the incidence of metastasis from carcinoma cervix represents 15%, and that most metastases appear within 5 years of completion of therapy. Freedman et al reported a case in which a patient with cervical cancer developed brain metastases within 1 week of diagnosis. Brain metastases in cervical cancer are generally a late event that occurs as a part of a disseminated disease. The median interval between the diagnosis of cervical cancer and the documentation of brain metastases is 18 months (range, 1 week to 78 months). The patients in this study developed metastasis after 37, 19, 13, and 15 months of diagnosis.

There is a correlation between the incidence of distant metastasis and the size of the cervical carcinoma and the tumour volume. Eifel et al reported that the incidence of distant metastasis was 9% when the tumour measured less than 3 cm as opposed to 36% in patients with a tumour of more than 3 cm. All 4 patients in this study had a tumour measuring more than 4 cm at the time of presentation.

Lymph node involvement is found in 50% of patients with cervical cancer who develop brain metastases, and histology tends to be poorly differentiated. Fagundes et al reported 18 (1.4%) cases of secondary tumours of the brain among 1211 patients with cervical cancer. An analysis of the primary-stage of disease in the 18 patients found that 4 patients had stage IB disease, 3 had stage IIA, 5 had stage IIB, 6 had stage III, and none had stage IV. In the present study, 2 patients had moderately differentiated disease, while 2 had poorly differentiated disease. Three patients had stage IIB disease and 1 patient had IIB disease.

Robinson and Morris reviewed 25 cases reported in the literature. In their study, 15 cases were squamous cell carcinoma, 5 were adenocarcinoma, 3 were carcinoid tumour, 1 was adenosquamous, and 1 was mixed carcinoid/adenocarcinoma. The histological type, however,
cannot predict whether the tumour will metastasise to the brain. In the present series, 3 patients had squamous cell carcinoma and 1 had adenocarcinoma.

The most common symptoms of brain metastases from cervical cancer that have been reported include headache (34.0%), hemiparesis (25.8%), mental status change (22.7%), monoparesis (14.4%), nausea (9.2%), vomiting (8.2%), gait disturbance (5.2%), and vertigo (3.1%). In this study, 3 patients complained of headache, 1 also had nausea, 1 also complained of vomiting, and 1 also had left-sided hemiparesis; the fourth patient presented with convulsion and hemiparesis. Brain metastases must be suspected in all patients with cancer who develop signs and symptoms of raised intracranial pressure, neurological deficits, seizures, or impaired memory.

Delattre et al, on analysing the distribution of secondary tumours in the brain, concluded that brain metastases were more frequent at the frontal and parietal lobes than at the temporal or occipital lobes. All patients in this study had multiple brain metastases that involved all lobes of brain.

Badib et al have shown that patients who are treated with radiation alone are more prone than those treated with surgery or combined therapy to have distant metastases without involvement of local pelvic structures. Rotman et al in a Radiation Therapy Oncology Group study suggested that distant metastases are more likely in patients undergoing pelvic irradiation alone than those undergoing extended-field treatment (i.e., combined pelvic and para-aortic nodal irradiation). In contrast to this suggestion, Haie et al reported that there was no differences in the incidence of distant metastasis or in survival in patients treated with extended pelvic irradiation than in other patients.

Approximately 72% (485/674) of patients in this study were treated with radiation alone, whereas the remaining 18% (189/674) received chemotherapy — either neoadjuvant or adjuvant to radiation therapy. Para-aortic irradiation was performed only in patients who had intraabdominal lymph nodes either in an ultrasonogram or in a CT scan. Perez et al reported that the incidence of distant metastasis was low when the primary tumour is controlled in the pelvis; if the primary tumour is not controlled and the stage of disease is advanced, the incidence of distant metastasis is consistently high. Contradictory to this finding, the primary tumour in this study was controlled in 2 of the 4 patients. One of these 2 relapsed and the other 2 patients had persistent residual disease.

Write et al suggested that haematogenous spread of the cervical carcinoma occurs first in the lungs and then in the brain. In contrast, all of the patients in this study first had brain metastases, although 1 of them was found to also have lung metastasis later.

The majority of studies in the literature report a very poor prognosis and a short survival time for patients with brain metastases from cervical carcinoma, and they consider this to be an incurable disease with no satisfactory therapeutic guidelines. Cormio et al reported a median survival of 4 months in 14 patients and suggested that neuropsychological resection should be considered in cervical carcinoma with brain metastases in the absence of any other systemic disease or in emergency situations as a palliative therapy. Ikeda et al reported a 3-month median survival in 8 patients. Robinson and Morris discussed 1 patient who survived for 6 years after complete surgical excision and radiotherapy for a single brain metastasis from cervical cancer. Veith and Odman reported the longest survival time, of 10 years, in 1 patient with a single brain lesion.

In this study, all 4 patients had multiple brain metastases and received palliative radiation therapy to the whole brain. The first patient survived for 4 months with good symptomatic control and then she was lost to follow-up; the second patient died after receiving 3 fractions of radiation; the third patient died after 2 months of treatment; and the fourth patient’s condition worsened while she was receiving treatment but she is alive with disease.

**CONCLUSION**

Although rare, intracranial metastases are encountered in patients with cervical carcinoma because survival from the primary tumour is prolonged by the availability of improved treatment facilities. Thus, a high degree of suspicion about metastasis should always be maintained, and if patients develop symptoms, they should be subjected to thorough investigations without delay. The optimal management of cervical carcinoma with brain metastases from a review of the literature is radiotherapy. Radiotherapy improves neurological function in 50% of patients with brain metastases from solid tumours but the median survival is poor (range, 2 to 5 months) and 30% to 50% of patients die as a result.
REFERENCES