

## LATE BRAIN METASTASES FROM BREAST CANCER: CLINICAL REMARKS ON 11 PATIENTS AND REVIEW OF THE LITERATURE

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**Aims and background:** Late brain metastases from breast cancer are a rare event. Only a few cases have been reported in the English literature. The authors describe the clinical and pathological remarks, together with treatment modalities, removal extent and overall survival, of 11 patients in whom brain metastases were detected more than 10 years from the primary tumor.

**Patients and methods:** Between January 1997 and April 2001, we hospitalized 11 patients, all females, with a histologically proven diagnosis of brain metastasis from breast invasive ductal carcinoma. We defined 'late metastasis' as those metastases that appeared at least 10 years after the breast cancer diagnosis. The median age at the moment of brain metastasis diagnosis was 59 years (range, 47-70), with a median latency time from breast cancer diagnosis of 16 years (range, 11-30).

**Results:** Ten patients underwent surgery followed by adjuvant radiotherapy (whole brain radiotherapy). Two of them received, after whole brain radiotherapy, stereotaxic radio surgery treatment. One patient had stereotaxic brain biopsy, performed by neuronavigator, followed by palliative corticosteroid therapy. Median survival after brain metastasis diagnosis was 28 months (range, 3 months-4 years).

**Conclusions:** Although late brain metastases are a rare event, specific neurologic symptoms and neuroradiological evidence of a cerebral neoplasm should be correlated to the presence of a cerebral metastasis, in a patient with a previous history of breast cancer. The longer latency time from breast cancer to brain metastasis could be explained by the "clonal dominance" theory and by different genetic alterations of the metastatic cell, which could influence the clinical history of the disease.

**Key words:** breast cancer, chemotherapy, late brain metastases, radiotherapy, stereotactic radiosurgery, surgery.

### Introduction

Breast cancer is the first cause of death for cancer in woman. In Italy, the incidence is 60-80 new cases over 100,000 per year<sup>1</sup>. Most deaths are the result of a metastatic dissemination, the most common evolution of the neoplasm. Breast cancer metastases involve lymph nodes, skin, bone, lungs, liver and brain<sup>2</sup>. Brain metastases are diagnosed in patients with breast cancer at a rate of 10%-20%, making breast cancer the second most common source of brain metastasis, although autopsy data demonstrate that the true prevalence is 30%<sup>3</sup>.

We consider the rare event of 'late brain metastasis' of breast cancer, defined as metastases that appear at least 10 years following breast cancer diagnosis. We describe 11 consecutive cases that have come to our observation.

### Patients and methods

Between January 1997 and April 2001, we hospitalized 11 patients (all females) with a histologically proven diagnosis of brain metastasis from breast cancer (Table 1). We defined 'late metastasis' those metastases that appeared at least 10 years after the breast cancer diagnosis. Brain metastases were the first metastatic event in the clinical history of these patients, in whom there had no previous local-regional relapses. In 10 patients, there were only brain metastases, and in 1 patient there

was also an extracerebral dissemination of the disease. All patients had been previously treated for premenopausal invasive ductal breast cancer. The brain metastasis histology was matched with the breast histological specimen and confirmed the same cellular origin. The median age at the moment of the brain metastasis diagnosis was 59 years (range, 47-70). There was a median latency time from breast cancer treatment till brain metastasis diagnosis of 16 years (range, 11-30).

As regards the breast cancer TNM Status, 3 patients had been classified as T2N0M0, 3 patients as T2N1M0, 3 patients as T2N2M0 and 2 patients as T3N0M0. After histological examination of the specimens, 8 patients had grade 1 and 3 patients had grade 2. Estrogen receptor status was positive in all patients (mean value, 39.5 fmol/mg; range, 8-78). Progesterone receptors were positive in 6 patients (mean value, 15.3 fmol/mg; range, 8-22) and negative in the other 5. In 7 patients, surgical resection was made via a quadrantectomy, 4 patients underwent mastectomy and relative axillary lymphonodectomy.

All the patients underwent adjuvant local radiotherapeutic treatment based on an average value of 4800 cGy fractioned in 6 weeks (range, 4600-5000 cGy). Subsequently, all of them had been submitted to a polychemotherapy treatment with the FEC schedule. At the end of this multimodality treatment, there was an apparently total regression of the disease, according to the clinical and radiological follow-up of the patients.

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**Table 1 - Patient characteristics**

No.	Age (yr)	TNM stage	Positive lymph nodes	Estrogen receptors (fmol/mg)	Progesterone receptors (fmol/mg)	MIB 1 (%)	Grading	Breast cancer treatment	Latency time from breast cancer to brain metastases	Brain metastasis localization	Symptoms	Treatment	Exitus (mo)
1	47	T2N0M0	-	8	-	20	G 1	Quadrantectomy + RT	11 years	Right frontal lobe	Hemiparesis seizures	Surgical removal + WBRT	43
2	59	T2N0M0	-	15	-	20	G 2	Quadrantectomy + RT	11 years	Right temporal lobe	Endocranial hypertension, aphasia, seizures	Surgical removal + WBRT	40 s
3	53	T2N0M0	-	10	-	15	G 1	Quadrantectomy + RT	13 years	Right occipital lobe	Endocranial hypertension, hemianopsia	Surgical removal + WBRT	48
4	56	T2N1M0	2	32	-	25	G 1	Quadrantectomy + RT	14 years	Left frontal lobe	Hemiparesis, seizures	Surgical removal + WBRT	28
5	58	T2N1M0	2	70	8	25	G 1	Quadrantectomy + RT	13 years	Right temporal lobe	Endocranial hypertension, hemiparesis, aphasia, seizures	Surgical removal + WBRT	37
6	59	T2N1M0	1	43	22	18	G 1	Quadrantectomy + RT	15 years	Right cerebellar hemisphere	Endocranial hypertension, ataxia, seizures	Surgical removal + WBRT	28
7	60	T2N2M0	4	12	-	22	G 2	Quadrantectomy + RT	15 years	Right frontal lobe + right temporo-thalamic area + cerebellar vermian	Endocranial hypertension, hemiparesis, aphasia, seizures	Surgical removal with fronto-temporal craniotomy and suboccipital median craniotomy + WBRT + SRS	23
8	65	T2N2M0	3	52	10	24	G 1	Mastectomy + RT	21 years	Right frontal lobe + right temporo-thalamic area + cerebellar vermian	Endocranial hypertension, hemiparesis, aphasia, seizures	Surgical removal with fronto-temporal craniotomy and suboccipital median craniotomy + WBRT + SRS	15
9	70	T2N2M0	5	78	17 fmol/mg	20	G 1	Mastectomy + RT	30 years	Disseminated metastases	Endocranial hypertension, hemiparesis, hemianopsia, seizures	Betamethazone 4 mg x 2/die	3
10	63	T3N0M0	-	60	15	25	G 1	Mastectomy + RT	18 years	Left temporal lobe	Endocranial hypertension, hemiparesis, aphasia, seizures	Surgical removal + WBRT	26
11	61	T3N0M0	-	55	20	20	G 2	Mastectomy + RT	16 years	Right cerebellar hemisphere	Endocranial hypertension, ataxia, seizures	Surgical removal + WBRT	19

WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery.

The follow-up for all the patients was 10 years, and there was no regrowth of the neoplasm, tested by clinico-radiological examinations and routine serum tumor marker control.

The diagnosis of brain metastasis was based on clinical symptoms and neuroimaging, using MRI with gadolinium administration, followed in the last 5 patients by MRI spectroscopy and functional MRI to define critical areas. Histopathological examination of tumor specimens was performed in all the patients, and a comparison was made with the primary breast tumor.

Cytoreductive surgery was obtained by the use of microsurgical methods and tools, using the 'no touch technique'. The extent of the surgical removal was evaluated by the intraoperative impression of the neurosurgeons and by postoperative MRI examination with gadolinium performed within 48 h of surgery. A brain biopsy was performed with a neuronavigation system (Stealth Station-Mach 3, Sofamor-Danek) in 1 patient.

After surgical removal, we submitted all patients to whole-brain radiotherapy (WBRT), using a LINAC (30 Gy in 15 fractions of 2 Gy/day). The time between surgery and radiotherapy was 26 days (range, 23-30). The 2 patients with 3 metastases and a thalamic residual, after surgical treatment, were treated with stereotactic radiosurgery (SRS) (with a dose of 24 Gy) 16 and 18 days after surgery and 3 weeks later were given WBRT.

The postoperative clinical status was evaluated by Karnofsky performance status (KPS) and serial MRI examination, during a follow-up period that lasted until the death of the patient.

## Results

First clinical symptoms were characterized by seizures in 10 patients, endocranial hypertension symptoms in 9 patients, hemiparesis in 7, aphasia in 5, hemianopsia in 2, and ataxia in 2.

As regards the brain metastasis location, 8 patients presented a single lesion, whereas in 3 patients multiple areas were affected. The single metastasis involved in 1 patient the right frontal lobe, in 1 case the left frontal lobe, in 3 cases the temporal lobes (2 right and 1 left), in 1 case the right occipital lobe, and in 2 cases the right cerebellar hemisphere. As regards the patients with multiple metastases, 2 cases presented a supra- and infratentorial involvement with 3 lesions (right frontal lobe, right temporo-thalamic area and cerebellar vermis), and 1 patient had disseminated brain metastases.

All the patients were surgically treated, except the patient with disseminated cerebral metastasis. The latter underwent palliative corticosteroid therapy (betamethasone, 4 mg  $\times$  2/d), followed by a brain stereotaxic biopsy performed with the neuronavigator. This patient was also the only one who presented extracerebral metastases: bone (dorso-lumbar vertebrae and pelvis) and lung (multiple miliary metastases of both lungs) in-

volvement. The 2 patients with 3 metastases were operated with a fronto-temporal craniotomy and a suboccipital median craniotomy performed in the same surgery. The thalamic lesion was not removed.

Surgical removal of the brain metastases was grossly total in all the patients with single lesions. The 2 patients with multiple cerebral metastases, who had another tumor location (1.5 cm in maximum diameter) in the right thalamus, were successfully treated with SRS (with a dose of 24 Gy) 16 and 18 days after surgery and 3 weeks later with WBRT, with total regression of the lesions. The average hospitalization period after surgical treatment was 3 days. In 1 case, the patient was hospitalized for 8 days for a wound sepsis.

Median survival after brain metastasis diagnosis was 28 months, ranging from 3 months (the patients with disseminated cerebral and extracerebral metastases) to 4 years. Systemic disease led all the patients to exitus, except for the patient with disseminated brain metastases in whom death was due to endocranial hypertension.

Postoperative KPS was 90-100 in all the patients, except the 1 with disseminated metastases (KPS 60).

## Discussion

In Italy, 7 out of 100 women have during their life a breast cancer, and the neoplasm is responsible for 18% of female mortality<sup>1</sup>. The median latency between breast cancer diagnoses and brain metastasis from breast cancer is 34 months<sup>3</sup>.

We have reported our experience about patient characteristics and disease course in the presence of 'late brain metastasis' from breast cancer. We defined 'late metastasis' as those metastasis that appear at least 10 years later after breast cancer diagnosis.

Undoubtedly, this is a rare event, because only a few studies<sup>4,5</sup> have addressed late cerebral metastasis from breast cancer in the literature. However, if a patient's clinical history reports a surgical treatment for breast cancer, even if more than 10 years before, in the presence of specific neurologic symptoms and neuroradiological evidence of a cerebral neoplasm, we should always keep in mind that it might be a late cerebral metastasis of breast cancer. Those symptoms in our series are represented by endocranial hypertension (headache, vomiting), seizures, hemiparesis, ataxia, hemianopsia and aphasia. Kath and Hoffken<sup>6</sup> reported in their study that over 90% of breast cancer metastasis can be detected by medical history and clinical examination alone. Unfortunately, the finding may be of limited significance: about 45% of the patients who have a relapse in breast cancer does not return until the next regular check-up, although they have complaints<sup>6</sup>. In late brain metastasis, we have to consider a main difference: the average length of the follow-up after a breast cancer treatment is generally 10 years, so after that time many patients are lost to follow-up. For this reason, we believe that the follow-up, in patients treated for breast cancer, even with apparently total regression of the dis-

ease, should be extended beyond the routine 10 years.

The management of cerebral breast cancer metastasis is based on multimodality treatment. The aim of the surgical treatment in patients with late brain metastasis is to obtain immediate symptom relief and local control of the disease. According to our experience, surgery should not be reserved only for patients with a single brain lesion but also for patients with multiple cerebral metastases (if they are not more than 3) and with systemic disease under control. Most of the lesions of our series were surgically and safely accessible due to neuronavigation techniques and neuroimaging fusion with functional MRI, which give us information about the exact localization of the lesion and allow us to operate without damaging healthy areas close to the lesion. Several studies have shown how patients with single brain metastases who have undergone surgical resection and WBRT have a longer survival than those who received biopsies and WBRT<sup>7,8</sup>.

The role of adjuvant WBRT has been analyzed by several studies and it is still debated, because most of them did not demonstrate any survival benefit<sup>3,9-11</sup>. The only prospective randomized study, including 9 patients with single brain metastases from breast cancer who underwent total surgical resection and who were then randomized to undergo either observation or adjuvant WBRT, revealed a significantly less frequent recurrence in the WBRT group (18%) than in the observation group (70%;  $P < 0.001$ ). However, overall survival did not differ significantly between the two groups, even though the incidence of neurologic death was also lower in the WBRT group (14% vs 44%,  $P = 0.003$ ). The conclusion was that WBRT should be given routinely<sup>12</sup>.

SRS was used in our series to operate on residual tumor in the thalamic area that surgical treatment could not safely remove. Moreover, the advantages of SRS include a lower risk of hemorrhage, infection and tumor spread, as well as lower costs because hospitalization is not required. We associated SRS to WBRT because several studies have reported a survival benefit over patients given WBRT alone and an improved performance status<sup>13,14</sup>.

The multimodality treatment is the golden standard in the treatment of brain metastases from breast cancer, al-

lowing a longer survival and a good KPS. Considering that brain metastases represent a significant health care problem, it is important to find prognostic factors and the most adequate treatment for these patients. In accordance with the results of other studies, a good KPS<sup>15,16</sup> and no signs of extracerebral metastases<sup>15-17</sup> represent the most important prognostic factors. However, a prognostic question remains: is survival in patients with late brain metastasis different from that of patients with early brain metastasis? The literature reports a median survival ranging from 16 to 21 months in patients treated with surgery plus radiotherapy<sup>18,19</sup>. Median survival in our patients was longer (28 months), but it is difficult to draw any statistical conclusion regarding the difference because of the small number of patients with late brain metastases that comprised our study group.

Metastasis is a highly selective and multistep process, involving complex interactions between tumor and host cells<sup>20-22</sup>. Survival of a minor subpopulation of cells with increased metastatic potential is favored within the population of heterogeneous primary tumor cells<sup>21,23</sup>. According to the clonal evolution theory<sup>24</sup>, this cell clone, usually the most aggressive one, has an additional selective growth advantage over its nonmetastatic counterparts: the capacity to overgrow the primary tumor and to metastasize: the "clonal dominance" theory<sup>25</sup>. Metastatic cell clones are characterized by increased genetic instability and the accumulation of genetic alterations affecting various genes. Studies have demonstrated that genetic events significantly correlate with decreased postmetastatic survival and that such alterations seem to have a specific influence on the aggressive behavior of metastases<sup>21,26,27</sup>. Possibly, late brain metastases from breast cancer have specific genetic alterations which are different from those of non-late brain metastases. It is possible that a longer latency time from breast cancer to brain metastasis is due to this biological difference, which also confers a different malignant behavior to the metastases in turn connected to a specific and probably different prognosis. In this light, it is interesting to note that, among our 11 cases, there were no grade 3 or ER-negative tumors. We hope that further studies will improve our understanding of this unusual metastasizing behavior in breast carcinoma.

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