

Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients. Clinico-pathological remarks on our series of seven cases and critical review of the literature

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ABSTRACT

Aims and background. The aim of the study was to evaluate the treatment of the extracranial metastases from glioblastoma multiforme in the elderly, discussing their uncommon occurrence and their pathogenesis.

Methods. The authors report seven cases of elderly patients (mean age, 69 years), with an initial diagnosis of cerebral glioblastoma multiforme, treated by a grossly total surgical removal and followed by adjuvant radiotherapy (64 Gy in 6 weeks, using Linac) and adjuvant chemotherapy (temozolomide both concomitant and sequential to radiotherapy).

Results. All patients presented a postoperative course characterized by good functional and clinical conditions (Karnofsky performance scale ≥ 70), which remained unchanged for a mean period of about 21 months (range, 16-23), with no neuroradiological signs of lesion regrowth. After this interval, new clinical signs occurred, and their clinical and radiological investigation showed metastatic repetitions in different sites: lung, liver, humerus and lymph nodes. All the metastases were surgically treated, but regrowth of the brain tumor and progression to deep important neural structures caused the patients' exitus after a mean interval of about 10 months (range, 8-12) from the diagnosis of metastasis.

Conclusions. We found 128 cases of extra CNS metastases in the English literature. The main features of the patients of the previous reports and of those of the present series were analyzed. The main modalities of glioblastoma multiforme spread, the few theories about the rarity of metastasis, and the probable biological, histological and immunogenetic mechanisms involved in the pathogenesis are described. Although several studies have reported a poor outcome in elderly patients, they affirm that the treatment of those with a Karnofsky performance status >60 should be just as aggressive as in younger patients. This allows them to obtain a longer survival time and to also treat metastases, which are uncommon particularly in the elderly.

Introduction

Glioblastoma multiforme (GBM) is a highly malignant glioma with a low potential to metastasize outside the confines of the central nervous system. Although the rarity of this condition is well documented in the literature, patients now have a longer survival than in the past due to improvement in treatment modalities (Figures 1-2). Thus, we can note a significant increase in the incidence of GBM cases with extracranial repetitions. The first documented metastatic glial tumor was described by Davis in 1928¹ under the diagnosis of spongioblastoma multiforme. If we consider that the

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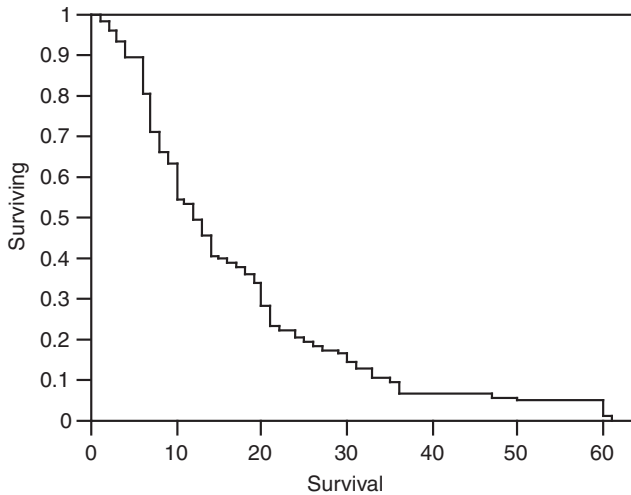


Figure 1 - Kaplan-Meier curve showing the overall survival.

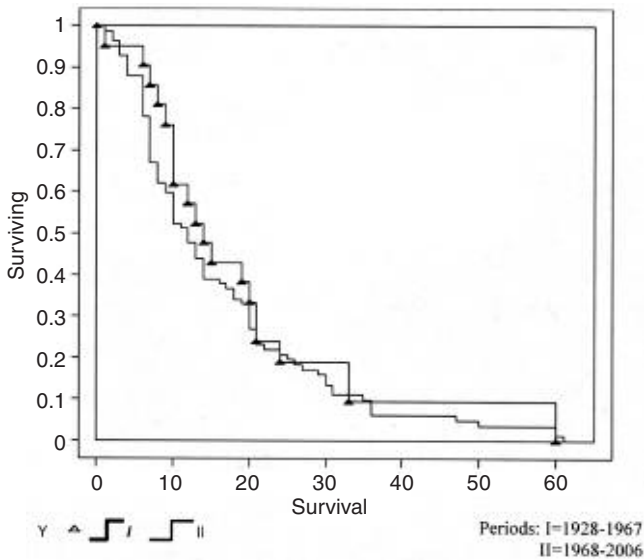


Figure 2 - Kaplan-Meier curve showing the survival of the patients in the two periods.

reported frequency of extraneural metastases was 0.44% in 1966², we can point out a sensitive increase until the present value of about 2%³.

We present 7 cases of GBM in elderly patients with distant metastases to the lung, liver, arm and lymph nodes. The potential pathogenetic mechanisms, the main routes of spread to extracranial sites, and the problems related to treatment in elderly patients are discussed.

Materials and methods

Case 1. A 66-year-old man presented a right frontal lobe lesion, which histologically proved to be a GBM. Gross total removal of the tumor was performed. The patient underwent adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with the administration of temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then sequentially (200 mg/m²/die for 5 days in each cycle of 28 days, for 6 cycles).

MRI-imaging follow-up at 16 months did not reveal any signs of local recurrence, the Karnofsky performance status (KPS) was 80, but the patient started to present hemoptysis and cough. He was thus studied with a thoracic CT scan that revealed a left apical lung lesion. The patient underwent a lung lobectomy. The histological examination showed the same features of the primary tumor, and a diagnosis of GBM metastatic lesion was made. A whole-body CT scan did not evidence additional lesions. Six months later the primary brain tumor presented a regrowth located in the corpus callosum and central ganglia; his conditions deteriorated and he died after 3 months (Table 1).

Case 2. A 74-year-old woman was treated for a right temporal lobe GBM. A craniotomy was performed, followed by a grossly total resection. She was given adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then se-

Table 1 - Our case series

Case No., age, sex	GBM localization	Metastatic localization, and time of occurrence (mo)	CNS GBM progression from diagnosis of metastasis (mo)	Death of the patient after CNS progression (mo)	Overall survival (mo)
Case 1, 66, M	R frontal lobe	Lung, 16	6	3	25
Case 2, 74, F	R temporal lobe	Liver, 18	6	2	26
Case 3, 67, F	L frontal lobe	Humerus, 19	8	3	30
Case 4, 72, M	R occipital lobe	Lung, 21	7	3	31
Case 5, 63, M	R temporal lobe	Lung, 19	8	2	29
Case 6, 70, F	R frontal lobe	Lymph nodes, 20	8	2	30
Case 7, 69, M	R temporal lobe	Lung, 23	9	3	35

R, right; L, left.

quentially (200 mg/m²/die for 5 days in each cycle of 28 days, for 6 cycles).

The postoperative course was uneventful, the KPS was 80, but 18 months later she presented icterus. Serum tests revealed increased pathological levels of bilirubin and γ GT. Abdominal CT scan demonstrated the presence of an hepatic mass, which was surgically removed. Histological examination confirmed the diagnosis of metastatic GBM. A whole-body CT scan did not reveal the presence of other metastatic lesions. A brain MRI performed 6 months later showed regrowth of the lesion, involving the deep structures. The patient died 2 months later (Table 1).

Case 3. A 67-year-old man underwent surgery with grossly total removal of a left frontal lobe GBM. He underwent adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then sequentially (200 mg/m²/die for 5 days in each cycle of 28 days, for 6 cycles). He had a stable postoperative course and no other clinical events for 19 months, with a KPS of 80.

After this period, he experienced a pain which irradiated to the right arm. CT scan demonstrated the presence of a lesion in the right humerus that was removed by surgical excision. The histologic diagnosis was GBM metastasis. Whole-body CT scan did not report other different metastases. Eight months later, the original tumor showed regrowth with progression to deep structures, and the patient died after 3 months (Table 1).

Case 4. A 72-year-old man was admitted for a right occipital GBM (Figures 3-6), and a grossly total excision was performed (Figures 7-8). He underwent adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then sequentially (200 mg/m²/die for 5 days in each cycle of 28 days, for

6 cycles). His clinical situation remained stable as the MRI follow-up confirmed, with a KPS of 80. However, 21 months later he developed hemoptysis and cough, which was studied by a thoracic CT scan. A neoplastic lesion was found in the left lung (Figures 9 A-B). A

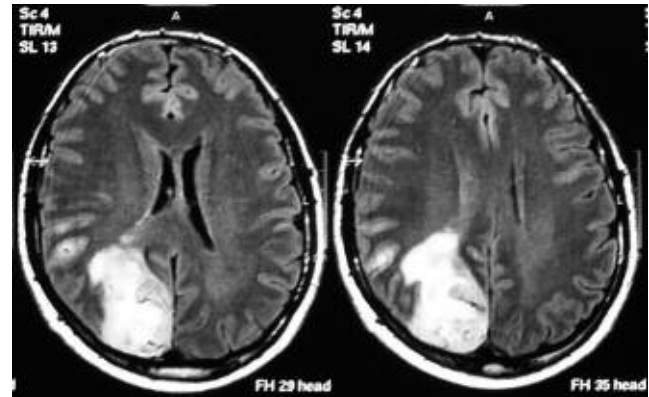


Figure 4 - T1-weighted axial MRI FLAIR sequences showing the tumor lesion before the surgery.

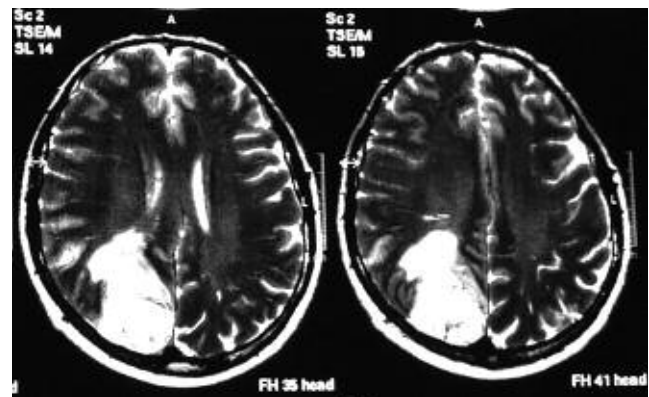


Figure 5 - T2-weighted axial MRI sequences showing the glioblastoma multiforme in the right occipital lobe before the surgical operation.

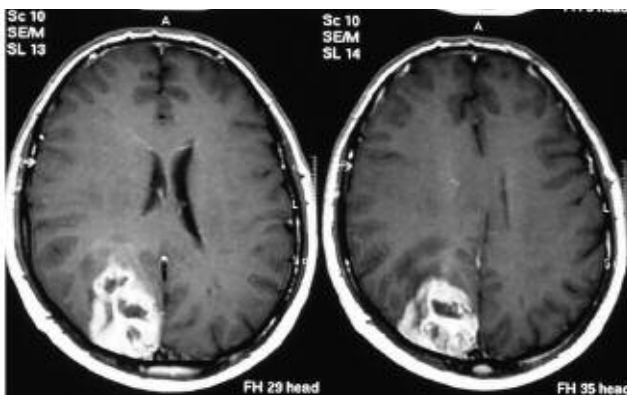


Figure 3 - T1-weighted axial MRI sequences with contrast enhancement showing the glioblastoma in the right occipital lobe before the surgery.

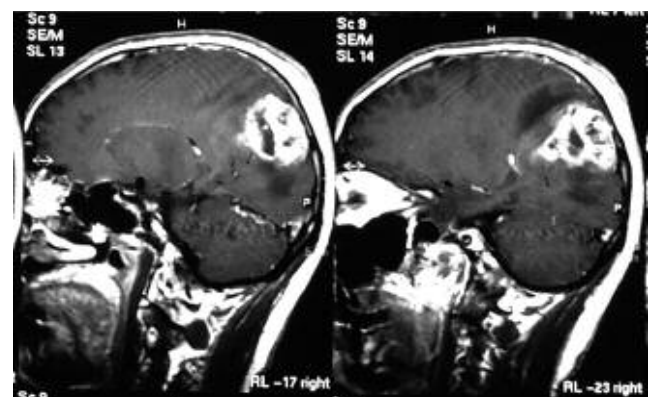


Figure 6 - T1-weighted sagittal MRI sequences with gadolinium administration showing the tumor before surgery.

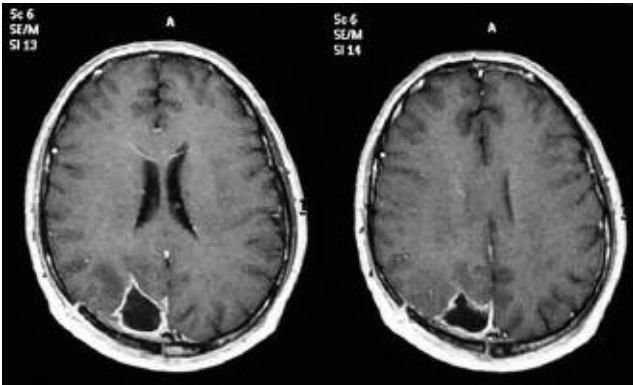


Figure 7 - T1-weighted axial MRI sequences with contrast enhancement showing the brain after total surgical removal of the glioblastoma.



Figure 8 - T1-weighted sagittal MRI sequence showing the brain after the surgery.

lobectomy was performed, and histology showed the features of a GBM metastasis. Whole-body CT scan did not reveal other metastases. After 7 months his clinical conditions worsened because of brain tumor regrowth involving important deep structures. The patient died 3 months later (Table 1).

Case 5. A 63-year-old man was treated by grossly total resection of a right temporal lobe GBM. He underwent adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then sequentially (200 mg/m²/die for 5 days in each cycle of 28 days, for 6 cycles). The postoperative course was un-

eventful with no other clinical manifestations for 19 months, with a KPS of 80. After this period, he began to experience hemoptysis and cough. A thoracic CT scan demonstrated a neof ormation in the apical pulmonary lobe. The patient underwent a lung lobectomy, and the histological diagnosis was a GBM repetition. Whole-body CT scan did not show any metastatic lesions in other tissues. Eight months later, the original tumor had regrown and reached important deep structures. The patient died in only 2 months (Table 1).

Case 6. A 70-year-old woman required radical surgical removal of a right frontal GBM. The woman underwent adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then sequentially (200 mg/m²/die for 5 days in each cycle of 28 days, for 6 cycles). Her overall condition remained unchanged for 20 months, with a KPS of 80. After this period, a tumefaction appeared in the lateral-cervical lymph nodes. A biopsy subsequently showed metastatic GBM. Whole-body CT scan did not show any other tumor lesions.



A



B

Figure 9 - Angio CT-scan showing the metastatic lesion from GBM in the left lung at two different transversal sections: lower section (A) and upper section (B).

A tumor regrowth in the frontal region made a second craniotomy necessary. The excision was grossly total, but after 8 months, deeper structures were involved. The patient died 2 months later (Table 1).

Case 7. A 69-year-old man was admitted for the surgical treatment of a cerebral tumor localized in the right temporal lobe. A grossly total excision was performed, and the diagnosis established the presence of a GBM. The man underwent adjuvant radiotherapy (64 Gy in 6 weeks using Linac) and adjuvant chemotherapy with temozolomide, first concomitantly to radiotherapy (75 mg/m²/die), then sequentially (200 mg/m²/die for 5 days in each cycle of 28 days, for 6 cycles). Postoperatively, there were no complications; KPS was 80. After a period of 23 months, the patient manifested hemoptysis and cough. Thoracic CT scan showed a pulmonary lesion in the apical area of the left lung. The whole pulmonary lobe was surgically removed. The histological diagnosis was GBM metastasis. A whole-body CT scan did not show any other metastatic lesions.

The right temporal lobe was again involved by tumor regrowth, which was treated by a second craniotomy and a new surgical removal. Nine months later the tumor showed progression to deep structures, and exitus occurred after 3 months (Table 1).

Literature review

In the English literature, to the best of our knowledge, 128 cases of extra CNS metastases from GBM have been reported, including our series (Table 2^{1,2,4,5-14,25-99}). Of these, we know the age of 127 patients, the sex of 123, and the survival of 103. There were 82 males and 41 females (M/F ratio, 2:1). The average age at GBM diagnosis was 40 years (range, 3-74; Table 3). The mean overall survival was 17 months (range, 1-60; Figure 1). Twenty-one cases were reported from 1928 to 1967, and 107 from 1968 to 2006 (Table 3). The mean age in the first period (i.e., 1928-1967) was 34 years (range, 6-61) and in the second period, 42 years (range, 3-74; Table 3). The sex distribution was 12 males and 9 females in the first and 70 males and 32 females in the second period (Table 3). The mean survival in the first was 19 months and in the second period, 16 months (even though these values were not statistically relevant, logrank, 0.417) (Figure 2).

Table 2 - Division of the patients according to the period of diagnosis (1928-1967 and 1968-2006), sex and age

	Total period (1928-2006)	Period 1 (1928-1967)	Period 2 (1968-2006)
No. of cases	128	21	107
Sex			
Male	67%	57%	69%
Female	33%	43%	31%
Mean age, yr	40 (range, 3-74)	34 (range, 6-61)	42 (range, 3-74)

Discussion

GBM is a highly malignant primary brain tumor. According to the characteristic behavior of these neoplasms, the occurrence of extracranial metastases is a very uncommon event, with a reported frequency in the literature of less than 2%³. Several attempts have been made to explain the rarity of extraneural metastases. Neidhart *et al.*⁴ described the following six reasons: the absence of lymphatic vessels in the CNS, intracranial perivascular spaces do not communicate with extracranial fluid space, the connections between the subarachnoid space and extracranial lymphatic vessels are very sparse, intracerebral veins are thin walled and would probably collapse from compression before a tumor's penetration⁴⁻⁶, meningeal tumors grow on the dura mater but remain only on the surface, dural veins are protected by a dense connective tissue^{4,6}.

GBM has a poor prognosis and presents an average survival time of approximately 1 year^{3,7}. Extracerebral metastases usually occur in regional lymph nodes (51%), particularly in the cervical group, in lungs and pleura (60%), and in the skeleton (31%), where vertebral bodies are the most involved. Bone metastases from GBM can be differentiated in lytic or sclerotic lesions on neuroimaging, and they are usually seen as a multiple extracranial spread. Only particular cases present an isolated vertebral localization (i.e., axis)⁵. Other target tissues for metastases are the liver (22%), the operative flap, dural veins, meninges, the scalp, the kidney, the orbit⁴, the spleen⁵, and the heart⁷.

The tumor is able to use several routes to metastasize, and we can describe five main ways⁴: hematogenous spread via the vessels of the primary tumor, hematogenous spread after tumor invasion of the dural veins, hematogenous and/or lymphogenous spread after infiltration of the skull and extracranial soft tissues, spread via the cerebrospinal fluid, spread via ventriculoatrial or ventriculo-pleural shunts.

Hematogenous and/or lymphogenous spread after infiltration of the skull and extracranial soft tissues represents the most common route, above all in patients who have undergone a surgical intervention. In fact, the operation alters the brain anatomy and gives the tumor the possibility to reach the extracranial soft tissue and to gain access to blood or lymphatic vessels. This is the main reason why so many different metastases to lymph nodes have been demonstrated^{4,8,9}. The hematogenous system is the preferential way involved in lung, osseous and spleen metastases. When the vertebrae are involved, the glioma cells probably enter the Batson plexus (which is situated in the anterior lumbar cord) and disseminate in the cerebrospinal fluid. The capacity of the Batson plexus to give blood to the inferior vena cava and also to lumbar and sacral vertebrae allows the formation of metastases in the lung and liver and in the lumbar and sacral vertebrae⁵.

Table 3 - Literature review of studies of extra central nervous system metastases from glioblastoma multiforme

Case No.	Investigator(s)	Patient's age, sex	Site	Survival from primitive GBM (mo)
1	Davis ¹	31, F	R Arm, L lung, R scapula, ribs	8
2	Kohlmeier ²⁵	38, M	Lung, pleura	12
3	Brandt ²⁶	53, M	Lung, kidney	24
4	Nowotny ²⁷	33, F	L retroauricular and cervical lymph nodes	21
5	Cross ²⁸ and Cooper Case 2 (1958)	20, M	Lungs, orbit, abdominal wall	9
6	Zeitlhofer ²⁹	40, F	Retroauricular and cervical. Lymph nodes	60
7	Wolf ³⁰	14, F	Lungs, pleura, ribs, vertebra, sternum, mediastinum, para-aortic lymph nodes	13
8	Gropp ³¹	48, M	Heart (R ventricle)	1
9	Bogdanovich ³²	61, F	Lungs	6
10	Dewart ³³ or Thiry ³⁴	57, F	Liver	>60
11	Ehrenreich ³⁵ or Feigin case 8 (1958)	44, M	R Lung	10
12	Feigin ³⁶ case 12 (1958)	6, M	L Lung	15
13	Garret ³⁷	55, F	Cervical lymph nodes	10
14	Giok ³⁸	25, F	Lungs	33
15	Grampa ³⁹	40, M	L kidney	7
16	Brodskaja ⁴⁰	24, M	L supraclavicular and cervical lymph nodes	10
17	Ley ⁴¹ case 2 (1961)	22, M	Cervical lymph nodes	33
18	Labitzke ⁴² or Smith case 9 (1969)	21, M	Lung, paratracheal, hilar and cervical lymph nodes	21
19	Nigogosyan ⁴³ case 1 (1962)	40, M	Lungs, vertebra, sternum, lymph nodes	14
20	Schejbal ⁴⁴	9, F	R cervical lymph nodes	19
21	Wisioł et al. ⁴⁵	31, M	Vertebra, acetabula	20
22	Smith ⁴⁶ case 1 (1969a)	52, M	Lung, mediastinal lymph nodes	60
23	Smith ⁴⁶ case 2 (1969a)	38, M	Hilar lymph nodes	9
24	Smith ⁴⁶ case 3 (1969a)	24, M	Lung	18
25	Smith ⁴⁶ case 4 (1969a)	43, M	Liver	6
26	Smith ⁴⁶ case 5 (1969a)	45, M	Liver	6
27	Smith ⁴⁶ case 6 (1969a)	6, M	L lung	7
28	Smith ⁴⁶ case 7 (1969a)	58, M	Liver	6
29	Smith ⁴⁶ case 8 (1969a)	29, M	Lung, periaortic and cervical lymph nodes	10
30	Smith ⁴⁶ case 10 (1969a)	55, M	Ribs	13
31	Smith ⁴⁶ case 11 (1969a)	54, M	Lung	8
32	Smith ⁴⁶ case12 (1969a)	45, M	Cervical lymph node	21
33	Smith ⁴⁶ case13 (1969a)	36, M	Vertebrae, acetabulum	12
34	Smith ⁴⁶ case14 (1969a)	63, M	Lung, liver, adrenal gland	1
35	Smith ⁴⁶ case15 (1969a)	44, M	Liver	8
36	Smith ⁴⁶ case 16 (1969a)	49, M	Liver, pancreas, cervical lymph nodes, sternum	16
37	Smith ⁴⁶ case 17 (1969a)	42, M	Lungs, cervical lymph nodes	50
38	Smith ⁴⁶ case 18 (1969a)	63, F	Lungs, vertebrae (T10-11)	11
39	Smith ⁴⁶ case19 (1969a)	42, F	Cervical lymph node	8
40	Smith ⁴⁶ case 20 (1969a)	38, M	Lung, pleura, hilar lymph nodes	20
41	Smith ⁴⁶ case 21 (1969a)	36, F	Ribs, vertebrae, cervical and mediastinal lymph nodes	13
42	Smith ⁴⁶ case 22 (1969a)	64, M	Liver, lung	10
43	Smith ⁴⁶ case 23 (1969a)	36, M	Vertebrae	14
44	Anzil ⁴⁷	54, F	Liver, vertebra (T11)	13
45	Dalla Pria ⁴⁸	40, F	R arm, R. haunch	2
46	Dalmer ⁴⁹	39, M	Cervical lymph nodes	6
47	Wakamatsu ^{50,51}	22, M	R lung, pleurae, pericardium, diaphragm	9
48	Komatsu ^{52,53}	18, F	L cervical lymph nodes	7
49	Dolman ⁵⁴	35, F	L intraparotid lymph nodes	3
50	Johnson ⁵⁵	46, M	Lungs, hilar lymph nodes, liver	36
51	Nikkanen ⁵⁶	12, F	Lungs, skeleton, cervical lymph nodes	7
52	Yao ⁵⁷	18, M	Lung, thyroid gland, neck, paratracheal and mediastinal lymph nodes	19
53	Hulbann ⁵⁸	63, M	R lung, bronchial lymph nodes, vertebra	2
54	Montaut ⁵⁹ case1 (1976)	23, M	Lungs, liver, cervical lymph nodes	14
55	Schuster ⁶⁰ case 6 (1976)	20, M	L cervical lymph nodes	17
56	Schuster ⁶⁰ case 7 (1976)	55, M	R cervical lymph nodes	18
57	Russell ⁶¹	25, M	Lungs, pleurae, pericardium, L. pulmonary hilar lymph nodes	>60
58	Russell ⁶¹	70, F	Pleurae, pericardium	6
59	Russell ⁶¹	3, F	Lungs, pleurae, pulmonary hilar lymph nodes	31

(continued)

(continued) - Table 3

Case No.	Investigator(s)	Patient's age, sex	Site	Survival from primitive GBM (mo)
60	Russell ⁶¹	7, F	Liver, adrenal medulla, hilar lymph nodes, pleurae, vertebra	NA
61	Russell ⁶¹	16, F	R Pleurae, peritoneum, diaphragm, lumbar region	36
62	O'Connor ⁶²	53, F	L supraclavicular lymph nodes, pleura	7
63	Terheggen ⁴	12, M	Bone marrow, pubic and ischiac bones, L ileum	10
64	Pasquier ⁶³	21, F	Liver, L submandibular lymph nodes	NA
65	Slowik ⁶⁴ case 1 (1980)	35	Bones, soft tissues, sinus vertebrae	20
66	Slowik ⁶⁴ case 2 (1980)	35	Bones, soft tissues, sinus vertebrae	20
67	Slowik ⁶⁴ case 3 (1980)	35	Bones, soft tissues, sinus vertebrae	20
68	Slowik ⁶⁴ case 4 (1980)	35	Bones, soft tissues, sinus vertebrae	20
69	Mousavi ⁶⁵	55, F	Bone marrow, liver	4
70	Dietz ⁶⁶	24, M	Thoracic vertebrae, sternum	6
71	Yung ⁶⁷ case 1 (1983)	57, M	Bone marrow, L femur, R sacroiliac joint, ribs, R humerus, pleura	NA
72	Yung ⁶⁷ case 2 (1983)	24, F	Bone marrow	10
73	Sadik ⁶	48, M	Lumbar vertebra	NA
74	Steinbok ⁶⁸	27, F	Cervical lymph nodes	22
75	Wakabayashi ⁶⁹	43, M	Peritoneal cavity	NA
76	Yokoyama ¹⁴	22, F	Hilar lymph nodes, lung, pleura, sternal bone marrow, liver	4
77	Ogata A ⁷⁰	68, M	Lungs, bronchial lymph nodes, liver, kidney, heart, spleen	8
78	Trattinig S ⁷¹	29, M	Cervical lymph nodes, bones	NA
79	Gamis ²	11, F	Thoracic bones, humerus, calvarium, facial bones, mandible, femurs, tibias, pelvis, shoulders, manubrium, L iliac crest, ankles, L foot	6
80	Newton ⁷² case 1(1992)	13, M	Peritoneal cavity, omental	NA
81	Newton ⁷² case 2 (1992)	9, F	Peritoneal cavity, omental	NA
82	Zappia ⁷³	39, M	Submandibular, jugulodigastric, deep cervical, parotid chains lymph nodes	NA
83	Malca ⁷⁴	46, M	Thoracic, lumbar and sacral vertebrae, ileum, femur, ribs, pleurae	27
84	Chesnut ⁷⁵	42, M	Cervical vertebrae	14
85	Gonzales Campora ⁷⁶	47, M	Cervical and supraclavicular lymph nodes	12
86	Minami ⁷⁷	9, M	Meninges, spinal metastases	NA
87	Mihara ⁷⁸	35, F	Vertebra (T1)	14
88	Shuto ⁷⁹	42, F	Liver, skull	NA
89	Granjon ⁸⁰	50, M	Parotid gland, lung, pleura, endobronchial masses	7
90	Jonas ⁸¹	48, F	Liver	4
91	Vural, Hagmar ⁸ case 1 (1996)	40, M	R side of neck	47
92	Wallace ⁹ case 1 (1996)	41, M	Neck, cervical and supraclavicular lymph nodes, extraocular muscle, R eye	NA
93	Wallace ⁹ (1996) case 2	39, M	R orbit, preauricular lymph nodes	7
94	Al-Rikabi ⁸²	4, M	L cervical lymph nodes	NA
95	Fecteau ⁸³	18, F	Omentum, stomach, abdominal wall, pelvis	NA
96	Greif ⁸⁴	51, M	Pleurae, lungs, liver	7
97	Datta ⁸⁵	35, F	R cervical lymph nodes	10
98	Waite ⁸⁶	40, M	L parotid region	>24
99	Frappaz ⁸⁷	52, M	L ribs, lumbar vertebra, R lung	12
100	Widjaja ⁸⁸	58, M	Liver, spleen	NA
101	Beauchesne ⁷	54, M	Dorsolumbar vertebrae, iliac bone, lung, heart	10
102	Park ¹² case 1 (2000)	31, M	Vertebrae, humerus	4
103	Park CC, Hartmann C et al. ¹² case 2 (2000)	31, M	Neck, pelvis	7
104	Park ¹² case 3 (2000)	27, M	R lung	7
105	Park ¹² case 4 (2000)	25, F	Parotid gland, neck	21
106	Park ¹² case 5 (2000)	60, M	Hip, cervical vertebrae	21
107	Laraqui ⁸⁹	40, M	Lung, endobronchial masses	NA
108	Hata N ⁹⁰	NA	Lung, lymph nodes	NA
109	Kuhn ⁹¹ case 2 (2003)	58, M	R parotid gland	NA
110	Yasuhara ¹⁰	47, F	Spleen, lung	6
111	Ueda ¹³	42, M	Cervical lymph nodes, thoracic vertebrae, L clavicle, epicardium, R kidney, pancreas, liver, L cervical and auricle soft tissue	NA
112	Erdem ⁹²	37, F	Infratemporal fossa, R orbit, lateral and medial pterygoid muscles, R carotid artery	NA
113	Fabj ⁹³	43, M	Lumbar vertebrae (L1,L3)	NA
114	Montagne ⁹⁴	74, M	Vertebrae, lungs, mediastinal lymph nodes	3

(continued)

(continued) - Table 3

Case no.	Investigator(s)	Patient's age, sex	Site	Survival from primitive GBM (mo)
115	Utsuki ⁵	42, M	Axis	>36
116	Chivukula ⁹⁵	62, M	R lung	NA
117	Mirzayan ¹¹	30, M	Bones (lumbar and thoracic vertebrae), L 7 th costovertebral junction, nodal, paravertebral and mediastinal metastases	NA
118	Tuominen ⁹⁶	25, M	Mediastinum	61
119	Taha ⁹⁷	33, M	Parotid gland, cervical lymph nodes	NA
120	Rajagopalan ⁹⁸	60, M	Lumbar and sacral vertebrae, epidural soft tissue	NA
121	Didelot ⁹⁹	74, M	Bone marrow, lung, mediastinal lymph nodes	3
122	Piccirilli case 1 (2006)	66, M	Lung	25
123	Piccirilli case 2 (2006)	74, F	Liver	26
124	Piccirilli case 3 (2006)	67, F	Humerus	30
125	Piccirilli case 4 (2006)	72, M	L lung	31
126	Piccirilli case 5 (2006)	63, M	Lung	29
127	Piccirilli case 6 (2006)	70, F	Cervical lymph nodes	30
128	Piccirilli case 7 (2006)	69, M	Lung	35

R, right; L, left; NA, not available.

Hematogenous spread can follow particular vein connections: this is the case of the axis metastasis. According to Utsuki *et al.*⁵, there could be some connections between part of the meningeal venous system and cranio-cervical venous system, which is connected to the internal vertebral venous plexus. The internal vertebral venous plexus flows back to the anterior and posterior surface of the cervical vertebrae, and there is also blood flow to the body of the axis⁵.

The so-called "drop metastases", due to metastatic dissemination with drainage of the CSE, as well as for the placement of ventricular systemic shunts¹⁰, are a well-documented event^{4,11}, but tumor expansion through the cerebrospinal circulation remains an unusual way.

Various hypotheses have been made to find a pathogenesis for the metastasis phenomenon. Interesting considerations surely derive from Park *et al.*¹². They suggested that the metastatic potential of GBM might be correlated with particular molecular features, P53 gene mutations and differential clonal selection^{3,12,13}. In fact, some metastases arise from genetically altered subclones of the primary tumor. Several biological and molecular studies¹³ have closely examined the different patterns of genetic expression between the primary tumor and some metastatic samples, using the cDNA microarray technique. They showed the following common results in both: the overexpression of insulin growth factor and a decrease of DNA-PK genetic expression, which is a DNA-dependent protein kinase involved in DNA repair mechanisms. The first probably plays a role in tumor progression; the second contributes to the malignant transformation of the glioma.

In other words, the present study underlines the similar patterns of genetic expression in intracranial tu-

mors as well as in metastases, suggesting that distant dissemination is the consequence of direct infiltration of tumor cells into extracranial blood vessels¹³.

An alternative explanation for the major tendency to metastasize is related to the appearance of a sarcomatous component in the original glioblastoma^{10,14}. In fact, we know that the gliosarcoma can metastasize more easily than other malignant gliomas. Moreover, patients with extracranial metastases from GBM with a sarcomatous component have a worse prognosis than patients with other gliomas. Most of the previously reported cases did not present a sarcomatous component in the early state, so it is thought that adjuvant radiotherapy and chemotherapy may have caused changes in the histological features¹⁰. All our patients presented a primary GBM and none of them showed a sarcomatous component after the histological examination. All of them received adjuvant radiotherapy and chemotherapy, but most of them did not undergo a second surgical removal of the brain lesion, which allowed us to verify histologically if a sarcomatous transformation took place. The only two patients who underwent a second surgical approach at the brain did not present any sarcomatous cells. Moreover, histological examination of metastatic GBM did not report any sarcomatous elements.

In relation to a study of 1977¹⁵, some authors examined the different immunologic responsiveness of GBM to several antigens in long- and short-term survivors. The experiments demonstrated at the beginning an anergic reaction, but after a relative short period, a progressive increase in immune responsiveness in all tests performed *in vivo* and *in vitro*. This last event probably represents a host immune attempt to arrest tumor proliferation. This is only a transitory phase for the short-

term survivors but represents the expression of a different immunogenetic pattern for the long-term survivors. In fact, particular antigens were present only in the cells of the long-term survival glioblastoma and were not seen in short-term survival GBM material. In the same way, a meningioma-related dicentric chromosome marker appeared only in the cells of long-surviving glioblastoma patients. Another important consideration derives from the comparison of PAGE (polyacrylamide gel electrophoretic) separation of serum: in fact, between their long- and short-surviving patients there was a significant quantitative difference in the measurement of two prealbumin components, and the α 1-acid glycoprotein/prealbumin ratio gave a sensitive index of the degree of malignancy¹⁵.

The elderly age of our patients is another important point of discussion. In fact, several authors have confirmed a growing incidence of tumors in elderly patients¹⁶⁻¹⁹. In particular, a study conducted in France between 1983 and 1990^{16,18} showed an increase of 5% per year in the incidence of malignant astrocytomas in the population over 65 years of age. We also have to consider the great increase in life expectancy of the population of industrialized countries. This fact probably created a large potential target sample for this neoplasm¹⁸. The increasing incidence of primary and malignant brain tumors seems to be specific in elderly patients^{18,19}, and this observation can only partially be attributed to the extensive use of new diagnostic neuroimaging like MRI and CT.

Elderly patients with a diagnosed GBM may often present a concomitance of important diseases such as diabetes, chronic broncho-pulmonary disease, ischemic heart disease, and hypertension. These factors can determinate a shorter survival. The other situations characterized by a poor survival in elderly patients without such diseases can be explained by a less aggressive multimodality treatment that the neurosurgeon chooses for the lower KPS generally observed in elderly patients^{18,20,21}. Some studies, only in particular cases, have evidenced that multimodality treatment could be less effective in elderly patients for the presence of specific mutations able to render tumor cells more resistant to adjuvant chemotherapy (p-53 mutations)^{18,22} and radiotherapy (deletions in chromosome 10)^{18,23}.

These considerations persuaded us to perform macroscopically complete surgical debulking, according to the concept that if the extent of the surgical removal is greater, the outcome is better for the patient^{18,24}. In fact, radical removal of GBM through an aggressive approach can delay tumor recurrence and reinforce the effect of adjuvant therapy. For these reasons, according to our experience, elderly patients, in a good functional state of health, should be treated in the same way as younger patients with the same diagnosis¹⁸.

In the past, the mean survival time of a patient with GBM did not exceed 6 months, but today this time can reach and also surpass 2 years. Our patients had an av-

erage survival time of 29 months (range, 25-35), although they were all elderly patients. Such a long survival time shows that the chosen treatment was appropriate for these patients.

Metastasis always preceded regrowth of the primary GBM (mean value, 7 months; range, 6-9). Nevertheless, in each case death was the result of cerebral GBM regrowth involving important deeper structures. Although the literature confirms the scarce tendency to metastasize, we have to report an important documented increase. In the 40 years between 1928 and 1967 in the literature, 21 cases of GBM extra-CNS metastases were reported, whereas in the 39 years between 1968 and 2006 there were 107 cases, about five times more. Advances in the multimodality treatment of gliomas, the earlier diagnosis due to a wide diffusion and improvement in neuroimaging techniques, and the subsequent longer patient survival may partially justify the growing incidence of extracranial metastases, from the value of 0.44%, reported by Smith *et al.* in 1969², to the present value of 2%³.

This phenomenon may also depend on the potential modification of the histological and genetic features of primary GBM. This new aspect adds another conditioning element to the GBM prognosis: metastasis treatment.

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