Particular aspects of cerebral metastases secondary to malignant melanoma in comparison with other brain metastases

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Abstract: Authors present a retrospective study of 427 patients with brain metastases admitted and treated in third and fourth neurosurgical departments of Emergency Clinical Hospital "Bagdasar-Arseni" Bucharest, from January, 2005 until December, 2014. 62.1% of all patients were men and 37.9% were women, with a medium age of 56.8 years, ranging between 17 and 85 years. 311 patients (72.8%) had a single metastasis, 79 patients (18.5%) developed 2 or 3 metastases and 37 patients (8.7%) had more than 3 metastases. The biggest four metastases in multiple cases were noted in database regarding location, either reported to left / right hemisphere, either related to site (frontal parietal etc.), and dimensions. In the case of malignant melanoma (22 men and 24 women) the status of the primary tumor was noted: the malignant melanoma was operated in 32 cases (69.6%) and in 7 patients (15.2%) the primary tumor was not operated. In another 7 cases the status of the primary tumor was not noted. The most frequent location for malignant melanoma was the legs in women and anterior thorax in men. In conclusion, cerebral metastases from malignant melanoma have most frequent intratumoral hemorrhages, comparative with other primary sources. Common primary sites founded in this study is legs in women and anterior thorax in men. Treatment of cerebral metastases is complex, multimodal, implying neurosurgeons, oncologists and radiotherapists.

Key words: brain metastases, malign melanoma, intratumoral hemorrhages.

Introduction

Brain metastases are the most frequent cerebral tumors and represent the main cause for morbidity and mortality among patients with systemic cancer. Between 20 – 40% of patients develop one or more brain metastases during neoplastic disease. The most of the brain metastases arise from lung cancer, breast cancer, malign melanoma and kidney cancer.

All studies report a maximum incidence in sixth and seventh decades of life. Among all systemic cancer, malign melanoma has the greatest propensity for brain metastases.

Modern treatment for brain metastases includes currently not only whole brain radiotherapy, but more complex approach, consisting in classic surgery, stereotactic radiosurgery and chemotherapy.

Surgical resection represents the gold standard for brain metastases therapy, because it provides local control of diseases, releases the symptoms and accurate establish histopathological diagnosis. Unfortunately, not all patients with brain metastases are good candidates for surgical treatment.

Material and methods

Authors present a retrospective study of 427 patients with brain metastases admitted and treated in third and fourth neurosurgical departments of Emergency Clinical Hospital "Bagdasar-Arseni" Bucharest, from January, 2005 until December, 2014. Clinical data were collected from clinical observation sheets and surgical protocols recorded for each patient, including demographic data (age, sex), symptoms, Karnofsky Performance Scale, number and location of tumors, systemic disease, imaging, surgical treatment and outcome. Furthermore, location of primary cancer was noted for malign melanoma, as well as the presence of intratumoral hemorrhage visible on CT or MRI scan.

Results

62.1% of all patients were men and 37.9% were women, with a medium age of 56.8 years, ranging between 17 and 85 years. Demographic data are shown in table 1, figure 1. The maximum incidence of brain metastases was observed in sixth and seventh decades of life, 35.4% and 30.7% respectively, as it is shown in table 1, figure 2.

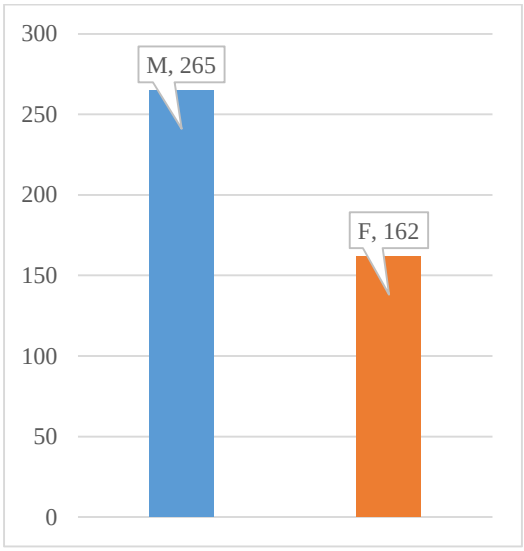

Figure 1 - Sex distribution

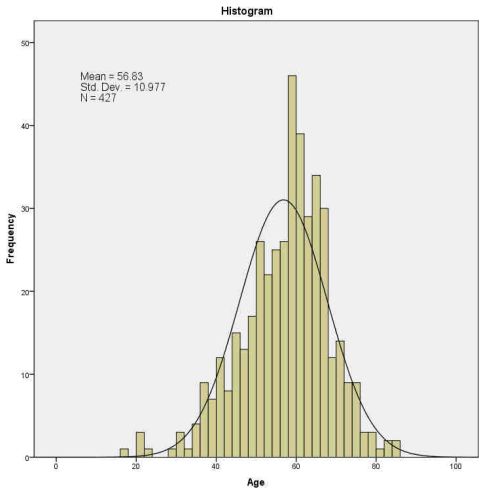

Figure 2 - Histogram from age distribution

311 patients (72.8%) had a single metastasis, 79 patients (18.5%) developed 2 or 3 metastases and 37 patients (8.7%) had more than 3 metastases. The biggest four metastases in multiple cases were noted in database regarding location, either reported to left / right hemisphere, either related to site (frontal parietal etc.), and dimensions. In 70.3% of cases (300 patients) tumors were located supratentorial, and in 18.5% (79 patients) brain metastases were located infratentorial. Both supra- and infratentorial location was seen in 11.2% of cases (48 patients) (Figure 3).

The medium size of the largest metastasis was 31.6 mm (varying from 4 to 80 mm). The medium size for the second metastasis was 10.6 mm, 9 mm for third tumor and 8.9 mm for fourth tumor.

Lung cancer was the starting point for brain metastases in almost half of the cases (196 patients, 45.9%), and most of them were men (84.7%). Next source for brain metastases was breast cancer (68 patients, 15.9%) 95.6% of the patients with breast cancer were women and 4.4% were men (3 patients). The third starting point for cerebral metastases was malignant melanoma (46 patients, 10.8%). Other primary sites were noted: colon cancer (24 patients), kidney cancer (19 patients), ovarian cancer (8 patients), cervix cancer (7 cases), and prostate cancer (4 cases). In 40 patients (9.4%) the investigations failed to reveal the source for brain metastases (Table 2, Figure 4).

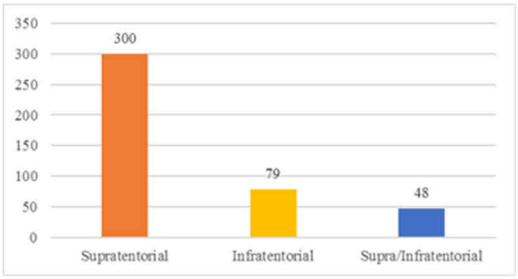

Figure 3 - Location of cerebral metastasis

TABLE 1

Characteristics of patients with cerebral metastasis

Characteristic of patients with brain metastasis		Count
Sex	*M*	*265 (62.1%)*
	F	*162 (37.9%)*
Age	*<20 years*	*3 (0.7%)*
	21-30 years	*6 (1.4%)*
	31-40 years	*27 (6.3%)*
	41-50 years	*72 (16.9%)*
	51-60 years	*151(35.4%)*
	61-70 years	*131(30.7%)*
	71-80 years	*33 (7.7%)*
	>81 years	*4 (0.9%)*
Number of brain metastases	*1*	*311 (72.8%)*
	2	*50 (11.7%)*
	3	*29 (6.8%)*
	>3	*37 (8.7%)*
Location	*Supratentorial*	*300 (70.3%)*
	Infratentorial	*79 (18.5%)*
	Supra/Infratentorial	*48 (11.2%)*
Intracranial hypertension		*402 (94.6%)*
Neurological deficits	*Hemiparesis*	*130 (30.7%)*
	Hemiplegia	*28 (6.6%)*
Seizures	*Generalized seizures*	*51 (12.0%)*
	Focal seizures	*45 (10.6%)*
Facial nerve palsy		*24 (5.6%)*
Cranial nerve palsies		*36 (8.5%)*
Aphasia	*Broca's aphasia*	*46 (10.8%)*
	Werniche's aphasia	*16 (3.8%)*
	Dyshartria	*14 (3.3%)*
Memory disorders		*41(9.6%)*
Visual problem		*49 (11.5%)*
Personality disorders		*36 (8.5%)*
Confusion		*34 (8.0%)*
Bone metastasis		*17 (4.0%)*
Lung metastasis		*38 (8.9%)*
Liver metastasis		*18 (4.2%)*
Kidney metastasis		*5 (1.2%)*
Genital metastasis		*10 (2.3%)*
Adrenal metastasis		*9 (2.1%)*
Other organs		*11 (2.6%)*

TABLE 2

Primary site of cancer

	TOTAL PACIENTS	MASCULIN	FEMININ
Lung cancer	*196 (45.9%)*	*166 (84.70%)*	*30 (15.30%)*
Breast cancer	*68 (15.9%)*	*3 (4.4%)*	*65 (95.6%)*
Melanoma malign	*46 (10.8%)*	*22 (47.8%)*	*24 (52.2%)*
Kidney cancer	*19 (4.4%)*	*15 (78.9%)*	*4 (21.1%)*
Colon cancer	*24 (5.6%)*	*15 (62.5%)*	*9 (37.5%)*
Unspecified cancer	*1 (0.2%)*	*1 (100%)*	*0 (0%)*
Prostate cancer	*4 (0.9%)*	*4 (100%)*	*0 (0%)*
Ovary cancer	*8 (1.9%)*	*0 (0%)*	*8 (100%)*
Unknown cancer	*40 (9.4%)*	*30 (75%)*	*10 (25%)*
Sarcoma	*2 (0.5%)*	*1 (50%)*	*1 (50%)*
Laryngeal cancer	*2 (0.5%)*	*2 (100%)*	*0 (0%)*
Uterine cancer	*7 (1.6%)*	*0 (0%)*	*7 (100%)*
Bladder cancer	*2 (0.5%)*	*2 (100%)*	*0 (0%)*
Mediastinal cancer	*2 (0.5%)*	*2 (100%)*	*0 (0%)*
Malignant timoma	*1 (0.2%)*	*0 (0%)*	*1 (100%)*
Testicular cancer	*1 (0.2%)*	*1 (100%)*	*0 (0%)*
Gastric cancer	*3 (0.7%)*	*1 (33.3%)*	*2 (66.7%)*
Thyroid cancer	*1 (0.2%)*	*0 (0%)*	*1 (100%)*
Total	**427 (100.0%)**	**265 (62.1%)**	**162 (37.9%)**

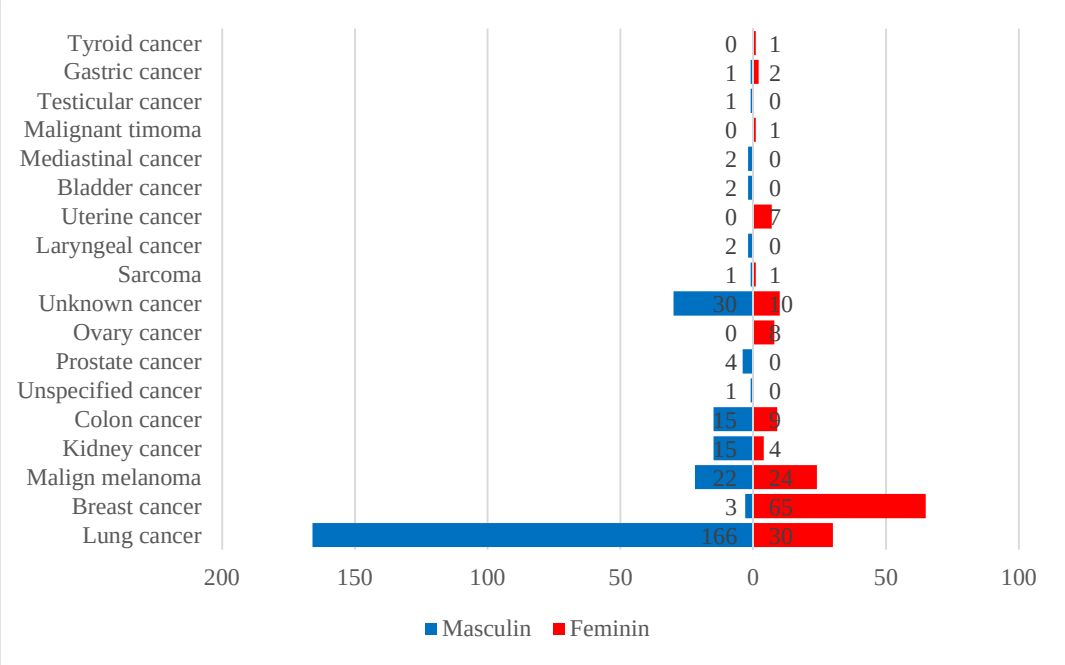

Figure 4 - Primary site

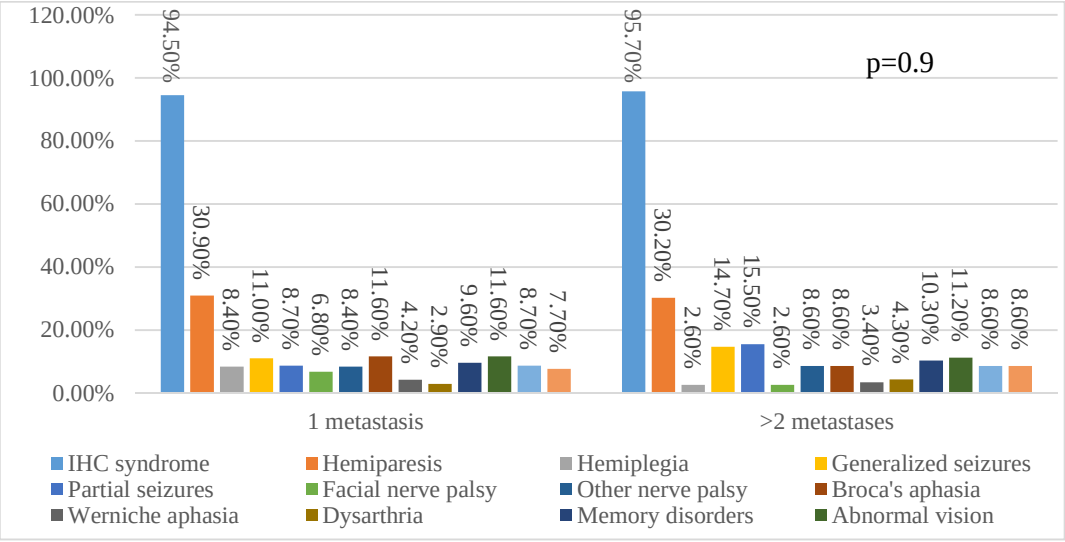

Figure 5 - Differences in symptomatology between patients with single metastasis and patients with multiple metastases

The most frequent symptoms were related to raise of intracranian pressure, founded in 94.6% of the patients. Motor deficits (paresis or palsy) were noted in 37.3% of cases (158

patients) and 22.6% of patients presented with seizures. Altered consciousness was encountered in 34 cases (8%), with giant metastases or posterior cranial fossa locations (Figure 5). Differentiated analysis of patients with one vs multiple metastases failed to reveal any statistical significant difference regarded to symptomatology (p=0.99), as shown in figure 5.

In the case of malignant melanoma (22 men and 24 women) the status of the primary tumor was noted: the malignant melanoma was operated in 32 cases (69.6%) and in 7 patients (15.2%) the primary tumor was not operated. In another 7 cases the status of the primary tumor was not noted. The most frequent location for malignant melanoma was the legs in women and anterior thorax in men, as shown in figure 6.

Cerebral imaging (CT or MRI scan with and without contrast enhancement) revealed intratumoral hemorrhage in 13 cases of brain metastases secondary to malignant melanoma, which meant the highest incidence, followed by cerebral metastases from lung cancer, with 3 cases of intratumoral hemorrhage (Figure 7).

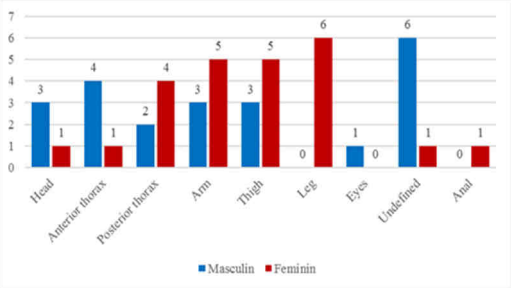

Figure 6 - Location of malign melanoma

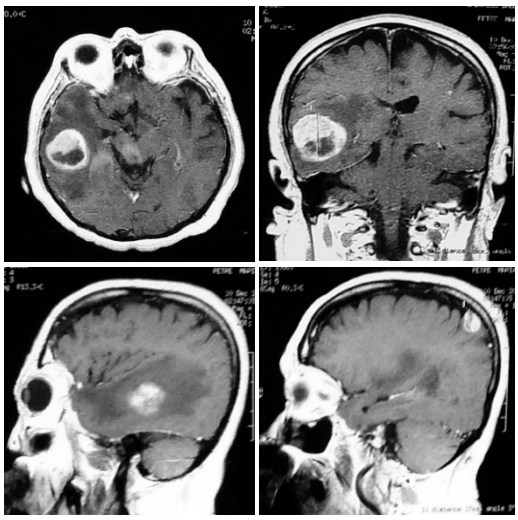

Figure 7 - MRI aspect of intratumoral hemorrhage (brain metastases from malignant melanoma)

All patients received steroids, while anticonvulsants were administrated in patients with supratentorial metastases. 335 of all patients (79.2%) underwent surgery for brain metastases. Surgical resection was performed in 34 of all patients diagnosed with malignant melanoma (73.9%), while surgery was not considered an option in 4 patients with multiple brain metastases, who had a poor biologic status. 1 patient refused surgery and was referred to oncologist. 8 patients underwent stereotactic gamma-knife radiosurgery.

Most patients had a good postoperative outcome. Only in 6.8% of cases the neurologic status worsened. The most common postoperative complication was cerebral hematoma, encountered in 17 patients (4.7%). Worsening of motor and sensitive deficits was noted in 8 cases (2.2%). 7 patients were complicated with pneumonia and 1 patient developed pulmonary embolism.

Discussions

Cerebral metastases are the most frequent tumors of the brain. They arise mainly from lung cancer (50%), breast cancer (15-20%), malignant melanoma (5-20%), and colon and kidney cancer (1, 2). Common clinical manifestations derive from raising of the intracranian pressure, focal neurologic deficits, seizures and altered consciousness.

Occurrence of brain metastases dramatically lowers the survival rate. If untreated, medium survival is approximately one month. Corticotherapy increase survival at 2 months (3). Association of corticotherapy with whole brain radiotherapy increase survival at 3 to 6 months (4-7). Surgical resection of the tumors raise life expectancy at 9 – 14 months, depending of primary cancer, Karnofsky Performance Scale, presence or absence of other systemic metastases (6-10). Major changes in the treatment for brain metastases had seen over time. The main goals of the treatment are lowering morbidity and mortality, with improvement of quality of life. Corticotherapy relief symptomatology by reducing peritumoral edema (11, 12). All patients in this study received steroids (dexamethasone sodium phosphate 8 mg daily). Surgical treatment is usually indicated in patients with Karnofsky Performance Scale > 70, with a single brain metastasis, which can be approached such that no additional motor or sensitive deficit be caused postoperative. Cerebral metastases are usually well demarcated form surrounding cerebral tissue. The 3 main goals of the surgical treatment are establishing of accurate histologic diagnosis, quick relief of symptoms and local cure of disease. Modern surgery, using of microsurgical techniques, neuronavigation and intraoperative monitoring had lead today to drops of intra- and postoperative complications (13, 14) and dramatically decreased immediate postoperative mortality under 1% (15). Patchell, Tibbs, 1990 (7) showed that surgical resection of brain metastases increases survival in comparison with whole brain radiotherapy alone (7). Furthermore, whole brain radiotherapy after surgical removal reduces the risk of recurrence compared with surgery alone (16).

Stereotactic radiosurgery (SRS), used since 1980 in North America (17) revolutionized treatment for cerebral metastases and not only. In the present, prospective randomized studies shows that, for selected cases, with 3 or 4 brain metastases, smaller than 2 cm, stereotactic radiosurgery combined with whole brain radiotherapy increase survival in comparison with WBRT alone (18, 19). Stereotactic radiosurgery has several advantages, such as: it is easily tolerated by patients, can treat deep sites or tumors located in eloquent areas, that cannot be approached surgical, and may be tried in treatment of some cerebral metastases considered radioresistant, such as those derived from malignant melanoma and kidney cancer (20). Postoperative radiation has the main goal to destroy residual tumoral cells from tumor bed or other occult locations. Patchell et all showed that when surgical treatment were applied alone, without WBRT, tumor recurred in medium in 27 weeks after surgery in 46% of patients, in whom complete surgical resection was confirmed on MRI.

Postoperative WBRT decreased recurrence at 10% and prolonged time of recurrence over 52 weeks (16).

Conclusions

Cerebral metastases from malignant melanoma have most frequent intratumoral hemorrhages, comparative with other primary sources. Common primary sites founded in this study is legs in women and anterior thorax in men. Treatment of cerebral metastases is complex, multimodal, implying neurosurgeons, oncologists and radiotherapists. Surgical resection combined with postoperative radiotherapy (WBRT or SRS) represent the gold standard of treatment for brain metastases. In cases of multiple brain metastases, the particular metastasis which is responsible of main symptomatology has surgical priority and should be resect first.

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