

Therapeutical Attitude and Analysis of Results in Brain Metastases

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Abstract: Objectives - The aim of this study is to assess therapeutic outcomes in patients presenting with brain metastases as the first manifestation of malignancies either as a final stage in the evolution of malignancies. Materials and methods - We've performed a complex retrospective study on a total of 81 patients with brain metastases treated in Medical Oncology Clinic of the Emergency County Hospital Craiova between 1 January 2005-31 December 2010. Results - The average age of women (55 years) was statistically significantly low compared to men (64 years) ($p = 0.000$). The most affected age group was 51-60 years in women with maximum frequency of breast cancer and 61-70 years for men, with predominance of lung cancer. Most cases were presented with multiple metastases (90.12%) and the average latency-free interval from primary tumor detection to onset of symptoms was 29.8 months. Clinical manifestations, in most cases, occurred in less than 6 months after diagnosis of the primary tumor being a consequence of the evolution of disease at distance (36 patients / 62 patients in oncological evidence 58.06%) and 12 months after diagnosis survival rate was low being detected in patients with a controlled primary tumor and distant resumption of the disease (14 patients / 62 patients in oncological evidence-22.58%). Median survival in patients with irradiated brain metastases was 7 months. Multivariate statistical analysis of the survival rate has detected statistically significant differences depending on the type of the primary tumor ($p = 0.000$) and the manner of the onset of brain metastases as the first manifestation or evolution of neoplastic disease ($p = 0.000$). Survival was affected, without statistical significance threshold, by the number of metastases, patient gender and the loco-regional status of the primary tumor.

KEYWORDS: Brain metastases, treatment, latency-free interval, survival rate

Introduction

Approximately 25% of cancer patients develop brain metastasis and patients diagnosed with melanoma (50%), lung cancer (30-80%) and breast cancer (20%) have the highest risk of metastasis. On the other hand tumors such as testicular (15%), oropharyngeal and skin carcinoma rarely metastasize (1). Estimated to the new cases of cancer in the United States in 2003, an estimated 60,000 cases of brain metastases were found. But analysis of data obtained from the necropsy detected a total of 170,000 brain metastases.

The incidence of multiple brain metastases is greater than the single metastases these being present in 50-70% of patients. Most published studies show that patient gender does not influence the overall incidence of brain metastases. In general, the differences that arise are due the predominance of a particular type of cancer in one sex. Thus, lung cancer and melanoma develop brain metastases more frequently in males and breast cancer develops brain metastases in women.

The patient's age is one of the factors that influence the incidence of brain metastases,

being more common in adults than in children, with a peak incidence ($> 60\%$) being reached in the age group of 50-70 years [1, 2,3,4].

Brain metastases may involve any of the three compartments of the brain (dura mater, leptomeninges, subarachnoid space or brain parenchyma), being located mainly at the cerebral hemispheres and in particular the left hemisphere (85% of brain metastases) and at the junction between the white and gray substance, where the vessel lumen is narrowed and blood flow slowed down [4,5].

Survival of patients with brain metastases is influenced by their number, and metastases are unique the prerogative of colorectal cancer and renal cell carcinoma and multiple metastases are the prerogative of lung cancer, breast cancer and malignant melanoma [6].

Materials and Method

Despite the high incidence of brain metastases (occurring in 10-30% of patients with cancer in their lifetime and are found in 25-40% of cases at necropsy), in the literature there are few published studies that address the incidence, methods of diagnosis, treatment and side effects of irradiation treatment.

The aim of this study is to analyze incidence, etiopathogenesis, diagnostic methods, therapeutic conduct and analysis of treatment results in patients presenting with brain metastases as the first manifestation of malignancies either as a final stage in the evolution of malignancies.

The objectives of this study are:

1. Demographic study of patients with brain metastases diagnosed in the period 2005-2010.
2. Findings of the applied treatment.
3. Evaluation of prognosis and survival rate of patients.

We conducted a complex prospective study on a number of 81 patients with brain metastases treated in the Oncology Clinic, Radiotherapy Department of the Emergency County Hospital Craiova between 1 January 2005-31 December 2010. We excluded a number of 11 patients who

were uncooperative or declined the completion of the irradiation treatment.

Data were collected from clinical observation sheets and sheets of radiotherapy treatment monitoring and statistical processing of the database was performed using the SPSS program version 19 and Excel 2010. For the analysis of patient survival the "Kaplan-Meier" curves were used with testing the statistical significance of the difference by Log Rank test.

The symptoms for which patients were presented at admission were: in 50.61% of cases (41 patients) experienced headache, a percentage of 29.62% of the cases (24 patients) showed signs of the outbreak, a percentage of 13.58% of the cases (11 patients) experienced headache and central type vomiting part of the intracranial hypertension syndrome and in 6.17% of cases (5 patients) experienced deterioration of intellect. (Fig.1)

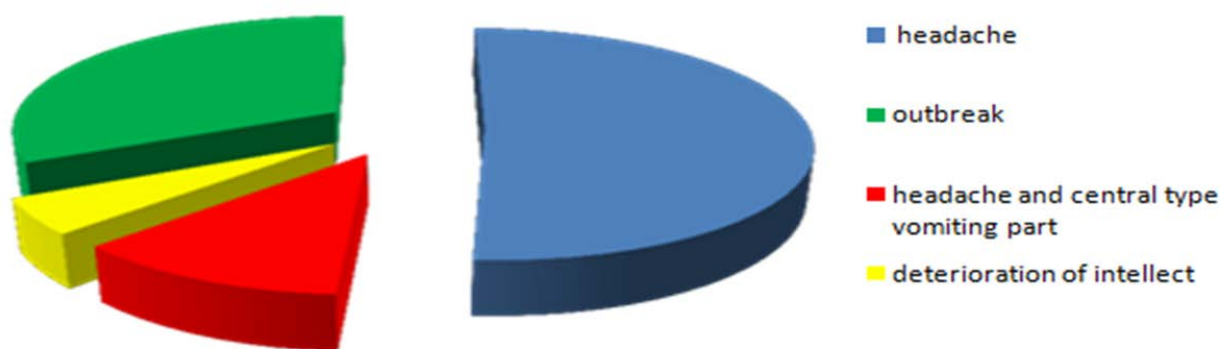


Fig.1: Percentage representation of symptoms at admission

In order to establish the diagnosis Computer tomography with contrast was performed in all

patients on admission, including patients admitted through the emergency room. (Fig.2).

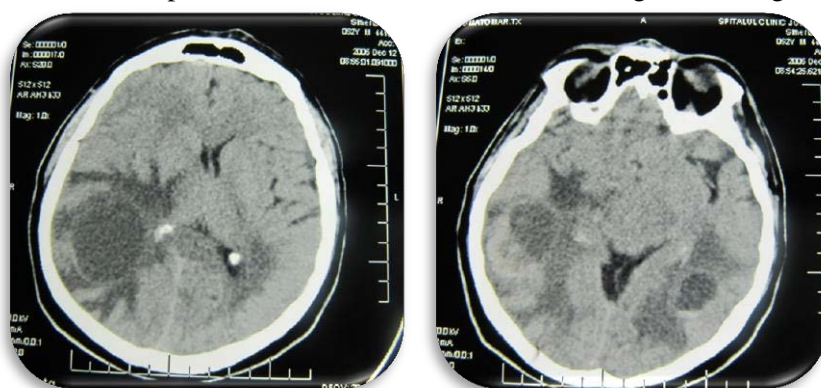


Fig.2: Brain metastases predominantly cystic temporal lobe bilaterally with perilesional edema in a patient diagnosed with lung cancer right upper lobe.

MRI examination was performed only in selected cases, 16 patients (19.75%) with

uncertain imaging diagnosis or computed tomography. (Fig.3 a, b and Fig.4. a, b, c, d, e, f) .

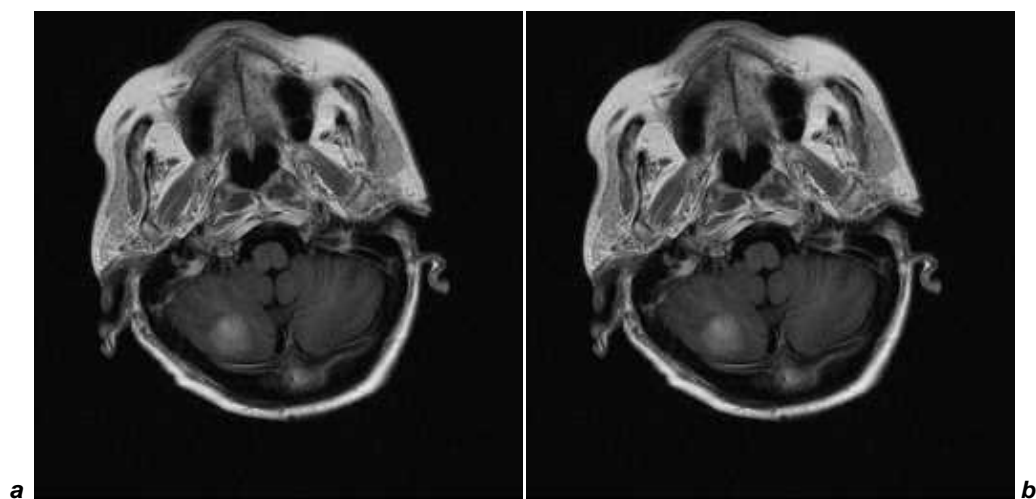
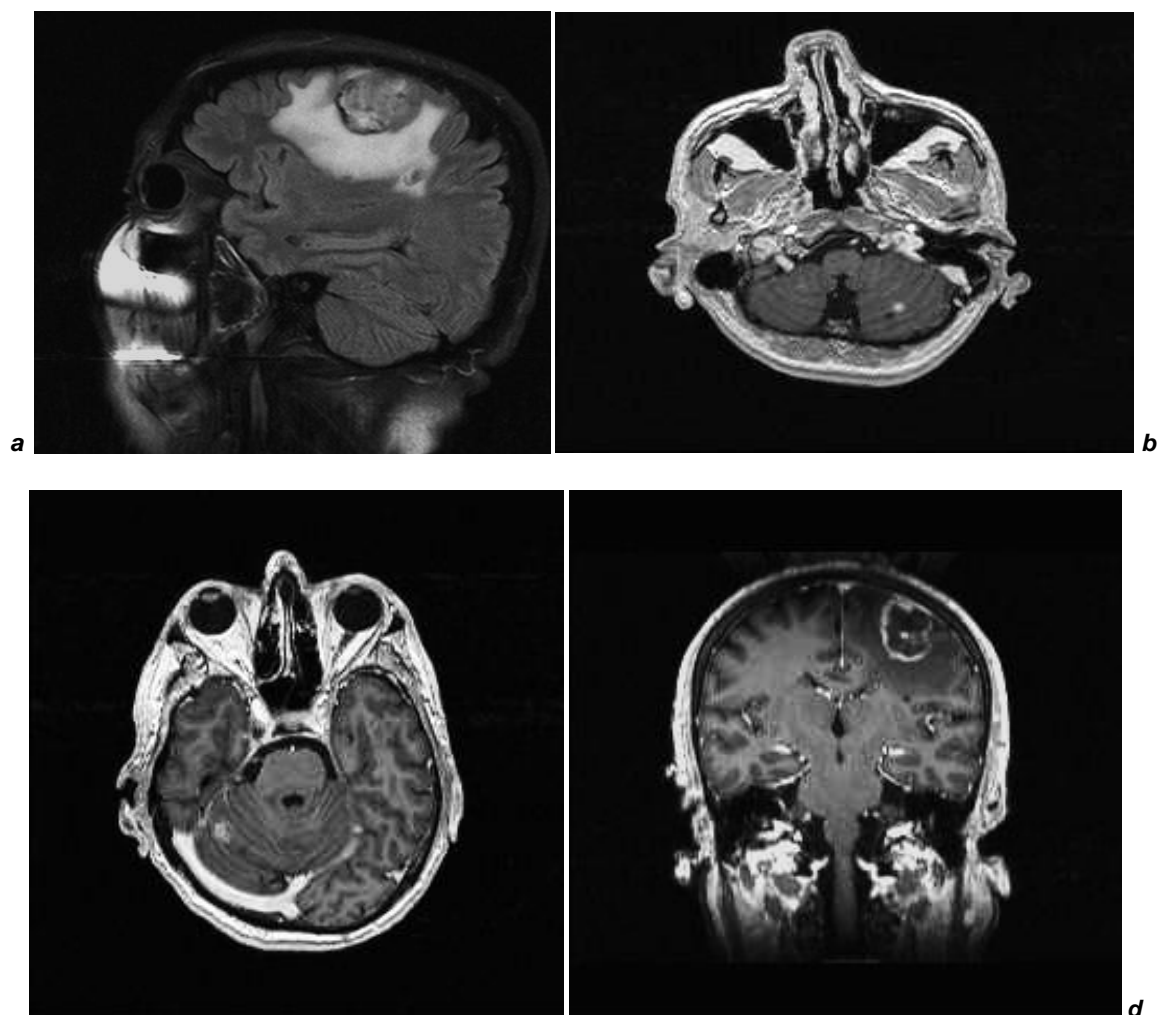


Fig.3 a, b: Infratentorial brain metastasis - native MRI sequences (a) and postcontrast (b) - right cerebellar hemisphere nodular mass with necrosis from treated breast cancer.



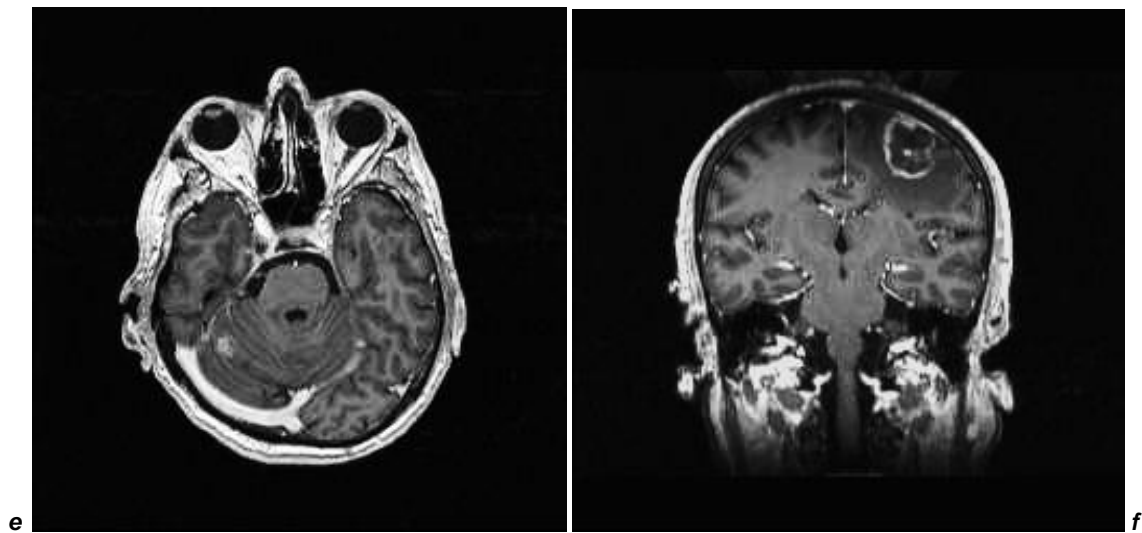


Fig.4 a, b, c, d, e, f: Native and postcontrast MRI brain study in a patient with metastatic lung cancer and multiple bleeding metastasis located infra and supratentorial

Control computer tomographic examination was carried out 2-3 months after irradiation, only 69.13% (56 patients), the remaining 30.86% (25 patients) didn't present for the imaging control. Whereas most patients had multiple metastases, radiotherapy was the main therapeutic method. Only in 8 patients, who initially were suspected with primary brain tumor after imaging examination, surgery was practiced, and pathological examination of those tumors revealed they were metastases with lung cancer starting point. We mention that including this category of patients, where surgery was practiced as a first therapeutic gesture benefit from adjuvant external beam radiotherapy. We have no data on patients with solitary brain metastases diagnosed with imaging methods that had indication to address the Bagdasar-Arseni Neurosurgery Department in order to perform gamma knife radiotherapy, and to compare therapeutic efficacy of the two methods, gamma knife radiotherapy vs external beam radiotherapy. During the period 1 January 2005 - December 31, 2010 a total of 81 patients received irradiation treatment in the Radiotherapy Compartment of the Oncology Clinic at the Emergency County Hospital ECraiova, the treatment being carried out in most patients (68 patients-83.95%) with a cobalt therapy machine type Theratron 75 and Varian linear accelerator, E = 6 Mv (13 patients, 16.05%). Irradiation was performed in the

supine position by two opposite and parallel fields. The radiation dose was 30 Gy administered in 10 fractions (3 Gy / fraction) in 12 days. Simultaneously with symptomatic treatment, cerebral depletion (mannitol 20% 125ml), antiinflammatory (Dexamethasone 8 mg) and painkiller if needed. In patients with major neurological deficits: hemiplegia, aphasia, phenomena of intracranial hypertension hospitalized in the Medical Oncology Clinic, an emergency depleted treatment was established with Mannitol 20% 125ml administered 1-3 times per day depending on the severity of the case and Dexamethasone 8 mg administered 1-3 times per day.

Results

During the period 1 January 2005 - December 31, 2010 a total of 81 patients diagnosed with brain metastases were treated and a number of 11 cases were excluded from the study due to non-cooperation or refusal of treatment.

Distribution of the 81 cases studied in this period was as follows: in 2005 there were registered a total of eight new cases, in 2006 a total of nine new cases, in 2007 a total of 11 new cases, in 2008 a total of 14 new cases, in 2009 a total of 18 new cases and 2010 a total of 21 new cases. (Fig.5)

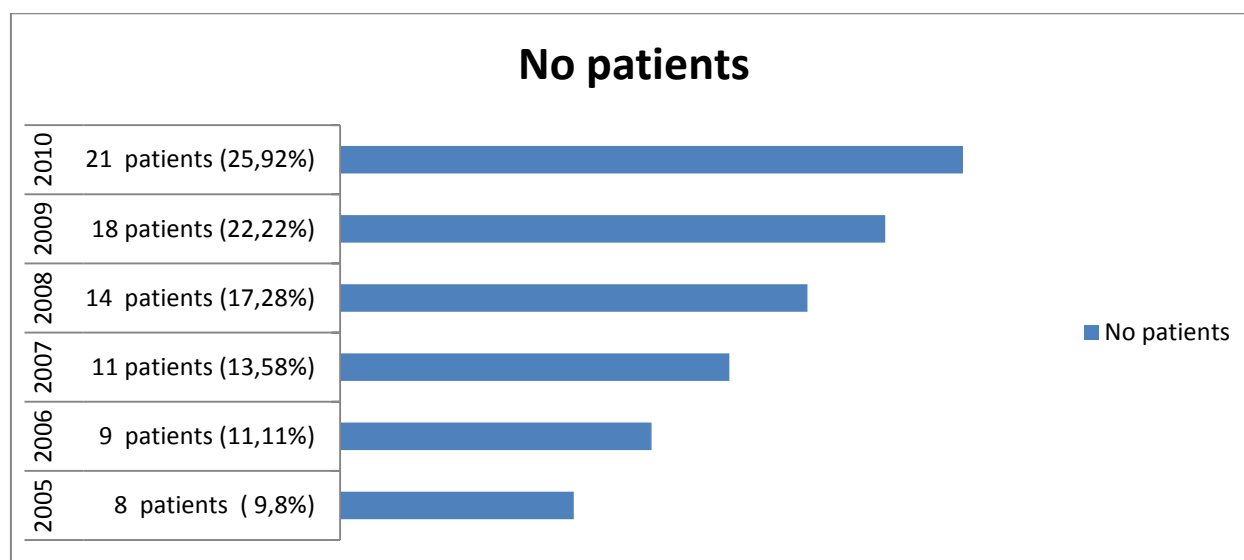


Fig.5: Distribution per years of study batch of patients

Of the 81 patients, 48 patients were male, accounting for 59.25% of cases, with a predominance of metastases from lung cancer, and 33 patients were female, accounting for 40.75%, with a predominance of metastases originating from breast cancer. Male / female ratio was 1.4 / 1. Regarding the age, we recorded a maximum frequency in age groups 61-70 years with 35 cases, representing 43.20% and 51-60 years with 29 cases, accounting for 35.80%, with a mean age of 60.34 years (SD = 8.708), with minimum 32 years and maximum 79 years ($p = 0.057$).

In the age group 61-70 years we have seen a predominance of males with 23 cases (65.71%) than females with 12 cases (34.28%) and the age group 51-60 years the ratio is reversed with predominance of females with 18 cases

(62.06%) compared to 11 cases in males (37.93%). The differences are due to lung cancer predominance in group 61-70 years and breast cancer in the age group 51-60 years.

Analysis by gender revealed that the age group below age 65 (37 patients, 46.67%) there is a predominance of females: 24 patients (64.86%) compared with 13 patients (35.13%) in men, while in the age group over 65 years (44 patients, 54.32%) report changes, predominantly male, 32 patients (72.72%) than female, 12 patients (27, 27%).

Comparing the average age between the sexes using t test we found that the average age of women ($M = 55.04$, $SD = 8.05$) was significantly lower ($p = 0.000$) than men ($M = 64.17$ $SD = 8.05$) (Fig.6)

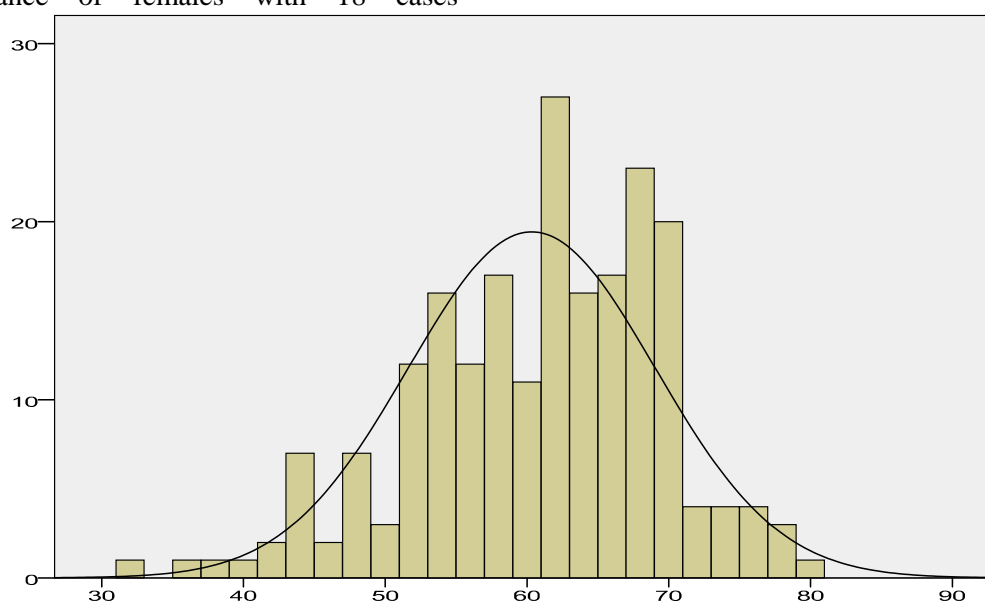


Fig.6: Average age of the lot (mean 60,34±8,708)

Depending on the starting point of the metastases, lung cancer was ranked first with a percentage of 45.67% of the cases (37 patients), followed by metastases with starting point breast cancer in 32.09% cases (26 patients), digestive tract cancer cases were responsible for 3.70% of brain metastases (3 patients), renal neoplasm 2.46% (2 patients), melanoma 2.46% (2 patients) and in 13.58% of cases (11 patients) the point of departure could not be said (Fig.7)

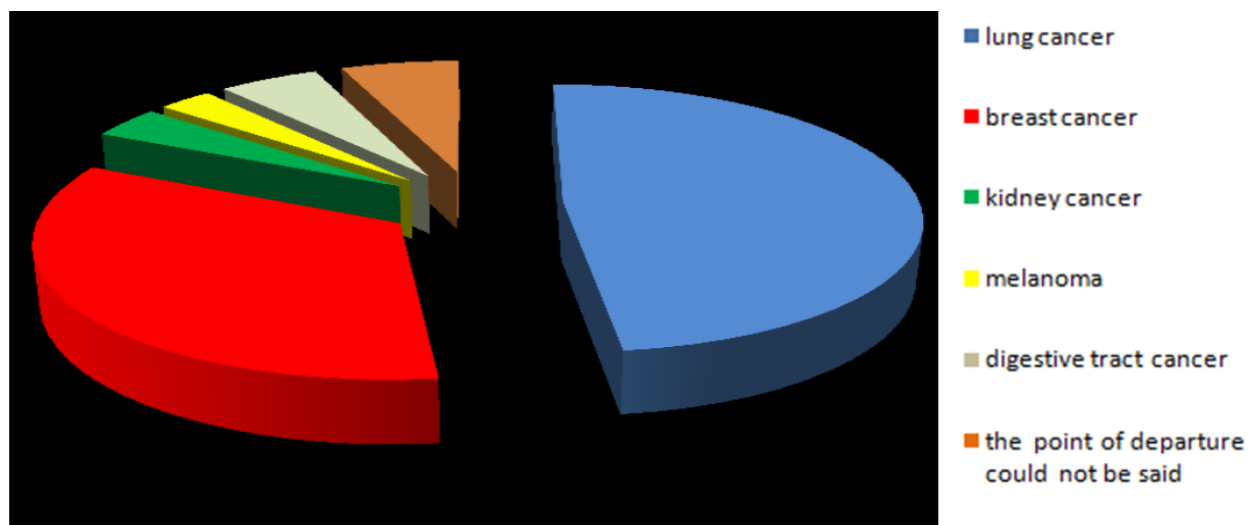


Fig.7: Graphical representation of the distribution of cases by the starting point

Of a total of 37 metastases from lung cancer starting point, 6 cases (16.21%) were registered in females and 31 (83.78%) males. In the case of the 26 patients with brain metastases with starting point breast cancer, they were present only in women and in the case of brain metastases with starting point kidney cancer, digestive cancer and melanoma they were found only in males with 3 cases, respectively two cases of kidney cancer and melanoma. In the case of the 11 patients with metastatic unspecified starting point were 10 male patients (90.90%) and 1 female patient (8.2%).

Taking into question the age and variety of primary tumor we have seen a maximum

frequency of lung cancer in men in the age group 61-70 years (23 patients / 31 cases, 74.19%) and of breast cancer in women in group age 51-60 years (18 patients / 26 cases, 69.23%). The duration of the latency interval from the detection of primary tumor to the onset of symptoms ranged from 0 to 85 months, depending on the type of the primary tumor, with a mean free latency interval of 29.8 months, which up showed a negative correlation ($p = 0.000$) between age and free range, thus in patients with lower age the free interval is increased and those with increased age the free interval is lower (Fig.8)

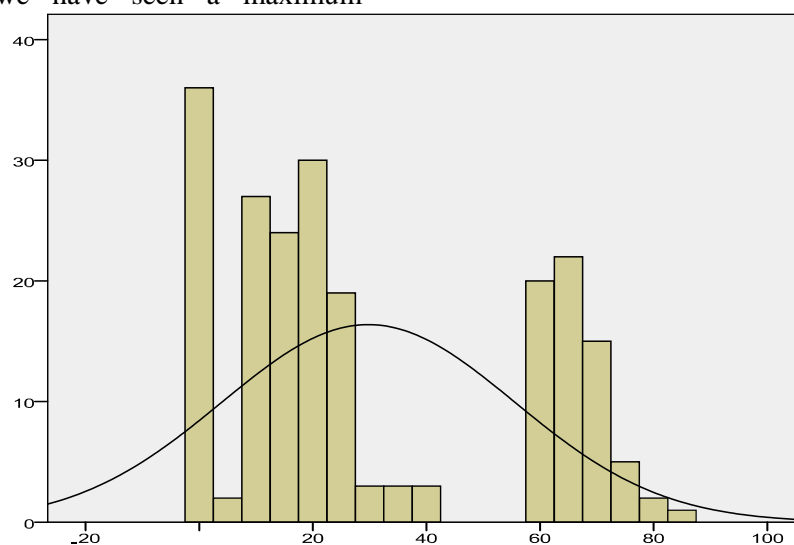


Fig.8: Average latency-free interval (mean 29.8 ± 25.817)

In terms of number of brain metastases was detected a predominance of multiple brain metastases throughout the group (73/81 patients, 90.12%), including univariate statistical analysis based on patient sex: male sex being predominance detected 44 cases of multiple brain metastases / 48 patients (91.66%), and encountered similar phenomenon in women 29cazuri / 33 patients (88.87%).Throughout the lot single brain metastases were found only in 8/81 patients (9.87%) with an identical distribution between sexes and 4 cases in men (8.4%) and 4 cases in women (12.12%) (Fig.9)

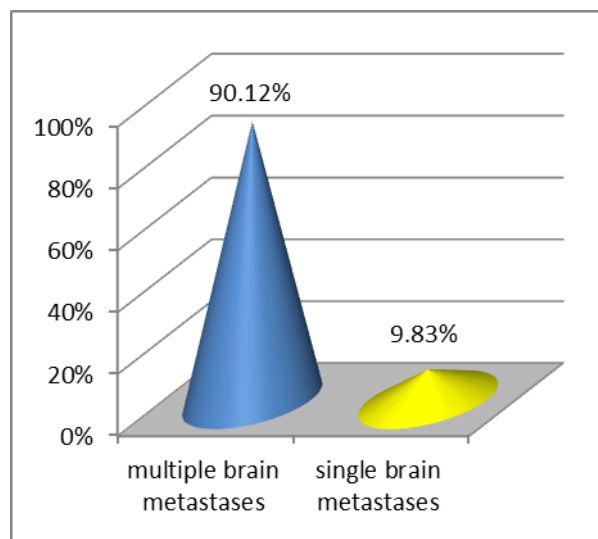


Fig.9. Graphical representation of distribution batch depending on the number of metastases

The vast majority of metastases were localized supratentorial, representing 83.95% of the cases (68 patients), the most common being localized in the frontal lobe, respectively 52.94% (36 patients), followed by those located in the the parietal lobes 35.29% (24 patients), and in a small percentage of 5.44% (8 patients) localized in the the temporal lobes, detectable with a slight predominance of left hemisphere.A small percentage of 9.87% (8 patients) of brain metastases were located subtentorial and only 6.17% of the cases (5 patients) were located both supratentorial metastases and subtentorial.From the total of 81 patients studied 11 patients (13.58%) were initially hospitalized in Neurology Clinic with a suspected stroke, being diagnosed as brain metastases with starting point undefined, 8 patients (9.87%) were hospitalized in Neurosurgery Clinic Bagdasar Arseni Bucharest with a suspected primitive brain tumor that after surgery were found to be brain metastases with starting point lung cancer

and 62 patients (76.54%) presented in the Medical Oncology Clinic at the time of occurrence of neurological symptoms, being with the primary tumor in the oncology records that suggest the presence of brain metastases as an evolution of the disease (Table 1).

Table 1: Distribution of patients under study

Clinic	No. patients	%
Neurology	11	13.58
Neurosurgery	8	9.87
Oncology	62	76.54

Statistical analysis detected a statistically significant difference ($p = 0.000$) between the group of patients who presented with uncontrolled primary tumor aspect of further development of the evolution of the disease by brain metastases (36 patients, 58.06%) compared with the 26 patients (41.93%) who had primary tumor controlled with the resumption of the evolution of disease through the development of brain metastases

Brain metastases in most cases were clinically manifested at an interval of less than 6 months from the onset of primary tumor through the distant evolution of the disease (36 patients / 62 cases in evidence-oncological 58.06%) and 12 months survival rate from diagnosis was low, being registered in patients with controlled primary tumor and distant resumption of evolution of the disease (14 patients / 62 cases in evidence oncological -22.58%) which proves the aggressive nature of brain metastases.

From the total of 81 patients treated by "whole brain" radiotherapy, in 65 patients (80.24%) of the cases was achieved complete or partial remission of neurological symptoms and 14 patients in this group (21.53%) complete remission of the disease was clinical and imagistic with disappearance of symptoms over several months. But in 16 patients (19.75%) symptoms were aggravated by the disease evolution, which was confirmed by imaging methods.

During and in the first days post irradiation various acute side effects occurred as follows: headache, nausea in 73 patients (90.12%), redness and skin peeling hairy head to 63 patients (77.77%), abnormal view 32 patients (39.50%).

Alopecia was observed in all patients and sudden neurological damage to over half of patients, respectively in 43 patients (53.08%). Late side effects were found in patients with a survival greater than a year, respectively in 12

patients (14.81%), manifested by reducing storage capacity in 7 patients and in 5 patients slowness in thinking.

Statistical analysis of survival

Statistical analysis of the survival data was performed in all patients. We studied survival rate using the Kaplan-Meier method. The

median overall survival was 9.59 months (survival minimum recorded was 1 month and maximum of 48 months) and median survival of 7 months. At 12 months after diagnosis the percentage of survivors was decreased, 20.98% (17 patients), which demonstrates the aggressive nature of brain metastases (Fig.10).

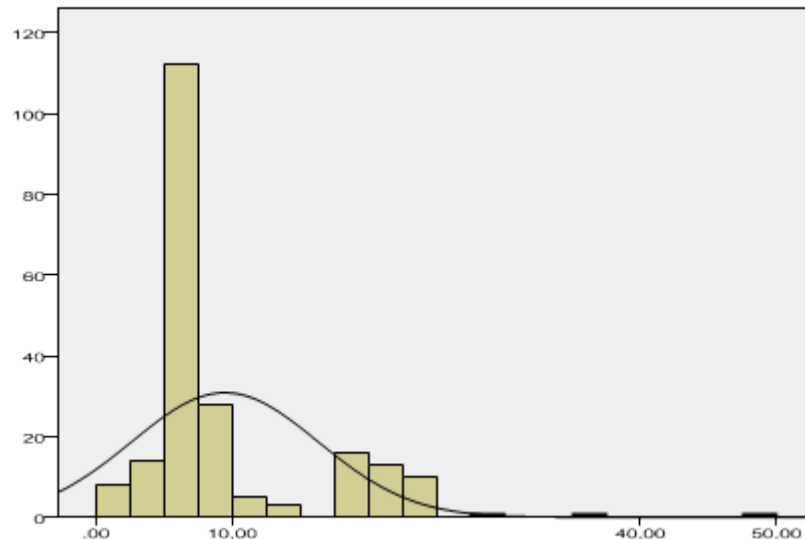


Fig. 10: Overall survival (mean 9,47±6,848)

Median survival in patients with brain metastases differs significantly depending on the type of primary tumor ($p = 0.000$): lung cancer median survival of 7 months, breast cancer median survival of 18 months, digestive cancers

median survival of 6 months, kidney cancer median survival 3 months, melanoma median survival of 5.1 months median survival in unspecified starting point was 6 months (Fig.11).

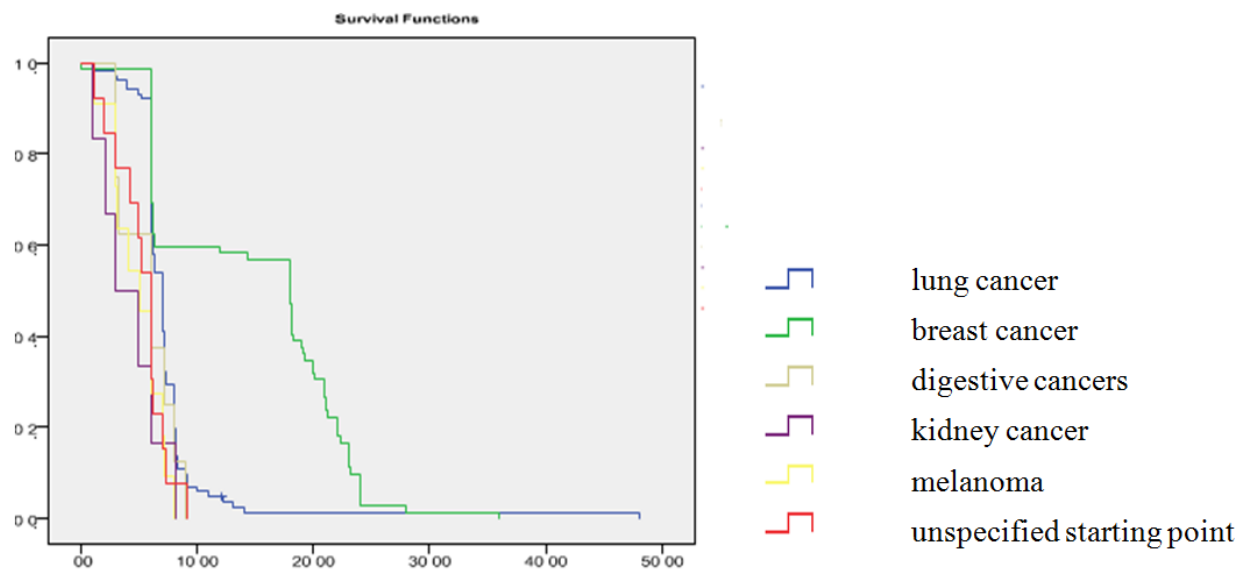


Fig. 11: Median survival depending on the starting point of metastasis

Median survival for single metastases was 14 months and for the multiple of 8.3 months with no statistically significant difference in the number of metastases ($p = 0.088$).

Survival is influenced by the number of metastases and the sex of the patients as such: in female patients with single metastases median survival was 18 months in patients with multiple metastases 7.2 months ($p = 0.280$) and in male

patients with single metastases have a median of 7.2 months in patients with multiple metastases of 6.2 months ($p = 0.724$), which is understandable considering the favorable prognosis of breast cancer in women predominantly, comparing with poor prognosis of lung cancer recorded mainly in males (Fig.12).

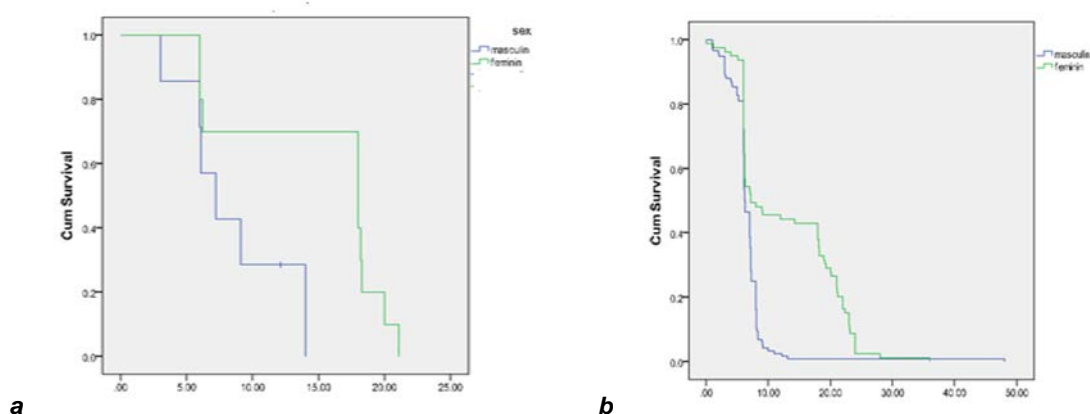


Fig. 12: Median survival depending on the number and sex of the patient metastasis: a. multiple brain metastases b. single brain metastases

Median survival is influenced without being detected statistically significant differences in function of the control of the primary tumor, so a controlled primary tumor in patients with distant resumption of the evolution of disease

through brain metastases was 7.2 months while those with uncontrolled primary tumor who continued the distant evolution of disease by brain metastases was 6.1 months (Fig.13).

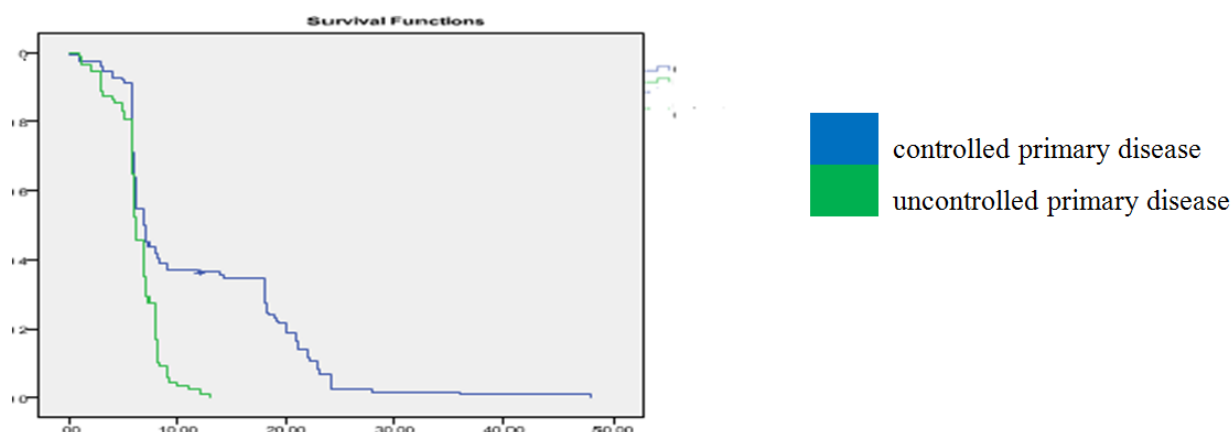


Fig. 13: Median survival of patients with primary disease controlled and uncontrolled primary disease

Survival of patients whose brain metastasis was the first manifestation of primary tumor was significantly reduced compared with that of patients who have brain metastases occurred after a disease-free interval of more than one year ($p = 0.000$). Thus, the median survival in patients whose disease onset was brain

metastasis was 6.2 months, in those under one year free interval (continuation of distant evolution of the disease) of 6.1 months, in patients with open interval over a year (resumption of distant evolution of the disease after initial therapy) recorded the longest median survival 7.2 months (Fig.14).

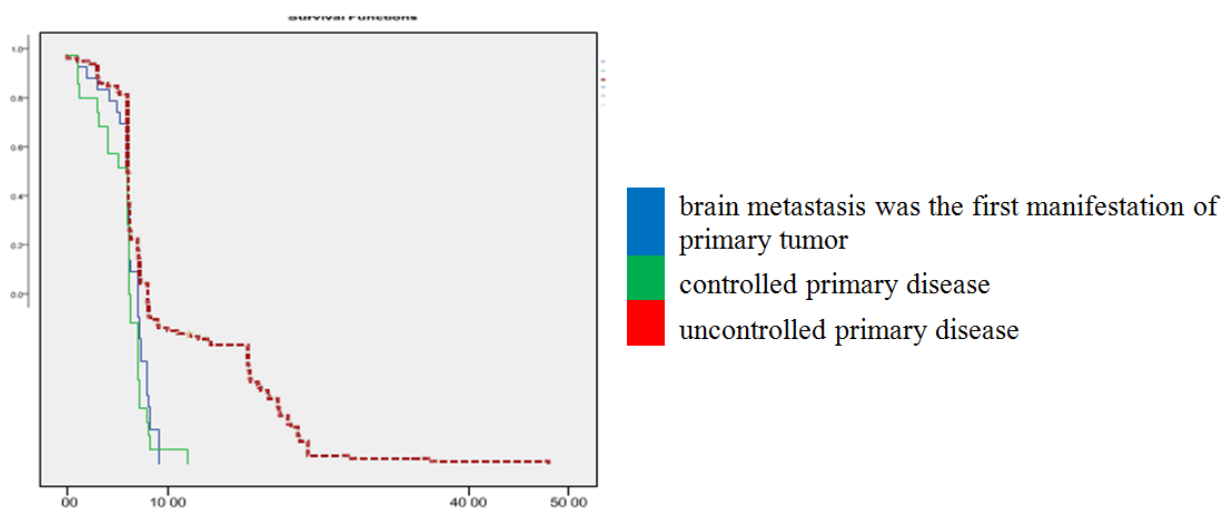


Fig. 14: Median survival depending on disease free interval

Discussion

The incidence of brain metastases is 12 / 100,000 people per year, and 25% -35% of patients diagnosed with neoplastic localization develop brain metastases, and in 6-8% of patients with brain metastases, the primary cancer remains unknown until the patient died (1,2,3).

Brain tumors affect the population regardless of age or sex and is an important cause of morbidity and mortality. Thus it can directly affect an eloquent area (speaking, motility etc.) or can be lying next to them, and with how much younger the person is, the neurologic sequelae are more severe and the patient needs special support from family and society [7,8]. The most important factors for a favorable prognostic are good functional status, the presence of a single brain metastasis, systemic absence of metastases, controlled primary tumor and age 60-65 years [9, 10].

Brain metastases, especially the multiple produce symptoms both by destruction of the brain, and by compression, the intracranial hypertension manifests itself through headaches, vomiting, papilledema, disorders of consciousness, cardiovascular and respiratory disorders, seizures, generalized [11-15].

The investigation of choice in the imaging diagnosis of brain metastases is magnetic resonance imaging, where brain metastases are described as injuries that capture contrast, vasogenic edema and if it is not available CT scanning allows the diagnosis [16-20].

Therapeutic strategy is conditioned by the number of brain metastases (single or multiple)

extracranial extension of the disease and performance status of the patient [21, 22, 23].

The majority of brain metastases are located supratentorial (about 2 / 3- 3/4 of cases), especially in the frontal and parietal lobes.

Surgery is possible in a small number of cases as it is limited to unique metastases, localized in accessible areas in patients with good performance status (Karnofsky score > 70), and age less advanced, without visceral metastases, and controlled primary tumor. Surgery will be completed mandatory by radiotherapy. [24,25].

The indications of radiotherapy are dictated by the degree of neurologic status of the patient, a profoundly altered general status involving a reduced chance of improvement. Objective of the radiotherapy treatment is to improve neurological recovery with improvement of headache, the movement disorders or psychiatric disorders, data published in the magazines reading a response rate to 70-90% of cases. [32-36]. Corticosteroids (dexamethasone) reduce peritumoral edema and intracranial pressure relieving headache (75,76,77). Anticonvulsant therapy is required in patients who have already had a seizure to the time of diagnosis of brain metastases. (79,80). Chemotherapy did not demonstrate efficacy in the adjuvant treatment or concomitantly with radiotherapy because of the blood brain barrier, although MRI exams and CT imaging reveal increased permeability at the level of brain metastases [26-31].

The average age of all patients was 60 years, but the average age of women (55 years) was lower compared to men (54 years), being reached the threshold statistical significance ($p = 0.000$) with a male / female 1.4 / 1. In discussing

sex, age and variety of tumor have detected a maximum frequency of lung cancer in men in the age group 61-70 years and of breast cancer in women in the age group 51-60 years.

Most patients were presented with multiple metastases (90.12%) and poor general condition with a poor prognosis, which required whole brain irradiation. The results obtained are overlapping but those in the literature with neurological symptoms resolved in 80.24% of cases (65 patients) and 14 patients in this group was complete remission and imaging confirmed.

Average latency-free interval from primary tumor detection to onset of symptoms was 29.8 months, up showed a negative correlation between age and free interval, in patients with lower age free interval is increased, and at the increased age free range is lower.

But in the most cases, brain metastases were clinically manifested at an interval of less than 6 months from the onset of primary tumor, through distant evolution of the disease (36 patients / 62 cases in evidence-oncological 58.06%) and the 12 months after of diagnosis the survival rate being registered was low in patients with controlled primary tumor and distant resumption of the evolution of disease (14 patients / 62 cases in evidence oncological -22.58%).

The median survival of 7 months, is higher than in specialized studies that show a median survival of 6 months.

Multivariate statistical analysis has detected the survival rate statistically significant differences depending on the manner the primary tumor and brain metastases debut as the first manifestation of neoplastic disease or its evolution.

Thus, median survival was 18 months in the breast cancer, 7 months in lung cancer seven months, 6 months in digestive tract cancer and metastases with undefined starting point, 5.1 months in the melanoma and 3 months in kidney cancer ($p = 0.000$).

Survival of patients whose brain metastasis was the first manifestation of the disease (6.2 months) was significantly reduced compared to patients whose brain metastases occurred after a disease-free interval of less than one year (6.1 months) or over one year (7.2 months) ($p = 0.000$).

On multivariate statistical analysis of survival rates were not statistically significant differences detected depending on the number of metastases and sex of patients, respectively locoregional status of the primary tumor.

Median survival for single metastases was 14 months and for the multiple 8.3 months ($p = 0.088$).

Survival is influenced by the number of metastases and patient sex: female patients with single metastases median survival was 18 months, in patients with multiple metastases 7.2 months ($p = 0.280$) and in male patients with unique metastases median survival was 7.2 months in patients with multiple metastases of 6.2 months ($p = 0.724$), due to favorable to prognosis of breast cancer in women predominantly, comparativ with poor prognosis of lung cancer in men. Median survival in patients with primary tumor controlled and distant resumption of the evolution of disease was 7.2 months while those with uncontrolled primary tumor with continued evolution of the disease was 6.1 months.

Conclusions

The gender distribution of the study group showed a slightly higher incidence to male patients, with a male / female ratio of 1.4 / 1.

The average age of all patients was 60 years, but the average age of women (55 years) was low compared to men (54 years), being reached the threshold statistical significance ($p = 0.000$). The most affected age group was 51-60 years for women and 61-70 years for men.

Lung cancer (48.11%) and breast cancer (36.96%) were the main starting points for brain metastases.

In discussing sex, age and variety of tumor we have detected a maximum frequency of lung cancer in men in the age group 61-70 years and of breast cancer in women in the age group 51-60 years.

Headache was the predominant symptom in the clinical picture of our casework being present in 41 patients (50.61%), followed in order by signs of outbreak (29.62%), vomiting (13.58%) and intellectual deterioration (6.17%).

Most cases were presented with multiple metastases (90.12%), single metastases are present only 9.87% of patients in the study.

Average latency-free interval from primary tumor detection to onset of symptoms was 29.8 months, up showed a negative correlation between age and free interval in patients with lower age free interval is increased, and at the age grown free range is lower.

All brain metastases, regardless of origin, size and the number receiving treatment irradiation dose of 30 Gy in palliative / 10 fractions / 12

Brain metastases were clinically manifested in most cases at an interval of less than 6 months from the onset of primary tumor through resumption of distant evolution of the disease (36 patients / 62 cases in evidence-oncological 58.06%) and 12 months survival rate was registered lower in patients with controlled primary tumor (14 patients / 62 cases in evidence oncological -22.58%) which proves the aggressive nature of brain metastases. Median survival of patients with brain metastases was irradiated was 7 months.

Multivariate statistical analysis has detected the survival rate statistically significant differences depending on the type of primary tumor ($p = 0.000$) and the manner the onset of brain metastases as the first manifestation of neoplastic disease or its evolution ($p = 0.000$).

Survival was influenced without the reached threshold of statistical significance of the number of metastases ($p = 0.088$) and patient gender (male $p = 0.724$, female $p = 0.280$) and the locoregional status of the primary tumor, primary tumors uncontrolled with continued of the evolution of disease or primary tumor controlled with the resumption of distant evolution of disease ($p = 0.724$).

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