LUCIAN BLAGA UNIVERSTY OF SIBIU

"Victor Papilian" Faculty of Medicine of Sibiu

Abstract of the Doctoral Thesis

MANAGEMENT OF BRAIN METASTASES IN ADULT PATIENTS

Scientific coordinator,

Prof. dr. Pereanu Marcel

Ph.D student,

Vitan Codruta Marina

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Introduction

The development of brain metastases is one of the most devastating complications of malignant tumor progression. Brain is locked into a rigid box so any increase in intracranial volume is incompatible with life (7).

Brain metastases incidence

The incidence of brain metastases varies considerably, accurate data is extremely difficult to obtain as dependent mainly addressing system and investigation of all malignancies. Literature data obtained after surgery in patients stable clinical status, have suggested that brain metastases are relatively infrequent relative to 1 – 10 against primary brain tumors.

Further data showed that brain metastases occur up to 10 times more common than primary tumors. In a cohort study conducted in Netherlands in 2002 showed that 8,5% of cancer patients develop brain metastases. This study showed a cumulative incidence in a 5 years period estimated at 16%, 10%, 7%, 5% and 1% in patients with lung cancer, renal carcinoma, breast cancer and colorectal carcinoma. This estimates of incidences for specific pathologies could be applied to estimate new cases of cancer in the United States in 2003, leading to an estimated 60000 cases of brain metastases. However, on the basis of the data obtained at necropsy the number of cases with brain metastases exceed 170000(1,2,3,4).

Approximately 25% of cancer patients will develop brain metastases. Patients with melanoma (50%), lung cancer (30-50%) and breast cancer (20%) have the highest risk of metastases. On the other hand, testicular tumors (15%), oropharynx carcinoma and skin carcinoma rarely metastasize to the brain (1).

The incidence of multiple brain metastases is higher than that of single metastases which are present in 50-70% of patients (5,7,8,12).

Most published studies show that patients gender does not influences the overall incidence of brain metastases. Generally, differences occur due to the predominance of a certain type of cancer one sex. So lung cancer and melanoma brain metastasize more frequently in males and breast cancer is the leading cause of brain metastases in women (13).

Patient's age is one of the factors influencing the incidence of brain metastases, which are more common in adults than in children.

In adults the maximum incidence (›60%) is observed in the age group of 50-70 years. In patient over 70 years is a decrease incidence (13).

Etiopathogeny

Pathophysiology of brain metastases is a complex multistep process, mediated by molecular mechanisms; from the primary body cancer cell must transform, grow and be transported to the CNS where they can lay dormant for different period time before the invasion and growth continues.

The dissemination is done through blood circulation, lymphatic or venous circulation.

Metastatic process includes a series of complex events involving sequential subpopulations of tumor cells. Metastatic cells that colonize the brain "escape" from the primary tumor, penetrate into lymphatic or venous system of the organ, than enter the right heart and through the pulmonary artery reaches the lung or pass foramen ovale into the systemic circulation; once in the systemic circulation they reach the brain circulation, penetrate the brain capillaries or venules, cross the vessel wall and into the brain where it develops micrometastases (14,15).

Brain metastases may involve any of the three compartments of the brain: dura mater, leptomeningis (subarachnoid space) or brain parenchyma.

Metastases initially affects one compartment and then invades then invades the others as they grow in size.

Parenchymal lesions can occur anywhere in the central nervous system, but most are supratentorial brain metastases; the most common location is in the cerebral hemispheres (85% of all brain metastases) at the junction between gray and white matter, where the vascular lumen is narrowed and blood flow slowed (14,23).

Number of brain metastases

The survival of patients with brain metastases is influenced by the number of brain lesions.

The literature discusses of single brain metastases (when there is only one lesion) and solitary brain metastases (when single brain location is known as the only place of metastatic disease) (16).

Multiple metastases occur frequently in lung cancer, breast cancer and melanoma. Single metastases occur in colorectal and renal carcinoma (24).

Histology

The surface of the brain suffers chnges that can plead for brain metastases: swelling more or less important, predominantly in the hemisphere where metastases is, often can be observed a herniation of temporal lobe with torsion of brainstem. In addition to cerebral edema the brain surface may have dirty yellowish area with dark points, brown, often delimitated and where the brain is soft almost crumbly. In section we can see one or more tumors, well circumscribed in the same lobe or widespread, in various sizes and aspects.

Metastases can develop in any part of the brain and they have a distribution in relation to vasculature and are more common in the left hemisphere and the boundary between the cortex and white matter (13,25,26).

Although macroscopic the brain metastases are well defined, there is a microscopic diffusion of tumor cells along the perivascular spaces surrounding brain tissue with perivascular sleeves form composed of neoplastic cells.

There can be isolated following histological types: epithelial type, gelatinous, encephalomalacia, hemorrhage, glial, perivascular, encephalitis and melanin (25,26).

Symptoms

In the evolution of cancer about 2/3 of the metastases become clinically apparent and may be the first manifestation of cancer. Any neurological symptoms in a patient with cancer must be considered and investigated as a brain metastases (1).

Signs and symptoms in cerebral metastatic disease occur through two mechanisms: the emergence of intracranial hypertension or development of the brai metastases.

Signs and symptoms caused by intracranial hypertension

Intracranial hypertension is manifested by a wide variety of signs and symptoms: headache, vomiting, papilledema, impaired consciousness, cardiovascular and respiratory disorders, generalized seizures (29,30,31).

Headache is a characteristic symptom of intracranial hypertension, is part of the semiology of all brain tumors, regardless of the nature and location.

In patients with brain metastases headache occurs early in 40-50% of cases. It is present more frequently with multiple metastases and those located in the posterior fossa. Headache can be diffused, permanent, gradually increased in intensity and may sometimes be accompanied by other sings of intracranial hypertension as nausea, vomiting and visual disturbance without value in locating metastases (24,27,31,32,33).

Vomiting often are late, appearing in two thirds of cases in the morning without preliminary nausea and abdominal discomfort. Relieves vomiting and dehydration

headache they produce cause transient improvement intracranial hypertension syndrome (29).

Papilledema generally occurs in advanced stages and is present at 15-25% of patients with headaches. Usually causes changes in visual field. When recently installed (1 month to 10 weeks), accompanied by nausea, vomiting, and "voltage" headache papilledema is predictive for brain metastases (24,29,33).

Disorders of consciousness in characterized by a lack of interest, inactivity, decline of intellectual functions, somnolence, stupor, unconsciousness and coma (24,29).

Signs and symptoms caused by metastases development

Brain metastases can determine by the mechanical action focal seizures, focal deficit syndromes with impaired balance or gait, slurred speech or visual and sensory disorders, solitary cranial nerves touches and psycho-behavioral disorders.

Secondary signs of outbreak irritation or neural distruction are cognitive impairment, moderate or severe hemiparesis, ataxia, aphasia, papilledema, visual field changes and consciousness changes (24,29).

Clinical examination

Clinical examination of the patient is very important. It has to be done systematically, patiently and competently, but mostly complete and without bothering the patient.

Medical history is an important part of the neurologic examination, is the subjective part of the examination providing data from the patient or his family when his condition does not allow a proper contact with the examining physician.

Neurological examination in patients with clinical apparent metastases aims:

- The location of the lesion or lesions causing symptoms

- Identify the pathophysiological mechanism
- The effect of lesion: with/without mass effect
- Differential diagnosis
- Establish the necessary investigations (39).

Imaging investigation

Computer tomography

Computer-assisted tomography fundamentally contributed to the diagnosis of the primary and secondary brain tumors. The CT scan can determine the exact location, shape, extension, number, sometimes the nature of expansive process and associated changes of the ventricular system.

Cerebral CT has diagnostic sensitivity of 90 % and a specificity of about 75 % and can detect tumors less than 5 mm in diameter, allowing early diagnosis (40,41,42,43).

Magnetic resonance

MRI is superior to the CT scan examination, shows more clearly the existence of brain metastases, surrounding edema and anatomical relationships with underlying structures.

The protocol used by most clinicians includes sequences T1, T2 and post-contrast T1.

Brain metastases are presented as lesions which capture the contrast, localized at the interface between the white and the gray matter with marked vasogenic edema (43,44,45,46,49,50).

Other imaging techniques used in to detect brain metastases are perfusion MRI, MRI spectroscopy, diffusion MRI and PET (positron emission tomography) (16,51,52,53,57,59,61)

Principles of treatment

The goal of treatment is to prolong survival and improve symptoms. Treatment strategy depends on the number of brain metastases (single vs. multiple), the extension of extracranial primary malignancy and the patient's performance status.

Symptomatic treatment

Antiedematous treatment

The firs way of therapeutic approach in patients with symptomatic brain metastases focuses on combating peritumoral brain edema.

Corticosteriods reduce peritumoral edema, mass efect and descrease intracranial pressure, relieving headache and neurological symptoms. The most common commonly used corticosteroid is Dexamethasone.

If symptoms improve with other treatment methods, corticosteroids should be stopped (75,76,77).

Anticonvulsant treatment

The need for anticonvulsant medication is clear in patients who have experienced a seizure by the time their brain tumor diagnosed. Although many clinicians routinely prescribe prophylactic anticonvulsant therapy for patients with brain metastases, evidence –based medicine does not support this practice (79,80).

Systemic treatment: chemotherapy

Chemotherapy has a limited role in the treatment of brain metastases, his effectiveness in the adjuvant treatment after surgery or radiotherapy being unproven. This lack of effectiveness is partly due to the blood brain barrier, although CT and MRI examinations should reveal increased permeability imaging of the brain metastases (72,82,92).

Loco-regional treatment

Surgery

Surgery is reccomanded to a small number of cases being indicated in single brain metastases located in an accesible location, in patients without visceral metastases, to those whose primary neoplasia is controlled locally and Karnofsky score›70 (33,90,92,94).

Radiotherapy

Radiation therapy is a physical method of treatment comprising administering an amount of radiant energy to a defined target volume, while protecting the surrounding healthy tissue.

Radiotherapy is the treatment of choice for patients who require palliative care for neurological symptoms.

The main goal of radiation therapy is to improve neurological status, with relief of headache, movement disoredres or mental disorders.

Response rate is between 70-90 % of cases. Improvement of neurological function depends on the patient's neurological status at the beginning of radiation therapy. The neurological damage is more severe the chances for improvement are shorter (107,108,109,110,112,114).

Research direction

Brain metastases are the most common solid intracranial tumors identified in adults; occur as a result of hematogenous dissemination in 10 – 30% of patients with cancer during lifetime and are fonud in 25 – 40% of cases at necropsy. The growing prevalence of neoplasms leads to an increasing number of brain metastases.

Brain metastases represent a difficult diagnostic and therapeutic management issue for the doctor. The diagnosis of brain metastases is devastating both for the patient - effectively represents an emotional issue, physically debilitating and greatly influencing the survival – and relatives with significant impact on quality of life.

The Aim of Study

The purpose of this study is to analyze the incidence, etiology, main cancer that causes brain metastases, diagnostic methods, therapeutic approach in patients who present with suspected brain metastases are the first manifestation of cancer, either as final stage in the evolution of cancer.

We also analyzed the adherence to the radiant treatment, the therapeutic results in terms of improvement of neurological symptoms, survival and quality of life and side effects.

The thesis emphasizes the importance of radiation side effects whereas to fight off those effects is a major challenge.

Finally we analyzed the prognostic factors and compared with the data obtained from the literature.

The Objectives of the Study

The objectives of this study are:

1. Establish/confirm the diagnosis of brain metastases
2. Demographic study of patients with brain metastases diagnosed between 2009 – 2012.
3. Develop diagnostic and therapeutic algorithm.
4. Assessing the imaging used in the diagnosis of brain metastases.
5. Assessment of the treatment results.
6. Evaluation of prognosis and survival of the patients with brain metastases.

Material and methods

We performed a complex prospective study a total of 243 patients who presented in the department of Neurology, Neurosurgery and Oncology of County Emergency Hospital of Sibiu in the period 1st January 2009 – 31st December 2012 with suspected brain metastases.

We excluded a total of 31 uncooperative patients or who refused the irradiation.

Diagnostic criteria that we had in view were:

1. General clinic investigation - performed for all patients
2. Specialized neurological examination - performed for all patients
3. CT exam – performed for all cases
4. Nuclear magnetic resonance – only in selected cases in other medical centers

For data collection we developed a model for individual data recording for each case.

Data were entered into the computer database tables in Microsoft Excel module of the Microsoft Office 2010. Statistical analysis was performed using SPSS version 19 and Excel 2010.

For the analysis of patients survival we used "Kaplan-Meier" survival curves with statistical significance test of difference through the Log Rank test.

Irradiation treatment

Radiation therapy has been the main method of treatment in brain metastases, most cases taken to study posing with multiple metastases, poor general condition and a poor prognosis.

Irradiation treatment was performed in the department of radiation oncology of County Emergency Hospital of Sibiu with an Theratron Elite 100 telecobaltotherapy device.

The irradiation plan and the simulation were performed using MCR SIMULIX device

From 1st November 2009 to 31st December a total of 212 patients benefited from irradiating treatment. Patients with relatively good general condition, with lesser severity of neurological disorders and which could move were irradiatede on an outpatient basis.

Irradiation was performed in supine position, with two opposite and parallel fields. Irradiation is carried out at a total dose of 30Gy/10 fractions (3 Gy/fraction) in 12 days

Antiedematous treatment

Treatment of cerebral depletion was applied to all patients in the study in the firs 4 – 5 days of radiotherapy. Patients with major neurological deficits: hemiplegia, aphasia, phenomena of intracranial hypertension hospitalized in the Oncology department had the depletion therapy emergency instituted. Treatment consisted of 20% Mannitol 125 ml 1 – 3 times a day depending on the severity of the case and Dexamethasone 80 mg 1 – 4 times a day.

Histopathology

Histopathological examination was possible only in 8 patients with brain metastases who initially suspected a primary brain tumor and subsequently underwent surgery. Intraoperative tissue samples were taken and pathological examination revealed that starting point was lung cancer in all cases.

Symptoms

Symptoms for which patients were presented at admission were as follows: in 50,94% of cases patients presented headache, in 32,07 % of cases focal signs, 11,79 % headache and vomiting of central type and in 5,18 % of cases damaged intellect.

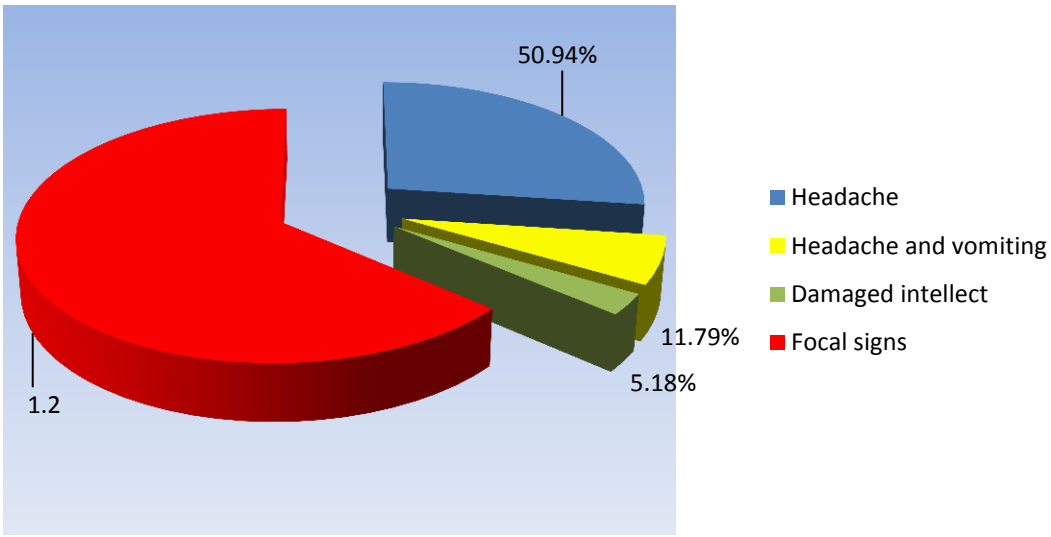

Fig 1: Percentage distribution of symptoms in admission

Imaging examination

Computer tomographic examination was performed in all patients on admission. In patients admitted to emergency performed by initially examining native CT. CT with contrast was the investigation of choice in our study.

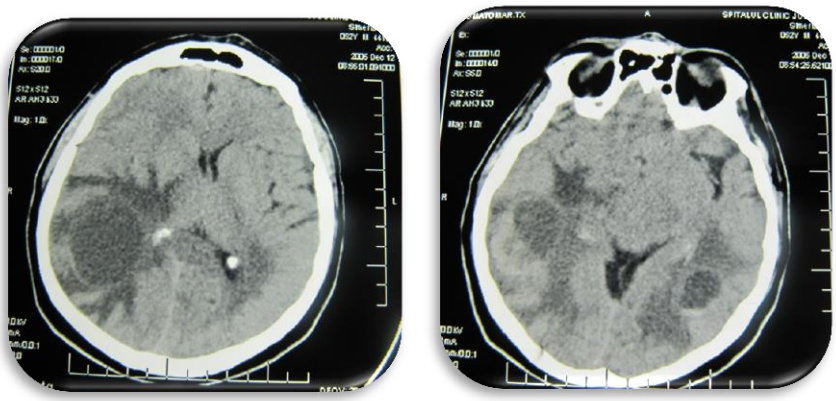

Fig 2. Brain metastases bilateral temporal with important perilesional edema in a male patient 65 years old with known right upper lobe cancer

CT examination of control was performed 4 weeks after completion of irradiation only to 72% (153) of patients, the other 28% (59%) opted for not coming to reschedule.

IRM

Nuclear magnetic resonance examination has been carried out only in selected cases in other medical centers. 42 (20%) of patients had such imaging examination.

Results

During the period 1st January 2009 – 31st December 2012 there was a total of 243 patients diagnosed with brain metastases. There were excluded from the study a total of 31 cases due to non-cooperation or refusal of treatment.

Annual distribution of cases studied

The distribution of the 212 cases in the studied period was as follows: in the year 2009 we studied 67 new cases, in 2010 51 cases of brain metastases, in 2011 a total of 53 cases and in 2012 a total of 41 new cases.

Group structure according to sex

Of the total of 212 patients 123 were men, representing 58,01% and 89 were women representing 41,99%. Male/female ratio was 1,4/1.

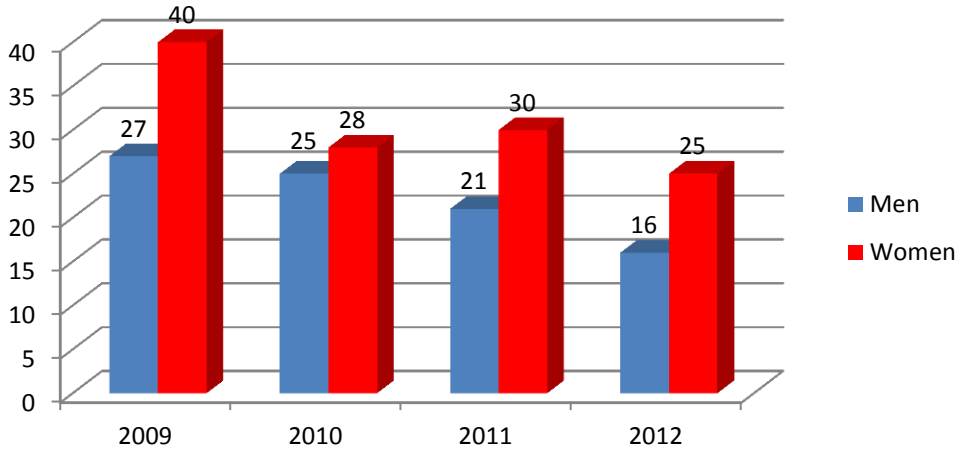

Fig. 3 Annual cases distribution according to sex

We have noted an increased frequency of men in brain metastases from lung and a predominance in women's metastases from breast neoplasms.

Group structure according to age

Regarding age we recorded a maximum frequency in age groups 61 – 70 years with 103 cases accounting for 48,58% and 51 – 60 years with 67 cases accounting for 31,60%. In the age group 61 – 70 years I noticed a male sex predominance with 77 cases (74,75%) versus female sex with 26 cases (25.24%), while in the age group 51 – 60 the ratio reverses: 41 women (61,19%) compared to 26 men (38,80%).

The differences are due to increased incidence of lung cancer at the age of 61 – 70 and breast cancer at the age of 51 – 60.

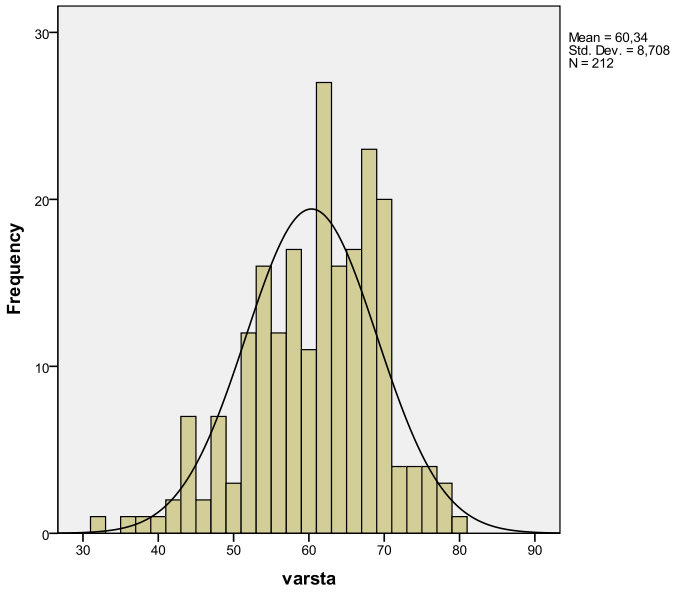

Fig. 4 Mean age of the group

The average age for the entire group of 212 patients was 60,34 years (SD=8,708) with a minimum age of 32 years and a maximum age of 79 years (p=0,057).

Casework analysis by gender revealed that in the age group ‹65 years there is a female sex predominance: 80 (37,73%) cases versus 64 cases (30,18) in men, while the age group › 65 years ratio changes.

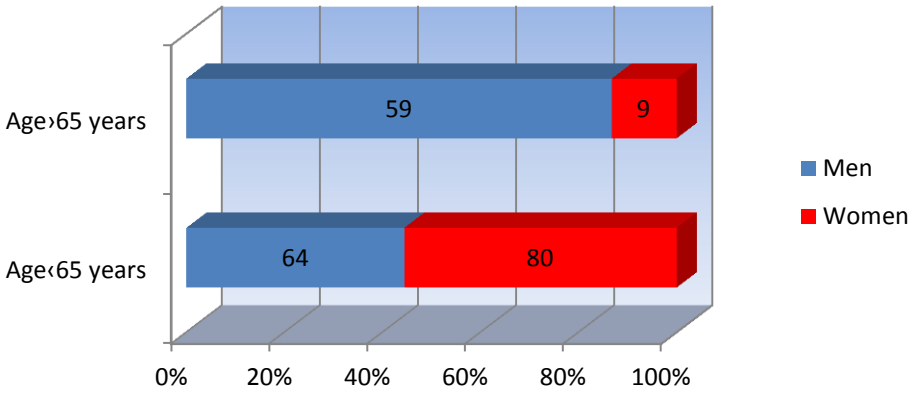

Fig.5 Graphical representation of group distribution according to age and sex

Comparing the mean age between the two genders 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).

Taking into question the variety of the primary tumor we observed a maximum frequency of lung cancer in males in the age group 61 – 71 years and of breast cancer in female at the age of 51 – 60 years.

Primary tumor variety	**Age and sex**											
	20-30 years		31-40 years		41-50 years		51-60 years		61-70 years		71-80 years	
	F	M	F	M	F	M	F	M	F	M	F	M
Lung	0	0	0	0	0	0	7	14	5	61	0	15
								21		**66**		**15**
Breast	0	0	4	0	16	0	31	0	21	0	0	0
				4		**16**		**31**		**21**		
Digestiv	0	0	0	0	0	0	0	2	0	6	0	0
								2		**6**		
Renal	0	0	0	0	0	0	0	2	0	4	0	0
								2		**4**		
Melanom	0	0	0	0	2	3	2	4	0	0	0	0
						5		**6**				
Unspecified starting point	0	0	0	0	0	0	1	4	0	6	0	2
								5		**6**		**2**
Total	0	0	4	0	18	3	41	26	26	77	0	16

Tabel 1. The frequency of brain metastases by gender, age and variety of primary tumor

Group distribution according to the primary tumor

Depending on the starting point the broncho-pulmonary tumors were ranked first with a share of 48,11% of cases, followed by metastases with starting point of breast tumors in 33,96% of cases, digestive tract 3,77%, kidney 2,83% and 6,13% of cases the starting point could not be specified.

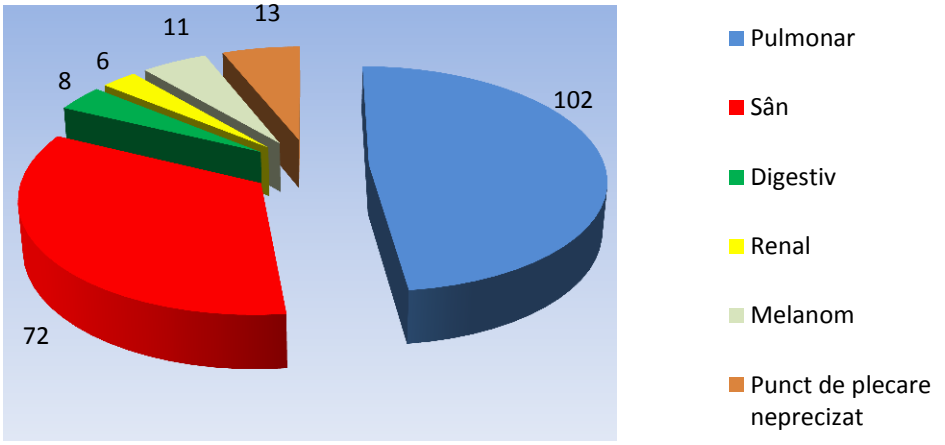

Fig. 6 Graphical representation of the distribution of cases according to the starting point

Out of 102 brain metastases with lung starting point 12 (11,77%) cases were in females and 90 (88,23%) men. In the case of secondary determinations with starting point breast cancer the wide range of work was represented by males and in the case of brain metastases with kidney and digestive starting point all cases were in males (6 and 8 cases). Tumors with unspecified starting point determined metastases in 1 (7,70%) female patient and 12 (92,30%) male.

Distribution of cases according to time elapsed from primary tumor signs to the onset of neurological symptoms caused by brain metastases

The period of time elapsed from detection of primary tumor to neurological symptoms of brain metastases ranges from 0 to 84 months depending on the type of primary tumor.

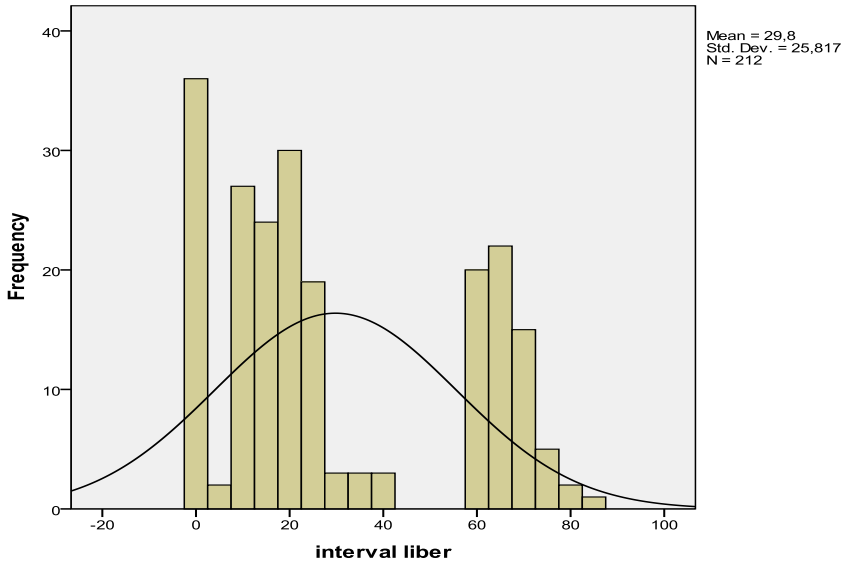

Fig. 7 Mean of the free interval

There was an average of 29,8 months free interval. Free range media did not differ significantly in the four-year review (p=0,177).

The trend of difference between the two genders is kept every year under study, the biggest difference was found in 2012 (63,94-10,92=53,02).

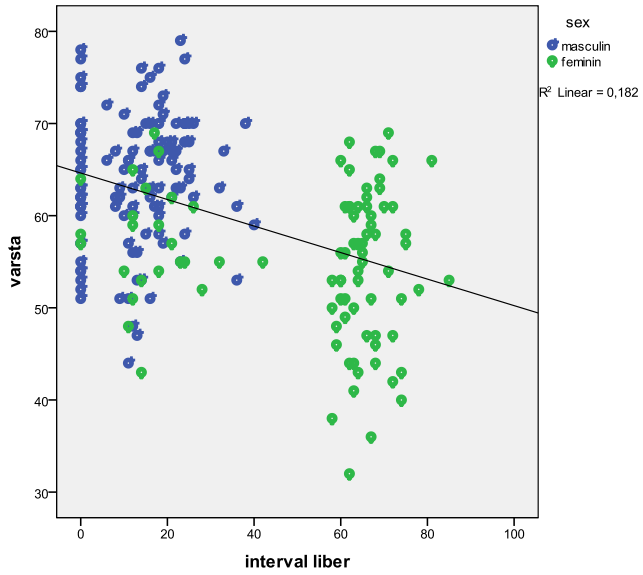

Fig.8 The evolution of the free interval

There was a negative correlation (r=-0,427, p=0,000) between age and free range, in patients with lower age the free interval is increased and in those with greater age the free interval is lower. Once the age increases the diseases free interval decreases.

Group distribution accounting number of brain metastases

Regarding the number of brain metastases we observed a predominance of multiple metastases rate of 92% compared to single metastases present only in 8% of cases.

In male patients 5,96% of metastases were single and in 91,98% of cases were multiple. In female patients the multiple metastases appeared in 88,79% of cases and the single metastases in 11,24% of cases.

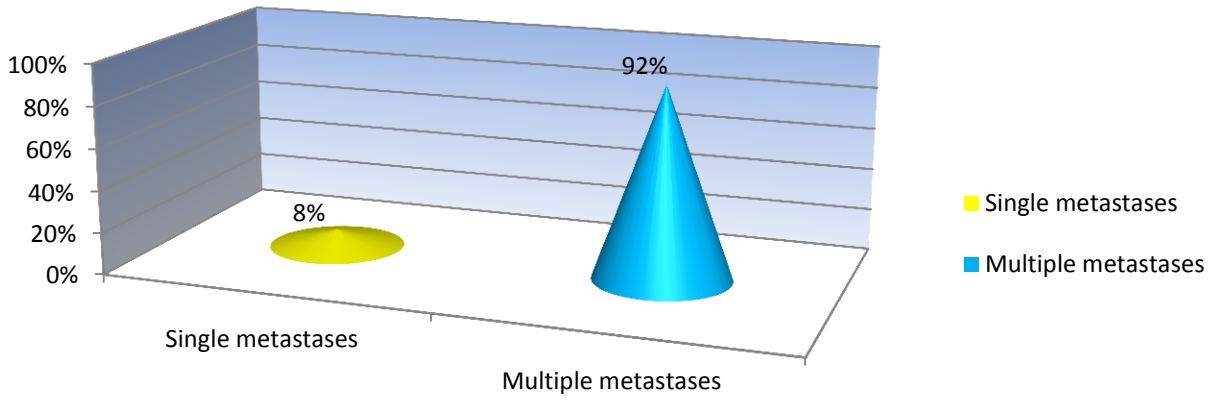

Fig. 9 Graphical representation of the distribution group by number of metastases

Group distribution according to the location of brain metastases

The vast majority of metastases were located supratentorial, representing 83,96% of cases. In 10,86% of cases were found infratentorial metastases and only 5,18% of the metastases were located both supratentorial and infratentorial.

In terms of frequency of unique brain metastases location the 17 single brain metastases were mostly located supratentorial (79%). In the supratentorial location the

most common were front lobes (10, 58,82%) followed by the parietal lobes(7, 41,17%). In my study there is a slight predominance of the left hemisphere.

The distribution of cases studied

Of the total number of 212 patients taken to study 36 (16,98%) were initially admitted in the Neurology Clinic with suspicion of stroke, 8 patients (3,77%) were admitted to the Neurosurgery Clinic with suspected primary brain tumor and which after surgery have proved to be metastases and 168 patients (79,25%) presented in the Oncology Clinic being already in oncological record with primary tumor at the time of the appearance of neurological symptoms that suggested the presence of brain metastases.

Clinica	Number of patients	%
Neurology	36	16.98
Neurosurgery	8	3.77
Oncology	168	79.25

Tabel 2. The distribution of patients in the study

Group structure according to the control of primary malignancy

88 patients representing 41,51% showed primary tumor controlled, while 124 patients representing 58,49% had uncontrolled primary tumor. We can say that there is a statistically significant difference between patients with controlled primary tumor and those with uncontrolled primary tumor (p=0,000).

Radiotherapy results

Of the total of 212 patients treated by whole brain radiotherapy in 176 cases (83%) we achieved complete or partial remission of neurological symptoms and in 36 (16,98%) of cases the disease has evolved. 132 (62,25%) patients achieved a partial remission with improvement of symptoms and in 44 (20,75%) cases the remission was complete with the disappearance of symptoms over several months.

Side effects of radiotherapy

Side effects of radiation reflected both on patient's general condition as well as on irradiated area.

During irradiation and in the early days post irradiation occurred several acute side effects: headache at 205 patients, erythema of the scalp in 167 cases, peeling hairy head in 180 cases, nausea in 104 cases and visual disturbances in 67 cases.

Boldness was observed in all patients and sudden deterioration in neurological status was noted in more than half of the patients (121 cases).

In the studied period we met late side effects in 29 (13,67%) patients who survived more than a year. 21 patients accused memory loss and 8 patients experienced slowness in thought after a period of about 8 months after end of treatment.

Statistical analysis of survival

Statistical analysis of survival data was performed in all patients. For survival study we used Kaplan-Meier method. Mean overall survival was 9,59 months (minimum recorded survival was 1 month and maximum of 48 month) and median survival of 7 months.

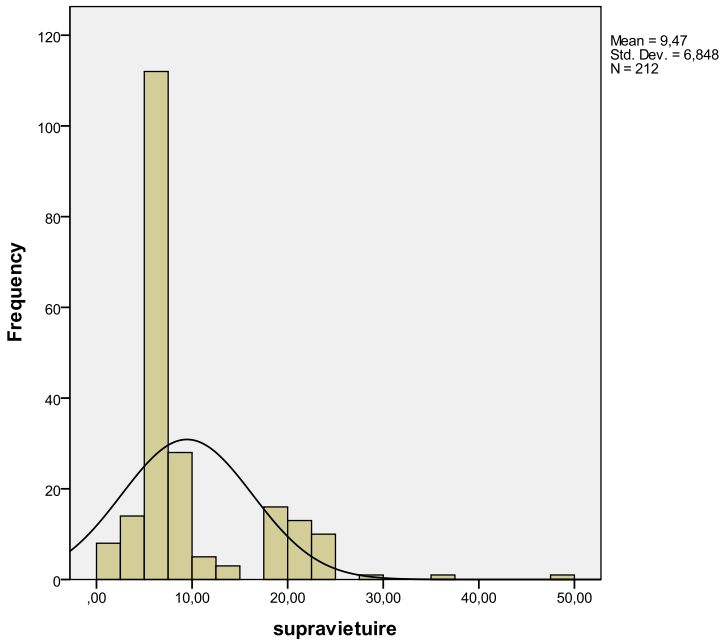

Fig 10. Mean overall survival

Median survival in patients with brain metastases varies significantly depending on the type of primary tumor (p=0,000): lung cancer median survival 7 month, breast cancer median survival 18 months, digestive cancer median survival 6 month, renal cancer median survival 3 month, melanoma median survival 5,1 month and unspecified starting point median survival 6 month.

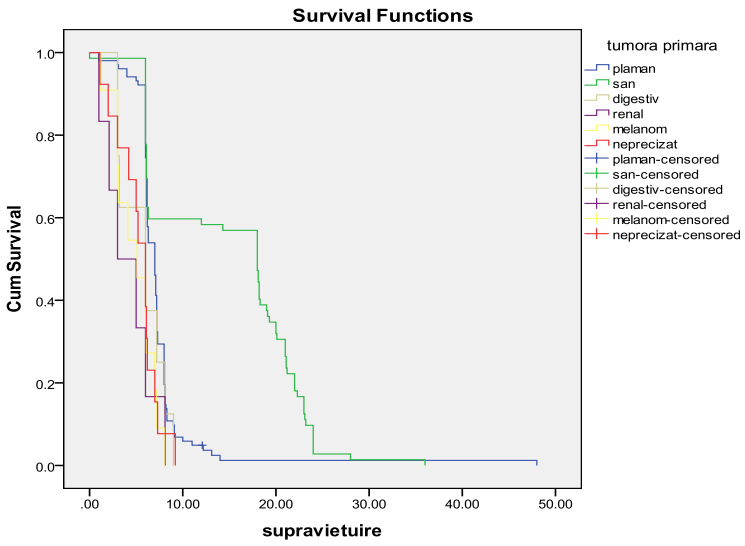

Fig 11. Median survival according to starting point

Median survival for single metastases was 14 month and for multiple metastases 8,3 months, without significant statistical difference according to number of metastases (p=0,048).

Survival is influenced by the number of metastases and sex of the patient as follows: for female patients with single metastases median survival was 18 months and for those with multiple metastases 7,2 months (p=0,280) and male patients with single metastases had a median survival of 7,2 months and those with multiple metastases had a median survival of 6,2 months (p=0,724).

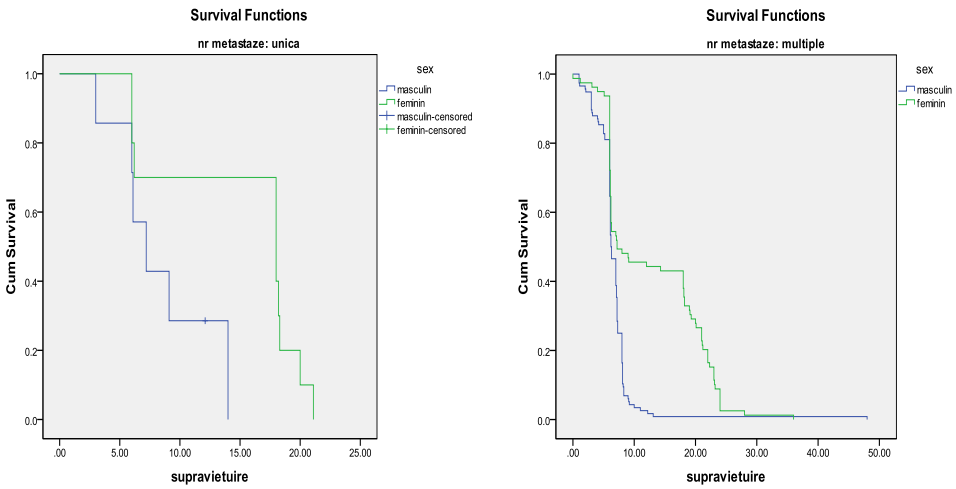

Fig 12. Median survival according to the number of metastases and patients sex

Median survival in patients with controlled primary disease was 7,1 months while those with uncontrolled primary disease had a median survival of 6,2 months.

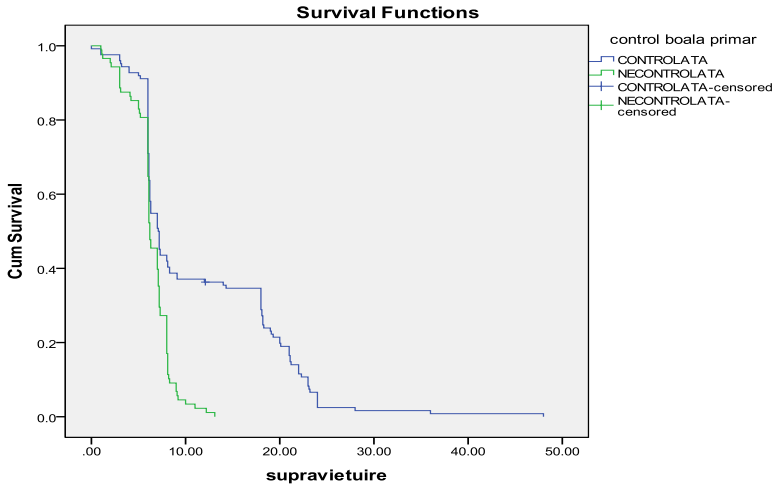

Fig 13. Median survival according to primary disease control

Survival of patients whose brain metastases represented the firs manifestation of the primary tumor was significantly lower than that of patients whose brain metastases occurred after a disease-free interval of more than a year (p=0,000).

Median survival in patients whose disease onset was brain metastases was 6,2 months and in those under one year free interval was 6,1 months and in patients with over one year free interval we recorded a median survival of 7,2 month.

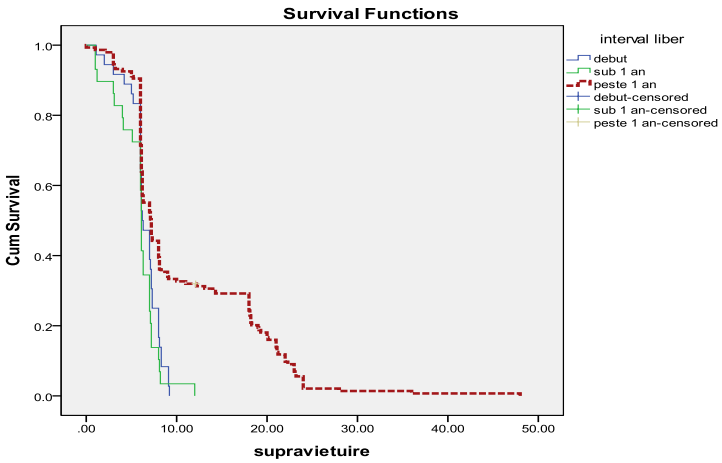

Fig 14. Median survival according to free interval of disease

Debates

Brain metastases are the most feared complication of generalized malignancy and the most intracranial tumors in adults. Brain metastases are more frequently since the survival was prolonged at patients with cancer. Any neurological symptoms in a patient with cancer should be considered and investigated as brain metastases,

Brain metastases are a difficult problem of diagnosis and therapeutic management for the physician for the patient and emotional and physically debilitating issue that influences in large extend the survival.

Imaging diagnosis of brain metastases is achieved by nuclear magnetic resonance, which is the currently investigation of choice. If magnetic resonance is not available (as in our case), computed tomography exam allows the diagnosis of brain metastases in most patients.

Note that in any clinical suspicion of brain metastases must be done as soon as possible one of this investigation. Any delay may lead to exceeding the useful therapeutic moment.

Therapeutic strategy depends on number of brain metastases (single or multiple), the extracranial extension of surgical resection is recommended in a small number of

cases, because is indicated in single brain metastases located in accessible areas, in patients with no systemic metastases and controlled primary tumor, patients with satisfactory general condition and to those with less advanced age. Surgery must be completed by radiotherapy.

In our study we found only 8 cases that only intraoperative were histologically proved to be brain metastases with the most common starting point lung. The surgery was carried out imagistic supposing the presence of a primary brain tumor the disease and the patient's performance status.

Most cases were presented with multiple metastases, poor general condition, with a poor prognosis which has required whole brain radiotherapy. The results are superimposable on the literature with a remission of neurological symptoms has been registered in 87% of the cases

The median survival of 7 month is higher to that of the studies showing a median survival of 6 month.

The dose of 30Gy/10 fractions, 12 days brought us satisfaction, therefore we recommend to be still use.

Conclusions

1. Sex distribution of the study group showed a higher incidence in male patients, with a men/women ratio of 1,4/1.
2. The average age of all patients include in the study was 60,34 years, the average age of women (M=55,04, SD=8,05) was significantly lower (p=0,000) than of men (M=64,17, SD= 8,05).
3. Most affected age group was 51 – 60 years for women with 41 cases and 61-70 years for men with a total of 77 cases.
4. Lung cancer (48,11%) and breast cancer (36,96%) were the main starting point for brain metastases in our study.

5. In terms of sex, age and variety of primary tumor we observed a maximum frequency of lung cancer in males in the age group 61-70 years and of breast cancer for women in the age group 51-60 years.
6. Most cases presented with multiple metastases (92%), single metastases being present only in 8% cases in this study.
7. In most cases (69,34%) brain metastases were clinically manifested at an free interval of one year from the beginning of the primary cancer, the latency period ranging from 0-85 months depending on the type of primary tumor.
8. Intermittent headache was the predominant clinical symptom of our casework being present in 108 cases (50,94%), followed in order by focal signs (32,07%0, vomiting (11,79%) and intellectual deterioration (5,18%).
9. In our study there is a statistically significant difference between patients with controlled primary tumor and those with uncontrolled primary malignancy (p=0,000), meaning that the average age of patients with uncontrolled primary tumor (M= 63,08, SD=7,705) is significantly higher than those with controlled primary disease (M=58,40, SD= 8,8883).
10. All brain metastases regardless of the size and number received palliative radiotherapy with a total dose of 30 Gy/10 fractions/12 days.
11. Encephalon irradiation was well tolerated in most cases and could be performed on an outpatient.
12. All patients experienced acute side effects during irradiation and in the early days of treatment: 100% boldness, scalp erythema 93%, 85% peeling hairy head skin, 97% headache, 57 % neurological damage, 49% nausea, 32% disturbance of view.
13. Late side effects occurred in13,67% of patients : decreased memory in 3,77% of patients and slowness in thinking in 9,90% of cases in about 8 months after radiotherapy.
14. Radiation therapy in the only active treatment outside of surgery in our study.

15. Most patients included in study were diagnosed in advanced stages, with short survival. We noted the low percentage of survivors (21,69%) at 12 months after diagnosis; this demonstrates the aggressiveness of brain metastases.
16. We observed a negative correlation (r=-0,427, p=0,000) between age and free range, in patients with lower age the free-interval is increased and in those with increased age free-interval is lower.
17. Median survival of patients with irradiated brain metastases enrolled in this study was 7 months, the shortest survival recorded was 1 months and the longest 48 months.
18. Median survival in our patients with brain metastases varies significantly depending on the type of primary tumor (p=0,000): lung cancer median survival 7 month, breast cancer median survival 18 months, digestive cancer median survival 6 month, renal cancer median survival 3 month, melanoma median survival 5,1 month and unspecified starting point median survival 6 month.
19. Survival was significantly influenced by patients sex (p=0,000), the women had a median survival of 7,2 months and men of 6,3 months.
20. Survival was influenced by the number of metastases (p=0,048), median survival for single metastases was 14 month and for multiple metastases 8,3 months.
21. Patients who underwent surgery before irradiating treatment had a median survival of 6,2 months.
22. An early diagnosis and aggressive treatment led to remission of neurological phenomena (HIC syndrome, motor deficit) in 83% of cases and improved the quality of life.

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