ORIGINAL ARTICLE

UDC: 616.831:616-033.2
DOI: https://doi.org/10.2298/VSP220316081N

Current approaches to the treatment of metastatic brain tumors

Sadašnji pristupi lečenju metastatskih promena na mozgu

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Abstract

Background/Aim. About 10% of patients diagnosed with systemic cancer had brain metastases in the central nervous system. Patients with diseased lungs, breasts, urinary and digestive tract, as well as melanoma of the skin, are increasingly treated by neurosurgeons due to their dissemination and creation of secondary deposits in the brain. The aim of the study was to assess the efficacy of treatment modalities for patients with brain metastasis according to their type – solitary or multiple, and also to the primary cancer site. **Methods.** The retrospective study was performed at the Clinic for Neurosurgery and the Clinic for Oncology from 2018 to 2020. One hundred and eleven patients with solitary changes in the brain and 122 patients with multiple changes were examined. **Results.** It was found that multiple metastases were more common in primary lung cancer, while single metastases were more common in adenocarcinoma. However, patients with primary adenocarcinoma died in a significantly higher number. **Conclusion.** Surgery and radiation remain the cornerstone of therapy for symptomatic lesions. We should strive to improve surgical techniques in the direction of less damage to the surrounding healthy tissue. Radiosurgery, as well as whole brain radiotherapy, remains the basic form in the treatment of multiple metastases.

Key words:
brain neoplasms; mortality; neoplasm metastasis; neurosurgical procedures; radiotherapy; treatment outcome.

Apstrakt

Uvod/Cilj. Oko 10% bolesnika sa dijagnozom sistemskog karcinoma imalo je metastaze u mozgu u centralnom nervnom sistemu. Bolesnici sa obolelim plućima, dojkama, mokraćnim i digestivnim traktom, kao i oni sa melanomom kože, sve češće se, zbog širenja metastaza i stvaranja sekundarnih naslaga u mozgu, leče kod neurohirurga. Cilj rada bio je da se proceni efikasnost modaliteta lečenja bolesnika sa metastazama u mozgu prema njihovom tipu – solitarne ili multiple, kao i prema lokalizaciji primarnog karcinoma. **Metode**. Retrospektivna studija rađena je na Klinici za neurohirurgiju i Klinici za onkologiju u periodu od 2018. do 2020. godine. Pregledano je 111 bolesnika sa solitarnim promenama na mozgu i 122 bolesnika sa višestrukim promenama. **Rezultati.** Utvrđeno je da su višestruke metastaze bile češće kod obolelih od primarnog karcinoma pluća, dok su pojedinačne metastaze bile češće kod obolelih od adenokarcinoma. Međutim, preminuo je značajno veći broj bolesnika sa primarnim adenokarcinomom. **Zaključak.** Hirurgija i zračenje ostaju kamen temeljac terapije simptomatskih lezija. Potrebno je težiti unapređenju hirurške tehnike u pravcu što manjeg oštećenja okolnog zdravog tkiva. Radiohirurgija, kao i radioterapija celog mozga, ostaju osnovni oblici u lečenju višestrukih metastaza.

Ključne reči:
mozak, neoplazme; mortalitet; neoplazme, metastaze; neurohirurške procedure; radioterapija; lečenje, ishod.

Introduction

In addition to primary brain tumors, such as meningiomas, gliomas, and astrocytomas, recently, more and more people with metastatic changes, i.e., secondary lesions, have been contacting a neurosurgeon. About 10% of patients diagnosed with systemic cancer develop brain metastases in the central nervous system (CNS). The most common tumors that metastasize to the brain are lung, breast, kidney, and colon cancers [1]. Lung cancer metastases are the most common, even though the incidence of breast cancer is increasing, and melanoma represents a greater predisposition than all systemic types of cancer that lead to brain metastasis. As for breast cancer control, although different factors contribute to varying degrees in different countries, it is mainly due to increased breast awareness, early detection, and the provision of the most appropriate therapy to women with the disease are present [2]. About 16% of the

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world's population is covered by registration systems that provide cancer incidence statistics, while mortality data are available for about 29%. The incidence and mortality from breast cancer vary significantly depending on the world region [3]. Eighty percent of brain metastases are localized in the hemisphere, 15% are localized at the cerebellar level, and 5% at the bone level. Brain metastases are the most common neurological complication of systemic cancer and have a very poor prognosis. Lately, the management of patients with brain metastases has become more important due to the increased incidence of these tumors and the prolonged survival time of the patient that accompanies the increased control of systemic carcinoma [4]. Importantly, progress has been made in understanding molecular biology underlying the initial development and eventual proliferation of brain metastases [5].

The first step in fighting metastases is to discover the mechanism of their occurrence. It was previously thought that metastatic cancer cells attach to cells (neurons) of the grey and white masses of the brain. The researchers confirmed that in more than 95% of cases, cancer cells do not start growing in the brain tissue but on the walls of the blood vessels in the brain. British scientists have discovered how cancer cells attach to the blood vessels of the brain and lead to metastasis in this vital human organ. By studying the pathways of metastasis, a group of scientists found that cancer cells attach to the blood vessels of the brain using integrins, a proteins widely distributed in nature. Integrins enable contact of cells with surrounding tissues and the exchange of intercellular signals. Authors believe that removing integrins from the surface of cancer cells prevents tumor metastasis. With the development of drugs that block integrins, progress can be made in the fight against metastases [6].

Symptoms of brain tumors are manifested in the form of headaches that change depending on the time of day, weather changes, epi attacks, numbness, numbness or weakness of one half of the body, nausea accompanied by vomiting, memory loss, speech problem, and mood swings. Clinical examination with neurological examination and monitoring of patients with primary processes on organs with possible dissemination of secondary changes represents an initial step in the prevention of multiple dissemination. The precise diagnosis of the present secondary changes in the brain, as well as their number and size, are set after the magnetic resonance imaging (MRI) of the brain. A study by Aslan et al. [7] showed that the application of magnetic resonance spectroscopy and dynamic sensitive contrast parameters could help distinguish high-grade glioma from solitary metastasis in 97% of cases.

The fact is that more than half of all metastases occurred within three years [8], so we advise that follow-up be started in the early periods after diagnosis.

There are four main ways to treat brain cancer: radiation, i.e., radiotherapy (RT), surgery, treatment with cytostatics (chemotherapy), and immunotherapy, as well as a combination of all or any individual therapy. Treatment of brain tumors through immunotherapy is based on stimulating or establishing the ability of the immune system to fight infections and the progression of cancer cells [9].

Treatment options for patients with cerebral metastases are limited and mainly depend on the number and size of lesions and the progression of the primary metastatic disease [10].

With multiple changes, the use of the Gamma Knife® has greatly improved and advanced the treatment of these patients. Radiosurgical (RS) treatment of brain metastases results in survival times that are favorably compared to historical experience in patients treated with whole brain RT (WBRT) or surgical resection alone [11]. Indications for using a Gamma Knife® are that the changes are well limited, the size of the change does not exceed 35 mm, and there is no large perifocal edema. The dose usually used is from 16 to 140 Gy. Gamma Knife® surgery is widely used for a number of neurological disorders. However, little is known about its long-term complications, such as carcinogenic risks, as described in the study by Wang et al. [12].

The problem is the secondary changes of larger dimensions, which are not subject to Gamma Knife® treatment. Then the methods of combined treatment are resorted to. If the patient's condition is satisfactory and the primary process is in remission, a large secondary deposit surgery is performed first, followed by RT.

There is no way to know exactly how long someone will live with brain metastases. It depends on many factors, including the type of primary process, the number of brain tumors, and the treatments used. The median and one-year survival rates initially in patients with metastases were ten months and 41%, respectively. The median time to metastasis in patients with the localized disease was 28 months [8].

Therefore, as we continue to strive for better access to and advancement in technology, improved survival in these settings should be achieved through increased awareness of cancer and its potential for successful treatment [13].

Methods

The retrospective study was carried out at the Clinic for Neurosurgery and the Clinic for Oncology, University Clinical Center Niš, Serbia, from 2018 to 2020. One hundred and eleven patients with solitary changes in the brain and 122 patients with multiple changes were examined. In all patients, in addition to multislice computed tomography (MSCT) of the brain or MRI of the brain, MSCT of the lungs and echocardiography or MSCT of the abdomen were performed. Patients with a solitary change were treated at the Clinic for Neurosurgery using operative treatment. Patients with multiple brain changes, who were not indicated for surgical treatment, were referred to the Clinic for Oncology, where they were treated with RT and chemotherapy. Patients with multiple changes, small diameter, good general condition, and remission of the primary disease were treated with Gamma Knife® at the Institute of Neuroradiology Belgrade.

Statistical analysis

Qualitative data were expressed as frequencies and percentages, while quantitative data were presented as mean and standard deviations. The normality of distribution was tested by the Kolmogorov-Smirnov test. Variables were compared by a two-tailed Student's *t*-test for continuous variables for normal distribution or the Mann-Whitney *U* test for continuous variables of non-normal distribution. The chi-square (χ^2) test and Fisher test were used for categorical variables. Statistical analyses were performed using the statistical software SPSS Statistics 22.0 (SPSS, Inc., Armonk, NY, USA). All *p*-values presented were 2-tailed, and $p < 0.05$ was considered statistically significant.

Results

In the three-year period (2018–2020), there were 111 patients with one operated metastasis in the examined population, among whom there were 70 (63.1%) men and 41 (36.9%) women. There was no significant difference in age structure by sex ($p = 0.071$).

A total of 9 patients died, of whom 7 (77.8%) were men and 2 (22.2%) women, but without statistical significance ($p = 0.340$).

There was no significant difference in the distribution of patients by sex according to the examined years ($p = 0.100$) or age structure ($p = 0.156$). In relation to the distribution of metastasis localization, there was no statistically significant difference in the three examined years. The number of deceased patients by age was equal without significant difference ($p = 0.984$) (Table 1).

There was also no statistically significant difference in the distribution of exitus in individual metastases, depending on the localization of the primary process ($p = 0.216$) (Table 2).

In the examined group in the three years, there were 122 patients with multiple metastases, among which there were 68 (55.7%) men and 54 (44.3%) women. There was no significant difference in age structure by sex ($p = 0.480$).

There was no significant difference in the distribution of patients by sex according to the examined years ($p = 0.202$) nor by age structure ($p = 0.698$). In relation to the distribution of localization of primary cancer, there was no statistically significant difference in the three examined years ($p = 0.501$). The number of deceased patients by age was equal without significant difference ($p = 0.744$) (Table 3).

In patients with multiple brain metastases, a significant difference in the number of deaths was found depending on the localization of primary cancer ($\chi^2 = 11.816$; $p = 0.037$). Patients with primary carcinoma of the digestive tract died in a significantly higher number ($p = 0.037$) (Table 4).

It was also shown that a significantly higher number of deceased patients were treated with RT than with the surgical approach ($\chi^2 = 33.213$; $p < 0.001$) (Table 5).

A significant difference in the existence of single or multiple metastases depending on the primary process was found ($\chi^2 = 35.041$; $p < 0.001$). Multiple metastases are more common in primary lung cancer, while single metastases are more common in digestive tract carcinoma (Table 6).

A significant difference in the distribution of metastatic changes in the three years was also observed ($\chi^2 = 11{,}768$; $p = 0.019$). Oligometastases were more prevalent in 2020, while multiple metastases were present in 2018 (Table 7).

Table 1

Data according to the years of examination of patients with one brain metastasis

Parameter	2018	2019	2020	*p*-value
Gender				
m	17 (48.6)	28 (70.0)	25 (69.4)	0.100
f	18 (51.4)	12 (30.0)	11 (30.6)	
Age (years)	65.74 ± 7.61	65.40 ± 10.46	61.50 ± 12.30	0.156
Localization				
digestive tract	7 (20.0)	13 (32.5)	14 (38.9)	
kidney	0 (0.0)	1 (2.5)	2 (5.6)	
breast	11 (31.4)	7 (17.5)	5 (13.9)	0.345
melanoma	4 (11.4)	2 (5.0)	4 (11.1)	
lungs	13 (37.1)	17 (42.5)	11 (30.6)	
Exitus	3 (8.6)	3 (7.5)	3 (8.3)	0.984

m – male; f – female. All results are given as number (percentage) except age which is shown as mean ± standard deviation.

Table 2

Distribution of the deceased according to the localization of the primary cancer

Localization	Deceased patients		*p*-value
	no	yes	
Digestive tract	32 (94.1)	2 (5.9)	
Kidney	2 (66.7)	1 (33.3)	
Breast	23 (100.0)	0 (0.0)	0.216
Melanoma	9 (90.0)	1 (10.0)	
Lungs	36 (87.8)	5 (12.2)	

All values are expressed as numbers (percentages).

Table 3

Data according to the years of examination of patients with multiple metastases

Parameter	2018	2019	2020	*p*-value
Gender				
m	34 (55.7)	19 (47.5)	15 (71.4)	0.202
f	27 (44.3)	21 (52.5)	6 (28.6)	
Age (years)	63.28 ± 11.17	64.85 ± 11.12	62.33 ± 11.84	0.698
Primary digestive tract carcinoma	2 (3.3)	2 (5.0)	2 (9.5)	
Localization of primary cancer				0.501
breast	8 (13.1)	6 (15.0)	2 (9.5)	
liver	1 (1.6)	0 (0.0)	0 (0.0)	
melanoma	5 (8.2)	2 (5.0)	5 (23.8)	
lungs	43 (70.5)	28 (70.0)	12 (57.1)	
urinary	2 (3.3)	2 (5.0)	0 (0.0)	
Therapy				
gamma	28 (45.9)	14 (35.0)	8 (38.1)	0.529
radiant	33 (54.1)	26 (65.0)	13 (61.9)	
Exitus	20 (32.8)	16 (40.0)	8 (38.1)	0.744

m – male; f – female. All results are given as number (percentage) except age which is shown as mean ± standard deviation.

Table 4

Distribution of deaths by localization of primary cancer in patients with multiple brain metastases

Localization	Deceased patients		*p*-value
	no	yes	
Digestive tract	1 (1.3)	5 (11.4)	0.037
Breast	14 (17.9)	2 (4.5)	ns
Liver	0 (0.0)	1 (2.3)	ns
Melanoma	8 (10.3)	4 (9.1)	ns
Lungs	53 (67.9)	30 (68.2)	ns
Urinary	2 (2.6)	2 (4.5)	ns

ns – non significant. All values are expressed as numbers (percentages).

Table 5

Distribution of the deceased according to the type of therapy

Therapy type	Deceased patients		*p*-value
	no	yes	
RT	47 (60.3)	3 (6.8)	< 0.001
WBRT	31 (39.7)	41 (93.2)	

RT – radiotherapy; WBRT – whole brain RT. All values are expressed as numbers (percentages).

Table 6

Distribution of localization of primary cancers

Localization	Single metastases	Multiple metastases	*p*-value
Lungs	41 (36.9)	83 (68.6)	
Breast	23 (20.7)	16 (13.2)	
Melanoma	10 (9.0)	12 (9.9)	< 0.001
Urinary	2 (2.7)	4 (3.3)	
Digestive tract	34 (30.6)	6 (5.0)	

All values are expressed as numbers (percentages).

Table 7

Distribution of metastatic changes according to the years of examination

Metastases type	2018	2019	2020	*p*-value
Single	35 (37.8)	40 (35.1)	36 (45.6)	0.019
Multiple	61 (48.4)	40 (35.1)	21 (26.6)	

All values are expressed as numbers (percentages).

Discussion

About 10% of patients diagnosed with systemic cancer have brain metastases in the CNS. Diseased lungs, breasts, urinary and digestive tract, as well as melanoma of the skin, are increasingly treated by neurosurgeons due to their dissemination and creation of secondary deposits on the brain. Lungs, breasts, and skin (melanoma) are the most common sources of brain metastases, and up to 15% of patients' primary site remains unknown [14]. Early diagnosis and suspicion of this dissemination in primary metastases enable surgical intervention followed by oncological treatment, which, together, prolong the patient's life. The average survival time with brain metastases is usually less than a year. However, when only isolated metastases (oligometastases) are found and are able to be treated, over 60% of people have the chance of surviving two years or longer [15].

In our study, in the three-year period (2018–2020) in the examined population, there were 111 patients with one operated metastasis, among which there were 70 (63.1%) men and 41 (36.9%) women. There was no significant difference in the age structure according to gender or concerning the existence of the primary process in the examined period. The optimal management of brain metastases remains controversial. WBRT and local treatment or surgery or RS are the cornerstones of treatment. Combination treatment can improve both overall survival and local control in patients with a single metastasis but also leads to the benefit of local control in patients with two to four lesions [16].

In patients with primary metastases caused by adenocarcinomas, it often happened that the patient underwent surgery for a change in the brain of unknown etiology and that the pathohistological (PH) finding gave us guidance in further examination. Before neurosurgical treatment, such patients were not treated by a gastroenterologist, but their treatment in that direction began only after the obtained PH findings. In the last few decades, surgical resection has evolved into a standard treatment that has led to improved clinical outcomes in carefully selected patients with brain metastases [17].

Fatal outcomes occurred in nine patients, with no significant differences in the distribution of exitus according to the location of metastases (p = 0.216). Kanner et al. [18] believe that aggressive intervention may be indicated for selected patients with well-controlled systemic cancer and good performance status in whom CNS disease poses the greatest threat to functionality and survival. Furthermore, Kuo and Recth [19] believe that an aggressive therapeutic approach for at-risk patients, which includes a combination of either surgery or stereotactic RS and WBRT, can improve survival and reduce the risk of CNS progression.

In the same period, 122 patients with multiple metastases were treated, among whom 68 (55.7%) were men and 54 (44.3%) women. Here, too, we did not have a significant statistical difference in terms of age structure, sex, and distribution of primary processes. Patients with primary carcinoma of the digestive tract died in significantly higher numbers. Kocher et al. [20] believe RS in patients with one to three cerebral metastases leads to significant survival benefits only in younger patients with low systemic tumor load compared with WBRT alone.

The results of treated patients with multiple metastases showed that a higher number of patients who received standard RT (WBRT) died than those patients treated with Gamma Knife® (RS). That can be explained by the fact that patients in better grades (Karnofski scale used) were referred to Gamma Knife® therapy, along with younger patients, compared to patients treated with standard radiation therapy. Métellus et al. [21] suggest that therapeutic decision is subject to multidisciplinary analysis, taking into account established prognostic factors, including general patient status, extracerebral disease status, and clinical and radiological presentation of lesions.

The study showed that multiple metastases were more prevalent in primary lung cancer, while single metastases were more prevalent in carcinoma of the digestive tract. A study by Hoffman et al. [22] showed that RS is an effective therapy for selected patients with newly diagnosed or recurrent brain metastases from lung cancer. Since the fatal outcome was most prevalent in patients with multiple brain metastases where carcinoma of the digestive tract was the primary process, we assume that the diagnosis of carcinoma of the digestive tract is much more difficult to come by. Attempts to detect a primary tumor are most often in vain, however, because its origin is established in only 13% of patients, regardless of diagnostic methods used [23]. The symptoms of the gastrointestinal tract are very non-specific, patients do not recognize them often, and only when the disease has progressed is the right diagnosis made. Advanced adenocarcinoma causes multiple changes in the brain, so the applied therapy does not ensure satisfactory success, and the patient quickly reaches a lethal outcome. These patients are treated with WBRT. Sahgal et al. [24] believe that WBRT is associated with toxicity that may influence the decision to use WBRT, and, therefore, acute side effects of WBRT and more serious late side effects of neurocognitive impairment and leukoencephalopathy should be considered. Hepatocellular carcinoma is the most common primary malignancy of the liver and the third leading cause of cancer-related death [25].

Regarding the three-year cross-section of treated patients at the Clinic for Neurosurgery in Niš, it was noticed that multiple changes were more often diagnosed during 2018, and individual metastases were more common in 2020. That supports the fact that the observation and follow-up of patients with primary cancers are more adequate and better. Modern diagnostic procedures, such as the use of MRI, have made it possible for changes in the brain to be detected earlier and, as individual secondary deposits in the brain, to be treated surgically. Sharma et al. [26] suggest improving primary healthcare, especially when it comes to breast cancer, believing the mortality rate would then decrease and the survival period would greatly increase.

From the aforementioned, we see that the optimal treatment of brain metastases is still controversial, although there is a clear role of RT in the treatment of this disease. Specific treatment recommendations depend on

different clinical parameters and patient preferences. Consistently, multiple studies of WBRT have shown improved local control and reduced progression elsewhere in the brain but no overall survival benefit and concern for the poorer neurocognitive outcome. However, both new drugs and technological advances in the provision of RT aim to reduce the neurocognitive consequences of WBRT. Stereotactic RS has been shown to improve overall survival in patients with a single brain metastasis compared with WBRT [27].

Conclusion

Treatment options for patients with cerebral metastases are limited and mainly depend on the number and size of lesions as well as the degree of evolution of the primary disease. Surgery and radiation remain the cornerstone of therapy for symptomatic lesions. We should strive to improve surgical techniques in the direction of causing less damage to the surrounding healthy tissue. RS, as well as WBRT, remain the basic form in the treatment of multiple metastases.

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Revised on March 16, 2022
Accepted on July 29, 2022
Online First August 2022