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SURGICAL TREATMENT OF SOLITARY BRAIN METASTASES

A.V. Stanishevskiy, Sh.Kh. Gizatullin, A.V. Smolin, E.V. Kryukov

Main Military Clinical Hospital named after Academician N.N. Burdenko, Ministry of Defense of Russia; 3 Gospitalnaya Sq., Moscow 105094, Russia

Contacts: Artem Vadimovich Stanishevskiy, *a-stan@mail.ru*

Background. Brain metastasis occurs in 10–30 % of patients with different malignances. Despite of successes, achieved in the treatment of extracranial malignances in last decade, tendency to increase of the survival and duration of the disease-free period in patients with brain metastasis is absent. Several treatment modalities have been proposed: chemotherapy, radiation, immune and target therapy, stereotactic radiosurgery, different types of surgical procedures, however, an optimal combination of these methods remain unclear.

The aim of the study: to summarize experience of multimodal treatment of patients with brain metastases in hospital with opportunity of both surgical removal, chemo- and radiotherapy and review literature on the topic.

Materials and methods. The retrospective analysis of medical data of patients with brain metastases performed with assessment of: localization of primary tumor, metastasis volume, localization, median survival duration from metastasis revealing due to different types of therapy, main period of recurrences and hospital state duration, early and late complications. Inclusion criteria were: patients with surgical treatment of brain metastases, availability of medical data. Exclusion criteria were: multiple brain metastases, contraindications for surgical treatment, sensitive to chemo- and radiation therapy malignances (leukoses, lymphoma, germinative tumors etc.). The extent of metastasis resection was assessed by postop CT and MRI with intravenous enhancement or by operation records. Fluorescent intraoperative navigation with 5-aminolevulinic acid was used for further evaluation of tumor borders. In case of localization of metastasis in motor or eloquent regions intraoperative electrophysiological monitoring acquired. Few operations for metastasis localized in speech zones were made with "asleep – awake – asleep" method. Follow-up assessed by questioning of patients and their relatives. Statistical analyzes performed in IBM SPSS Statistics 23.

Results. 52 patients meet criteria and were included to the study. Male to female ratio was 1 : 1, main age – 60 years. The most common sources of brain metastases were (in decreasing order) melanoma, lung cancer, kidney cancer, breast cancer, colorectal cancer, prostate cancer, ovarian cancer and uterus cancer. Two patients had 2 brain metastases at the time of assessment, other 50 – single. Most common localizations of brain metastases (in decreasing order) were: parietal lobe, frontal lobe, cerebellum hemispheres, occipital lobe, temporal lobe, ventricular system and brain meninges. In 46 % of cases metastases significantly involves motor or eloquent areas of brain. Median volume of metastasis was 11 cm^3; midline shift appeared in 65.4 % of cases; 6 patients have hemorrhage in the tumor, 2 – seizures, 2 – occlusive hydrocephalus. Main Karnofsky performance index – 73.8. Gross total resection performed in 84.6, subtotal – in 7.7 % of cases. Intraoperative fluorescent navigation used in 73 %. In 10 cases metastasis localized in motor and sensory areas, all these cases were treat with intraoperative neurophysiological monitoring. Postoperative hemiparesis noticed in 1 patient; 3 surgeries performed with awake; no postop aphasias mentioned. Follow-up was assessed in 44 patients, 20 of them were dead at the time of the study. Correlation of median survival rates with primary tumor localization performed. The following prognostic factors for brain metastases have been identified: its morphology and volume, extent of resection, Karnofsky performance index and early complications.

Conclusions. Most patients with brain metastasis are in satisfactory condition at the initial examination. Most frequent primary tumor localization: melanoma and lung cancer, they are characterized by poorer prognosis. Most metastasis are supratentorial, intracranial hypertension is obvious. Metastasis localization, time from its evaluation to surgery, significant functional areas involvement and primary tumor resection aren't fluent on survival.

Key words: metastasis, chemotherapy, radiation therapy, tumor, brain, melanoma, cancer, adenocarcinoma

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BACKGROUND

Ten to thirty percent of patients with different cancers develop brain metastases (BMs) [1, 2]. Only in 9 % of patients previously diagnosed with cancer, cerebral lesions are associated with primary cerebral tumors. The most common origins of BMs include lung cancer, melanoma, kidney cancer, breast cancer, and colorectal cancer [3].

According to the World Health Organization, the predicted global cancer burden will increase in 2012–2030. As of 2016, 19.1 % of all primary tumors are diagnosed at stage III, another 20.5 % – at stage IV. BMs are believed to be the most severe cancer complication significantly reducing the quality of life and characterized by high death rates.

The aim of the study: to analyze the experience of multimodal treatment for BMs in a multidisciplinary hospital and to summarize relevant scientific literature on current trends in BMs therapy.

MATERIALS AND METHODS

We performed retrospective analysis of medical records of patients treated between December 20, 2013 and January 1, 2020 at the Department of Neurosurgery and Department of Radiology, Main Military Clinical Hospital named after Academician N.N. Burdenko.

Inclusion criteria were as follows:

- patients over 18 years with BMs;
- available data on patient's condition upon admission to hospital, as well as detailed information on treatment, its duration, and complications. Patient's condition was evaluated using the Modified Rankin Scale (mRs) upon admission and discharge;
- available results of preoperative contrast-enhanced magnetic resonance imaging (MRI).

Exclusion criteria were as follows:

- multiple BMs;
- no history of BMs removal.

In addition to that, we surveyed relatives of the study participant to collect the information on their outpatient treatment, BMs recurrence, time and cause of death.

The extent of BMs resection was assessed using postoperative computed tomography (CT), contrast-enhanced MRI, and the analysis of surgical intervention protocols.

Fluorescence diagnostics (FD) – fluorescent intraoperative navigation with 5-aminolevulinic acid – in addition to contrast-enhanced MRI was used in patients with no clear boundaries between metastasis and normal brain tissue. It was also used in patients whose were located in sensory, motor or eloquent areas of the brain, in addition to intraoperative electrophysiological monitoring (IOM) that ensured more precise identification of tumor boundaries and increases extent of resection. IOM was used for patients with located in the motor and sensory areas of the brain cortex, while patients with in the eloquent areas underwent awake surgery.

To assess median overall survival, patients were divided into 3 groups: with from melanoma, from lung cancer, and from other primary tumors (Table 1).

Table 1. *The assessment of overall survival in patients with melanoma, lung cancer and another metastasis*

Morphology of metastasis	Number of patients, %	Overall survival median, months	95 % CI
Melanoma	14	6.7	2.8–10.7
Lung cancer	14	9.6	5.4–13.8
Other*	24	13.4	7.4–19.4

**Cancer localization, number of patients (%): kidney cancer – 7, breast cancer – 6, rectal cancer – 5, prostate cancer – 3, ovarian cancer – 2, uterus cancer – 1.*

Data processing and analysis was performed using the IBM SPSS Statistics 23 software. We performed Kaplan–Meier analysis to calculate median overall survival of patients with from melanoma, lung cancer, and other cancers.

RESULTS

A total of 52 patients with met the inclusion criteria and had all necessary medical information, including protocols of surgical interventions and results of pre- and postoperative examinations (CT and contrast-enhanced MRI of the brain).

Age and gender distribution of study participants is shown in Table 2. the majority of patients were admitted to hospital in a satisfactory condition (score 80–100 on the Karnofsky scale). Six (11.5 %) patients had hemorrhage into the tumor; 2 (3.85 %) patients had seizures; and 2 (3.85 %) patients had occlusive hydrocephalus.

Table 2. *The gender and sex characteristics of included patients*

Parameter	Value
Number of patients (%): male female	 24 (46) 28 (54)
Age median (95 % CI), years	61.5 (56.5–63.1)
Karnofsky Index, %	70 (70–80)

Note. *95 % CI – confidence interval (possibility level 95 %).*

The most common origins of in our patients were melanoma, lung cancer, kidney cancer, and breast cancer. Forty-four (84.6 %) patients had supratentorial tumors; 2 (3.85 %) patients had intraventricular tumors; and 2 (3.85 %) patients had solitary metastases located along the dura mater, initially diagnosed as meningiomas (Tables 3, 1).

Twenty-four (46.2 %) patients had in the functional areas of the brain. Thirty-four (65.4 %) patients presented with severe peritumorous edema that caused compression and shift of adjacent brain structures.

All patients underwent multimodal treatment, including excision followed by chemotherapy (CT), radiotherapy (RT) or both when indicated (Table 4).

Table 3. *The characteristics of cerebral metastases*

Parameter	Number of cases	
	abs.	%
Primary tumor:		
Melanoma	14	26.9
Lung cancer	14	26.9
Kidney cancer	7	13.5
Breast cancer	6	11.6
Rectal cancer	5	9.6
Prostate cancer	3	5.8
Ovarian cancer	2	3.8
Uterus cancer	1	1.9
Localization of metastasis:		
Parietal lobe	18	34.6
Frontal lobe	14	26.9
Cerebellum hemispheres	8	15.5
Occipital lobe	6	11.6
Temporal lobe	2	3.8
Ventricular system	2	3.8
Dura mater	2	3.8
Functional zones involvement		
Motor and sensory zones	10	19.2
Speech zones	6	11.6
Other*	6	11.6
Away SFA	30	57.6
Midline shift		
Takes place	34	65.4
None	18	34.6
Metastasis volume** mediane (95 % CI), cm^3	11 (10.1–19.8)	

Note. *SFA – significant functional areas.*
**Localization (significant functional areas): visual cortex, basal ganglia, cerebellum nuclei.*
***Metastasis volume evaluate as ABC/2, where A, B, C – sizes of metastasis due to three MRI planes.*

Forty-five (87 %) operations were performed with intraoperative FD (iFD). Among 22 (42.3 %) patients with affecting functionally significant areas of the brain, 10 (19.2 %) patients had their tumors located in the motor and sensory zones of the cortex, whereas 6 (11.5 %) patients had tumors in the eloquent areas. All 10 patients were operated on with intraoperative electrophysiological monitoring; 2 (3.85 %) patients of them developed transient hemiparesis that was partially regressed after postoperative Dexamethasone therapy; 1 patient developed persistent central hemiparesis that existed until patient's death 7.5 months postoperatively. Three patients with located in the eloquent areas underwent awake brain surgeries. None of them developed aphasia in the postoperative period. Among those who had conventional surgery, 3 patients presented with aphasia. In 2 of them, it resolved spontaneously within 1 week postoperatively, while 1 patient had persistent motor aphasia.

We managed to survey relatives of 44 study participants to obtain the information on their survival and complications developed after discharge. For the rest of the patients, we used only medical records.

The following complications were observed in the early postoperative period: ventilator-associated pneumonia ($n = 2$), intracerebral hemorrhage ($n = 2$), and meningoencephalitis ($n = 2$) (Table 5).

The survival analysis showed that patients with from melanoma and lung cancer had worse prognosis than other patients.

Linear regression analysis demonstrated that several factors significantly affected postoperative survival, including morphology and volume, brain compression and shift extent of BMs resection, patient's condition upon admission to hospital (Karnofsky score), and early complications.

DISCUSSION

Despite the advances in the treatment of extracerebral tumors achieved in the last 10 years, still significantly affect patient survival and their quality of life [5, 6]. There has been a paradoxical increase in incidence of metastatic lesions to the central nervous system along with the development

Table 4. *The characteristics of treatment modalities of brain metastases*

Parameter	Number of cases	
	abs.	%
Surgery		
Extent of resection:		
total	43	82.7
subtotal	9	17.3
Using of fluorescence guidance	45	87
Using of INM (in case of SFA involvement):		
motor and sensory zones evolvement	10	3
awake surgery	19.2	5.8
Radiation therapy		
Takes place	19	36.5
None	17	32.7
Data absent	16	30.8
Time after surgery, days	**Mediane**	**95 % CI**
	32	20–47
Chemotherapy		
Takes place	25	48
None	10	19.2
Data absent	17	32.8
Time after surgery, days	**Mediane**	**95 % CI**
	22	19–32

Note. *INM – intraoperative neuromonitoring; SFA – significant functional areas of the brain.*

Table 5. *The characteristics of post-op period*

Parameter	Value
Follow-up: duration mediane (95 % CI), month exitus lethalis*, *n* (%)	 6.5 (6.3–13.5) 20 (38.5)
Overall treatment duration mediane (95 % CI), day	17.5 (17.2–22.0)
Earlier complications, *n* (%)	6 (11.5)

**Causes of death: 1 patient died from myocardial infarct, mortality was associated with intracranial tumor progression – 19 cases (with extracranial progression – 13, with multiple cerebral metastasis formation and leptomeningeal spreading – 6).*

of effective treatments for primary tumors [7]. Without treatment, median overall survival after detection does not exceed 4–6 months [8].

In our study, primarily originated from lung cancer, breast cancer, melanoma, colorectal cancer, and kidney cancer, which is consistent with the results of other studies [7].

Treatment of patients with requires a multidisciplinary approach and combine the efforts of neurosurgeons, oncologists, neuroradiologists, and a number of other specialists.

Indications for surgery (evidence level A) include solitary, satisfactory condition of the patient (Karnofsky score >70), and absence of extracerebral metastases. Excision of solitary not only increases patient survival, but also improves their quality of life by eliminating intracranial hypertension and giving the opportunity to discontinue steroids. Several studies suggest that the excision of the most clinically significant in patients with multiple is appropriate [9]. Ensuring an acceptable quality of life after surgery is a priority task for a surgeon, even more important than supramarginal resection in patients with tumors located in the functionally significant areas of the brain. In such patients, it is recommended to use IOM and awake surgery. Tumor location in the functionally significant brain areas presumably does not affect postoperative survival, which can probably be attributed to the widespread use of IOM in combination with neuronavigation and microsurgical techniques allowing extensive tumor resection with a minimal risk of neurological deficit. the majority of in this study (82.7 %) were gross totally resected, which became possible primarily due to iFD that allowed us to estimate tumor invasion in case of infiltrative BMs.

Since metastatic brain lesions can progress very rapidly, adjuvant therapy should be initiated as soon as possible after surgery. Therefore, it is optimal to treat patients with BMs in multidisciplinary hospitals that can provide adjuvant immediately after BMs removal.

One of the issues in BMs treatment that has not yet been addressed is low permeability of the blood-brain barrier (BBB) [10] for most antitumor drugs. W.M. Pardridge (2005) demonstrated that 98 % of chemotherapeutic agents approved by FDA do not cross the BBB [11]. This problem was partially solved (at least for glioblastoma) by a modified method of regional (intracarotide) chemoinfusion with temporary BBB disruption [12, 13]. It was found that intraarterial administration of bevacizumab ensures higher concentration of this drug in the brain tissue than intravenous administration [14].

Immune checkpoint inhibitors appear to be a promising treatment for cancers with BMs [15]. However, none of the patients from this study received these drugs.

The issue of optimal combination of different variants of CT and RT with targeted therapy, stereotactic radiosurgery, and novel treatments is still being discussed [16–18].

Whole brain radiation therapy is a basic treatment for patients with BMs. Researchers are currently trying to develop ways to overcome neurotoxic effects of RT, in particular cognitive impairment. NRG Oncology CC001, a randomized phase III trial, demonstrated that hippocampal avoidance during whole brain radiation therapy plus memantine significantly reduce cognitive impairments in patients after treatment [19].

Stereotactic radiosurgery has shown its effectiveness as a pre- and postoperative RT method that reduces the incidence complications associated with radiation [20, 21]. Moreover, stereotactic radiosurgery is believed to be an optimal method for multiple BMs. In this study, none of the participants underwent stereotactic radiosurgery in the pre- and postoperative periods.

Radiation necrosis after RT also remains one of the challenges. Recent studies analyzed the efficacy of bevacizumab [22] and hyperbaric oxygen therapy [23] has been studied as a supplementary treatment, and in patients with refractory tumors as an alternative to pulse steroid therapy.

MRI-guided laser interstitial thermal therapy (MRgLITT) is one of the novel minimally invasive methods used for BMs treatment [24, 25]. Although the theoretical basis of this method was developed in the 1970s, the largest case series published by 2015 included no more than 20 patients. This method is currently used as an additional option in combination with surgery, RT, and CT, but not as an independent treatment [26]. According to the literature, MRgLITT is recommended for patients with primary and recurrent deep BMs with a diameter of 1–3 cm, as well as tumors resistant to RT [7]. The authors are not aware whether MRgLITT is currently used in any healthcare institution in the Russian Federation.

Despite the existence of clinical guidelines regulating treatment of patients with metastatic brain lesions, there are very few studies with a high level of evidence analyzing treatment outcomes in patients with BMs. An optimal approach can be found in prospective studies involving larger groups or in meta-analysis of accumulated data.

CONCLUSION

Brain metastasis being more typical for melanoma and lung cancer and are characterized by a poorer prognosis. Most BMs are supratentorial and often cause compression and dislocation of adjacent brain structures. Neither location of BMs, nor their proximity to the functionally significant areas affected patient survival. It is important to mention that there were no patients with brain stem tumors in our sample, and the time between BMs detection and their excision did not exceed 76 days. Linear regression analysis demonstrated that several factors significantly affected postoperative survival, including BMs morphology and volume, compression and dislocation of brain structures, effectiveness of tumor excision, patient's condition upon admission to hospital (Karnofsky score), and early complications.

Study limitations. Despite a significant number (about 350) of patients with BMs treated in the Centers of Neurosurgery and Radiology over the last 7 years, only 54 of them met the inclusion criteria. Further division of the sample into subgroups for comparison made some findings insignificant. In this study, we used no differentiation between patients with various morphological types of lung cancer, characterized by different proliferative activity of the primary tumor, sensitivity to systemic and radiation therapy and, as a result, prognosis.

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Authors' contributions
A.V. Stanishevskiy: obtaining data and statistical analysis, article writing;
Sh.Kh. Gizatullin: research idea of the study, scientific editing of the article, overall leadership;
A.V. Smolin: research design of the study, statistical analysis, scientific editing of the article;
E.V. Kryukov: scientific editing of the article, overall leadership.

ORCID of authors
A.V. Stanishevskiy: https://orcid.org/0000-0002-2615-269X
Sh. Kh. Gizatullin: https://orcid.org/0000-0002-2953-9902
A.V. Smolin: https://orcid.org/0000-0002-3023-0515
E.V. Kryukov: https://orcid.org/0000-0002-8396-1936

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