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Cerebral Metastases as a Cause of Non-Traumatic Intracranial Hemorrhage: Long-Term Results of Surgical Treatment

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ABSTRACT

Hemorrhages from brain tumors are the second most frequent cause of spontaneous intracerebral hemorrhages, with metastatic tumors more often leading to hemorrhages. We have studied the long-term results of surgical treatment of metastatic brain lesion complicated by hemorrhage in the tumor. Materials and methods. From 2005 to 2013, 264 patients from three clinical centers were operated on, of which 87 (32.95%) recorded hemorrhages from metastases. All metastatic tumors and associated hematomas were removed microsurgically, while block removal of neoplasms was performed in 195 (73.9%) patients, in 69 (26.1%) neoplasms were removed by fragmentation. Patients were stratified according to the histological structure of the primary tumor, and also divided into classes of RPA (recursive partition analysis). The interval of observation of patients (from the operation to a clinically significant event) ranged from 1 to 72 months, the median of observation was 22.6 months. Such aspects of treatment as the frequency of local relapses, the median of non-progressive and overall survival after surgical removal of metastases were retrospectively studied. **Results.** Local relapses occurred in 14 (16.1%) patients from the group of patients with tumor hemorrhages and 47 (26.6%) in the remaining cohort of patients with cerebral metastases ($\chi 2$ = 3.59, p = 0.059; φ = 1.97, p> 0.05). The local recurrence rate was 11.7% with block removal of metastases, and 25.9% with fragmentary removal ($\chi 2$ = 2.804, p = 0.095, φ = 1.597 p> 0.05). The medians of non-progressive and overall survival after surgery among all patients did not exceed 4.9 and 9.3 months, respectively, while the minimum values were observed with metastatic melanoma (1.6 and 6.0 months, respectively) and class III of RPA (3.6 and 6.5 months, respectively). **Conclusion.** Surgical treatment is an effective option in patients with symptomatic hemorrhagic metastases, allowing to achieve similar results in the frequency of local relapses and life expectancy of patients after surgery, in comparison with a group of patients without intracerebral hemorrhages from metastases.

Keywords: intracerebral hemorrhage, intracranial hemorrhage, local recurrence, brain metastases.

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INTRODUCTION

Essential arterial hypertension is the leading cause of intracerebral nontraumatic cerebral hemorrhage among patients over 18 years old, arteriovenous malformations and bursting aneurysms are rarer [11]. However, the proportion of spontaneous intracerebral hemorrhages in brain tumors can reach up to 2.4% - 4.4% of all intracerebral hemorrhages [5, 8, 15]. It should be noted that intracranial hemorrhages more often develop with metastatic lesions (up to 14% of all cancer patients with cerebral metastases) than with primary brain tumors (about 0.8% of patients with gliomas, glioblastomas and other morphological types of CNS tumors) [10] . Brain hemorrhages from metastases of malignant neoplasms (MN) account for about 1% of all intracerebral hematomas undergoing surgical treatment [8], while cerebral metastases of the most common MNs such as melanoma [3] and renal cell cancer [4] are most often prone to hemorrhages , and hemorrhages in lung cancer and breast cancer are somewhat less common [10, 19].

However, there are currently no studies demonstrating the effect of spontaneous intracerebral hemorrhage in brain tumors on the survival of cancer patients.

PURPOSE OF THE STUDY

To study the results of surgical treatment and the survival of patients with metastatic brain lesion complicated by cerebral hemorrhage.

MATERIALS AND METHODS

A multicenter (n = 3) retrospective study was conducted on the long-term results of surgical treatment of patients (n = 264) who underwent surgical removal of malignant tumors from the brain from one or several metastases from 2005 to 2013, while 87 (32, 95%) of patients with metastatic brain lesion were complicated by hemorrhage. All metastatic tumors and associated hematomas were removed by microsurgery, with block MN removal performed in 195 (73.9%) patients, neoplasms were removed by fragmentation in 69 (26.1%) patients. Before

the operation, all patients underwent magnetic resonance imaging (MRI) with intravenous contrast; also, patients underwent computed tomography of the head in the first day after surgery; Patients underwent MRI with contrast enhancement, first 1 month after the operation and then every three months in the period of subsequent monitoring of the tumor process in order to control local relapses and / or disease progression. The interval of observation of patients (from the operation to a clinically significant event) ranged from 1 to 72 months, the median of observation was 22.6 months. A clinical study did not compare different treatment regimens, and therefore no measurable indicators and statistical hypotheses were previously determined. Patients were stratified according to the histological structure of the primary tumor, and also divided into classes of RPA (recursive partition analysis) [2]. An intragroup analysis of the studied parameters was carried out in patients with metastatic brain lesion with (n = 87) and without (n = 177) cerebral hemorrhage. The method for determining the reliability of the compared features was selected depending on the data being analyzed. To compare survival between groups, we studied the cumulative data of overall survival (OS) and progression-free survival (PFS) of the disease (from the day of surgery) according to the Kaplan-Mayer method. Reliability between groups was evaluated using a logarithmic rank test (Cox-Mantel test) and Gehan-Breslow-Wilcoxon test. The study was carried out in accordance with the principles of the Helsinki Declaration of the World Association "Ethical Principles of Scientific and Medical Research with the Participation of a Person", the legislation of the Russian Federation - Federal Law dated 21.11.2011 No. 323-ФЗ "On the Basics of Protecting the Health of Citizens in the Russian Federation" and " The rules of clinical practice in the Russian Federation", approved by Order of the Ministry of Health of the Russian Federation No. 266 dated 06/19/2003, and other applicable regulatory requirements for conducting clinical trials and observation programs in the Russian Federation. The patient monitoring protocol and examination program were approved by local ethics committees.

RESULTS

Characterization of patients

Among 264 patients with MN of various locations with cerebral metastases (see table 1), the most common were lung cancer (n = 59, 22.3%), breast cancer (n = 51, 19.3%), melanoma (n = 49, 18.6%). Hemorrhagic metastases most often occurred in melanoma (n = 26; 29.9%), kidney cancer (n = 17; 19.5%) and lung cancer (n = 13; 14.9%). The class I of RPA group (more favorable prognosis) was 11.5% (n = 10) of patients with cerebral hemorrhage among these patients, the class II of RPA group (intermediate prognosis) was 56.3% (n = 49), the class III of RPA group (unfavorable prognosis) - 32.2% (n = 28).

Table 1. Clinical characteristics of patients included in the study.

Index	metastatic brain lesion		hemorrhagic metastases	
	n	%	n	%
nature of metastatic lesion				
Single metastasis	192	72,7	66	75,9
Multiple metastases	72	27,3	21	24,1
Histological type of primary tumor				
Melanoma	49	18,6	26	29,9
Non-seminomatous tumor of the testis	12	4,5	7	8,0
Squamous cell carcinoma of the cervix or vagina	25	9,5	4	4,6
Renal cell carcinoma	34	12,9	17	19,5
Lung cancer	59	22,3	13	14,9
Mammary cancer	51	19,3	8	9,2
Ovarian cancer	21	8,0	5	5,7
Soft tissue sarcoma	13	4,9	7	8,0
RPA Groups				
I class (more favorable prognosis)	37	14,0	10	11,5
II class (interim forecast)	148	56,1	49	56,3
Class III (unfavorable prognosis)	79	29,9	28	32,2

Asymptomatic metastases were only in 2 (2.3%) patients with hemorrhagic metastases. Hemorrhage, macroscopically not exceeding the limits of metastasis itself, occurred in 29 (33.3%) distant metastases; hemorrhage went beyond the boundaries of distant metastatic foci with the formation of intracerebral hematomas of various periods of limitation in the remaining 58 (66.7%) cases. The most common hematomas with a volume of up to 11 ml were found in 54 (93.1%) patients, hemorrhages with a volume of 51 to 80 ml were noted in 4 (6.9%) patients (2 patients with melanoma, 2 patients with kidney cancer). Hemorrhages in all these 4 (4.6%) cases were of the nature of acute hematoma.

RESULTS

Early postoperative mortality (within the first 6 days after surgery) was recorded in 5 (5.7%) of 87 patients, while all patients had several unfavorable prognostic factors: age over 50, Karnovsky index of 40% or less, general condition on the ECOG-WHO scale – 2 or less points.

Table 2. Clinical characteristics of patients with hemorrhages from brain tumors

Primary tumor	type of hemorrhage		surgical technique		or tal ity	ro lo gi ca l de	oc al re cu rr en
	intratumo ral	hematoma	block deletion	fragmenta tion removal			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Melanoma	6 (20,7)	20 (34,5)	17 (28,3)	9 (33,3)	2 (40,0)	5 (38,5)	8 (57,1)
Non-seminomatous tumor of the testis	2 (6,9)	5 (8,6)	4 (6,6)	3 (11,1)	-	1 (7,7)	1 (7,1)
Squamous cell carcinoma of the cervix or vagina	1 (3,4)	3 (5,2)	2 (3,3)	2 (7,4)	1 (20,0)	1 (7,7)	-
Renal cell carcinoma	8 (27,6)	9 (15,5)	15 (25,0)	2 (7,4)	1 (20,0)	2 (15,4)	2 (14,3)
Lung cancer	3 (10,3)	10 (17,2)	8 (13,3)	5 (18,5)	1 (20,0)	1 (7,7)	2 (14,3)
Mammary cancer	4 (13,8)	4 (6,9)	5 (8,3)	3 (11,1)	-	1 (7,7)	-
Ovarian cancer	3 (10,3)	2 (3,4)	4 (6,6)	1 (3,7)	-	-	-
Soft tissue sarcoma	2 (6,9)	5 (8,6)	5 (8,3)	2 (7,4)	-	2 (15,4)	1 (7,1)
Total:	29	58	60	27	5	13	14

Positive neurological dynamics after surgery was noted in 69 (79.3%) patients, an increase in neurological deficit was noted in 13 (14.9%) patients. The number of patients with local relapses was 14 (16.1%) patients from the group of patients with tumor hemorrhages and 47 (26.6%) in the rest of the cohort of patients with cerebral metastases ($\chi2 = 3.59$, $p = 0.059$; $\varphi = 1\ 97$, $p > 0.05$). An intragroup analysis of factors in patients with hemorrhage into a metastatic brain tumor was performed. The highest proportion of local relapses developed in patients with melanoma metastases - in 8 (30.8%) of 26 patients ($\chi2 = 5.92$, $p = 0.016$; $\varphi = 2.306$, $p > 0.05$). Hemorrhages in metastasis, local relapses with an intratumoral form were noted in 3 (10.3%) of 29 patients, local relapse was noted in 11 (19.0%) of 58 patients with the formation of metastatic hematomas ($\chi2 = 1,064$, $p = 0.303$; $\varphi = 1.095$, $p > 0.05$). The removal technique also correlated with the frequency of local relapses: it was 11.7% with block removal (7 out of 60 patients), while with fragmentary - 25.9% (7 out of 27 patients); $\chi2 = 2.804$, $p = 0.095$, $\varphi = 1.597$ $p > 0.05$). However, this circumstance may be associated with the nature of invasive growth and / or aggressiveness of the tumor, which makes block removal of the tumor impossible.

Overall and progression-free survival

When comparing cumulative indicators of OS (9.0 months and 9.3 months) and PFS (4.9 months and 4.3 months), these parameters were comparable in patients with metastatic brain lesion with and without tumor hemorrhage (see table 3), while the median OS after surgical removal of metastasis had a maximum value of 19.1 months in the group of patients with breast cancer.

Table 3. Cumulative survival rates for patients with metastatic brain lesion with and without tumor hemorrhage

Indicator	no hemorrhage into the tumor (n=177)		with tumor hemorrhage (n=87)	
	median, months		median, months	
	PFS	OS	PFS	OS
Histological type of primary tumor				
Melanoma	1,9	7,1	1,6	6,0
Non-seminomatous tumor of the testis	5,9	8,0	6,1	8,6
Squamous cell carcinoma of the cervix or vagina	4,5	7,0	4,0	6,6
Renal cell carcinoma	4,3	11,4	4,5	10,0
Lung cancer	5,9	12,9	5,7	13,5
Mammary cancer	10,0	20,3	10,5	19,1
Ovarian cancer	9,1	16,0	9,5	14,7
Soft tissue sarcoma	7,5	15,3	7,8	15,5
RPA groups				
I class (more favorable prognosis)	10,2	13,9	10,0	13,4
II class (interim forecast)	9,8	11,4	9,5	12,8
Class III (unfavorable prognosis)	3,2	6,9	3,6	6,5
Intergroup analysis				
All patients (n = 264)	4,9	9,0	4,3	9,3

When analyzing survival after surgery in patients with cerebral hemorrhage, significant differences were found between groups of patients stratified by the histological principle: the median OS in melanoma and non-seminomatous testicular tumor was significantly lower in comparison with OS in patients with breast, ovarian and soft tissue sarcomas (see table 4). Analysis of survival data depending on RPA also revealed a significant decrease in OS in patients assigned to class III (poor prognosis) compared with class I and II on RPA.

Table 4. Statistical comparison of overall survival in patients with cerebral hemorrhage

Groups to compare	Confidence indicator	
	the criterion of Cox–Mantel	Gehan-Breslow-Wilcoxon criterion
Histological type of primary tumor		
melanoma vs renal cell carcinoma	p = 0,0692	p = 0,0431
melanoma vs lung cancer	p = 0,0472	p = 0,0326
non-seminomatous tumor of the testis vs renal cell carcinoma	p = 0,1086	p = 0,0936
non-seminomatous tumor of the testis vs lung cancer	p = 0,0668	p = 0,0486
renal cell carcinoma vs lung cancer	p = 0,0708	p = 0,0612
renal cell carcinoma vs ovarian cancer	p = 0,0504	p = 0,0433
ovarian cancer vs breast cancer	p = 0,0491	p = 0,0418
soft tissue sarcoma vs breast cancer	p = 0,0634	p = 0,0502
RPA groups		
I class vs II class	p = 0,1191	p = 0,1011
I class vs III class	p = 0,0359	p = 0,0313
II class vs III class	p = 0,0368	p = 0,0285

DISCUSSION

Spontaneous intracerebral hemorrhage may be associated with intracranial tumor in approximately 7% of all cases, with acute neurological symptoms observed in less than 3% of cases [15]. On the other hand, according to clinical and pathological studies, intratumoral hemorrhages occur in a quarter of all patients with metastatic brain tumors, which indicates their relatively asymptomatic course [7, 9]. However, in our study, the absence of symptoms occurred in only 2 (2.3%) patients. Among the common metastatic brain tumors, metastases of melanoma, kidney cancer, lung cancer [14, 16, 20] most often lead to intracranial hemorrhages, which is fully consistent with the structure of patients in our cohort.

The main goal of the operation is local control, which helps to improve the quality and life expectancy of the cancer patient. After surgical treatment and the subsequent course of radiation therapy to the area of metastatic brain lesion, the local relapse rate is from 10% to 34% [12, 13, 18]. In our study, the local relapse rate was 12.6%. From the point of view of reducing the risk of developing local relapse, block removal of metastasis is most preferable: according to our study, the specific gravities are 11.7% and 25.9% for block and fragmentary removal, respectively [1, 19]. The most probable reasons for the reduction in the frequency of local recurrence of metastases with hemorrhages are their better delimitation from brain tissue during perifocal hemorrhage, which contributes to better intraoperative ablastics, as well as impaired blood supply and necrosis of the metastatic focus during hemorrhage, which helps to reduce the invasive potential of the tumor. Incomplete removal of intracerebral tumors, including metastatic origin, increases the risk of repeated hemorrhage [6]. Before the advent of stereotactic radiosurgery as one of the most promising methods of treating cerebral metastases, the frequency of hemorrhage in the tumor was about 7.4%; however, after carrying out radiosurgical treatment, this indicator doubled (up to 18.5%), while approximately one third of the patients showed pronounced focal symptoms. It should be noted that the frequency of bleeding after radiosurgery increases with an increase in the volume of metastases, an increase in the number of isocenters, and an increase in the maximum radiation dose [17]. This fact leaves the place of classical neurosurgery in the treatment of patients with a high risk of developing hemorrhage in cerebral metastases as the safest method of treatment; however, stratification of risk factors is the subject of further research.

CONCLUSION

The results of treating patients with hemorrhage in a metastatic brain tumor are comparable with the results of similar treatment in the absence of hemorrhage in cerebral metastases. A relatively more favorable clinical prognosis was noted in patients who did not suffer from melanoma or a non-seminomatous testicular tumor, having an intratumoral hemorrhage and belonging to class I and II of RPA. Moreover, even in patients with severe functional impairment (class III of RPA), which is usually caused by a neurological deficit, or in patients with metastatic melanoma, relatively satisfactory treatment results can be achieved.

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