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Outcome comparison of treatment of brain metastases in hypofractionation and staged radiosurgery

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Abstract. Brain metastases occur in 20–40% of cancer patients. The main methods of treatment are neurosurgical intervention, radiation therapy, and stereotactic radiosurgery is actively developing. The advantage of radiosurgery is non-invasiveness, the effectiveness of exposure to foci and the low probability of radiation reactions after treatment. However, in patients with a tumor volume exceeding 3 centimeters in diameter, with radiosurgical doses (>18 Gy), the risk of post-radiation complications is subsequently high, therefore radiosurgical methods of hypofractionation and staged radiosurgery are increasingly used.

The research included a group of patients (46 people) who underwent treatment by the method of staged radiosurgery and a group of patients (27 people) who underwent hypofractionation. The clinical study was conducted at the Leksell Gamma Knife Icon installation (Stockholm, Sweden). The summed dose was in the range from 16 to 30 Gy.

The purpose of research: to study and compare the results of the use of hypofractionation methods and staged radiosurgery for brain metastases.

Keywords: stereotactic radiosurgery, staged radiosurgery, hypofractionation, brain metastases, radiation reactions, gamma knife.

1. Introduction

Oncological diseases are among the most common diseases in the world, from which, according to The Global Cancer Observatory, more than 9.9 million people died in 2020 [1]. The characteristic features of cancer are rapid cell division, the ability to penetrate into surrounding tissues, as well as metastasize to other organs. Brain metastases (BMs) are the most common tumors of the central nervous system. Approximately 20–40% of all cancer patients have BMs [2]. Brain metastases are most often observed in patients with lung cancer, breast cancer and melanoma [3–4]. The use of radiation in the treatment of BM has evolved from the use of only irradiation of whole–brain to combine irradiation and stereotactic radiosurgery. In 1951, Lars Leksell created the first prototype of a gamma knife, where cobalt-60 was used as photon sources, and with it a new direction in medicine – stereotaxic or high-precision radiosurgery [5]. Gamma knife radiosurgery and SRS are currently the main methods of treating BMs. Stereotactic radiosurgery is recommended to be used as an alternative to surgical intervention in metastases, when surgical intervention can cause complications.

Radiosurgery is determined by the effectiveness of exposure to foci and the low probability of post-radiation reactions. However, it is worth noting that a large tumor volume exceeding 3 cm in diameter is not suitable for radiosurgical treatment, since when radiosurgical doses (more than 18 Gy) are summed up in the treatment of such volumes, the risk of post-radiation complications is high. Usually, to solve this problem, stereotactic radiation therapy in hypofractionation mode or multimodal approaches combining stereotactic radiosurgery with surgical intervention or traditional radiation therapy are used. In recent years, in the treatment of such patients, the use of staged radiosurgery, summing up small doses with a time interval of 1 to 4 weeks, has been of interest. In this regard, it is of interest to study the effectiveness of the use of stereotactic radiosurgery in the hypofractionation mode and staged radiosurgery, which allow you to bring a high dose in several sessions and minimize the radiation load on normal brain tissues.

The aim of the study is to evaluate the results of treatment in hypofractionation mode and staged radiosurgery.

2. Methods and Materials

From 2011 to 2022 in the treatment and diagnostic center of the Medical Institute Berezin Sergei conducted a retrospective analysis, which included 73 observations of patients with secondary brain lesion (91 lesions). The median age of patients at the time of the 1st session of stage radiosurgery/hypofractionation was 58 years (range 30–84 years). The study groups were dominated by patients with breast cancer – 40% of patients. Significantly less often, the source of brain metastases were: lung cancer – 16%, melanoma – 11%, gastrointestinal cancer - 8, uterine cancer – 8%, kidney and bladder cancer 4% of the case. In 11% of patients, metastases were a manifestation of primary multiple cancer. In one case, brain metastases were the primary manifestation of the disease.

All patients underwent clinical neurological study with an assessment of the functional status of Karnovsky (KPS) >50. Magnetic resonance imaging (MRI) was performed on a Magneton Avanto (Siemens, Germany) 1.5 T T2-weighted images with 2 mm thickness, magnesium/gadovist T1-weighted images with 1 mm thickness. The resulting images were imported into the planning station Leksell Gamma Plan 11.1, where treatment plans were created.

The treatment was carried out at the Leksell Gamma Knife Icon (Stockholm, Sweden) in the mode of hypofractionation (HF) or staged radiosurgery (ST). Patients were fixed using the Leksell G Frame or individual thermoplastic mask. The treatment regime was chosen taking into account the clinical picture: the presence of a single or multiple metastatic lesions, as well as the attachment of hearths to critical brain structures.

The HF method is applied to 31 foci in three or five sessions each day or every other day. The edge dose ranged from 5 Gy to 8 Gy. The total focal dose (TFD) ranged from 18 Gy to 25 Gy. The ST method covers 60 foci in two and three stages with a time interval of 1 to 4 weeks. The limit dose was in the range of 8 to 12 Gy. TFD ranged from 20 Gy to 36 Gy.

Control of perifocal edema was carried out by the introduction of glucocorticosteroid (dexamethasone), the dose and duration of the course determined individually depending on the clinical picture of the disease, neurological deficiency and the severity of perifocal edema. The evaluation of the local control of the treatment was carried out on the basis of the MRI and volumetric analysis of foci at all stages of the treatment.

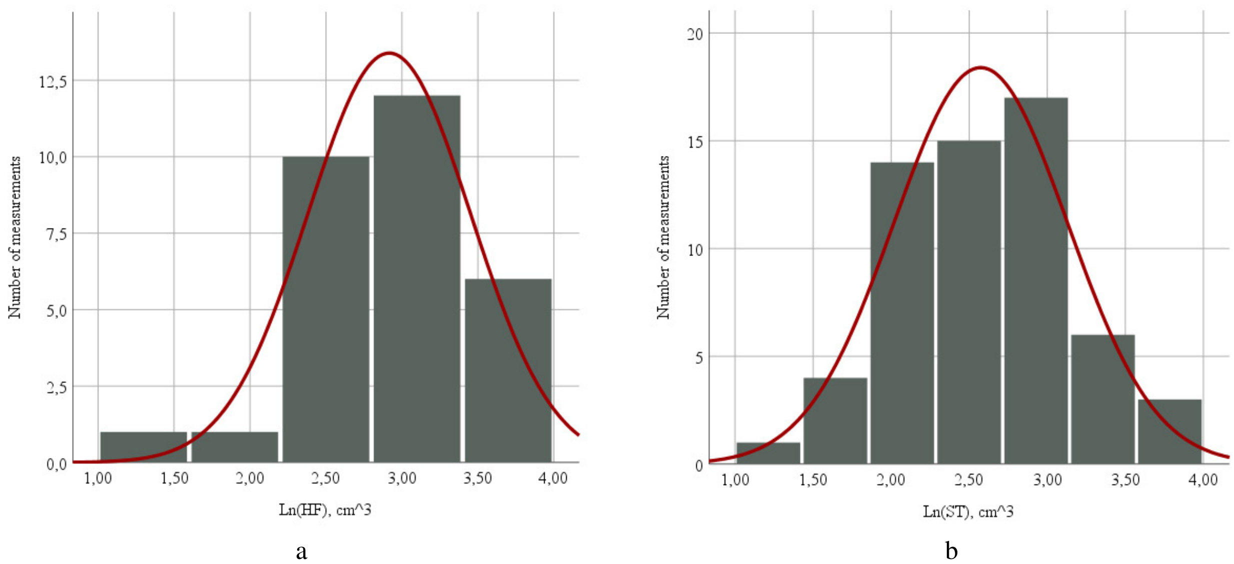

Fig.1. Histograms of the lognormal distribution of the volume of foci in the treatment by hypofractionation (a) and staged radiosurgery (b).

3. Results

3.1. Treatment outcomes

Testing the hypothesis of normal distribution using the Kolmogorov-Smirnov criterion showed that all samples of measured values of the volumes of metastatic foci are subject to a lognormal distribution. Therefore, to calculate the main characteristics of the samples obtained, it was necessary to use formulas for estimating the mean and standard deviation of lognormal samples [6]. Fig.1a, Fig.1b, as an example, shows histograms of the lognormal distribution of the volume of foci at the time of treatment by hypofractionation and staged radiosurgery.

The average values, standard deviations, minima, maxima and medians of metastasis volumes at the time of hypofractionation treatment and at the time of control after 2, 4, 5 and 9 months are shown in Table 1.

Table 1. Statistical data on the volume of foci in hypofractionation

	Average, cm^3	Standard deviations, cm^3	Min, cm^3	Max, cm^3	Median, cm^3
V HF	21	12	3	54	19
V 2 months after HF	12	15	1	71	7
V 4 months after HF	11	14	2	28	8
V 5 months after HF	9	12	2	19	5
V 9 months after HF	9	8	2	21	7

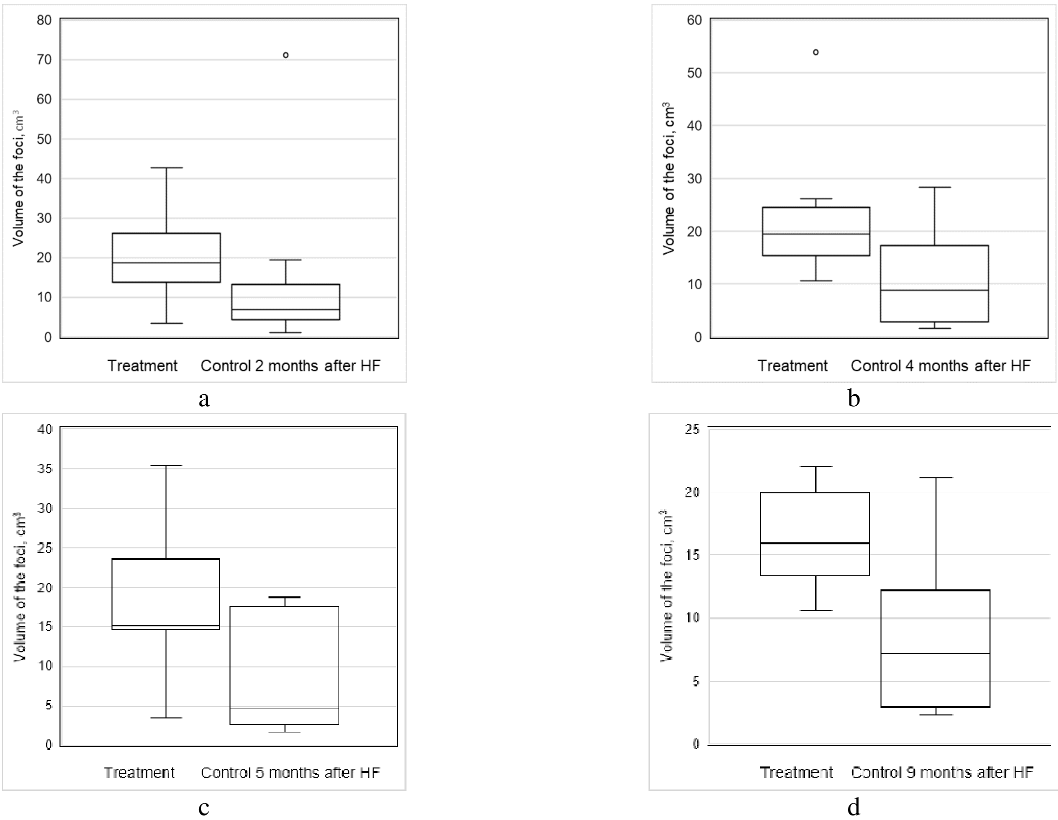

Fig.2. Changes in the volume of irradiated metastases 2 months (a), 4 months (b), 5 months (c) and 9 months (d) after treatment by hypofractionation.

At the time of control MRI, 93% of patients had a decrease in the volume of irradiated metastases by an average of 48%. In the study group, 2 cases of radionecrosis were recorded. In the first case, the volume of the irradiated focus at the time of treatment was 43 cm^3, the summed total dose was 24 Gy. At the time control, after 2 months, the volume of the focus increased to 71 cm^3. In the second case, after adding 24 Gy to the volume of the focus equal to 10 cm^3, we recorded a gradual increase in volume in the sixth and ninth months after treatment, the volume of the foci was 14 cm^3 and 21 cm^3, respectively. This increase is explained by the appearance of moderate radiation reactions corresponding to the timing of the treatment. It is worth noting that two cases with the continued growth of previously treated foci were recorded in the study group. With the help of PET/CT of the brain with tyrosine, the continued growth of metastases was differentiated 1.5 years after treatment with summed total focal dose of 24 Gy at 50% isodose. The radiopharmaceutical accumulation index was 2.82 and 2.04, respectively. Fig.2 shows graphs of changes in the volumes of irradiated metastases by hypofractionation two, four, five and nine months after the treatment.

Basic data on the volumes of metastases at the time of treatment by the method of staged radiosurgery and at the time of control after 2, 4, 6 and 9 months are shown in Table 2.

Table 2. The main statistical data of volumes at the stage radiosurgery

	Average, cm^3	**Standard deviations, cm^3**	**Min, cm^3**	**Max, cm^3**	**Median, cm^3**
V 1st ST	16	12	3	43	13
V 2 months after ST	10	21	0	48	4
V 4 months after ST	6	9	0.4	21	3
V 6 months after ST	4	8	0.3	15	2
V 9 months after ST	3	7	0.2	10	1

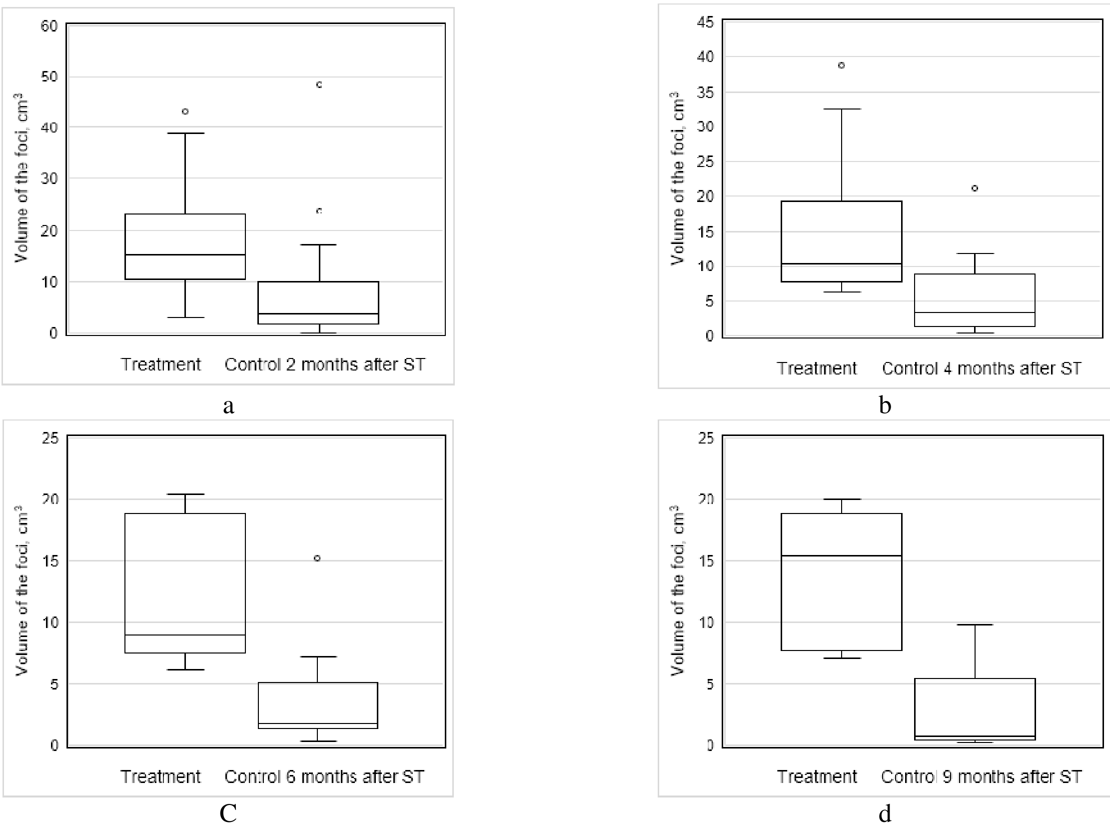

Fig.3. Changes in the volume of irradiated metastases 2 month (a), 4 months (b), 6 months (c) and 9 months (d) after treatment by staged radiosurgery.

At the time of control MRI after 2, 4, 5 and 9 months, 91% of patients had a decrease in the volume of irradiated metastases by an average of 64%. In the study group, cases of the development of radionecrosis were also recorded, the development period, of which was 2 and 4 months. I would like to note that with an increase in the marginal dose (10–12 Gy) and a decrease in the time interval between treatment stages (up to 14 days), the risk of post-radiation reactions is higher than with smaller marginal doses (8–10 Gy). Note that the appearance of moderate radiation reactions corresponds to the timing of the treatment. Also, in the study group, there was one case of regression of the focus, two months after treatment. Fig.3 shows graphs of changes in the volumes of irradiated metastases two, four, six and nine months after the treatment with staged radiosurgery.

Using a variance analysis of the volume values obtained at the time of treatment and control MRI between the two methods, a significant difference in the obtained average values was shown. For example, the average values at the time of the control MRI after 2 months between the methods differ significantly (the calculated value of the Fisher criterion of 18.25 is significantly greater than the critical 2).

4. Conclusion

Many patients with brain metastases have a hard time tolerating long-term treatment sessions, especially those with low Karnovsky's functional status or impaired neurocognitive function, therefore it is rational to apply treatment methods in several fractions with a high cumulative foci dose. With the development of technology, stereotactic radiotherapy in hypofractionation mode and staged radiosurgery are now such methods. They provide an opportunity to deliver a high therapeutic dose to the hearth for several fractions with minimal lesions of the surrounding healthy tissues. These methods also allow adaptive planning of treatment for each patient at each stage of stereotactic radiosurgery, which allows to take into account the specific response to the treatment of each hearth, as well as significantly reducing the load on the surrounding brain tissue.

The available data in the study are heterogeneous in terms of tumor volumes, the number and size of treated metastases, the difference in their morphological types, the total doses and the number of fractions, as well as the parallel treatment used. Despite this, hypofractionation and staged radiosurgery in most cases stabilize or reduce the volume of foci, with radionecrosis recorded in only 8% of the irradiated foci.

In the course of the study, it was found that staged radiosurgery provides satisfactory indicators of local control and is comparable to the hypofractionation method of treating large intracranial metastases in the absence of surgical removal. According to preliminary data, the development of radiation reactions during staged radiosurgery using higher marginal doses is higher than with hypofractionation. However, in the study group of hypofractionated patients, two cases with the continued growth of previously treated foci were recorded.

5. References

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