Original article

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Hypofractionated radiotherapy of patients with glioblastoma: the first experience in Ukraine and prospects view

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Objective: To assess the survival of patients (pts) with newly diagnosed glioblastoma (GBM) in groups with hypofractionated regime radiotherapy, standard fractionationated regime radiotherapy and whole brain irradiation.

Materials and methods: A retrospective non-randomized single-center study of 205 pts with GBM grade 4 according to the WHO classification treated in Romodanov Neurosurgery Institute named after Acad. A.P. Romodanov National Academy of Medical Science of Ukraine (2014–2020). The mean age of pts 53.8 years (95% CI 52.1 - 55.5); there were 114 men (55.6%) and 91 women (44.4%). According to the regimen radiotherapy (RT), pts were divided into 3 groups: 49 (23.9%) pts (standard RT: 2.0 Gy per fraction in 30 fractions, total dose 60.0 Gy) – group "sRT", 110 (53.7%) pts (hypofractionated RT: 3.5 Gy per fraction in 15 fractions, total dose 52, 5 Gy) - group "hRT", 46 (22.4%) pts – group "WBRT" (whole brain radiation). Differences in progression-free survival (PFS) and overall survival (OS) between the three groups were analyzed using Kaplan–Meier survival curve, log-rank test and Pearson Chi-square test.

Results: The median OS is 15,0 (95% CI 14,1 – 17,1), 16,5 (95% CI 14,1 – 18,8) and 8,7 (95% CI 7,5 – 9,5) months for sRT, hRT and WBRT, respectively. There is a significant difference in OS for sRT and hRT compared to WBRT (p=0.00000), without difference in OS between sRT and hRT (p=0.06757). The median PFS in sRT and hRT does not differ significantly: sRT – 9.0 (95% CI 9.0 - 10.0) months; hRT – 9.0 (95% CI 8.0 - 10.0) months. The median OS for WBRT is 5.1 (95% CI 4.0 - 6.0) months. There is a significant difference in PFS for sRT and hRT compared to the WBRT (p=0.00000), without difference in PFS between sRT and hRT (p=0.43374). The risk of death for WBRT compared to sRT is 2.5 times higher (HR 2.5 [95% CI, 1.45 - 4.46)) and 3.5 times higher compared to the hRT group (HR 3.5 [95% CI, 2.09-5.88)). The risk of progression for WBRT is 2.8 times higher (HR 2.78 [95% CI, 1.63-4.74)) compared to sRT, and 3.1 times higher (HR 3.12 [95% CI, 1.91-5.10)) compared to hRT.

The broad implementation of hRT into clinical practice is specific to all modern radiation oncology. This trend is currently underway due to the specific positive clinical effects of hRT, which are discussed in detail in our publication.

Conclusions: Our study demonstrates comparable survival outcome between sRT and hRT groups. This is an argument in favor of the feasibility of using hRT as a part of multimodal GBM treatment in terms of oncological outcomes. Further studies are needed to identify specific stratification groups of GMB patients with the greatest survival and quality of life benefits due to hRT.

Key words: *neoplasms; glioblastoma; radiotherapy; radiation dose hypofractionation; survival analysis*

Introduction

Glioblastoma (GBM) is a malignant brain tumor in adults characterized by an extremely aggressive course and resistance to treatment. This explains the negative prognosis for this category of patients, with low chances of long-term survival [1]. Standardized multimodal treatment of newly diagnosed GBM (primary GBM) involves the maximal safe surgical resection with adjuvant chemoradiotherapy according to the Stupp protocol. In 2005, R. Stupp *et al*. in a prospective randomized study, it was first demonstrated that the combining alkylating chemotherapy (CT) with temozolomide and radiation therapy (RT) increased the median overall survival (OS) in GBM by 2.5 months compared to RT alone [2]. Studies proving the positive effect of adjuvant RT both in monotherapy and in combination with BCNU-CT on

the survival of patients with malignant gliomas were first carried out almost 50 years ago [3].

A population-based study published in 2020 by E. Burton *et al*. analysed the US National Cancer Database (NCDB) with a cohort of 17,451 adults with GBM from 2005–2012. It was shown that the inability to perform standard RT is associated with decreased survival [4]. In 80% of cases, GBM recurrence occurs in the irradiated area [5]. At the same time, the recurrence rate of GBM is extremely high (about 90%), but there is still no standard treatment for recurrent GBM [6]. Reoperation may be considered for about 25% of patients with recurrent GBM because of the high probability of significant postoperative neurologic deterioration. Futhermore, despite significant technological advances in modern radiation oncology, reirradiation is associated with a high risk of radiation toxicity, in particular, radiation-induced brain necrosis [6, 7].

Therefore, RT is now an indispensable component of multimodal treatment of patients with GBM. The relevance of the problem of improving the effectiveness of RT in neuro-oncology is beyond doubt. Recently, alternative approaches to standard RT (sRT) (2,0 Gy per fraction over 6 weeks; total dose 60,0 Gy), in particular, different modes of irradiation (hypofractionation, hyperfractionation, total dose increase, use of boost, etc.) have been studied. This publication analyses our own experience of using hypofractionated RT (hRT, radiation with increased dose per fraction and reduced number of radiation fractions) in the adjuvant treatment of patients with primary GBM in terms of oncological outcomes, namely the impact on survival. The view of hRT, presented in the current professional literature, is also demonstrated.

The aim is to investigate the survival of patients with newly diagnosed glioblastoma in groups with hypofractionated radiation, standard fractionation and whole brain radiation.

Materials and methods

Study participants

A retrospective non-randomized single-center study of 205 patients with newly diagnosed and verified GBM, treated at the Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine in the period from 2014 to 2020.

At the time of the last contact within the framework of the study (September 9, 2021 – the right-censoring point), 41 (20.0%) patients were alive, 164 (80.0%) had died.

The analysis was conducted as part of the research work of the Institute of Romodanov Neurosurgery Institute named after Acad. A.P. Romodanov National Academy of Medical Science of Ukraine "To study the effectiveness of adjuvant immunotherapeutic and radiotherapeutic technologies in the complex treatment of malignant glial brain tumors" (chief scientific officer of the topic - Dr. habil. med., Prof. Oleksandr Y. Glavatskyi). The study was approved by the Committee on Ethics and Bioethics of the institution (Minutes № 3 dated June 6, 2016).

Written informed consent for the study was obtained from all patients in accordance with the World Medical Association Declaration of Helsinki on the Ethical Principles for Medical Research Involving Human Subjects (1964-2008), directive of the European Society 86/609 on humans participation in medical and biological research, as well as by order of the Ministry of Health of Ukraine, as amended, No. 690 dated from 23. 09. 2009.

Criteria for iclusion in the study:

- age of patients ≥18 years;
- informed and voluntary written consent to treatment, desire and ability to comply with study and follow-up procedures;
- life expectancy >3 months;
- pathohistologically confirmed diagnosis of GBM;
- Karnofsky Performance status (KI) ≥60 score (%).

Characteristics of the group

The average age of patients in the total cohort was 53.8 years (95% confidence interval (CI) – 52.1–55.5), median – 55 years. There were 114 (55.6%) men, 91 (44.4%) women.

According to the volume of surgical resection, the distribution was as follows: 82 (40.0%) patients had the tumor removal in the perifocal zone (gross total resection), 23 (11.2%) underwent subtotal tumor removal, 69 (33.7%) had partial tumor removal, 31 (15.1%) had stereotaxic biopsy.

In all cases, the diagnosis of GBM of grade 4 according to the WHO classification was verified pathomorphologically after surgical treatment.

Given that the vast majority of the cohort belongs to the period prior to the widespread introduction of molecular genetic studies into clinical practice (primarily regarding the methylation status of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter, isocitrate dehydrogenase (*IDH*) gene mutation), we have limited data on the distribution of patients according to these indicators. This publication provides data on the distribution of patients according to *MGMT* gene promoter methylation status in the overall cohort, taking into account the predictive value of this feature in response to alkylating CT [8]. Molecular genetic markers such as 1p/19q codeletion and mutational status of the *IDH* gene were considered as important prognostic factors in previous WHO classifications of central nervous system tumors, but in the 2016 classification, these features have become disease- defining features and are therefore no longer prognostic within a given disease subtype [9].

In the cohort studied, data on *MGMT* gene promoter methylation status were absent for more than half of patients (106 (51.7%) of 205 patients). In 99 (48.3%) of 205 cases when such a diagnosis was made, the distribution of *MGMT* gene promoter methylation status was as follows: 46 (22.4%) had no *MGMT* gene promoter methylation, 53 (25.9%) had *MGMT* gene promoter methylation.

Clinical management (e.g., treatment decisions) was performed by a multidisciplinary neuro-oncology team.

Characteristics of the cohort are shown in ***Table 1 and 2***.

This article contains some figures that are displayed in color online but in black and white in the print edition.

Table 1. Characteristics of the cohort (n=205)

Indicator	Standard RT, n= 49	Hypofractionated RT, n= 110	Whole brain irradiation, n= 46	Total
Sex:				
men	25 (12,2%)	48 (23,4%)	18 (8,8%)	91 (44,4%)
women	24 (11,7%)	62 (30,2%)	28 (13,7%)	114 (55,6%)
Volume of resection:				
gross total resection	23 (11,2%)	59 (28,8%)	0 (0%)	82 (40,0%)
subtotally	11 (5,4%)	12 (5,8%)	0 (0%)	23 (11,2%)
partially	10 (4,9%)	29 (14,2%)	30 (14,6%)	69 (33,7%)
stereotaxic biopsy	5 (2,4%)	10 (4,9%)	16 (7,8%)	31 (15,1%)
Age, years:				
≤59	33 (16,1%)	73 (35,6%)	29 (14,2%)	135 (65,9%)
>59	16 (7,8%)	37 (18,1%)	17 (8,3%)	70 (34,2%)
GBM localisation:				
lobar	32 (15,6%)	76 (37,1%)	5 (2,4%)	113 (55,1%)
median distribution	17 (8,2%)	34 (16,6%)	11 (5,4%)	62 (30,2%)
multifocal process	0 (0%)	0 (0%)	30 (14,6%)	30 (14,6%)
Karnofsky Performance status (%)				
90	13 (6,4%)	33 (16,1%)	0 (0%)	46 (22,4%)
80	24 (11,7%)	46 (22,4%)	2 (1,0%)	72 (35,1%)
70	11 (5,4%)	22 (10,7%)	17 (8,3%)	50 (24,4%)
60	1 (0,5%)	9 (4,4%)	27 (13,2%)	37 (18,1%)
CT:				
was not carried out	44 (21,4%)	100 (48,8%)	26 (12,7%)	35 (17,1%)
was carried out:	5 (2,4%)	10 (4,9%)	20 (9,8%)	170 (82,9%)
temozolomide CT	38 (18,5%)	87 (42,4%)	16 (7,8%)	141 (68,8%)
PCV CT	6 (2,9%)	13 (6,3%)	10 (4,9%)	29 (14,1%)

Table 2. Age, Karnofsky Performance status, and radiation treatment parameters

Indicator	Standard RT, n= 49		Hypofractionated RT, n= 110		Whole brain irradiation, n= 46	
	Mean value	Median	Mean value	Median	Mean value	Median
Age, years	52,8 (49,6–55,8)	54,0 (49,0–58,0)	54,0 (51,8–56,3)	55,0 (52,0–58,0)	54,4 (50,1–58,7)	58,0 (51,0–60,0)
Karnofsky Performance status, %	80,0 (77,9–82,1)	80,0 (80,0–80,0)	79,4 (77,6–81,0)	80,0 (80,0–80,0)	64,6 (63,0–66,2)	60,0 (60,0–70,0)
BED 11, Gy	70,9 (70,9–70,9)	70,9 (70,9–70,9)	69,2 (69,2–69,2)	69,2 (69,2–69,2)	35,8 (34,1–37,4)	36,4 (36,4–36,4)
Total dose, Gy equivalent to 2,0 Gy radiation regimen	60,0 (60,0–60,0)	60,0 (60,0–60,0)	58,6 (58,6–58,6)	58,6 (58,6–58,6)	30,3 (28,9–31,7)	30,8 (30,8–30,8)
PTV (planning tumor volume), $см^3$	98,1 (92,7–103,4)	95,2 (88,3–102,5)	103,6 (96,6–112,0)	94,4 (90,7–105,2)	1530,3 (1476,1–590,6)	1522,9 (1448,1–1581,3)
Number of fractions	29,7 (29,0–30,0)	30,0 (30,0–30,0)	14,9 (14,8–15,0)	15,0 (15,0–15,0)	6,4 (5,6–7,2)	5,0 (5,0–5,0)

Note: 95% confidence intervals are given in brackets.

Study design

Patients were divided into three groups according to the RT regimen: 49 (23.9%) patients (sRT group) – standard regimen (30 fractions, dose per fraction – 2.0 Gy, total dose – 60.0 Gy), 110 (53.7%)) patients (group of hRT) - hRT (15 fractions, dose per fraction - 3.5 Gy, total dose - 52.5 Gy), 46 (22.4%) patients (WBRT group) - whole brain irradiation due to the multifocal or diffuse nature of the spread 4–6 fractions; total mean dose 30,3 Gy) tumor process. Irradiation was performed using a Trilogy linear accelerator (USA, 6 MeV). In standard and hypofractionated regimens, irradiation was performed using IMRT (intensity modulated radiotherapy), which is a more advanced RT compared to 3D conformal RT. The main advantages of IMRT include homogeneous dose distribution in the radiation target, the ability to deliver the dose to the radiation target in the most sparing way to the structures and tissues adjacent to the radiation site. In addition, this method is associated with a reduction in the duration of the radiation treatment session, which reduces the radiation burden on the patient and allows more efficient use of treatment facility resources. Whole brain irradiation was performed using of conformal opposing fields (conformal beam irradiation).

CT was used in most patients (170 (82.9%)), in particular alkylating CT (temozolomide) - in 141 (68.8%), PCV CT - in 29 (14.1%). In 35 (17.1%) patients, adjuvant RT was performed in mono-regimen.

The following CT regimens were used in 141 (68.8%) patients who received temozolomide-CT:

– concomitant (temozolomide – 75 mg/m^2 of body surface, daily during the entire course of RT) – 137 (66.8%) patients;

– adjuvant maintenance regimen (temozolomide – 150–200 mg/m^2 of body surface in cycles of 5 days every 28 days after the end of RT) – 112 (54.6%) patients.

The combination of concomitant and adjuvant maintenance regimen was applied to 109 (53.2%) patients.

The distribution of patients according to the number of cycles of adjuvant maintenance temozolomide-CT was as follows:

– <6 cycles – 34 (16.6%) patients (9 (4.4%) from the sRT group, 23 (11.2%) from the hRT group, 2 (1%) from the WBRT group);

– 6–10 cycles – 50 (24.4%) patients (11 (5.4%) from the sRT group, 36 (17.6%) from the hRT group, 3 (1.5%) from the WBRT group);

– >10 cycles – 28 (13.7%) patients (8 (3.9%) from the sRT group, 17 (8.3%) from the hRT group, 3 (1.5%) from the WBRT group).

In all cases, CT was performed in the absence of contraindications.

Statistical analysis

Survival analysis was performed using the Kaplan–Meier method, the log-rank test, and the χ^2-test.

The OS indicator was defined as the time from the date of surgery to death, the PFS indicator (progression-free survival) - from the date of surgery to clinical and radiological confirmation of progression or death.

Hazard ratio (HR) was calculated with 95% CI.

The statistical significance of the results was determined by comparing the p-value indicators with the defined critical level of acceptance/rejection of statistical hypotheses α=5%.

Statistical calculations were performed using specialized software Statistica 64 ver.10.0.1011.0 StatSoft Inc.

Results and discussion

Analysis of overall survival

In the sRT group with a median follow-up time of 24.4 months, the median OS was 15.0 (95% CI – 14.1–17.1) months, in the hRT group with a median follow-up time of 22.3 months was 16.5 (95% CI - 14.1–18.8) months. The median OS for the WBRT group was 8.7 (95% CI – 7.5–9.5) months. The median follow-up time for this group is not reached during uncensored observations.

The median OS for the total cohort was 14.1 (95% CI – 12.8–15.5) months. The median follow-up for the combined group of sRT and hRT was 23.8 months. This indicator is calculated excluding the WBRT group, as the inclusion of such a group distorts this indicator for the total cohort.

The χ^2-test showed the presence of a statistically significant difference in OS between sRT and WBRT and between hRT and WBRT (χ^2=41.31794, df=2, p=0.00000) ***(Fig. 1)***. The OS data, depending on the radiation regimen, are shown in ***Fig. 2–4***.

Calculations using the logrank test revealed no statistically significant difference in OS between the sRT and hRT groups (p=0.06757) ***(Fig. 5)***. There is a clear trend towards an increase in OS in the hRT group after reaching the median compared to the other study groups.

Analysis of progression-free survival

Median PFS was 9.0 (95% CI 9.0–10.0) months in the sRT group, 9.0 (95% CI 8.0–10.0) months in the hRT group, and 9.0 (95% CI 8.0–10.0) months, in the WBRT group 5.1 (95% CI – 4.0–6.0) months ***(Fig. 6)***. For the total cohort, the median PFS was 8.8 (95% CI – 7.0–9.0) months.

The analysis revealed the presence of a statistically significant difference in PFS between the sRT and WBRT groups, between hRT and WBRT (χ^2=42.13263, df=2, p=0.00000) ***(***see ***Fig. 6***). There was no statistically significant difference in PFS between the sRT and hRT groups (Logrank test p=0.43374) ***(Fig. 7).***

The results of calculations of survival rates in the groups are shown in ***Table. 3.***

Analysis of death risk ratio and progression depending on the radiation regimen

Patients in the WBRT group had 2.5 times higher risk of death (HR - 2.5 (95% CI - 1.45–4.46)) compared to the sRT group and 3.5 times higher (HR - 3.5 (95% CI – 2.09–5.88)) – compared to the hRT group.

Given the OS data in the study groups (see ***Fig. 1***), the assessment of the death risk ratio in patients of the sRT and hRT groups is not correct due to the absence of a statistically significant difference in the risks and the value of HR (0.73 (95% CI – 0.51–1.03)).

The risk of progression for the WBRT group was 2.8 times higher (HR – 2.78 (95% CI – 1.63–4.74)) compared to the sRT group and 3.1 times higher (HR – 3.12 (95% CI – 1.91–5.10)) – compared to the hRT group.

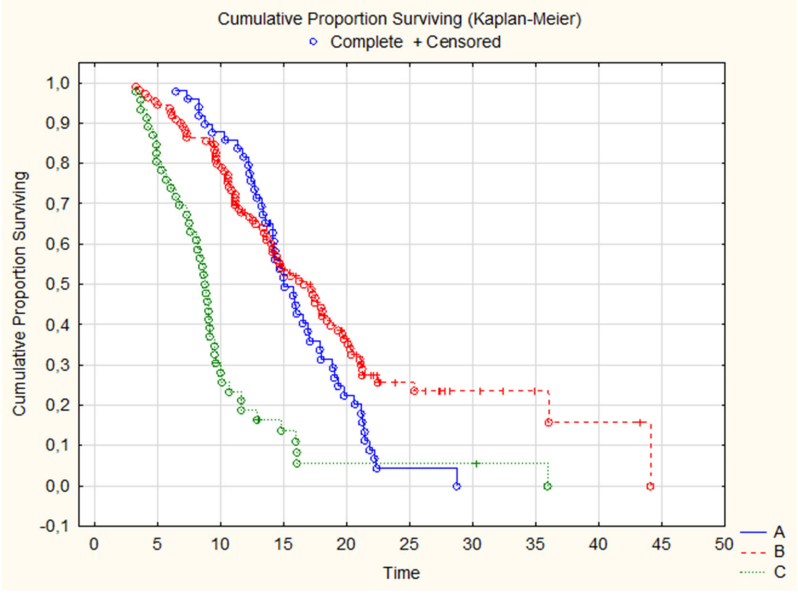

Fig. 1. Kaplan–Meier curves of OS of 205 patients with GBM in the groups of standard radiation regimen (A), hypofractionated RT (B) and whole brain irradiation (C)

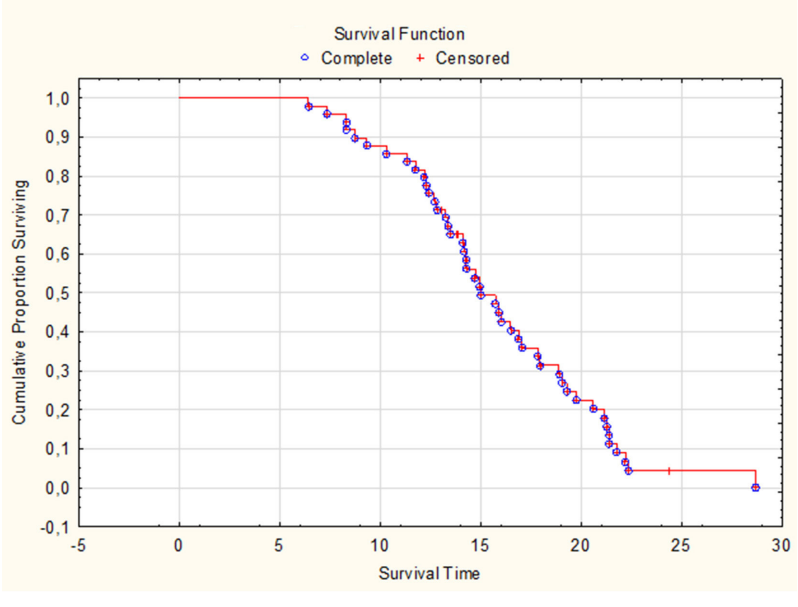

Fig. 2. Kaplan–Meier curve of OS of 49 patients with GBM in the group of standard RT fractionation

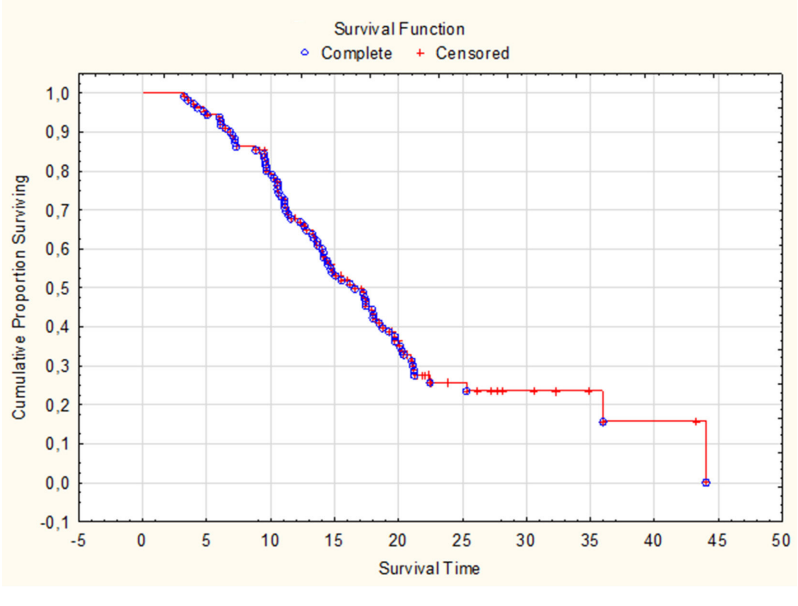

Fig. 3. Kaplan–Meier curve of OS of 110 patients with GBM in the group of hypofractionated RT

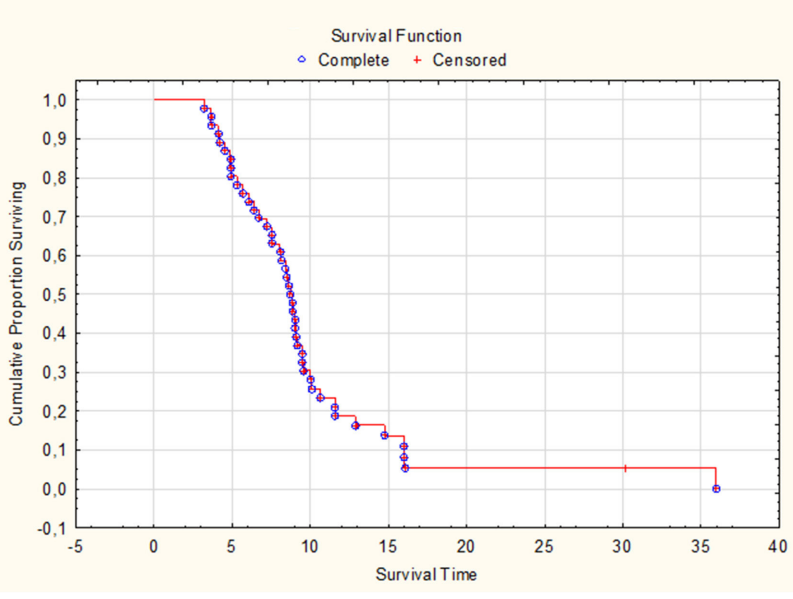

Fig. 4. Kaplan–Meier curve of OS of 46 patients with GBM in the whole brain irradiation group

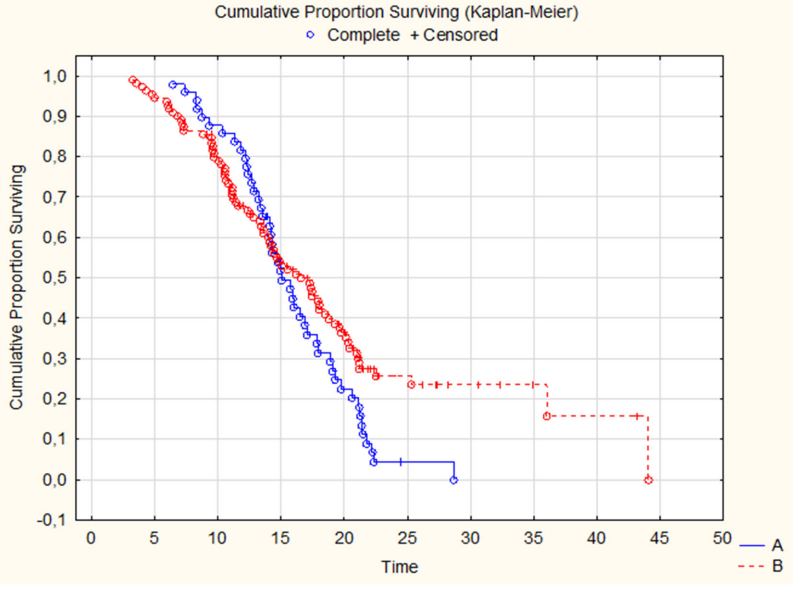

Fig. 5. Kaplan–Meier curves of OS of patients with GBM in the group of standard radiation regimen (A) and hypofractionated RT group (B)

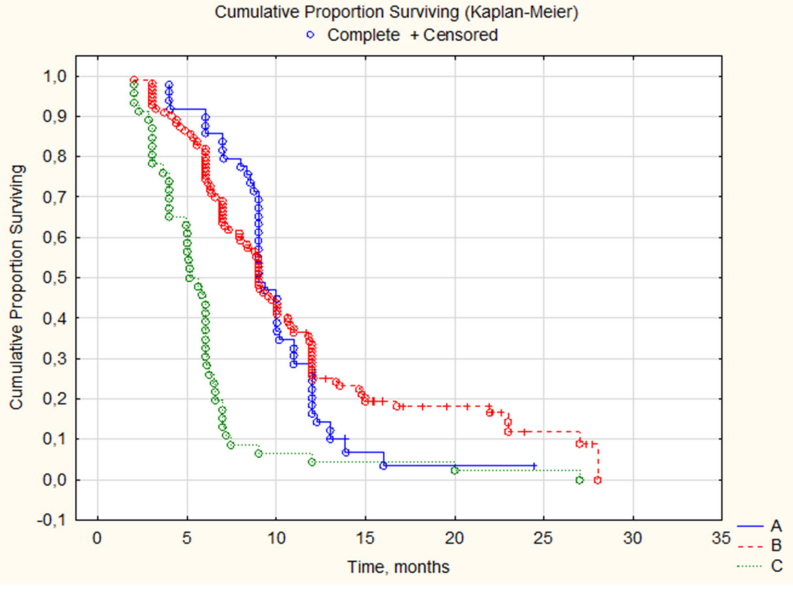

Fig. 6. Kaplan–Meier curves of PFS for patients with GBM in the groups of standard radiation regimen (A), hypofractionated RT (B) and whole brain radiation (C)

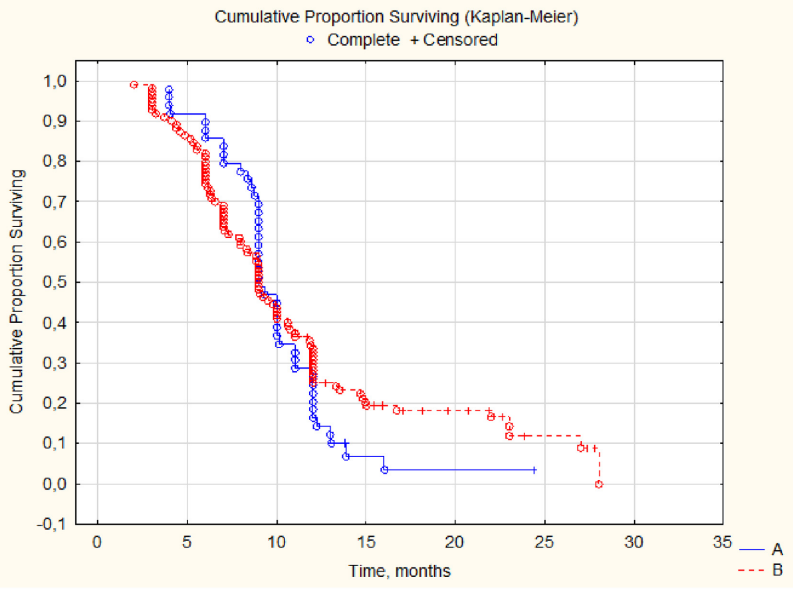

Fig. 7. Kaplan–Meier curves of PFS of patients with GBM in groups of standard radiation regimen (A) and hypofractionated RT (B)

Table 3. Survival in the studied groups, months

Indicator	sRT, n=49	hRT, n=110	Overall population, n=205
Median OS	15,0 (14,1–17,1)	16,5 (14,1–18,8)	14,1 (12,8–15,5)
Median PFS	9,0 (9,0–10,0)	9,0 (8,0–10,0)	8,8 (7,0–9,0)
Median follow-up time	24,4	22,3	23,8*

Notes. * For the combined sRT and hRT group, without the WBRT group (explanation in the text). 95% CI are given in brackets.

The estimate of the risk ratio between the sRT and hRT groups is not correct, taking into account the value of HR (0.89 (95% CI – 0.64–1.24)).

During the follow-up period, there was no case of severe radiation toxicity grade ≥3 according to CTC (Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0)), with clinical deterioration requiring hospitalisation and intensive care, and radiation complications that would threatened the patient's life. Radiation reactions were controlled by steroid and symptomatic therapy. The details of this aspect, as well as the impact of the quality of life of the radiation regimens will be the subject of a separate publication.

The debate about the place of hypofractionation in the radiation treatment of neuro-oncology patients continues. This is evidenced by recently published systematic reviews and meta-analyses [10–15].

The widespread introduction of the hypofractionated approach in clinical practice is characteristic of modern radiation oncology, and is not related only to individual nosologies or the preferences of individual specialists. This trend is due to a number of objective reasons.

In 2021, D. Rodin *et al*. published the results of anonymous survey "Hypofractionated radiotherapy in real clinical settings: the ESTRO-GIRO international survey" of 2316 radiation oncologists in 2018–2019 under the initiative of ESTRO-GIRO (The European Society for Radiotherapy and Oncology's Global Impact of Radiotherapy in Oncology [16]. Among the specialists surveyed, more than half (58.1%) belonged to the academic community (affiliated with the university), most respondents worked on high-tech equipment, including linear accelerator (93.3%), CT-3D planning (90.0%) and IMRT (85.0%). The survey covered all world regions according to World Bank classification and included the following categories: clinical experience, economic and resource impact, professional culture, patient opinion. Analysis of the results of the global professional community survey revealed progress in general perception and consistency of the use of hRT in palliative care, but showed significant differences in the determination and indications in non-palliative clinical scenarios, as well as across geographic regions and income groups. The authors argue that the findings suggest that the need to develop interventions aimed at supporting clinical decision-support and focusing on training should be developed to address gaps in physician knowledge and patient awareness, with a focus on countries with low- and lower-middle-income. Improving the global implementation of hypofractionation has been noted as an important step towards increasing availability and access to treatment.

In 2015, the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) investigated the medical and

economic benefits of increasing radiotherapy use in low- and middle-income countries. The group developed a model using the average number of radiation fractions per course of RT, taking into account tumor type and other individual clinical data. When the two radiation regimens were equally effective, the lower number of fractions was preferred. The results of the study showed that the lowest level of use of hRT is observed in regions with limited access to high-tech equipment [17]. The ESTRO-GIRO study confirmed that limited access to modern radiation technologies is the major barrier to the use of hypofractionated irradiation schemes [16]. The ability to use IMRT was found to be one of the strongest predictors of the use of hypofractionation regimens in non-paliative radiation therapy. In the study by D. Dearnaley *et al*. (2016) it is demonstrated that the use of IMRT in conventional RT is associated with a reduction in radiation toxicity by more than 50% [18]. Consequently, the regimen of fractionation has less effect on radiation toxicity than the degree of precision of dose delivery to the target of irradiation.

Thus, optimizing the implementation of hRT in clinical practice is not only associated with tactical advantages, but can also have a strategic impact on the efficiency of the global medical system functioning.

In neuro-oncology, the search for more effective treatment of patients with GBM remains the subject of special attention of researchers, since the 5-year survival rate for this patients does not exceed 10% even in the case of using innovative personalized therapy. In terms of changing approaches to RT in patients with brain tumors, one of the biggest prejudices regarding the wider introduction of hypofractionated radiation regimens is radiation toxicity, although recently hypofractionated RT regimen for certain categories of patients with GBM is considered more optimal. This applies primarily to patients with the least favorable prognosis (elderly and with a limited functional capacity (poor-prognosis patients)) [19–21]. On the other hand, the possibility of significantly reducing the duration of RT contributes to wider implementation of hypofractionation for the treatment of neuro-oncology patients with higher chances of survival. The work of P. Chidle *et al*., published in 2022, is devoted to this category of patients, in which they compared the results of hypofractionated (total dose 50.0 Gy in 20 fractions) and conventional (total dose 60.0 Gy in 30 fractions) RT regimens in patients with GBM of young age with better performance status (young and fit patients). It was found that hRT can provide equivalent treatment results and reduce the burden of the treatment process compared to standard RT in young patients with GBM with better performance status [22].

In 2020, J.-C. Trone *et al*. published a systematic review and meta-analysis on the use of hRT in patients with GBM, which is one of the most thorough [11]. 2283 publications were analyzed from 1985 to 2020. The authors concluded that, because some studies were randomized and there were some concerns about the quality of most reports, it is difficult to clearly define the place of hypofractionation in GBM, but the results suggest that hRT provides a comparative survival rate with shorter duration of the radiation regimen. In a system analysis, L. Guo *et al*. (2021) [14] evaluating the efficacy of hRT in newly diagnosed GBM without age restrictions, found that by reducing the overall duration of treatment, hypofractionation can not only increase tumor cell killing through a higher dose per fraction, but also reduce the need for medical resources. In contrast to sRT, hRT is associated with a tendency to improve prognosis in GBM.

Our findings are consistent with the results of current publications devoted to hRT in patients with GBM. Analysis of a cohort of 205 patients with GBM, allocated according to the adjuvant RT regimen, showed that survival (both OS and PFS) in the groups of sRT and hRT did not differ significantly. In contrast, patients who underwent WBRT had worse survival than patients in the sRT and hRT groups.

Only our initial results were analyzed. It is advisable to carry out a more detailed analysis with a focus on the sRT and hRT groups. It is necessary to compare the impact of these regimens on patients' quality of life, radiation toxicity, to investigate the predictive effect on treatment outcomes and risk ratios. Such an analysis will enable us to detail our experience with hRT in patients with GBM.

It is well known that only randomization guarantees an equal distribution of all characteristics in the study groups and allows conclusions to be drawn about causal relationships associated with treatment efficacy. However, it is randomized controlled trials that are criticized for the lack of external validity, i.e., it is not clear how far the results of a particular trial can be extended to the general population, given the selectivity of involvement in randomized trials [23,24]. Non-randomized trials are an alternative, but there is a risk that the analysing groups will differ in characteristics, affecting the results of the study. Multiple regression models are usually used for non-randomized trials, but the so-called propensity score analysis (PSA) is increasingly used. This method provides an assessment of treatment outcomes by taking into account the influence of covariates characterizing the sample [25,26]. This justifies the expediency of our use of the propensity score method for further analysis, but it should be taken into account that using such an approach will significantly limit the sample size and, hence the power of statistical methods.

It is clear that we do not provide a systematic review in this publication, but only highlight the views on hypofractionation in modern radiation oncology. Currently, there is a clear trend towards the wider use of hypofractionation in RT of neuro-oncology patients. A consensus on such an approach continues to be sought. On the one hand, the standard radiation regimen has proven itself to be satisfactory in terms of efficacy and safety for decades, on the other hand, this fractionation regimen has been introduced into clinical practice based on studies dating back to the earliest stage of radiation oncology development (almost 100 years ago) [27, 28].

Given the innovative advances associated with the technological capabilities of modern radiation oncology, a paradigm shift in relevant clinical approaches is required. The precision of irradiation is now incomparably higher than in those times when the radiation regimen (30 fractions with 2.0 Gy per fraction) became standard for adjuvant RT in patients with GBM. Despite the ongoing search for a more effective

treatment for malignant gliomas, there has been no significant progress in the treatment of this category of patients by any approach.

Hypofractionation can reduce the time of the patient's stay in the clinic, minimize the epidemiological risk (including coronavirus infection (COVID-19), decrease burden on the medical staff and caregivers, and optimize the use of technology. Halving the radiation exposure time (from 6 to 3 weeks) is associated with increased patient comfort, especially considering that the survival rate of most patients with GBM is 12–18 months. A shorter course of radiation treatment reduces the burden on the global health care system. If implemented effectively, hRT can optimise the provision of care to cancer patients within the framework of the National Health System of Ukraine. However, researchers emphasize the lack of high-level consensus. First of all, this is due to the insufficient number of clinical trials with a high level of evidence. Therefore, one of the urgent tasks for neuro-oncology is to conduct large-scale prospective randomized trials on hypofractionated RT, allow to create the practical clinical guidelines with a consensus level close to 100%.

There are concerns about a possible increase in radiation toxicity when using higher dose per fraction and reduction of the radiation time. There is a need for a better understanding of exactly which radiobiological effects are associated with a change in the RT fractionation regimen. The problem of individual radiosensitivity is worth considering in this regard. There is reliable evidence of considerable variability in individual radiosensitivity, which affects the results of RT. In this connection, another important question arises related to radiobiological research: how is the radiosensitivity of the tumor and the patient correlated? The answer to this question will bring the choice of the most optimal fractionation regimen by unifying the approaches to the individualisation of RT of patients.

All of the above suggests that hRT in patients with GBM is associated with certain clinical benefits that needs to be further analyzed. In our opinion, more extensive study can help to identify the categories of patients who will benefit the most from the use of hRT, which will be accompanied by a positive impact on survival and quality of life.

Conclusions

The results of our study show comparable survival outcome between the sRT and hRT groups, which determines the feasibility of using hRT as a part of the multimodal therapy of primary GBM.

The median OS in patients of the sRT, hRT, WBRT groups was 15.0 (95% CI – 14.1–17.1) months, 16.5 (95% CI – 14.1–18.8) months, 8.7 (95% CI – 7.5–9.5) months, respectively. The median OS for the total cohort was 14.1 (95% CI – 12.8–15.5) months.

According to OS, the sRT and hPT groups were not statistically significantly different (p=0.06757), but compared to the WBRT group, a statistically significant difference was established (p=0.00000).

For the sRT and hRT groups, the median PFS was 9.0 (95% CI – 9.0–10.0) and 9.0 (95% CI – 8.0–10.0) months, respectively, for the WBRT group was 5, 1 (95% CI – 4.0–6.0) months.

According to PFS, the sRT and hRT groups were significantly different from the WBRT group (p=0.00000), but not from each other (p=0.43374).

The risk of death was 2.5 times higher (HR - 2.5 (95% CI - 1.45–4.46)) for the WBRT group compared to the sRT group and 3.5 times higher (HR – 3.5 (95% CI – 2.09–5.88)) compared to the hRT group.

The risk of progression for the WBRT group was 2.8 times higher (HR – 2.78 (95% CI – 1.63–4.74)) compared to the sRT group and 3.1 times higher (HR – 3.12 (95% CI – 1.91–5.10)) – compared to the hRT group.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed on patients during the study comply with the ethical standards of institutional and national ethics committees, the 1964 Declaration of Helsinki and its amendments or similar ethical standards. The study was approved by the Committee on Ethics and Bioethics of Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine (Minutes No. 3 dated June 6, 2016).

Informed consent

Informed and voluntary written consent to participate in the study was obtained from each patient.

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