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DIFFERENTIAL TREATMENT EFFECTS OF STANDARD AND HYPOFRACTIONATED RADIATION REGIMENS IN GLIOBLASTOMA PATIENTS

Background. The identification of the subgroups with differential treatment effects (DTE) is important for decision-making in personalized treatment. The DTE analysis assists in identifying patients who are more likely to benefit from a particular treatment regimen. The **aim** of the study was to analyze DTE in terms of the survival of glioblastoma (GBM) patients in the groups of standard radiotherapy (SRT) and hypofractionated radiotherapy (HRT) by the multicluster modeling of homogenous groups while retaining the statistical characteristics of the overall primary study cohort. **Patients and Methods.** T**he** cohort of 159 patients with newly diagnosed GBM stratified according to the radiotherapy regimen (HRT group (n = 110/69.2%); SRT group (n = 49/30.8%)) was evaluated retrospectively. Forty-eight subgroups (multiclusters) were created by enumerating all possible combinations of 5 significant covariates (age, sex, the radicality of the surgical resection, chemotherapy, and Karnofsky performance status) of the Cox model. The DTE for the cancer-specific survival (CSS) within 48 modeled multiclusters were studied by comparing the interpolated Weibull CSS curves according to the Kolmogorov — Smirnov test. **Results.** The findings showed that the SRT group was superior to the HRT group by CSS only in 3 of the modeled clusters presenting clinical scenarios with a non-radical tumor resection, no chemotherapy, and low Karnofsky functional status (≤ 70 scores) (Cluster 10: male aged < 60; Cluster 21: female aged ≥ 60; Cluster 22: male aged ≥ 60). Most of the studied clinical variants (45 of 48 multiclusters) did not demonstrate a significant difference when comparing the interpolated Weibull curves of the CSS for the SRT and HRT groups according to the Kolmogorov — Smirnov test ($p \geq 0.05$). **Conclusions.** We propose a novel multicluster modeling approach that addresses DTE in relatively small samples of GBM patients receiving SRT or HRT. This original analytical method can be taken into consideration while designing new well-powered prospective trials aimed at the subgroup analysis in GBM patients who will be most beneficial from personalized treatment strategies.

Keywords: differential treatment effects, subgroup analysis, glioblastoma, hypofractionated radiation therapy.

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The personalized therapeutic approach taking into account the individual features of cancer patients is an important prerequisite for the successful treatment outcome. The analysis of the concordance between the therapeutic effect and the specific characteristics of the patients through the subgroup analysis becomes increasingly relevant, especially within the framework of controlled clinical trials [1—3]. The identification of the subgroups of patients that account for treatment effect heterogeneity (differential treatment effects (DTE)) and are likely to benefit more from certain therapeutic modalities represents an indispensable basis for the practical realization of the precision medicine concept [4]. This is especially true for radiation oncology, which rapidly acquires personalized features. The current high-tech accelerators allow for the precise dose delivery to the target and the real-time adjustment of the radiation schedule according to the anatomical changes in patients and tumors during the course of radiation therapy (RT) [5, 6]. On the other hand, the technological improvements result in broader application of modified RT regimens, in particular hypofractionated RT (HRT), allowing to complete RT course faster [7].

Glioblastoma multiforme (GBM) is the most common and aggressive malignant brain tumor in adults. RT as an indispensable component of the complex treatment of GBM has demonstrated a positive impact on the patient's survival and the admissible toxicity profile in multiple studies [8].

The use of HRT as an alternative to the standard RT regimen (SRT) in elderly patients and/or patients with a low functional status has been approved by the consensus of the professionals and regulated by the current guidelines (NCCN, SNO, EANO) [9—11].

At the same time, the question remains open whether HRT could be beneficial in fit and young patients who have prognostically higher survival chances [12, 13].

The present study is based on a suggestion that there are certain subgroups of GBM patients with potential survival benefits depending on the RT regimen used (i.e., HRT *vs.* SRT). In other words, we assumed the existence of the DTE across outcomes depending on the applied RT regimen. Due to the lack of a unified approach to the analytical tools for subgroup analysis, we propose an original methodology based on the multicluster modeling of homogenous groups while retaining the statistical characteristics of the overall primary study population.

The aim of the study was to analyze the differential treatment effect in terms of the survival of GBM patients in SRT and HRT groups by the multicluster modeling of homogenous groups while retaining the statistical characteristics of the overall primary study population.

Materials and Methods

The data of the retrospective single-center study of the cohort of 159 GBM patients treated at the State Institution "Romodanov Neurosurgery Institute, National Academy of Medical Sciences of Ukraine" in 2014—2020 are presented. The diagnosis of GBM was verified histopathologically after the resection or stereotactic biopsy of the primary tumor. Patients were stratified according to the RT regimen: SRT — 49 (30.8%) patients and HRT — 110 (69.2%) patients.

The patients were treated on a linear accelerator "Trilogy" (USA) (6 MeV). The intensity-modulated RT (IMRT) method was applied. The radiation regimens were as follows:

SRT: total dose 60.0 Gy delivered in 30 fractions, 5 days a week, 2.0 Gy per fraction;

HRT: total dose 52.5 Gy delivered in 15 fractions, 5 days a week, 3.5 Gy per fraction.

Inclusion criteria:

- males and females aged above 18 years;
- anticipated survival time of more than 3 months;
- histopathologically confirmed diagnosis of GBM (diffuse glioma grade 4 according to the WHO classification);
- supratentorial location of tumor;
- Karnofsky performance status ≥ 60; performance status according to ECOG scale ≤ 1;
- patients who received a course of the adjuvant RT (either SRT, 60.0 Gy delivered in 30 fractions, or HRT 52.5 Gy delivered in 15 fractions)
- voluntary informed written consent to participate in the study; willingness and ability to comply with the procedures of the study and the follow-up.

The study was approved by the Committee on Ethics and Bioethics of the Institute (Meeting Minutes No. 3 of June 6, 2016).

The distribution of the patients under study according to their major characteristics is given in Table 1.

The data on the methylation of the promoter of the *MGMT* gene were not available for most patients in the SRT group (33 cases; 67.4%) and the significant number of patients in the HRT group (44 cases; 40%). In 8 (16.3%) patients in the SRT group and 43 (39.1%) patients in the HRT group, the promoter of the *MGMT* gene in tumors was methylated. Non-methylated status of the promoter of the *MGMT* gene was confirmed in 8 (16.3%) cases in the SRT group and 23 (20.9%) cases in the HRT group. The statistical assessment for group homogeneity according to the methylation status of the promoter of the *MGMT* gene was not provided because of the shortage of such data for most cases in this study. Due to the same reasons, this feature was not included as a covariate in further analysis.

The descriptive statistics of this patient population is presented in detail in our previous papers [14, 15].

Statistical analysis. The following algorithm was used for testing the H0 hypothesis as to the presence of DTE when the HRT and SRT regimens were used in GBM patients:

1. The regression semiparametric model of the Cox proportional risks is built for the sample stratified by the SRT and HRT groups aimed at the detection of the covariates affecting the baseline risk of survival for these two groups, which may be different.

2. A whole set of possible clusterization variants according to the detected statistically significant covariates is generated by the enumeration of all their values.

3. The baseline survival separately for the SRT and HRT groups is then interpolated by the Weibull function opening up the possibility to use calculations for determining the survival curves, which in the SRT and HRT groups simulate the risk inherent to each of the 48 homogeneous clusters.

4. The interpolated curves of the baseline functions of cancer-specific survival (CSS) for SRT and HRT groups are used for calculating the survival curves (S_g) for each separate homogeneous cluster by the Cox model formula:

Table 1. **Patients' characteristics**

Characteristics	Overall study population	SRT group	HRT group	*p*
Mean age, years (95% CI)	53.6 (51.8—55.4)	52.8 (49.6—55.8)	54.0 (49.0—58.0)	0.56 Mann — Witney test
Gender:				
males	86 (54.1%)	24 (49.0%)	62 (56.4%)	0.38828
females	73 (45.9%)	25 (51.0%)	48 (43.6%)	0.38871 χ2-test (Pearson Chi-square; M-L Chi-square)
Radicality of surgery:				
total + subtotal resection	105 (66.0%)	34 (69.4%)	71 (64,6%)	0.55163
partial resection + stereotactic biopsy	54 (34.0%)	15 (30,6%)	39 (35.4%)	0.54968 χ2-test (Pearson Chi-square; M-L Chi-square)
Karnofsky performance status:				
≤ 70	43 (27.0%)	12 (24.5%)	31 (28.2%)	0.62843
> 70	116 (73.0%)	37 (75.5%)	79 (71.8%)	0,62639 χ2-test (Pearson Chi-square; M-L Chi-square)
Adjuvant chemotherapy:				
temozolomide	125 (78.6%)	38 (77.6%)	87 (79.1%)	0.97049
PCV	19 (12.0%)	6 (12.2%)	13 (11.8%)	0.97079
not used	15 (9.4%)	5 (10.2%)	10 (9.1%)	χ2-test (Pearson Chi-square; M-L Chi-square)

$$S_g = S_{bg}^{\gamma}$$

where

$$\gamma = e^{\Sigma_i \beta_i k_i},$$

g — feature of the SRT or HRT group; S_{bg} — curves for the baseline functions of CSS for the SRT and HRT groups interpolated by the Weibull function; β_i — regression coefficients assessed in the Cox model; k_i — corresponding values of the covariates (1 or 0) depending on the selected cluster.

5. The distributions obtained for the SRT and HRT groups in each cluster are finally compared using the Kolmogorov — Smirnov test since the survival curves are in fact the corresponding functions of the probability distributions.

To accept/reject the H0 hypothesis stating that there is no differential treatment effect in the SRT and HRT groups, a significance $\alpha_{crit} = 0.05$ was set.

The assumption of the risk proportionality hypothesis was tested using the Schoenfeld residuals analysis (since this assumption is the underlying assumption of the Cox model). The graphical representations of the Schoenfeld residuals, which show a separate residual for each subject according to a separate covariate, do not show a non-random pattern (i.e., a pattern of changes in the residuals), which indicates that the assumption of proportionality of risks is not violated. Schoenfeld's residuals test did not reveal a statistical significance of $p < 0.05$ for all the regression variables studied determined by the Cox proportional hazards model, which confirms the hypothesis that the risks of these covariates are proportional.

The primary data were collected and prepared in MS Excel. The data were analyzed using STATISTICA 64 v.12.5.192.0 Windows NT 6.2.

Results and Discussion

The survival of the patients in the study population has been analyzed in detail in our previous paper [14]. Earlier, we also analyzed the factors (covariates) affecting the survival of GBM patients [15]. We demonstrated the following selected clinical factors as significant covariates in the semiparametric regression model of Cox proportional risks: age ($p = 0.003$), gender ($p = 0.02$), radicality of surgery ($p = 0.002$), chemotherapy ($p < 0.0000001$), and Karnofsky functional status ($p = 0.0003$). Nevertheless, the log-rank test showed no significant difference in overall survival (OS) ($p = 0.07$), progression-free survival (PFS) ($p = 0.43$), or cancer-specific survival (CSS) ($p = 0.07$) between the SRT and HRT groups.

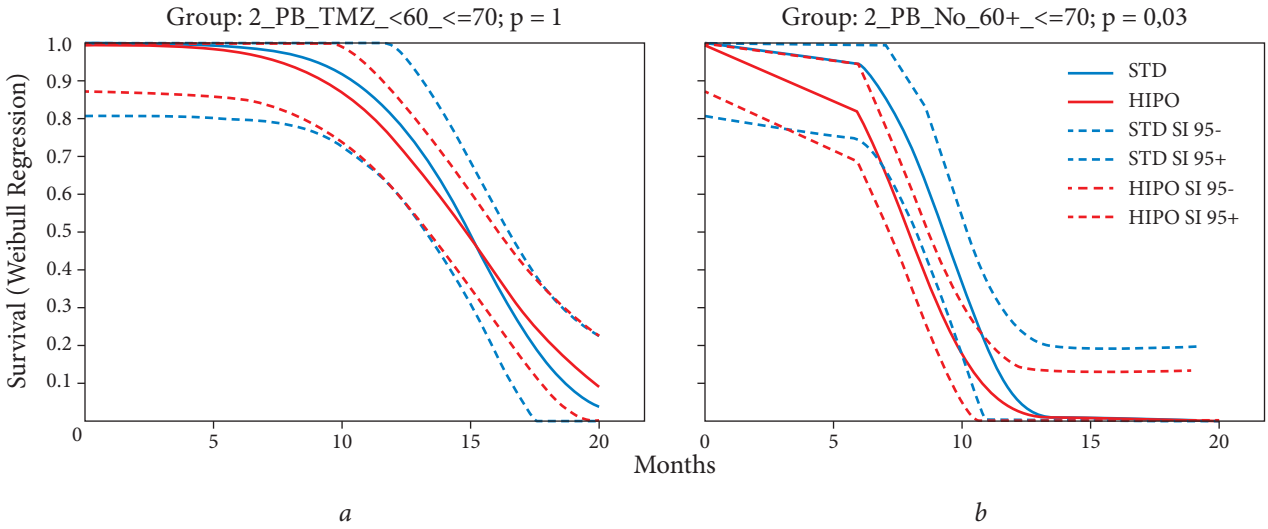
The analysis of the Kaplan — Meier curves for OS, PFS, and CSS in the SRT and HRT groups demonstrated that these curves had intersection points close to the median values. At the same time, the shape of these curves demonstrated that the SRT group has survival benefits over a span before the intersection point, while the situation changes to reverse when the median is attained. A log-rank test will be useful for detecting the possible difference between two Kaplan — Meier curves when the risk of the event for one of the groups is consistently higher throughout the entire period of study. However, this is not the case when the survival curves are intersected [16, 17].

Meanwhile, the inconsistency in the risk coefficient in the case of the intersecting Kaplan — Meier curves does not mean that a log-rank test itself is ineffective. In the case of crossing survival curves, a log-rank test may lose its power in providing a significant comparison of the treatment outcomes. In such a situation, alternative methods of analysis could exist allowing for better results [18].

In light of the foregoing, we attempted to search for the methodology aimed at overcoming the limitations of a log-rank test in a situation of crossing survival curves using more powerful methods of statistical analysis. We hypothesized that certain combinations of clinical factors may impact the survival in the SRT and HRT groups.

To check this hypothesis, we attempted to use the method of simulation of multicluster samples for analyzing our data. The total number of patients in our study was rather small (n = 159) excluding the delineation of the real subgroups that could be sufficient for assuring the required statistical power.

First, using the statistically significant covariates determined by the Cox model in our previous study, we generated all 48 possible clinical variants of clusterization. An important prerequisite for the correct extrapolation of the multicluster simulation to the real cohort is that artificially generated clusters are not only homogenous relative to the delineated factors affecting the survival but also retain the statistical characteristics of the overall primary study population relative to these selected factors.



The interpolated CSS (in months) curves (Weibull's regression) with 95% confidence intervals for cluster 1 (*a*) and cluster 21 (*b*) in the SRT and HRT groups

Examples of the clusterization variants:

Cluster 1: female, age < 60, non-radical tumor resection, chemotherapy with temozolomide, Karnofsky functional status ≤ 70.

Cluster 24: male, age ≥ 60, radical resection of primary tumor, without chemotherapy, Karnofsky functional status ≤ 70.

Cluster 48: male, age ≥ 60, radical resection of primary tumor, without chemotherapy, Karnofsky functional status > 70.

The results of testing the H0 hypothesis as to the DTE in SRT and HRT by the algorithm above demonstrated that only in three variants of covariate combination (variants 10, 21, 22) out of 48 possible combinations, the H0 hypothesis should be rejected (Table 2). For all other 45 clinical variants, the H0 hypothesis assuming that there is no significant difference in CSS between the SRT and HRT groups is accepted.

Figure, *a* demonstrates the interpolated CSS curves for cluster 1 (female, age < 60, non-radical tumor resection, temozolomide chemotherapy, Karnofsky functional status ≤ 70)). According to the Kolmogorov — Smirnov test, $p = 1.0$. Therefore, the H0 hypothesis implying that there is no significant difference between CSS in the SRT and HRT groups is accepted.

Figure *b* demonstrates the interpolated CSS curves for cluster 21 (female, age ≥ 60, non-radical tumor resection, without chemotherapy, Karnofsky functional status ≤ 70). According to the Kolmogorov — Smirnov test, $p = 0.03$. Therefore, the H0 hypothesis implying that there is no significant difference between CSS in the SRT and HRT groups is rejected. The interpolated CSS curves (Weibull regression) demonstrate the benefit to survival in the SRT group.

The p values for the Kolmogorov — Smirnov test in the SRT and HRT groups for different baseline risk functions interpolated by the Weibull distribution are given in Table 3.

Since the results outlined above may depend on the precision of the approximation of the base-

Table 2. **Clinical variants wherein the H0 hypothesis as to the CSS distribution in the SRT and HRT groups is rejected**

Cluster No.	Covariates				
	Gender	Age, years	Radicality of surgery	Chemotherapy	Karnofsky functional status
10	Male	< 60	Non-radical	Not performed	≤70
21	Female	≥ 60	Non-radical	Not performed	≤70
22	Male	≥ 60	Non-radical	Not performed	≤70

line survival curves, we performed an additional analysis. Instead of the exact Weibull approximation, we used a simple linear interpolation between the adjacent points of the survival curves in the groups under study. Since the linear interpolation is sensitive to accidental outliers (deviations), it may be considered a "rough" estimate compared to Weibull's approximation. The results of the cluster estimation are summarized in Table 4.

As seen from Tables 3 and 4, the number of clusters with $p > 0.05$ for the Kolmogorov — Smirnov test (i.e., the clusters that share the same distribution) is different depending on the interpolation used (Weibull's or linear). Based on the comparison between the results obtained by Weibull's or linear interpolation, we may state that the variants sharing significant p values of the Kolmogorov — Smirnov test ($p < 0.05$) assessed by both interpolation methods can be considered more confident as to the rejection of the H0 hypothesis of no significant difference between CSS in the SRT and HRT groups (variants 10, 21, and 22).

Table 3. ***P* values* for the Kolmogorov — Smirnov test in the SRT and HRT groups for different baseline risk functions interpolated by Weibull distribution**

Age	Gender	Male				Female			
	Karnofsky functional status	≤70		>70		≤70		>70	
	Radicality of surgery**	PB	TS	PB	TS	PB	TS	PB	TS
<60	Chemotherapy with temozolomide	0.981	0.976	0.946	0.706	0.997	0.867	0.804	0.635
	Chemotherapy PCV	0.271	0.550	0.622	0.896	0.423	0.734	0.799	0.974
	Without chemotherapy	0.039	0.124	0.156	0.370	0.085	0.219	0.268	0.544
≥60	Chemotherapy with temozolomide	0.888	0.993	0.997	0.892	0.971	0.987	0.968	0.737
	Chemotherapy PCV	0.137	0.335	0.395	0.706	0.240	0.504	0.574	0.865
	Without chemotherapy	0.019	0.055	0.075	0.201	0.033	0.108	0.134	0.330

Notes: * If $p > 0.05$ for the Kolmogorov — Smirnov test, the SRT and HRT groups share the same Weibull distribution. ** Radicality of surgery: PB — partial surgical resection + biopsy; TS — total + subtotal resection of tumor.

Table 4. ***P* values* for the Kolmogorov — Smirnov test in the SRT and HRT groups for different baseline risk functions linearly interpolated**

Age	Gender	Male				Female			
	Karnofsky functional status	≤70		>70		≤70		>70	
	Radicality of surgery**	PB	TS	PB	TS	PB	TS	PB	TS
<60	Chemotherapy with temozolomide	0.054	0.273	0.260	0.220	0.163	0.261	0.259	0.223
	Chemotherapy PCV	0.000	0.000	0.001	0.010	0.000	0.002	0.003	0.042
	Without chemotherapy	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000
≥60	Chemotherapy with temozolomide	0.009	0.092	0.139	0.259	0.039	0.243	0.267	0.230
	Chemotherapy PCV	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.007
	Without chemotherapy	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000

Notes: * If $p > 0.05$ for Kolmogorov — Smirnov test, the SRT and HRT groups share the same distribution. ** Radicality of surgery: PB – partial surgical resection + biopsy; TS – total + subtotal resection of tumor.

A rationale for interpreting the obtained results of statistical calculations is relevant to the principle of conservatism envisaging the decisions minimizing the risk of bias as to the established DTE as a component of the subgroup analysis. Consequently, only in cases when the H0 hypothesis is accepted by both analytical methods, we will assume the difference in CSS in the SRT and HRT groups as non-significant (in fact, as absent).

According to the results of the statistical analysis, the following clinical variants should be considered the least doubtful (by Kolmogorov — Smirnov test $p \geq 0.05$ coinciding for both interpolation methods — Weibull's or linear) as to the absence of the significant difference in CSS for SRT and HRT:

- All cases where the patient is younger than 60 years and receives temozolomide chemotherapy, regardless of sex, the radicality of the surgical treatment, as well as the Karnofsky performance status score before RT.
- All cases where the patient (male or female) belongs to the age group of 60 years and older and receives chemotherapy, except for those cases where non-radical tumor removal combines with a low Karnofsky performance status score (≤ 70 points) before RT.

As stated above, this study is a logical extension of our previous survival analysis of the same patients population based on the standard approach [14, 15].

Our current approach was employed to decide whether certain subgroups with survival advantages depending on the used RT regimen (SRT or HRT) exist within the overall population of 159 GBM patients. We suggest that such an approach allows approximating subgroup analysis, and the presence of DTE within small-size samples is important for the clinical trials related to the malignant diseases that are not highly prevalent in the general population, in particular, GBM. In such cases, it is highly improbable to generate within the plausible timeframe real subgroups of the size providing the required statistical power. Our methodological approach based on simulating multicluster homogeneous subgroups retaining the statistical characteristics of the overall primary study population allows for overcoming these limitations. Nevertheless, this approach itself has several inherent limitations related both to the assumptions of the Cox proportional risks methods and the inaccuracies of one or another interpolation technique.

Usually, a subgroup analysis envisages the division of the general cohort into subgroups according to some defined factors (parameters). We realize that the approach that we have suggested should not be considered an accepted subgroup analysis *per se*. In this context, it is worth mentioning the propensity score analysis that could be used for studying the treatment effects within certain groups of patients, although it does not represent a sort of subgroup analysis as such [19].

On the other hand, the dominating belief is that prospective randomized clinical trials are to be considered as reference ones in terms of the level of evidence of the results obtained. Contrary to this view, the point of the current discussion is whether the accepted practice of the direct extrapolation of the randomization results to the general population is correct in all aspects [20—22].

We must admit that many questions related to the subgroup analysis and the assessment of the DTE remain open. This is partly due to the methodology and analytical tools of the corresponding studies. Nevertheless, the growing relevance of such studies in the context of personalized treatment is beyond doubt.

It should also be mentioned that the terms of subgroup analysis and DTE themselves have not yet become widespread among the relevant specialists and sometimes these terms are perceived ambivalently. Moreover, no unified view as to which statistical methods could be most appropriate for such an analysis has been elaborated.

Anyway, despite the difficulties and the lack of unification, such studies become increasingly relevant in the context of personalized medicine. Subgroup analysis allows for substantiating the before-developed hypothesis on different treatment outcomes in specified subgroups of patients providing the required level of evidence.

In the context of personalized medicine, there are several advantages of subgroup analysis [3, 23, 24].

A subgroup analysis might be helpful to better identify patients who benefit more from the specific treatment regimen paving the way for developing personalized treatment accounting for the specific profiles of patients. Moreover, the analysis

of subgroups can provide insight into the mechanisms underlying the treatment effects with a better understanding of how the specific factors affect the treatment outcome.

Nevertheless, such an analysis has certain pitfalls and shortcomings partly due to the underpowered statistics resulting in misinterpretation caused by multiple comparisons with an increased chance of false-positive and false-negative results. Therefore, the correct interpretation of the results of subgroup analysis with inferences on the individual therapeutic approaches represents a challenging task [25—27].

Despite all the difficulties, subgroup analysis is becoming more widespread in clinical trials, in particular, in neuro-oncology. Recently, Toms et al. [28] presented the data of *post-hoc* subgroup analysis applied to the phase II randomized clinical trial demonstrating a significant survival benefit in GBM patients treated with alternating electric fields of a low intensity and intermediate frequency in combination with temozolomide compared to temozolomide alone when a compliance threshold of 50% was set.

It should be emphasized the advantage of subgroup analysis allowing for delineating certain profiles of patients that potentially fit most for personalized targeted treatment in terms of the specific features selected for the analysis. Such an approach was successfully used by Georgescu [29] who demonstrated the importance of the molecular classification of GBM based on MAPK pathway activation for delineating the subgroups of GBM patients that could respond differently to targeted therapy.

The analysis presented in our study is in line with the current trends in neuro-oncology aimed at the personalization and optimization of the multimodal treatment of GBM. Although this analysis is based on a sample of a sufficient size (159 patients) and employs evidence-based analytical tools, we are well aware that the results obtained should be interpreted with caution and using a conservative approach. It should be warned that our subgroups were not obtained by the true subdivision of the cohort but were simulated by the Cox model with the Weibull approximation retaining the statistical characteristics of the overall primary study population.

In most (45 out of 48) simulated clusters (clinical variants), no significant benefit of one of the RT regimens has been demonstrated. All three clusters wherein the significant benefit of SRT was demonstrated shared such features as non-radical resection, absence of chemotherapy, and low functional status of the patient. On the contrary, in all cases of patients younger than 60 years and treated with temozolomide, the survival in the SRT and HRT groups did not differ significantly independently of the gender, radicality of surgery, and Karnofsky functional status before RT (Table 2).

At the same time, according to the guides reflecting the actual neuro-oncological consensus with a high evidence-based level, such factors as the low functional status and the elderly age of GBM patients are associated with the negative prognosis, and therefore HRT is recommended for these patients [9—11].

However, the attempts to improve treatment outcomes for GBM patients, especially those with poor-prognosis high-grade glioma, cannot be considered successful justifying the current concept of the incurability of GBM patients as such with all the efforts focusing on the supportive treatment aimed at prolonging the life of these patients by the maintenance of their quality of life [30—32].

To sum up, the studies employing subgroup analysis determining DTE represent a promising direction in modern neuro-oncology. Its application in well-powered trials involving GBM patients should be considered as a priority allowing for increasing the evidence for the personalized treatment strategies. Our new analytical approach can be taken into consideration during the creation of a more robust design of prospective clinical trials, including those exploring subgroups of patients who will benefit most from modified RT regimens. Not less important is assessing risks and limitations in HRT of certain categories of patients.

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ДИФЕРЕНЦІЙОВАНИЙ ЕФЕКТ ЛІКУВАННЯ ПРИ ЗАСТОСУВАННІ СТАНДАРТНОГО І ГІПОФРАКЦІЙНОГО РЕЖИМІВ ОПРОМІНЕННЯ У ПАЦІЄНТІВ З ГЛІОБЛАСТОМОЮ

Стан питання. Визначення підгруп пацієнтів згідно диференційованого ефекту лікування (ДЕЛ) є важливою передумовою ефективності персоналізованої терапії. Аналіз ДЕЛ допомагає виявити саме тих пацієнтів, які з більшою ймовірністю отримають користь від певної схеми лікування. **Мета**. Дослідити ДЕЛ за канцерспецифічною виживаністю (КСВ) пацієнтів з гліобластомою (ГБ) в групах стандартної променевої терапії (СПТ) та гіпофракційної ПТ (ГПТ) шляхом мультикластерного моделювання однорідних вибірок зі збереженням статистичних характеристик первинної вибірки. **Матеріали та методи**. Ретроспективно оцінено когорту 159 пацієнтів з уперше діагностованою ГБ, стратифікованою за режимом ад'ювантної ПТ: група СПТ (n = 49/30,8%) та група ГПТ (n = 110/69,2%). Сорок вісім підгруп (мультикластерів) були створені шляхом перерахування усіх можливих комбінацій 5 статистично значущих коваріатів моделі Кокса (вік, стать, радикальність хірургічної резекції, хіміотерапія та статус Карновського). В межах змодельованих 48 кластерів проаналізовано ДЕЛ у групах СПТ і ГПТ за допомогою порівняння інтерпольованих кривих Вейбулла для КСВ за критерієм Колмогорова — Смірнова. **Результати**. Виживаність у групі СПТ у порівнянні з групою ГПТ переважала лише в трьох досліджених кластерах (кластер 10: чоловік віком <60 років; кластер 21: жінка віком ≥60 років; кластер 22: чоловік віком ≥60 років) за умови наявності таких факторів як нерадикальна резекція первинної пухлини, відсутність хіміотерапії та статус Карновського ≤ 70 балів. Натомість у більшості досліджуваних клінічних сценаріїв (45 із 48 кластерів) не було зафіксовано статистично значущої різниці в інтерпольованих кривих Вейбулла КСВ груп СПТ і ГПТ за критерієм Колмогорова — Смірнова ($p \geq 0,05$). **Висновок**. Запропонований нами новий підхід мультикластерного моделювання дозволяє дослідити ДЕЛ у значно гетерогенних та відносно невеликих когортах пацієнтів з ГБ в залежності від застосованого режиму ад'ювантної ПТ (гіпофракційний проти стандартного режиму). Цей оригінальний аналітичний підхід може бути врахований при розробці дизайну майбутніх досліджень, спрямованих на визначення підгруп пацієнтів з ГБ, які отримають найбільшу користь від певних персоналізованих стратегій лікування.

Ключові слова: диференційований ефект лікування, підгруповий аналіз, гліобластома, гіпофракційна променева терапія.