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Relationship of carbohydrate metabolism indicators during adjuvant radiotherapy and survival in patients with glioblastoma

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ABSTRACT

Despite the improvement of treatment methods, survival of patients with glioblastoma is still low. Glioblastoma is the most common brain tumor.

Objective. To study carbohydrate metabolism in patients with glioblastoma during adjuvant external beam radiation therapy and its impact on survival.

Material and methods. The study included 66 patients with glioblastoma (Karnofsky score ≥80%) who underwent hypofractionated adjuvant external beam radiation therapy (single focal dose 2.5—3Gr). Patients received dexamethasone 4—8 mg daily throughout the entire course of irradiation.

Results. High level of glycated hemoglobin (Hb_{A1c}) was observed in 33.3% of patients with glioblastoma undergoing irradiation. Cumulative survival was 17 months (95% CI 13.7-20.3). Two indicators had a significant negative impact on cumulative survival: age of patients (HR 1.04; 95% CI 1.01—1.08; p=0.02) and level of Hb_{A1c} (HR 1.94; 95% CI 1.23—3.06; p=0.005). Cumulative survival was significantly (p=0.022) higher in patients younger 53 years compared to older people (18 months and 14 months, respectively). Cumulative survival was 20 months among patients whose Hb_{A1c} did not exceed the upper reference value (<5.8%). Survival was higher (p=0.017) in these ones compared to patients with Hb_{A1c} ≥5.8% (13 months). According to multivariate Cox regression model, high Hb_{A1c} was the only significant negative predictor of cumulative survival (HR 3.35; 95% CI 1.14—9.81; p=0.027).

Conclusion. High Hb_{A1c} is unfavorable predictor of cumulative survival in patients with glioblastoma and Karnofski score ≥80% undergoing adjuvant hypofractionated irradiation regardless their age.

Keywords: *glioblastoma of the brain, adjuvant irradiation, age, glycated hemoglobin, cumulative survival.*

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Introduction

Glioblastoma is the most common brain tumor [1]. Thus, the problems associated with its treatment are extremely important. Over 70% of patients with newly diagnosed glioblastoma receive combined treatment including adjuvant external beam radiotherapy (aEBRT) in addition to resection [2]. Despite certain improvements in the treatment of this tumor, the outcomes are still disappointing. Indeed, most authors reported life expectancy in patients with glioblastoma up to 11—14.9 months [2—5]. Some recent data indicate increment of 2-year survival from 7% to 22%. The main reasons of this success are considered to be patient age < 60 years and, less often, chemotherapy with temozolomide [2]. It was found that life expectancy is significantly shorter in patients aged 60 years and older [6]. Age as a predictor of treatment outcome in patients with glioblastoma has been known for more than a decade. Nevertheless, pathogenesis of this effect has not yet been elucidated.

High radioresistance is considered to be one of the main factors determining low efficacy of treatment. Radioresistance may be caused by carbohydrate metabolism disorders, i.e. hyperglycemia. The last one follows dexamethasone therapy in patients with glioblastoma in addition to other things [7]. Almost all patients with glioblastoma have received glucocorticosteroids since the middle of the last century (most often dexamethasone synthesized in 1958) [8]. The indication is severe edema of brain matter adjacent to peripheral part of glioblastoma. The cause

of edema is considered to be violation of blood-brain barrier permeability in tumor vessels. Dexamethasone restores blood-brain barrier due to activation of occludin and reinforcement of binding of VE-cadherin with endotheliocyte cytoskeleton [8]. Hypofractionated aEBRT overcomes radioresistance via increase of single focal dose. However, hypofractionation has not yet become widespread in clinical practice [6].

Carbohydrate metabolism disruption can also negatively affect the results of surgical treatment in patients with glioblastoma. More common neurological impairment was established in patients with postoperative hyperglycemia [4]. These postoperative events complicate adjuvant treatment including aEBRT. In turn, refusal from aEBRT decreases life expectancy in patients with glioblastoma. In this regard, analysis of the role of carbohydrate metabolism disorders in pathogenesis of reduced survival in patients with glioblastoma is important.

The purpose of the study was to study carbohydrate metabolism in patients with glioblastoma during adjuvant external beam radiotherapy and its impact on survival.

Material and methods

The study included 66 patients who underwent aEBRT in 4—8 weeks after resection of glioblastoma. There were 35 men and 31 women. Median age of patients was 58 (52—63) years. Karnofsky score immediately before aEBRT was ⩾ 80%.

We planned aEBRT in accordance with the recommendations of the European Organization for Research and Treatment (EORTC). Medium hypofractionation was used (single focal dose 2.5—3 Gy). Irradiation was continued up to total focal dose of 54—60 Gy. All patients received decongestant therapy (daily intramuscular injection of dexamethasone 4—8 mg) throughout the entire postoperative period including time interval for aEBRT. We excluded patients who underwent extended biopsy instead of resection. Chemotherapy with temozolomide throughout the period of aEBRT was administered only in 3 patients younger 60 years. Thus, we were not able to analyze influence of this factor on survival.

Serum insulin (reference values 21.5—122 pmol/l), C-peptide (reference values 1.77—3.51 ng/ml), glycated hemoglobin Hb_{A1c} (reference values 4.4—5, 8%) and glucose (reference values 4—5.9 mmol/l) were assessed before and after completion of aEBRT. Mean values were subsequently used to analyze their prognostic significance.

Statistical analysis was performed using the IBM SPSS Statistics software v25 (IBM Corporation, USA). Quantitative variables were described as medians and quartiles. Survival was analyzed using Kaplan—Meier curves. Influence of quantitative and qualitative factors on survival was assessed using univariate and multivariate Cox regression models. The null hypothesis was rejected at p-value<0.05.

Results

Cumulative survival was 17 months (95% CI 13.7—20.3) **(Fig. 1)**. One-year and two-year survival rates were 67.7% (95% CI 56.3—79.1%) and 30% (95% CI 18.1—41.9%), respectively.

During the period of aEBRT, high serum insulin (124—410.5 pmol/l) was observed in 6.7% of patients, high serum glucose (6.2—10.4 mmol/l) — in 16.1% of patients, high serum C-peptide (3.55—5.09 ng/ml) — in 23% of patients. High Hb_{A1c} (5.85—10.4%) was the most common (33.3% of patients). At the same time, medians of all above-mentioned parameters of carbohydrate metabolism were within reference values in all patients **(Table 1)**.

Influence of gender, age, serum insulin, C-peptide, Hb_{A1c} and glucose on survival of patients with glioblastoma who underwent hypofractionated aEBRT was analyzed using univariate Cox regression model **(Table 2, Fig. 2)**. Only two indicators had significant negative impact on cumulative survival: age of patients (HR 1.04. 95% CI 1.01—1.08; p=0.02) and Hb_{A1c} (HR 1.94, 95% CI 1.23—3.06; p=0.005).

Considering these data, we compared Kaplan—Meier cumulative survival depending on age and Hb_{A1c}.

Cumulative survival in patients aged <53 years significantly differed from that in patients aged ⩾53 years (p=0.022, Breslow test). Median survival was 18 (95% CI 10.324—25.679) and 14 (95% CI 10.828—17.172) months, respectively **(Fig. 3)**. One-year (12 months) and two-year (24 months) survival rates were also higher

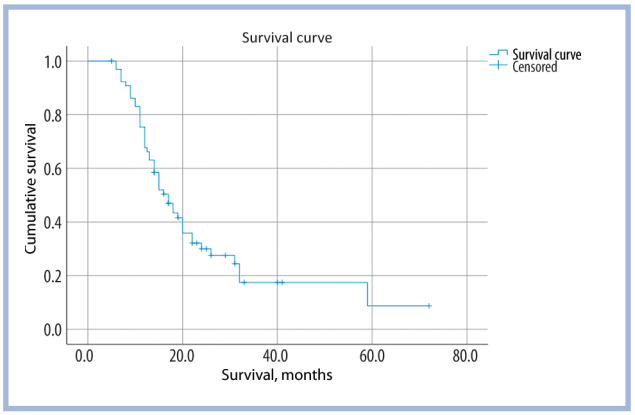

Fig. 1. **Kaplan-Meier cumulative survival of patients with glioblastoma after hypofractionated adjuvant external beam radiotherapy.**

Table 1. **Carbohydrate metabolism parameters analyzed in patients with glioblastoma**

Variable	Study group (n=66)		
	n	μ±σ	Me
Age, years	66	57.2±9.8	58.0 (52.0; 63.0)
Insulin, pmol/l	45	84.93±64.36	71.00 (52.5; 95.0)
C-peptide, ng/ml	42	3.069±1.006	2.863 (2.24; 3.98)
Hb_{A1c}, %	36	5.92±1.20	5.60 (5.38; 5.88)
Glucose, mmol/l	62	5.34±1.17	5.10 (4.65; 5.50)

Table 2. **Impact of some indicators of carbohydrate metabolism during hypofractionated adjuvant external beam radiotherapy on survival of patients with glioblastoma (univariate and multivariate Cox regression analysis)**

Variable	Univariate analysis HR (95% CI)	*p*	Multivariate analysis HR (95% CI)	*p*-value
Gender	0.67 (0.38; 1.21)	0.183	1.21 (0.49; 3.0)	0.683
Age	1.04 (1.01—1.08)	0.02	1.04 (0.97; 1.11)	0.23
Insulin	0.99 (0.99—1.004)	0.63	1.008 (0.99—1.02)	0.12
C-peptide	1.23 (0.84—1.79)	0.29	0.78 (0.45—1.36)	0.39
Hb_{A1c}	1.94 (1.23—3.06)	0.005	3.35 (1.14—9.81)	0.027
Glucose	1.06 (0.77—1.45)	0.75	0.65 (0.33—1.29)	0.22

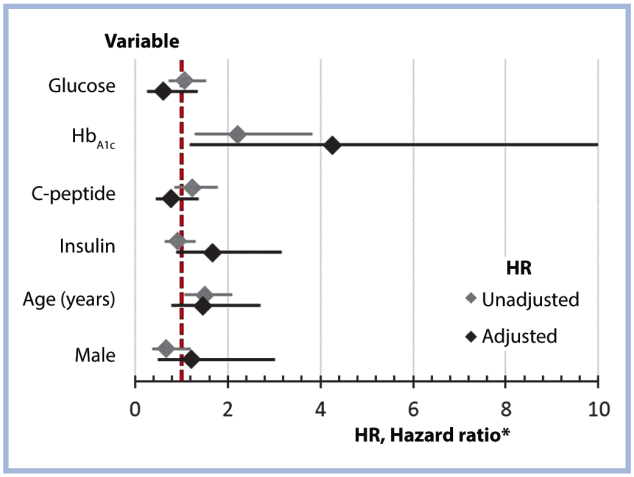

Fig. 2. **Adjusted and unadjusted hazard ratio for standardized indicators. Standardization was carried out according to equation (X–M)/SD).**

in patients aged <53 years **(Table 3)**. However, statistical analysis revealed that only one-year survival in patients aged <53 years was significantly higher (94.7% (84.7—100%) and 56.5% (42.2—70.8%) years, respectively).

There were significant differences in cumulative survival (p=0.017, Breslow test) between patients with normal (<5.8%) and elevated Hb_{A1c} (20 (95% CI 15.744—24.256) and 13 (95% CI 8.954—17.046) months, respectively) **(Fig. 4)**.

Annual and 2-year survival of patients with Hb_{A1} <5.8% was 83.3% (68.4—98.2%) and 38.7% (18.3—59.1%), respectively. These values were insignificantly higher than in patients with Hb_{A1c} ⩾5.8% (54.5% (25.1—84.0%) and 18.2% (0—41.0%), respectively) **(Table 4)**.

At the final stage of the study, we analyzed the impact of above-mentioned variables on survival using multivariate Cox regression model **(Table 2)**. The only significant factor negatively affecting survival was Hb_{A1c} during hypofractionated aEBRT (HR 3.35, 95% CI 1.14—9.81; p=0.027).

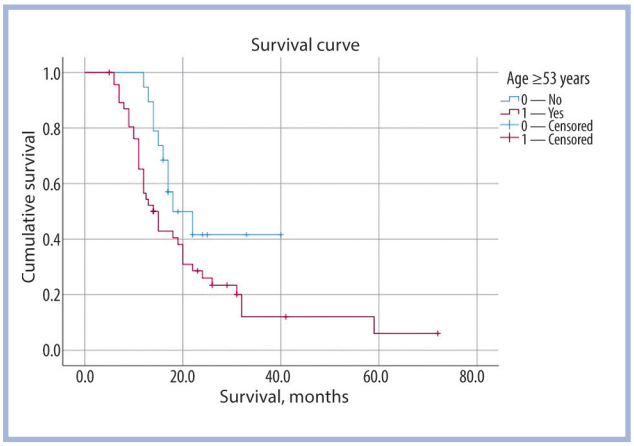

Fig. 3. **Age-adjusted cumulative survival of patients with glioblastoma after hypofractionated adjuvant external beam radiotherapy.**

Table 3. **Age-adjusted one- and two-year survival of patients with glioblastoma after adjuvant external beam radiotherapy**

Age, years	Survival, months	Survival (95% CI), %
<53	12	94.7 (84.7—100)
	24	41.6 (16.8—66.3)
⩾53	12	56.5 (42.2—70.8)
	24	26.0 (12.8—39.1)

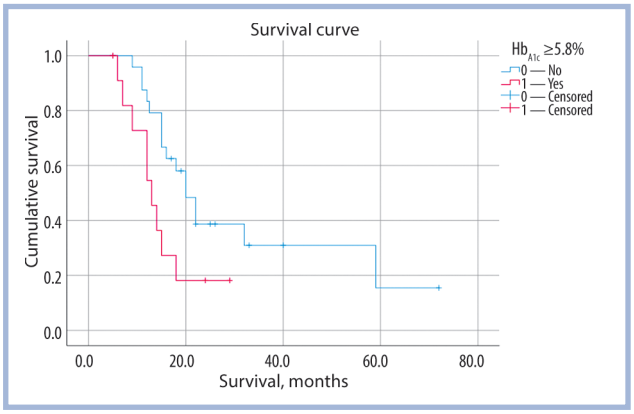

Fig. 4. **Cumulative survival of patients with glioblastoma after hypofractionated adjuvant external beam radiotherapy depending on Hb_{A1c}.**

Table 4. **Annual and two-year survival of patients with glioblastoma undergoing hypofractionated radiotherapy depending on Hb_{A1c}**

Hb_{A1c}, %	Survival, months	Survival (95% CI), %
<5.8	12	83.3 (68.4—98.2)
	24	38.7 (18.3—59.1)
⩾5.8	12	54.5 (25.1—84.0)
	24	18.2 (0—41.0)

Discussion

Despite improvement of treatment methods, survival of patients with glioblastoma is still low and does not exceed 11—14 months [2—5]. Age and functional state significantly affect survival in these patients. For example, median survival for patients aged 20—44 years is 21.5 months, 45—64 years — 15.5 months, over 65 years — only 10.5 months [2].

In case of unsatisfactory functional state (Karnofsky score < 50%), survival most often does not exceed 2.3 months regardless of age [9]. In our study, we excluded this negative factor and enrolled only patients with Karnofsky score ⩾ 80% in 4—6 weeks after resection of glioblastoma. In our opinion, this approach led to a rather high cumulative survival rate of 17 months, as well as one- and two-year survival rates of 67.7 and 30%, respectively.

The relevance of this study was confirmed by common carbohydrate metabolism disorders during aEBRT for glioblastoma (6.7—33.3% of our patients). High (⩾5.8%) Hb_{A1c} was the most common disorder (33.3%). Statistical analysis of influence of carbohydrate metabolism disorders on survival of patients with glioblastoma undergoing hypofractionated aEBRT revealed high Hb_{A1c} as significant negative prognostic factor. Indeed, median survival in patients with Hb_{A1c} ⩾5.8% was only 13 months. This value was significantly lower compared to patients with normal Hb_{A1c} (20 months).

There are certain data on negative effect of carbohydrate metabolism disorders on treatment outcomes in neuro-oncology [10—12]. Thus, type 2 diabetes mellitus is detected in approximately 12.6% of patients with glioblastoma. Moreover, hyperglycemia is a consequence of therapy with high daily doses of dexamethasone in 20% of these cases [7, 13, 14]. Survival of patients with glioblastoma and normoglycemia is 11—20 months. In case of concomitant hyperglycemia, this value is only 5—9.6 months [3, 5, 7, 14]. Severity of hyperglycemia also affects life expectancy in patients with glioblastoma, i.e. negative effect is only observed in serum glucose > 6.3 mmol/L [13]. Even short-term hyperglycemia contributes to decrease of survival of patients with glioblastoma from 16.7 to 8.8 months [15].

It is believed that Hb_{A1c} more correctly characterizes carbohydrate metabolism disorders and mean serum glucose for previous 2—3 months. Moreover, elevated Hb_{A1c} can indicate not only diabetes mellitus, but also insulin resistance [11]. In turn, high Hb_{A1c} in cancer patients with insulin resistance positively correlates with mortality rate. Pathogenesis of negative impact of carbohydrate metabolism disorders, including those caused by dexamethasone, on treatment outcomes in patients with glioblastoma has not yet been clearly established. There is evidence that hyperinsulinemia can increase proliferative potential of glioblastoma cells [13] through activation of EGFR and insulin-like growth factor type 1 (IGF-1) [16]. Moreover, high level of glycolytic enzymes (enolase 1 type) in glial tumor cells following hyperglycemia ensures their ability for invasive growth [17, 18].

The above-mentioned facts deserve a special attention due to the so-called Warburg effect in tumor cell metabolism. This last one is characterized by excessive absorption of glucose under anaerobic glycolysis. As a result, tumor cells accumulate lactate that also ensures their high proliferative potential. Proliferative processes imply intensive neoangiogenesis with anaerobic glycolysis as the main source of energy [19]. Some authors suppose that hyperglycemia can cause high radioresistance of glioblastoma cells due to active DNA repair and suppression of apoptosis [13, 15]. These assumptions are supported by the fact that suppression of glycolysis in tumor cells caused by *IDH-1* gene mutation reduces radioresistance of glioblastoma [20—22]. All these data require careful analysis of the effect of carbohydrate metabolism disorders during aEBRT on survival of patients with glioblastoma.

An important feature of carbohydrate metabolism disorders is microcirculatory lesion including central nervous system. There are reasons to assume a combined pathogenic effect of carbohydrate metabolism disorders and irradiation during aEBRT for brain glioblastoma. As a result, more severe irradiation-induced lesion of brain matter up to necrosis and reduction of life expectancy are possible [23].

Out study also confirms previous data on significant effect of age on survival of patients with glioblastoma [12]. In our study, age was associated with significant (p=0.022) reduction of overall survival from 18 (<53 years) to 10 months (⩾53 years) and one-year survival from 94.7 to 56.5%. Two-year survival was higher in patients younger 53 years old. However, statistical analysis found no significant differences in 2-year survival. Multivariate Cox regression analysis revealed only high Hb_{A1c} as significant negative predictor of survival (HR 3.35, 95% CI 1.14—9.81; p=0.027) while significance of age was not confirmed in this sample size. In our opinion, this fact can be considered as evidence of less effect of age on survival in patients with glioblastoma and postoperative Karnofsky score > 80% after previous hypofractionated aEBRT. As a result, only carbohydrate metabolism disorders negatively affect survival, and high Hb_{A1c} is the most informative parameter of these disturbances in patients with glioblastoma. Carbohydrate metabolism disturbances throughout the period of aEBRT may be due to perioperative therapy with high daily doses of dexamethasone. In our opinion, it is necessary to develop certain measures regulating dexamethasone therapy and correct hyperglycemia in patients with glioblastoma undergoing aEBRT. Perhaps, this approach per se can increase survival in patients with glioblastoma.

Conclusion

Elevated Hb_{A1c} during hypofractionated aEBRT in patients with glioblastoma and Karnofsky score ⩾80% receiving dexamethasone in a daily dose of 4—8 mg is an unfavorable factor reducing survival regardless of age. In this regard, reasonable administration of certain dose of dexamethasone, careful monitoring and, if necessary, correction of carbohydrate metabolism disorders seem advisable in these patients. These measures will positively affect treatment outcomes in patietns with glioblastoma undergoing aEBRT.

Author contribution:
Concept and design of the study — Balkanov A.S.
Collection and analysis of data — Rozanov I.D., Glazkov A.A.
Writing the text — Balkanov A.S., Rozanov I.D.
Editing — Balkanov A.S.

No conflict of interests to declare.

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COMMENT

The article is devoted to features of carbohydrate metabolism and their impact on life expectancy in patients with glioblastoma undergoing aEBRT. There are more and more data on the impact of carbohydrate metabolism disorders and insulin resistance on development and growth of various malignancies including glioblastoma. Dexamethasone therapy is one of the main factors provoking hyperglycemia. Despite the widespread use of dexamethasone in chemo- and radiotherapy for glioblastoma, few studies were devoted to the effect of carbohydrate metabolism and dexamethasone therapy on survival since the 1960s. To date, insufficient attention is paid to carbohydrate metabolism abnormalities in patients with glioblastoma. Patients with severe hyperglycemia (>10-12 mmol/l) are referred to endocrinologists. The study included 66 patients with glioblastoma who underwent radiotherapy after previous neurosurgical treatment. All patients received dexamethasone. The authors assessed carbohydrate metabolism including serum insulin, C-peptide and glycated hemoglobin in all patients. Multivariate Cox regression analysis revealed only high Hb_{A1c} as significant negative predictor of survival. The disadvantage of this study is non-inclusion of other prognostic factors (localization of tumor, surgery, influence of chemotherapy, somatic status of patients and so on). The article is interesting for neurosurgeons, radiotherapists, oncologists and endocrinologists. Better survival associated with lower glycated hemoglobin in this study, as well as serum glucose in previous reports provide evidence for intensifying glycemic profiling, analysis of target parameters of carbohydrate metabolism and targets for personalized administration of dexamethasone in patients with glioblastoma. Further prospective large-scale studies are needed.

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