Chapter 8

Concurrent Thermochemoradiotherapy in Glioblastoma Treatment: Preliminary Results

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Abstract

Glioblastoma is the most frequent and aggressive primary brain tumor. The patient can be alive with this pathology using the modern standard of intensive combined treatment less than 2 years. Between December 2013 and August 2017, 30 patients with newly diagnosed supratentorial glioblastoma had received concomitant chemoradiotherapy with transcranial radiofrequency hyperthermia. The gross total or the subtotal resection of the tumor was made previously in all cases. The median follow-up time after operation achieved 12 months (95% confidence interval (CI): 8.5–23 months) in this study. The median disease-free survival time was 9.6 months (95% CI: 7.2–19.0 months). The median overall survival time of patients included in the study was 23.4 months. No increase in the systemic side effects of chemotherapy was found compared with the frequency described in the population. Preliminary results had shown that the usage of concomitant thermochemoradiotherapy with transcranial radiofrequency hyperthermia improves progression-free survival rates. Overall survival rates also tended to increase. Given the absence of severe complications, it is necessary to continue research to achieve statistically significant results.

Keywords: glioblastoma, newly diagnosed glioblastoma, concurrent thermochemoradiotherapy, local hyperthermia, radiofrequency hyperthermia, hyperthermic radiosensitization, hyperthermic chemosensitization

1. Introduction

The median survival time of patients diagnosed with glioblastoma multiforme (GBM) without any treatment is up to 3 months after diagnosis [1]. Modern multimodal treatment including surgery and adjuvant chemoradiotherapy with subsequent chemotherapy results in longer survival. However, the median survival does not exceed 2 years [2–4]. According to population-based studies, the overall 1-, 2-, and 3-year survival rates are approximately 40, 15, and 7–8%, respectively, and the 5-year survival rates range between 0.05 and 5.5% [1, 5–7].

Glioblastoma multiforme is divided into primary and secondary morphological subtypes. Primary GBM accounts for 80–90% of malignant gliomas. They arise de novo and are common in older adults (mean age 55–62 years). Secondary GBMs represent progression from astrocytoma or oligodendroglioma. They manifest in younger adults (mean age 40–45 years) and have a lesser degree of necrosis [8–10]. Various genetic disorders characteristic of the primary and secondary subtypes of glioblastoma have been identified, of which the presence of IDH1/2 mutation is the most reliable molecular marker that is determined in all cases of secondary GBMs, while only about 5% of primary glioblastoma have IDH mutations [1, 11–13]. Several studies have shown that IDH1/2 mutations are positive molecular-genetic prognostic markers. IDH1/2 mutations make the tumor cells more susceptible to genetic rearrangements caused by oxidative stress, thus being a driving force for the development of gliomas. On the other hand, tumor cells containing IDH1 mutations become more susceptible to antitumor therapy, which confers cytotoxicity through the generation of reactive oxygen species [14]. Patients with glioma harboring IDH mutation show a significantly better survival than those with an IDH wild-type glioma (24–36 months vs. 9–15 months). The 5-year survival rate is nearly zero for patients with primary GBM and up to 80% for patients with secondary GBM [12, 15]. In accordance with the updated 2016 edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), glioblastomas are classified into glioblastoma, IDH wild-type, glioblastoma, IDH-mutant, and glioblastoma NOS. The not-otherwise specified (NOS) is reserved for situations where there is either insufficient material or the facilities for testing for the specific genotype are not available [16].

Promoter methylation of the gene encoding the DNA repair enzyme O(6)-methylguanine DNA methyltransferase (MGMT) is a favorable molecular-genetic prognostic/predictive marker for patients with GBM. Approximately 50% of newly diagnosed GBMs have MGMT gene promoter methylation. MGMT promoter methylation correlates with a low level of MGMT gene expression and may be a predictive marker of sensitivity to alkylating agents, resulting in an almost twofold increase in the median survival after chemoradiotherapy [8, 17]. In addition, the presence of mMGMT is associated with an improved survival of GBM patients regardless of the treatment strategy and reflects a generally more favorable tumor phenotype [15]. The presence of 1p19q co-deletion (loss of heterozygosity on the 1p and 19q chromosome arms) is typical for oligodendroglial tumors and indicates a more favorable prognosis. However, in patients with glioblastoma, the 1p/19q co-deletion may not be associated with survival benefit [18]. The identification of molecular-genetic biomarkers considerably increased our current understanding of glioma genesis. However, further studies are required to identify new biomarkers to define the clinical and biologic subtypes of glioblastoma [1, 8, 13].

Multimodal treatment including surgery and adjuvant chemoradiotherapy with subsequent chemotherapy is the mainstream treatment modality for GBM. Surgery provides material for histological and genetic examinations as well as reduces intracranial pressure in most patients with intracranial hypertension. The gross total or the subtotal tumor resection is an important prognostic factor. Surgery followed by antitumor therapy increases survival rates of these patients [19]. However, aggressive surgery within eloquent areas can worsen the neurological outcome and performance status of patients, thus decreasing overall survival [20, 21]. Moreover, the infiltrative tumor growth beyond the contrast-enhancing areas and the presence of tumor cells in the areas of perifocal edema dictate the need for further antitumor therapy [22]. Survival of patients treated with surgery alone is less than 6 months [23].

Adjuvant radiation therapy at the standard total dose of 60 Gy prolonged overall survival to 10 months. However, tumor recurrence affected about 90% of patients who received radiation therapy [1, 24]. The use of hyperfractionation or dose escalation beyond 60 Gy conferred no survival benefit. Dose escalation up to 90 Gy led to a decrease in 1- and 2-year survival rates [25, 26]. Attempts to escalate the total dose using brachytherapy and radiosurgery also showed no benefit over the standard external beam radiation therapy [27–29].

In the randomized study, concurrent chemoradiation therapy with subsequent adjuvant chemotherapy with temozolomide (TMZ) led to an increase in the overall survival of GBM patients only up to 14.5 months [30]. The use of anti-angiogenic therapy (bevacizumab) in patients with recurrent glioblastomas resulted in survival benefit, with the median overall survival rate from 19.6 to 21.5 months [4, 31, 32]. However, two large randomized phase III trials showed no improvement in overall survival between patients with newly diagnosed GBM receiving and not receiving bevacizumab. The median overall survival of these patients did not exceed 17 months [3, 33].

In recent decades, new approaches to GBM treatment including new drugs, and various biological and physical modifiers have been actively developed. Studies on cell cultures and animal models have shown that low intensity and 200 kHz alternating electric fields have antitumor activity due to mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis [34, 35]. In a large prospective randomized phase III trial, tumor-treating fields (TTFields) were compared with standard chemotherapy for patients with recurrent GBM. The trial indicated that TTFields had an equivalent efficacy when compared with palliative chemotherapy; however, the quality of life was better in the TTFields group [36]. In patients who underwent surgery and standard chemoradiotherapy, TTFields administered concomitantly with temozolomide significantly improved the median overall survival compared with temozolomide alone (20.5 vs. 15.6 months) [37]. Based on the results obtained, TTFields were included in the standard for the treatment of newly diagnosed GBM in the United States [38].

Experimental studies have shown that high temperatures can directly induce damage to glioma cells and result in radio- or chemosensitization [39–43]. Unlike healthy tissues, tumors have an increased thermal sensitivity, which is caused by biophysical differences between

healthy and tumor cells associated with a low efficiency of ATP production in tumor cells. Under conditions of ATP deficiency, the active transport of ions through the cell membrane is violated and its membrane potential is reduced, thus resulting in higher conductivity and dielectric permittivity in cancer tissue than in normal tissue [44, 45].

As recognized in the early 1970s, the main molecular event underlying the biological effects of local hyperthermia (LHT) in a clinically significant temperature range (39–45°C) is protein damage, including denaturation, exposure to hydrophobic groups, and aggregation with proteins not directly altered by hyperthermia [46–48]. Hyperthermia (temperature above 43°C) causes a large number of macromolecular changes that lead to cell death through extensive protein denaturation and necrosis. Although significantly fewer macromolecular changes occur in the 40.5–42°C range, these changes are still numerous. They occur in different cell components and lead to apoptotic cell death [46, 48–50].

Protein aggregation and denaturation have a significant impact within the cell nucleus. Changes in nuclear proteins, especially those involved in DNA transcription, replication, and repair, cause the inhibition of replication forks and lead to chromosomal aberrations, genomic instability, abnormal chromosome segregation, and cell death [46, 47, 49–52]. Cell membranes are also extremely sensitive to heat stress due to the complex molecular composition of their lipids and proteins. Under the action of LHT, the gel-to-liquid crystal lipid phase transition occurs and the proteins lose their structure, thus resulting in an increased permeability of the cell membrane. The ion balance (Na^+, Mg^{2+}, K^+, Ca^{2+}) in cells and in the extracellular environment is changed, although these changes are not the main mechanism of hyperthermic cell death [49, 52].

Ion imbalance results in significant changes in the mitochondrial membrane potential and disturbance of mitochondrial respiration, causing an increase in the activity of oxygen radicals and a decrease in the level of oxygen consumption in malignant cells [52, 53]. Depolarization of the mitochondrial membrane and the resulting release of oxygen radicals change the oxidation-reduction status of cells and stability of proteins, increasing their sensitivity to LHT. The accumulation of lipid peroxidation changes the distribution of Ca^{2+} and activates the Ca^{2+}-dependent apoptotic pathway. These effects contribute to the protein-unfolding effects of hyperthermia and contribute to effects observed in the nucleus [46, 49].

Irreversible changes in the structure of the protein appear to occur at a temperature of 40°C [54–57]. This temperature threshold also temporarily increases the activity of heat shock genes that encode heat shock proteins (HSPs). The effect of HSPs may depend on their location: intracellularly located HSPs have a protective function, including the correction of misfolded protein molecules, the prevention of aggregation, the transport of proteins, and the restriction of apoptosis. Intracellularly located Hsp70 can act as a cell survival protein by inhibiting the permeability of lysosomal membranes. It also protects tumor cells from monocytic cytotoxicity mediated by tumor necrosis factor [58]. However, HSPs may possess both anti-apoptotic (Hsp27, Hsp70, and Hsp90) and proapoptotic effects (Hsp60 and Hsp10) [59, 60]. Finally, cell death due to apoptosis can occur through various mechanisms and, perhaps, HSPs cannot provide protection against all these mechanisms [61]. In contrast to intracellular HSPs, membrane-bound and extracellular HSPs may have an immunostimulating effect [50]. Heat

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has been found to act as the main stimulator of HSP expression and immune stimulation. Hyperthermia treatment at 43.5°C enhances cytotoxicity by antibodies monospecific to specific tumor antigens, suggesting that LHT is capable of enhancing specific immune responses against tumor-associated cell membrane antigens [58, 62].

A simplified view that LHT can lead to immune suppression via induction of thermo-tolerance in tumor cells has been accepted for many years [52, 58]. It is becoming increasingly apparent that in addition to general and limited immune suppression, LHT treatment can lead to specific activation of the immune system by inducing certain modifications of the tumor cell surface and various forms of cell death. Studies have shown that even local exposure to LHT can lead to systemic tumor control by activating the innate immune system [50, 52, 58].

Despite convincing biological justifications, the enthusiasm for the clinical use of LHT as monotherapy has decreased due to the fact that heating of human tumors to cytotoxic temperatures between 42 and 45°C is difficult or almost impossible. In living tissues heated for more than a few minutes, convective heat losses occur near large blood vessels (diameter of ~0.5 mm). Such blood vessels act as a heat sink, and one can expect a temperature drop of up to 50% [63]. Blood flow provides up to 90% of heat removal. A 10-fold increase in blood flow in response to LHT can occur due to the compensatory expansion of arteries and intensive perfusion, especially in normal tissues [64–66].

Intratumoral blood flow varies considerably depending on the tumor type. Moreover, even within the same tumor, the distribution of the vasculature and blood flow is very heterogeneous. Contrary to the general notion that the blood flow in tumors is less than that in normal tissues, blood flow in many tumors, especially in small tumors, is actually greater than that in the surrounding normal tissues under normal conditions. Typically, the bloodstream of the tumor usually decreases as the tumor grows. While studies in small animals suggest that LHT induced a decrease in blood flow at 42–43°C, there is evidence that tumors in large animals and, more importantly, human tumors, are significantly less sensitive to LHT. In general, clinical studies do not suggest a reduction in tumor perfusion at temperatures up to 44°C [67].

An increased blood flow can increase tumor growth, as well as the risk of hematogenous metastases, suppressing the possible therapeutic effect of LHT [48, 52, 68]. However, a high blood flow can have the opposite effect: a high blood flow provides a more intensive exposure to chemotherapy and, through increased oxygenation, sensitizes tumor tissue to radiotherapy [69].

A mild temperature (39–42°C), which is not optimal for the induction of direct cell death or damage to the vascular system of the tumor, is effective in enhancing tumor response to radiation therapy or chemotherapy [70]. Many conditions that contribute to radioresistance, including hypoxia, acid medium, and S-phase of the cell cycle, either increase sensitivity to LHT or do not change it [50, 52, 70, 71]. LHT-induced increase in tumor perfusion leads to an increased tumor tissue oxygenation and an increased tumor radiosensitivity [72].

Under the influence of LHT, both the intrinsic chemical activity of cytostatics and the degree of their penetration into cells increase due to the activation of membrane transport, and the direct effect of LHT is much higher in hypoxic tissues, in which chemoresistance is observed [47, 71].

The mechanism of enhanced cytotoxicity can include the increase in intracellular accumulation of chemotherapeutic drugs, the inhibition of DNA repair, and S-phase cell cycle block, when cells are most sensitive to heat. In addition, LHT increases the production of free radicals and can reverse drug resistance [47, 49, 50].

Based on clinical data demonstrating the synergistic antitumor effect of noninvasive radiofrequency hyperthermia used in combination with chemotherapy and radiotherapy for tumors from various sites and recurrent glioblastomas, the goal of the study was to evaluate the effectiveness and safety of LHT combined with concurrent chemoradiotherapy for newly diagnosed glioblastoma.

2. Methods

2.1. Study population

Between December 2013 and August 2017, 30 patients with newly diagnosed and histologically verified supratentorial GBM were included into the study. All patients underwent gross total or subtotal microsurgical removal of the tumor. Patients with the evidence of recent hemorrhage on baseline magnetic resonance imaging (MRI) of the brain, metal implants, and concurrent severe, intercurrent illness were excluded from the study. The study was approved by the Ethics Committee of Cancer Research Oncology of Tomsk National Research Medical Center. All patients provided informed written consent before being included in the study.

2.2. Study design and treatment

This uncontrolled cohort study aimed to assess the tolerability and efficacy of concomitant transcranial local radiofrequency hyperthermia combined with radiotherapy and chemotherapy with temozolomide to treat newly diagnosed glioblastoma after surgical treatment. The IDH mutation status was determined using immunohistochemical staining with the anti-human IDH1 R132H. Methylation of O6-methylguanine-DNA methyltransferase (MGMT) was evaluated using a quantitative methyl-specific polymerase chain reaction in real time. To assess surgical outcomes, postoperative contrast-enhanced MRI of the brain was used.

External beam radiation therapy (2.0 Gy per fraction, 5 days per week to a total dose of 60 Gy) was delivered using Theratron Equinox device. Chemotherapy with temozolomide was administered at a dose of 200 mg/m^2/day for 5 days for every 28-day cycle. The first course of chemotherapy was administered a week after starting radiation therapy. Patients received local hyperthermia beginning from the second week of administering external beam radiotherapy (**Figure 1**). Local hyperthermia was given two times a week for 60 min. The interval between local hyperthermia session and radiation therapy was 20–40 min.

Local hyperthermia was given using Celsius TCS system, which uses electromagnetic waves with a frequency of 13.56 MHz (radio waves) for energy transfer. The area of heating

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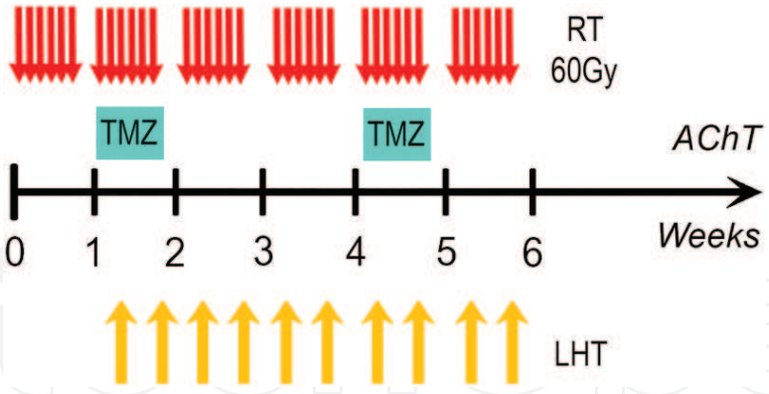

Figure 1. The protocol for transcranial local radiofrequency hyperthermia combined with radiation therapy and chemotherapy with temozolomide.

exceeded the largest tumor diameter by at least 3 cm and increased proportionally to the tumor depth. The heating temperature was gradually increased, focusing on the patient's tolerability of the procedure in accordance with the protocol recommended by the device manufacturer [73].

The applied energy of the electromagnetic field was increased during seven sessions and was dependent on the patients' tolerance. In subsequent treatment sessions, the power did not increase. The duration of the treatment session ranged between 20 and 60 min and the absorbed power during one session was from 42 to over 324 kJ. To prevent thermal burns of the skin and subcutaneous tissue, the surface of the electrodes was cooled by circulating deionized water at a temperature of 12–16°C.

2.3. Patient surveillance and follow-up

Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required before starting concurrent thermochemoradiotherapy (TCRT). All patients underwent a detailed history and physical examination before treatment. Control blood and urine tests were performed every week of thermochemoradiotherapy. The neurological and neuro-ophthalmic evaluations were performed before and after completion of treatment.

Overall survival and time to tumor progression/recurrence are the most important criteria for the assessment of response to adjuvant therapy in patients with GBM. All patients were followed up in the outpatient clinic setting. To assess treatment outcomes, contrast-enhanced MRI was performed a month after completion of treatment, every 3 months in the first 2 years and every 6–12 months thereafter. All MR images were evaluated using Response Assessment in Neuro-oncology criteria, RANO [74]. In case of suspicion of tumor progression, an extraordinary MRI was performed. When a patient did not show up for a scheduled appointment, information on the patient's health status was requested in his family relatives.

Adverse effects of radiation therapy were evaluated using RTOG/EORTC Scoring Criteria (1995), and side effects of chemotherapy were assessed using the NCIC-CTC grading scale. Thermal damage to the skin was classified according to the depth of the lesion.

2.4. Statistical analysis

Progression-free survival and overall survival were assessed using clinical and molecular-genetic prognostic factors.

Statistical analysis was done using statistical software for Microsoft Office Excel 2010 (Microsoft Corporation) and Statistica 10.0 (StatSoft).

2.5. Results

Between December 2013 and August 2017, 30 patients with newly diagnosed supratentorial glioblastoma were included into the study. Eight patients underwent gross total tumor resection, and 22 patients underwent subtotal resection. The status of IDH mutation and MGMT promoter methylation was analyzed in 73% of patients. Mutation of IDH was found in one patient. The frequency of MGMT promoter methylation was 54.5%. There were 19 male and 11 female patients aged from 21 to 71. The highest frequency of glioblastoma occurred in the age range of 50–61 (median age 56 years). Tumor involvement of more than one lobe was the most common. Tumors that infiltrated the parietal, temporal, and frontal lobes occurred less frequently. The medial structures and the occipital lobe were the least frequent sites in which cancer developed (**Figure 2**).

The median Karnofsky Performance Status (KPS) score was 85% (range 40–90%, 95% CI: 60–90%) (**Figure 3**).

The average time from diagnosis to start of radiation therapy was 5.4 weeks. (95% CI: 4.5–6.5 weeks). Three patients who underwent subtotal tumor resection had disease progression at the time of initiation of adjuvant therapy.

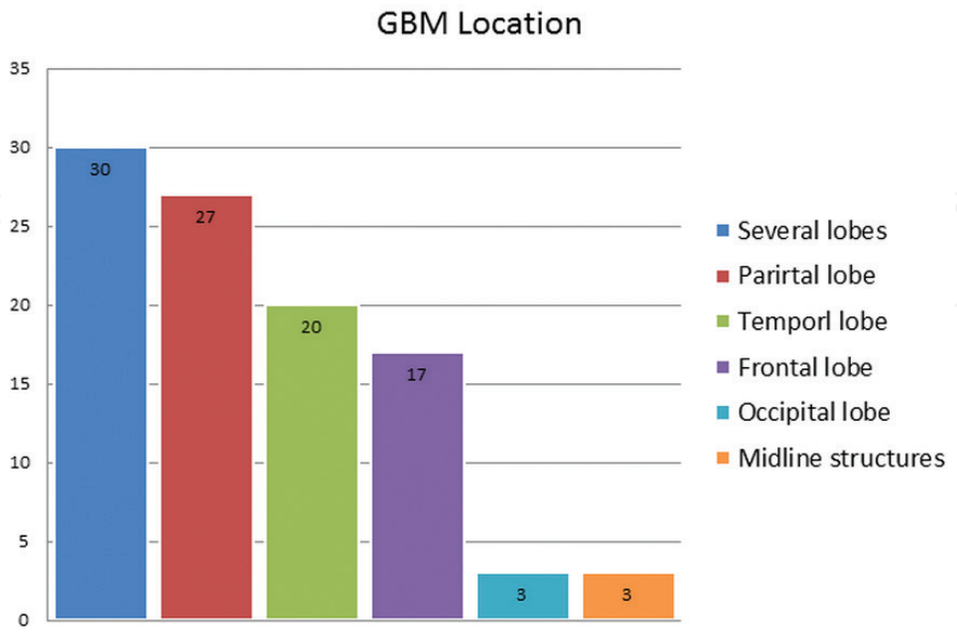

Figure 2. GBM location in patients enrolled into the study.

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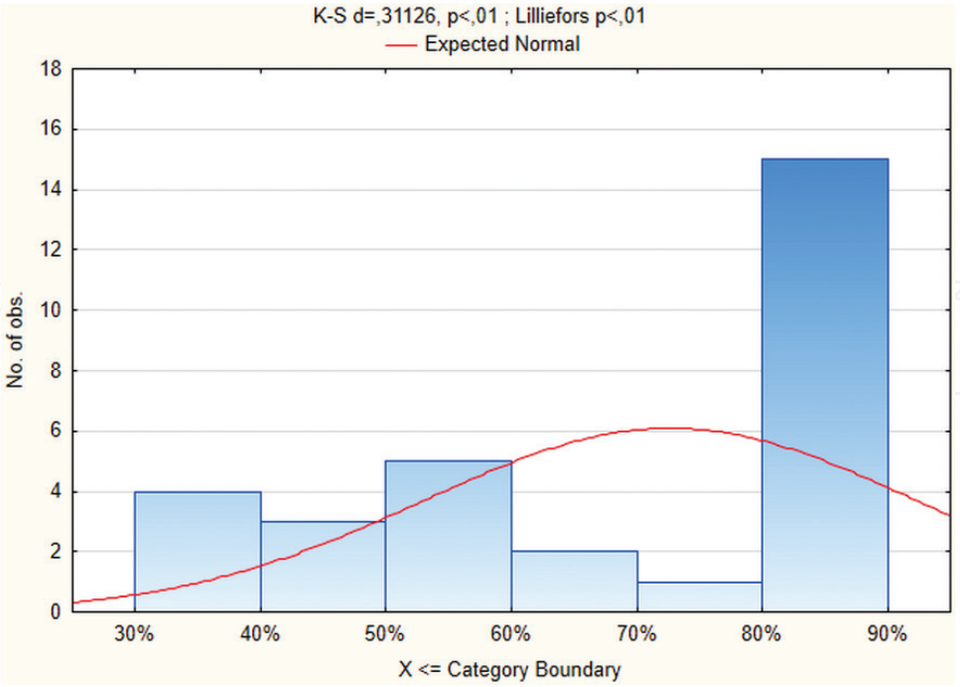

Figure 3. Karnofsky performance status score.

2.6. Treatment

Of the 30 patients included into the study, 29 completed concurrent thermochemoradiotherapy (TCRT). One patient discontinued adjuvant chemotherapy after 42 Gy radiotherapy and eight sessions of local hyperthermia because of tumor progression. In this case, disease progression was diagnosed before starting TCRT. Two patients lost to follow-up after assessing immediate response to TCRT.

Patients who completed TCRT continued to receive chemotherapy with temozolomide at a dose of 200 mg/m^2 per day for five consecutive days in a 28-day cycle. Three patients died within 2 months after completion of treatment with no evidence of disease progression. Among the patients who died, one patient had extensive destructive pneumonia, one patient had severe neutropenia and thrombocytopenia, and another one patient had psycho-organic syndrome occurring during atrophy of the brain.

Patients who had disease progression underwent surgery and second-line chemotherapy. Repeated radiation therapy at a total dose of 40 Gy was administered to patients who developed disease progression 1 year after completion of adjuvant radiation therapy.

2.7. Treatment outcomes

Progression-free survival and overall survival were the primary end points in evaluating treatment response in the study. The median follow-up time was 12 months (range 4–51 months; 95% CI: 8.5–23 months). The median disease-free survival was 9.6 months (95% CI: 7.2–19.0 months), and recurrence most often occurred within 6–12 months after treatment (**Figure 4A**).

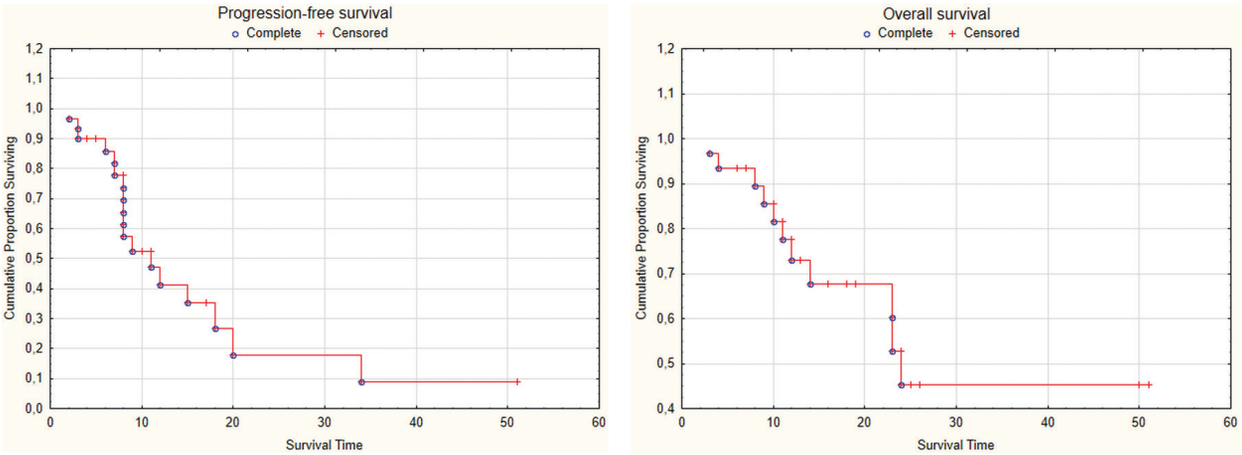

Figure 4. Survival of GBM patients who received concurrent thermochemoradiotherapy. (A) Progression-free survival and (B) overall survival.

The 1-year disease-free survival rate was 41.3 ± 10.6%. Five patients were followed up for more than 24 months. One patient developed recurrent disease 34 months after diagnosis.

During the follow-up period, 11 patients died. Most deaths were registered within 6–12 months (five patients) and 12–24 months (four patients). The median overall survival time was 23.4 months. The 1-year survival rate was 73 ± 8.8%. Four patients had no evidence of recurrence 24 months after completion of treatment (**Figure 4B**).

2.8. Safety and tolerability

Treatment tolerance was assessed by monitoring changes in the functional and neurological status of patients and comparing complications from chemotherapy and radiotherapy.

Most patients had no changes in the functional performance status assessed by the Karnofsky scale before and after TCRT. In three patients with low KPS score (40%) due to neurological deficit, concurrent TCRT led to an increase in KPS score to 60%. One patient had disease progression during TCRT, and his KPS score decreased from 80 to 40%.

Changes in the KPS status before and after TCRT are shown in **Figure 5**. An increased functional activity of patients was observed; however, differences were not statistically significant ($p > 0.05$).

The assessment of neurological symptoms before and after TCRT showed no changes in neurological deficit in most patients. Neurological symptoms were transient in three cases and regressed after vascular therapy in two cases. Worsening of neurological symptoms was observed in three patients. One of these patients discontinued radiotherapy at a total dose of 42 Gy because of disease progression. In two remaining patients, an increase in neurological symptoms was not associated with tumor progression and was characterized by the occurrence of extrapyramidal symptoms in one case and behavioral disorders in another case. Both patients had a history of chronic cerebral ischemia. Regression of focal neurological symptoms manifested as a decrease in the severity of pyramidal symptoms was registered after TCRT

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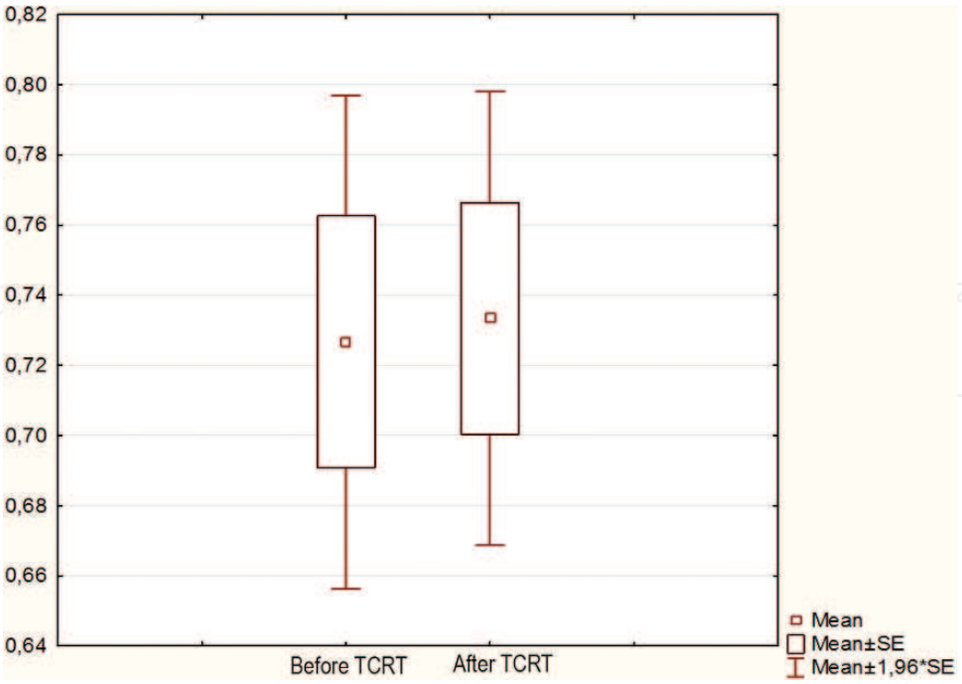

Figure 5. Functional activity of patients before and after TCRT.

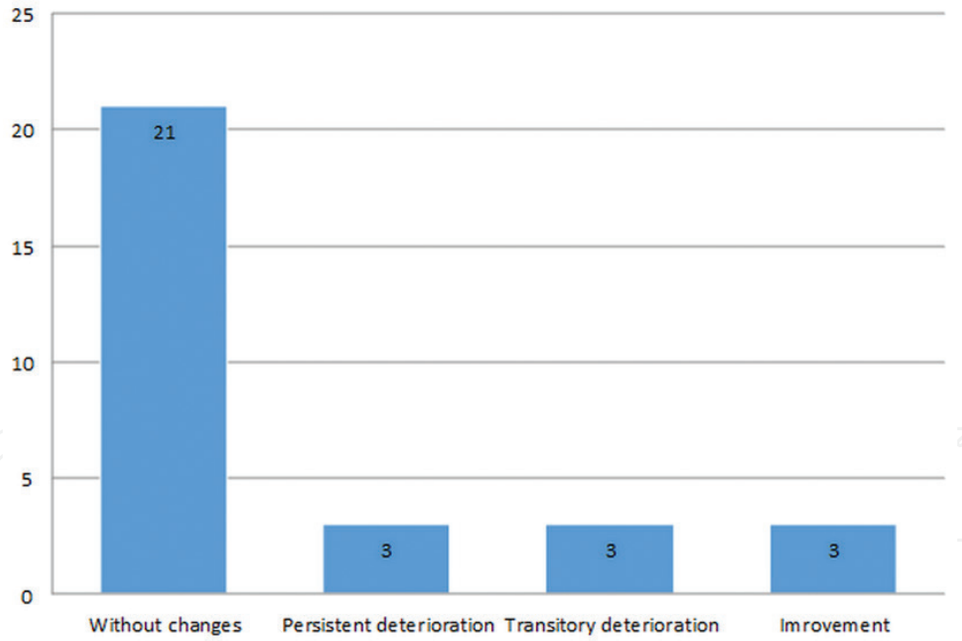

Figure 6. Changes in neurological symptoms after TCRT.

in two patients, and as an improved extremity muscle strength and regression of convulsive syndrome in one patient, thus increasing KPS status from 40 to 60%. The patient characteristics with respect to changes in neurological symptoms are shown in **Figure 6**.

Gastrointestinal toxicity manifested with diarrhea, nausea, or loss of appetite was founded in four (13.3%) patients. Grade 3/4 toxicity was not registered. Hepatotoxicity manifested by a

selective and sustained rise of serum alkaline phosphatase (ALP) activity that was noted in 13 (43.3%) patients. When the level of serum ALP activity was 2.5 times higher than the normal limits, chemotherapy temporarily stopped, and the correction with hepatic protectors was performed.

Hematologic toxicity in the form of grade 1/2 leukopenia, grade 1/2 thrombocytopenia, and grade 1 anemia was observed in 10 (33.3%) patients. Grade 3/4 leukopenia and thrombocytopenia were diagnosed in two (6.7%) patients. Clinical manifestations of grade 3/4 hematological toxicity were characterized by increased hemorrhage, microhematuria, and thrombocytopenic purpura. In one patient, hematoma formation in the tumor bed required surgery. There were no cases of febrile neutropenia. In the cases of grade 3/4 hematologic toxicity, chemotherapy with a reduced dose of temozolomide continued after achieving absolute neutrophil count of >1500 cells/μl and platelet count of >100,000 cells/μl. There were no cases of chemotherapy termination because of hematological toxicity.

Grade 1–2 infectious complications after the completion of chemotherapy were revealed in three (10%) patients. These complications were manifested by chronic pyelonephritis, bronchitis, and oropharyngeal candidiasis and were managed by antibacterial and antifungal therapy. Within a month after completion of TCRT, two patients developed severe infections (pneumonia), requiring hospitalization and prescription of antibiotic therapy. Both patients received dexamethasone at a dose of 16 mg/day intramuscularly.

Acute radiation-induced skin damage was observed in all patients. Allopecia was observed in 29 (96.7%) patients, and a second-degree skin radiation reaction was observed in one case (3.3%). Complications associated with hyperthermia in the form of thermal injury of skin (up to 2 cm in diameter) were diagnosed in three (10%) patients. They did not cause deterioration in the physical status of patients. Treatment was conservative, and interruption or cessation of treatment was not required. One patient developed inconsistency of a postoperative scar with the formation of a cerebrospinal fluid leak. In this case, the excision and suture of the liquor fistula were performed, liquorrhea was stopped, and TCRT was successfully completed.

3. Discussion

Several randomized studies showed a significant increase in the overall and disease-free survival of GBM patients receiving LHT [75, 76]. Seventy-nine patients with newly diagnosed glioblastoma were randomized to receive either interstitial high-frequency hyperthermia in combination with brachytherapy or interstitial brachytherapy alone. The median time to disease progression was longer and the median overall survival was higher in the LHT + brachytherapy group than in the group with brachytherapy alone (35 vs. 57 weeks and 76 vs. 85 weeks, respectively) [75]. Based on the study, interstitial high-frequency hyperthermia for GBM treatment was approved by the Food and Drug Administration (FDA). However, the invasive nature of LHT limited its use by two procedures to prevent complications associated with the installation of antennas and determined the impossibility of combining LHT with external beam radiation therapy.

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The effectiveness of magnetic hyperthermia combined with fractionated stereotactic radiotherapy for recurrent GBM was evaluated in a large two-center study [76]. Patients underwent stereotaxic intratumoral injection of a fluid containing magnetic nanoparticles (MNPs), followed by heating in an alternating magnetic field. Side effects were moderate, and no serious complications were observed. The median overall survival time from the diagnosis was 23.2 months. Thus, thermotherapy involving the use of alternating magnetic field in conjunction with MNPs was proven to be an effective method for treating patients with GBM. However, current limitations to the use of magnetic hyperthermia for thermotherapy of GBM patients include the high concentration of MNPs required to generate hyperthermia precluding the use of MRI, as well as the effective delivery of the MNPs [77].

Modern systems for performing deep LHT allow for noninvasive heating of the tumor. In such systems, the electrical parameters of the circuit are automatically measured and individually adjusted to ensure control and high efficiency of the procedure. Temperature monitoring in tumor tissue is provided by calculation based on the measurement of absorbed energy and tissue impedance [66, 68].

There are a number of disadvantages of LHT: the excessive heating of subcutaneous fat, instability in a radiofrequency field and its dependence on the size of electrodes, their location, distance between them, and on the dielectric parameters of tissues, as well as the ease of the formation of the "hot spots," that is, the maximum electrical field in places with a high dielectric contrast [64, 78, 79].

There are published data indicating that the conductivity of the cerebrospinal fluid is at least four to six times higher than that of the gray and white matter. Thus, it is reliable to predict the presence of "hot spots" along the gray matter-cerebrospinal fluid (CSF) boundary, as well as along white matter-CSF boundary. Moreover, the induced electric field distribution is highly nonuniform. The electric field direction plays a significant role: the internal and near-surface electric field is higher in a tissue with low conductivity and lower in a tissue with high conductivity. As a result of tissue heterogeneity, the electric field in the brain does not decrease smoothly with distance from the transducers, as it would in a homogeneous tissue. In addition, electric field "hot spots" can occur far from the arrays, giving rise to a complex spatial distribution [80, 81].

This nonuniformity of the electric field determines high safety requirements for LHT, as it has a number of negative effects on neuronal structures and functions, causing disturbances in electrochemical depolarization, transmembrane ion transport, and destruction of cellular signaling mechanisms and mitochondrial functions. Despite the fact that irreversible changes in the protein structure occur at temperatures above 40°C [55, 56], this temperature threshold also activates heat shock proteins to increase thermal tolerance and enhance cell protection [82]. Since irreversible changes in normal nerve tissue are detected after hyperthermia at 42–42.5°C for 40–60 min [56, 57], the brain temperature should not exceed 42°C.

The attempts to use noninvasive magnetic resonance thermometry during transcranial radiofrequency LHT were unsuccessful, because it was impossible to combine an electromagnetic LHT device with an MRI system. Invasive thermometry for LHT is time-consuming, uncomfortable,

and risky for the patient. Considering these data, we conducted a study simulating radiofrequency deep LHT using a realistic bioequivalent phantom. Results of thermometry showed that the temperature in the normal brain substance and cerebrospinal fluid did not exceed the physiologic parameters. The rise in the tumor temperature enhanced the efficacy of radiotherapy [83].

Several clinical studies on transcranial radiofrequency hyperthermia for relapsed malignant brain tumors showed a low frequency of objective response (from 7 to 25% of cases) and the median overall survival time of 6–9 months after the onset of hyperthermia [84–86]. It was difficult to determine the effectiveness of treatment, since there were no data on the overall survival from the time of surgical treatment.

A preliminary analysis of the results of this uncontrolled cohort clinical trial showed that at a median follow-up of 12 months, the median progression-free survival was 9.6 months in patients who received TCRT (CI 95%: 7.2–19.0 months). These results were better than those described in the randomized study conducted by Stupp [30], who reported that the median disease-free survival time was 6.9 months (95% CI: 5.8–8.2 months) and 7.1 months (95% CI: 5.9–8.2 months) in GBM patients treated with Stupp regimen and tumor-treating fields, respectively [30, 37]. The median overall survival time of patients included in the study was 23.4 months. However, the result was not statistically significant because the median follow-up was up of 12 months.

Given a small number of patients included in the study, the evaluation of molecular-genetic prediction factors (IDH mutations and MGMT methylation) was important to avoid errors associated with a disproportionate number of patients with a favorable prognosis. The molecular-genetic features of tumors in patients enrolled in the study could not be the cause of improved survival. However, the study demonstrated a high frequency of subtotal tumor resections, which was a negative predictor factor [1].

Since radiofrequency hyperthermia was administered locally, an increase in the systemic side effects of chemotherapy compared with the frequency described in the population was not determined. The appearance of neurologic toxicity during chemotherapy with temozolomide not described in the previous studies [30] was more likely to be associated with an increase in edema and ischemic disorders. This was confirmed by the fact that neurological toxicity was mainly observed during the second course of chemotherapy, when external beam radiation dose accumulated. However, none of the patients had evidence of ischemic stroke.

Concurrent hyperthermia and chemoradiotherapy did not result in an increased frequency of local injuries associated with transcranial local radiofrequency hyperthermia [79]. However, it is necessary to pay attention to the fact that during TCRT, one patient developed a fistula in the area of a postoperative scar, which indicated an impairment of reparative processes.

4. Conclusion

Preliminary results of the analysis of 30 patients with supratentorial newly diagnosed glioblastoma who received adjuvant thermochemoradiotherapy using transcranial radiofrequency

hyperthermia showed an increase in progression-free survival rates. Overall survival rates also tended to increase. Given the absence of severe complications, it is necessary to continue research to achieve statistically significant results.

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