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Repetitive resection and intrasurgery radiation therapy of brain malignant gliomas: history of question and modern state of problem

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ABSTRACT

Numerous studies have shown that the degree of primary resection of malignant gliomas of the brain (MG) directly correlates with rates of relapse-free and overall patient survival. Currently, there is no unequivocal opinion regarding the indications and effectiveness of repeated resection in relapse of MG after combined treatment. Surgical intervention, taking into account the pathomorphological features of these tumors, is not healing and should be supplemented with certain methods of adjuvant treatment.
The article reviews and analyzes publications devoted to repeated resection and various methods of intraoperative radiation therapy in the treatment of MG.
Based on the analysis, the authors of the article came to the conclusion that it is advisable to start their own research on the use of intraoperative balloon brachytherapy in the treatment of recurrent MG based on modern technological solutions.

Keywords: glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, radiation therapy, brachytherapy, intraoperative radiation therapy.

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Abbreviations

3MG — malignant gliomas
GB — glioblastoma
AA — anaplastic astrocytoma
AO — anaplastic oligodendroglioma
FEBRT — fractionated external-beam radiotherapy
TFD — total focal dose
OS — overall survival
IRT — intraoperative radiotherapy
IBEB — intraoperative balloon electronic brachytherapy

Malignant brain gliomas are a group of intracerebral tumors with rapid progression and infiltrative growth that determines their unfavorable prognosis in most cases. Glioblastoma (GB) is the most common, anaplastic astrocytoma (AA) and anaplastic oligodendroglioma (AO) are less common[1]. Annual incidence of MG is 4—6 cases per 100,000 that accounts about 40% of all primary brain tumors. Incidence of MG is less only that of brain metastases of tumors growing outside central nervous system [2]. MG resection is not curative, although numerous studies have shown that surgical intervention is necessary and type of resection directly affects recurrence-free and overall survival [3—7]. According to the majority of recommendations, patient should continue treatment within 4—6 weeks after surgery in accordance with one or another adjuvant treatment protocol depending on histological and molecular genetic profile of the tumor [8, 9]. This management is based on detrimental effect irradiation and chemotherapy on residual macro- and microscopic elements of the neoplasm in peritumorous tissue of the brain. Fractionated external-beam radiotherapy is included into the majority of protocols. Irradiation should be implemented on modern equipment with available 3D modeling of irradiation zone. However, the majority of MG recur within 6–7 months after adjuvant therapy in resection edge and within 2–3 cm from this edge [10–13]. In case of recurrent MG, redo surgery can imply biopsy for morphological verification of recurrent tumor or resection of the maximum safe volume of the neoplasm. Candidates for redo resection are 20–30% of patients with recurrent MG [14]. There is currently no unequivocal opinion regarding the indications and effectiveness of repeated resection for recurrent MG. Postoperative median survival in patients with recurrent GB is 8—12 months as a rule [15, 16], in patients with AA — 12—18 months [17—19]. There is currently no convincing evidence that these results are better than would be expected after radio- and/or chemotherapy alone. However, redo surgery may be beneficial for some patients (for example, in those with symptomatic mass- effect). The most significant clinical predictor of better survival after redo surgery is high Karnofsky score [14, 16—18, 20]. Other favorable prognostic factors are young age, longer interval after the first operation and redo resection grade [21—23].

One study showed that ependymal spread of the tumor is the most important negative prognostic factor in patients undergoing redo surgery for glioblastoma [24]. Particular caution is required in patients with preoperative intake of bevacizumab due to the risk of impaired wound healing.

Optimal methods and modes of adjuvant treatment after surgery for recurrent MG are still unclear [16].

Fractionated external-beam radiotherapy is recognized as an effective treatment for newly diagnosed MG. According to the literature, effective total focal dose of FEBRT in this case is 60–84 Gy. FEBRT after MG resection significantly improved overall survival. Repeated FEBRT for recurrent tumors is undesirable since local recurrence occurs within 6—7 months after surgery as a rule and repeated irradiation is associated with advanced risk of severe post-irradiation reaction. Radiosurgery is advisable only in some cases of recurrent MG due to infiltrative growth, dimensions and severity of lesion.

Intraoperative radiotherapy may be effective for local tumor control in patients with recurrent MG. IRT implies irradiation of tumor bed and residual macro- and microscopic tumor elements. Early postoperative irradiation can stop and disrupt proliferation of residual tumor cells. Moreover, effective dose exposure around post-resection cavity is achieved. At the same time, surrounding brain tissue is not exposed under advanced irradiation that significantly reduce irradiation-induced necrosis. In addition, high single doses can cause local and systemic immune responses followed by activation of cytotoxic function [25, 26].

Japanese researchers M. Abe et al. were ones of the first who reported the use of IRT in neuro-oncological practice in 1971. They described 2 cases of recurrent malignant intracerebral tumors [27]. Irradiation was carried out using cobalt-60 (^{60}Co) facility and betatron with various electron energies. In the first case, resection of fibrosarcoma of occipital lobe was performed in a 57-year-old woman (single irradiation course with a dose of 3500 P, irradiation field collimator of 8 cm and electron beam energy of 18 MeV). Postoperative period was uneventful. Satisfactory clinical outcome was stable within 5 months after surgery. In the second case, resection of recurrent GB of the right frontal lobe in a 37-year-old woman was followed by single course of radiotherapy (dose of 4000 R, irradiation field collimator of 4 cm, electron beam energy of 12 MeV). Clinical deterioration after 2 months required redo craniotomy. Irradiation-induced necrosis without signs of local recurrence was observed. The patient died in 87 days after surgery on the background of permanent fever. Autopsy was not performed.

N. Sakai et al. reported encouraging results of surgical treatment of MG with IRT in 1991 [28]. IRT was used in 32 out of 73 patients with histologically confirmed AA and GB. In all cases, maximum safe resection and FEBRT (TFD 30 Gy for 25 fractions or 61 Gy for 10 fractions) were followed by chemotherapy with nimustine (ACNU). Repeated craniotomy and IRT with doses of 10—50 Gy (mean 26.7 Gy) per one course were performed in 1 week after surgery using a microtron (MM-22, ScanditronixAB, Sweden). In patients after IRT, 24- and 36-month survival was 57.1 and 33.5%, respectively (mean 26.2 months). In other patients, these values were significantly lower (23.6 and 13.1%, respectively, $p<0.01$) (mean 20.7 months).

M. Matsutani et al. have applied IRT in 170 patients (85 gliomas, 81 cerebral metastases, 4 other neoplasms) using Shimadzu-20 MeV betatron (Shimadzu, Japan) with electron beam energy of 8—20 MeV for the period 1977—1990. Spatial shape of electron beam was changed by various conical applicators. Resection of intracerebral tumor was followed by filling of post-resection cavity by moistened sterile swabs. Intraoperative irradiation (15—30 Gy for 5—10 min) involved brain tissue at a depth of 1—2 cm from resection edge. There are interesting results in a subgroup of 30 patients with newly diagnosed and recurrent GB who underwent IRT (mean dose 18.3 Gy) combined with FEBRT (mean dose 58.5 Gy, range 30—80 Gy). Median recurrence-free and overall survival was 73 and 119 weeks, respectively. Annual, 2- and 3-year survival was 97, 61 and 33%, respectively [29].

A. Fujiwara et al. used FEBRT combined with IRT in 20 out of 36 patients with MG [30]. A balloon was placed inside post-resection cavity immediately after resection of tumor. This balloon resulted a regular rounded shape of the cavity. IRT (20—25 Gy) was performed using a linear accelerator (Toshiba, Japan) with 80% of isodose within 1.8—3.3 cm from the edge of residual cavity under ultrasonic control. All patients received TFD of 40—50 Gy for 20—25 courses in 2 weeks after surgery. Radiotherapy was followed by chemotherapy with ACNU, cisplatin and carbaplatin. Better median survival after IRT compared with the control group was reported (14 and 10 months, respectively). Some trials did not demonstrate significant efficacy of IRT. In 2002, K. Nemoto et al. reported the results of treatment of 21 patients with GB and 11 patients with AA [31]. Excision was followed by IRT of the tumor bed using a linear accelerator (mean dose of 14.9 Gy, range 12—15 Gy). FEBRT with TFD of 60 Gy was performed in 2 weeks after surgery. In patients with AA, annual, 2- and 5-year survival rates were 81, 43, and 21%, respectively. In patients with GB, these values were 70, 18, and 6%, respectively. There were no significant between-group differences.

Spanish researchers reported the results of combined treatment of 17 patients with MG (7 GB, 4 AA, 6 AO) using IRT. Irradiation was carried out immediately after resection of the neoplasm on a linear electron accelerator with a beam energy of 12—18 MeV. A radiation energy beam was formed by conical applicators. ILT with single fraction of 10—15 Gy was used in patients with recurrent tumors and previous external radiotherapy. A dose of 15—20 Gy was used in primary patients. Total resection of macroscopic tumor volume was achieved in 14 patients. In other cases, there was tumor biopsy only. IRT of tumor bed involved surrounding brain tissue within 1—2 cm from the edge of resection cavity. Postoperative combined treatment of newly diagnosed MG and IRT implied fractional irradiation of the whole brain with a TFD of 45—50 Gy and intraoperative irradiation of postoperative cavity and 2—3 cm of surrounding tissue with a dose of 15 Gy.

Patients with recurrent MG had previous external fractional irradiation with a TFD of 50—60 Gy by the moment of IRT. A 18-month survival was 56% in patients with MH who received the combined treatment for the first time and 47% in those with recurrent MG [32].

In 2005, P. Schueller et al. reported the results of IRT in 71 patients with MG [33]. The study included 26 patients with various anaplastic gliomas (AA, AO) and 45 patients with GB. The maximum safe microsurgical resection of supratentorial malignancies was performed under computed navigation. IRT (dose of 20 Gy) was performed in 52 patients with a newly diagnosed tumor using an original neuronavigation device to guide the irradiating beam. Subsequently, FEBRT with TFD of 60 Gy was administered. The study also enrolled 19 patients with recurrent MG who underwent IRT with irradiation dose of 20—25 Gy. Mean survival in patients with AA was 14.9 months, in patients with GB — 14.2 months. A 2-year survival rates were 26.9 and 6.8%, respectively (p=0.0296). Thus, there were no advantages of IRT over FEBRT for OS in this trial. K. Takakura and O. Kubo irradiated 55 MG patients using spherical applicators. A 2-year survival was 89% in patients with AA and 42% in patients with GB. These data exceeded the control values from the Japanese registry of tumors (77 and 21%) [34].

In 2012, I. Zamzuri et al. reported a case report of a 42-year-old patient with GB who underwent resection of about 80% of tumor in accordance with intraoperative assessment [35]. Redo craniotomy and IRT with a dose of 10 Gy were performed in 2 weeks after initial operation. They used an equipment of the Zeiss company (Germany) with a spherical applicator. FEBRT of the whole brain with a TFD of 40 Gy was combined with chemotherapy (temozolomide). There were no clinical and tomographic signs of recurrence within 2-year follow-up period.

There were 24 patients with recurrent GB who were treated at the Johns Hopkins Hospital (USA) for the period 2000–2004. GliaSite radiation therapy system (RTS) was applied [36]. GliaSite balloon was placed inside the post-resection cavity immediately after removal of tumor. Injection port connected to the balloon was taken out subcutaneously in the scalp. Then, the balloon was filled with an isotonic sodium chloride solution through this port so that the surfaces of balloon and post-resection cavity fit snugly over each other over the entire area. Surgeries were completed in standard fashion. Adequacy of balloon localization and isodose curves were assessed using postoperative CT data. Drainage of isotonic sodium chloride solution from the balloon was followed by its filling with radioactive drug Iotrex (iodine-125; ^{125}I). Balloon brachytherapy has been carried out for several days in accordance with specialized algorithms for dose calculation. Mean dose was 53.1 Gy (standard deviation 9.2 Gy, range 29.9–80 Gy). Symmetrical dose distribution was achieved in all 24 patients that emphasizes the advantage of balloons over flat and spherical applicators. Moreover, balloons are more suitable for cavities with complex spatial configuration as the most common result of resection. Median OS was 23.3 months compared to 18 months after redo FEBRT of GB (according to the literature) [37]. A serious drawback of this method is the need for redo surgery to remove GliaSite balloon. In addition, the patient should be isolated from others for radiation safety. Considering these disadvantages, manufacturing of GliaSite was discontinued in 2008.

In 2018, F.A. Giordano et al. reported phase I—II results of the INTRAGO trial. This study was started in 2014 and devoted to analysis of the efficacy of IRT with INTRABEAM system (Zeiss, Germany) in patients with newly diagnosed GB. Literature review preceded the study. There was an important conclusion in this review that the majority of studies performed before 2014 had single-center design and small sample size. FEBRT was carried out using various models of linear accelerators as a rule. The researchers faced with low accuracy in FEBRT planning, difficult choice of adequate collimators, etc. These features significantly reduced the effectiveness of the treatment [38]. F.A. Giordano et al. performed IRT using INTRABEAM system (Zeiss, Germany) with solid-state spherical applicators, which were inserted into the post-resection cavity at the final stage of surgery. IRT with a single dose of 20 Gy on the applicator surface was made in 3 patients. Subsequently, the dose was increased up to 30 Gy and 40 Gy in other patients. Dose escalation was carried out in the absence of so-called dose-limiting toxicity. The authors determined this parameter as the absence of impaired wound healing and need for surgical debridement, IRT-associated hemorrhage and ischemia, symptomatic irradiation-induced necrosis as indication for surgery, need to interrupt external irradiation. Further adjuvant chemoradiotherapy with temozolomide was carried out in accordance with the protocol generally accepted in neurooncology. This protocol was proposed by R. Stupp et al. in 2005 [39]. The objective of the study was analysis of effective and safe dose for IRT. The trial enrolled 15 patients older than 45 years (median 62 (46—72) years) by the moment of publication. According to postoperative MRI data, total resection (over 98% of the tumor) was achieved in only 2 patients. There was no methylation of MGMT gene promoter in 10 patients. Median of local progression free survival was 17.8 months (95% CI 9.7—25.9) in 12 patients who underwent treatment with full observance of the research protocol. Median of recurrence-free period in the entire group was 11.3 months (95% CI 5.4—17). It was associated with distant local progression outside the primary tumor. The authors concluded that IRT is predominantly advisable for local GB. Dose-limiting toxicity was not observed. Therefore, the authors concluded that selected dose range was relatively safe [40].

In 2009, S. Bensaleh et al. published a review devoted to the use of balloon brachytherapy (MammoSite system) for early breast cancer [41]. This device is a balloon connected to a double-lumen catheter. The balloon is placed inside the post-resection cavity in the mammary gland immediately after removal of tumor. Filling of the balloon by a fluid through the catheter resulted inflation of the balloon and its close contact with the walls of post-resection cavity. Irradiation plan was made using CT data. Irradiation involved tissues within 1 cm from the balloon surface. The balloon was filled by radioactive iridium-192 (^{192}Ir) through a separate port for these purposes. TFD of 34 Gy was achieved for 10 fractions (twice a day) with subsequent elimination of the balloon. S. Bensaleh et al. analyzed 11 trials and found that MammoSite system and methods of external accelerated partial irradiation result similar 3- and 5-year disease-free survival in patients with early breast cancer. A significant drawback of this method is the need for the

MammoSite system to remain in the body for at least 2 days. Some authors reported the risk of infectious complications 16%.

In 2011, D.J. Scanderberg et al. reported a 47-year-old man with recurrent AO of the right frontal lobe. Contura device (SenoRx, USA) originally developed for IRT of local breast cancer was applied in this patient [42]. This device consists of balloon-applicator connected to a multi-lumen catheter for introduction of radiation sources. The equipment is applied for high-dose radiotherapy (HDR). Balloon-applicator was placed in post-resection cavity at the final stage of surgery. Computed tomography of the brain, planning and implementation of balloon brachytherapy with a single focal dose of 20 Gy at a distance of 1 cm from the balloon surface were performed in 24 hours after surgery. The balloon was eliminated immediately after brachytherapy. Follow-up period was 6 months. The authors reported no signs of recurrence and any postoperative complications.

There has been a significant improvement of IRT in the treatment of MG over the past few decades. This is facilitated by the introduction of innovative equipment for radiotherapy, rapid development of pre- and intraoperative neuroimaging technologies, as well as software for conformal planning of radiotherapy.

One of the latest achievements in oncological radiology is equipment for intraoperative balloon electronic brachytherapy (IBEB) Xoft ElectronicBrachytherapy System, Axxent (Xoft Inc., USA). This system is equipped by own miniature x-ray source that allows direct irradiation of the tumor bed. Unlike conventional high-dose brachytherapy methods, the Axxent device does not require the use of radioactive isotopes, heavy shields or capital equipment. A miniature x-ray tube with a voltage of 50 kV placed at the end of the source delivers radiation through the applicator during brachytherapy procedure. The source is designed for maximum irradiation of tissue around the applicator. Balloon spherical applicator consists of an inflatable balloon made of silicone elastomer with a contrast agent in the wall of the balloon and multi-lumen catheter with three ports. The balloon is filled only with sterile isotonic solution. The middle port is connected to the central cavity and designed for introduction of x-ray source during radiotherapy. Inflated balloon results a boundary with surgical cavity and provides a clear shape of this cavity for delivering the prescribed irradiation dose during radiotherapy. Radiotherapist and medical physicist jointly draw up a treatment plan to deliver the prescribed dose to the target tissue volume [43].

There are data on improved outcomes of the treatment of various oncological diseases using IBEB implemented on the equipment of the Xoft company [44–48].

Undoubtedly, the problem of MG management is still far from being solved, since the most difficult mechanisms of neuro-oncogenesis are still unclear. Moreover, there are no effective methods from the category of chemotherapy, targeted molecules, etc. Many tumors are initially unresectable and/or characterized by primarily multiple growth.

Developing technologies for surgical and radiological control of local MG recurrence should be investigated regarding their safety and efficacy. Even total resection of these tumors does not result complete recovery and should be supplemented by adjuvant treatment considering the features of these neoplasms. Numerous studies have shown that quality of primary resection directly correlates with overall and recurrence-free survival. Radiotherapy also improves survival rates.

Type of resection of recurrent MG is still debatable. Chemotherapeutic agents, target molecules, immunotherapy methods and tumor treating fields (TTFs) are characterized by moderate efficacy. Repeated external irradiation is not always applicable because of early recurrence and high risk of severe irradiation-induced necrosis.

Conclusion

The authors of this article believe that radical resection with intraoperative balloon electronic brachytherapy may be effective and safe in patients with local recurrence of malignant glioma. We started the use of intraoperative balloon electronic brachytherapy for recurrent MG using an Axxent device (Xoft Inc., USA) in order to analyze this approach (registration certificate of the Russian Federation for medical device dated 04.17.2015 No. RZN 2015/2593). This study will include adults with recurrent malignant glioma after combined treatment. All patients will undergo maximum and safe neoplasm resection followed by immediate intraoperative balloon electronic brachytherapy (Xoft equipment) with a prescribed single dose of 20 Gy on the surface of the applicator balloon. Recurrence-free and overall survival, as well as side effects will be analyzed. We will use clinical and tomographic control with contrast-enhanced and perfusion magnetic resonance imaging of the brain within 24 hours after surgery and then contrast-enhanced and perfusion magnetic resonance imaging of the brain and, according to indications, positron emission tomography of the brain with 18-FDOPA every 3 months until tumor recurrence (in accordance with Response Assessment in Neuro-Oncology criteria). Monthly assessment of Karnofsky score, general and neurological status are scheduled.

Future study is intended to analyze the effectiveness and safety of intraoperative radiotherapy in the treatment of malignant gliomas of the brain.

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