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INFLUENCE OF PERITUMORAL EDEMA ON THE OUTCOME OF RADIOTHERAPY OF SUPRATENTORIAL NONCYSTIC GLIOBLASTOMA MULTIFORME

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The lifetime of an OH radical is 10-5 sec., i.e. ten billion times longer than the lifetime of a free electron, and most authors stress its indirect mechanism of DNA destruction as a predominant one in the radiation treatment of glioblastoma multiforme (GBM). Although the concentration of OH radicals in brain edema is increased, the edema remodels the zone of tumor infiltration and prepares the ground for exterritorialization of tumor regions planned for irradiation, influencing the possibility of rapid recurrences.

The aim of the paper was to establish the impact of peritumoral edema on the time to recurrence of glioblastoma multiforme, survival, type and incidence of postirradiation complications.

Sixty patients with total resection of supratentorial noncystic GBM were treated after a month with 60 Gy of radiation therapy, out of which one half to the therapeutic volume (TV) and the other half to the clinical target volume (CTV), and upon completion all of them were given the BCNU protocol. According to the recommendations by RTOG (Radiation Therapy Oncology Group), surgically treated patients were divided into those with edema below 25 cm^3; 25-75 cm^3; and finally those over 75 cm^3.

Patients with peritumoral edema of over 75 cm^3 had statistically significantly faster relapse, had poorer Karnofsky score, progression of peritumoral edema, and higher mortality if radiotherapy was delivered only to the CTV. Dispersion of radiation in the TV does not reduce the incidence of cutaneous postirradiation effects and cannot be justified for edemas smaller than 25 cm^3. *Acta Medica Medianae 2011;50(3):5-9.*

Key words: *glioblastoma multiforme, radiotherapy, peritumoral edema, survival, radiation complications*

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Introduction

Glioblastoma multiforme (GBM) is the most malignant tumor of the central nervous system (CNS), and the third most malignant tumor among all tumors in humans. It is associated with a high mortality of 77%; in the USA alone, around 13.000 people die of the disease a year (1). It is a primary tumor originating from glial cells, characterized by a high degree of infiltration of brain structures thanks to disadhesion, proteolysis of the extracellular matrix, locomotion, and angiogenesis. The result is the presence of tumor cells even in the contralateral brain hemisphere, and on account of that GBM is believed to be a diffuse disease. In spite of maximal resection, GBM recurs after a couple of months already, and half of the affected die in the first year of diagnosis in spite of a reoperation.

Radiation treatment has a huge significance in the postoperative management of the affected. Deviations in the effects of radiation of GBM of similar dimensions, sites, and Karnofsky performance scores (KPS) open the question of impact of peritumoral edema on the effects of radiation. Since the lifetime of an OH radical is 10-5 sec., i.e. ten billion times longer than the lifetime of a free electron, most authors stress its indirect mechanism of DNA destruction as a predominant one in the radiation treatment of GBM. Although peritumoral edema increases the presence of OH radicals via increased water concentration, and thus potentiates treatment effects, brain edema pushes away the zone of tumor infiltration and enhances exterritorialization of tumor islets planned to be irradiated and promotes fast recurrence of the tumor. Although some authors believe that a vasotoxic tumor effect on the adjacent or more distant peritumoral portions of the brain parenchyma constitutes the essence of a brain edema, some authors consider brain edema as an expression of immediate coexistence of tumor cells and brain tissue, and that the degree of brain edema is directly proportional to the presence of cellular tumor infiltration (2). In that

context, instead of classical conformal irradiation with 60 Gy delivered to the tumor volume alone, radiation therapy extended beyond the tumor volume to involve the zone of edema and 1cm safety margin is usually recommended (therapeutic volume, TV) (3).

Aim

The paper aims to assess the impact of peritumoral edemas in variable degrees on the effects of radiation therapy of surgically treated supratentorial noncystic GBM, monitoring the time to relapse, length of survival, and presence of complications.

Methods

The study enrolled 60 patients treated at the Clinic of Neurosurgery, Clinical Centre Niš, in the period from January 2006 to November 2007, for primary brain noncystic supratentorial glioblastoma multiforme (GBM). Contrast-enhanced brain CT was performed in all patients, and then the volume of peritumoral edema was determined (computer-assisted, based on the RTOG – Radiation Therapy Oncology Group guidelines), stratifying the patients into three groups: those with small edema (<25 cm^3); intermediate edema (25-75 cm^3); and large edema (>75 cm^3). The principle of total macroscopic tumor resection was implemented in all patients. The Karnofsky Performance Score (KPS) was determined pre- and postoperatively monthly for the first three months, and every three months later on for 18 months after surgery. Contrast-enhanced control brain CT was performed immediately before discharge, and postoperatively every three months, recording radiologic complications, edema, recurrences and similar. The time to relapse was monitored and correlated with the degree of peritumoral edema. Thirty surgically treated patients were randomly selected a month after surgery to receive 60 Gy to the Clinical Target Volume (CTV; the tumor zone extended by 2cm to include possible microscopic infiltration); the other 30 cases were the controls, receiving 60 Gy to the therapeutic volume (TV; involving not only the tumor volume plus 2cm margin, but also the zone of edema with additional 1 cm margin). All these patients were treated chemotherapeutically with BCNU after radiation treatment. The period of postoperative surveillance was 13 months on the average (range, 6-54 months). Tumor volume was determined. The size of peritumoral edema was correlated with the time to relapse and survival length, depending on the radiation therapy utilized. Radiation complications were also recorded. The results were statistically processed using the Kaplan-Meier regression and survival curve, linear regression test, and Pearson's chi-square test.

Results

The studied patients were aged over 52.4 years on the average, with preoperative KPS of 76, predominantly frontal (n=19) and temporal (n=17) disease sites, and in 2 cases the tumor involved both hemispheres.

The mean value of primary GBM volume was 31.4cm^3 (9.4–126.2 cm^3), and mean value of peritumoral edema was 54.8 cm^3 (1.1–272.1 cm^3). The distribution of patients by edema volume (<25 cm^3: 25-75 cm^3: >75 cm^3) was 8:11:11 in the CTV group and 10:9:11 in the TV group.

The mean volume of peritumoral edema immediately before radiation therapy in the CTV group was 53.4 cm^3 (1-260.8 cm^3), while in the TV group it was 56.1 cm^3 (5-272.1 cm^3; p=0.39; r^2=0.0011); the samples were thus homogenous, without any statistically significant difference.

In the group of patients where radiation therapy was delivered to the tumor zone and margins of up to 2cm (CTV), mean CTV value was 219.7 cm^3 (94-416 cm^3), compared to statistically significantly different values in the TV group irradiated to the field 1 cm beyond the edema borderline, where the mean edema value was 343.5 cm^3 (147-452 cm^3).

First relapses of the tumors with peritumoral edema below 25 cm^3 were recorded in the fourth month, with an abrupt rise from the seventh month, without any statistically significant difference between CTV and TV. A similar trend was observed in the patients with edemas of 25-75 cm^3, while in those with edemas over 75 cm^3 a significant difference was observed in the speed of relapsing (Figure 1).

The group of patients with CTV had median lethality of 50% of patients (L50) at 9 months, 12 month survival was observed in 26.4% of all patients, while 6.6% survived for 18 months. In the TV group, L50 was observed in the 11 month, 12 month survival was 33.6%, and 18 month survival was observed in 13.2% of patients surgically treated for GBM (p<0.01). A statistically longer survival in the TV group was observed in those with edema volume of 25-75 cm^3, as well as in those over 75 cm^3 (Figure 2).

KPS was statistically significantly higher in all TV subgroups. Mean KPS in the first 6 months of operation in the subgroup with edema <25 cm^3 was 93:82; in those with edema 25-75 cm^3 it was 84:78; and in those with edema volume >75 cm^3 it was 72:51 (p<0.01).

Regarding complications, the following were observed:

- Early cutaneous complications such as early erythema, dry desquamation, pigmentation, reduction of sebaceous and sweat glands, epilation in 73% in the CTV group, and in 76.5% in the TV group (without statistical significance).
- Early CNS complications in the form of brain edema with CT and clinical signs (headache, emesis, papilledema) of increased intracranial pressure in 12 patients (40%) in the CTV group, i.e. in 8 cases (72.7%) with preoperative edema volume >75 cm^3 and 3 cases (27.7%) with 25-75 cm^3 edemas. At the same time, in the TV group, this complication was observed

in 6 patients (54.4%) in the subgroup with >75 cm^3 preoperative edemas, and in only 2 cases (22.2%) in the subgroup with 25-75 cm^3 edemas. The observed values in both instances suggested a statistically significant difference – a lower percentage of patients with increased intracranial pressure in the TV group.

- Early delayed reactions in the form of nausea, emesis, dysarthria, dysphagia, cerebral ataxia and nystagmus, were observed in the CTV group in 22 patients (73.3%) and in 24 cases (80%) in the TV group and did not have any statistical significance.
- Late delayed reactions in the form of epilepsy were observed in the CTV group in the period of 18 months in 5 patients (16.66%), out of which in 4 cases not until the eight month within the CT verification of relapse. At the same time, epilepsy was observed in the TV group in 3 patients (10%), exclusively among those with primary peritumoral edemas >75 cm^3 (1 grand mal, 2 jacksonian forms).
- Postirradiation necrosis in CTV was observed in 3 patients (10%), out of which in 2 cases from the subgroup with <25 cm^3 edema volume, while the same complication was recorded in 2 patients (6.66%) in the TV group (1 from the <25 cm^3 subgroup, and 1 from the 25-75 cm^3 subgroup) (Figure 3).

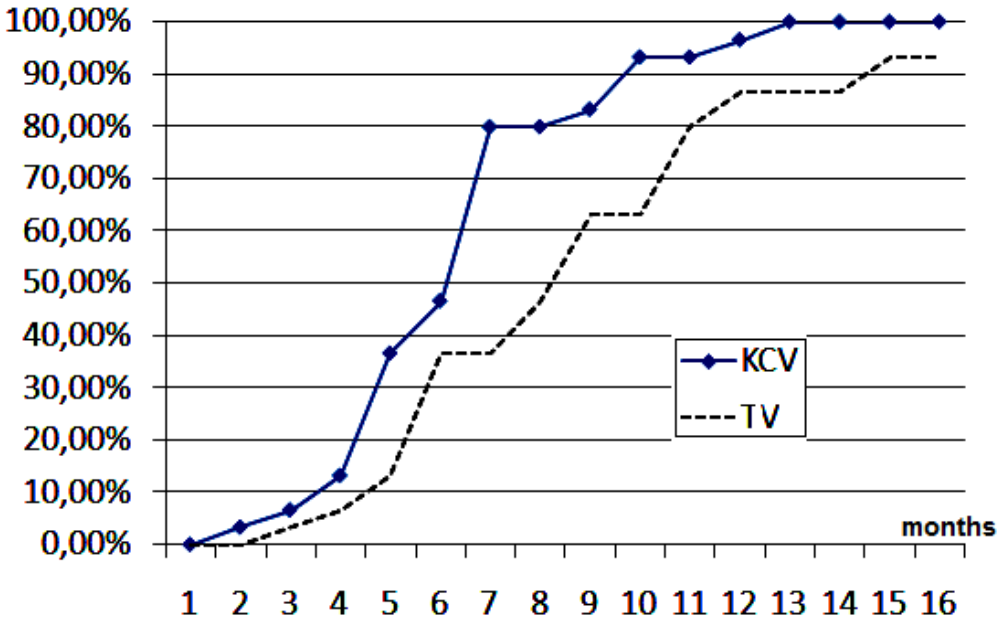

Figure 1. Speed of relapse of GBM in the group of patients with peritumoral edema over 75cm^3 in volume (p<0,01)

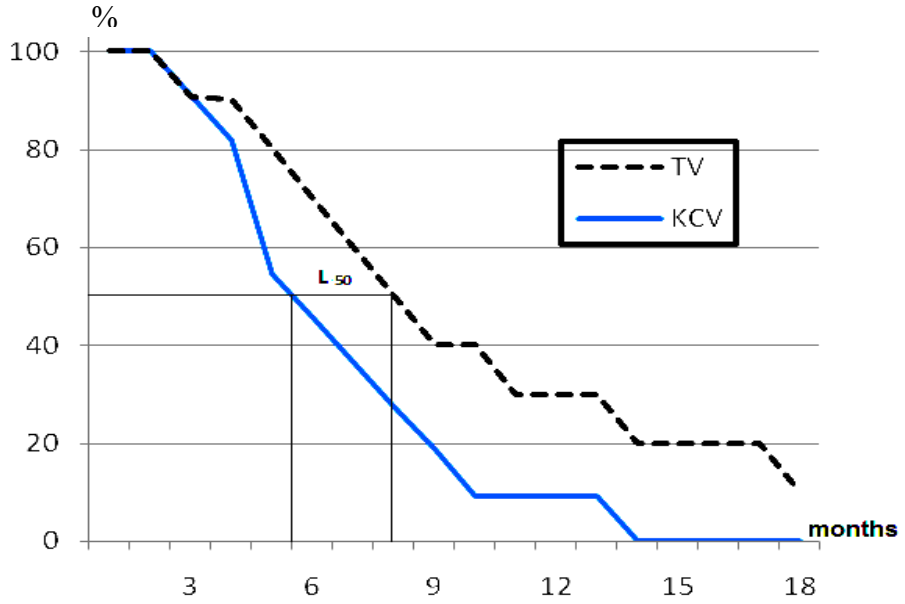

Figure 2. Length of survival in patients surgically treated for GBM, with peritumoral edema over 75 cm^3, depending on the radiation type (p<0,01)

Figure 3. Postcontrast brain CT in a patient with postirradiation necrosis in the CTV group with edema 25-75 cm^3 in volume

Discussion

Glioblastoma multiforme (GBM) is the most malignant brain tumor in adults (4). The survival associated with GBM does not exceed one year. Factors influencing survival are patient age, KPS, radicality of surgical resection, completion of radiation and chemotherapy, use of corticosteroids (5,6). The impact of the degree of peritumoral edema is still a matter of debate, although some authors have cited the papers in which the size of brain edema has been regarded as an adverse prognostic factor (7). The analysis has been thus incited dealing with the question whether particular radiation doses to the edematous brain are able to disrupt the hematoencephalic barrier and accelerate tumor invasion; or, on the contrary, whether radiation is able to contribute to the regression of cytotoxic edema via the destruction of tumor cells in the infiltration zone (8-10).

Dispersion of radiation to a wider zone (TV), involving not only the zone of macroscopically visible tumor, but also the zone of purported infiltration enlarged by the edema zone and a safety margin of 1 cm, was shown in this paper to be more effective regarding the quality and length of survival of patients with total resection of supratentorial noncystic GBM. It was obvious that a slighter reduction of radiation intensity conditioned by the enlargement of treatment zone did not reduce cytotoxicity below the level of efficacy, simultaneously inactivating most peripheral islets of the tumor infiltration. That is the reason why the degree of peritumoral edema at the moment of surgery and in the period preceding radiation treatment is an important prognostic parameter about which precise information should be sought on contrast-enhanced CT or magnetic resonance imaging of the brain. Radiation treatment following here described TV group model is also able to reduce the rate of delayed severe complications of radiation, especially in the group of tumors with peritumoral edema exceeding 75 cm^3 in volume.

Conclusion

The degree of peritumoral edema is an important prognostic factor regarding the length of survival and quality of life of all patients undergoing total resection of supratentorial GBM.

The patients with peritumoral edemas over 75cm^3 in volume relapse faster, (which is of statistical significance), they have poorer Karnofsky performance score, progression of peritumoral edema, and higher mortality if radiation treatment is delivered only to the CTV. Dispersion of radiation in TV does not reduce the incidence of cutaneous postirradiation effects and cannot be justified for edemas below 25cm^3 in volume, but it is very significant for the reduction of number of severe and delayed complications in tumors with large edemas.

References

1. Liang BC, Thornton AF Jr, Sandler HM, Greenberg HS. Malignant astrocytomas: Focal tumor recurrence after focal external beam radiation therapy. J Neurosurg. 1991 ; 75(4)**:** 559–63. [CrossRef] [PubMed]
2. Seidel C, Dörner N, Osswald M, Wick A, Platten M, Bendszus M, et al. Does age matter? - A MRI study on peritumoral edema in newly diagnosed primary glioblastoma. BMC Cancer. 2011 Apr 12 ; 11(1): 127 - 31. [CrossRef] [PubMed]
3. Kamoun WS, Ley CD, Farrar CT, Duyverman AM, Lahdenranta J, Lacorre DA, et al. Edema control by cediranib, a vascular endothelial growth factor receptor-targeted kinase inhibitor, prolongs survival despite persistent brain tumor growth in mice. J Clin Oncol. 2009 ; 27: 2542–52. [CrossRef] [PubMed]
4. Gorlia T, van den Bent MJ, Hegi ME, Mirimanoff RO, Weller M, Cairncross JG, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. Lancet Oncol. 2008 ; 9(1): 29-38. [CrossRef] [PubMed]
5. Hammoud MA, Sawaya R, Shi W, Thall PF, Leeds NE. Prognostic significance of preoperative MRI scans in glioblastoma multiforme. J Neurooncol. 1996 ; 27(1): 65-73. [CrossRef] [PubMed]
6. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol. 2004 May 1 ; 22(9): 1583-8. [CrossRef] [PubMed]
7. Schoenegger K, Oberndorfer S, Wuschitz B, Struhal W, Hainfellner J, Prayer D, et al. Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma?. Eur J Neurol. 2009 ; 16(7): 874-8. [CrossRef] [PubMed]
8. Chang EL, Akyurek S, Avalos T, Rebueno N, Spicer C, Garcia J, et al. Evaluation of peritumoral edema in the delineation of radiotherapy clinical target volumes for glioblastoma. Int J Radiat Oncol Biol Phys. 2007 May 1 ; 68(1): 144-50. [CrossRef] [PubMed]
9. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery. 2008 Mar ; 62(3): 564-76. [CrossRef] [PubMed]
10. Lu S, Ahn D, Johnson G, Law M, Zagzag D, Grossman RI. Diffusion-tensor MR imaging of intracranial neoplasia and associated peritumoral edema: introduction of the tumor infiltration index. Radiology. 2004 ; 232(1): 221–8. [CrossRef] [PubMed]

UTICAJ PERITUMORSKOG EDEMA NA ISHOD RADIOTERAPIJE SUPRATENTORIJALNOG NECISTIČNOG GLIOBLASTOMA MULTIFORME

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Život OH radikala inosi 10-5 sek. i deset milijardi puta je duži od života slobodnih elektrona, pa većina autora njegov indirektni mehanizam destrukcije DNK ističe kao dominantan u radioterapiji glioblastoma multiforme (GBM). Iako je koncentracija OH radikala u moždanom edemu povećana, edem remodelira zonu tumorske infiltracije i stvara uslove za eksteritorijaciju tumorskih područja određenih za zračenje i time utiče na mogućnost brzih recidiva.

Cilj rada bio je da utvrdi uticaj peritumorskog edema na brzinu recidiviranja glioblastoma multiforme, dužinu preživljavanja, tip i učestalost postiradijacionih komplikacija.

Radioterapijom u dozi 60 Gy tretirano je za mesec dana 60 bolesnika sa totalnom resekcijom supratentorijalnog necističnog GBM, od čega polovina na terapijski volumen (TV), a druga polovina na klinički ciljni volumen (KCV), a svi nakon toga BCNU protokolom. Prema preporukama RTOG (Radiation Therapy Oncology Group) operisani su podeljeni u grupu sa edemom ispod 25 cm^3, 25-75 cm^3, preko 75 cm^3.

Rezultati i diskusija: Bolesnici sa preko 75 cm^3 peritumorskog edema beleže statistički brži recidiv, lošiji Karnofsky performans skor, progresiju peritumorskog edema i veću smrtnost ukoliko se zračenje primeni samo na KCV. Disperzija zračenja kod TV ne smanjuje učestalost kutanih postiradijacionih efekata i nema opravdanja u primeni kod edema manjeg od 25 cm^3. *Acta Medica Medianae 2011;50(3):5-9.*

***Ključne reči**: glioblastoma multiforme, radioterapija, peritumorski edem, preživljavanje, komplikacije začenja*