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Tumour surface area as a prognostic factor in primary and recurrent glioblastoma irradiated with ^{192}Ir implantation

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Background

To evaluate the impact of tumour surface area (TSA) on survival of patients treated with ^{192}Ir implantation for glioblastoma multiforme (GBM).

Methods/Materials

The analysis of survival and prognostic factors was performed based on a retrospective study group of 120 patients (74 males and 46 females; mean age 53 years; mean KPS score 74.6) irradiated with ^{192}Ir for GBM between 1999 and 2003. There were 72 (60%) patients with recurrent and 48 (40%) with primary inoperable tumour. Patients with recurrences were initially treated with surgery and external beam radiotherapy (EBRT; mean total dose (MTD) 53.5Gy). Individuals with primary inoperable glioblastoma underwent EBRT (MTD 37.2Gy) after brachytherapy completion. All patients were irradiated with ^{192}Ir with a total dose of 15Gy given in 5 fractions.

Results

For the total group of patients 1-year and 2-year survival were 22% and 11%, respectively, with a median survival time (MST) of 6.1 months. The multivariate Cox analysis of the best fit ($\text{Chi}^2=22.98$, $p=0.000041$) distinguished such variables as: patient age ($p=0.002$), performance status ($p=0.04$) and tumour surface area ($p=0.04$) to significantly affect survival. Patients with $\text{TSA}<90\text{cm}^2$ had better prognosis compared to those with $\text{TSA}>90\text{cm}^2$ ($p<0.001$).

Conclusions

Tumour surface area is an independent prognostic factor in patients irradiated with ^{192}Ir for glioblastoma multiforme. TSA less than 90cm^2 predicts significantly longer survival and appears to be a more powerful prognostic variable than tumour volume.

Key words

glioblastoma • tumor surface area • tumor volume • prognostic factors

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BACKGROUND

Despite aggressive standard treatment (surgery followed by external beam irradiation and chemotherapy in specified cases) glioblastoma multiforme (GBM) tumours have remained incurable and highly lethal. Interstitial brachytherapy is an established treatment option in selected patients with recurrent [1–3] and primary [4–6] malignant gliomas, enabling the deposition of a high radiation dose within the target volume, while sparing surrounding normal tissues. Local recurrence after implantation in a characteristic form of tumour regrowth within or at the margin of an irradiated field is the most common cause of treatment failure [7,8].

Searching for clinical and histological variables affecting survival in patients with malignant glioma is virtually a procedure leading to the optimal choice of therapeutic strategy and thus an improvement of treatment results. The prognostic criteria published by the Radiation Therapy Oncology Group (RTOG) in its recursive partitioning analysis (RPA) of randomized malignant glioma trials [9] are currently obligatory and indicate such variables as lower histological grade, greater extent of surgical resection, younger age, high Karnofsky Performance Status (KPS) score and favourable neurological state to predict better survival outcomes. More recently, tumour volume has been reported to be a significant prognostic factor in patients with both primary [10] and recurrent [11] glioma treated with brachytherapy techniques. However, the prognostic effect of tumour volume has been proven to disappear when patients are stratified using the RTOG's RPA criteria [10].

As suggested by inhomogeneous contrast enhancement on MRI images of GBM [12], a dynamic increase in its volume finds expression in a marginal expansion and a cumulative contribution of necrosis, haemorrhage foci as well as vascular and cystic areas in the central part of the tumour. Therefore, we hypothesized that a parameter that could better describe the population of viable proliferating malignant glioma cells, and consistently responsible for clinical effects, is not the total volume of the tumour but rather its surface area, which reflects the most external, actively growing portion of the neoplasm. Thus, the aim of this study was to evaluate the impact of the tumour surface area on survival of patients with both primarily inoperable and recurrent glioblastoma irradiated with ^{192}Ir implantation.

METHODS AND MATERIALS

Patient data

Between July 1999 and December 2003, 219 patients were treated with ^{192}Ir implantation for recurrent or primary malignant brain tumour at the Chair and Clinic of Oncology and Brachytherapy. In this group, the stereotactic biopsy results confirmed glioblastoma multiforme in 120 cases. Other tumours were histologically classified as: anaplastic astrocytoma (43 patients), metastasis (25 pts.), anaplastic oligoastrocytoma (14 pts.), anaplastic oligodendroglioma (10 pts.), anaplastic ependymoma (6 pts.) and gliosarcoma (1 pt.). The study group consisted of 120 patients with the diagnosis of glioblastoma multiforme: 48 (40%) had primarily inoperable tumour and were referred for EBRT after completion of brachytherapy; 72 (60%) had recurrent tumour and were previously treated with a combination of surgery and external beam radiotherapy (EBRT). The mean time to relapse was 68.7 weeks, range 4.7–232. In all patients conformal EBRT techniques and megavoltage linear accelerators were used. The EBRT total doses for primarily inoperable tumours ranged between 20 and 54Gy (mean 37.2 ± 11.2) given in 1.8–4.0Gy-size fractions to the tumour volume with a 3cm margin. The EBRT total doses for initially resected GBMs ranged between 20 and 60Gy (mean $53.2 \text{Gy} \pm 12.3$) given in 1.8–4.0Gy-size fractions to the primary tumour volume with the same margin.

Patients were selected for brachytherapy according to the following criteria: pathologic confirmation of GBM, $\text{KPS} \geq 50$, unifocal (except for 2 patients) supratentorial disease of a maximum size $\leq 6\text{cm}$, with no involvement of the corpus callosum, informed patient consent to implantation. The applicability of the method was assessed in each case by the radiation oncologist together with the neurosurgeon.

The clinical patient characteristics are given in Table 1. Seventy-four males (62%) and 46 females (38%) were implanted. The mean age of patients was 53.2 ± 11.6 years (range 28–76). The mean KPS score was 74.6 ± 14.1 (range 50–100).

Implantation and irradiation procedure

A day prior to implantation all patients underwent magnetic resonance imaging (MRI) with contrast medium (1.5 T scanner, Siemens). T1-weighted images (3mm-spaced) were substantially

Table 1. Patient characteristics (n=120).

| Variable | Value | |
|----------------------|-----------|----------|
| Age [years] | | |
| Mean | 53.2±11.6 | |
| Range | 28–76 | |
| KPS | | |
| Mean | 74.6±14.1 | |
| Range | 50–100 | |
| Sex | | |
| Male | 74 | (62.0%) |
| Female | 46 | (38.0%) |
| Tumour | | |
| Primarily inoperable | 48 | (40.0%) |
| Recurrent | 72 | (60.0%) |
| < 30cm ³ | 38 | (32.5%)* |
| ≥ 30cm ³ | 79 | (67.5%)* |
| < 90 cm ² | 59 | (50.4%)* |
| ≥90cm ² | 58 | (49.6%)* |

n=117.

transferred to the computer treatment planning system (BrainLAB, AG, Germany), in which tumour volume and the objects required for the fusion of MRI with CT scans (the eyeballs and pineal gland) were outlined by the radiation oncologist. On the day of implantation computed tomography (CT) was carried out using the stereotactic frame (BrainLAB, AG, Germany) affixed to the skull under local anaesthesia. CT images (5mm-spaced) were also transferred to the BrainLAB system and, after delineation of the fusion objects, they were automatically superimposed onto corresponding MRI scans. After image fusion the radiation oncologist together with the neurosurgeon planned the biopsy trajectory and radiation dose distribution. Stereotactic implantation was executed in the operating room under sedoanalgesia and preceded by tumour biopsy. A plastic tube (a canal for an internal catheter) was introduced through the skull twist drill hole to the determined depth and the tube's ends sutured to the scalp. The wound was protected with a chamber dressing fulfilled with crystalline penicillin, and corticosteroids as well as prophylactic antibiotics (3rd generation cephalosporin) were administered to patients until brachytherapy completion. The treatment started 1–2 days after implantation. Patients were irradiated in the brachytherapy room using the MicroSelectron

HDR (GENIE, Nucletron, The Netherlands). The ¹⁹²Ir stepping source was afterloaded into the internal catheter inserted directly before treatment into the implanted plastic tube and taken out after each fraction. Once brachytherapy had been completed, plastic tubes were removed by the radiation oncologist and the scalp wound was sutured.

The prescribed total radiation dose was 15Gy given in 5 fractions (1 fraction per day) to the volume of enhancing recurrent tumour or to the volume of enhancing primary tumour with a margin of 5mm. The radiation dose distribution parameters are given in Table 2. In each case we endeavoured to achieve conformity index (CI; the ratio of treated volume to target volume) <2.5 and coverage factor (CF; the proportion of the target volume covered by the reference isodose) >95%. In order to improve the dose distribution 33 patients (27%) were implanted with two catheters. Additionally, the minimal dose (D_{min}) within the target volume was determined, but it did not influence dose distribution planning.

Tumour volume and tumour surface area determination

Tumour volumes (TV) were calculated automatically by the BrainLAB software based on enhancing lesions manually delineated on MRI scans.

In order to determine tumour surface areas (TSA) the MRI slices with outlined target volumes were exported into the 3DDoctor software (Able Software Corp, USA) in the BMP format. Subsequently the bitmap series was transformed into the DICOM format and pixel sizes as well as interslice distances were edited. Finally the software algorithms of the formation of spatial tumour images (using the function of automatic segmentation and rendering) enabled the calculation of TV and TSA with a triangulation method (Figure 1).

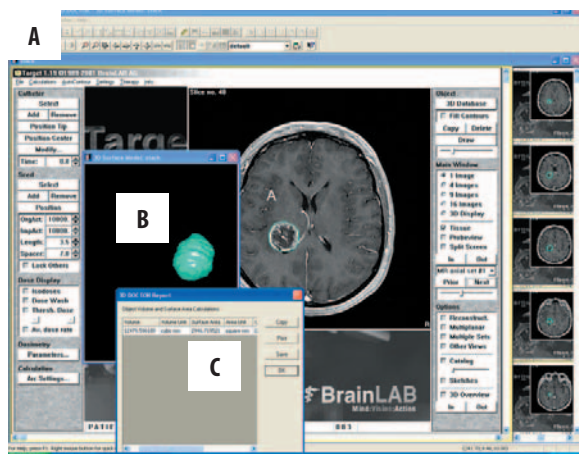
Additionally, we introduced a parameter called "sphericity index" (SI) to describe the irregularity of the tumour shape and also assess its impact on survival. We defined SI as a quotient of two surface areas: of the tumour, and of a sphere having the same volume.

Statistical methods

The correctness of TSA calculations was estimated by determining the correlation between TVs

Table 2. Dose distribution parameters.

| | Mean | Minimum | Maximum | Standard deviation |
|-----------------------|------|---------|---------|--------------------|
| Conformity Index [%] | 2.3 | 1.3 | 7.6 | 0.8 |
| Coverage Factor | 96.7 | 83.0 | 100.0 | 3.2 |
| D _{min} [Gy] | 11.0 | 5.0 | 19.0 | 3.1 |

**Figure 1.** 3DDoctor software – delineated MRI image of a tumour (A), spatial image (B) and results of TV and TSA calculations (C).

calculated with the 3DDoctor software and those obtained from the BrainLAB system using linear regression analysis.

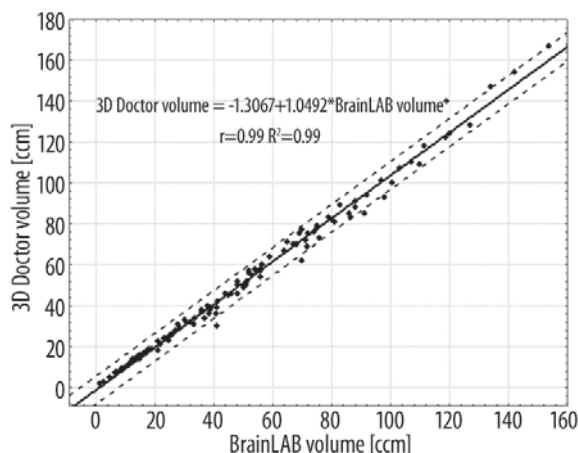
The Kaplan-Meier method was employed to assess survival rates from the day of implantation to the time of patient death or the date of the analysis. Survival data of the specified subgroups of patients were compared using the log-rank test. In order to evaluate variables affecting survival, univariate and multivariate analyses were performed using the Cox proportional hazards model. The fitting of multivariate analyses was estimated with the Chi² test.

All statistical analyses were performed using the software Statistica 7.1 (StatSoft Inc., Tulsa, USA).

RESULTS

We analysed 117 cases (97.5%) out of the 120 that entered the study due to the impossibility of retrieving radiological data of 3 patients. The mean follow-up time was 8.9 months (range 0.3–70.8). There were 4 censored and 113 complete observations.

The mean TV computed with the 3DDoctor software was 50.6cm³±34.2 (range 1.5–153), corresponding to a sphere diameter of approximately

**Figure 2.** Relationship between tumour volumes calculated with the 3DDoctor software and tumour volumes obtained from the BrainLAB system.

4.3cm±1.13 (range 1.5–6.8). The mean TSA was 94.5cm²±51.4 (range 4.3–247). There was a high correlation between TVs calculated with the 3DDoctor software and those obtained from the BrainLAB system (R=0.99; p<0.001; Figure 2). Thus, we assumed that TSA assignment was not burdened with a meaningful error. Tumour volumes were stratified as <30cm³ and ≥30cm³. There were 38 (32.5%) analysed patients with TV <30 cm³ and 79 (67.5%) with TV ≥30cm³. Tumour surface areas were stratified as <90 cm² and ≥90cm². There were 59 (50.4%) patients with TSA <90cm² and 58 (49.6%) with TSA ≥90cm². The calculated tumour parameters are given in Table 3.

For the total group of 120 patients 1-year and 2-year survival were 22% and 11%, respectively, with a median survival time (MST) of 6.1 months (range 0.26–70.8; Figure 3). For the subgroup of patients suffering from recurrent GBM 1-year survival was 26%, 2-year survival 13%, and MST 6.9 months (range 0.36–70.8). For the subgroup of primary GBMs they were, respectively, 17%, 7%, and 4 months (range 0.26–30.1). There was a statistically significant difference in survival between the subgroups (p=0.0038; Figure 4).

Since individuals with recurrent tumours had longer survival than those with primarily

Table 3. Tumour parameters.

| | Mean | Minimum | Maximum | Standard deviation |
|--|------|---------|---------|--------------------|
| Tumour volume [cm ³] | 50.6 | 1.5 | 153.8 | 34.2 |
| Tumour surface area [cm ²] | 94.5 | 4.3 | 247.0 | 51.4 |
| Sphericity index | 1.5 | 1.24 | 2.6 | 0.26 |

Table 4. Univariate analysis of prognostic variables – Cox proportional hazards model.

| | Beta coefficient | Standard error | Hazard ratio | p |
|--|------------------|----------------|--------------|-------|
| Age | 0.03 | 0.01 | 1.03 | 0.001 |
| KPS | -0.03 | 0.01 | 0.97 | 0.003 |
| Tumour volume [cm ³] | 0.03 | 0.01 | 1.03 | 0.001 |
| Tumour surface area [cm ²] | 0.01 | 0.002 | 1.01 | 0.002 |
| Coverage Factor | -0.05 | 0.14 | 0.95 | 0.69 |
| Conformity Index [%] | 0.03 | 0.16 | 1.03 | 0.85 |
| Dmin [Gy] | 0.003 | 0.001 | 1.00 | 0.09 |
| Sphericity index | 0.44 | 0.38 | 1.5 | 0.2 |

Table 5. Multivariate analysis of prognostic variables – Cox proportional hazards model ($Chi^2=22.98; p=0.000041$).

| | Beta coefficient | Standard error | Hazard ratio | p |
|---------------------|------------------|----------------|--------------|-------|
| Age | 0.03 | 0.01 | 1.03 | 0.002 |
| KPS | -0.02 | 0.01 | 0.98 | 0.04 |
| Tumour surface area | 0.004 | 0.0001 | 1.004 | 0.04 |

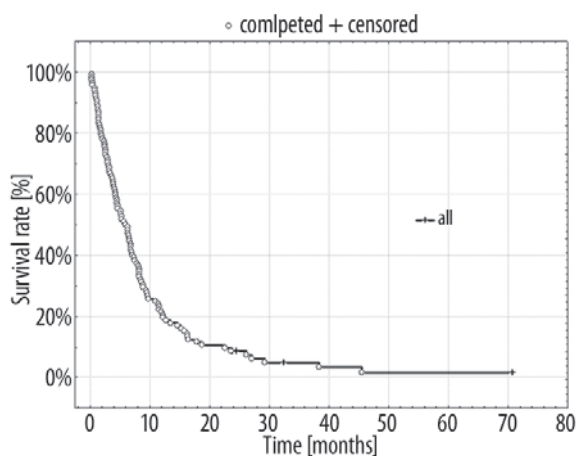


Figure 3. Survival of the total group of patients (n=120).

inoperable GBMs we decided to analyse both subgroups together. Only after combining them did a statistical significance of prognostic factors, other than age and KPS score, appear. As shown in Table 4, in the univariate Cox mod-

el there were four variables which we identified to significantly affect survival: patient age ($p=0.001$), performance status ($p=0.003$), tumour volume ($p=0.001$) and tumour surface area ($p=0.002$). No radiation dose distribution parameters (CI, CF, D_{min}) appeared to predict survival. The two multivariate Cox analyses performed displayed different fit determined by the Chi² test. The analysis of better adjustment ($Chi^2=22.98; p=0.000041$) distinguished such variables as: patient age ($p=0.002$), performance status ($p=0.04$) and tumour surface area ($p=0.04$; Table 5) to be significant and independent predictors of survival. Patients with TSA $<90\text{cm}^2$ had significantly better prognosis compared to those with TSA $\geq 90\text{cm}^2$ ($p=0.00038$). One-year and 2-year survival and MST for the former subgroup were 38%, 19% and 8.5 months, whereas the corresponding values for the latter subgroup were 10%, 2% and 4.5 months (Figure 5). In the multivariate Cox analysis of worse fitting ($Chi^2=22.78; p=0.000045$) patient age, KPS score

Table 6. Multivariate analysis of prognostic variables – Cox proportional hazards model ($Chi^2=22.78; p=0.000045$).

| | Beta coefficient | Standard error | Hazard ratio | p |
|---------------|------------------|----------------|--------------|-------|
| Age | 0.03 | 0.01 | 1.03 | 0.001 |
| KPS | -0.02 | 0.01 | 0.98 | 0.05 |
| Tumour volume | 0.01 | 0.003 | 1.001 | 0.04 |

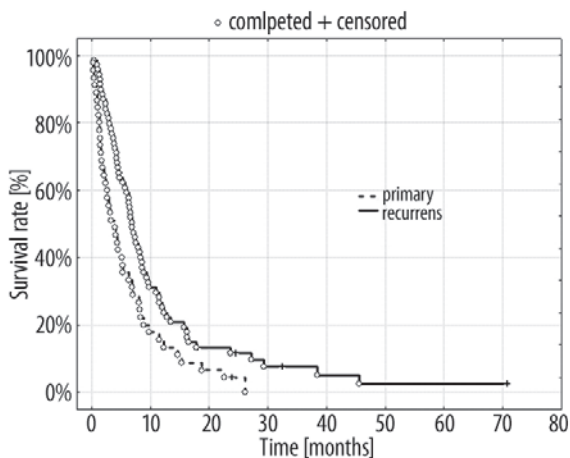


Figure 4. Survival of patients according to tumour characteristic. Solid line – patients with recurrent tumours; dashed line – patients with primarily inoperable tumours. Log-rank test was significant ($p=0.0038$).

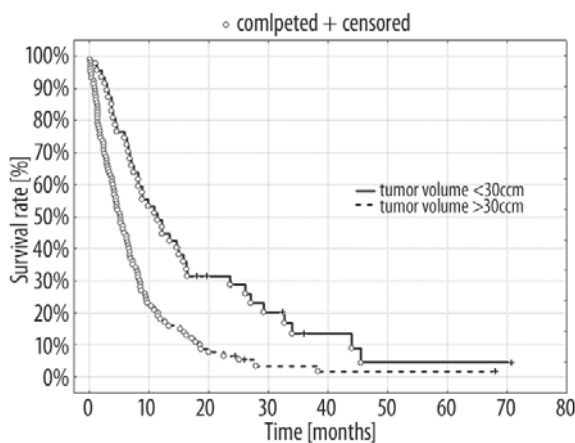


Figure 6. Survival of patients according to tumour volume. Solid line – patients with TV $<30cm^3$; dashed line – patients with TV $\geq 30cm^3$. Log-rank test was significant ($p=0.0003$).

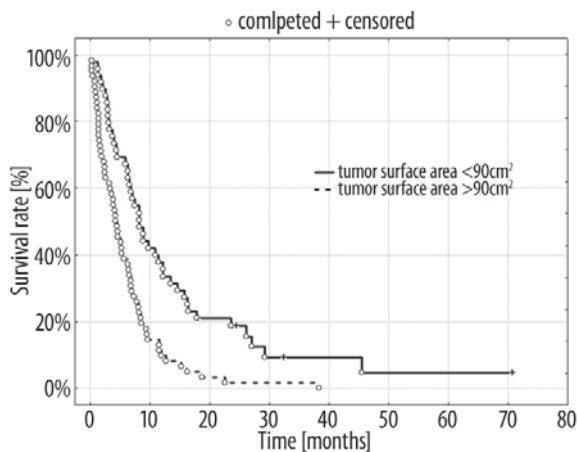


Figure 5. Survival of patients according to tumour surface area. Solid line – patients with TSA $<90cm^2$; dashed line – patients with TSA $\geq 90cm^2$. Log-rank test was significant ($p=0.0038$).

and tumour volume appeared to significantly affect survival ($p=0.001, 0.047$ and 0.042 , respectively; Table 6). Patients with smaller TVs ($<30cm^3$) displayed significantly better survival outcomes ($p=0.0003$; 1-year and 2-year survival and MST were 48%, 25% and 11.4 months, respectively) compared to those with TVs $\geq 30cm^3$ (17%, 5% and 5.3 months, respectively; Figure 6).

DISCUSSION

The complex biological characteristics of GBM, including high proliferation rate [13], striking motility [14], great contribution of hypoxic cells [15] and rapid neoangiogenesis [16], is commonly considered to be responsible for the invariably poor prognosis of affected patients. Determining variables that would relate to natural GBM features as well as being clinically available seems to be a key to the choice of optimal patient management. The tumour surface area reflects the marginal tumour expansion and can be relatively easily obtained from MRI data. Since the radiographic image of GBM suggests that its central portion is mainly occupied by necrotic, vascular, haemorrhage and cystic areas, we assumed that the most external tumour layer, which TSA mathematically describes, might determine treatment failure. In fact, we demonstrate in our study that TSA is an independent prognostic factor in implanted GBM patients. In this highly selected and uniformly treated group TSA less than $90cm^2$ predicts significantly better prognosis than TSA $\geq 90cm^2$. Indeed, the statistical analysis also confirmed the recent reports on the prognostic value of GBM volume [10,11]; however, the Chi^2 test indicated TSA as a parameter that better describes

survival outcomes of patients treated with brachytherapy techniques. Our findings seem to be consistent with the conclusions of the RTOG recursive analysis. Its results did not identify tumour size itself as a factor of prognostic value [9], but, similarly to other studies [17–19], distinguished the extent of GBM surgical resection as one of the survival predictors. One can assume that the unfavourable effect of insufficient cytoreduction on survival results from the presence of residual disease mainly on the periphery of the originally detected tumour. In this context both the completeness of neoplasm tissue removal and TSA describe the impact of marginal tumour zone on treatment efficiency.

In our opinion TSA appeared to be a prognostic variable since it relates not only to a peripheral purely cellular active layer of neoplasm but it also reflects, which may be even more important, a characteristic GBM feature of massive microscopic invasion. As several histological analyses have shown, malignant gliomas cannot be considered as strictly solid tumours since they display an enormous capacity for intracerebral dissemination [20–22]. Experimental studies have demonstrated that the size of the area of microscopic tumour cell invasion remains relatively stable and is approximately 2.5 times greater than the area outlined by the solid tumour mass [23]. TSA may give us then indirect information, which we cannot obtain from radiographic data (CT/MRI), of the extent of GBM spread and thus may be helpful in predicting patient prognosis. Spectacular examples of this dependence were in our study two cases of multifocal disease. Although this is a condition commonly considered to be a contraindication to brachytherapy, we decided to implant two young patients with bifocal GBM and a high KPS score. The volumes of single foci were small but their total TASs were high, which found a reflection in the short survival times of both patients (1.1 and 5.6 months).

It is a little surprising that the study results did not confirm the impact of the tumour shape (expressed as the sphericity index) on survival, especially as the irregular pattern of infiltration has been stressed to be one of GBM's features unfavourably affecting patient prognosis. However, if we assume that the extent of the spread of neoplasm cells depends on TSA, the shape of a given tumour area seems to have minor importance.

Since the commonly used imaging modalities (CT/MRI) do not allow one to assess precisely

the boundaries of malignant glioma, TSA may be considered as a kind of indicator of the intracerebral extent of a tumour and thus a predictor of survival in patients treated with brachytherapy for primary and recurrent glioblastoma. To our best knowledge this is the first study demonstrating significantly better prognosis for a GBM surface area less than 90cm².

CONCLUSIONS

Tumour surface area is an independent prognostic factor in patients with primary and recurrent glioblastoma irradiated with ¹⁹²Ir implantation. TSA <90cm² predicts significantly better survival, with a median survival time of 8.5 months. TSA appears to be a more powerful prognostic variable than tumour volume.

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