The Importance of Tumor Volume in the Prognosis of Patients with Glioblastoma

Comparison of Computerized Volumetry and Geometric Models

Georgios Iliadis[1], Panagiotis Selviaridis[2], Anna Kalogera-Fountzila[3], Anna Fragkoulidi[4], Dimos Baltas[5], Nikolaos Tselis[5], Athanasios Chatzisotiriou[2], Despina Misailidou[1], Nikolaos Zamboglou[5], George Fountzilas[4]

Background and Purpose: The importance of tumor volume as a prognostic factor in high-grade gliomas is highly controversial and there are numerous methods estimating this parameter. In this study, a computer-based application was used in order to assess tumor volume from hard copies and a survival analysis was conducted in order to evaluate the prognostic significance of preoperative volumetric data in patients harboring glioblastomas.
Patients and Methods: 50 patients suffering from glioblastoma were analyzed retrospectively. Tumor volume was determined by the various geometric models as well as by an own specialized software (Volumio). Age, performance status, type of excision, and tumor location were also included in the multivariate analysis.
Results: The spheroid and rectangular models overestimated tumor volume, while the ellipsoid model offered the best approximation. Volume failed to attain any statistical significance in prognosis, while age and performance status confirmed their importance in progression-free and overall survival of patients.
Conclusion: Geometric models provide a rough approximation of tumor volume and should not be used, as accurate determination of size is of paramount importance in order to draw safe conclusions in oncology. Although the significance of volumetry was not disclosed, further studies are definitely required.

Key Words: Glioblastoma multiforme · Volumetry · Survival analysis · Volumio · Prognostic factors

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Tumorvolumen als prognostischer Faktor für Patienten mit Glioblastoma. Vergleich der computerbasierten Volumetrie mit geometrischen Modellen

Hintergrund und Ziel: Die Bedeutung des Tumorvolumens als prognostischer Faktor für maligne Gliome ist nach wie vor umstritten. In dieser Studie wurden eine computerbasierte Methode zur Beurteilung des Tumorvolumens anhand von magnetresonanztomographischen Bildern bei Patienten mit Glioblastoma multiforme (GBM) durchgeführt und mittels einer Überlebensanalyse die prognostische Bedeutung präoperativer volumetrischer Daten untersucht.
Patienten und Methodik: 50 Patienten mit GBM, welche zwei unterschiedliche Chemotherapieregime erhalten hatten, wurden retrospektiv analysiert und die Tumorvolumina durch verschiedene geometrische Modelle sowie eine spezielle Software (Volumio) gemessen. Alter, Performance-Status, Tumorlokalisation sowie Art der Exzision wurden in der multivariaten Überlebensanalyse berücksichtigt.
Ergebnisse: Die angewandten sphäroiden und rektangulären geometrischen Modelle überschätzten das Tumorvolumen, wohingegen die ellipsoiden Modelle die beste Annäherung im Vergleich zu Volumio ermöglichten. Das Tumorvolumen erwies sich nicht als statistisch signifikanter Prognosefaktor. In der multivariaten Analyse bestätigte sich die Bedeutung des Alters und des Performance-Status für das progressionsfreie Überleben und das Gesamtüberleben der Patienten.

[1]Department of Radiation Oncology, "Papageorgiou" General Hospital, Thessaloniki, Greece,
[2]Department of Neurosurgery, "AHEPA" Hospital, Aristotle University of Thessaloniki, School of Medicine, Greece,
[3]Department of Radiology, "AHEPA" Hospital, Aristotle University of Thessaloniki, School of Medicine, Greece,
[4]Department of Medical Oncology, "Papageorgiou" General Hospital, Aristotle University of Thessaloniki, School of Medicine, Greece,
[5]Department of Radiation Oncology, Klinikum Offenbach, Germany.

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Schlussfolgerung: Geometrische Modelle bieten eine ungenaue Messung des Tumorvolumens und sollten in der klinischen Praxis nicht zur Anwendung kommen, zumal die präzise Erfassung der Tumorgröße von entscheidender onkologischer Bedeutung ist. Obwohl die vorgelegten Daten den Einfluss des Tumorvolumens als statistisch nicht signifikant zeigten, sind weitere Studien bezüglich der Bedeutung dieses Parameters notwendig.

Schlüsselwörter: Glioblastoma multiforme · Volumetrie · Überlebensanalyse · Volumio · Prognostische Faktoren

Introduction

Glioblastoma is one of the most devastating tumors. Despite modern radiotherapy techniques [4, 5, 7, 8, 16, 19] and various chemotherapeutic regimens [10, 17, 22], the overall survival remains poor, with a median survival of 12–15 months and a small fraction of patients living > 2 years. The most important prognostic factors, which have so far been identified and are well established in the literature, include the age and the performance status (PS) [4, 13–15]. It has long been held that tumor volume comprises an important factor as well, although the importance of this belief remains contradictory in brain tumor research [6, 23, 24].

Several attempts have been described correlating outcome with tumor volumetry data. Volume has been estimated using formulas and assuming that the shape of the tumor was rectangular, spherical, or ellipsoid. There are two issues, however, concerning the importance of tumor volume. On the one hand, the less accurate geometric tumor measurements in most of these studies may cause inconsistent and less reliable results. In order to eliminate subjectivity, computerized image processing has been developed [1, 3, 20, 21]. On the other hand, even with accurate assessments, the importance of this factor per se is again contradictory in the literature. Preoperative tumor volume of high-grade gliomas correlated significantly with patient survival in one study [24], whereas it had no effect in another [13].

In the present study, we retrospectively reviewed data from patients suffering from glioblastoma in order to assess the effect of preoperative tumor volume on their survival. Tumor volumes were estimated with the traditional geometric models along with an application that was particularly developed for this reason aiming to overcome the frequently encountered problem of the heterogeneity of radiologic examinations.

Patients and Methods

Patients and Treatment

50 patients with glioblastoma multiforme (WHO [World Health Organization] grade IV) were treated between December 2000 and March 2007 in our institution and were included in two different chemotherapy treatment protocols. All received chemotherapy concurrent and adjuvant to radiation therapy: 24 patients with temozolomide and irinotecan and 26 patients only with temozolomide. All patients underwent partial-brain radiotherapy with linear accelerator to a median total dose of 60 Gy (20–62 Gy).

Tumor Volumetry and Geometric Tumor Volume Measurements

For our measurements, we used the T1-weighted gadolinium-enhanced magnetic resonance (MR) images, acquired within 1 week before surgery. The tumor was considered to be the contrast-enhancing area, including any region of central necrosis. All images were assessed by the same experienced radiation oncologist.

Geometric Models Estimation

Tumor volume was initially calculated using the spheroid, ellipsoid, and rectangular formulas. Briefly, according to the spherical model, the volume is defined as $1/6\ \pi D^3$, where D is the diameter of the maximum cross-sectional area on the MR image [24]. The ellipsoid model defines volume as $1/6\ \pi$ ABC, where A, B, C represent diameters in the three axes of the tumor [6]. Finally, the rectangular formula estimates the volume as a multiplication of the three diameters ABC [1].

Computer-Based Tumor Volume Estimation

Since the preoperative scans were only available in hard copies, these were digitized by means of a commercial high-resolution scanner and then saved in "tiff" (tagged image file) format. This resulted in each image including multiple slices of a particular MR sequence. In order to create a separate image for each MR slice and to convert these images to the widely used DICOM (Digital Imaging and Communications in Medicine) format, a specialized software called dMed (pi-Medical, Athens, Greece) was used, by means of which the original "tiff" images were cut down into smaller images, which now included only one MR slice per image (Figure 1). dMed allows image rotation with an accuracy of a tenth of a degree. In this way, slight differences in image orientation during scanning can be anticipated. Subsequently, the tools from the dMed software were used in conjunction with the scale marked on the MR scan to calculate the true pixel dimensions (x, y). Finally, the sum of the slice thickness plus the slice spacing (z) noted on the MR slices was manually added to the DICOM header. At that point, usable DICOM images were available and were imported into a different software called Volumio (MedCom, Darmstadt, Germany) for further calculations. In Volumio (Figure 2), the investigator would then contour the VOI (volume of interest) on each MR slice. Once the contouring of the VOI was complete, the software was able to calculate the volume of the VOI using the following formula:

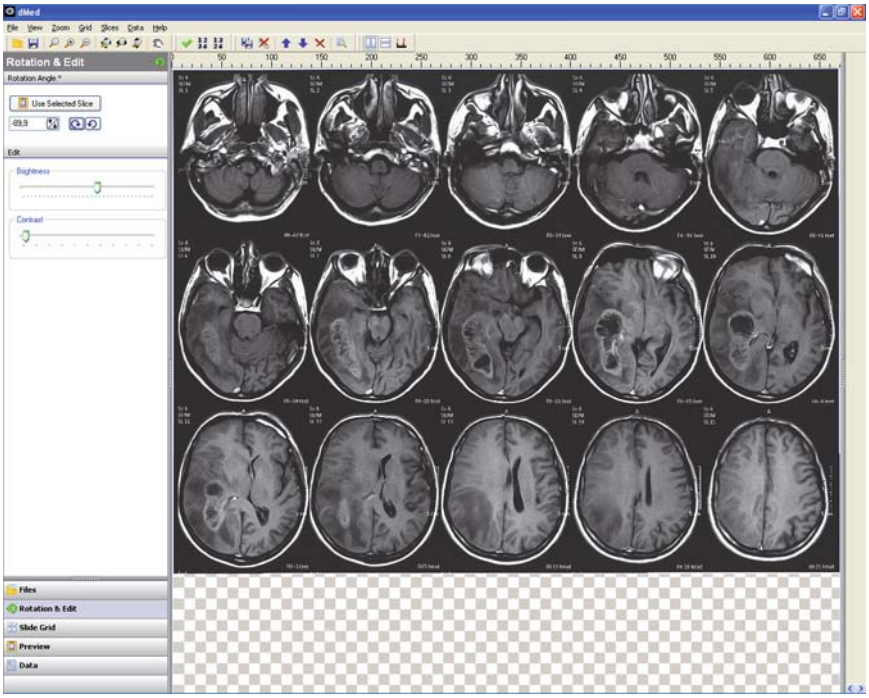


Figure 1. dMed user interface.

Abbildung 1. dMed-Nutzerschnittstelle.

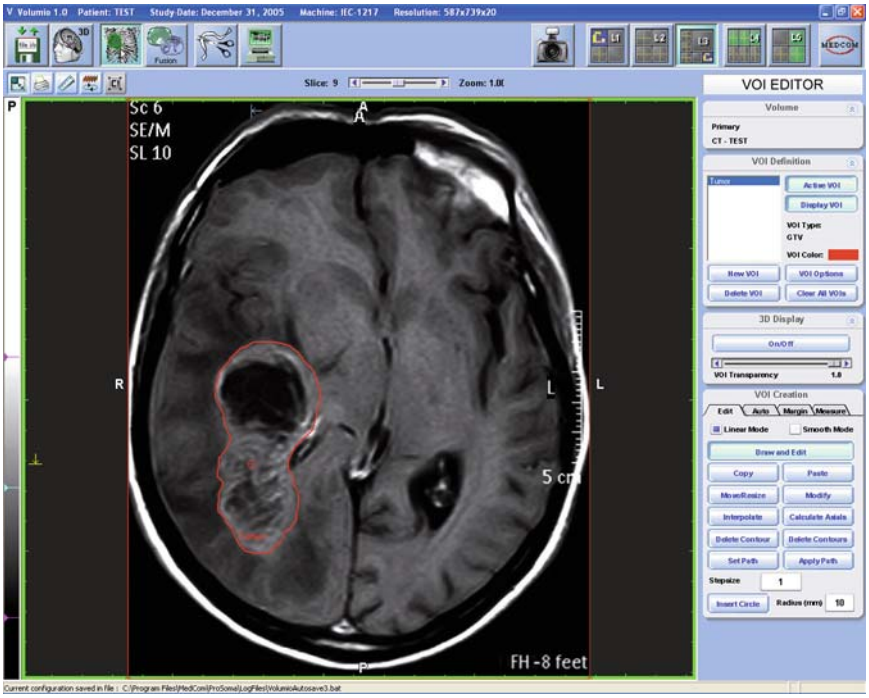


Figure 2. Volumio user interface.

Abbildung 2. Volumio-Nutzerschnittstelle.

$$V = \Sigma S_i * z,$$

where V is the volume of the VOI, S_i the surface included by the contour of the VOI on each slice, and z the slice thickness. The accuracy of this method is inversely proportional to slice thickness.

Statistical Analysis

Correlation of the geometric models with the actual tumor volume, as estimated by using our software (Volumio), was performed using the Spearman correlation coefficient method. Agreement of the mathematically calculated volume with the computer-estimated volume was assessed through the Bland-Altman method. Moreover, tumors were separated in two categories based on the median value of each method of volume estimation. Agreement of the categorized tumor volume was assessed by the kappa coefficient method. The overall agreement was also evaluated.

The Kaplan-Meier method was used to estimate survival and progression-free survival (PFS) time distributions. Comparisons were performed using the log-rank test.

Univariate Cox analysis was performed in order to investigate the impact of tumor volume, as assessed by the software, on patient survival. Multivariate Cox analysis followed. Variables included were sex, age, PS (0–1/2–3), type of excision (biopsy/subtotal/total), group of treatment (chemotherapy with temozolomide and irinotecan or only with temozolomide), and tumor volume (above median, below median) as given by all methods under consideration. Variables selection was performed by the backward selection method based on the likelihood ratio test.

For all tests, $\alpha = 0.05$ level of significance was used. Analysis was conducted using SPSS 16 (SPSS Inc., Chicago, IL, USA).

Results

The patients' characteristics are shown in Table 1, along with tumor location

and PS. There were 34 males and 16 females with a median age of 59 years. The preoperative PS was < 2 in 36 (72%). All patients had surgical tissue diagnosis. 47 had undergone craniotomy and open biopsy followed by maximum feasible tumor resection (18 complete resections, 13 partial resections, and 16 biopsies) and three received stereotactic biopsies (Table 2). The median follow-up was 29.7 months (2–32 months).

Table 1. Selected patient characteristics. PS: performance status.
Tabelle 1. Patientendaten. PS: performance status.

	Patients n (%)
Age (years) [median (range)]	59 (34–76)
Sex	
Male	34 (68)
Female	16 (32)
PS	
0	23 (46)
1	13 (26)
≥ 2	14 (28)
Location	
Temporal	21 (42)
Parietal	17 (34)
Occipital	3 (6)
Frontal	9 (18)
Deep	3 (6)

Table 2. Treatment.
Tabelle 2. Behandlungsdaten.

Treatment	Patients n (%)
Surgery	
• Complete resection	18 (36)
• Partial resection	13 (26)
• Biopsy	16 (32)
• Stereotactic biopsy	3 (6)
Radiotherapy	
• Total dose (Gy) [median (range)]	60 (20–62)
Chemotherapy	
• Temozolomide + irinotecan	24 (48)
• Temozolomide	26 (52)

Table 3. Tumor dimensions before surgery.
Tabelle 3. Präoperative Tumorausmaße.

	Median (range)
Diameter	
Maximum (cm)	4.8 (2.2–7.9)
Mean (mm)	4.1 (1.9–6.0)
Volume	
Ellipsoid (cm^3)	36.7 (3.7–111.2)
Spheroid (cm^3)	57.9 (5.6–258.0)
Rectangular (cm^3)	70.2 (7.0–212.5)
Volumio (cm^3)	33.9 (3.4–95.9)

Estimation of Tumor Volume

Tumor volume as evaluated by the various geometric models as well as our software (Volumio) is shown in Table 3. The correlation between Volumio and each geometric model is depicted in the scatterplots in Figure 3 and the average of ellipsoid, spheroid, rectangular volume and volumetry against the corresponding difference is shown in Figure 4. It is clearly indicated that the spheroid and rectangular models overestimate tumor volume (median volume was 70.2 and 57.9 ml for rectangular and spheroid vs. 36.7 and 33.9 ml for the ellipsoid and the Volumio, respectively), whereas the ellipsoid model offers the best approximation. In order to evaluate the effect of tumor volume, patients were divided into two subgroups (large/small tumors), with the median volume, according to each model, as the cutoff point. In this way, the kappa coefficient between the Volumio and the spheroid was 0.76 ($p < 0.001$) with an overall agreement of 88% versus 0.84 ($p < 0.001$) for the ellipsoid and rectangular with an agreement of 92%.

Length of Survival

Median PFS for all patients was 11.4 months (range, 5.8–16.9 months), 15.4 (5.4–25.4 months) for the small-tumor subgroup and 9.4 (5–13.8 months) for the bigger ones (Figure 5). Median overall survival for all patients from the time of operation was 13.8 months (9.4–18.2 months); 13.8 (12–15.6 months) and 15 (6.3–23.7 months) for small and large tumors, respectively (Figure 6).

Analysis of Factors of Survival

As shown in Table 4 concerning univariate Cox analysis, tumor volume, as estimated by all models, was not found to be a significant predictor for patient survival (although with Volumio the hazard ratio attained a value of 1.31 vs. 1.08/1.09/1.08 for ellipsoid, spheroid, and rectangular models, respectively). In the multivariate analysis which followed (Table 5), the well-established parameters of age and functional status were confirmed to comprise significant predictors for PFS and overall survival, as well as the type of treatment followed. Sex and type of excision did not show any prognostic significance.

Discussion

The issue of whether initial tumor volume has an important contribution to patient survival is highly controversial. This paper correlates preoperative tumor volume, assessed by various geometric models and a specialized software tool used in our institution, with the survival time of patients harboring glioblastomas. The conclusion is that the spheroid and the rectangular models greatly overestimate tumor volume and this difference was amplified in the large tumor group. Inter-

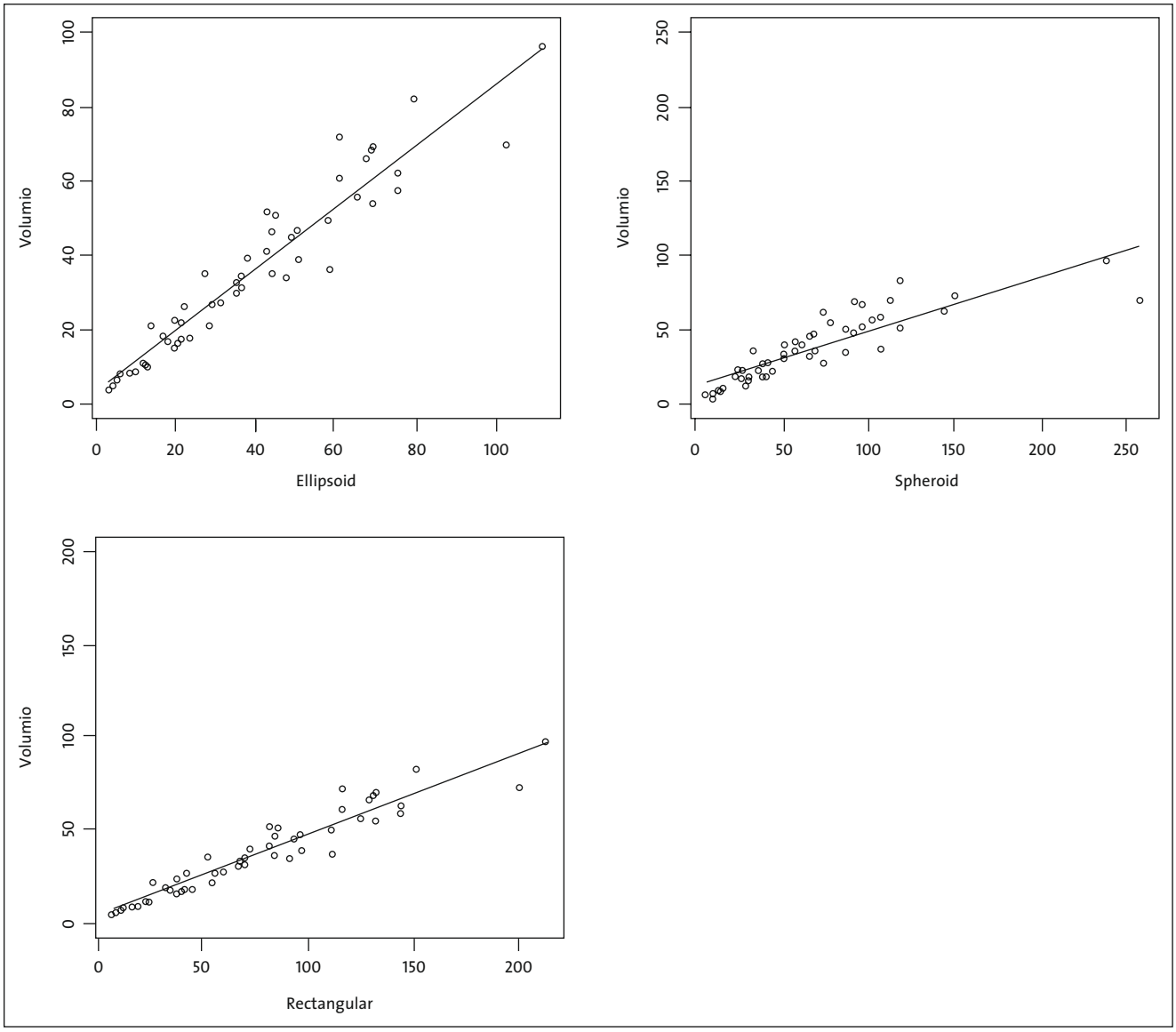


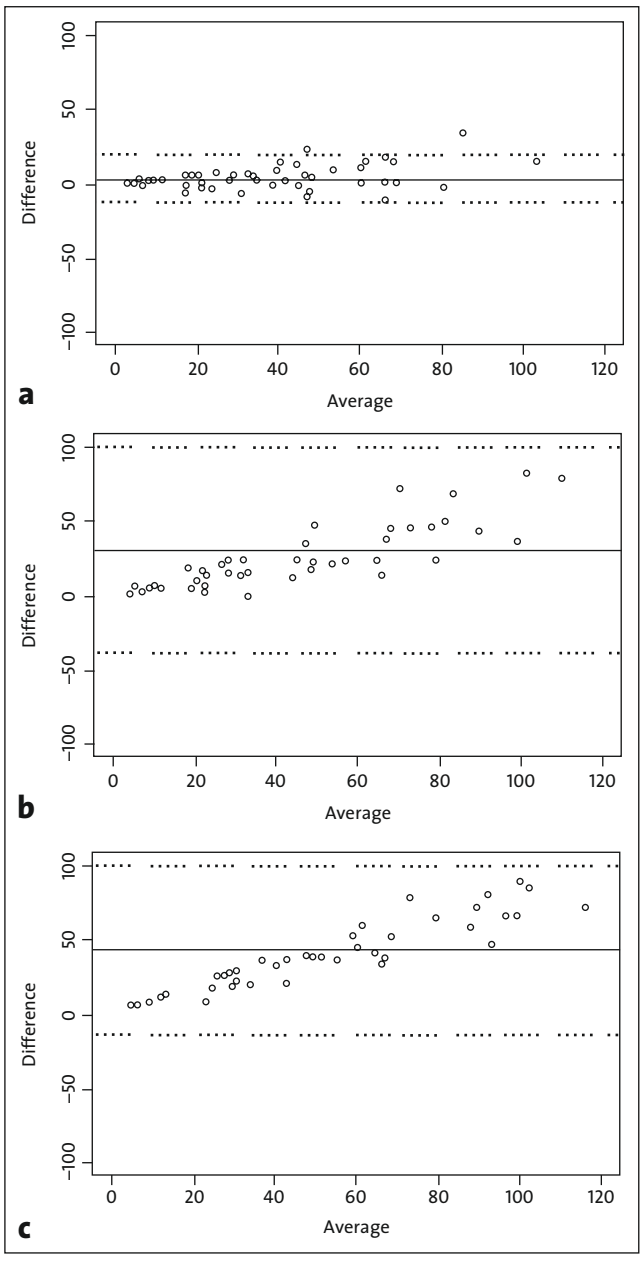
Figure 3. Linear regression analysis for the volume estimated by Volumio against the volume calculated by the geometric formulas. Volumio = 2.54 + 0.84*ellipsoid, Volumio = 11 + 0.37*spheroid, Volumio = 2.54 + 0.44*rectangular.

Abbildung 3. Lineare Regressionsanalyse für die durch Volumio gemessenen Volumina im Vergleich zur Volumenkalkulation auf der Basis geometrischer Modelle. Volumio = 2,54 + 0,84*ellipsoid, Volumio = 11 + 0,37*sphäroid, Volumio = 2,54 + 0,44*rektangulär.

estingly, the ellipsoid model provided the best approximation compared to our software.

In a large tertiary neurooncologic center, MRI scans are highly heterogeneous (hard copies or compact disks, different slice thickness, orientation, etc.) and a tool for accurate quantitative volume information is needed. Assumptions based on visual intraoperative impression of tumor removal or qualitative rough comparison between pre- and postoperative scans, are considered obsolete and result in erroneous estimation of tumor volume. For all these reasons, we had to develop a method for processing the images in order to obtain a uniform neuroimaging data file for the quantitative grading of glioblastomas. In addition, although similar software is readily included in most radiotherapy treatment-planning systems, this tool may easily be used by other physicians implicated in oncologic practice.

There are certainly some drawbacks which are difficult to overcome. As it has been pointed out in a study similar to ours [3], factors which may cause variations in the determined volume and should be taken into consideration, are the zoom, window and level settings, resolution of the image, tilt of the patient's head, or even the amount of contrast medium given.



Figures 4a to 4c. Average of ellipsoid (a), spheroid (b), rectangular (c) volume and Volumio against the corresponding difference. Solid horizontal line corresponds to the mean difference, while the dotted horizontal lines correspond to mean difference ± 2 SD (standard deviations). Inspecting plots b and c, it is obvious that spheroid and rectangular models overestimate tumor volume. Specifically, the larger the tumor volume, the greater the overestimation.

Abbildungen 4a bis 4c. Durchschnittliche Volumina nach der ellipsoiden (a), sphäroiden (b) und rektangulären (c) Methode sowie auf der Basis von Volumio gegen die jeweils entsprechenden Differenzen. Die durchgehende horizontale Linie entspricht der durchschnittlichen Differenz. Die gepunktete horizontale Linie zeigt die durchschnittliche Differenz ± 2 SD (Standardabweichungen). Die Plots b und c zeigen, dass die Tumorgröße von den sphäroidalen und rektangulären geometrischen Modellen überschätzt wird, wobei die Abweichung analog der Tumorgröße zunimmt.

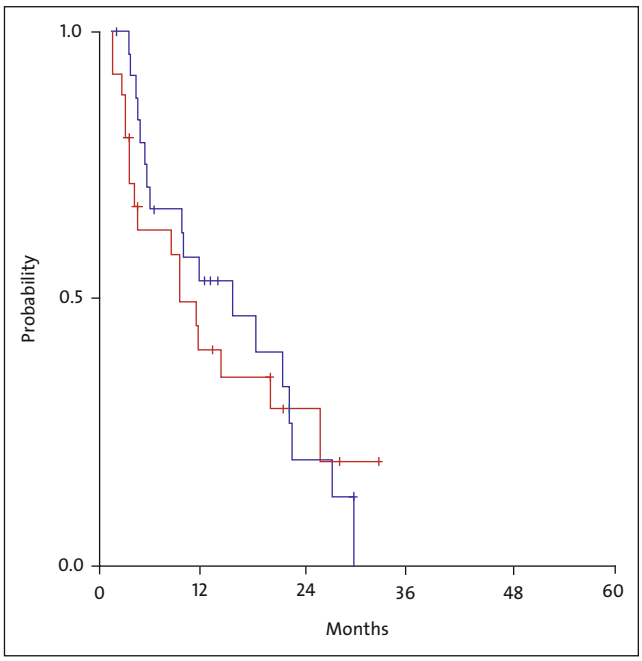


Figure 5. Progression-free survival for patients with Volumio-estimated tumor volume above median (red line) versus patients with Volumio-estimated tumor volume below median (blue line).

Abbildung 5. Progressionsfreies Überleben für Patienten mit Volumio-Tumorvolumina über dem Median (rote Linie) im Vergleich zu Patienten mit Volumio-Tumorvolumina unter dem Median (blaue Linie).

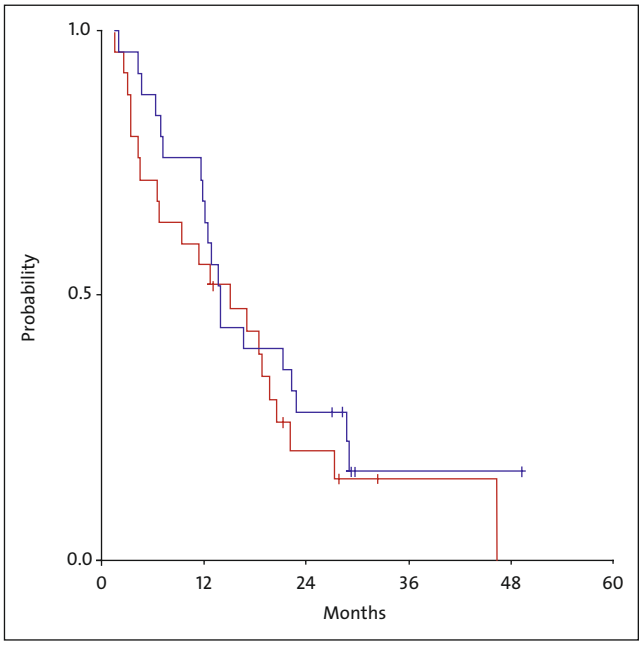


Figure 6. Overall survival for patients with Volumio-estimated tumor volume above median (red line) versus patients with Volumio-estimated tumor volume below median (blue line).

Abbildung 6. Gesamtüberleben für Patienten mit Volumio-Tumorvolumina über dem Median (rote Linie) im Vergleich zu Patienten mit Volumio-Tumorvolumina unter dem Median (blaue Linie).

Regarding the technical aspect of volumetric estimation, in previous studies [12, 18], the tumor outlines were first traced on the films and were afterwards digitized. By following this procedure it is impossible to realize possible mistakes during digitization, since the actual tumor cannot be concurrently observed on the CT (computed tomography) or MRI scans and the electronic images produced. So even if the traced contours are correct, this method of measurement cannot be validated. Moreover, this procedure is time-consuming and there is no flexibility in adjusting the contour.

In another study of Shi et al. [21], MRI scans were directly incorporated from the scanner in the personal computer application program, thus obviating the need for slide scanning. This method is far more accurate, as it bypasses the usual errors upon image manipulation, but there is the prerequisite of performing the MRI scan in the same institution and having all files in DICOM format. Moreover, this method cannot be used in order to perform retrospective studies as one should be able to take advantage of previous hard-copy data files.

Concerning the impact of the actual volume on prognosis, we concluded that, despite the inaccuracies stemming from the various methods of volumetric assessment, when tumors are grouped according to size, the correlation between the various techniques is very strong. In other words, the distinction of large and small tumors remains the same, independently of the appreciation method. Subsequently, it seems straightforward that the introduction of tumor volume as a categorical variable in survival data does not yield a statistically significant difference, whatever the estimation method may be.

Table 4. Univariate Cox analysis for the association of tumor dimensions and prognosis. All hazard ratios (HR) correspond to the comparison of tumor categories based on the median of each measure. Tumor dimensions, calculated by any of the considered methods, were not shown to affect patients' prognosis (all p-values > 0.05). CI: confidence interval; PFS: progression-free survival.

Tabelle 4. Univariate Cox-Analyse für die Korrelation zwischen Tumorgröße und Prognose. Hazard Ratios (HR) entsprechen dem Vergleich von Tumorkategorien auf der Grundlage der Medianwerte der einzelnen Tumorausmaße. Die Tumorgröße, gemessen durch die angewandten Methoden, erwies sich als ohne signifikante prognostische Bedeutung (alle p-Werte > 0,05). CI: Konfidenzintervall; PFS: progressionsfreies Überleben.

	Survival HR	95% CI for HR	p-value	PFS HR	95% CI for HR	p-value
Mean diameter	1.08	0.58–1.99	0.815	0.96	0.49–1.88	0.913
Maximum diameter	1.09	0.59–2.02	0.783	0.93	0.48–1.82	0.838
Ellipsoid	1.08	0.58–1.99	0.815	0.96	0.49–1.88	0.913
Spheroid	1.09	0.59–2.02	0.783	0.93	0.48–1.82	0.838
Rectangular	1.08	0.58–1.99	0.815	0.96	0.49–1.88	0.913
Volumio	1.31	0.71–2.42	0.396	1.15	0.59–2.23	0.682

Table 5. Multivariate Cox analysis. CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; PS: performance status.

Tabelle 5. Multivariate Cox-Analyse. CI: Konfidenzintervall; HR: Hazard-Ratio; PFS: progressionsfreies Überleben; PS: Performance-Status.

	Survival HR	95% CI for HR	p-value	PFS HR	95% CI for HR	p-value
Treatment			0.022			0.581
Temozolomide	1	–		1	–	
Temozolomide + irinotecan	2.24	1.12–4.47		0.82	0.39–1.69	
Age	1.03	1.00–1.07	0.039			
PS			< 0.001			0.005
0 or 1	1	–		1	–	
2 or 3	4.35	1.93–9.78		3.63	1.49–8.84	
Tumor size			0.151			0.155
Below median	1	–		1	–	
Above median	1.76	0.81–3.81	0.151	1.78	0.81–3.92	

In the study of Xue & Albright [24], the authors concluded that the accurate preoperative measurement of tumor volume by planimetry (computer-based three-dimensional reconstruction) is an important prognostic factor in high-grade gliomas. It is of notice that this effect was not statistically significant for the geometric models. This group used a previously described application [1, 2] and they found that the inaccuracies of the rectangular and spherical geometric models were too great to allow practical use in quantifying CT volume. In this paper, however, the method according to which regions of interest were delineated is not mentioned (contrast enhancement, margins, etc.), especially when the population of the study is not uniform, comprising anaplastic astrocytomas and glioblastomas altogether.

In another retrospective and well-documented study [13], preoperative tumor volume, accurately determined by volumetry, did not impart a significant effect on survival. As in most similar studies, age and functional PS were the main predictors of outcome. Finally, in a very promising recent study [11], tumor delineation is accomplished by the aid of SPECT (single-photon emission computed tomography) and MRI, underlining the technical difficulties presented.

One should be very cautious when interpreting survival data. Although the idea of identifying a parameter as statistically significant may seem very attractive, other factors may impart a more decisive effect on survival. Since our purpose was to evaluate the prognostic significance of preoperative tumor volume alone, we chose not to present differences in other parameters (RPA [recursive partitioning analysis] classes, grading, MGMT [methylguanine methyltransferase] promoter status, oligodendroglial component, LOH [loss of heterozygosity] 1p19q efficacy or side effects of chemotherapeutic agents). The variation in prognosis and survival is most likely related to the biological behavior of these tumors. It is also probable that postoperative tumor volume may be a more decisive factor for survival than the preoperative one [9]. Our study certainly points out that precise volume determination is indispensable in brain tumor research and patient follow-up.

Conclusion

By means of a versatile image analysis application, it was feasible to import hard-copy studies into a computer-based system and to estimate the tumor volume in a group of patients suffering from glioblastoma. In the survival analysis which followed, though, tumor size did not reach statistical significance. More studies are certainly needed in order to decipher the factors influencing the evolution of malignant gliomas, which should be based undoubtedly on an objective and precise way of determining tumor volume.

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Address for Correspondence
Georgios Iliadis, MD
Stratigou Sarafi 3
55132 Thessaloniki
Greece
Phone (+30/2310) 400177, Fax 442415
e-mail: iliadisg@the.forthnet.gr