

Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma?

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Background: Peritumoral brain edema in glioblastoma patients is a frequently encountered phenomenon that strongly contributes to neurological signs and symptoms. The role of peritumoral edema as a prognostic factor is controversial.

Materials and Methods: This multi-centre clinical retrospective study included 110 patients with histologically proven glioblastoma. The prognostic impact on overall survival of pre-treatment peritumoral edema detected on MRI-scans was evaluated. All patients had preoperative MRI, surgery, histology, and received standard treatment regimens. Edema on MRI-scans was classified as minor (< 1 cm), and major (> 1 cm).

Results: Our results confirm that peritumoral edema on preoperative MRI is an independent prognostic factor in addition to postoperative Karnofsky performance score (KPS), age, and type of tumor resection. Patients with major edema had significant shorter overall survival compared to patients with minor edema.

Conclusion: This easily applicable early radiological characterization may contribute to a more subgroup oriented treatment in glioblastoma patients for future trials, as well as in clinical routine.

Introduction

Glioblastoma is the most common malignant primary brain tumor in adults. Prognosis of glioblastoma patients is dismal with a median survival of approximately 1 year [1,2]. However, patient outcome is variable with a small fraction of long-term survivors [3,4]. To evaluate predictors of individual outcome in glioblastoma patients, several clinical, radiological, molecular, and histological factors have been identified. Important factors are age, KPS (Karnofsky performance score), extent of tumor resection, radio-chemotherapy, and corticosteroid use [5–9]. Molecular alterations, such as EGFR and MGMT promoter status are under investigation [10–12].

Peritumoral brain edema in glioblastoma patients is a frequently encountered phenomenon. It is considered as vasogenic; however, mechanisms of tumor related brain

edema are complex and probably because of several cellular mechanisms [13].

Its prognostic value at diagnosis, as well as in the course of disease is still a matter of discussion. Peritumoral edema may cause severe neurological signs and symptoms, and remains a challenge in the treatment of glioblastoma patients. Some studies report that the severity of brain edema at diagnosis is a negative prognostic factor [14,15]. Other studies show no prognostic impact [7]. However, there is no agreement on how peritumoral edema should be measured or classified on MRI-scans.

The purpose of this study was to evaluate the degree of peritumoral edema as prognostic factor for survival in glioblastoma patients. The peritumoral edema was measured on first diagnostic MRI with an easy applicable and simple technique. Moreover, results from Pope *et al.* [15], using a similar radiological technique for the measurement of peritumoral edema, are re-evaluated.

Methods

This multi-centre retrospective study included 110 patients with primary glioblastoma. All patients

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underwent initial neurosurgical tumor intervention between 1995 and 2005. Surgery was categorized as total, subtotal, or biopsy. All tumor specimens were histologically confirmed as glioblastomas according to the WHO classification [1,2].

Postoperative KPS was assessed 10–14 days after surgery [16]. Patients underwent standard treatment with radio-chemotherapy.

The preoperative MRI-studies were performed at different institutions. MRI scans had different slice thicknesses and slice distances. However, minimum protocol included axial T1-weighted sequences with and without contrast enhancement, and a T2-weighted or flair sequence for the assessment of edema and vascularity. Peritumoral edema was defined as a region of increased T2 signal intensity on the tumor margin. In most of the patients, axial scans were available, some also had additional coronal sequences. If this was the case, both axial and coronal sequences were analyzed. Measurement was performed at the maximum extent of the peritumoral edema evaluable on the MRI scans.

Edema extending < 1 cm from the tumor margin was defined as minor, and edema extending more than 1 cm from the tumor margin as major (Fig. 1).

Tumor size was measured as unidimensional largest diameter in cm on T2-weighted images. Two groups were defined, using the mean value of 4.3 cm as cut-off point (tumors ≤ 4 cm and tumors > 4 cm). Contrast

enhancement – grading was not possible because of the retrospective character of this study and the availability of mostly hard copies. Moreover, different MRI machines, contrast media, as well as application schedules were applied.

Only treatment naive patients, with respect to anti-tumor and anti-edema therapy, were included. Steroid use before first radiological diagnosis in a single patient cannot be ruled out, but was not documented and seems improbably prior to MRI confirmation of a cerebral tumor mass.

The end-point of the study was overall survival, which was measured from the day of surgery (equivalent to the day of diagnosis) until death of the patient. Survival beyond the end of the observational period (last follow-up visit) was considered as censored observation.

Kaplan–Meier method was used to generate survival plots. The prognostic value of the factors of interest was assessed with Cox proportional hazards regression models [17]. Overall and partial measures of dependence (*R*-squared values) were computed according to Kent and O’Quigley [18,19].

All reported *P*-values are results of two-sided tests. *P*-values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using spss (SPSS Inc., Chicago, IL, USA) or sas (SAS Institute Inc., Cary, NC, USA).

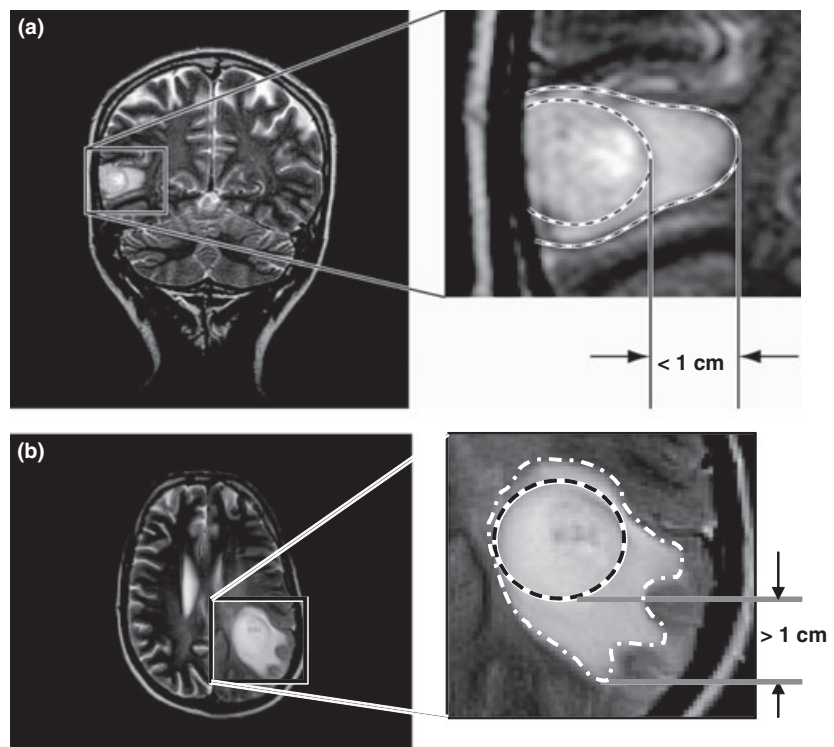


Figure 1 Measurement of peritumoral edema by means of MRI T2 (coronal/axial) weighted images. (a) Coronal T2-weighted images showing peritumoral edema extending less than 1 cm from the tumor margin, which was defined as minor edema. (b) Axial T2-weighted images showing peritumoral edema extending more than 1 cm from the tumor margin as major, which was defined as major edema.

Results

The main characteristics of the patients are summarized in Table 1. Out of 110 patients, 71 (64.5%) were male and 39 (35.5%) were female (gender ratio: 1.8). Fifty-three (48.2%) patients were ≤ 60 years and 57 (51.8%) were > 60 years (median age 60.1 years; range: 27.3–84 years). During the observation period, 92 patients died whilst 18 patients were still alive (follow up time minimum 5 days, maximum 1354 days, median 293 days). Median postoperative KPS was 90% (range 50–100%). Eighty-three (85%) patients had a KPS ≥ 80 and 15 (15%) a KPS < 80 . In 12 cases, KPS was not estimated. The MRIs of 24 (22%) patients showed minor edema and in 86 (78%) patients, major edema. Fifteen (14%) patients had biopsy only, 58 (53%) patients had subtotal, and 36 (33%) had total tumor resection. In 56 patients, tumor size was measured. Twenty-five (45%) patients had tumors ≤ 4 cm and 31 (55%) patients had tumors measuring > 4 cm.

Eighty-four (77%) patients received radiotherapy and adjuvant chemotherapy with alkylating agents. Nine (8%) patients had radiotherapy, and one patient chemotherapy only. Nine (8%) patients had surgical tumor resection only. Out of these, one patient refused any further treatment, three died shortly after surgery, and four were included in the study after tumor resection and had not received any adjuvant treatment at end-point. Six (5.5%) patients had biopsy only, and in one case, information on adjuvant radio-chemotherapy was not available.

Table 1 Patients characteristics are described with absolute frequencies, percentages and, if applicable, minimum and maximum values

Factors of interest	n	%
<i>Age of patient (years)</i> (Range 27.3–84.0, Median 60.1, Mean 58.7)		
≤ 60	53	48.2
> 60	57	51.8
<i>Gender</i>		
Female	39	35.5
Male	71	64.5
<i>Karnofsky performance score</i> (n = 98) (Range 50–100, Median 90)		
< 80	15	15.3
≥ 80	83	84.7
<i>Edema</i>		
Minor edema (≤ 1 cm)	24	21.8
Major edema (> 1 cm)	86	78.2
<i>Tumor resection</i> (n = 109)		
Total	36	33
Subtotal	58	53.2
Biopsy	15	13.8
<i>Tumor size (cm)</i> (n = 56) (Range 1.0–7.0, Median 5.0, Mean 4.3)		
≤ 4	25	44.6
> 4	31	55.4

Looking at the distribution of patient characteristics in the edema subgroups, patients with minor edema showed larger percentage of younger age and smaller tumors. The percentage of patients receiving total, subtotal resection, or biopsy is approximately equal in both groups (Table 2). Correlation of factors showed a weak correlation between edema grade and tumor diameter ($r = -0.33$ $P = 0.001$). Between age-subgroups and KPS-subgroups, no significant correlation could be found ($r = -0.159$ $P = 0.117$).

Table 2 Distribution of patient characteristics in edema subgroups (absolute frequencies, percentages)

Factors of interest	Minor edema	Major edema
<i>Age of patient (years)</i>		
	n = 24	n = 86
≤ 60	15 (62.5%)	38 (44.2%)
> 60	9 (37.5%)	48 (55.8%)
<i>Gender</i>		
	n = 24	n = 86
Female	12 (50%)	27 (31.4%)
Male	12 (50%)	59 (68.6%)
<i>Karnofsky performance score</i>		
	n = 19	n = 79
< 80	2 (10.5%)	13 (16.5%)
≥ 80	17 (89%)	66 (83.5%)
<i>Tumor resection</i>		
	n = 24	n = 85
Total	8 (33.3%)	28 (32.9%)
Subtotal	12 (50%)	46 (54.1%)
Biopsy	4 (16.7%)	11 (12.9%)
<i>Tumor size</i>		
	n = 13	n = 43
≤ 4	9 (69.2%)	16 (37.2%)
> 4	4 (30.8%)	27 (62.8%)

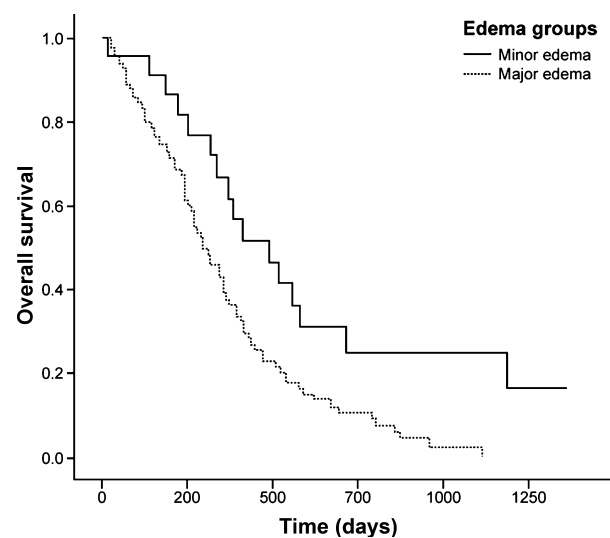


Figure 2 Kaplan–Meier estimated survival curves for the edema subgroups (minor edema < 1 cm and major edema > 1 cm).

Table 3 Hazard ratios, 95% confidence intervals (CI), and *P*-values of four univariate and a multiple Cox model are given. Partial adjusted R^2 values are added for the latter

Factors of interest	Univariate Cox models		Multiple Cox model		
	Hazard ratio (95% CI)	<i>P</i> -value	Hazard ratio (95% CI)	<i>P</i> -value	Partial R^2
Age of patient					
> 60/≤60	1.83 (1.21–2.77)	0.004	1.54 (0.986–2.41)	0.058	2.9%
Karnofsky performance score					
< 80/≥80	3.26 (1.79–5.92)	< 0.0001	2.74 (1.48–5.08)	0.001	7.9%
Peritumoral edema					
Major/minor	2.17 (1.23–3.80)	0.006	2.51 (1.30–4.81)	0.006	11.0%
Tumor resection					
Biopsy/total	2.98 (1.55–5.74)	0.0002	4.90 (2.33–10.3)	< 0.0001	17.6%
Subtotal/total	0.87 (0.54–1.40)		0.87 (0.53–1.42)		

Univariate analysis revealed that patients with major edema had significantly shorter survival than patients with minor edema ($P = 0.006$) (Fig. 2). A high KPS ($\geq 80\%$) (< 0.0001) and younger age (≤ 60 years) ($P = 0.004$) were positive clinical factors, associated with longer survival. Glioblastoma patients with biopsy only had a significantly worse outcome as compared to patients with total/subtotal resection ($P = 0.0002$). Preoperative tumor size had no significant impact on survival.

Multivariate analysis showed that postoperative KPS > 80 , tumor resection, and minor edema on pre-treatment MRI are independently associated with longer survival.

Adjusted R^2 measure showed that these four prognostic factors explained 36.8% of the variability in the overall survival time. The partial adjusted R^2 for edema alone after accounting for the effects of age, KPS, and tumor resection was 11% (Table 3).

Discussion

Several studies have elaborated neuroradiological imaging properties as prognostic factors in glioma patients. Tumor size, extent of necrosis, extent of peritumoral edema, contrast enhancement, location, and others have been examined [20,21]. In a large series of 416 glioblastoma patients, Lacroix *et al.* found five independent predictors: age, KPS, contrast enhancement, extent of necrosis on preoperative MRI, and extent of resection. Extent of edema was not found to be an independent prognostic factor in multivariate analysis [7]. The evaluation of the extent of edema in this series was modified and based on a study by Hammoud *et al.* who introduced three edema grades (grade I = amount of edema is less than tumor volume, grade II = amount of edema equal to tumor volume, grade III = amount of edema is larger than tumor volume) using volumetric data [14]. However, Hammoud's study reported brain edema as significant

prognostic factor with the moderate edema group having a significantly better outcome than the large edema group. In conclusion: these two scoring systems of peritumoral edema are bound to a time-consuming procedure, and do not seem to yield data that is reproducible.

In contrast, the evaluation system of peritumoral edema in our study is measured in centimeter from the outer ring of the tumor margin, followed by grouping into a minor (< 1 cm) and major (> 1 cm) edema. A similar scoring system for preoperative brain edema in patients with high-grade gliomas was introduced by Pope *et al.* They used imaging definitions with a clear score description (0 = no edema, 1 = bright T2 signal intensity with no mass effect and architectural deterioration and not extending more than 1 cm; 2 = edema > 1 cm) [15]. In this study, the extent of edema turned out to be an independent prognostic factor in patients with glioblastoma.

Thus, in the literature, results concerning the prognostic impact of brain edema in glioblastoma patients have not been conclusive and uniform. Many different scoring systems make comparison between studies and validation of results difficult. Our study confirms the results of Pope *et al.* applying a similar scoring system. Both our and Pope *et al.*'s [15] study establishes that peritumoral edema is an independent prognostic factor for survival in glioblastoma. The pathophysiological mechanisms of pre-treatment peritumoral edema leading to a worse prognosis need to be elucidated in further studies.

Extent of resection has a statistical significant impact on overall survival. In this sample, we observed that glioblastoma patients with biopsy had a significantly worse outcome compared to patients with partial or total resections. Comparing the patient subgroups with partial and total resections, we did not find a significant difference of outcome. This observation was previously shared [22], whereas recent studies reported a better outcome for patients with total resection [7,9]. This

might be because of recently more accurate pre- and post-operative tumor volume measurements and documentation.

Tumor size at first radiological diagnosis had no significant impact on survival, as reported by Hammoud *et al.* [14], and Kreth *et al.* [22], although they used different measurement techniques. We found that larger tumors were more probably to have major edema (Table 2). This positive weak correlation seems feasible, but remains pathophysiologically unclear.

For use in everyday clinical setting, selection of radiological parameters that are easily determined from routine scans is preferable, whereas volumetric analysis is bound to specific computer systems, and is a rather time-consuming procedure. In this respect, we recommend this radiological scoring system for evaluation of the extent of pre-treatment brain edema in glioblastoma. Our study confirms peritumoral edema as an independent prognostic factor, as previously published by Pope *et al.* [15]. This easily applicable early radiological characterization may contribute to a more subgroup oriented treatment approach in glioblastoma patients for future trials as well as in clinical routine.

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