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*Clinical Study*

# Influence of extent of surgery and tumor location on treatment outcome of patients with glioblastoma multiforme treated with combined modality approach

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*Key words:* extent of surgical resection, tumor location, glioblastoma multiforme, radiation therapy, chemotherapy

**Summary**

Between 1988 and 1991, eighty-six patients with glioblastoma multiforme were evaluated in order to define the influence of extent of surgery and tumor location on treatment outcome. Patients underwent surgery followed by postoperative hyperfractionated radiotherapy and chemotherapy delivered according to one of two consecutive protocols. Surgery consisted of biopsy in 25 (29%) patients and subtotal or gross total tumor resection in 61 (71%) patients. Frontally located tumors were noted in 26 (30%) patients and other tumor locations were noted in 60 (70%) patients. Patients having more radical surgery had longer median survival time (MST) and higher 1- and 2-year survival rates than those with biopsy only (56 vs 29 weeks, respectively; 62% and 23% vs 16% and 0%, respectively; p = 0.00000). Patients having frontally located tumors had longer MST and higher 1- and 2-year survival rates than those with other tumor locations (101 vs 47 weeks, respectively; 76% and 44% vs 37% and 2.5%, respectively; p = 0.00001). Multivariate analysis confirmed that extent of surgery and tumor location were independent prognostic factors in patients with glioblastoma multiforme. Regarding progression-free survival, patients having more radical surgery had longer median time to tumor progression (MTP) than those with biopsy only (33 weeks vs 21 weeks, respectively). Also, progression-free survival at 1 year was higher in radically resected group than in biopsy only group (20% vs 0%, respectively; p = 0.00000). Patients with frontally located tumors had longer MTP (42 weeks) and higher progression-free survival at 1 year (42%) than those with other tumor location (28 weeks and 1.7%, respectively; p = 0.00002). Multivariate analysis confirmed that the extent of surgery and tumor location are independent prognosticators in patients with glioblastoma multiforme treated with combined modality approach using progression-free survival as an endpoint.

## Introduction

A variety of factors which predict for survival of patients with glioblastoma multiforme (GBM) were identified from data obtained from large multiinstitutional prospective randomized studies as well as those done in a retrospective way [1–13]. Age and performance status were identified as the most important, although some studies indicated that extent of surgery and tumor location influenced survival [14–16]. Interfraction interval, when multiple fractions per day (MFD) during radiotherapy (RT) are employed, could also influence survival of patients with GBM [8].

Extent of surgery as a prognostic factor has been debated for decades, but its determination is still imprecise. Computerized tomography (CT) and magnetic resonance imaging (MRI) substantionally changed the diagnostic approach, but their limits are already recognized [17, 18]. Even technical advances (besides stereotaxy) like computer-assisted laser resection and perioperative cortical sensory and motor mapping did not improve the ability of radical surgical resection to extend survival time [15, 19, 20].

Finally, there is an extensive body of data in the literature with conflicting results. Both single and multiinstitutional studies did not confirm the influence of the extent of surgery on survival of patients with GBM treated with surgery, postoperative RT, with or without chemotherapy (CHT) [4, 10, 14, 21, 22–25]. Some studies did not provide statistical analysis, and in some lesser extent of surgery negatively correlated with survival only when adjuvant therapy was excluded from regression model statistics. Walker *et al.* [1] reported on the results of The Brain Tumor Cooperative Group (BTCG) (formerly The Brain Tumor Study Group – BTSG) study 69-01 where surgical biopsy negatively correlated with the length of survival. Using the Cox model, Gehan and Walker [14] reported that biopsy was negatively correlated with survival, but only when adjuvant therapy was excluded from the analysis. When adjuvant therapy was added, the extent of surgery did not influence the outcome and the addition of adjuvant therapy (RT and CHT) significantly improved survival.

The European Organization for Research and Treatment of Cancer (EORTC) reported on the data of their study showing that extent of surgery did not influence the length of postoperative survival [4]. Similar conclusions were drawn by Coffey *et al.* [15] and Kinsella *et al.* [26].

In contrast, there are reports suggesting a benefit for patients treated more aggressively. Jelsma and Bucy [9] reported better survival for patients who had a more extensive surgical approach than that observed in patients treated with external decompression or biopsy. Analyzing results on 554 patients enrolled in a joint Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (RTOG/ECOG) protocol, Chang *et al.* [5] found statistically significant increase in survival in a group of patients treated with a more extensive surgical approach than in those with limited surgery. Also, retrospective analysis of CT data of subsets of patients enrolled into various BTSG studies showed a correlation between the extent of surgery (or presence of residual tumor mass on postoperative CT scan) and survival [6, 27].

A number of studies did not include tumor location in the data analysis [6, 24–27], while some did [5, 10, 15, 21, 23]. From the latter group, no consistency could be found regarding the influence of tumor location on the survival of patients with GBM. Jelsma and Bucy [9] reported on longer survival in patients with non-central tumor location and extensive resection, although tumor sites in the relatively small biopsy and partial resection groups were not defined. Miller *et al.* [12] analyzed results obtained on 82 patients with high-grade gliomas (66 of whom were grade 4). After both univariate and multivariate analysis, tumor location was not found to be important prognostic factor.

Since there are a lot of conflicting data regarding the role of the extent of surgery and tumor location in patients with GBM, the aim of present study is to explore the influence of the extent of surgery and tumor location on survival/progression-free survival in patients with GBM treated with surgery, postoperative radiotherapy and chemotherapy.

## Material and methods

Eighty-six patients with glioblastoma multiforme (GBM) treated with surgery, postoperative radiotherapy (RT) employing multiple fractions per day (MFD) and adjuvant or concurrent chemotherapy (CHT) that entered into two consecutive studies were eligible for this analysis. The patients were grouped according to the extent of surgery (gross total tumor resection, GTR; subtotal resection, STR; biopsy, B), tumor location (frontal, F; temporal, T; parietal, P; occipital, O) and known prognostic factors such as age, performance status, as well as those that might have influence on survival such as interfraction interval or tumor size.

Thirty-seven patients received hyperfractionated radiation therapy (HFX RT) that consisted of tumor dose (TD) of 52.80 Gy in 44 fractions in 22 treatment days in 4.5 weeks, 1.2 Gy fractions b.i.d. to a treatment volume consisting of all visible tumor on contrast enhanced computerized tomography (CT) scan + surrounding edema + 2-cm margin, after which reduced fields (tumor + 2-cm margin) was used to treat with additional TD of 19.20 Gy in 16 fractions in 8 treatment days in 1.5 week, 1.2 Gy fractions b.i.d., with interfraction interval of 4.5–6 hours. Total TD was 72 Gy in 60 fractions in 30 treatment days in 6 weeks. Four weeks after completion of HFX RT patients underwent CHT which consisted of BCNU 50 mg/m$^2$, days 1–3, Vincristine 1.4 mg/m$^2$ (max. 2 mg), day 1, Procarbazine 50 mg/m$^2$, days 1–7, and Cisplatin 20 mg/m$^2$, days 1–3. Cycles were repeated every 4 weeks to a maximum of 6 cycles or until tumor progression was noted.

Forty-nine patients received accelerated hyperfractionated radiation therapy (ACC HFX RT) with concurrent CHT. TD was 66 Gy in 44 daily fractions in 22 treatment days in 4.5 weeks, 1.5 Gy fractions b.i.d. with interfraction interval of 4.5–6 hours to a treatment volume consisting of all visible tumor on contrast enhanced CT scan + 2-cm margin. BCNU 80 mg/m$^2$ and hydroxyurea 800 mg/m$^2$ were both given on treatment days 1.6.11.16. and 21 during the RT course. Drugs were given 3–4 hours after the first daily fraction.

Differences in patient characteristics between groups were evaluated by chi-square test. Survival times were calculated by the Kaplan-Meier method [28], and diferences between survival curves were analyzed by the generalized Wilcoxon test. The interaction of each potential prognostic factor and their effect on survival were analyzed using the Cox proportional hazards model [29]. All statistical analyses were carried out using a computer program HALBAU[1].

## Results

### *Patients characteristics*

Between January 1, 1988 and December 31, 1991,

*Table I.* Pretreatment characteristics

| Characteristics | | No. of pts (%) |
|---|---|---|
| SEX | M | 50 (58) |
| | F | 36 (42) |
| AGE (yrs) | < 60 | 50 (58) |
| | ≥ 60 | 36 (42) |
| ECOG PS | 0–1 | 52 (60) |
| | 2–3 | 34 (40) |
| SURGERY | B | 25 (29) |
| | GTR + STR | 61 (71) |
| RADIOTHERAPY | HFX RT | 37 (43) |
| | ACC HFX RT | 49 (57) |
| LOCATION | Frontal | 26 (30) |
| | Temporal | 22 (26) |
| | Parietal | 30 (35) |
| | Occipital | 8 (9) |
| INTERFRACTION INTERVAL (hours) | 4.5–5.0 | 33 (38) |
| | 5.5–6.0 | 53 (62) |
| SIZE | ≤ 4 cm | 33 (38) |
| | ≥ 5 cm | 53 (62) |

HFX = hyperfractionation; ACC HFX = accelerated hyperfractionation; ECOG PS = Eastern Cooperative Oncology Group Performance Status; B = biopsy; STR = subtotal resection; GTR = gross total tumor resection.

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*Table 2.* Distribution of patient characteristics by the extent of surgery

| | Characteristics | B | GTR + STR | $\chi^2$ |
|---|---|---|---|---|
| | | No. (%) | No. (%) | |
| SEX | M | 15 (60) | 35 (57) | |
| | F | 10 (40) | 26 (43) | n.s. |
| AGE (yrs) | < 60 | 10 (40) | 40 (66) | |
| | ≥ 60 | 15 (60) | 21 (34) | n.s. |
| ECOG PS | 0–1 | 2 (8) | 50 (82) | |
| | 2–3 | 23 (92) | 11 (18) | $p < 0.005$ |
| LOCATION | Frontal | 4 (21) | 22 (36) | |
| | Other | 21 (84) | 39 (64) | n.s. |
| SIZE | ≤ 4 cm | 7 (28) | 39 (64) | |
| | ≥ 5 cm | 18 (72) | 22 (36) | $p < 0.01$ |
| RT | HFX | 14 (56) | 23 (38) | |
| | ACC HFX | 11 (44) | 38 (62) | n.s. |
| INTERFRACTION INTERVAL (hours) | 4.5–5.0 | 6 (24) | 27 (44) | |
| | 5.5–6.0 | 19 (76) | 34 (56) | n.s. |

HFX = hyperfractionation; ACC HFX = accelerated hyperfractionation; ECOG PS = Eastern Cooperative Oncology Group Performance Status; B = biopsy; GTR = gross total tumor resection; STR = subtotal resection.

eighty-six patients with GBM that entered into two consecutive studies on the use of surgery, postoperative radiation therapy employing multiple fractions per day and adjuvant or concurrent chemotherapy were eligible for this analysis. Patients characteristics are given in Table 1.

Distribution of patients characteristics by the extent of surgery is given in Table 2. Sex, age, tumor location, type of radiation therapy, and interfraction interval were well balanced between biopsy (n = 25) and more extensive (n = 61) surgical subgroups, although the preponderance of young indi-

*Table 3.* Distribution of patients characteristics by tumor location

| Characteristics | Frontal | Other | $\chi^2$ | |
|---|---|---|---|---|
| | No. (%) | No. (%) | | |
| SEX | M | 18 (69) | 32 (53) | |
| | F | 8 (31) | 28 (47) | n.s. |
| AGE | < 60 | 19 (73) | 31 (52) | |
| | ≥ 60 | 7 (27) | 29 (48) | n.s. |
| ECOG PS | 0–1 | 22 (84) | 30 (50) | |
| | 2–3 | 4 (16) | 30 (50) | $p < 0.01$ |
| SIZE | ≤ 4 cm | 16 (62) | 30 (50) | |
| | ≥ 5 cm | 10 (38) | 30 (50) | n.s. |
| SURGERY | B | 4 (16) | 21 (35) | |
| | GTR + STR | 22 (84) | 39 (65) | n.s. |
| RT | HFX | 10 (38) | 27 (45) | |
| | ACC HFX | 16 (62) | 33 (55) | n.s. |
| INTERFRACTION | 4.5–5.0 | 9 (35) | 24 (40) | |
| INTERVAL | 5.5–6.0 | 17 (65) | 36 (60) | n.s. |

HFX = hyperfractionation; ACC HFX = accelerated hyperfractionation; ECOG PS = Eastern Cooperative Oncology Group Performance Status; B = biopsy; GTR = gross total tumor resection; STR = subtotal resection.

*Table 4.* Survival

| Characteristics | | No. pts. | MST (weeks) | % Survival at | | Univariate p | Multivariate p |
|---|---|---|---|---|---|---|---|
| | | | | 1 yr | 2 yr | | |
| STUDY | HFX | 37 | 44 | 32 | 8.1 | 0.02347 | 0.00090 |
| | ACC HFX | 49 | 56 | 61 | 25 | | |
| SEX | M | 50 | 52 | 48 | 20 | 0.62135 | excluded |
| | F | 36 | 54 | 50 | 8.1 | | |
| AGE (years) | < 60 | 50 | 57 | 57 | 28 | 0.00034 | 0.01167 |
| | ≥ 60 | 36 | 41 | 36 | 2.8 | | |
| ECOG PS | 0–1 | 52 | 57 | 63 | 25 | 0.00000 | 0.88960 |
| | 2–3 | 34 | 36 | 26 | 0 | | |
| LOCATION | frontal | 26 | 101 | 76 | 44 | 0.00001 | 0.00001 |
| | other | 60 | 47 | 37 | 2.5 | | |
| SIZE | ≤ 4 cm | 46 | 55 | 57 | 20 | 0.02451 | 0.81060 |
| | ≥ 5 cm | 40 | 45 | 39 | 9.8 | | |
| SURGERY | GTR + STR | 61 | 56 | 62 | 23 | 0.00000 | 0.00030 |
| | B | 25 | 29 | 16 | 0 | | |
| INTERFRAC. | 4.5–5.0 | 33 | 59 | 73 | 19 | 0.00027 | 0.00006 |
| INTERVAL | 5.5–6.0 | 53 | 44 | 33 | 16 | | |

HFX = hyperfractionation; ACC HFX = accelerated hyperfractionation; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GTR = gross total tumor resection; STR = subtotal resection; B = biopsy.

viduals is in the more extensive surgical subgroups. Patients having higher performance status were treated more often with more radical surgery than with biopsy, contrary to patients with lower performance status who were treated more often with biopsy ($p < 0.005$). Also, patients with tumors ≤ 4 cm were treated more often than those with tumor ≥ 5 cm with biopsy only ($p < 0.01$).

*Table 5.* Progression-free survival

| Characteristics | | No. pts. | MTP (weeks) | % Progression-free at 1 year | Univariate p | Multivariate p |
|---|---|---|---|---|---|---|
| STUDY | HFX | 37 | 29 | 11 | 0.59719 | excluded |
| | ACC HFX | 49 | 31 | 16 | | |
| SEX | M | 50 | 29 | 14 | 0.32404 | excluded |
| | F | 36 | 31 | 14 | | |
| AGE (years) | < 60 | 50 | 33 | 20 | 0.00022 | 0.04394 |
| | ≥ 60 | 36 | 25 | 5.6 | | |
| ECOG | 0–1 | 52 | 34 | 23 | 0.00005 | 0.056208 |
| PS | 2–3 | 34 | 20 | 0 | | |
| LOCATION | frontal | 26 | 42 | 42 | 0.00002 | 0.00008 |
| | other | 60 | 28 | 1.7 | | |
| SIZE | ≤ 4 cm | 46 | 31 | 20 | 0.01163 | 0.37778 |
| | ≥ 5 cm | 40 | 28 | 7.5 | | |
| SURGERY | GTR + STR | 61 | 33 | 20 | 0.00000 | 0.00045 |
| | B | 25 | 21 | 0 | | |
| INTERFRAC. | 4.5–5.0 | 33 | 37 | 21 | 0.00083 | 0.01816 |
| INTERVAL | 5.5–6.0 | 53 | 27 | 9.4 | | |

HFX = hyperfractionation; ACC HFX = accelerated hyperfractionation; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GTR = gross total tumor resection; STR = subtotal resection; B = biopsy.

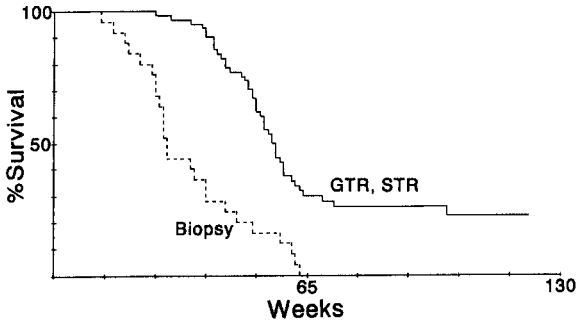


*Fig. 1.* Survival according to the extent of surgery.

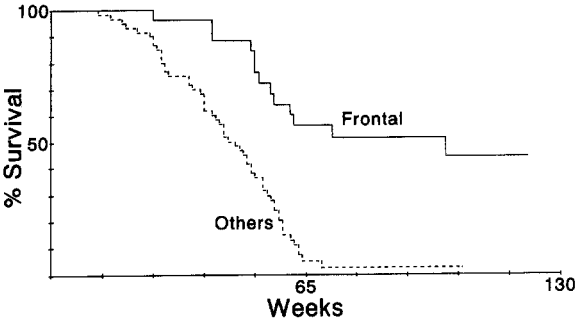


*Fig. 2.* Survival according to tumor location.

Distribution of patients characteristics by tumor location is given in Table 3. Sex, age, extent of surgery, type of radiation therapy, and interfraction interval were well balanced between frontal (n = 26) and other tumor locations (n = 60). Patients with frontal tumors had higher performance status more often than those with other tumor location ($p < 0.01$).

Patients treated with ACC HFX RT achieved better results than those treated with HFX RT (Tables 4 and 5). The balance between the two regimens is similar between biopsy and open surgery groups (Tables 4 and 5).

*Survival*

Patients having more extensive surgery had longer median survival time (MST) and higher 1- and 2-year survival rates than those with biopsy only (56 vs 29 weeks, respectively; 62% and 23% vs 16% and 0%, respectively; $p = 0.00000$) (Fig. 1). Patients having frontally located tumors had longer MST and higher 1- and 2-year survival rates than those with other tumor locations (101 vs 47 weeks, respectively; 76% and 44% vs 37% and 2.5%, respectively; $p = 0.00001$) (Fig. 2). Multivariate analysis confirmed that extent of surgery and tumor location are independent prognostic factors, together with age and interfraction interval, while ECOG PS and tumor size were found not (Table 4).

*Progression-free survival*

Patients having more extensive surgery had longer median time to tumor progression (MTP) and higher progression-free survival (PFS) rate at 1 year than those with biopsy only (33 weeks and 20% vs 21 weeks and 0%, respectively; $p = 0.00000$) (Fig. 3). Patients with frontally located tumors had a longer MTP and a higher PFS at 1 year than those with any other tumor location (42 weeks and 42% vs 28 weeks and 1.7%, respectively; $p = 0.00002$) (Fig. 4). Multivariate analysis showed that extent of surgery and tumor location were independent prognosticators, as well as age and interfraction interval, while ECOG PS and tumor size were not (Table 5).

## Discussion

The benefit of surgical resection in patients with GBM remains controversial, although reduction of tumor burden could be theoretically supported from a cytokinetic point of view [30], and aggressive resection of GBM should be associated with longer survival times. Findings of Wood *et al.* [6] support the view that significantly longer survival is obtained when CT scan did not show residual contrast-enhanced mass. This is further supported by the data that the size of contrast-enhanced tumor mass correlated with time to tumor progression [31, 32], although other do not share the same experience [33].

The influence of extent of surgery on survival of patients with GBM has been documented over the years [1, 5, 6, 9, 27]. In a retrospective analysis of 285 consecutive adult patients with supratentorial malignant glioma (188 of whom were GBM), Winger *et al.* [7], using a multivariate analysis, showed that the extent of surgery was significantly independent var-

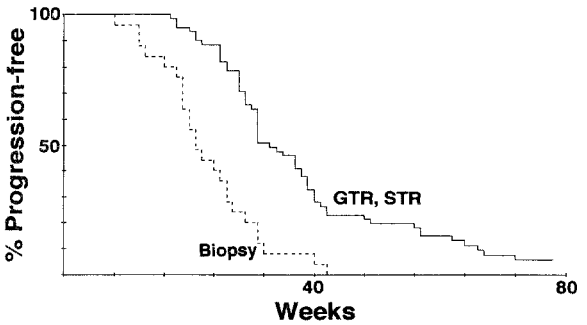


*Fig. 3.* Progression-free survival according to the extent of surgery.

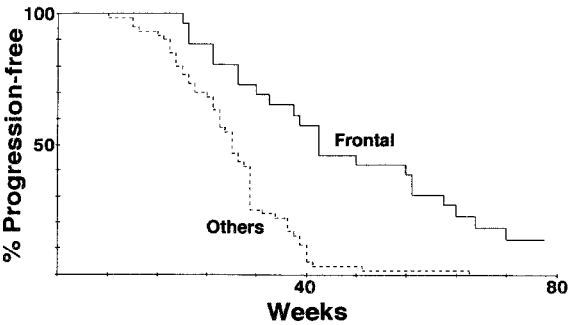


*Fig. 4.* Progression-free survival according to tumor location.

iable influencing survival. Patients with gross total resection lived significantly longer than those undergoing biopsy only. MST for patients with biopsy only was 19 weeks, for those with partial resection with or without lobectomy 41 and 47 weeks, respectively ($p = 0.2106$), and for those with gross total resection 76 weeks ($p = 0.001$).

Miller *et al.* [12] reported on results obtained on eighty-two patients with high-grade gliomas (sixty-six of whom were grade 4). The twenty-three patients who were treated with gross total surgical resection had a median survival time of 51 weeks, which was less but not significantly different from MST of 54 weeks obtained in 50 patients who underwent subtotal resection. The six patients with biopsy only had a MST of only 12 weeks, which was significantly worse than that obtained with more extensive surgery ($p = 0.04$).

Devaux *et al.* [11] recently reported on the influence of the extent of surgery in 196 newly diagnosed patients with cortical and subcortical grade IV gliomas. Patients undergoing resection of contrast-enhancing mass (documented by CT and MRI) and postoperative RT lived longer than those undergoing biopsy only and RT (MST: 50.6 weeks and 33.0 weeks, respectively; Smirnov test, $p = 0.0380$). This observation, however, was not confirmed in grade 3 lesions ($p = 0.746$).

Simpson *et al.* [16] reported on 645 patients with GBM that entered into three consecutive Radiation Therapy Oncology Group (RTOG) studies (7401, 7918, 8302). Patients undergoing total resection had a MST of 11.3 months compared with 6.6 months for patients with biopsy only. A significant difference in median survival was also found for partial resection versus biopsy only (10.4 vs 6.6 months, respectively; $p = 0.0001$).

The results of our series confirm the importance of the extent of surgery as prognostic factor in patients with GBM. Patients undergoing more extensive surgery (gross total tumor resection or partial resection) had longer MST and 1- and 2-year survival rates than those with biopsy only ($p = 0.00000$) as well as longer MTP and higher 1-year PFS ($p = 0.00001$). Multivariate analyses using both survival and progression-free survival as endpoints confirmed these observations.

Results of this study regarding the influence of the extent of surgery on survival and progression-free survival of patients with GBM confronted with those supporting the view of the use of lesser aggressive surgical approach [4, 10, 15, 21–26]. Kelly *et al.* [19] reported on the lack of difference in the average survival period between patients with intraaxial brain neoplasms (including 26 GBM) treated with computer-assisted laser resection and irradiation, and those with tumors located in more favorable locations treated by conventional surgery and RT.

In a review of studies over a 50-year period assessing the association between the long-term survival and type of surgical management in adults with supratentorial intermediate or high-grade astrocytomas, Nazzaro and Neuwelt [34] concluded that there is little justification for belief that there is a definite relationship between increasing patients survival times and aggressive surgical treatment if patients receive postoperative RT.

Recently, Kreth *et al.* [13] reported on a retrospective study assessing the influence of the extent of surgery on survival of patients with GBM treated

between 1986 and 1991. The treatment variable biopsy versus resection did not reach prognostic relevance and authors concluded that results of their series place doubt on concept of treating GBM with aggressive cytoreductive surgery.

Definition of exact tumor location still carries some problems. CT/MRI have revolutionalized diagnostic approach in neuro-oncology, although high grade gliomas may fail to enhance on CT scans. Tumor cells may extend beyond the area of CT contrast enhancement or hypodensity [17]. Similar situation is observed with T2-weighted MRI [18], it is, therefore, not surprising that many studies gave little attention to tumor location, not including it in the data analysis [6, 27], or reporting the data on the influence of tumor location on survival made by univariate but not multivariate analysis [10, 21, 23]. Of those addressing the role of tumor location, almost all examined the association between survival and extent of surgery, Gehan and Walker [14] as well as Coffey *et al.* [15] reported on the influence of tumor location on survival, but not the extent of surgery. Also, Devaux *et al.* [11] found, in grade IV tumors, that cortical location was associated with the longest survival (MST, 44.3 weeks) and a midline location was associated with the shortest survival (MST, 15.6 weeks) ($p = 0.0638$).

On the other hand, Chang *et al.* [5] find that tumor location was not associated with different survival. Kreth *et al.* [13] also did not find any difference in survival when tumor location was analyzed (lobar vs midline, and left vs right hemisphere). However, recently the report of Simpson *et al.* [16] on a large number of patients confirmed the importance of tumor location. Patients with frontal lobe tumors survived significantly longer (median, 11.4 months) than those with temporal (median, 9.1 months) or parietal (median, 9.6 months) lobe lesions ($p = 0.01$).

Results of the current study support the view that tumor location is an important prognostic factor. Patients with frontally located tumors achieved the best results and there is a statistically significant difference between these patients and those with other tumor locations regarding both MST and 1- and 2-year survival rates ($p = 0.00001$) as well as MTP and PFS at 1 year ($p = 0.00002$). Multivariate analyses using both survival and progression-free survival as endpoints confirmed these observations.

In conclusion, it is typically although perhaps not universally accepted that removal of the gross tumor predicts for a longer survival time and a longer time to symptomatic recurrence. Even if this was not true, there is no reason not to try to debulk as much of a tumor as can safely be done, and the results of our study support the necessity of performing more radical surgery, whenever possible. This study has also shown that patients with frontally located tumors must be considered as favourable subgroup since this location carries the best prognosis. These results could serve as a basis for the design of future GBM trials stratifying patients according to the extent of surgery and tumor location in addition to age and performance status as the most important prognosticators. Attempts to further evaluate the role of surgical resection and tumor location in patients harbouring GBM in a prospective randomized fashion are now in progress.

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