Impact of Peritumoral Edema on Overall Survival in Glioblastoma Multiforme

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OBJECTIVE
The aim of the present study was to investigate the relationship between peritumoral edema and overall survival in glioblastoma multiforme (GBM).

METHODS
Total of 101 patients with radiologically or pathologically GBM were included in this study. Data of patient age, sex, tumor dimensions, and preoperative peritumoral edema were analyzed.

RESULTS
While average survival was 16.67±3.99 months (95% confidence interval [CI]: 8.85-24.49 months) and 1- and 3-year survival rates were 50% and 16.7%, respectively, for patients without edema, average survival was 13.74±1.95 months (95% CI: 9.91-17.58 months) and 1- and 3-year survival rates were 35.6% and 8.5%, respectively, for patients with edema. No statistical difference between them was found (p=0.297).

CONCLUSION
Prognostic value of edema for survival could not be determined in this retrospective analysis of homogeneous group of patients with isolated GBM.

Keywords: Glioblastoma multiforme; peritumoral edema; survival.

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ORIGINAL ARTICLE

Introduction
Although brain tumors are a significant morbidity and mortality reason relatively common in adults, metastatic tumors are seen most frequent in brain.[1] More than half of brain tumors are malign glioms (WHO Grade III-IV) and approximately 3/4 of them are grade IV glioblastoma multiforme (GBM).[2] While it can be seen at every age, it peaks between 45 and 55 years of ages.

GBM’s standart treatment is surgical. The main aim of surgical treatment is a complete surgical excision which has a direct relationship with disease-free survival and overall survival.[3,4] However, because GBM has a high local recurrence rate, there is a need for adjuvant therapies after surgical treatment. In the Stupp and his colleagues’ joint randomized phase III study with European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) groups, it is shown that adding temozolomide (TMZ) (75 mg/m²) which is an oral alkylating agent and 5 cures (150–200 mg/m²) of adjuvant therapy simultaneously to the standart conventional radiotherapy (RT) extends the survival significantly compared...
to the RT alone. Nowadays, GBM patients’ stand-
art treatment is determined like “complete surgical
excision+simultaneous chemoradiotherapy+adjuvant
chemotherapy”.[5,6]

In high grade tumors, age, KPS, histology, resection
width, duration of symptoms, neurological-functional
mental state and tumor’s crossover to the opposite lobe
are defined prognostic factors.[7–11] Our intention in
this study is to observe peritumoral edemas’ effect to
the survival in GBM.

Materials and Methods

101 patients that medical inoperable ones’ GBM diag-
nosis were made by radiologically, operated ones’ GBM
diagnosis were made by pathologically and RT and si-
multaneously chemotherapy (CT) were applied and
monitored for adjuvant therapy, are included in this
study. The patients age, sex, tumor’s dimensions and
peritumoral edema were recorded.

Treatment

Computer tomography scans were done for RT appli-
catons. The mass or mass loge was fusioned with MRG
which had had before surgical treatment. Brainstem,
lenses, optical nerves, pituitary gland and optical chi-
asm were contoured as critical organs.

The 3 dimensional conformal radiotherapy
(3DRT) or intensity modulated radiotherapy (IMRT)
techniques were used. In RT planning, if there wasn’t
an edema, the mass or mass bed was described as the
GTV2 in terms of gross tumor volume (GTV),
if there was an edema, it is described as the GTV1
including that. The clinical tumor volume (CTV)
was forged with 2 cm margins given to the GTV1 or
GTV2. The CTV was excluded from anatomic barri-
ers if there was not an extension. The planned target
volume (PTV) was forged with 0.5 cm margins given
to the CTV. 2 Gy each for 23 fractions total 46 Gy
were given to the PTV1, 2Gy/7 fractions total 14 Gy
were given to the PTV2 and grand total tumor dose
reached to 60 Gy. Everyday orally 75mg/m² TMZ was
applied as simultaneously CT. After RT, once in 28
days, 5 days long 150–200mg/m² TMZ was applied
for 5 cures.

Follow-up

After RT, clinical examination, complete blood test and
MRG controls were done with 2 months periods. The
overall survival was accepted as the time between diag-
nosis and last control or death date.

Statistical methods

The obtained data was loaded to the SPSS 13.0 softwere.
The Kaplan-Meier test was used for survival times. The
prognostic factors were calculated with the long-rank
test. P<0.05 was accepted as significant.

Results

39% (39) of 101 patients that involved to the study were
females and 61% (62) of them were males. The age av-
erage was 62.72±13.56 (7–88). 15 (15%) patients were
<50 years old, 86 (85%) of them ≥50 years old.

The average tumor size was 4.03±1.46 cm (1.5–8.0)
and at 59 (58%) patients ≤4 cm and at 42 (42%) of
them >4 cm. Because they were medical inoperable
at 23 (23%) patients diagnosis was made by radiologi-
cally. 23 (23%) of the 78 (77%) patients who were op-
erated, only biopsy was applied. Subtotal excision was
made to 21 (21%) patients and total excision was made
to 34 (33%) of them. The drawn volumes at the RT
planning; the mass was 92.03±107.58 (13.65–721.21)
cm³, PTV 0–46 544.88±240.19 (50.91–1257.85) cm³
and PTV 46–60 319.45±172.32 (19.81–899.96) cm³. If
it was evaluated based on sex; while the average sur-

vival at females was 13.45±2.13 (95% CI: 9.28–17.63)
months, and 1 and 3 years survival rates were 33.6%
and 5.7% respectively, the average survival at males was
13.95±2.06 (95% CI: 9.91–17.98) months and 1 and 3
years survival rates were 37.7% and 9%, and there were
no statistically difference between them. If the survival
was evaluated based on age; while the average sur-

vival was 24.83±3.01 (95% CI: 18.91–30.75) months, 1 and 3
years survival rates were 33.6% and 5.7% respectively, the average survival at males was
13.95±2.06 (95% CI: 9.91–17.98) months and 1 and 3
years survival rates were 37.7% and 9%, and there were
no statistically difference between them. If the survival
was evaluated based on tumor size; while at the patients ≤4 cm the average survival
was 8.13±2.24 (95% CI: 3.72–12.53) months, 1 and 3
years survival rates were 35.9% and 14% respectively,
at the patients >4 cm survival was 11.49±1.62 (95% CI:
8.32–14.67) months, 1 and 3 years survival rates were
39.5% and 0%. A significant relation between tumor
size and survival couldn’t be found (p=0.0404). While
the average survival at the patients who were treated
without surgical operation was 9.50±2.05 (95% CI:
5.46–13.53) months, 1 and 3 years survival rates 24.8%
and 0% respectively, the average survival at the pa-
tients who were applied biopsy and subtotal excision
was 11.88±1.62 (95% CI: 8.38–14.50) months, 1 and 3
years survival rates were 39.1% and 3.3% respectively, the average survival at the patients who were applied total excision was 19.62±3.82 (95% CI: 12.13–27.12) months, 1 and 3 years survival rates were 39.3% and 23.9% respectively and, a statistically significant relation between them couldn't be found (p=0.099).

While there was no peritumoral edema at 15 (15%) patients, at 86 (85%) of them there was an edema and the average volume of the edema was 145.71±133.92 (0.0–549.80) cm³. If the survival was evaluated for peritumoral edema at the GBM patients; while the average survival was 16.67±3.99 (95% CI: 8.85–24.49) months, 1 and 3 years survival rates were 50% and 16.7% respectively at the patients without edema, the average survival was 13.74±1.95 (95% CI: 9.91–17.58) months, 1 and 3 years survival rates were 35.6% and 8.5% respectively at the patients with edema and, there wasn't a statistical difference between them (p=0.297) (Figure 1).

If the peritumoral edema was evaluated for sex; while there was no peritumoral edema at 5 female patients, at 34 of them there was an edema. The edema seen rate was 87%. The average survival of female patients without edema was 21.40±7.32 (95% CI: 7.04–35.75) months, 1 and 3 years survival rates were 50% and 25%, the average survival of female patients with edema was 11.44±1.91 (95% CI: 7.69–15.20) months, 1 and 3 years survival rates were 33.8% and 0% respectively. There was no statistical difference between two groups (p=0.145). While the edema wasn't observed at 10 male patients, at 52 of them it was observed. The edema rate at male patients was 83%. The average survival of male patients without edema was 13.79±4.18 (95% CI: 5.58–22.0) months, 1 and 3 years survival rates were 50% and 12.5%, the average survival of male patients with edema was 14.42±2.64 (95% CI: 9.23–19.61) months, 1 and 3 years survival rates were 34% and 10.4% respectively. There was no statistical difference between two groups (p=0.406). If all groups compared with each other, there was no statistical difference between them (p=0.619).

If the peritumoral edema was evaluated for age; while there was no peritumoral edema at 4 patients under ages of 50, at 11 of them there was an edema and, edema seen rate was 73%. The average survival was 19.98±8.0 (95% CI: 4.30–35.66) months, 1 and 3 years survival rates were 40% and 40% respectively at patients with >4 cm tumor and an edema. The average survival was 14.77±2.42 (95% CI: 10.02–19.51) months, 1 and 3 years survival rates were 35.5% and 10.2% respectively at patients with a ≤4 cm tumor without an edema. There was no statistical difference between two groups (p=0.426). While there was no edema at 9 patients with a tumor >4 cm, at 33 of them there was an edema. The edema seen rate was 79%. The average survival was 14.12±4.05 (95% CI: 6.16–22.08) months, 1 and 3 years survival rates were 34.3% and 0% respectively at patients with a >4 cm tumor and an edema. There was no statistical difference between two groups (p=0.034).

If the peritumoral edema was evaluated for tumor size; while there was no edema at 6 patients with a tumor ≤4 cm, at 53 of them there was an edema. The edema seen rate was 90%. The average survival was 14.77±2.42 (95% CI: 10.02–19.51) months, 1 and 3 years survival rates were 40% and 40% respectively at patients with a ≤4 cm tumor without an edema. The average survival was 14.12±4.05 (95% CI: 6.16–22.08) months, 1 and 3 years survival rates were 35.5% and 10.2% respectively at patients with a >4 cm tumor without an edema. There was no statistical difference between two groups (p=0.426). While there was no edema at 9 patients with a tumor >4 cm, at 33 of them there was an edema. The edema seen rate was 79%. The average survival was 14.12±4.05 (95% CI: 6.16–22.08) months, 1 and 3 years survival rates were 34.3% and 0% respectively at patients with a >4 cm tumor and an edema. There was no statistical difference between two groups (p=0.034).
between two groups (p=0.141). If all groups compared with each other, there couldn’t be found a statistical difference (p=0.259).

If it was evaluated for surgical operation; because 23 (23%) of the patients were accepted as medical inoperable, the diagnoses were made radiologically. While at 6 of these patients there was no edema, at 17 of them there was an edema. The edema seen rate was 74%. The average survival was 12.10±4.91 (95% CI: 2.47–21.73) months, 1 and 3 years survival rates were 33.3% and 0% respectively at the group with no edema. The average survival was 8.55±2.21 (95% CI: 4.21–12.89) months, 1 and 3 years survival rates were 26.8% and 0% respectively at the group with an edema. There was no statistical difference between two groups (p=0.141). If all groups compared with each other, there couldn’t be found a statistical difference (p=0.167). Table 1 demonstrates that in the comparison of the patients who have whole brain RT after surgical treatment and the patients who didn’t have any adjuvant therapy. But, because of the brain's tolerance dosage, lower dosages were used at these wide area irradiations. Later, at the otopsy series, by reason of the disease’s recurrences’ 90% were being at the first 2 cm and were being shown the tumor cells’ existence in the peritumoral edema tissue, it was started to apply higher dosages to more limited areas and it was determined that there was an advantage on survival with these applications.[12] However it was tried many agents for a systemic treatment, the breaking point at this field which is determining nowadays’ standards was held by Stupp and his colleagues[5] in 2005 by the application of 75 mg/m² TMZ simultaneously with 60 Gy RT. The most evident response was seen at the patients who had MGMT mutation. Today, even though many tests were made with new technologies and new devices like dosage escalation and/or additional dosage stereotactic boost, there is no randomized evidence that shows efficacy of over 60 Gy dosages yet.

It was come to a certain point at systemic treatment as well as local treatment on GBM and it couldn’t be gone beyond Stupp’s study.[6] It is similar for prognostic factors. The RPA classification is still remains the feature of being the most used and the most valid classification. The age, performance state, resection width, duration of symptoms, neurologic-functional mental state and tumor’s cross over status to the other lobe are the best known prognostic factors. The publications about the peritumoral edema’s being a prognostic factor question that’s our study’s main goal as well, are controversial. Although it is already known that there are tumoral cells surrounding the tumor’s edema and included to the RT literature, being inevitable of the local recurrences directed us to search this subject.

The necrosis MR is one of the pathognomonic factors for GBM, too. Also, the peritumoral edema’s being wide situation at these tumors is a frequent situation at diagnosis phase or at the patients not having steroids. It is being thought that the widespread edema at the diagnosis phase is related with the tumor’s biological behaviour. Wu and his colleagues reported that at the retrospective analysis which they examined 109 patients’ with malignant glioma preoperative MR images, the edema and necrosis were negative prognostic indicators for overall survival. Also, they suggested these tumor cells in the peritumoral edema area could be related to the unresponsiveness to the treatment. It was indicated that this peritumoral edema’s effect was controversial in the Liu and his colleagues’ study.[13] Even it was stated
that the radiological differences of the malign gliomas including histological differences could be causing this debate. The sharpness of the boundaries of the edema surrounding the mass was also examined but it lost the meaningfulness in the multivariant analysis.

Wu CX and his colleagues[14] study, the enhancement extent was associated with the OS of the patients with malignant glioma on univariate analysis, while it failed to retain its significance on multivariate analysis. Schoenegger K et al.[15] results confirm that peritu-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics and results of log-rank univariate analysis for overall survival.</th>
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<tbody>
<tr>
<td>Peritumoral edema</td>
<td>n</td>
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<tr>
<td>General</td>
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</tr>
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<tr>
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<td>≥50</td>
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<td>Tumor size</td>
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<td>≤4 cm</td>
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</tr>
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<td>&gt;4 cm</td>
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<td>Yes</td>
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</table>
moral 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.

The results of our study are inconclusive; the available evidence does not certainly support or rule out an association between pre-operative peritumoral edema and overall survival (p=0.297). However, the patients under 50 years with no edema had significant long overall survival compared to patients 50 years old and over with edema (p=0.034).

For a conclusion, the edema’s prognostic value couldn’t be determined on the survival in the retrospective analysis of our homogeneous group formed from isolated GBM patients. There is a need for randomized studies with higher patient numbers for researching this subject.

Disclosure Statement

The authors declare no conflicts of interest.

References


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