Accepted Manuscript

Title: Role of Mass Effect, Tumor Volume and Peritumoral Edema Volume in the Differential Diagnosis of Primary Brain Tumor and Metastasis

Author: Mustafa Mahmut Baris Ahmet Orhan Celik Naciye Sinem Gezer Emel Ada

PII: S0303-8467(16)30247-5
DOI: http://dx.doi.org/doi:10.1016/j.clineuro.2016.07.008
Reference: CLINEU 4458

To appear in: Clinical Neurology and Neurosurgery

Received date: 2-5-2016
Revised date: 1-7-2016
Accepted date: 2-7-2016

Please cite this article as: Baris Mustafa Mahmut, Celik Ahmet Orhan, Gezer Naciye Sinem, Ada Emel. Role of Mass Effect, Tumor Volume and Peritumoral Edema Volume in the Differential Diagnosis of Primary Brain Tumor and Metastasis. Clinical Neurology and Neurosurgery http://dx.doi.org/10.1016/j.clineuro.2016.07.008

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Role of Mass Effect, Tumor Volume and Peritumoral Edema Volume in the Differential Diagnosis of Primary Brain Tumor and Metastasis

Mustafa Mahmut Baris¹, Ahmet Orhan Celik², Naciye Sinem Gezer¹, Emel Ada¹

1. Department of Radiology, Faculty of Medicine, Dokuz Eylul University Hospital, Izmir, Turkey
2. Department of Radiology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey

**Corresponding author:** Mustafa Mahmut Baris

**Address:** Department of Radiology, Faculty of Medicine, Dokuz Eylul University Hospital, Mithatpasa Cad. 35340 Inciralti-Izmir, Turkey

**E-mail:** mustafamb1@yahoo.com

**Residential Telephone:** +90 506 7516285

**Business Telephone:** +90 232 4125901

mustafamb1@yahoo.com
aorhancelik@gmail.com
drsinemgezer@gmail.com
emel.ada@deu.edu.tr
Highlights

- Definition of mass-edema index which is a new differential diagnosis tool.

- Metastases have higher mass-edema index than primary brain tumors.

- Volume measurement of brain tumors is a useful tool in differential diagnosis.
Abstract

Introduction

The differentiation of metastatic and primary brain tumors with certainty is important since clinical management and treatment of these two types of tumors are radically different.

The purpose of the present study was to evaluate the effect of peritumoral edema volume, tumor volume and mass effect of tumor on differential diagnosis of metastatic and primary brain tumors. Also we have planned to investigate if the relationship between edema volume and mass affect can contribute to the differential diagnosis.

Material and Methods

We retrospectively reviewed MR images of patients with primary (n=40) and metastatic (n=40) intra-axial supratentorial brain tumor. Supratentorial primary solitary brain tumor group was also subdivided as GBM subgroup (n=24) and other than GBM subgroup (n=16) for statistical analysis. Metastasis at suitable localization which can lead to midline shift (due to mass effect) were selected. Tumor volume, peritumoral edema volume and mass-edema index (peritumoral edema volume / tumor volume) were calculated. Displacement of the midline structures (subfalcian herniation) was measured.

Metastasis, GBM and other than GBM groups were evaluated for subfalcian shift, shift grade, tumor volume, peritumoral edema volume and mass-edema index by using Kruskal-Wallis test after Bonferroni correction. Mann-Whitney U-test was used to analyse subfalcian shift, tumor volume, peritumoral edema volume and mass-edema index of primary tumor and metastasis groups since the data was not normally distributed. Shift grade of the two groups was analysed with chi-square test.

Results

Midline shift, tumor volume and mass-edema index were significantly different between metastasis and primary tumor groups (p=0.001, p<0.001, p=0.001 respectively). Midline shift and tumor volume of the primary tumor group were greater than metastasis group while mass-edema index was less. Shift grade of metastasis and primary tumor groups was also significant (p=0.041). A midline shift more than 5 mm (grade 2) was more common
in primary tumors. There was no significant difference between GBM and other than GBM groups.

**Conclusion**

Measurement of midline shift, tumor volume and mass-edema index may contribute to the differential diagnosis of brain metastasis from primary brain tumors. Also mass-edema index can be a useful tool for differential diagnosis in the future. But further studies with larger series are needed.

**Keywords:** Brain neoplasms; magnetic resonance imaging; metastasis; volume measurement.
1. Introduction

The differentiation of metastatic and primary brain tumors with certainty is important since clinical management and treatment of these two types of tumors are radically different [1, 2]. Yet, it is often difficult to differentiate a solitary brain metastasis from glioblastoma multiforme (GBM) based on conventional magnetic resonance (MR) imaging characteristics such as signal-intensity and contrast enhancement patterns alone [3-6].

Metastatic and primary brain tumors are both surrounded by extensive peritumoral edema [7]. In previous studies, it is reported that pathophysiology of peritumoral edema is different in brain metastasis than it is in primary brain tumors [2]. Metastasis is expansive and displaces the surrounding brain tissues rather than invading them [8-12]. Thus peritumoral edema area of metastatic brain tumors consists of vasogenic edema essentially [13-15]. On the other hand, GBM typically grows infiltratively and invades the surrounding tissues [7]. For this reason peritumoral edema area of metastatic brain tumors also contains peritumoural infiltrating neoplastic cells localized along the perivascular spaces [13-15]. Furthermore, Ludwig et al. found that peritumoral edema extension in metastatic and primary brain tumors is associated with different nitric oxide synthase (NOS) isoenzymes [16].

The purpose of the present study is to evaluate the effect of peritumoral edema volume, tumor volume and mass effect of tumor on differential diagnosis of metastatic and primary brain tumors. Also we planned to investigate if the relationship between edema volume and mass affect can contribute to the differential diagnosis.

To the best of our knowledge, ours is the first study in English literature that compares the peritumoral edema volume of metastatic and primary brain tumors.
2. Material and Methods

2.1. Patients

This study was conducted with institutional review board approval. We retrospectively searched the imaging database of our radiology department for cranial magnetic resonance (MR) images of the patients with metastatic or primary brain tumor. The patients who had only CT investigation before treatment without MR examination were not included in the study. Posterior fossa tumors and extra-axials masses were excluded from the study. Hemorrhagic tumors were also not included in the study since peritumoral edema would indirectly be affected. Solitary primary tumors were selected. In the other group metastasis at suitable localization (such as frontal, parietal, parieto-occipital or parietotemporal lobe) which can lead to midline shift (due to mass effect) were selected. We stopped to search the database when the number of patients reached forty in both groups (primary brain tumor group and metastasis group). Forty patients with intra-axial supratentorial primary brain tumor and forty patients with intra-axial supratentorial metastatic brain tumor constituted the study group. Supratentorial primary brain tumor group was subdivided as GBM subgroup and other than GBM subgroup. Information on histopathological type of tumor was obtained from pathology reports.

2.2. MRI protocol

MR examinations were performed on a 1.5T scanner (Gyroscan Achieva or Intera, Philips, Best, the Netherlands) equipped with a head coil in the axial plane. All of the examinations were acquired by using our standard protocol for the assessment of brain tumors. The images included axial proton-density and T2-weighted turbo spin-echo (TSE) (dual-echo spinecho) (slice thickness: 5 mm; intersection gap: 1 mm; field of view: 230 mm; matrix: 320 x 512; TR: 4000 ms; TE: 20/120 ms; NEX: 2; flip angle: 90), axial fluid-attenuated inversion-recovery (FLAIR) (slice thickness: 5 mm; intersection gap: 1 mm; field of view: 230 mm; matrix: 256 x 256; TR: 6000 ms; TI:2000 ms; TE:120 ms; NEX: 2), sagittal T1-weighted (slice thickness: 5 mm; intersection gap: 1 mm; field of view: 250 mm; matrix: 256 x 256; TR: 596 ms; TE:15 ms; NEX: 2; flip angle: 69) and post contrast sagittal and axial T1-
weighted sequences (slice thickness: 5 mm; intersection gap: 1 mm; field of view: 230 mm; matrix: 256 x 256; TR: 650 ms; TE: 15 ms; NEX: 2; flip angle: 69).

2.3. Measurement

Tumor volume and peritumoral edema volume were measured using Lesion Annotation & Volume Assessment (LAVA) software (Medical Image Mining Laboratories, Llc 400 Columbus Avenue, Valhalla, New York, United States). Tumors were annotated slice by slice on axial post contrast T1-weighted images and total volume was calculated automatically by the software. FLAIR and T2-weighted TSE sequence images were used for peritumoral edema volume measurement by the same method (Figure 1). “Mass-edema index” was calculated according to the equation of “mass-edema index = peritumoral edema volume / tumor volume”.

Axial FLAIR sequence was used to measure subfalcian herniation. The degree of midline shift was categorized as grade 1 herniation when the displacement from midline was absent or less than 5 mm and as grade 2 herniation when the displacement was 5 mm or more.

2.4. Statistical analysis

Statistical analysis was performed using statistical package for social sciences version 15.0 (SPSS, Chicago, IL, USA). Metastasis, GBM and other than GBM groups were evaluated for subfalcian shift length, shift grade, tumor volume, edema volume and mass-edema index by using Kruskal-Wallis test after Bonferroni correction. Mann-Whitney U-test was used to analyse subfalcian shift, tumor volume, edema volume and mass-edema index of primary tumor and metastasis groups since the data was not normally distributed. Shift grade of the two groups was analysed with chi-square test. A p-value less than 0.05 was considered significant.
3. Results

3.1. Findings

There were 21 female, 19 male patients in metastasis group. Primary tumor group consisted of 24 female and 16 male patients. The mean age of metastasis and primary tumor groups were 59 (29 - 81 years) and 55 (14 and 82) respectively.

In metastasis group, 40 lesions of 40 patients were evaluated. Brain lesions were the metastasis of lung cancer (n=20), breast cancer (n=10), renal cell cancer (n=2), colon cancer (n=2), pancreas cancer (n=1), malignant fibrous histiocytoma (n=1), bladder cancer (n=1), adenocarcinoma of lung (n=1), and adenocarcinoma of unknown origin (n=2). In primary tumor group 40 lesions of 40 patients were measured. Pathological diagnoses were glioblastoma multiforme (GBM) (n=24), oligodendroglioma (n=4), anaplastic oligoastrocytoma (n=4), gliosarcoma (n=3), hemangiopericytoma (n=1), astrocytoma (n=1), primary lymphoma of CNS (n=1), pleomorphic xanthoastrocytoma (n=1) and dysembryoplastic neuroectodermal tumor (n=1).

Metastases were at the parietal lobe in 15 patients, at the frontal lobe in 16 patients, at the temporal lobe in 1 patient, at the parieto-occipital lobe in 7 patients and at the frontoparietal lobes in 1 patient. Primary tumors were at the parietal lobe in 10 patients, at the frontal lobe in 17 patients, at the temporal lobe in 3 patients, at the frontoparietal lobes in 4 patients and at the frontotemoral lobes in 2 patients.

The mean tumor volume and peritumoral edema volume of metastases were 12.0 cm$^3$ and 38.6 cm$^3$ respectively. In primary tumor group, mean tumor volume and peritumoral edema volume were 26.1 cm$^3$ and 37.9 cm$^3$ respectively. When GBM and other than GBM subgroups were evaluated, the mean tumor volume was 26.2 cm$^3$ and peritumoral edema volume was 37.7 cm$^3$ in GBM subgroup. In other than GBM subgroup, the mean tumor volume was 26.0 cm$^3$ and mean peritumoral edema volume was 38.1 cm$^3$. Maximum peritumoral edema volume was reaching to 151 cm$^3$ in metastasis group while it is 126 cm$^3$ in GBM subgroup (Table 1).
According to our observation, peritumoral edema can reach more extensive levels in patients with metastatic brain tumors. Yet, it is not causing to midline shift.

A midline shift was not detected in 23 (57.5%) of metastatic tumors and in 9 (22.5%) of primary tumors. The mean value of midline shift of metastasis and primary tumor groups were 2.0 mm and 5.2 mm respectively. When GBM and other than GBM subgroups were analyzed the mean values of shift were 5.2 mm and same in both of the subgroups. In metastasis group 34 (85%) of patients were in grade 1 subfalcian herniation group while 6 (15%) of patients were in grade 2. In primary tumor group, GBM subgroup has 15 (62.5%) patients in grade 1 herniation and 9 (37.5%) patients in grade 2 herniation group while other than GBM subgroups has 10 (62.5%) patients in grade 1 herniation group and 6 (37.5%) patients in grade 2 herniation group.

Mass-edema indexes of metastasis and primary tumor groups were 9 and 2.5 respectively. Mass-edema indexes of the GBM and other than GBM subgroups were 2.1 and 3.1 respectively (Table 1).

3.2. Statistical results

Statistical evaluation of the data revealed that midline shift, tumor volume and mass-edema index were significantly different between metastasis and primary tumor groups (p=0.001, p<0.001, p=0.001). However there was no significant difference in midline shift, tumor volume and mass-edema index between GBM and other than GBM subgroups. Midline shift and tumor volume of the primary tumor group were greater than metastasis group while volume index was less. Difference in shift grade of metastasis and shift grade of primary tumor groups was also statistically significant (p=0.041). A midline shift more than 5 mm (grade 2) was more common in primary tumors. There was no significant difference in edema volume between the groups (GBM, other than GBM and metastasis groups) (p=0.954).

Also statistical analysis performed for evaluation of metastatic and primary brain tumors in same tumor location. Primary tumors and metastasis in same localization (e.g. frontal lobe, parietal lobe… etc.) were selected. Statistical evaluation was performed for tumor volume, peritumoral edema volume and mass-edema index differences. For frontal lobe localization, tumor volume was significantly different between metastasis and primary tumor group (p= 0.14). It was the same for parietal lobe also (p=0.01). Mass-edema index was also statistically different between metastasis and primary tumor group in frontal lobe localization.
(p=0.06). But mass-edema index was not statistically significantly different between two groups for parietal lobe localization (p=0.129). For other localizations, numbers of lesions were not enough to evaluate. No statistically significantly difference was found for peritumoral edema volume between metastasis and primary tumor groups in frontal or parietal lobe localization.

4. Discussion

The present study demonstrated that midline shift, tumor volume and mass-edema index were significantly different between metastatic and primary brain tumors.

The differentiation of metastatic and primary brain tumors with certainty is important since clinical management and treatment of these two types of tumors are radically different [1, 2]. Metastases and high-grade gliomas are the most common intra-axial brain tumors (3,17). In many clinical settings, especially in patients with multiple lesions, the diagnosis of brain metastasis is usually straightforward and uncomplicated. However, it is often difficult to differentiate a solitary brain metastasis from a high grade glioma based on the imaging findings alone and applied MRI techniques, such as MR spectroscopy and perfusion imaging have been reported to be of value in this regard (3).

All aggressive brain tumors, such as malignant gliomas and metastatic tumors produce brain edema regardless of their cell type of origin (18). Papadopulos et.al (18) mentioned the differences in the molecular mechanisms of metastatic and primary brain tumor edema in their study that published in 2004. Law et.al (19) was mentioned that T2 weighted areas of hyperintensity seen in peritumoral regions surrounding metastases is likely to be due to vasogenic edema associated with the leakiness of abnormal capillaries of metastatic tumors and on the other hand in high-grade gliomas, the enhancing portion of the tumor demonstrates breakdown of the blood-brain barrier. Additionally, some studies that focusing peritumoral area for differential diagnosis have been performed like the study of Tsuchiya et al. Tsuchiya et al. evaluated fractional anisotrophy (FA) maps of diffusion tensor images of the enhancing tumor and peritumoral area in both brain metastasis and high grade glioma in 2005, but found no significant differences in FA values. Also in 2002 Meng Law et al. mentioned that, perfusion-weighted and spectroscopic MR measurements in the peritumoral region can be used to demonstrate differences in solitary metastasis and high grade gliomas. According to
study of Tang et al. in 2006, the key to making the distinction between these two entities appears to lie in detecting the changes within the peritumoral area (17). In metastases, this area consists essentially of vasogenic edema, while in gliomas; this may also contain neoplastic cells (3,17,19-22). So there are differences in molecular and macroscopic mechanism of peritumoral edema occurrence between metastasis and primary brain tumors. This made us thought there might be a difference in peritumoral edema volume and mass effects also. All these studies focused on to peritumoral region for differential diagnosis but none of them mentioned volume measurement and give quantitative volume values. One of the strong sides of our study is giving quantitative measurements of edema volume, mass volume and mass-edema index of metastatic and primary brain tumors. All the studies mentioned above define some differences in the peritumoral edema of metastasis and primary brain tumors. But when it comes to volume of peritumoral edema we found no significant difference between the groups.

Also we were evaluated the midline shift of two group and find that shift in primary tumor group is significantly grater than in the metastasis group. This can be explained by malign tumor cells in edema. But we also found strong correlation with tumor volume and shift length in the primary tumor group(r:0,718). So we have concluded that reason for greater midline shift in primary tumor group may be the result of greater tumor volume. Tang et al. mentioned that there is relatively greater extracellular water content in peritumoral vasogenic edema related to a metastasis compared with glioma. But we found no difference in peritumoral edema volume of the metastasis, GBM and other than GBM primary tumor group statistically. Therefore peritumoral edema which contains neoplastic cells may does not affect edema volume in the primary tumor group.

The major limitations of our study are different kinds of tumors in primary brain tumor group and different localizations of tumors. Patient groups that consist of solitary brain metastasis and solitary glioblastoma in same localization with similar tumor volume can be chosen for further studies. Randomized larger series that comparable according to age, sex and location are needed. But our study showed the differences of primary brain tumors and metastasis with quantitative volume measurements and made the definition of mass-edema index.

Another limitation of our study was retrospective nature of the study.
Strong side of our study is definition of mass-edema index. The index was made by dividing edema volume to tumor volume. The index was statistically significantly different in metastasis, GBM and other than GBM primary tumors group. Mass-edema index is significantly different in metastasis group than total primary tumor group statistically. In previous studies, it is reported that pathophysiology of peritumoral edema is different from each other in metastatic and primary brain tumors [2]. Metastasis is expansive and displaces the surrounding brain tissues rather than invading them [8-12] thus peritumoral edema area of metastatic brain tumors consists essentially of vasogenic edema [13-15]. On the other hand, GBM typically grows infiltratively and invades the surrounding tissues [7]. For this reason peritumoral edema area of metastatic brain tumors also contains peritumoural infiltrating neoplastic cells localized along the perivascular spaces [13-15]. But as we mentioned above, we found no difference in peritumoral edema volume of the metastasis, GBM and other than GBM primary tumor group statistically. Mean peritumoral edema volume of each group was similar (Table 1). On the other hand, mean tumor volumes of metastasis and primary tumor groups were different. We thought that lower mass-edema index in primary tumor groups might be the result of higher tumor volumes in that group. As far as our knowledge this definition is first in literature and there is no study that gives measurement of mass-edema index. This study suggests that mass-edema index can be a useful tool for differential diagnosis.

5. Conclusion

As a conclusion, measurement of midline shift, tumor volume and mass-edema index may contribute to the differential diagnosis of brain metastasis from primary brain tumors. Also mass-edema index can be a useful tool for differential diagnosis in the future. But further studies with larger series are needed.

Acknowledgements

The Editors gratefully acknowledge the assistance of Prof.Dr.Hülya Ellidokuz, who performed the statistical evaluation of the data.

No funding to declare.
Authors’ Contributions M.M.B.: provided the conception and design of the study, acquisition of data, analysis and interpretation of data, volum measurements, drafting the article, revised it critically for important intellectual content, and final approval of the version to be submitted; A.O.C.: supplied the acquisition of data, volum measurements, drafting of manuscript; N.S.G.: provided the revised the article critically for important intellectual content, E.A..: provided the conception and design of the study.

Conflicts of interests/disclosures

All authors have no conflict of interest to report
References


Table Legends

Table 1. Distribution of lesions according to displacement severity (midline shift), tumor volume, mass-edema index and tumor localization is shown in the table below.

Figure Legends

Figure 1. Tumor volume and peritumoral edema volume measurements that were done by using Lesion Annotation & Volume Assessment (LAVA) software are shown in the figure below. Fig.1A) Peritumoral edema measurement, Fig.1B) Tumor volume measurement.
**Table 1:** Distribution of lesions according to displacement severity (midline shift), tumor volume, mass-edema index and tumor localization is shown in the table below.

<table>
<thead>
<tr>
<th>Tumor volume(cm³)</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>0.10</td>
<td>12</td>
<td>75.74</td>
</tr>
<tr>
<td>GBM</td>
<td>4.52</td>
<td>26.2</td>
<td>66.7</td>
</tr>
<tr>
<td>Other than GBM</td>
<td>3.32</td>
<td>26.0</td>
<td>93.0</td>
</tr>
</tbody>
</table>

**Peritumoral edema volume(cm³)**

<table>
<thead>
<tr>
<th>Tumor volume(cm³)</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>0.67</td>
<td>38.6</td>
<td>151.55</td>
</tr>
<tr>
<td>GBM</td>
<td>0.93</td>
<td>37.7</td>
<td>126.48</td>
</tr>
<tr>
<td>Other than GBM</td>
<td>2.74</td>
<td>38.1</td>
<td>122.88</td>
</tr>
</tbody>
</table>

**Mass-edema index**

<table>
<thead>
<tr>
<th>Tumor volume(cm³)</th>
<th>Min</th>
<th>Mean</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>0.09</td>
<td>9</td>
<td>68.43</td>
</tr>
<tr>
<td>GBM</td>
<td>0.10</td>
<td>2.1</td>
<td>7.67</td>
</tr>
<tr>
<td>Other than GBM</td>
<td>0.05</td>
<td>3.1</td>
<td>12.59</td>
</tr>
</tbody>
</table>

**Tumor location**

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Other locations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>16(40%)</td>
<td>15(37.5%)</td>
<td>9(22.5%)</td>
</tr>
<tr>
<td>GBM</td>
<td>10(25%)</td>
<td>6(15%)</td>
<td>8(20%)</td>
</tr>
<tr>
<td>Other than GBM</td>
<td>7(17.5%)</td>
<td>4(10%)</td>
<td>5(12.5%)</td>
</tr>
</tbody>
</table>

**Displacement (Shift)**

<table>
<thead>
<tr>
<th>Displacement (Shift)</th>
<th>Shift&lt;5 mm (Grade 1)</th>
<th>Shift&gt;5 mm (Grade 2)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>34(85%)</td>
<td>6(15%)</td>
<td>40(100%)</td>
</tr>
<tr>
<td>GBM</td>
<td>15(37.5%)</td>
<td>9(22.5%)</td>
<td>24(60%)</td>
</tr>
<tr>
<td>Other than GBM</td>
<td>10(25%)</td>
<td>6(15%)</td>
<td>16(40%)</td>
</tr>
<tr>
<td>Total</td>
<td>59(73.75%)</td>
<td>21(26.25%)</td>
<td>80(100%)</td>
</tr>
</tbody>
</table>

*Other locations; temporal lobe, frontoparietal lobe, parietooccipital lobe, frontotemporal lobe.