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Quantitative CT Volumetric Measurement of Peritumoral Edema Assists in Differentiate Between Primary Brain Tumor and Solitary Metastatic Brain Tumor

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Abstract

Brain imaging is necessary in clarifying intracranial pathology that produces clinical symptoms to the patients. The CT brain scan is a fast, simple and safe valuable neuroimaging tool that provides diagnosis. Brain tumors are a common disease that cause severe neurological symptoms and neurological deficits which require urgent treatment. Primary brain tumors such as the glioma group and meningioma as well as metastatic brain tumor are among the three most prevalent type of brain tumor encountered everywhere in the world, including Thailand. If a brain tumor has specific characteristic such as pathognomonic findings like meningioma, CT brain scans can give the right diagnosis and lead to treatment. However, glioma tumors, particularly glioblastoma multiforme (GBM), the most commonly encountered, have no pathognomonic characteristic along with solitary metastatic brain tumors. Both gliomas and metastatic tumors usually have hypodensity in the gray matter and heterogeneously enhancement surrounded by vasogenic edema. Both tumors have a significantly different prognosis and treatment method via surgery, radiation therapy and chemotherapy. Therefore, we quantitatively measured vasogenic edema on a CT scan to help differentiation between primary brain tumor and solitary brain metastasis.

Objective: To evaluate the ratio between peritumoral edema volume and tumor volume acquired from a CT brain scan to help differentiate primary brain tumor from solitary metastatic brain tumor.

Materials and Methods: Our institutional review board approved this study, and we performed our study in Siriraj hospital. A total of 60 patients (30 patients with primary brain tumor and 30 with solitary metastatic brain tumor) CT brain scan was retrospectively studied before any treatment or surgical biopsy was performed. Clinical data were reviewed from electronic medical records and CT brain scans from the Picture Archiving and Communication System (PACS) in the hospital.

The tumor volume and perilesional edema volume were measured. Then, the peritumoral edema volume: tumor volume ratios were calculated. A Mann–Whitney U test and ROC curve analysis was applied for statistical analysis. P<0.05 was accepted as statistically significant.

Results: Median (min, max) peritumoral edema volume (PTV): tumor volume (TV) ratio of primary brain tumors and metastatic brain tumors were 0.802 (0.024, 3.48) and 3.136 (0.12, 28.27), respectively. The difference was statistically significant (p<0.001).

Conclusion: CT volumetric measurement of the PTV/TV ratio used in solitary brain tumors can be used as a surrogate marker in differentiation of metastatic tumors from primary brain tumors.

Keywords: Peritumoral edema; Primary brain tumor; Metastatic brain tumor; CT brain scan

Introduction

Brain tumors can be divided into primary and secondary brain tumors, with differences in prognosis, management, and plan of further investigation. For the time being, the most specific method after neuroimaging to differentiate between primary and metastatic brain tumors is tissue histopathology. In some clinical settings, especially in patients with multiple intracranial mass lesions and history of extracranial primary malignancies, the diagnosis of brain metastasis may be uncomplicated. However, it is often to have first met neurologists due to neurological symptoms and further neuroimaging investigation shows solitary mass lesion in the cranial cavity that is difficult to differentiate between a solitary brain metastasis from primary brain tumor, especially a high grade tumor which often sharing common imaging findings such as hypodensity to the gray matter, heterogeneously enhancement and surrounded by vasogenic edema.

From prior studies, applied advanced MRI techniques, such as MR spectroscopy and perfusion imaging, have been reported to be of value in differentiating between brain metastasis and high grade primary brain tumors [1-6]. According to previous study by Hakyemez et al. [1], using MRI in evaluating the peritumoral edema/tumor area ratio was significantly higher in metastatic brain tumors than in high-grade gliomas (the peritumoral edema: tumor area ratio was 0.69 ± 0.41 in high-grade gliomas and 2.41 ± 1.63 in metastases (p< 0.001)). Moreover, in a study by Chen et al. [2], glioblastoma multiforme (GBM) was more likely to have the area of peritumoral T2 prolongation ≤ the area of the tumor in the section where the tumor showed maximal diameter, and metastatic tumors were more likely to have the area of peritumoral T2 prolongation > the area of the enhancing tumor. However, there is limited amount of MRIs in Thailand and almost all of them are distributed in only the large cities. Moreover, due to long waiting times, some elderly patients cannot tolerate the long duration of MRI study. On the contrary, CT scanners are widely accessible and have a short scan time and can tolerate and differentiate normal brain tissue and intracranial pathology by means of morphology of lesion and density differences.

Thus, our objective was to determine if the ratio of peritumoral vasogenic edema volume (PTV) and primary brain tumor and metastatic brain tumor volume (TV) from CT findings also help differentiation between primary and metastatic brain tumor.

Materials and Methods

Patients

The CT images of patients with brain tumors, who were treated in Siriraj hospital between January 2007 to June 2013, were retrospectively analysed. Patients who had multiple lesions, prior brain surgery, prior brain radiotherapy, chemotherapy or history of steroid use at the time of CT scans, were not included in the study. Histopathological diagnosis was obtained after surgery was performed. After this step, 60 patients were randomly selected, 30 patients with primary brain tumor (20 male and 10 female patients aged between 5-74 years, mean age 44.5 ± 20.98) and 30 patients with metastatic brain tumor (18 male and 12 female patients aged between 30-77 years, mean age 56.73 ± 11.77) (Table 1,2). According to WHO's classification, the primary brain tumors were distributed as follows: grade IV glioblastoma (n=16), grade IV gliosarcoma (n=1), grade IV medulloblastoma (n=1), grade III anaplastic ependymoma (n=1), grade III anaplastic oligodendroglioma (n=1), high grade glioma grade III (n=1), germinoma (n=1), grade II oligodendroglioma (n=2), grade II oligoastrocytoma (n=1), grade I hemangioblastoma (n=2), and grade I pilocytic astrocytoma (n=3) (Table 3). The distribution of primary cancers associated with metastatic brain lesions came were as follows: lung (n=16), breast (n=6), uterus (n=2), colon (n=1), stomach (n=1), liver (n=1), shoulder (n=1), not definite (n=2) (Table 4).

Table 1: Demographic data, tumor volume, peritumoral edema volume, and peritumoral edema: tumor volume ratio of primary and metastatic tumors.

	Primary (n = 30)	Metastasis (n = 30)	*p*-value
Age† (years)	44.5 ± 20.98	56.73 ± 11.77	0.008
Sex (n): Male Female	20 (66.7%) 10 (33.3%)	18 (60%) 12 (40%)	0.592
Tumor volume# (cm^3)	34.86 (3.13, 122.55)	20.42 (2.40, 136.12)	0.04
Peritumoral edema volume# (cm^3)	29.23 (1.25, 132.13)	95.98 (5.25, 199.09)	0.001
Peritumoral edema: tumor volume ratio#	0.802 (0.024, 3.48)	3.136 (0.12, 28.27)	<0.001
#Median (Min, Max) †Mean ± SD			

Table 2: Tumor location.

Location	Metastasis (n = 30)		Primary (n = 30)		Total	
	number	%	number	%	number	%
Cerebellum	6	20	5	16.7	11	18.3
Corpus callosum	0	0	1	3.3	1	1.7
Cortical	1	3.3	8	26.7	9	15
Deep gray matter	3	10	6	20	9	15
Gray-white junction	19	63.3	9	30	28	46.7
White matter	1	3.3	1	3.3	2	3.3

Table 3: Pathohistology, location, tumor volume, peritumoral edema volume, and peritumoral edema: tumor volume ratio of the primary tumors.

No.	Pathohistology	Location	Tumor volume (cm^3)	Edema volume (cm^3)	Ratio
1	Anaplastic ependymoma gr.III	Deep gray matter	122.55	88.09	0.72
2	Anaplastic oligodendroglioma at least gr.III	Deep gray matter	14.48	8.24	0.57
3	Glioblastoma gr. IV	White matter	108.77	77.90	0.72
4	Glioblastoma gr. IV	Deep gray matter	52.45	81.01	1.54
5	Glioblastoma gr. IV	Gray-white junction	72.93	48.65	0.67
6	Glioblastoma gr. IV	Cortical	50.31	92.08	1.83
7	Glioblastoma gr. IV	Gray-white junction	3.13	8.04	2.57
8	Glioblastoma gr. IV	Cortical	46.73	67.40	1.44
9	Glioblastoma gr. IV	Gray-white junction	68.12	74.23	1.09
10	Glioblastoma gr. IV	Cortical	7.20	18.78	2.61
11	Glioblastoma gr. IV	Cerebellum	23.53	23.44	1.00
12	Glioblastoma gr. IV	Cortical	65.10	40.49	0.62
13	Glioblastoma gr. IV	Gray-white junction	26.81	93.37	3.48
14	Oligodendroglioma gr.II	Cortical	3.48	1.25	0.36
15	High grade glioma gr.III-IV	Deep gray matter	32.00	13.57	0.42
16	Oligoastrocytoma gr.II	Cortical	31.13	1.49	0.05
17	Hemangioblastoma	Cerebellum	8.70	25.20	2.90
18	Glioblastoma gr. IV	Cortical	13.46	1.30	0.10
19	Gliosarcoma gr.IV	Gray-white junction	71.38	132.13	1.85
20	Pilocytic astrocytoma gr.I	Gray-white junction	6.84	23.34	3.41
21	Medulloblastoma gr.IV	Cerebellum	14.57	9.03	0.62
22	Glioblastoma gr. IV	Corpus callosum	25.32	58.75	2.32
23	Oligodendroglioma at least gr.II	Gray-white junction	3.34	9.54	2.85
24	Pilocytic astrocytoma gr.I	Deep gray matter	57.56	1.41	0.02
25	Germinoma	Deep gray matter	48.31	33.25	0.69
26	Glioblastoma gr. IV	Gray-white junction	76.75	67.96	0.89
27	Hemangioblastoma gr.I	Cerebellum	36.39	7.69	0.21
28	Pilocytic astrocytoma gr.I	Cerebellum	48.66	14.46	0.30
29	Glioblastoma gr. IV	Cortical	33.32	75.90	2.28
30	Glioblastoma gr. IV	Gray-white junction	98.91	40.80	0.41

Table 4: Pathohistology, location, tumor volume, peritumoral edema volume, and peritumoral edema: tumor volume ratio of metastatic tumors.

No.	Pathohistology	Primary cancer	Location	Tumor volume (cm^3)	Edema volume (cm^3)	Ratio
1	Poorly differentiated carcinoma	Lung	Cerebellum	6.15	23.61	3.84
2	Carcinoma	Not definite	Cerebellum	43.78	5.25	0.12
3	Adenocarcinoma	Lung	Cerebellum	14.85	18.74	1.26
4	Adenocarcinoma	Colon	Gray-white junction	30.40	100.95	3.32
5	Carcinoma	Breast	Gray-white junction	39.97	86.64	2.17
6	Adenocarcinoma	Stomach	Gray-white junction	2.40	67.73	28.27
7	Adenocarcinoma	Breast	Deep gray matter	11.21	147.43	13.15
8	Poorly differentiated carcinoma	Lung	Gray-white junction	41.62	99.36	2.39
9	Non small cell carcinoma	Lung	Gray-white junction	46.23	101.85	2.20
10	Adenocarcinoma	Breast	Gray-white junction	6.67	131.08	19.67
11	Endometrioid adenocarcinoma	Uterus	Gray-white junction	14.73	116.15	7.89
12	Pulmonary adenocarcinoma	Lung	Gray-white junction	31.23	41.05	1.31
13	Hepatocellular carcinoma	Liver	Gray-white junction	47.00	108.20	2.30
14	Adenocarcinoma	Lung	Gray-white junction	26.64	52.46	1.97
15	Adenocarcinoma	Lung	Gray-white junction	28.07	23.79	0.85
16	Adenocarcinoma	Lung	Gray-white junction	4.50	92.61	20.59
17	Adenocarcinoma	Lung	Cerebellum	21.23	11.19	0.53
18	Adenocarcinoma	Not definite	Gray-white junction	25.81	106.18	4.11
19	Adenocarcinoma	Lung	Cerebellum	7.63	11.05	1.45
20	Poorly differentiated carcinoma	Lung	Deep gray matter	63.33	120.41	1.90
21	Adenocarcinoma	Lung	Gray-white junction	19.61	199.09	10.15
22	Adenocarcinoma	Lung	Cerebellum	30.58	13.86	0.45
23	Adenocarcinoma	Lung	Gray-white junction	2.75	9.82	3.56
24	Adenocarcinoma	Breast	Gray-white junction	17.23	63.08	3.66
25	Adenocarcinoma	Lung	Deep gray matter	8.22	59.97	7.29
26	Adenocarcinoma	Lung	Cortical	4.11	111.89	27.26
27	Adenocarcinoma	breast	Gray-white junction	41.94	123.74	2.95

28	Malignant fibrous histiocytoma	Shoulder	Gray-white junction	17.51	100.92	5.76
29	Small cell carcinoma	Uterus	White matter	136.12	107.53	0.79
30	Mammary carcinoma	Breast	Gray-white junction	16.08	136.54	8.49

CT Imaging and Processing

The examinations were performed using one of three CT scanners: Siemens 64-slice dual-source CT, GE LightSpeed VCT 64-slice CT or a single-slice helical CT scanner (Tomoscan AV1, Philips medical systems). Images were acquired by using a standard protocol for assessment of intracranial lesions with section thickness 1.25 or 1.5 mm. The volume of tumors and perilesional edema was generated using a volume rendering application known as Advantage workstation program (AW Volume Share 5, GE Healthcare). The images were set at a window width of 100 and window level 35, which were set automatically by the software. The measurements were recorded by two readers (neuroradiologists with 22 years' experience and one with 15 years' experience), who were blinded from patient data that was randomly mixed between the two groups of patients. For tumor volume measurements, the region of interest (ROI) was highlighted by enhancing portions, including cystic portion of the tumor (Figure 1,3). For perilesional edema volume, the ROI was the abnormal hypodense area around the tumor, which included the volume of tumor (Figure 2,4). Then, calculated volume was minus with the tumor volume, resulted in peritumoral edema volume. In cases in which the outline of peritumoral edema was unclear, the outline was made by narrowing the CT window setting based on a consensus of the two readers. Then the peritumoral edema and tumor volume ratio calculated according to the following equation:

$$\text{Peritumoral edema volume (PTV): tumor volume (TV) ratio} = \frac{\text{peritumoral edema volume}}{\text{tumor volume}}$$

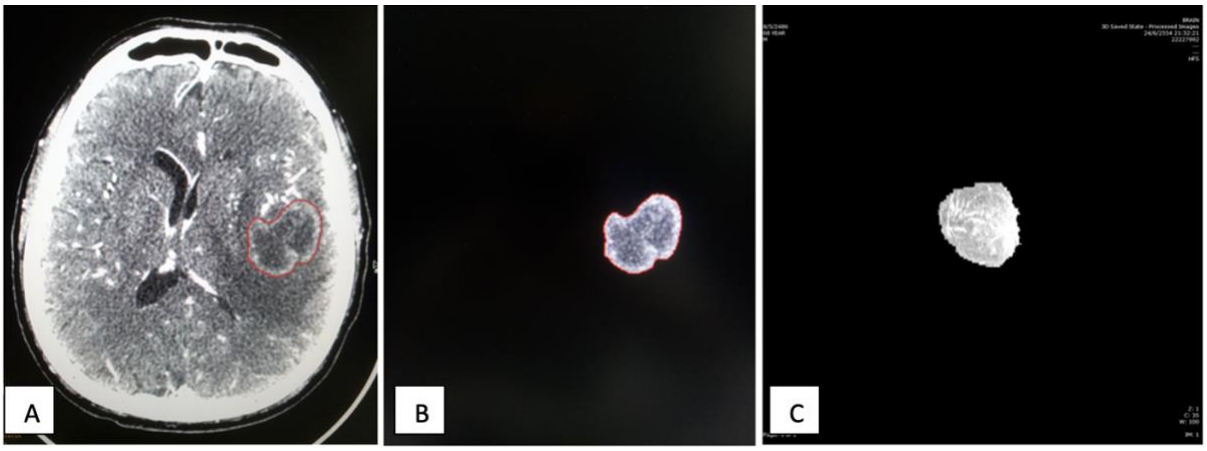

Figure 1: Glioblastoma WHO gr.IV **(A,B):** region of interest for tumor volume measurement; **(C):** 3D volume rendering of tumor volume.

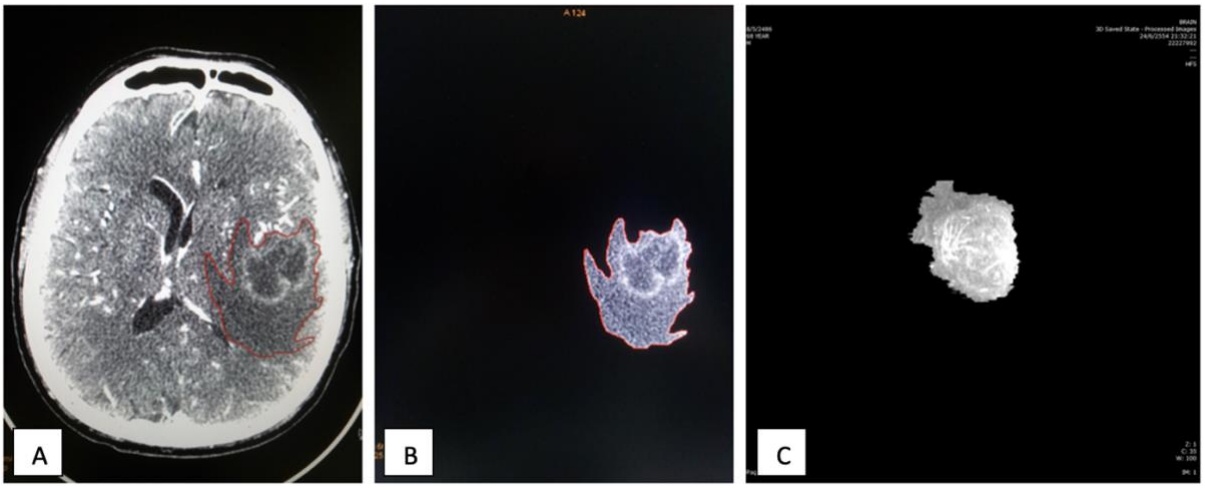

Figure 2: Glioblastoma WHO gr.IV **(A,B):** region of interest for total volume measurement (peritumoral edema volume + tumor volume); **(C):** 3D volume rendering of total volume.

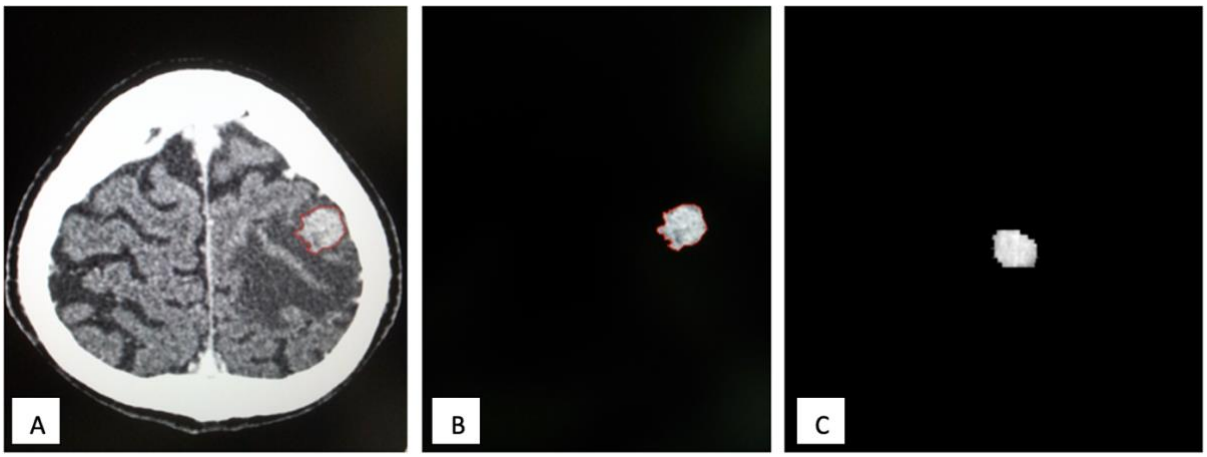

Figure 3: Solitary metastasis. **(A,B):** region of interest for tumor volume measurement; **(C):** 3D volume rendering of tumor volume.

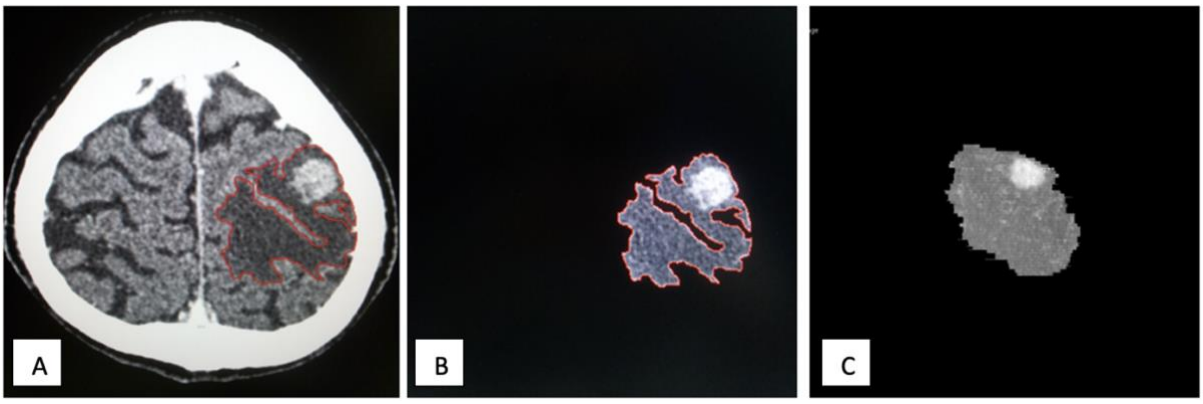

Figure 4: Solitary metastasis. (A, B) region of interest for total volume measurement (peritumoral edema volume + tumor volume). (C) 3D volume rendering of total volume.

Statistical Analysis

Mean and standard deviation were used to describe the age of the patients in each group and were compared using a student t-test. Sex, location of the tumor, and primary cancer associated with the metastatic brain lesion were described in percentage. The number of tumors at the gray-white matter junction in each group and sex of patients were compared using a Chi-square test.

Due to large variable of tumors and peritumoral edema volume, we used median to describe the data. The tumor volume, peritumoral edema volume, and peritumoral edema: tumor volume ratio were compared using the Mann-Whitney U test. A receiver operating characteristic (ROC) curve analysis was performed to assess whether there was a significant difference between the peritumoral edema: tumor volume ratios of the primary brain tumor and metastases. Sensitivity specificity was established to use as potential cut-off values to allow for differentiation between lesions (Figure 5). A difference of $p<0.05$ was considered statistically significant. And interobserver agreement was calculated using intraclass correlation coefficient.

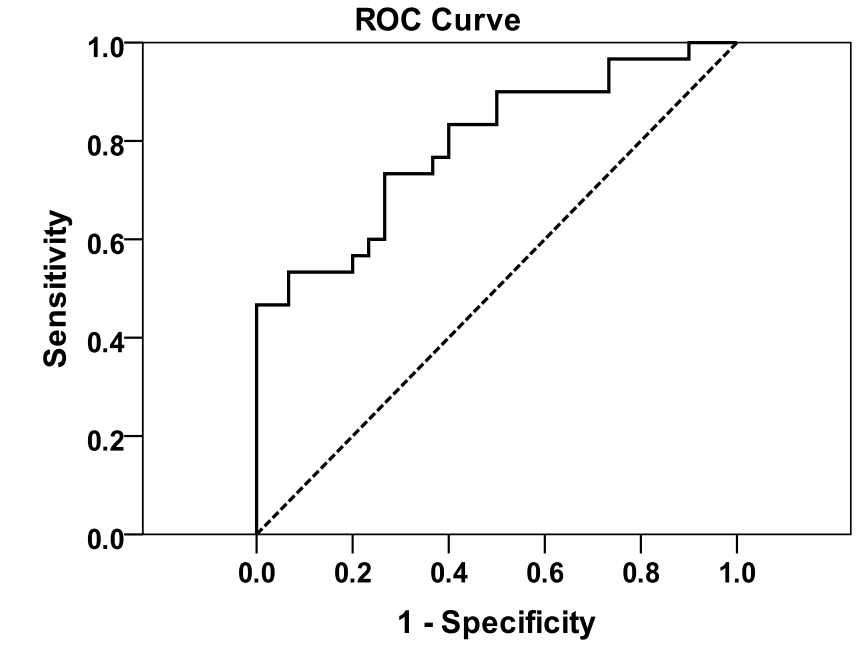

Figure 5: Results of ROC analyses of peritumoral edema: tumor volume ratios.

Results

Patient age data had normal distribution. The age of patients in the metastatic group was significantly higher than the primary tumor group (metastatic mean age = 56.73 ± 11.77, primary tumor mean age = 44.5 ± 20.98, $p = 0.008$). No difference between primary tumors and metastatic tumors regarding gender ($p = 0.592$) was observed. The number of tumors located at gray-white junction, was significantly higher in the metastatic group or 63.3% vs 30% in the primary tumor group ($p = 0.01$). There was consistency between the two separate measurements by both radiologists regarding tumor volume, peritumoral edema volume, and peritumoral edema: tumor volume ratio with an intraclass correlation coefficient of 0.999, 0.997 and 0.999 respectively.

Primary brain tumor sizes range from 3.13 and 122.55 cm^3 [42.41 ± 32.43 (mean ± SD), median = 34.86], peritumoral edema sizes were between 1.25 and 132.13 cm^3 [41.29 ± 35.91 (mean ± SD), median = 29.23], and the peritumoral edema: tumor volume ratio was between 0.024 and 3.48 [1.28 ± 1.06 (mean ± SD), median = 0.802].

For metastatic tumors, the tumor size ranged between 2.40 and 136.12 cm^3 [26.92 ± 26.04 (mean ± SD), median = 20.42], peritumoral edema sizes were between 5.25 and 199.09 cm^3 [79.74 ± 49.88 (mean ± SD), median = 95.98], and the peritumoral edema: tumor volume ratio between 0.12 and 28.27 [6.32 ± 7.80 (mean ± SD), median = 3.136].

The peritumoral edema volume and peritumoral edema: tumor volume ratio were significantly higher in metastatic tumors ($p = 0.001$ for peritumoral edema volume and $p<0.001$ for peritumoral edema: tumor volume ratio). The tumor size was larger in primary brain tumors ($p = 0.04$) and the area under the ROC curve for the peritumoral edema: tumor volume ratio was calculated as 0.794 (Figure 5). A cut-off value of >1.5 was obtained from ROC analysis of the peritumoral edema : tumor volume ratio and the sensitivity and specificity was 73.3% and 63.3%, respectively.

Discussion

The two most common intracranial neoplasms, brain metastasis and IDH wild type glioblastoma, make up more than 70% of all brain tumors. Among the glioma group, blood brain barrier (BBB) alterations are most prominent in glioblastoma multiforme (WHO IV, GBM), the most malignant form of brain tumor and associated with high morbidity and poor median survival [7,8]. Differential diagnosis between primary brain tumors and metastatic brain tumors is importance as there are different approaches of diagnosis, treatment, and follow-up procedures for each type. The fact that metastatic tumors are generally seen in patients with a history of primary malignancy with multiple lesions that are well-defined masses at the gray–white junction helps the diagnosis [9]. However, differentiatiating solitary metastatic tumors between unknown and primary brain tumors is difficult. Multiple previous studies have reported using applied MRI techniques, such as dynamic contrast susceptibility MRI, MR spectroscopy, perfusion imaging, DTI, to differentiate between brain metastasis and high grade primary brain tumors [1-6, 10-13]. CTs have a role in brain tumor imaging such as in case where a patient presents acute neurological deterioration, partial to noncooperation or when there are contraindications to a MR study. In such instances, CT brain is the first line of investigation imaging modality. CT brain scans can use density to differentiate tissues property such as solid, cystic portions, hemorrhage, calcification and edema of tumor from normal brain tissue. After iodinated contrast medium administration, reevaluation of the pattern of enhancement is used to make differential diagnosis [14]. Among the tissue properties, brain edema plays a role in the diagnosis of brain tumors and edema associated with brain tumors as they are vasogenic which contrasts other circumstances such as hypoxia- or hypoosmolality-induced edema of cytotoxic origin [15]. Basically, density of brain edema is less than normal brain tissue in both gray and white matter and vasogenic edema is confined to the white matter bundle distribution [16]. Previous studies mention the multiple utility of CT brain scans in detection of GBM and brain metastasis [8,14,17,18].

In our study the mean age of patients with metastatic tumor was higher than that of primary brain tumor. This can be explained by low incidence of metastatic tumor in young patients. The location of tumors at the gray-white junction has a higher incidence in metastatic tumor (63.3% in metastatic tumors and 30% in primary brain tumors), which correlates with prior studies.

In prior studies, the peritumoral edema: tumor area ratio was significantly higher in metastatic brain tumors than in high-grade gliomas [1,2]. Accordingly, in our study the peritumoral edema: tumor volume ratio measured by CT images was also significantly higher in metastatic brain tumors than in primary brain tumors. The difference between the peritumoral edema volume of primary brain tumors and metastatic tumors can be explained by the pathophysiological mechanisms of the blood-brain barrier [19]. In high-grade primary brain tumors, capillaries show different morphological characteristics and varying degrees of damage in the blood–brain barrier. Thus, capillary permeability may vary. In metastases, capillaries bear the morphology of the original systemic cancer and have no blood–brain barrier components with significant capillary fenestrations. This single capillary feature forms large vasogenic edema areas via significant increases in permeability [1]. Furthermore, low grade primary brain tumors usually show less degree of damage in the blood-brain barrier. In the present study, a statistically significant difference between peritumoral edema: tumor volume ratio was found in metastatic tumors compared to primary brain tumors, which supports the pathophysiological mechanism ($p<0.001$). These ratios were much higher in metastatic tumors than primary brain tumors and therefore should help differentiate the two.

There is a large variety of peritumoral edema volume in both primary and metastatic brain tumors. The peritumoral edema: tumor volume ratios of metastatic brain tumors were between from 0.12 to 28.27, mean PTV/TV=6.32, range 0.024 to 3.48, mean PTV/TV=1.28 in primary brain tumors. Some lesions with small peritumoral edema could be metastatic brain tumors and some lesions with large peritumoral edema could be primary brain tumors. However, the study suggests that a PTV/TV ratio greater than 3.5 means the possibility of brain metastasis is much high and should interpretation together with tumor morphology, contrast enhancement pattern, location of tumor as well as clinical context for the completeness.

Conclusion

The PTV/TV ratio a CT brain scan might provide additional helpful information such as a quantitative index that can effectively differentiate metastatic tumors from primary brain tumors. Thus, the PTV/TV ratio along with other CT images characteristic findings such as tumor morphology, contrast enhancement pattern, and location of tumor etc, and clinical context are recommended.

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