Rezk and Mokbel
Egyptian Journal of Neurosurgery (2023) 38:6
https://doi.org/10.1186/s41984-023-00193-1

Egyptian Journal of Neurosurgery

RESEARCH

Open Access

Stereotactic biopsy for multiple intra-axial brain lesions: impact on consequent treatment Regimen

Essam M. Rezk* and Essam Mokbel

Abstract

Background and objectives Multiple brain lesions represent a serious challenge in which biopsy is commonly the first step to help overcome patients' mental anxiety and decide the following treatment step. This study presents an effective decisional algorithm that could guide in dealing with such a challenge. We evaluate the feasibility and safety of frame-based stereotactic biopsy to obtain the histopathologic diagnosis of the multiple intra-axial brain lesions and to decide the further treatment.

Patients and methods Thirty-two patients with multiple intracerebral lesions underwent stereotactic serial biopsies for brain lesions at the Neurosurgery Department, Tanta University Hospital. All the stereotactic biopsies were obtained under local anesthesia using Riechert–Mundinger (RM) system or Cosman–Roberts–Wells (CRW) system.

Results The histopathological diagnosis revealed multifocal malignant gliomas in 43.75% of patients (18.75% anaplastic astrocytoma and 25% multiform glioblastoma) and metastatic tumor in 37.5% of patients (all were adenocarcinoma). In addition, 12.5% had multiple brain abscesses, and 6.25% had malignant lymphoma. We reported no mortality secondary to the surgical procedure.

Conclusions Stereotactic biopsy is considered the best choice to allow histopathologic diagnosis of multiple brain lesions with minimal morbidity and no mortality. Histopathologic findings gained with stereotactic procedures guided the choice of proper treatment thus eliminating the hazards associated with blind treatments.

Keywords Multiple brain lesions, Stereotactic biopsy, Decisional algorithm

Introduction

The differential diagnosis of multiple brain tumors includes multifocal glioma, metastatic brain tumors, multiple brain abscesses and multicentric lymphomas. In medulloblastomas and ependymomas, subarachnoid seedings can be detected as tumoral nodules along the brain and spinal cord. Multiple brain tumors can also be seen in tuberous sclerosis (subependymal tubers and subependymal giant cell astrocytomas) and neurofibromatosis type I (optic gliomas and hemispheric astrocytomas) [1]. Unfortunately, similar imaging features can be seen in many tumor-like lesions including multiple sclerosis tumefactive plaques, resolving hematomas, vascular malformations, opportunistic infections in HIV patients and even metabolic disorders [2].

Some of these cases could be appropriately diagnosed regarding the nature of their brain lesions after laboratory and clinical examinations, as in multiple sclerosis, secondary infective diseases, metastatic tumors, and systemic diseases affecting the brain [3]. However, some argue that the histopathologic diagnosis for the brain lesion itself is required for a variety of reasons:

*Correspondence:
Essam M. Rezk
es_moneer2000@yahoo.com; essam.rezk@med.tanta.edu.eg
Department of Neurosurgery, Faculty of Medicine, Tanta University, El-Gaish Street, Tanta 31527, Egypt

1. The primary tumor location will not be discovered in up to 15% of brain metastasis patients, despite thorough investigation [4].
2. Brain lesions may not be metastatic in about 11% of cases with a known history of systemic cancer [5].
3. Clinical impression based on advanced neuroimaging such as CT or MRI is not identical to a histopathological finding. Furthermore, the wide range of diseases seen in patients with multiple brain tumors highlights the importance of tissue diagnosis in avoiding the risks of therapy based solely on clinical laboratory and neuroimaging data. In practice, tumor-like lesions (such as the tumefactive plaque of multiple sclerosis) can be treated more conservatively, whereas tumors (such as lymphomas) should be treated aggressively. Misinterpretation could lead to overtreatment of a benign lesion or a considerable delay in getting a malignant one treated properly [3].
4. The current increase in the survival rate of patients with immunosuppressive and systemic diseases due to advances in diagnostic and therapeutic options resulted in increasing the variety of neuropathologic processes, thus demanding a thorough differential diagnosis of histopathology of intra-axial brain lesions [6].
5. For many cerebral space-occupying lesions diagnosed in CT scan or MRI, the histological diagnosis is the sole demonstrable confirmation of the disease, and treatment is based on this histopathological diagnosis [7–9].

The aim of this retrospective study was to determine the safety and feasibility of stereotactic biopsy for detection of the histopathological diagnosis of these multiple intra-axial brain lesions and to decide the further treatment plan through an effective decisional algorithm.

Patients and methods

Patient population and selection criteria

Patients with multiple intra-axial brain lesions and no neoplasms outside the nervous system were designated for our stereotactic biopsy protocol guided by our decisional algorithm (Fig. 1). Patients who met at least one of the following criteria were included in the study:

1. Lesions that are invasive but do not have a significant mass effect.
2. Lesions on CT or MRI that are poorly defined.
3. Suspicion of radiosensitive lesions, e.g., germinoma and lymphomas.
4. An undiagnosed intra-axial mass lesions in eloquent or deeply seated location that could not be diagnosed by craniotomy without high risk of morbidity.

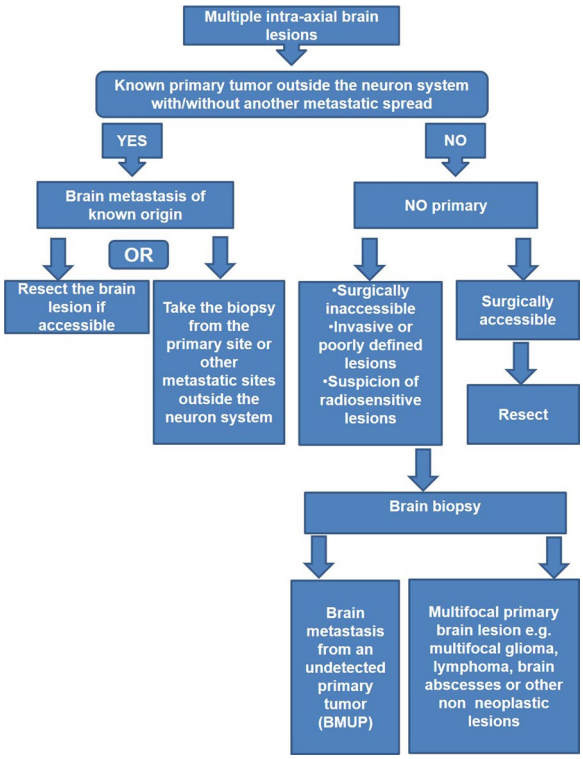

Fig. 1 A decisional algorithm to guide in dealing with multiple intra-axial brain lesions

The prerequisites for patients' selection.

- Karnofsky performance scale > 70.
- There are no systemic disorders that could be linked to the brain localization.
- There were no cerebral circulation disorders and no evidence of demyelinating diseases.

Between 2012 and 2021, two hundred ninety-five patients underwent stereotactic serial biopsy for brain lesions at the Neurosurgery department of Tanta University Hospital. Multiple intracerebral lesions were found in 32 patients. These patients ranged in age from 27 to 66 years old (mean age 51), 20 were males and 12 were females. The heralding symptoms included focal neurological deficits in 22 cases, intracranial hypertension in 14 cases, and epileptic seizures in 12 cases (Table 1).

Multiple intra-axial brain lesions were categorized as having three or more lesions in different cerebral lobes. The number of radiologically revealed lesions in each patient ranged from 3 to 8 (mean 4). Left hemisphere lesions found in 18 patients, 8 patients had right hemisphere lesions, and 6 patients had lesions in both hemispheres.

Table 1 Patients' and peri-operative characteristics

Patients (*n*)	**32**
Sex [*n* (%)]	
Male	20 (62.5%)
Female	12 (37.5%)
Median age (range [years])	51 (27–66)
Median number of lesions (range)	4 (2–8)
Side of tumor [*n* (%)]	
Right hemisphere	8 (25%)
Left hemisphere	18 (56.25%)
Both hemispheres	6 (18.75%)
Focal neurological deficit	
Yes	22 (68.75%)
No	10 (31.25%)
Symptoms of increased intracranial pressure	
Yes	14 (43.75%)
No	18 (56.25%)
Fits	
Yes	12 (37.5%)
No	20 (62.5%)
Median operating time in minutes (range)	75 (60–105)
Median number of biopsies (range)	6 (4–10)
Mortality & Mortality	
Biopsy-related hemorrhage	1 (3.12%)
Biopsy-related death	0

Vasogenic edema around the lesion was treated with a steroid dosage of 4 mg dexamethasone three times per day. Steroids should not be given to patients with suspected lymphomas if stereotactic biopsy is being considered since doing so would make the lesion radiographically fade.

Preoperative clinical assessment

Before the stereotactic brain biopsy technique, all patients had a clinical, laboratory, and radiological evaluation. High-risk patients with history of bleeding diathesis were excluded. Patients taking antithrombotic drugs were told to stop taking them at least 7 days before the biopsy. A Karnofsky Performance Scale (KPS) [10] was used to evaluate all patients before and after the surgical procedure.

The work has been carried out per The Code of Ethics of the World Medical Association (Declaration of Helsinki) for human research. All patients signed an informed consent after detailed explanation of procedure-related risks and agreed that their data would be used for scientific evaluation.

Table 2 Histopathological diagnosis in 32 patients with multiple intra-axial brain lesions made by stereotactic biopsy

Histological diagnosis	**Number of patients**	**Percent (%)**
Metastasis of unknown origin	**12**	**37.5**
Multifocal primary brain lesions		
[A] Multifocal malignant gliomas	**14**	**43.75**
Multiform glioblastoma	8	25
Astrocytoma (grade III)	6	18.75
[B] Abscess	**4**	**12.5**
[C] Malignant lymphoma	**2**	**6.25**
Total	**32**	**100**

Stereotactic technique

The Riechert–Mundinger (RM) or Cosman–Roberts–Wells (CRW) system was used for all stereotactic biopsies that were performed under magnetic resonance and CT image guidance for stereotactic localization. In each patient, a multiplanar reconstruction software called Praezis plus 3 (Inomed Company, Germany) was utilized to determine the optimal trajectory.

A direct trajectory via a single pial surface was chosen, and transgression of an ependymal surface was almost never required. All procedures were done under local anesthesia. Serial biopsies were obtained with a side-cutting needle along the maximal diameter of the lesion to acquire information about the zone of infiltration, vital neoplasm, and necrotic areas.

Histopathological assessments

The tissue samples were fixed in neutral buffered formalin at a 10% concentration before being submitted for histopathological analysis, with the exception of pus, which should be sent for antibiotic sensitivity testing and culture instead of formalin fixation. Hematoxylin and eosin (H&E) staining, as well as additional staining techniques such as immunohistochemical staining, was used to stain paraffin tissue slices. The histopathological diagnoses were based on 2016 Central Nervous System Tumor Classification system proposed by the World Health Organization (WHO) [11].

Results

The histopathological diagnosis of the biopsied lesions is shown in Table 2. The plan of the further treatment was guided by these histopathological findings. 14 patients (43.75%) had multifocal malignant gliomas, including anaplastic astrocytoma (18.75%) and multiform glioblastoma (25%). Multiple malignant gliomas were treated by chemotherapy and conventional

radiotherapy. 12 patients (37.5%) had metastatic brain tumor from pulmonary adenocarcinoma; a subtype of non-small cell pulmonary cancer with no metastasis to other body parts before the biopsy. All patients with metastatic brain tumors were treated by external brain radiation only. Furthermore, two patients (6.25%) had malignant lymphoma that did not respond to preoperative corticosteroid (Fig. 2). Multiple primary brain lymphomas were treated by external radiotherapy and chemotherapy.

Furthermore, four patients (12.5%) had multiple brain abscesses, and an abscess wall biopsy and an intra-abscess pus drainage were done to improve the clinical and neurological status (Fig. 3).

No mortality, because of the stereotactic biopsy procedure, was encountered; however, one patient, diagnosed with metastasis, had a small non-symptomatic intraparenchymal hematoma.

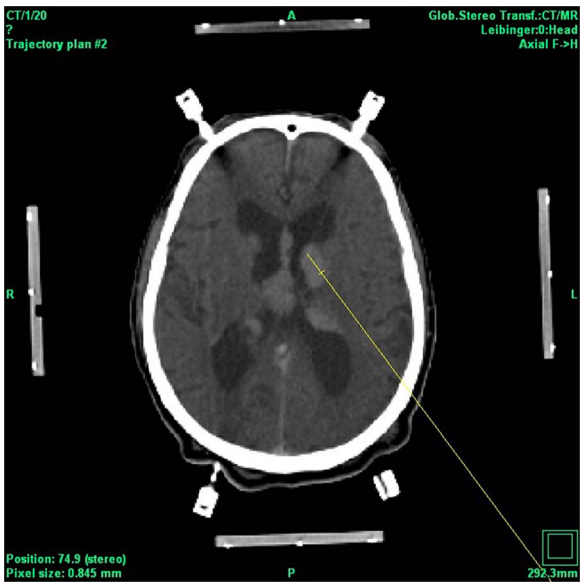

Fig. 2 An illustrative case. Screen capture from a preoperative CT stereotactic brain biopsy planning. Histological diagnosis was multiple primary brain lymphomas

Discussion

Multiple brain lesions are a serious challenge for any neurosurgeon. We usually suggest biopsy as a start to help overcome patients' mental stress and enable the design of the next treatment step.

In the current study, 10.85% (32 of 295 cases) of the lesions were multiple and the histopathologic diagnoses were as following: metastases (37.5%), glioblastoma multiform (25%), grade III astrocytoma (18.75%), abscess (12.5%) and malignant lymphoma (6.25%).

Meshkini et al. [12] previously reported that 7.6% (158 of 2081 patients) of the brain lesion biopsies were multiple lesions. Over half of these cases had low-grade multiple gliomas, while over one-fifth of the cases had multiple malignant gliomas. Moreover, 10.2% had malignant lymphoma, whereas 4.6% had metastatic tumor and 2.7% of the cases had multiple brain abscesses.

Moreover, Franzini et al. [13] recorded that out of 940 cases, 100 (10.6%) showed multiple lesions; 37% were malignant gliomas, 15% were brain metastases, 15% were primary lymphoma, 12% with low-grade gliomas, 10% had infectious disease ranging between brain abscess and viral multifocal encephalitis and 6% were ischemic lesions, and others showed rare lesions.

On the other hand, Calisaneller et al. [8] showed that from 100 brain lesion biopsies, only 4.25% of the cases were multiple. The histopathological diagnoses were

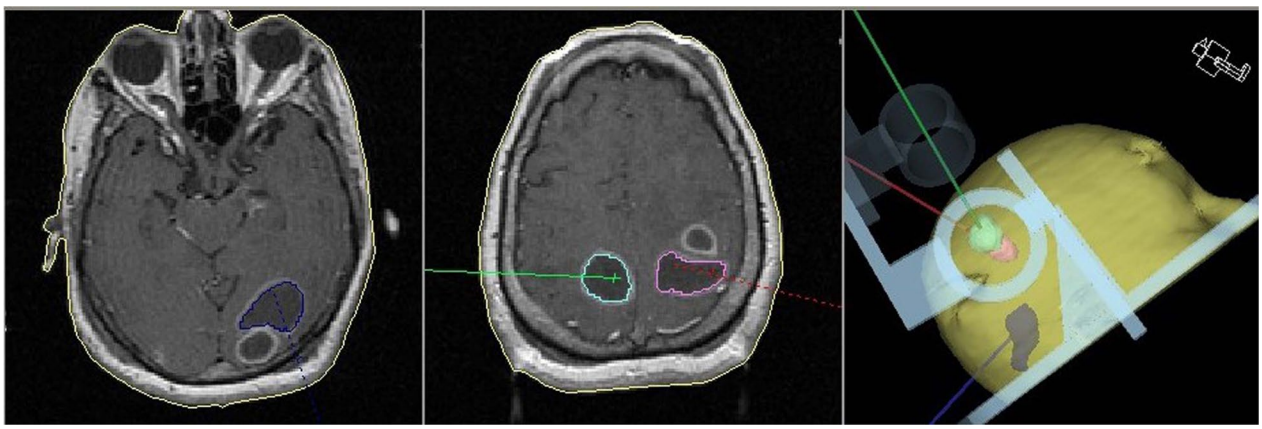

Fig. 3 An illustrative case. Preoperative stereotactic planning MRI and 3D simulation with 3 trajectories. Histological diagnosis was multiple brain abscesses

61.71% neuro-epithelial tumors, 8.51% metastases and 10.64% infectious lesions.

Metastatic brain tumors must be considered first when multiple brain lesions are identified. In a patient with a known systemic malignancy, diagnosing brain metastases is a simple affair that can be accomplished by obtaining a biopsy from an extracranial site, which has a lower biopsy-associated risk than a brain lesion [1].

Brain metastases of unknown primaries (BMUPs) are frequently underestimated. A two-to-three months window is usually accepted for detecting the primary origin, because the initial workup is occasionally delayed by attention to the brain tumor [14]. The management of BMUPs patients requires the resection of an accessible single brain metastasis to reach a histopathological diagnosis. Inaccessible tumors need a stereotactic biopsy, and if < 3 cm, they are treated with stereotactic radiosurgery (SRS). Whole brain radiotherapy (WBRT) is either an adjuvant therapy in these two categories or is the primary treatment option if the previous two conditions are not met [15]. A potentially unneeded craniotomy may be avoided when a "non-surgical" tumor type is diagnosed.

Small cell lung cancer responds well to fractionated radiation in most cases secondary lymphoma, choriocarcinoma, and testicular tumors, for example, usually respond to fractionated radiotherapy, focal radiation, or systemic chemotherapy. Melanoma, renal cell carcinoma, and non-small cell lung cancer, on the other hand, are typically thought to be chemoresistant, while melanoma, renal cell carcinoma, and sarcoma are thought to be resistant to normal fractionated radiation [16, 17]. According to studies, radioresistant renal cell carcinoma and melanoma are more vulnerable to radiosurgery than other cancers [18].

Multifocal gliomas are gliomas spreading through commissural or the fornix and the corpus callosum, through cerebrospinal pathways, and/or by local metastasis [19]. Multicentric gliomas should be distinguished from multifocal tumors. Multicentric gliomas are encountered infrequently, with reports suggesting they account for 0.15–8% of glial tumors [20, 21].

According to Kotwica and Papierz [20], a large percentage of multifocal or multicentric gliomas have been misdiagnosed as brain metastases based on CT imaging without histopathological confirmation. Multiple gliomas occur outside the cortical–subcortical borders, deep within the white brain matter, according to Ozawa et al. [2]. The histopathology of these tumors must be investigated in order to provide an accurate prognosis, and high doses of radiotherapy are required in cases of glioblastoma, even more so than in patients with brain metastases. In circumstances where surgical excision of the lesion is not an option, stereotactic biopsy is probably the best alternative for allowing histopathologic examination [22].

Differentiation among glioblastoma, brain metastasis, and lymphoma with conventional structural MR scanning alone also remains challenging because the three intra-axial tumors often show a similar appearance on structural MRI, so stereotactic biopsy should be considered to resolve this dilemma. Unlike other high-grade intracranial malignancies, lymphoma is treated without surgery using a combination of radiation and high-dose chemotherapy. Surgical intervention is mainly confined to obtaining tissue for histopathologic diagnosis by performing a biopsy [23].

It's hard to differentiate between a pyogenic brain abscess and a necrotic tumor when a brain lesion presents a ring-like enhancement pattern on CT scan and MRI. Distinguishing between these two situations is critical since they require a completely different therapeutic approach as well as a different prognosis. A systematic approach and evaluation of the patient's history can help narrow the differential diagnosis [24]. Although prior studies have shown the ability of Dynamic Susceptibility Contrast-Enhanced (DSC) Perfusion MRI to distinguish abscesses from glioblastomas and metastases, they had certain limitations [25, 26]. Therefore, in cases of suspected brain abscess, it is essential to drain the abscess beside taking a stereotactic biopsy of the abscess wall and administration of antibiotics to help improve the patients' clinical and neurological status.

Conclusions

Stereotactic biopsy is considered the best choice to allow histopathologic diagnosis of multiple brain lesions with minimal morbidity and no mortality. Histopathologic findings gained with stereotactic procedures guided the choice of proper treatment thus eliminating the hazards associated with blind treatments.

Abbreviations

RM	Riechert–Mundinger system
CRW	Cosman–Roberts–Wells system
HIV	Human immunodeficiency virus
CT	Computerized tomography
MRI	Magnetic resonance imaging
KPS	Karnofsky Performance Scale
H&E	Hematoxylin and eosin
BMUPs	Brain metastases of unknown primaries
SRS	Stereotactic radiosurgery
WBRT	Whole brain radiotherapy
DSC	Dynamic susceptibility contrast

Acknowledgements

Not applicable.

Author contributions
All authors have equally contributed to the study conceptualization, methodology, software, data curation, validation, writing— original draft, reviewing, and editing of the manuscript. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Tanta University.

Consent for publication
Not appilicable.

Competing interests
The authors have no conflict of interest to declare.

Received: 19 May 2022 Accepted: 12 July 2022
Published online: 13 February 2023

References

1. Soffietti R, Rudā R, Mutani R. Management of brain metastases. J Neurol. 2002;249:1357–69.
2. Ozawa Y, Machida T, Noda M, Harada M, Akahane M, Kiryu S, et al. MRI findings of multiple malignant gliomas: differentiation from multiple metastatic brain tumors. Radiat Med. 1998;16:69–74.
3. Huisman TAGM: Tumor-like lesions of the brain. Cancer Imaging. 2009; 9 Spec No:S10–3
4. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases: Histology, multiplicity, surgery, and survival. Cancer. 1996;78:1781–8.
5. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322:494–500.
6. Yamada K, Goto S, Kochi M, Ushio Y. Stereotactic biopsy for multifocal, diffuse, and deep-seated brain tumors using Leksell's system. J Clin Neurosci. 2004;11:263–7.
7. Hu LS, Baxter LC, Smith KA, Feuerstein BG, Karis JP, Eschbacher JM, et al. Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusio. AJNR Am J Neuroradiol. 2009;30:552–8.
8. Calişaneller T, Ozdemir O, Ozger O, Ozen O, Kiyici H, Caner H, et al. The accuracy and diagnostic yield of computerized tomography guided stereotactic biopsy in brain lesions. Turk Neurosurg. 2008;18:17–22.
9. Schmierer K, Scaravilli F, Barker GJ, Gordon R, MacManus DG, Miller DH. Stereotactic co-registration of magnetic resonance imaging and histopathology in post-mortem multiple sclerosis brain. Neuropathol Appl Neurobiol. 2003;29:596–601.
10. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984;2:187–93.
11. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803–20.
12. Meshkini A, Shahzadi S, Alikhah H, Naghavi-Behzad M. Role of stereotactic biopsy in histological diagnosis of multiple brain lesions. Asian J Neurosurg. 2013;8:69–73.
13. Franzini A, Leocata F, Giorgi C, Allegranza A, Servello D, Broggi G. Role of stereotactic biopsy in multifocal brain lesions: considerations on 100 consecutive cases. J Neurol Neurosurg Psychiatry. 1994;57:957–60.
14. Bartelt S, Lutterbach J. Brain metastases in patients with cancer of unknown primary. J Neurooncol. 2003;64:249–53.
15. Polyzoidis KS, Miliaras G, Pavlidis N. Brain metastasis of unknown primary: a diagnostic and therapeutic dilemma. Cancer Treat Rev. 2005;31:247–55.
16. Korinth MC, Delonge C, Hütter BO, Gilsbach JM. Prognostic factors for patients with microsurgically resected brain metastases. Oncol Res Treat. 2002;25:420–5.
17. Pollock BE, Brown PD, Foote RL, Stafford SL, Schomberg PJ. Properly selected patients with multiple brain metastases may benefit from aggressive treatment of their intracranial disease. J Neurooncol. 2003;61:73–80.
18. Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL. Stereotactic radiosurgery for patients with ???Radioresistant??? Brain Metastases Neurosurgery. 2002;51:656–67.
19. Bordignon KC, Neto MC, Ramina R, de Meneses MS, Zazula AD, de Almeida LGMP. Patterns of neuroaxis dissemination of gliomas: suggestion of a classification based on magnetic resonance imaging findings. Surg Neurol. 2006;65:472–7.
20. Kotwica Z, Papierz W. Cerebral and Cerebellar Glial Tumors in the Same Individual. Neurosurgery. 1992;30:439–40.
21. Kudo H, Tanaka M, Urui S, Suzuki H, Tamaki N, Matsumoto S. Multicentric Glioblastoma Multiforme Occurring in the Supra and the Infratentorial Regions. Neurol Med Chir (Tokyo). 1990;30:334–8.
22. Ampil F, Burton GV, Gonzalez-Toledo E, Nanda A. Do we need whole brain irradiation in multifocal or multicentric high-grade cerebral gliomas? Review of cases and the literature. J Neurooncol. 2007;85:353–5.
23. Herrlinger U, Schabet M, Clemens M, Kortmann R-D, Petersen D, Will BE, et al. Clinical presentation and therapeutic outcome in 26 patients with primary CNS lymphoma. Acta Neurol Scand. 1998;97:257–64.
24. Toh CH, Wei K-C, Chang C-N, Ng S-H, Wong H-F, Lin C-P. Differentiation of brain abscesses from glioblastomas and metastatic brain tumors: comparisons of diagnostic performance of dynamic susceptibility contrast-enhanced perfusion MR imaging before and after mathematic contrast leakage correction. PLoS ONE. 2014;9:e109172–e109172.
25. Chiang I-C, Hsieh T-J, Chiu M-L, Liu G-C, Kuo Y-T, Lin W-C. Distinction between pyogenic brain abscess and necrotic brain tumour using 3-tesla MR spectroscopy, diffusion and perfusion imaging. Br J Radiol. 2009;82:813–20.
26. Lai P-H, Chung H-W, Chang H-C, Fu J-H, Wang P-C, Hsu S-H, et al. Susceptibility-weighted imaging provides complementary value to diffusion-weighted imaging in the differentiation between pyogenic brain abscesses, necrotic glioblastomas, and necrotic metastatic brain tumors. Eur J Radiol. 2019;117:56–61.

Publisher's Note