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Value of Thallium-201 SPECT and SPECT/CT Brain Imaging in Differentiating Malignant From Nonmalignant Lesions: A Comparative Case-Series Study With Pathologic and/or Clinical Correlation

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Background Thallium-201 single-photon emission computed tomography/computed tomography (SPECT/CT) brain scan is an imaging modality which can be done to differentiate between malignant and nonmalignant lesions among patients with nonconclusive findings on conventional neuroimaging. This study describes the results of thallium-201 SPECT/CT brain imaging and relate it to histopathologic and/or clinical findings and evaluate the value of thallium-201 SPECT/CT brain imaging in differentiating malignant from nonmalignant lesions.

Methods This is a retrospective case series study of 10 patients with cerebral lesions who underwent thallium-201 SPECT/CT brain imaging in a hospital in the Philippines from 2010 to 2021.

Results A total of 10 patients underwent thallium-201 SPECT/CT brain scan. Six had negative results while 4 had positive results. All of the patients who had positive results were found to have malignancy, whether recurrent or newly diagnosed. All of the patients with negative scan were found to have either an infectious and inflammatory disease and responded to treatment albeit in different degrees. Two of the 10 patients underwent biopsy whose results were consistent with the thallium-201 SPECT/CT brain scan results.

Conclusion Thallium-201 brain scan combined with SPECT and SPECT/CT has been demonstrated to be useful in distinguishing malignant from nonmalignant lesions and is more cost-effective versus other imaging techniques. The findings in this study support the role of thallium scintigraphy in the diagnosis of patients with brain lesions most significantly when there is a need to differentiate between a malignant and benign condition.

Keywords Thallium; Tomography, emission-computed, single-photon; Neuroimaging; Brain tumor; Malignancy.

INTRODUCTION

The primary neuroimaging methods for the identification and localization of intracranial lesions are MRI and CT neuroimaging. Of the two, MRI is the imaging modality of choice to evaluate brain tumor location, size, and extent, mass effect, and involvement of critical structures [1]. However, there are instances where MRI cannot accurately determine characteristics of lesions to differentiate malignant lesions from nonmalignant ones. Primary central nervous system (CNS) lymphoma and various CNS infections may have indistinguishable characteristics of lesions on neuroimaging studies [2].

Brain biopsy remains to be the gold standard in the diagnosis of brain tumors, which is most often done at the time of tumor removal. Limitations on the use of brain biopsy include the hard-to-reach location of the tumor, patients who are poor surgical candidates, and when patient is not amenable to an invasive surgical procedure [3]. There are also instances such as in HIV patients particularly, it would be helpful in distinguishing parasitic infections from malignancies such as lymphoma where delaying treatment for a therapeutic trial would be detrimental.

Thallium-201 single-photon emission CT/CT (SPECT/CT) brain imaging has been reported to be more sensitive and specific in identifying carcinomatous cerebral lesions as compared to MRI, CT, or radionuclide studies using other radiotracers [4-9]. Separating malignant from benign lesions with thallium brain scans is based on the tracer activity imaged during the procedure. The normal absence of tracer uptake in the brain permits easier visualization of tumors and imaging of brain lesions has been the most common application of thallium in tumor imaging. There is differential washout of the tracer from malignant tumors versus normal brain tissues, with prolonged clearance in the former. Lymphoma has a moderate to intense tracer uptake while a CNS infection such as toxoplasmosis has absent uptake.

The aim of this retrospective study is to describe the results of thallium-201 SPECT/CT brain imaging and relate it to histopathologic and/or clinical findings and to evaluate the value of thallium-201 SPECT/CT brain imaging in differentiating malignant from nonmalignant lesions. This is the first study in the Philippines investigating the usefulness of thallium-201 SPECT/CT brain imaging.

MATERIALS AND METHODS

This is a retrospective case series of patients ages 18 years old and above with cerebral lesions who underwent thallium-201 SPECT/CT brain imaging at St. Luke's Medical Center−Global City, Philippines from 2010 to 2021. Patients who were not able to complete the thallium-201 brain imaging were excluded in the study.

Brain scintigraphy was performed using 4 mCi ±5% of thallium-201. Scanning was done using Siemens Symbia Intevo Bold or Siemens Symbia S dual-head hybrid SPECT/CT gamma camera (Siemens Healthineers, Erlangen, Germany) with a large field of view, low energy all purpose-parallel hole collimator. Images were acquired in continuous mode, non-circular orbit, 180 degrees, 32 views, 50 seconds per view with 128×128 matrix size. Initial planar images of the head were acquired 15 minutes post-intravenous injection of the radiotracer. Delayed planar images were acquired 90 minutes post-tracer injection. SPECT imaging of the head was done after the delayed scan and SPECT/CT was performed as needed. A positive thallium-201 SPECT brain imaging was interpreted based on the tracer uptake on the area of interest. All imaging findings were interpreted and reviewed by experienced nuclear medicine physicians.

The clinical protocol and all relevant documents were approved by the Institutional Ethics Review Committee. Each patient document was coded and does not contain any identifying information to ensure confidentiality.

The list of patients who underwent thallium-201 SPECT brain imaging were retrieved from the computerized database/online imaging portal of the hospital. Data were gathered from review of medical records and healthcare system. Data pertaining to the outcomes of patients who underwent thallium 201 SPECT/CT brain imaging were recorded in the researchers' database. This included patients' demographic profile, comorbidities, neurologic symptoms, brain scintigraphy result, other imaging/ancillary results, histopathologic findings and clinical diagnosis, management, interventions and clinical outcome.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. The thallium-201 SPECT/CT brain imaging findings were compared to the final diagnosis of the patients and to histopathologic findings, if available.

Chart review was done for all the patients included in this study. No direct contact was done between the researchers and the patients. Identifying data of the patients have not been included in the data collection form to maintain confidentiality. This study with reference number SL-21298 received ethical clearance from the Institutional Ethics Review Committee of St. Luke's Medical Center on October 2021. Informed consent was wavied by the Institutional Review Committee.

RESULTS

The characteristics of patients who underwent thallium-201 brain imaging are summarized in Table 1. Half of the population belong to the 41 to 50-year age group. Most of the patients (80%) were females. Three of the 10 patients had a known carcinoma. The most common complaint of the patients tested was headache.

Four patients rendered positive results with thallium-201 brain scan while the rest have negative results. Of patients with positive thallium-201 brain scan, 3 patients were diagnosed with brain metastasis while 1 patient was diagnosed with pilocytic astrocytoma. Among patients with negative thallium-201 brain scan results, 5 patients were diagnosed with CNS infec-

Table 1. Characteristics of patients who underwent thallium-201 brain imaging

Patient	Age (yr)	Sex	Comorbidities	Neurologic manifestations	Thallium-201 SPECT/CT	Histopathology	Diagnosis	Outcome
1	48	Male	Meningioma, post-resection	Asymptomatic	Negative	-	Tuberculous granuloma	Responded to treatment
2	32	Female	Lung cancer	Headache	Positive	-	Brain metastasis	Died
3	59	Female	Hypertension, diabetes mellitus	Blurring of vision	Negative	Chronic inflammation and gliosis	Neurocysticercosis	No response to treatment
4	29	Male	Cerebral toxoplasmosis	Headache; perseveration; unilateral weakness	Negative	-	Cerebral toxoplasmosis recurrence	Responded to treatment
5	72	Female	Breast cancer	Dizziness; vomiting; diplopia	Positive	-	Brain metastasis	Responded to treatment
6	41	Female	None	Dizziness	Negative	-	Tuberculous granuloma	Responded to treatment
7	49	Female	Cervical cancer	Memory lapses; change in sensorium	Positive	-	Brain metastasis	Refused treatment
8	48	Female	Hypertension	Headache; multiple craniopathies	Negative	-	Neurosarcoidosis	Responded to treatment
9	22	Female	None	Headache; dizziness	Positive	Pilocytic astrocytoma	Astrocytoma	Responded to treatment
10	48	Female	Hypertension	Headache; unilateral weakness	Negative	-	Tuberculous granuloma	Responded to treatment

SPECT/CT, single-photon emission computed tomography/computed tomography.

tion while 1 patient was diagnosed with an autoimmune disease.

Patients were treated according to their final diagnosis. Six patients had good response to treatment, 1 patient is still ongoing treatment, 1 patient had poor response to treatment, and 1 patient refused treatment. Patient 2 died while still initiating treatment.

Only two patients consented and underwent biopsy of the brain lesion. Patient 3 who had negative result in thallium-201 brain scan underwent excision of cerebellar mass showed chronic inflammation and gliosis on biopsy and was diagnosed with neurocysticercosis. Patient 9 who had positive thallium-201 brain scan revealed pilocytic astrocytoma on biopsy and was treated accordingly. Figs. 1 and 2 show the thallium-201 brain scan findings and the corresponding histopathologic images of the biopsied cerebral lesions confirming the diagnosis. The thallium SPECT/CT scan images of the rest of the patients are shown in Supplementary Figs. 1 and 2 (in the online-only Data Supplement).

DISCUSSION

Neurologists may be faced with a diagnostic dilemma when a patient's clinical and radiographic presentation may point to several possible etiologies. As physicians, coming up with an accurate diagnosis is very crucial because treatment may vary depending on the disease entity and delay in the diagnosis may consequentially worsen a patient's condition. In case where our primary neuroimaging does not provide us with a definite diagnosis and brain biopsy may not be an option in some patients, thallium-201 brain scan may be used to supplement the diagnosis.

In our case series, these patients had nonconclusive primary neuroimaging findings which made their neurologists proceed with thallium-201 brain imaging to further support the diagnosis. Thallium-201 brain scan was able to accurately validate whether the patients have malignant lesions versus non-malignant lesions such as infection and inflammation. This aided the physicians on the treatment plan for the patients, on which they responded albeit in different degrees.

One of the advantages of thallium-201 SPECT/CT brain imaging in comparison with other imaging modality is its mechanism in localizing malignant lesions [10]. Thallium-201 uptake in the brain is influenced by regional blood flow, blood–brain barrier (BBB) permeability, cellular metabolic activity, and the variability in Na^{+}-K^{+}-ATPase (adenosine triphophatase) activity [11-14].

The integrity of the BBB makes it possible for different radiopharmaceuticals to distinguish between lesions that are benign and malignant. Non-malignant entities incite inflammatory responses that interrupt with physiological brain func-

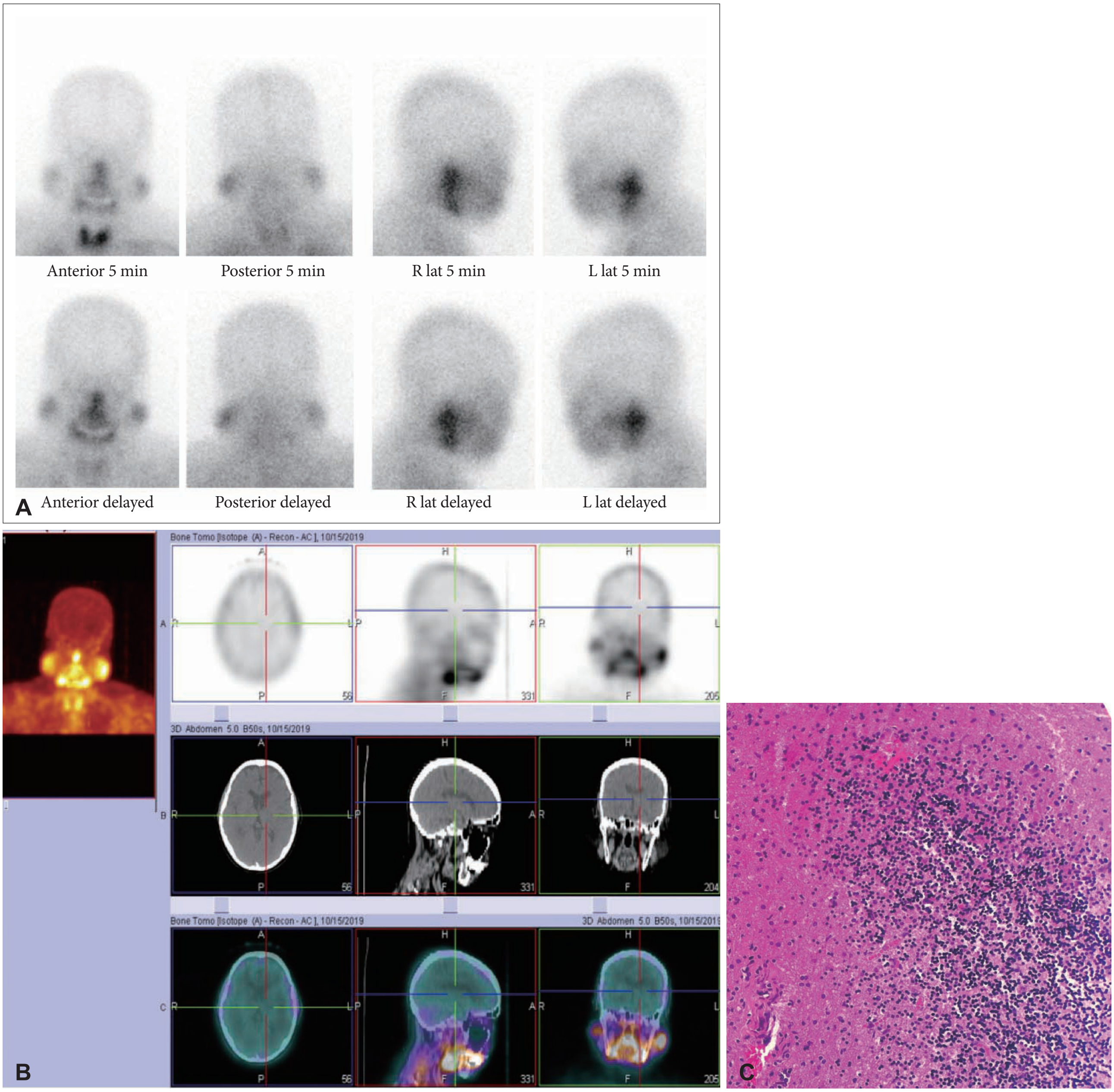

Fig. 1. Thallium-201 brain scan findings and histopathologic image of Patient 3. A and B: A negative thallium brain scintigraphy planar (A) and SPECT/CT images (B) showing no increased tracer accumulation. C: Cerebellar tissues with gliosis (H&E, ×10). SPECT/CT, single-photon emission computed tomography/computed tomography.

tions which eventually lead to their clinical presentations. These pathologies are met by an immune response which does not cause a disruption in the BBB, limiting them to their area of origin and minimizing deviations from the body's homeostasis as much as possible. Brain tumors, on the other hand, encroach on the supply of normal tissues for oxygen and nutritional sustenance. They secrete angiogenesis factors to support their rapid growth. Blood vessels formed in the tumor-host interface do not have tight junctions, which normally only allow small amounts of plasma filtered at a time. This leakiness allows for tumor metastasis and serves as the entry point for thallium-201. It would follow that malignant processes would present as thallium-avid lesions in the brain and benign processes do not get visualized. It is also good to note that increase in BBB permeability alone will not necessarily increase thallium-201 uptake in the brain as some nonmalignant lesions may have increase in BBB permeability but will still only have little or no uptake [10].

Variability in thallium-201 uptake may as well provide further information on the brain lesion being investigated. The

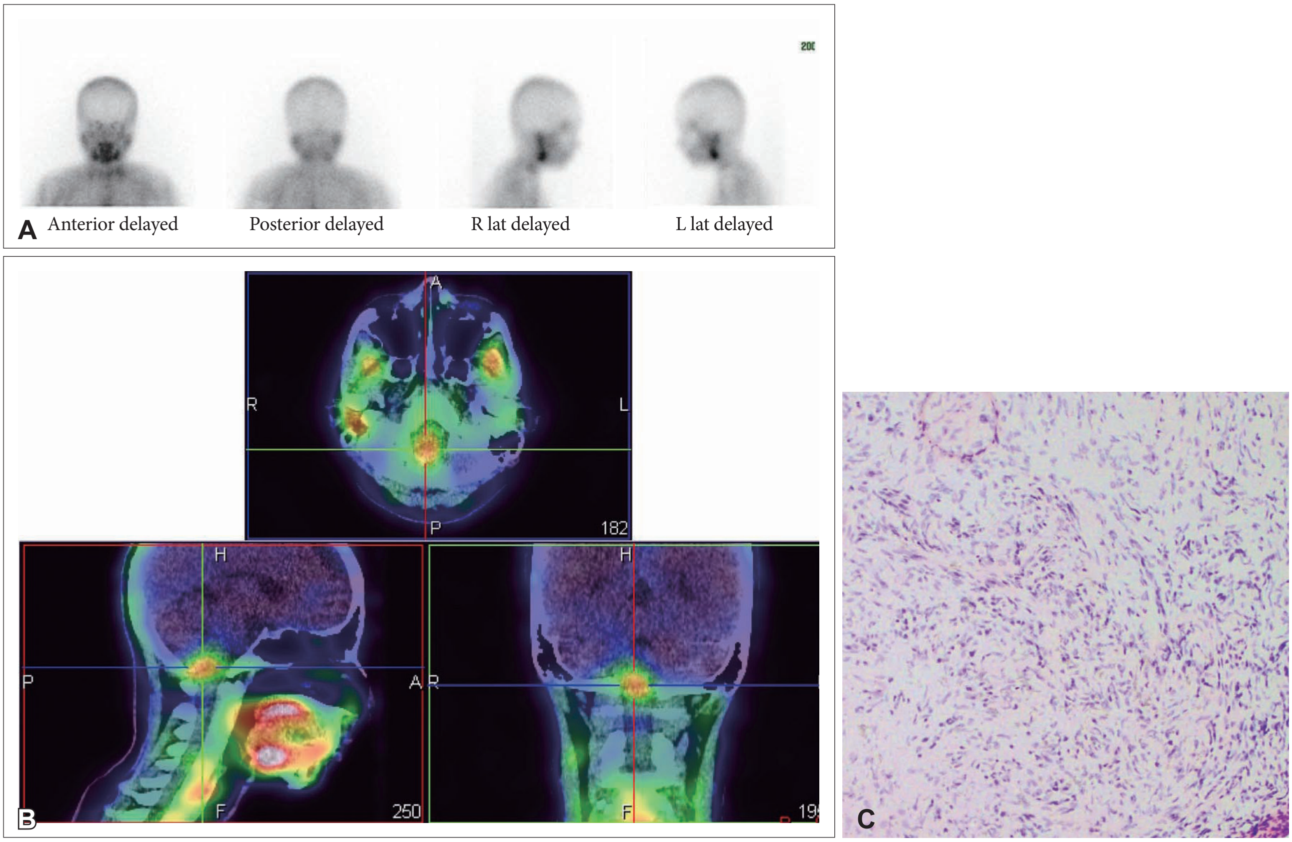

Fig. 2. Thallium-201 brain scan findings and histopathologic image of Patient 9. A: Initial planar images after 90 minutes of thallium-201 intravenous injection showing no focus of increased tracer uptake. B: SPECT/CT imaging with a focus of thallium-201 uptake in the cervicomedullary junction and right brachium pontis. C: Cellular portion of brain tissue populated by bland round and spindle cells (H&E ×100), immunohistochemistry results revealed positive GFAP and P16, focally positive SOX10, IDH1 negative, and retained nuclear staining on ATRX favoring the diagnosis of pilocytic astrocytoma. SPECT/CT, single-photon emission computed tomography/computed tomography.

early uptake is thought to be related to tumor vascularity and the disruption of the BBB. Delayed uptake depends on the metabolic activity of the Na^+-K^+-ATPase mechanism of transmembrane transport into viable tumor cells, which may also indicate the degree of tumor malignancy. Thallium uptake is found to be significantly increased in tumors expressing increased vascular endothelial growth factor (VEGF) compared to VEGF weakly positive meningiomas in both the early image and the delayed image [15]. These mechanisms explain how malignant lesions have higher tracer activity in thallium brain scans compared to benign pathologies. By evaluating early and delayed uptake with normal "background" activity in thallium brain scan with SPECT, researchers have also come up with a retention index which correlates with degree of aggressiveness in gliomas and even meningiomas, Ki-67 proliferative index and predicting progression-free survival which are helpful for pretreatment planning. The addition of SPECT or SPECT/CT to the thallium-201 brain scan planar images provides improved sensitivity resulting in improved detection and localization.

Though in this case series we did not have a patient with a case of radiation-induced necrosis, several studies reported use of thallium-201 SPECT/CT imaging in differentiating tumor recurrence from radiation-induced necrosis [14,16-18]. These two outcomes are most commonly encountered post-brain tumor treatment [19]. Their radiographic characteristics are similar and hard to distinguish on the conventional imaging which led to the use of several functional and physiologic imaging techniques to differentiate the two. A combination of MR spectroscopy and MR perfusion is commonly used but one of its disadvantages is its low accuracy when testing patients with coexisting tumor and necrosis [14]. In cases of malignant tumor recurrence, SPECT imaging will present with thallium-201 tracer uptake while radiation-induced necrosis will have no tracer uptake. In this case series, only Patients 1 and 2 had a history of cerebral lesion. Patient 1 had a resected meningioma and was found out to have a new cerebral lesion near the resected lesion during a surveillance MRI. No tracer uptake was seen on thallium-201 SPECT imaging thus new malignancy was ruled out. She was clinically diagnosed with tuberculous granuloma granuloma to which she responded to treatment with resolution of the previously noted cerebral lesion on repeat imaging posttreatment. Patient 2 was previously treated for cerebral toxoplasmosis then developed new-onset neurologic deficits. MRI showed new multiple scattered cerebral lesions that had no tracer uptake on thallium brain scan. Patient was managed for cerebral toxoplasmosis recurrence and responded to treatment with resolution of neurologic deficits and cerebral lesions.

The sensitivity and specificity of thallium-201 SPECT in detecting and differentiating brain tumors was evaluated by Dierckx et al. [20] which resulted to 71.7% and 80.9%, respectively. Similar results were seen in the study of Hussain and Hussain [6] on the clinical utility of thallium-201 SPECT alone in the diagnosis of AIDS-related primary CNS lymphoma which yielded a sensitivity of 77% and specificity of 81%, but the diagnostic accuracy improved to 100% when it was used together with the cerebrospinal fluid Epstein-Barr virus polymerase chain reaction results. In a different study done by Lorberboym et al. [5], thallium-201 brain SPECT had a higher overall sensitivity of 100% and specificity of 90% in differentiating primary CNS lymphoma from cerebral toxoplasmosis. MR spectroscopy, in comparison, has a sensitivity of 89.3% and sensitivity of 73.9% [21]. Given these values, thallium-201 brain scan can competitively be used as an imaging option when other imaging modality is not convenient.

Thallium-201 brain scan is also a more cost-effective option among the noninvasive imaging techniques. As can be seen in Table 2, the gross price of a thallium-201 brain scan combined with SPECT/CT just a little above the price of a single cranial MRI with contrast and costs 35% less than an MR spectroscopy with perfusion study. In the Philippine setting where cost can be an important factor in the choice of diagnostic procedure, this study further supports the use of thallium-201 SPECT/CT scan in the diagnosis of patients with brain lesions.

The limitation of this study is the small number of patients included in the study and only 2 of the patients underwent biopsy to confirm the diagnosis. Nonetheless, objective clinical findings were used for the patients with no histopathologic results. A prospective study involving a larger population of sample with correlation of histopathologic findings is recommended to extensively examine the utility of thallium-201 brain scan.

Table 2. Diagnostic neuroimaging procedure prices in a hospital in the Philippines

Diagnostic procedure	Prices (USD)
Thallium-201 brain scan	$432.50
Thallium-201 brain scan + SPECT/CT	$490.00
Cranial MRI with contrast	$440.00
Cranial MRI with MRS and MRP	$763.50

SPECT/CT, single-photon emission computed tomography/computed tomography; MRS, MR spectroscopy; MRP, MR perfusion

In conclusion, thallium-201 brain scan combined with SPECT and SPECT/CT has been demonstrated to be useful in determining the nature of brain lesions, capable of distinguishing malignant process from nonmalignant ones, and more cost-effective than other imaging techniques. Thallium-201 brain scan is a promising imaging modality to confirm diagnosis among patients with nonconclusive findings on conventional neuroimaging.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14791/btrt.2023.0022.

Availability of Data and Material

This database of the patients is under the ownership of the St. Luke's Medical Center - Global City. Inquiries regarding the access can be directed to the corresponding author.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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