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CLINICAL-PATIENT STUDIES

The role of ^{111}indium-octreotide brain scintigraphy in the diagnosis of cranial, dural-based meningiomas

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Abstract
Objective Meningiomas are common brain tumors with somatostatin receptors that bind octreotide. We report the use of ^{111}indium-octreotide brain scintigraphy (OBS) for the non-invasive differentiation of meningiomas from other cranial dural-based pathology.
Methods A retrospective analysis of our experience with OBS for non-invasive identification of meningiomas was performed. Two neuroradiologists, blinded to clinical data, utilized a standardized grading scheme to define the uptake of octreotide at 6 and 24 h post-administration. The correlation between (18) F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET), magnetic resonance imaging (MRI) scans, and octreotide uptake was assessed.
Results The cohort consisted of 50 patients having a mean age of 62.4 years and a median follow-up time of 24 months. Management consisted of biopsy (n = 4); resection (n = 10); observation (n = 16); radiosurgery (n = 21); and external beam radiotherapy (n = 3). OBS was correlated with MRI (n = 50); FDG-PET brain studies (n = 38); histology (n = 14), and angiography (n = 1). In cases where definitive diagnosis could be made, the sensitivity, specificity, positive and negative predictor values for OBS alone were 100; 50; 75; and 100, respectively. OBS provided false positive data in 3 patients (metastasis, chronic inflammation, lymphoma). Use of OBS with MRI to differentiate meningiomas from other lesions was highly significant ($P < 0.001$). FDG-PET correctly identified malignant pathology with 100% sensitivity and specificity.
Conclusion OBS may increase the diagnostic specificity of conventional MRI when differentiating meningioma from other dural-based pathologies, while the addition of FDG-PET differentiates benign from malignant lesions.

Keywords Brain · Dura · Meningioma · Octreotide · Scintigraphy · FDG-PET

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Introduction

Radiographic discrimination of meningiomas from other cranial dural-based lesions can be problematic. The widespread use of magnetic resonance imaging (MRI) has resulted in increased detection of patients harboring asymptomatic intracranial lesions. Following

the diagnosis of a cranial dural-based lesion(s), management is usually determined by a combination of factors such as clinical status (asymptomatic versus symptomatic), medical history, and neuroimaging qualities such as site, size, and imaging characteristics. While most of these lesions are benign in pathology (e.g. meningioma), occasionally the surgeon is faced with uncertainty when the dural-based lesion is not causing mass effect, has atypical imaging characteristics, or is present in the setting of extracranial tumors which have the potential to metastasize to the brain and its coverings. In this situation, we have used octreotide brain scintigraphy (OBS) in combination with (18)F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) in addition to routine neuroimaging modalities to further help with the non-invasive differentiation of meningiomas from other dural-based pathologies.

Since its initial description [1], many reports have documented the role of somatostatin receptor scintigraphy using ^{111}indium-octreotide in the pre-operative diagnosis [2–6] and the detection of recurrence [7] of cranial meningiomas.

In this retrospective report, we document our experience with the use of OBS and FDG-PET for the non-invasive differentiation of meningiomas from other cranial dural-based lesions.

Methodology

Analysis of the Brain Tumor Institute's Institutional Review Board approved database was performed over a 6-year interval (1998–2003) to identify patients who underwent octreotide brain scintigraphy to differentiate meningiomas from other cranial dural-based lesions. Only cranial dural-based lesion(s), in which the treating surgeon was uncertain of the diagnosis, were entered into the study. Detailed analysis of patient records inclusive of clinical presentation, management, neuro-imaging, and outcome data were performed. All neuroimaging [MRI, OBS and FDG-PET scans] were read by two independent neuroradiologists blinded to the clinical diagnosis of the patients. Three primary groups were analyzed: OBS and MRI (n = 50); OBS and histopathology (n = 14); and OBS; FDG-PET and MRI (n = 38).

Imaging techniques

Octreotide brain scintigraphy (OBS)

Octreotide scintigraphy was performed by intravenous administration of 6 mCi of [^{111}In-diethylentriamine-pentaacetic acid (DTPA)]-octreotide [Octreoscan®-Mallinckrodt Inc., St. Louis, MO], using an Ecam single photon emission computed tomography (SPECT) system [Siemens Medical, Malvern, PA], at 6 and 24 h post-administration. The images were reconstructed using filtered back projection and displayed via 128 × 128-matrix format. OBS uptake was classified qualitatively using the adjacent skull bone. Activity comparable to adjacent bone was classified as mild uptake, while activity higher than bone was classified as moderate uptake. Intense uptake was consistent with those tumors, which displayed OBS activity when the image was rewindowed to remove the adjacent bone. A positive OBS was recorded as intense or moderate uptake of the tracer.

Magnetic resonance imaging

MRI acquisition was obtained using a 1.5 Tesla Magnetom system (Siemens Medical, Malvern, PA), in axial and either sagittal or coronal planes, with T1 (both pre- and post-gadolinium-based contrast material), fast spin echo T2, FLAIR, and sometimes supplemental diffusion sequences. Fat suppressed post-contrast T1 weighted spin echo sequences were implemented for images centered about the orbital region. MRI results were classified as ''consistent with meningioma'' or ''not consistent with meningioma''.

Positron emission tomography (PET)

Forty minutes after intravenous administration of 10 mCi (370 MBq) of ^{18}F-FDG, PET-CT images were acquired using a Siemens Biograph 16 scanner with PET imaging time of 2–5 min per bed position, depending on patient weight and body habitus. Following image reconstructions, a standardized uptake value (SUV) for the lesion of interest was determined utilizing the iterative OS-EM algorithm (2 iterations, 8 subsets) and 6 mm post filter, with the CT data used for attenuation correction. SUV's were then categorized as mild (SUV < 5); intense (SUV > 5) and no uptake. Only intense FDG-PET uptake was recorded as a positive PET scan result.

Image qualitative analysis

Available scintigraphic, MRI, and PET images were individually reviewed by two blinded observers and assessed for being consistent, not consistent, or equivocal with classical scintigraphic or imaging appearances of meningioma. The following criteria were considered to be diagnostic of meningioma: (OBS) high avidity

(intense or moderate uptake) of ^{111}indium-octreotide relative to surrounding cranial or intracranial background signal levels; (MRI) dural-based lesion with homogeneous enhancement following intravenous contrast administration, with or without internal calcification on non-contrast computed tomography images, with T2 and FLAIR isointensity or subtly increased intensity, and residing in select intracranial positions known to be preferred by meningiomas (e.g. parasagittal, parafalcine, cerebral convexity, parasellar and skull base); (FDG-PET) low avidity (mild or no uptake) for FDG relative to surrounding cranial or intracranial signals. Such qualitative (OBS and MRI) and quantitative (FDG-PET) assessments were then combined with available histopathologic and angiographic information to calculate sensitivity, specificity, positive, and negative predictive values for octreotide brain scintigraphy as individual diagnostic modalities in the diagnosis of meningiomas. The diagnostic results from OBS, MRI, and PET were cross-tabulated in contingency tables. Their correlation was studied with sensitivity, specificity, and predictor values. Fisher's exact test was used to study their associations. All tests were two-sided. *P*-values less than 0.05 were considered statistically significant. The data analysis was completed with SAS 9.0 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 50 patients [female 35; male 15] who had OBS to differentiate meningiomas from other cranial dural-based lesions were identified. The mean age of the study cohort was 62.4 ± 14.5 years (range: 24–94) with a mean follow-up period of 24 ± 15 months (range: 0–74; median 24). The majority of the patients, 44 of 50 (88%) had single lesions (right: 24; left: 20); 4 patients had two lesions each while two others had multiple lesions (Cowden syndrome [PTEN mutation]; renal cell carcinoma).

The clinical presentation was varied; 14 patients presented with cranial nerve dysfunction inclusive of vision and hearing impairment, 9 patients with headaches, 8 with focal motor weakness, 4 with seizures, and 14 patients with incidental discovered tumors. Tumor location is listed in Table 1. Fifteen patients had a co-existing extracranial cancer (breast cancer-8; non-small cell lung cancer-2; melanoma-3; renal cell cancer-2), with 7 patients having tumors discovered incidentally as part of their staging.

Table 1 Location of dural lesions (n = 51) in 50 patients

Site	Number
Supratentorial	
Falcine	5
Sphenoid and orbit	3
Temporal fossa	4
Tentorium	6
Convexity	15
Cavernous sinus	6
Petrous ridge	1
Infratentorial	
CPA	8
Cerebellar convexity	3

Ten patients underwent craniotomy for resection of their tumor (subtotal-3; gross total-7), while 4 patients had frameless stereotactic biopsy of their lesions. A patient with multiple dural lesions was found to have dural venous varices on digital subtraction angiography. Twenty-four patients (48%) had primary radiation therapy or radiosurgery for treatment of their lesions, while 15 patients (30%) were managed non-operatively by serial neuroimaging (Table 2). A single patient with a tentorial meningioma who received fractionated stereotactic radiosurgery required permanent cerebrospinal fluid diversion to treat her hydrocephalus while another patient with concurrent frontal lymphoma (histologic diagnosis) and cerebellopontine angle meningioma required an Ommaya reservoir for chemotherapy. Correlations between definitive diagnosis of lesion and neuroimaging studies could be made in 15 patients (histology-14; angiogram-1) (Table 3), and correlations between MRI, OBS and FDG-PET studies were performed in 38 patients (Table 4).

Correlation of OBS and MRI

OBS was positive in 35 of 50 (70%) patients, while 7 (14%) patients had no uptake, and in 8 (16%) patients OBS uptake was inconsistent with meningioma (low

Table 2 Summary of patient management (n = 50)

Management	Number (%)
Observation	15 (30)[a]
Biopsy	4 (8)
Craniotomy	10 (20)
Radiation therapy	24 (48)
Gamma knife	18[b]
Cyberknife	3
Intensity modulated radiotherapy	1
External beam radiotherapy	2

[a]Stereobiospy (n = 2)

[b]Stereobiospy (n = 1)

Table 3 Correlation of final diagnosis with MRI, octreotide and PET imaging ($n = 15$)

Procedure	Diagnosis	Histologic subtype	OBS	FDG-PET	MRI	Status
Crani	Meningioma	Syncytial	Positive	Negative	MRI+	TP
Crani	[a]Meningioma	Syncytial	Positive	Positive	MRI+	TP
Crani	[a]Meningioma	Syncytial	Positive	Not done	MRI+	TP
Crani	Lung metastasis	NSC	Negative	Not done	MRI+	TN
Crani	RCC/meningioma	Collision tumor	Positive	Negative	MRI+	TP
Crani	Meningioma	Fibrous	Positive	Negative	MRI+	TP
Crani	Meningioma	Syncytial	Positive	Negative	MRI+	TP
Crani	Meningioma	Fibrous	Positive	Not done	MRI+	TP
Crani	Meningioma	Syncytial	Positive	Negative	MRI+	TP
Crani	Meningioma	Syncytial	Positive	Negative	MRI+	TP
SBx	Chronic inflammation	Non-tuberculous	Positive	Negative	MRI–	FP
SBx	Metastasis	NSC	Positive	Positive	MRI–	FP
SBx	PCNSL	B-cell	Positive	Positive	MRI–	FP
SBx	Carcinoma	Poorly diff	Negative	Negative	MRI+	TN
DSA	Venous varix	–	Negative	Negative	MRI+	TN

[a]Malignant

Crani, Craniotomy; SBx, stereobiopsy; DSA, digital subtraction angiogram; NSC, non-small cell carcinoma; MRI+, MR imaging consistent with meningioma; MRI–, MR imaging not consistent with meningioma; TP, true positive; FP, false positive; TN, true negative

Table 4 Correlation of MRI/FDG-PET/OBS scans ($n = 38$)

Neuroimaging	No.	Etiology & imaging characteristics
MRI+	31[a]	5-(MRI–); 3-(MRI+/–)
FDG-PET–	31	
OBS+	30[a]	
Concordance		
Classic meningioma (MRI+/FDG-PET–/OBS+)	25	1-chronic infection (false positive)
Positive OBS/FDG-PET (false positives)	4	2-malignant meningioma; 1-metastasis; 1-PCNSL
Negative OBS/positive FDG-PET	3	3-metastases
Negative FDG-PET/OBS	7	4-(MRI+); 3-(MRI+/–)

[a]Single patient with concurrent PCNSL (MRI–/OBS+/FDG-PET+) and meningioma (MRI+/OBS+/FDG-PET–)

MRI+/–, imaging characteristics consistent with either meningioma or schwannoma; MRI+, MR imaging consistent with meningioma; MRI–, MR imaging not consistent with meningioma

intensity and or incomplete uptake). All patients with positive OBS imaging had 100% concordance with their respective MRI studies for imaging characteristics consistent with meningioma ($P < 0.001$). Seven of the 35 (20%) patients died during the follow-up period from malignant meningioma ($n = 2$), natural causes ($n = 1$), uncontrolled extracranial metastatic disease [breast and melanoma with intracranial tumors FDG-PET negative] ($n = 2$), primary central nervous system (PCNSL) lymphoma ($n = 1$), or sequelae of colonic perforation associated with high dose steroid therapy for edema following radiosurgery ($n = 1$).

Correlation of OBS, MRI, FDG-PET and diagnosis ($n = 15$) (Table 3)

In this subgroup, a positive OBS was found to correlate with MRI, FDG-PET, and pathology findings in 12 of 15 (80%) of cases. In three cases, there was a false-positive OBS result (lung metastasis, chronic inflammation, primary central nervous system lymphoma [PCNSL]). In these cases, however, the MRI and FDG-PET findings correctly identified the lesions to have characteristics inconsistent with meningioma. In this subgroup, octreotide brain scintigraphy was found to have a sensitivity of 100%, specificity of 50%, positive predictive value of 75%, and negative predictive value of 100% when used alone to diagnose meningioma. The test differentiated meningioma from other dural-based pathology including a venous anomaly.

Correlation of OBS, FDG-PET and MRI scans ($n = 38$) (Table 4)

In 25 of 38 (66%) patients there was concordance with MRI, FDG-PET and OBS with a single patient in this group having a false positive result (chronic inflammation: OBS positive; FDG-PET negative). The 14 cases with discordant studies were as follows: 4 patients [MRI consistent with meningioma in 2 patients] with OBS and FDG-PET positive scans [malignant meningioma—histologic diagnosis ($n = 2$); non-small cell metastasis [histologic diagnosis—false positive] ($n = 1$); and PCNSL [histologic diagnosis—false positive] ($n = 1$). Three patients with inconsistent MRI features for meningioma and OBS negative, FDG-PET

positive, had dural-based metastases. A single patient had concurrent frontal PCNSL (OBS and FDG-PET positive) and cerebellopontine angle meningioma (OBS positive and FDG-PET negative) (Fig. 1).

Seven additional patients had negative OBS and FDG-PET scans with four lesions having MRI imaging characteristics consistent with meningioma, while in a further 3 patients the lesions were either meningiomas or schwannomas. Significant correlation of MRI and FDG-PET ($P = 0.0124$), OBS and PET ($P = 0.0118$) were recorded.

In 12 of the 50 patients who had no FDG-PET imaging, correlation with OBS and MRI was only performed. In 11 of 12 patients, MRI showed lesion(s) with imaging characteristics consistent with meningioma with a single lesion having imaging characteristics of either a schwannoma or meningioma. Nine of 12 patients had positive OBS. In the three negative OBS scans, one patient died from lung metastasis, a second patient had a cerebellopontine angle tumor treated by radiosurgery and a third patient had multiple dural venous varices.

Outcome analysis recorded 12 deaths (malignant meningioma-2; extracranial malignancies-7; natural causes-1; iatrogenic-1; co-existent meningioma and PCNSL-1); and unknown status in 2 patients. Analysis of the 36 alive patients MRI studies at last clinic follow-up recorded their lesions to be stable in 20 patients; decreased in size in 12 patients (radiosurgery only treatment), and no recurrence in 4 post-operative patients.

Discussion

The biochemical characteristics and distribution of somatostatin receptors in meningiomas have been well documented [8–10]. Somatostatin receptors are integral membrane glycoproteins with five subtypes presently cloned [11]. The somatostatin analog octreotide inhibits somatostatin binding to receptor subtype 2 [12]. Octreotide is a polar, water-soluble peptide consisting of eight amino acids that does not penetrate an intact blood–brain barrier (BBB). Recent reports documenting improved kinetics and binding affinity (multiple subtypes) of newer somatostatin receptor analogs [13, 14], is set to expand the role of this radiolabeled peptide in the emerging field of targeted radiotherapy [15].

With their high somatostatin receptor density and the fact that they are situated outside the BBB, intracranial meningiomas present ideal targets for octreotide brain scintigraphy. Generally, neuroendocrine tumors (growth-hormone secreting pituitary adenomas), lymphomas, meningiomas, and activated leucocytes as in sarcoidosis have an increased density of somatostatin receptors enabling their visualization with somatostatin analogs. The classic imaging signature of a benign meningioma is octreotide positive, FDG-PET negative. However, as reported in 2 of our patients, some meningiomas are known to be positive on FDG-PET including recurrent tumors, atypical and malignant, and angioblastic, syncytial or papillary subtypes [16].

In contrast to meningioma, the uptake of octreotide with intraparenchymal tumor visualization is dependent on tumor-related loss of integrity of the BBB. Somatostatin receptors are commonly found in 82% of low-grade gliomas, and rarely in WHO grade IV gliomas (glioblastoma multiforme, 2%) [8]. In Grade III astrocytomas an inverse relationship between epidermal growth factor and somatostatin receptors have been reported with both receptor types found in this

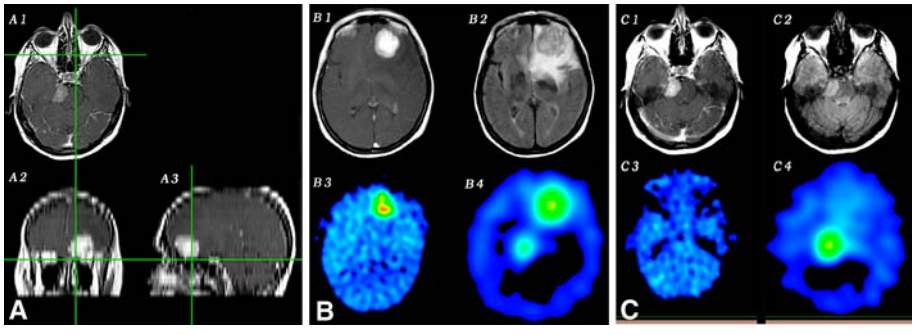

Fig. 1 Panel **A**: Axial gadolinium enhanced MRI scan (A1) showing patient with a petro-clival meningioma with corresponding coronal (A2) and sagittal (A3) reconstruction's showing opposite frontal dural-based lesion. Panel **B**: Axial images of right frontal dural-based lesion (lymphoma on biopsy). (B1) T1 weighted image (T1WI) with diffuse enhancement of the tumor. (B2) Fluid attenuation and inversion recovery (FLAIR) image of frontal lymphoma. (B3) FDG-PET showing high metabolic activity in tumor. (B4) OBS showing positive uptake in both tumor. Panel **C**: Axial images of left petro-clival meningioma. (C1) T1WI with diffuse enhancement of the tumor. (C2) FLAIR image of tumor. (C3) FDG-PET showing no metabolic activity in tumor. (C4) OBS showing positive uptake in tumor

tumor subtype [17]. Unlike a previous report [2], we recorded no difference in intensity of octreotide uptake related to the histologic subtype of meningiomas, however, this is most likely due to our small number of pathologically proven meningiomas.

The analysis of the subgroup of 15 patients with a definitive (radiographic or histologic) diagnosis, recorded a specificity of 50%, with the three OBS false positive patients having dural-based lesions which had MRI characteristics inconsistent with those typical for meningioma. However, there was 100% concordance between OBS and MRI in this subgroup, in cases where the MR imaging characteristics were consistent with meningioma. The results of the current study suggest a negative OBS rules out a meningioma if the lesion possesses imaging characteristics inconsistent with meningioma. However, it should be noted that a recent report recorded 88% positive expression of meningiomas analyzed for at least one of the five somatostatin receptor subtypes. Furthermore, the in-vitro antiproliferative activity of the somatostatin receptor reported in this study suggests potential future therapeutic options in the management of meningiomas [10].

Metastatic brain tumors may also possess somatostatin receptors and therefore may be visualized on OBS. One patient with renal cell cancer and a known asymptomatic frontal convexity meningioma (OBS positive and FDG-PET negative) became symptomatic following a bleed into the tumor with subdural extension of clot. Histological examination was consistent with renal cell metastasis and meningioma collision tumor [18]. Previous reports have documented the presence of somatostatin receptors in renal cell carcinoma independent of grade or stage in-vitro, but have failed to show in-vivo presence by positive scintigraphy [19, 20]. In addition, and unlike a previous report, which reported non-small cell lung brain metastasis as OBS negative [4], in this study one of three false positive OBS patients had a FDG-PET positive non-small cell lung metastasis.

The three false positive lesions had MRI imaging characteristics inconsistent with meningioma. The first patient, a 38-year-old female, presented with a crossed hemiparesis and an MRI which revealed an enhancing mass adjacent to the brain stem at the tentorial incisura; the second patient presenting with a hemiparesis, had an enhancing posterior frontal dural-based lesion and the third patient who presented with headaches and memory problems had two dural-based lesions in the frontal region (MRI-inconsistent with meningioma; biopsied) and cerebellopontine angle mass (MRI-consistent with meningioma). Frameless stereotactic biopsy was performed on all patients and the diagnoses were non-tuberculous chronic inflammation, lung metastasis and PCNSL, respectively. Previous reports have noted that OBS imaging may be positive in chronic granulomatous diseases; lung metastases and lymphoma [4, 12, 21].

Previous investigators have attempted to improve the specificity of somatostatin receptor imaging by comparing the uptake of octreotide of the tumor to background uptake ratio [2, 21, 22] and OBS to ^{99m}Tc-DTPA brain scintigraphy [2]. It has been previously reported that a semiquantitative analysis of simultaneously performed OBS and ^{99m}Tc-DTPA may be used to define an index which allows reliable diagnosis of false positive OBS secondary to BBB rupture. With a sensitivity of 100% and a specificity of 94% this index may accurately differentiate meningioma from other central nervous system tumors [2]. In the current study, FDG-PET was used and accurately predicted (100% sensitivity and specificity) the metabolic activity of all lesions including the 2 malignant meningiomas and 3 false positive patients. FDG-PET when used in combination with MRI and OBS helped to further differentiate classic meningioma from other dural-based lesions. In the patient with concurrent PCNSL and meningioma, both lesions were OBS positive, but the FDG-PET was positive only in the histologically confirmed lymphoma (Fig. 1).

The technique of OBS is a simple, non-invasive, and is an outpatient procedure that has no side-effects. Unlike magnetic resonance spectroscopy, it is currently fully reimbursed by Medicare. Cost effectiveness, however, may be influenced by the volume of patients scanned. Optimal scintigraphic images are usually obtained as early as 2–4 h following administration of ^{111}indium-octreotide. However, based on our experience with use of Octreoscan® optimal uptake is usually noted initially at approximately 6 h from administration of the tracer. Currently delayed imaging at 24 h has been recommended only for patients who harbor small meningiomas (volume < 5 ml) [23]. Although not found to be a problem in this study, a drawback of the SPECT method is its limited sensitivity in detecting small meningiomas.

The current report has several limitations in that the data was accrued in a retrospective fashion, the small number of patients with a definitive diagnosis ($n = 15$), that analysis of the additional patients (correlation of OBS, PET, and MRI $n = 38$) without histologic confirmation may not necessarily be valid, the paucity of false positive conditions such as sarcoidosis, meningeal lymphoma, and Cattleman's disease, and the inherent limitations of MRI and PET scanning may all serve to

limit the current reports findings. Based on the results of the present study, good correlation exists when an OBS positive study is recorded for a dural-based lesion with MRI characteristic of meningioma. Performance of FDG-PET will allow further non-invasive differentiation of benign versus malignant pathologies.

OBS may increase the confidence in the presumed diagnosis of meningioma in cases of dural-based lesion(s) where non-invasive management such as observation or stereotactic radiosurgery is considered. Also, although not the subject of this report, OBS potentially could be used to differentiate post-operative scar from tumor recurrence, reveal the true extent of calvarial meningeal meningiomatosis and differentiate acoustic schwannoma from meningioma, which may occur simultaneously in neurofibromatosis type 2.

Conclusion

Octreotide brain scintigraphy together with FDG-PET scanning may contribute to the increased diagnostic specificity of conventional MRI neuroimaging in the pre-operative discrimination of meningiomas from other dural-based pathology.

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