

Comparison of ^{99m}Tc Technetium Sestamibi Brain Single Photon Emission Computed Tomography (SPECT) with Computed Tomography (CT) & Magnetic Resonance Imaging (MRI) in Differentiating Tumor Recurrence From Radiation Necrosis in Post Therapeutic Gliomas

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Short Title: SPECT vs MRI and CT to differentiate radiation necrosis from recurrence in brain tumours

Abstract: Malignant gliomas account for 60% of all primary brain tumours routine treatment for gliomas consists of surgical resection, adjuvant radiotherapy and chemotherapy. During follow-up discrimination between tumour recurrence and Radiation necrosis is required. In the present study we compared ^{99m}Tc Sestamibi brain SPECT with CT & MRI in differentiating tumour recurrence from radiation necrosis in post therapeutic gliomas. Total of 36 patients of gliomas post surgery and Radiotherapy presenting with clinical deterioration willing to participate in the study were included. Out of 36 patients the sensitivity and specificity of ^{99m}Tc Sestamibi were 92.86% and 95.45%. Sensitivity and specificity of MRI were 92.86% and 72.73%. Sensitivity and specificity of CT were 92.86% and 63.64% respectively. In patients of glioma on follow-up, ^{99m}Tc Sestamibi Brain SPECT showed great diagnostic accuracy to discriminate tumour recurrence from radiation necrosis when compared to CT scan & MRI. ^{99m}Tc Sestamibi brain SPECT may be used as a useful tool in establishing prognosis of glioma patients at the end of radiation & chemotherapy.

Keywords: Gliomas, ^{99m}Tc Sestamibi, radiation necrosis, tumor recurrence MRI and CT

1. Introduction

Malignant gliomas account for 60% of all primary brain tumours. Patients having this tumour type have dismal prognosis. The mean survival is only from 2 to 3 months to 1 year⁽¹⁻³⁾.

Established treatment consists of surgical resection, adjuvant radiotherapy and chemotherapy with minor modification of this treatment approach depending on the specific type of tumour.

With the development of aggressive therapeutic trials, an increasing number of patients presenting after treatment with symptoms & signs that may be secondary to residual or recurrent tumour, or due to radiation induced necrosis.

Both MRI and CT localise brain tumours and define the extension of the tumoral mass into the surrounding normal tissue. Nevertheless, these techniques present some limitations, especially regarding patients follow-up after treatments when discrimination between tumour recurrence/persistence versus necrosis is required⁽⁴⁾. In such cases, nuclear functional imaging by SPECT and PET was successfully proposed to obtain a metabolic characterisation of the morphological lesions detected by MRI or CT scan.

The routinely used PET radio tracer Fluorine-18 Fluoro-Deoxy Glucose (FDG) proved to be useful to diagnose primary brain tumours and their recurrences; moreover, the entity of FDG uptake was found to correlate with brain tumour histology^(5, 6). However, FDG is physiologically taken by normal brain tissue, so this radio tracer is less accurate in detecting very low grade gliomas due to their relatively low target to background uptake ratio⁽⁷⁾. There are two main peaks of incidence: the former in childhood between 0 and 4 years, the latter in the elderly between 65 and 79 years^(8, 9, and 10).

To differentiate residual tumour from post-surgical/post radiation changes is also a diagnostic dilemma, but ^{201}Tl can be a candidate for problem solving. Radiation therapy for brain tumour, is associated with a delayed necrosis. Necrosis may be also delayed up to two or three months following radiation therapy. The necrotic area may also stimulate oedema in the surrounding tissue. On CT or MRI, this diagnostic difficulty comes from the disruption of the BBB that makes an abnormal contrast enhancement area in both conditions. ^{201}Tl uptake, increasing in comparison to the contralateral normal brain, is highly suggestive of recurrence. Necrosis and inflammatory-infectious processes may rarely show increased uptake of ^{201}Tl ⁽¹¹⁾. In view of better imaging characteristics and less radiation exposure

Volume 5 Issue 9, September 2016

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^{99m}Tc Sestamibi is used as a surrogate for Thallium-201. We evaluated the role of ^{99m}Tc Sestamibi Brain Single photon Emission computed tomography (SPECT) in differentiating tumour recurrence from radiation necrosis in post therapeutic glioma patients and compared to CT and MRI.

2. Material and Methods

It is a Prospective Cohort study conducted from 2006 to 2008 in 36 patients.

Post therapeutic Glioma patients presenting with clinical deterioration on follow up, who were investigated with CT and MRI and who were willing to give informed consent were included in the study.

Pregnant or Lactating woman, Patients with a history of hypersensitive to radiopharmaceutical were excluded from the study.

This SPECT Study was performed to differentiate neoplastic from a non-neoplastic aetiology of space occupying lesions (ISOLS) in the brain. ^{99m}Tc - Sestamibi is injected intravenously in an isolated room to a dose for adults 15-30mCi (555 MBq -1110 MBq). SPECT scan was performed on Siemens E Cam Gamma Camera (Dual Head). The patient's head was lightly restrained to facilitate patient cooperation in minimising motion during acquisition. Sedation was used following the injection of radiopharmaceutical in uncooperative patients.

Images were acquired in the following parameters: 64X64 matrix, 32 views, step & shoot, 25-30 seconds, circular and step and shoot method. Raw films will be reconstructed by filtered back projection method. Trans axial, coronal and sagittal views (Images) were analysed. ^{99m}Tc SESTAMIBI Tumour Brain SPECT compared with Computed Tomography & Magnetic Resonance Imaging. Radiologists, without their knowledge of SPECT results identified recurrence of tumour or radiation necrosis in CT & MRI.

3. Statistical Analysis

Data was entered in Microsoft excel spread sheet

Version 2000. Data was categorised as 1 for the presence of tumour and 0 for absence of tumour and then expressed in actual numbers. Using 2 x 2 table sensitivity and specificity were calculated based on the clinical status at 6 months.

4. Results

Out of 36 cases 25 were male and 11 were female. Demographic datamedian age of the patients is 50 (range 30 to 70). out of 36 cases 23 were WHO grade II tumours, 6 were WHO grade III and remaining 7 were WHO grade IV (glioblastoma multiforme). Out of 36 lesions, 20 were located in frontal lobe, 13 in Temporo parietal lobe and 3 in cerebellum.

Follow-up SPECT, CECT and MRI were done in these patients up on clinical deterioration. These patients were followed up. Positive for recurrence assumed to be predisposing factor for worsening clinical outcome.

Negative for recurrence assumed to be predisposing factor for better clinical outcome and stable lesion.

Out of these 36 cases on ^{99m}TcSESTAMIBI Tumour Brain SPECT 14 cases shown recurrence of tumour or tumour viability, rest of the 22 cases were reported as negative, these cases had very faint tracer or no tracer uptake in the suspicious region, compatible with radiation injury or no tumour recurrence (Table 1)

In 14 cases diagnosed by SPECT, 8 cases had a survival for a time period of 12 months on follow up, 5 patients survived for a period of (6-8) months and 1 patient died within a span of 6 months. Among the 22 cases reported as negative, 21 cases had shown lesions remained morphologically unaltered in a 12 month follow up period. There was no clinical deterioration in the patient condition, strongly favouring the diagnosis of radiation injury. One case which was reported as radiation injury has clinical deterioration and expired at 6 months.

Sensitivity and specificity of ^{99m}Tc SESTAMIBI tumour brain SPECT in differentiating radiation necrosis from tumor recurrence taking clinical deterioration as standard were 92.86 and 94.85% respectively (Table 2).

In CT suspicious lesion appears a considerable grey zone between the tumour, oedema and the surrounding normal brain parenchyma.

In total 36 cases, CT was positive for recurrence in 21 patients, out of which 13 had clinical deterioration at 6 months and 8 had stable disease at follow up after 6 months remaining 15 cases were reported as negative. (Table1)

Sensitivity and specificity of CT in differentiating radiation necrosis from tumor recurrence were 92.86% and 63.64% respectively.

MRI shows positive for tumour recurrence in 19 cases, negative in 17 cases. Out of the 19 cases thought to be positive for recurrence on MRI only 13 had clinical deterioration at 6 months and the rest 6 patients had stable lesion. (Table1). Sensitivity and specificity of MRI in differentiating radiation necrosis from tumor recurrence were 92.86% and 72.73% respectively.

5. Discussion

Radiation therapy and/or chemotherapy are the current mainstays of treatment for most brain stem gliomas. Functional imaging with PET and SPECT may provide direct information of tumour metabolism and tissue viability. There are various investigating modalities, to detect early recurrence or radiation necrosis. These are Computed Tomography, Magnetic Resonance Imaging, Radionuclide SPECT Imaging, and Magnetic Resonance Spectroscopy & Positron Emission Tomography.

Various imaging modalities for determination of treatment effect, tumour progression, and differentiation of recurrent tumour from radiation necrosis. The effects of treatment should ideally be visualised with the same imaging parameters that have been used before therapy.

However, there are several limitations inherent in each imaging modality. On contrast-enhanced MRI, residual tumour and post surgical changes can both result in abnormal enhancement. Therefore, MRI cannot be used postoperatively after day 3 and for several weeks because the surgical damage of the BBB, with subsequent leakage of contrast media, leads to a false-positive indicator of the presence of residual or recurrent tumour. Moreover, conventional MRI techniques usually fail to detect early effects of radiotherapy and chemotherapy because individual treatment effects are only visible after more than 12 months, with a substantial inter observer variability in the assessment of treatment response.

Especially after the application of biologically active agents (gene therapy vectors, toxins), the value of conventional MRI to detect -specific changes of tumour viability is limited.

In contrast, dynamic contrast enhanced MRI, as a surrogate marker for angiogenesis, is useful for monitoring anti angiogenic therapies in brain tumours. Moreover, diffusion-weighted MRI detects therapy-induced water diffusion changes and has been suggested to provide an early surrogate marker for quantification of treatment response.

It was found that low values for the ADC indicating high tissue viability imply better response to radiotherapy, whereas high ADC values indicating necrosis correlate with poorer response.

However, dexamethasone treatment significantly reduces the diffusivity of oedematous brain, thus confounding the interpretation of DWIs. Because MRS can reliably differentiate pure tumour, pure necrosis, and normal tissue, specific changes in tumour metabolite levels as detected by MRS may be predictive for the effectiveness of experimental treatment strategies.

However, MRS alone may not be particularly helpful because most patients have mixed histological findings comprised of necrosis and tumour giving rise to inconclusive findings. In contrast, progression from low-grade to high-grade gliomas leads to a characteristically increased concentration of choline and a reduced NAA peak with high diagnostic accuracy.

Due to the relatively high cortical background activity, [¹⁸F] FDG-PET is not suited to detect residual tumour after therapy. Similar to structural imaging, the effects of radio- and chemotherapy can be visualised by [¹⁸F] FDG-PET only after several weeks with a possible transient increase of [¹⁸F] FDG-uptake in the initial phase which is most likely due to infiltration of macrophages consuming [¹⁸F] FDG.

[¹⁸F]FDG-PET⁽¹²⁾ has a sensitivity of 75% and a specificity of 81% for the detection of recurrent tumour versus radiation

necrosis. Moreover, in patients after stereotactic radiotherapy for brain metastasis, co registration of [¹⁸F] FDG-%. Disadvantages of [¹⁸F] FDG-PET include accumulation of [¹⁸F] FDG in macrophages that may infiltrate the sites having received radiation therapy. Therefore, radiation necrosis may be indistinguishable from recurrent tumour. It should be noted that in patients receiving corticosteroids as symptomatic treatment evaluation of [¹⁸F] FDG-PET may be hampered by a reduced cortex-to-white matter ratio.

[¹¹C]MET-PET⁽¹³⁾ in contrast is much better suited to follow the effects of radiation therapy, which show as a reduction of relative methionine uptake, which may also be observed in animal models. Most importantly, [¹¹C] MET-PET⁽¹³⁾ successfully differentiates between recurrent tumour and radiation necrosis with the detection of recurrent tumour at high sensitivity and high specificity. Though combination of F18 FDG and C11 Methionine can accurately differentiate radiation necrosis from tumour recurrence of both low grade and high grade tumours the cost availability and short half life of C11 Methionine preclude using these agents. In our study we used easily available less costly Tc-99m-Hexakis-2-methoxy-2-isobutyl Isonitrile to study its ability to differentiate tumor recurrence from radiation necrosis.

Tc-99m-Hexakis-2-methoxy-2-isobutyl isonitrile (Tc-99m-sestamibi) (Tc-99m-MIBI) is a monovalent cation complex formed by a central technetium atom surrounded by six 2-methoxy-2-isobutyl isonitrile groups. This compound is also used extensively in myocardial perfusion imaging. Normal brain tissue shows minimal uptake of Tc-99m-sestamibi.

The normal physiologic distribution in the head and neck region is similar to that of thallium and includes the scalp, nasopharyngeal area, salivary gland, and the pituitary gland. There is notable significant choroid plexus uptake, much greater when compared to thallium-201.

It is postulated that after crossing the cell membrane MIBI is taken by the mitochondria in relation to negative electric potential. Normal myocardial uptake of MIBI depends on blood flow and the uptake of the mitochondria in metabolically active tissue. In brain tumours the mechanism of tumour uptake is also thought to be dependent on mitochondrial activity and the presence of P-glycoprotein.

In present study, clinically deteriorated Post therapeutic glioma patients are subjected to ^{99m}Tc SESTAMIBI Tumour Brain SPECT, This brain SPECT report is compared with Computed Tomography, Magnetic Resonance Imaging reports.

Yamamoto Y. et. al⁽¹⁴⁾ performed Dual SPECT with ^{99m}Tc-MIBI and ²⁰¹Tl in 21 patients suspected of having recurrent brain tumours. SPECT images were acquired 15 min (early) and 2 h (delayed) after injection. The ratio of the average counts for the region of interest in the lesion area and its mirror image in normal brain tissue was obtained. Early and delayed ratios were calculated. On the basis of histological and/or clinical findings, the final diagnosis was considered as recurrent tumours in 15 patients and radiation necrosis in six. Both ratios using ^{99m}Tc-MIBI and ²⁰¹Tl were

significantly higher in recurrent tumours than in radiation necrosis.

Based on a cut-off of 5.89 of the early ratio using ^{99m}Tc-MIBI to distinguish between recurrent tumours and radiation necrosis, the accuracy was 90%. Based on a cut-off of 6.77 of the delayed ratio using ^{99m}Tc-MIBI, the accuracy was 86%. The corresponding values using cut-offs of 2.40 and 1.85 with ²⁰¹Tl were 90% and 86%, respectively. However, within recurrent tumours, both ratios for ^{99m}Tc-MIBI were significantly higher than those for ²⁰¹Tl. Early ^{99m}Tc-MIBI SPET may be especially useful for the detection of recurrent tumours in patients who have previously undergone radiation therapy for brain tumours.

Patrick et al⁽¹⁵⁾ performed ^{99m}Tc-MIBI brain SPECT in glioma patients at the end of radiation therapy to see if it can aid in further management.

Patient survival after therapy for malignant gliomas has been correlated with a variety of factors including the type of tumour, age of the patient, histologic findings, score on the Karnofsky performance scale (KPS), and completeness of tumour resection; however, few investigators have MIBI brain SPECT; survival time assessed the utility of ^{99m}Tc-MIBI brain SPECT for this purpose.

Soler et al.⁽¹⁶⁾ analysed in a retrospective study the usefulness of MIBI SPECT in diagnosis of supra tentorial malignant gliomas recurrence versus radio necrosis. Actually, after conventional radiotherapy clinical deterioration may occur due to either tumour recurrence or radiation induced changes. In this work, 35 patients with clinical deterioration were studied; MIBI SPECT was performed contextually with CT scan. MIBI uptake was visually assessed by two blinded nuclear physicians. Semiquantitative analysis was applied by drawing regions of interest (ROI) and comparing tumour uptake to background and to the pituitary gland uptake. Pituitary gland is located outside the BBB and represents a site of MIBI physiological uptake. Moreover, a mathematical algorithm was used to calculate tumour volume. The functional indices and tumour evolution were statistically correlated to tumour recurrence proved by biopsy or by rapid clinical evolution. MIBI SPECT was true positive in 31 patients and true negative in 4 patients, without false positive or negative results. Nevertheless, in all but eight patients with recurrence CT scan was enabling to identify tumour viability. So, MIBI SPECT was proved to be more accurate than CT scan in detecting supra tentorial gliomas recurrences.

Our study results are also in line with previous studies

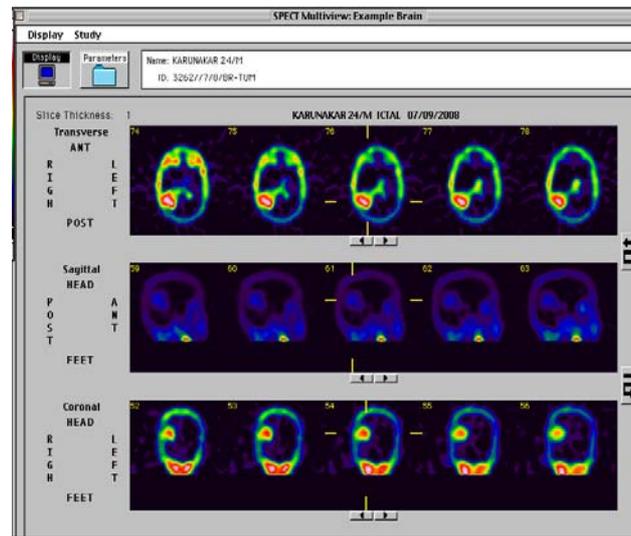


Figure 1: TC-99M Sestamibi Tumor Brain Spect Positive for Residual Tumor/ Tumor Recurrence/ Viability at Right Temporal Lobe

6. Conclusion

In post treatment glioma patients follow-up, ^{99m}Tc-SESTAMIBI tumour brain scintigraphy showed great diagnostic accuracy to discriminate tumour recurrence versus scar tissue when compared to CT scan & MRI. ^{99m}Tc-SESTAMIBI tumour brain SPECT proved efficient in differentiating tumour recurrence from tumour necrosis, in predicting survival in post treatment glioma patients and can be used in diagnostic dilemmas in centres where dual tracer PET-CT is not feasible.

Captions to illustrations:

Table1:

Total Cases	Computed Tomography (CT)	MRI	Single Photon Computed Tomography (SPECT)
36			
TP	13	13	13
FP	8	1	1
TN	14	16	21
FN	1	1	1
Sensitivity	92.86%	92.86%	92.86%
specificity	95.45%	63.64%	72.73%

Financial Support

Nil

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