DIRECT COMPARISON OF Tl-201 AND Tc-99m MIBI SPECT OF GLIOMA BY A RECEIVER OPERATING CHARACTERISTIC ANALYSIS

Y Shibata, M.D., Ph.D.,

T Yamamoto, M.D., Ph.D., S Takano, M.D., Ph.D., W Katayama, M.D.,

T Takeda*, M.D., Ph.D., A Matsumura, M.D., Ph.D.,

Department of Neurosurgery and *Radiology, Institute of Clinical Medicine, Graduate school of comprehensive human sciences, University of Tsukuba

Tennodai 1-1-1, Tsukuba, Ibaraki, 305-0005, Japan

Correspondence and whom reprint requests should be directed:

Yasushi Shibata, M.D., Ph.D.

Department of Neurosurgery, Institute of Clinical Medicine, University of Tsukuba

Tennodai 1-1-1, Tsukuba, Ibaraki, 305-0005, Japan

Tel: +82-298-533220

Fax: +82-298-533214

E-mail: yshibata@md.tsukuba.ac.jp

Abstract

The diagnostic value of SPECT has been evaluated using sensitivities and specificities with arbitrary cut off values. The diagnostic ability of Tl-201 SPECT and Tc-MIBI SPECT was directly compared for patients with an initial glioma using an receiver operating characteristic (ROC) analysis. The study population included 59 patients with gliomas. Tl and Tc-MIBI SPECT images were obtained 15 min (early) and 3 hours (delayed) after the intravenous injection of 74 MBq of Tl chloride or 740 MBq of Tc-MIBI using a multi-detector SPECT machine. The Regions of Interest were set on tumor and contra-lateral normal white matter and Tumor/Normal ratios were calculated. The area z-score (A_z) values were calculated from the areas under the ROC curves. All A_z values were high and no statistical difference was observed between each modality. Both Tl and MIBI SPECT are considered to be useful imaging modalities for the evaluation of glioma malignancies.

Key words: Glioma, Malignancy, Tl, Tc-MIBI, SPECT, ROC

Introduction

Single photon emission computed tomography (SPECT) is a valuable diagnostic modality for the evaluation of brain tumor malignancy and activity. Thallium-201 (Tl) SPECT and Technetium-99m methoxyisobutylisonitrile (Tc-MIBI) SPECT were clinically used to evaluate brain tumor malignancy and activity. In addition, both early and delayed images were taken depending on the preference of each institute. The results of SPECT examinations always include some false positive or false negative findings. The diagnostic value of brain tumor SPECT has been evaluated using sensitivities and specificities with arbitrary cut off values (*1*-*8*). These arbitrary cut off values depend on the measurement methods used by each institute, as a result, studies using these arbitrary cut off values are not useful for evaluating tumor malignancy at other institutes.

A receiver operating characteristic (ROC) analysis is useful for evaluating the diagnostic ability of different examinations that include some errors (*9*, *10*). In order to investigate the ability of each SPECT modality to evaluate tumor malignancy, each SPECT modality was directly compared for the patients with an initial glioma using an ROC analysis. The hypothesis is that the one SPECT modality is superior to any other modalities for grading glioma.

Patients and Methods

The study population included 59 patients with glioma who were admitted to

Tsukuba University hospital between 1999 and 2005 and who underwent SPECT imaging. None of the patients had received any previous radiation therapy to the brain and recurrent cases were excluded. Tl and Tc-MIBI SPECT images were taken before surgery, radiation or chemotherapy in most patients. The SPECT images were taken after surgery but before radiation or chemotherapy in one patient (Case 2). All pathological diagnoses were confirmed after the surgical removal of the tumor. The benign group included low grade astrocytomas (n=23) and a central neurocytoma (n=1) while the malignant group included anaplastic astrocytomas (n=10) and glioblastomas (n=25). The benign group included 13 men and 11 women, ranging from 3 to 59 years of age and the median age was 32 years old. The malignant group included 17 men and 18 women, ranging from from 7 to 79 years of age and the median age was 55 years old.

Tl SPECT and Tc-MIBI SPECT images were obtained 15 min (early) and 3 hr (delayed) after the intravenous injection of 74 MBq of Tl chloride or 740 MBq of Tc-MIBI using a multi-detector SPECT machine (E.CAM, Siemens Medical, Malvern, PA) and a high resolution collimator (LEHR, Siemens Medical, Malvern, PA). The Butterworth pre-correction filter and the Chang method were used for pre and post attenuation corrections. The Ramp filter was used for reconstruction. The image matrixes for Tl and MIBI SPECT were 64x64 and 128x128. The pixel sizes for Tl and MIBI SPECT were 6.61mm and 3.31mm. The slice thickness both of Tl and MIBI SPECT was 6.61mm.

The Regions of Interest (ROI) were set on tumor and contra-lateral normal white matter in reconstructed SPECT images. The ROIs were customized for each patient. In the cases with a hot tracer uptake into the tumor, the ROIs were placed at homogeneously high uptake areas. In cases with no tracer uptake, the ROIs were placed at suspected tumor areas using the MRI findings as references. All ROIs were selected by independent radiology technologists. Tumor/Normal (T/N) ratios were calculated as the ratios of radioactivity in the ROIs. The diagnostic abilities of the T/N ratios for malignancy were analyzed by an ROC analysis using the ROCKIT1.1B2 Beta and PlotROC.xls software programs (University of Chicago). The area z-score (A_z) values were calculated from the areas under the ROC curves and the diagnostic accuracy was compared between each imaging modality. Any differences in the A_z values were analyzed using the bivariate x^2 test.

Case 1

An eighteen-year-old male was admitted into the hospital complaining of a headache. An MRI showed a well demarcated intraventricular enhanced tumor (**Figure 1**). Early and delayed Tl SPECT demonstrated hot uptake at the tumor. The early and delayed Tl indices were 3.3 and 2.8. No uptake was seen in the early and delayed Tc-MIBI SPECT. Early and delayed MIBI index were 1.1 and 1.0. The tumor was surgically removed and the pathological diagnosis was confirmed as a central neurocytoma. Tumor recurrence has not been observed for several years without any additional therapy.

Case 2

A thirty-three-year-old male was admitted to the hospital complaining of a headache. An MRI revealed a well enhanced left frontal tumor. The tumor was surgically removed and the pathological diagnosis was glioblastoma. The post-operative MRI showed a small residual enhanced tumor detected at the corpus callosum (**Figure 2**). Both of early and delayed Tl and Tc-MIBI SPECT showed hot uptake at the residual tumor. Tc-MIBI SPECT demonstrated a more localized tumor, on the other hand Tl SPECT showed a larger tumor volume than that of the enhanced MRI. The early and delayed Tl indices were 3.1 and 3.5. Early and the delayed MIBI indices were 50 and 58, so the MIBI index were higher than Tl index. Although the patient was treated with radiation therapy and chemotherapy, the tumor progressed rapidly and he died about 1 year after the initial diagnosis.

Results

Figure 3 shows the ROC curves. The vertical axis is the true positive fraction (TPF) that means sensitivity and the horizontal axis is the false positive fraction (FPF) that is same value of 1-specificity. The ROC curve of the early MIBI shifted to upper right and the sensitivity was better than the other in the high FPF area, however the sensitivity was low in the low FPF area. The ROC curve of the delayed MIBI shifted to the upper left and showed well balanced high sensitivity and specificity. The ROC curves of the early and delayed Tl were almost same and showed lower sensitivity and specificity than that of the delayed MIBI in most areas.

The A_z values for the early Tl, delayed Tl, early MIBI, delayed MIBI were 0.90, 0.91, 0.87, and 0.93, respectively. All A_z values were high and no statistical difference was observed between each modality. The delayed MIBI had the highest A_z while the early MIBI had the lowest A_z. The delayed A_z values were higher than the early A_z values for both the Tl and MIBI SPECT. This tendency was dominant in MIBI SPECT although the difference was not statistically significant.

Discussion

Tl SPECT

Tl SPECT is useful for identifying the presence of a tumor (*11*), tumor malignancy (*1, 6, 12*) and for making a differential diagnosis to distinguish tumor recurrence from radiation necrosis (*6, 12, 13*). The Tl index, the ratio of radioactivity of ROI at the lesion and normal brain, was used to differentiate low and high grade glioma (*1*), recurrence and radiation necrosis (*2, 3*). The dynamic Tl SPECT is reported to be useful to evaluate tumor vascularity, histology and malignancy (*14, 15*). However there are some false positive and false negative cases reported (*6, 7, 12, 16, 17*). Inflammation after surgery or radiation is a major cause of false positive Tl uptake. The causes of false negative findings may include small tumor size, histological heterogeneity, cystic or necrotic components, or a low threshold of the detector or imaging (*18, 19*). Both of central neurocytoma and ganglioglioma are benign glioma. High

Tl uptake in a central neurocytoma and ganglioglioma were reported (*20*, *21*). High cell density and high metabolic rate are thought to explain the high Tl uptake in these low proliferative tumors. In the present series, one patient with a central neurocytoma showed high Tl uptake and no MIBI uptake (**Figure 1**). In this case, MIBI SPECT was more accurate than Tl SPECT to evaluate tumor malignancy, because central neurocytoma is a benign tumor. Pilocytic astrocytoma is one of the most benign gliomas and the Tl SPECT findings of a pilocytic astrocytoma are reported to show a variable uptake (*8*).

Tc-MIBI SPECT

Tc-MIBI SPECT is reported to be useful to diagnose brain tumor recurrence (*22, 23*), high S-phase fraction and aneuploidy (*24*), tumor volume and survival (*25, 26*), and, differential diagnosis of radiation necrosis (*27*). The Tc-MIBI index, the ratio of radioactivity of the ROI at the lesion and normal brain, was used to differentiate low and high grade gliomas (*28*), recurrence and radiation necrosis (*22*) and the estimation of the prognosis (*25, 26*). However there are some false positive and false negative cases reported (*23*). Tc-MIBI is concentrated in the mitochondria as the result of active diffusion due to increased metabolic needs (*22*). Tc-MIBI uptake is determined by tumor malignancy, viability, density, oxygenation, vascular supply, and blood brain barrier (BBB) disruption (*29*). These factors are not linearly correlated, because glioblastoma, the most malignant form of glioma, is pathologically heterogeneous including internal necrosis. False negative MIBI SPECT may occur due to the lack of contrast uptake on MRI and masked by other normal tissue uptake. This was seen in temporal and periventricular tumors (*23*), because Tc-MIBI is physiologically taken into the orbita, nasopharyngeal tissues, pituitary, scalp and choroid plexus (*30*). Some of the false positive results were due to recent radiation induced local disruption of the BBB (*23*).

The pixel size of MIBI SPECT was smaller than that of Tl SPECT in this study. Therefore, MIBI SPECT has a higher spatial resolution than Tl SPECT. This study investigated the diagnostic ability of SPECT for glioma malignancy. Higher spatial resolution might influence the diagnostic ability with small or heterogeneous tumors. However, all of the gliomas in this study were larger than the pixel size. In addition, most of the malignant tumors in this study were highly heterogeneous in both of MRI and SPECT. Only the higher spatial resolution of MIBI SPECT could not explain the slightly higher diagnostic ability of MIBI SPECT than that of Tl SPECT. Some authors have reported that Tc-MIBI SPECT has higher sensitivity and specificity than that of Tl SPECT for adult and childhood brain tumors and differential diagnosis of recurrence and radiation necrosis (*26, 27, 31*). However, other authors did not (*32*). This discrepancy may be caused by small and heterogeneous patient populations and arbitrary selected cut off values. In Tl SPECT there is some normal brain uptake, this makes T/N ratio low. Tc-MIBI has high photon energy level and higher tumor/background ratio in comparison with Tl SPECT and yields clear SPECT images and high sensitivity for malignant brain tumor (*22, 27, 31*).

P-glycoprotein is one of the drug efflux pumps in the cell membrane and it acts to remove Tc-MIBI from tumor cells (*33, 34*). Other studies have suggested that p-glycoprotein expression in malignant glioma is the cause of false negative with Tc-MIBI SPECT (*35-37*). The effect of p-glycoprotein expression on clinical Tc-MIBI SPECT images has been investigated, and this effect was negligible in the diagnosis of brain tumor malignancy (*38*). Henze also reported that p-glycoprotein efflux does not contribute to false negative MIBI SPECT, since MIBI washout did not occur between the early and late SPECT scans (*39*).

ROC analysis

Many facilities use a cut off value to evaluate tumor malignancy in Tl or MIBI SPECT (*1, 4-8*). Serizawa reported that simple inter-institutional comparisons of Tl indices are not possible because measurement methods are different in each institute (*7*).

Most diagnostic tests have some errors and the results are influenced by arbitrary selected cut off values. ROC analysis is useful to evaluate the diagnostic values of each examination that yield some false positive or false negative results (*9, 10*). Henze reported that ROC analysis comparing I-123-iodo-α-methyl-L-tyrosine (IMT), MIBI SPECT and F-18-fluorodeoxyglucose positron emission computed tomography (FDG PET) for detection of tumor progression in irradiated low-grade astrocytoma demonstrated that IMT yielded best diagnostic accuracy (*29*). ROC analysis has better diagnostic power than the arbitrary cut off method and independent disease prevalence and decision-making threshold (*29*). ROC analysis also provides adequate cut off value with appropriate sensitivity and specificity. Because SPECT image accuracy is dependent on SPECT machine quality, acquisition algorithm, and injected isotope dose, each facility should determine its own cut off value to provide an adequate diagnosis from an ROC analysis of own data.

Some facilities omitted the acquisition of delayed images due to their limited examination time. However, the current results demonstrated the superior diagnostic value of delayed images in both of Tl and MIBI SPECT. These results revealed both Tl and MIBI SPECT are useful for the diagnosis of gliomas. However, the SPECT study is not perfect, there are still some false positive and false negative findings. Multi-modality imaging studies may therefore help to diagnose brain tumors more correctly. If it is necessary to limit SPECT examinations due to medical economical issues related to the health insurance policy, then MIBI SPECT with a delayed acquisition is therefore considered to be the most reasonable choice.

In conclusion, both Tl and MIBI SPECT are useful imaging modalities for the evaluation of glioma malignancies. Delayed MIBI SPECT demonstrated a better diagnostic value for the patients with gliomas based on an ROC analysis, although no statistical significant difference was observed. The delayed images were better than the early images for both the Tl and MIBI SPECT. If it is necessary to limit SPECT examinations due to medical cost issues related to the health insurance policy, then MIBI SPECT with a delayed acquisition is therefore considered to be the most reasonable choice.

Acknowledgements

The authors would like to thank the neurosurgical and nuclear medicine technical staffs in Tsukuba University Hospital for their valuable help in conducting this study.

Legends of Figures

Figure 1

Upper left: T1 weighted MRI, Upper middle: Gadolinium-DTPA enhanced MRI, Upper right: T2 weighted MRI

Lower left: early and delayed Tl SPECT, Lower right: early and delayed Tc-MIBI SPECT

Intraventricular enhanced tumor in MRI. Hot uptake in early and delayed Tl SPECT. No uptake in early and delayed Tc-MIBI SPECT.

Figure 2

Upper left: T1 weighted MRI, Upper middle: Gadolinium-DTPA enhanced MRI, Upper right: T2 weighted MRI

Lower left: early and delayed Tl SPECT, Lower right: early and delayed Tc-MIBI SPECT

Small residual enhanced tumor at corpus callosum. Both of early and delayed Tl and Tc-MIBI SPECT showed hot uptake at residual tumor, however, MIBI index were higher than Tl index.

Figure3

ROC curves early and delayed Tl and Tc-MIBI SPECT. The vertical axis is true positive fraction (TPF) that means sensitivity and the horizontal axis is false positive fraction (FPF) that is the same value of 1-specificity.

References

1. Black KL, Hawkins RA, Kim KT, Becker DP, Lerner C, Marciano D. Use of thallium-201 SPECT to quantitate malignancy grade of gliomas. J Neurosurg. 1989;71:342-346.

2. Kosuda S, Shioyama Y, Kamata N, et al. [Differential diagnosis between recurrence of brain tumor and radiation necrosis by 201Tl SPECT]. Nippon Igaku Hoshasen Gakkai Zasshi. 1991;51:415-421.

3. Kosuda S, Fujii H, Aoki S, et al. Reassessment of quantitative thallium-201 brain SPECT for miscellaneous brain tumors. Ann Nucl Med. 1993;7:257-263.

4. Kahn D, Follett KA, Bushnell DL, et al. Diagnosis of recurrent brain tumor: value of 201Tl SPECT vs 18F- fluorodeoxyglucose PET. Am J Roentgenol. 1994;163:1459-1465.

5. Burkard R, Kaiser KP, Wieler H, et al. Contribution of thallium-201-SPECT to the grading of tumorous alterations of the brain. Neurosurg Rev. 1992;15:265-273.

6. Staffen W, Hondl N, Trinka E, Iglseder B, Unterrainer J, Ladurner G. Clinical relevance of 201Tl-chloride SPET in the differential diagnosis of brain tumours. Nucl Med Commun. 1998;19:335-340.

7. Serizawa T, Saeki N, Higuchi Y, et al. Diagnostic value of thallium-201 chloride single-photon emission computerized tomography in differentiating tumor recurrence from radiation injury after gamma knife surgery for metastatic brain tumors. J Neurosurg. 2005;102 Suppl:266-271.

8. Comte F, Bauchet L, Rigau V, et al. Correlation of preoperative thallium SPECT with histological grading and overall survival in adult gliomas. Nucl Med Commun. 2006;27:137-142.

9. Metz CE. ROC methodology in radiologic imaging. Invest Radiol. 1986;21:720-733.

10. Metz CE, A. HB, Jong-Her S. Maximum likelihood estimation of receiver operating characteristic (ROC) curves from continuously-distributed data. Statistics in Medicine. 1998;17:1033-1053.

11. O'Tuama LA, Janicek MJ, Barnes PD, et al. 201Tl/99mTc-HMPAO SPECT imaging

of treated childhood brain tumors. Pediatr Neurol. 1991;7:249-257.

12. Yoshii Y, Satou M, Yamamoto T, et al. The role of thallium-201 single photon emission tomography in the investigation and characterisation of brain tumours in man and their response to treatment. Eur J Nucl Med. 1993;20:39-45.

13. Schwartz RB, Carvalho PA, Alexander E, 3rd, Loeffler JS, Folkerth R, Holman BL. Radiation necrosis vs high-grade recurrent glioma: differentiation by using dual-isotope SPECT with 201TI and 99mTc-HMPAO. AJNR Am J Neuroradiol. 1991;12:1187-1192.

14. Ueda T, Kaji Y, Wakisaka S, et al. Time sequential single photon emission computed tomography studies in brain tumour using thallium-201. Eur J Nucl Med. 1993;20:138-145.

15. Sugo N, Yokota K, Kondo K, et al. Early dynamic 201Tl SPECT in the evaluation of brain tumours. Nucl Med Commun. 2006;27:143-149.

16. Buchpiguel CA, Alavi JB, Alavi A, Kenyon LC. PET versus SPECT in distinguishing radiation necrosis from tumor recurrence in the brain. J Nucl Med. 1995;36:159-164.

17. Rollins NK, Lowry PA, Shapiro KN. Comparison of gadolinium-enhanced MR and thallium-201 single photon emission computed tomography in pediatric brain tumors. Pediatr Neurosurg. 1995;22:8-14.

18. Kallen K, Burtscher IM, Holtas S, Ryding E, Rosen I. 201Thallium SPECT and 1H-MRS compared with MRI in chemotherapy monitoring of high-grade malignant astrocytomas. J Neurooncol. 2000;46:173-185.

19. Young RJ, Ghesani MV, Kagetsu NJ, Derogatis AJ. Lesion size determines accuracy of thallium-201 brain single-photon emission tomography in differentiating between intracranial malignancy and infection in AIDS patients. AJNR Am J Neuroradiol. 2005;26:1973-1979.

20. Kumabe T, Shimizu H, Sonoda Y, Shirane R. Thallium-201 single-photon emission computed tomographic and proton magnetic resonance spectroscopic characteristics of intracranial ganglioglioma: three technical case reports. Neurosurgery. 1999;45:183-187.

21. Kanamori M, Kumabe T, Shimizu H, Yoshimoto T. (201)Tl-SPECT, (1)H-MRS, and MIB-1 labeling index of central neurocytomas: three case reports. Acta Neurochir (Wien). 2002;144:157-163.

22. Soler C, Beauchesne P, Maatougui K, et al. Technetium-99m sestamibi brain single-photon emission tomography for detection of recurrent gliomas after radiation therapy. Eur J Nucl Med. 1998;25:1649-1657.

23. Le Jeune FP, Dubois F, Blond S, Steinling M. Sestamibi technetium-99m brain single-photon emission computed tomography to identify recurrent glioma in adults: 201 studies. J Neurooncol. 2006;77:177-183.

24. Ak I, Gulbas Z, Altinel F, Vardareli E. Tc-99m MIBI uptake and its relation to the proliferative potential of brain tumors. Clin Nucl Med. 2003;28:29-33.

25. Beauchesne P, Soler C. Correlation of 99mTc-MIBI brain spect (functional index ratios) and survival after treatment failure in malignant glioma patients. Anticancer Res. 2002;22:3081-3085.

26. Beauchesne P, Pedeux R, Boniol M, Soler C. 99mTc-sestamibi brain SPECT after chemoradiotherapy is prognostic of survival in patients with high-grade glioma. J Nucl Med. 2004;45:409-413.

27. Yamamoto Y, Nishiyama Y, Toyama Y, Kunishio K, Satoh K, Ohkawa M. 99mTc-MIBI and 201Tl SPET in the detection of recurrent brain tumours after radiation therapy. Nucl Med Commun. 2002;23:1183-1190.

28. Baillet G, Albuquerque L, Chen Q, Poisson M, Delattre JY. Evaluation of single-photon emission tomography imaging of supratentorial brain gliomas with technetium-99m sestamibi. Eur J Nucl Med. 1994;21:1061-1066.

29. Henze M, Mohammed A, Schlemmer HP, et al. PET and SPECT for Detection of Tumor Progression in Irradiated Low-Grade Astrocytoma: A Receiver-Operating-Characteristic Analysis. J Nucl Med. 2004;45:579-586.

30. Kirton A, Kloiber R, Rigel J, Wolff J. Evaluation of pediatric CNS malignancies with (99m)Tc-methoxyisobutylisonitrile SPECT. J Nucl Med. 2002;43:1438-1443.

31. O'Tuama LA, Treves ST, Larar JN, et al. Thallium-201 versus technetium-99m-MIBI SPECT in evaluation of childhood brain tumors: a within-subject comparison. J Nucl Med. 1993;34:1045-1051.

32. Nishiyama Y, Yamamoto Y, Fukunaga K, Satoh K, Kunishio K, Ohkawa M. Comparison of 99Tcm-MIBI with 201Tl chloride SPET in patients with malignant brain tumours. Nucl Med Commun. 2001;22:631-639.

33. Feun LG, Savaraj N, Landy HJ. Drug resistance in brain tumors. J Neurooncol. 1994;20(2):165-176.

34. Lehnert M. Multidrug resistance in human cancer. J Neurooncol. 1994;22(3):239-243.

35. Andrews DW, Das R, Kim S, Zhang J, Curtis M. Technetium-MIBI as a glioma imaging agent for the assessment of multi-drug resistance. Neurosurgery. 1997;40(6):1323-1332.

36. Ballinger JR, Sheldon KM, Boxen I, Erlichman C, Ling V. Differences between accumulation of 99mTc-MIBI and 201Tl-thallous chloride in tumour cells: role of P-glycoprotein. Q J Nucl Med. 1995;39(2):122-128.

37. Piwnica-Worms D, Chiu ML, Budding M, Kronauge JF, Kramer RA, Croop JM. Functional imaging of multidrug-resistant P-glycoprotein with an organotechnetium complex. Cancer Res. 1993;53(5):977-984.

38. Shibata Y, Matsumura A, Nose T. Effect of expression of P-glycoprotein on technetium-99m methoxyisobutylisonitrile single photon emission computed tomography of brain tumors. Neurol Med Chir (Tokyo). 2002;42:325-330.

39. Henze M, Mohammed A, Schlemmer H, et al. Detection of tumour progression in the follow-up of irradiated low-grade astrocytomas: comparison of 3-[123I]iodo-alpha-methyl-L-tyrosine and 99mTc-MIBI SPET. Eur J Nucl Med Mol Imaging. 2002;29:1455-1461.