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Original Article

To study the efficacy of thallium-201 as tumor seeking agent and to study its role in therapeutic response

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ABSTRACT

Background: Tumour seeking characteristics of TL-201 have been underutilized. The study was undertaken to evaluate the role of TL-201 scintigraphy in tumour imaging.

Methods: A total of 50 cases were studied over a period of 18 months (13 lymphomas, 11 breast carcinoma, 10 lung cancer, 6 of soft tissue sarcoma, 2 bone tumours and 4 cases each of thyroid and brain tumours). Thallium-201 chloride was injected IV in the dose range of 3–5 mCi. Imaging was done using Siemen's ECAM dual headed gamma camera. Mean tumour to background ratio (T/B ratio) was calculated for all the positive cases. Descriptive statistical analysis was carried out.

Results: Findings revealed a sensitivity of 94.12%, specificity 87.5%, PPV 94.12%, NPV 87.50% and accuracy of 92% for TL-201 tumour imaging. The mean T/B ratio for the true positive cases at 10 min and at 3 h was 1.81 and 1.99 respectively, the difference being 0.18 (P value < 0.001). Amongst them, the mean T/B ratios for low-grade tumours were 1.45 ± 0.32 at 10 min and 1.63 ± 0.38 after 3 h with difference of 0.176 ($P < 0.001$). For the high-grade tumours the ratios were 2.08 ± 0.35 and 2.26 ± 0.41 respectively with a difference of 0.186 ($P < 0.001$).

Conclusion: Thallium-201 scintigraphy is a useful tumour imaging modality in cases of thyroid, breast, brain, lung, soft tissue and bone tumours and lymphomas. A T/B ratio of 1.63 ± 0.38 in 3 h-delayed imaging is suggestive of low-grade tumours. For high-grade tumours a ratio of 2.26 ± 0.41 should be considered significant.

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Introduction

Thallium-201 is a mono-valent radioisotope and has biological properties very similar to potassium.^{1,2} The major role of thallium in nuclear medicine has been in myocardial perfusion imaging, parathyroid imaging and in assessment of viability post myocardial infarction. It was used for tumour imaging in late 1980s and early 1990s. However with the approval of FDG-PET in the imaging world, ²⁰¹Tl took a backseat due to the better biological distribution and resolution of F-18 FDG. However, it continued to have its role in intracranial brain tumours as FDG has physiologically high uptake in brain leading to poor tumour to background ratio (T/B ratio).

There is however enough literature suggesting that ²⁰¹Tl has a clinically relevant role in the oncology patient population. ²⁰¹Tl in many tumour types is an excellent radiopharmaceutical for evaluating the extent of the tumour, response of the tumour to therapy and distinguishing benign from malignant lesions.³ Rapid development of research using ²⁰¹Tl in different tumours had taken place during 1990s. The techniques for using ²⁰¹Tl in tumour imaging have also been modified using SPECT and various tumour to non-tumour uptake ratios.^{4,5}

Thallium still has the problems of poor resolution, however despite this it is currently being used to differentiate malignant from inflammatory lesions, to help in guiding biopsy accurately to malignant tissue,^{6–10} to differentiate kaposi sarcoma from inflammatory lesions in AIDS, to determine the grade of the tumour,^{11,12} to evaluate the response of pre-operative chemotherapy or radiotherapy to determine the presence of residual tumour or tumour recurrence,^{7,13} and to differentiate post-therapy tissue necrosis from local recurrence.^{14–16}

There are studies which show that ²⁰¹Tl better delineates viable tumour as compared to CT scan and Tc-99m HMPAO after radiotherapy.¹⁷ Thallium-201 SPECT has been found to be useful in differentiating benign from malignant breast masses especially in patients with dense breasts who have indeterminate mammograms.¹⁸ It has been found useful, even when compared with mammography in patients with normal breast density.¹⁹ The viable tumour burden in primary brain tumours is indicated better by thallium-201 scans as compared to other radionuclide studies. Steroid administration has lesser effect on TL-201 uptake and it complements well with the CT scan data (anatomical information).²⁰ PET facility is not available in all centres and we feel TL-201 has been under-utilized in tumour imaging. Also there are not enough Indian studies which lay down the various T/B ratios of malignant tumours using ²⁰¹Tl for diagnosing and grading malignancy. Hence this study was undertaken to study and revisit the role of thallium in tumour imaging.

Material and methods

1. A total of 50 cases who were referred from the oncology ward/OPD and who were willing to undergo thallium scanning were imaged with TL-201 in the Department of

Nuclear Medicine, over a period of 18 months. Written consent was taken for the procedure from all the patients. The study group consisted of patients in pre-treatment group referred for diagnostic workup and those in post-treatment group referred for either ruling out recurrence or to assess treatment response.

2. Thallium-201 chloride was injected IV in the dose range of 3–5 mCi. Imaging was done at 10 min and 180 min post injection using Siemen's ECAM dual headed gamma camera with energy centred on 80 keV and 160 keV with window widths of 20% and 15% respectively using low energy all purpose collimators. Static imaging was done for 5 min each time followed by whole body imaging with a speed of 8 cm/min.
3. T/B ratio was calculated for both 10 min and 3 h image. Region ratio protocol in the Siemen's software was used to calculate the ratio. Tumour ROI (region of interest) was drawn on the tumour over the pixels showing the maximum uptake and background ROI was drawn on the contra-lateral side in the same region. The images were studied and reported by two nuclear medicine physicians independently without the knowledge of histopathology report.
4. Mean T/B ratio was calculated for all the positive cases. Mean difference in the T/B ratio from early (scan at 10 min post injection) to late (scan at 180 min post injection) was calculated and the mean difference in ratio between high-grade and low-grade tumours was calculated. Any uptake seen with ratio more than 1 was considered positive scan and below 1 was considered negative scan.
5. Histopathology was used as gold standard for pretreatment cases and conventional imaging/histopathology for all the post treatment cases. Sensitivity, specificity, NPV and PPV was accordingly calculated.

To estimate sensitivity of thallium scan to detect malignancy as compared to gold standard with 10% absolute precision and 95% confidence interval, sensitivity considered from previous review as 90%,^{3,4,21} the minimum required sample size was 34 subjects with disease. We studied 50 consecutive cases out of which 34 had active disease. Descriptive statistical analysis was carried out. Results on continuous measurements were presented as mean $\pm$ SD (Min–Max) and results on categorical measurements were presented as number (%). Significance was assessed at 5% level. Between TB ratio early and late, Student's t test (paired) was used and between low grade and high grade, Student's t test (unpaired) was used to find out statistical significance. +Suggestive significance (P value: 0.05 < P < 0.10); *Moderately significant (P value: 0.01 < P $\leq$ 0.05); **Strongly significant (P value: P $\leq$ 0.01). The statistical software SPSS 15.0 was used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

Results

A total of 50 cases were studied over a period of one and half years. The mean age of patients studied was 50.2 years. There were 30 males and 20 females. 13 cases were of lymphomas, 11 cases of breast carcinoma, 10 cases of lung cancer, 6 cases of

Table 1 – Total number of positives and negatives (2 × 2 table).

	Malignancy present	Malignancy not present	Total
TL-201 scan positive	32 (64%)	2 (4%)	34
TL-201 scan negative	2 (4%)	14 (28%)	16
Total	34	16	50
Sensitivity = 94.12% (95% CI = 78.9–98.9); specificity = 87.5% (95% CI = 60.4–97.8%).			

soft tissue sarcoma, 2 cases of bone tumours and 4 cases each of thyroid and brain tumours. There were 27 pre-treatment cases referred during the diagnostic workup and 23 cases were post treatment, who were referred for evaluation of treatment response or to rule out recurrence. The study revealed a total of 34 positive scans and 16 negative scans. There were two false positives and two false negatives (Table 1).

Amongst the patients in pre-treatment group 3 patients had negative scan and rest had positive scans. Amongst the 3 negative scans 1 was true negative as it turned out to be benign breast nodule with no uptake of thallium and was benign on histopathology (Fig. 1). The other two were false negatives.

Both were cases of low grade NSCLC that was proved by histopathology (Fig. 2).

Among the post-treatment cases 8 patients were referred for suspicion of relapse/recurrence and 15 patients for assessing the treatment response. Among the 8 patients relapse was detected in 7 patients. Among these 7 patients where relapse was detected, 3 cases were of lymphomas, 2 cases carcinoma thyroid and one case each of breast and brain tumour (Figs. 3 and 4). Among the 15 patients referred for treatment response 14 showed good response to treatment (Fig. 6 shows case of brain tumour with good response to treatment) and 1 patient showed poor response and this was substantiated by histopathology/conventional imaging (Fig. 5).

Fig. 1 – Benign breast nodule right where the thallium scan is negative. There is no abnormal uptake seen in the right breast.

Fig. 2 – NSCLC right lung – false negative thallium scan. There is no abnormal uptake seen in the right lung.

Fig. 3 – Carcinoma right breast (operated). Thallium scan showing uptake in the outer quadrant of right breast with T/B ratio of 2.5. Relapse was confirmed by biopsy.

The mean T/B ratio was calculated for all the true positive cases at 10 min and at 3 h. The values were 1.81 and 1.99 respectively. The difference being 0.18 (P value <0.001) (Table 2). Amongst them the mean T/B ratios for low-grade

tumours was 1.45 ± 0.32 at 10 min and 1.63 ± 0.38 after 3 h with difference of 0.176 ($P < 0.001$). For the high-grade tumours the ratios were 2.08 ± 0.35 and 2.26 ± 0.41 respectively with a difference of 0.186 ($P < 0.001$). The difference in T/B ratios between the high grade and low grade were 0.62 and 0.63 for early and late respectively and that was also statistically significant ($P < 0.001$). The ratio was more for high-grade tumours than the low-grade tumours (Table 3). In addition amongst the positive cases mean T/B ratios for individual organs involved was calculated (Table 4). Breast and bone tumours had higher ratios than lymph nodes and lung.

The study showed that tumour imaging by ^{201}Tl had a sensitivity of 94.12%, specificity 87.5%, PPV 94.12%, NPV 87.50% and accuracy of 92%.

Discussion

The present work was carried out to study the role of thallium-201 scintigraphy in tumour imaging of breast, brain, thyroid, bone, soft tissue and lymphomas.

We calculated the T/B ratio for both 10 min and 3 h image by drawing the tumour ROI over the pixels showing the

Fig. 4 – Glioblastoma multiforme (operated). Scan shows abnormal uptake in the left parietal region with an early T/B ratio of 1.6 and late ratio of 2.5.

Fig. 5 – NSCLC left lung post surgery and post chemotherapy. Thallium scan shows uptake in the left lower lobe with an early T/B ratio of 2.3 and late T/B ratio of 2.5.

Fig. 6 – Astrocytoma right frontal region. Scan reveals no abnormal focus of uptake.

Table 2 – Mean tumour to background ratios for all the positive scans.

Positive cases	Number of patients	TB ratio early	TB ratio late	Difference	P value
Mean $\pm$ SD	32	1.81 $\pm$ 0.46	1.99 $\pm$ 0.50	0.18	<0.001**
95% CI	–	1.64–1.96	1.80–2.17		

** means strongly significant.

Table 3 – Mean TB ratios in high-grade and low-grade cases.

Positive cases	Number of patients (n = 32)	TB ratio early	TB ratio late	Difference	P value
Low grade	14	1.45 $\pm$ 0.32	1.63 $\pm$ 0.38	0.176	<0.001**
High grade	18	2.08 $\pm$ 0.35	2.26 $\pm$ 0.41	0.186	<0.001**
Difference	–	0.62	0.63	–	–
Significance	–	<0.001**	<0.001**	–	–

** means strongly significant.

maximum uptake and background ROI was drawn on the contra-lateral side in the same region. Most investigators recommend the ROI to be drawn over the highest pixel count whereas few are recommending ROI over the borders both inner and outer and then taking the average counts.^{6,14,22,23} Any uptake seen with ratio more than 1 was considered positive scan and below 1 was considered negative scan. Mean T/B ratio was calculated for all the positive cases. Mean difference in the T/B ratio from early to late was calculated and the mean difference in ratio between high-grade and low-grade tumours was calculated. The comparison of thallium uptake between tumour and adjacent normal or background

tissue or contra-lateral normal tissue has been recommended by various authors in order to differentiate normal from malignant lesions. There are various factors affecting the absolute values of these ratios. Important factors being site where ROI is drawn, the location of the lesion (if background has high blood pool or any surrounding inflammation), size of the lesion (more the number of pixels more accurate is the value) and presence of central necrosis. Ratios above 1.6–2.4 have been reported to indicate malignant lesions and lower counts indicating benign lesions or early recurrence. In this study the mean TB ratio for 3 h imaging was 1.99 with 95% CI of 1.8–2.17. The mean ratio for the low-grade tumours was 1.63 and for high grade was 2.26.

Few authors feel the ratios should always be interpreted with reservations as there is a significant overlap in these values between benign and malignant lesions.^{6,24} Ratios are more indicative if the tumour has not been treated previously. Most important to note that for a lesion which has been treated and found to be thallium negative, any positive scan subsequently indicates recurrence of malignancy, no matter how low the ratio is. With time the ratio increases as the tumour grows in size. Thallium uptake is also seen postoperatively and after chemotherapy due to granulation tissue and increased vascularity. Our study had two false positives – one was a case of breast carcinoma where thallium study revealed TB ratios in the range of 1.4–1.5, however the histopathology

Table 4 – TB ratios of tumours in positive cases – organ wise.

Site	Number of positive cases (n = 32)	TB ratio early	TB ratio late
Lung	9	1.66	1.84
Thyroid	3	2.03	2.17
Brain	3	1.88	2.08
Breast	6	2.10	2.30
LN	9	1.53	1.72
Soft tissue	1	1.80	1.95
Bone	2	2.28	2.48

Fig. 7 – Thallium scan shows hot focus in the amputation stump with a T/B ratio of 1.2. The histopathology revealed only granulation tissue.

Fig. 8 – Low-grade carcinoma right breast. Thallium scan showing low uptake.

and mammography ruled out recurrence and the other case was that of soft tissue sarcoma post treatment where histopathology revealed granulation tissue (Fig. 7). This increase in uptake decreases with time in benign lesions and hence on delayed imaging after 3 h T/B ratio will reduce.

But if there is residual disease or recurrence this ratio persists or increases on delayed imaging. Our study also showed similar trend. The ratios for the malignant cases at 10 min and at 3 h were 1.81 and 1.99 respectively and the increase was statistically significant.

The mean difference between the early and late T/B ratio for all positive cases was 0.18 ($P < 0.001$) (Table 2). For the low-grade tumours the difference was 0.176 and for high grade it was 0.186. The T/B ratio was more for high-grade tumours than the low grade ones (Table 3). Figs. 8 and 9 show scans of low-grade and high-grade tumours respectively. Identification of grade of tumour and histopathological type has been attempted by various investigators. Yamamoto et al. evaluated the uptake of ^{201}Tl and Tc-99m MIBI in different grades of primary lung cancer.²⁵ Mean $\pm$ SD values for the early and delayed ratio for ^{201}Tl in well-differentiated tumours were 2.19 ± 0.72 and 2.28 ± 0.71 respectively; in the moderately differentiated tumours it was 2.38 ± 0.83 and 2.48 ± 0.48 and 2.87 ± 0.75 and 3.60 ± 1.51 respectively in poorly differentiated malignancies. There was no significant difference in ratios detected in these three groups when $^{99\text{m}}\text{Tc}$ -MIBI was used. They concluded that ^{201}Tl is superior to $^{99\text{m}}\text{Tc}$ -MIBI in grading

Fig. 9 – High-grade carcinoma right breast. Thallium scan showing high uptake.

the histopathological differentiation of primary lung adenocarcinoma. Similar results were obtained by Takekawa et al.²⁶ They found that sensitivity of TL-201 scan was low for well-differentiated adenocarcinoma whereas in case of moderately and poorly differentiated adenocarcinoma the sensitivity was good. In the delayed scan images the ratios were very low in the well-differentiated tumours whereas the poorly differentiated ones had greater ratios. They also evaluated this parameter based on Na/K ATPase activity and found the ratio to be higher in tumours positive for Na/K ATPase. The results of both reports indicate that the uptake ratio of ²⁰¹Tl may be a non-invasive indicator of the grade of pathological differentiation of adenocarcinoma and provide insight into the relationship between ²⁰¹Tl uptake, grade of tumour and Na/K ATPase activity. In our study both the false negative scans were of low-grade lung cancer that was confirmed by histopathology and conventional imaging (Fig. 2).

In another study by Takekawa et al. where they studied 152 patients of lung cancer, it was found that the survival was longer in the group with low TL-201 uptake ratio as compared to the group with high uptake ratio ($P = 0.0138$ by the log rank test). The multivariate analysis further revealed that the uptake value also was an independent prognostic factor for survival. The authors in fact believe it to be a non-invasive marker in predicting the prognosis in carcinoma lung cases.²⁷

Our study has also demonstrated that higher the grade of tumour higher is the ²⁰¹Tl uptake. Quantifying the ²⁰¹Tl uptake hence is extremely useful in diagnosis as well as knowing the differentiation level of the tumour.

When it comes to bone and soft tissue tumours many authors have reported limitations of TL-201 scan. Otsuka et al. studied the TL-201 uptake patterns in 91 patients with soft tissue tumours, which included 19 malignant and 72 benign tumours and concluded that high TL-201 uptake is more frequently associated with malignant tumours. However, the difference of uptake was not statistically significant ($P = 0.72$). Size of tumour, location and physiological uptake in surrounding muscle were factors leading to this. They recommended that combination of imaging techniques be utilized in differentiating benign and malignant soft tissue tumours.²⁸ Sugawara et al. studied 175 cases of bone and soft tissue tumours and concluded that due to surrounding muscle uptake the clinical importance of TL-201 scintigraphy is questionable and delayed scan has little significance.²⁹ However, in our study which included total 8 cases of bone and soft tissue tumours, only one case was found to be false positive and that was a case of soft tissue sarcoma right leg that was operated and was scanned for detecting any residual tumour. The TB ratio was 1.2 (early) and 1.3 (late) and the histopathology revealed granulation tissue. Overall considering all the 50 cases the sensitivity and specificity of TL-201 was found to be 94.12% and 87.5% respectively.

Conclusion

1. The present study shows that thallium-201 scintigraphy is a useful tumour imaging modality in cases of thyroid, breast, brain, lung, soft tissue and bone tumours and lymphomas. It has a good sensitivity and specificity and this modality is

helpful in monitoring response to treatment and in detection of relapse in these cases. However, more studies are required with larger sample sizes to establish the use of TL-201 routinely in clinical practice.

2. The T/B ratio adds quantification parameter in evaluation of these tumours. A T/B ratio of 1.63 ± 0.38 in 3 h-delayed imaging is suggestive of low-grade tumours. For high-grade tumours a ratio of 2.26 ± 0.41 should be considered significant. In addition, in malignant cases there is increase in TB ratio by a mean value of 0.18 from early to late imaging.

Recommendations

We recommend that thallium-201 scintigraphy can be used as a tumour imaging modality in places where PET scan is not available. In combination with the conventional anatomical imaging methods it is useful in diagnosis and monitoring of patients of lymphomas, breast, bone, thyroid, lung, brain and soft tissue tumours. More studies with larger sample size are required to establish its role in routine practice and studies directly comparing thallium-201 and PET scan should be done.

Limitations

The sample size was limited to the duration of study and in that duration only 50 cases in total agreed to participate in the study. Hence it is felt inadequate for calculation of specificity as only 16 cases were free of malignancy. The sensitivity was also calculated with 10% absolute precision. Studies with larger sample size are recommended.

Conflicts of interest

The authors have none to declare.

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