Clinical significance of thallium-201 scintigraphy in bone and soft tissue tumors

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Abstract We evaluated sequential thallium scans on both early images (EI) and delayed images (DI) for 62 patients who had bone and soft tissue lesions. The purpose was to determine whether this technique could be used to ascertain accurately whether lesions were malignant or benign and to predict the response to chemotherapy. The thallium-201 chloride (201Tl) accumulation in malignant tumors and benign lesions was statistically different. Sensitivity, specificity, and accuracy for 201Tl scans in detecting malignant tumors was 94%, 65%, and 82%, respectively, for EI, and 94%, 85%, and 90%, respectively, for DI. On multivariate analysis, significant independent factors for 201Tl uptake were malignant lesions on EI and DI and high cellularity on EI. Thirteen patients with malignant bone and soft tissue tumors underwent 201Tl scans before and after preoperative chemotherapy. There was a good correlation between percentage of tumor necrosis and percentage change of accumulation in lesion-to-normal tissue ratio, and the correlation coefficient was higher on EI ($r = 0.801$) than on DI ($r = 0.664$). These results support the notion that 201Tl scintigraphy, although showing some false-positive and false-negative findings, is a useful tool in the evaluation of either malignant tumors or benign lesions. Furthermore, 201Tl scans on EI provide benefit concerning the evaluation of chemotherapeutic response in patients with malignant bone and soft tissue tumors.

Key words Thallium-201 · Malignant tumor · Chemotherapy

Introduction

Malignant bone and soft tissue tumors are relatively uncommon neoplasms. Most of them behave aggressively and rapidly progress in the absence of treatment. Delineation of the local extent of malignant tumors and their early detection are important for disease management.

Radionuclide scanning with technetium-99m methylene diphosphonate ($^{99m}$Tc-MDP) and gallium-67 ($^{67}$Ga) were previously used in the detection or management of bone and soft tissue tumors.6,9,10 However, detection was hard to achieve, and false-negative scans did occur.1,3,6,9,10,13 Because thallium-201 chloride (201Tl) has an affinity for a variety of neoplasms, there has been growing interest in using 201Tl for management of bone and soft tissue tumors since the early 1990s.1–3,5,7,8,11–18 Terui et al.18 showed that the sensitivity of detection with 201Tl was higher than that with 67Ga. Ramanna et al.13 reported that 201Tl scintigraphy was superior to 67Ga and $^{99m}$Tc-MDP scans in assessing the response of bone sarcomas to preoperative chemotherapy. However, this opinion was not long accepted because a series of studies then showed that 201Tl scintigraphy alone is not helpful in differentiating malignant tumors from benign lesions.1,3,14,16

With these considerations in mind, we investigated the performance of 201Tl scintigraphy for differentiating between malignant and benign lesions and for assessing the effectiveness of preoperative chemotherapy.

Materials and methods

Patient characteristics

A total of 62 patients (38 males and 24 females, aged 1–82 years) with various bone and soft tissue abnormalities were studied. There were 26 bone lesions (12 malignant tumors, 4 benign tumors, and 10 osteomyelitic lesions) and 36 soft tissue lesions (24 malignant tumors, 9 benign tumors, and 3 granulomatous lesions). Low-grade soft tissue sarcomas [American Joint Committee on Cancer (AJCC) G1/G2] were found in 8 patients (35%) and high-grade sarcomas (AJCC
G3/G4) were found in 15 patients (65%). All lesions ranged from 1 to 24 cm in diameter, with a median size of 9 cm. Lesions size was <5 cm in 11 patients (18%) and ≤5 cm in 51 patients (82%). Lesions were located on an extremity in 42 patients (68%) and the trunk in 20 patients (32%). A total of 46 patients (74%) had high cellularity, and 16 (26%) had low cellularity. Preoperative chemotherapy was undergone by 8 patients with malignant bone tumors (5 with osteosarcoma, 1 malignant fibrous histiocytoma, 1 primitive neuroectodermal tumor, and 1 multiple myeloma) and 5 patients with malignant soft tissue tumors (2 with synovial sarcoma, 1 malignant fibrous histiocytoma, 1 leiomyosarcoma, and 1 alveolar soft part sarcoma). These patients were evaluated both before and after chemotherapy. The preoperative chemotherapy was multidrug combination therapy: doxorubicin (60–90 mg/m²) and ifosfamide (12–16 mg/m²) with or without high-dose methotrexate (8–12 g/m²) and cisplatin (120 mg/m²). All drugs were administered intravenously.

Thallium scintigraphy

Radioisotope imaging sequences included whole-body scans and static scans of selected regions of interest (ROI) starting 5 min (early) and 2–3 h (delayed) after intravenous administration. Both early and delayed scintigraphic images were taken of all patients. The 201Tl dose was 0.185 MBq/kg for a maximum dose of 111 MBq and a minimum dose of 50 MBq. A scanning Anger camera (GCA901A/W2; Toshiba, Tokyo, Japan) at a speed of 20 cm/min was used for imaging. A large field-of-view rectilinear camera with a 3/8-in. sodium iodine crystal was used to obtain static views. Low-energy high-resolution collimators (Lehr model RDC-901HA; Toshiba, Tokyo, Japan) were used.

Image analysis

The amount of 201Tl uptake in the lesions was visually graded on a scale of 0 to 4 as defined by Menendez et al. Two observers (Y.G. and R.O.) without previous knowledge of the patient's outcome independently evaluated the extent of 201Tl uptake in each lesion. A grade of 0 indicated background activity; a grade of 1, equivocal activity; a grade of 2, definite activity but less than that of myocardium; a grade of 3, definite activity equal to that of myocardium; and a grade of 4, activity greater than that of myocardium. Uptake was considered positive if the scintigram demonstrated grade 2 or more on visual inspection and negative if the scintigram demonstrated grade 1 or less. The diagnostic sensitivity, specificity, and accuracy were calculated based on the grades obtained from visually assessing early and delayed images of all 62 patients. For quantitative evaluation, image data from the spot images were stored in the computer (GMS550U; Toshiba). On each image, one ROI was placed inside the outer border of the lesion and a second ROI of equal size was placed contralateral or adjacent to the lesion in a normal area. For each ROI, the average counts per pixel were calculated by the computer. The average counts in the ROI of the lesion divided by that from the contralateral or adjacent normal tissue area yielded a lesion-to-normal tissue (L/N) ratio. L/N ratio was obtained for both early and delayed images. Retention index (RI) was calculated using early and delayed ratio, as follows: RI (%) = (delayed ratio – early ratio)/early ratio × 100. We compared the prechemotherapy L/N ratio with the post-chemotherapy L/N ratio, and the percent change was defined as an alteration ratio, as follows: alteration ratio (%) = (prechemotherapy L/N ratio – postchemotherapy L/N ratio)/prechemotherapy L/N ratio × 100.

Histologic evaluation

The resected specimen was sliced coronally or axially to include the largest portion of the tumor. The slices were fixed in 10% neutral buffered formalin and embedded separately in paraffin. The sections were stained with hematoxylin and eosin and examined by an experienced pathologist (S.K.) who had no knowledge of the results of scintigraphic assessment. The lesions were investigated by macroscopic appearances and histological specimens. Cellularity was determined by the relations between the proportion of matrix component and of cellular component. Cellularity was considered high if the cellular component demonstrated 50% or more in the lesion and low if the matrix component demonstrated 50% or more.

Statistical analysis

The following baseline variables were considered for thallium uptake: histology (malignant or benign lesion), grade (high grade or low grade in soft tissue sarcomas), cellularity (high or low cellularity), size (≤5 cm or <5 cm), and site (extremity or trunk). Relationships between two variable quantities were analyzed by the Mann–Whitney U test. To establish a hierarchy among the variables of most important value, multivariate analysis using a logistic regression model was performed. A two-tailed P value <0.05 was considered significant.

The percentage of tumor necrosis was correlated with the percentage alteration ratio using Spearman’s rank correlation. Statistical analyses were performed by