Thallium-201 Scintigraphy in Pediatric Soft-Tissue Tumors

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Thallium-201 has been used as a tumor imaging agent in adults with lymphoma, brain tumors, thyroid carcinoma and bone sarcomas. The application of ^{201}Tl in pediatric oncology has been very limited. **Methods:** Whole-body ^{201}Tl studies were incorporated into the imaging protocols of 45 children with solid soft-tissue tumors. Bone and ^{67}Ga scans as well as ^{131}I-MIBG scans for patients with neuroblastoma were obtained. **Results:** Seventeen children with lymphoma, five with Hodgkin's disease and twelve with non-Hodgkin's lymphoma (NHL) were studied. All of the patients with Hodgkin's disease showed avid uptake of ^{201}Tl and ^{67}Ga. The six patients with B-cell NHL had positive ^{67}Ga scans and four had positive ^{201}Tl scans. There was variable uptake in T-cell and undifferentiated lymphoma with an overall sensitivity of 69% for ^{201}Tl and 85% for ^{67}Ga. In 14 patients with rhabdomyosarcoma, 10 (71%) had positive ^{201}Tl scans and 11 (79%) had positive ^{67}Ga images. Gallium and thallium scans detected lesions equally. There was poor uptake of ^{201}Tl in the six children with neuroblastoma. Primary tumor and metastases were detected more readily with the bone and MIBG scans. Three children with Wilms' tumor had poor or no uptake on ^{201}Tl images, two of three patients with histocytosis had no significant uptake and one patient had mild uptake of ^{201}Tl. One patient with primitive neuroectodermal tumor had positive ^{201}Tl and ^{67}Ga images and one patient with a neurofibrosarcoma had negative ^{201}Tl and ^{67}Ga images. There was no correlation with histological types of tumor or disease staging. **Conclusion:** This study shows significant uptake of ^{201}Tl in many pediatric solid soft-tissue tumors. Additional study is needed to determine ^{201}Tl effects on treatment response and tumor viability. Also, more studies are needed to assess ^{201}Tl delayed images to determine if there is more tracer concentration in the tumors.

Key Words: thallium-201 scintigraphy; gallium-67; soft-tissue tumors

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Thallium-201 chloride reportedly shows active accumulation in many solid tumors (*1,2*). Recent articles show that the degree of ^{201}Tl uptake in a tumor is more closely related to cell type than any other single factor (*3,4*). Thallium-201 imaging has been used in adults with cerebral tumors (*5,6*), primary bone tumors (*3,7,8*), primary carcinoma of the lung (*1,9*), lymphoma (*1,2,4,10,11*), breast tumors (*12*) and thyroid cancer (*1,13*). Recent data have shown applications in pediatric cerebral tumors (*14*), lymphoma and rhabdomyosarcoma (*15–17*).

We studied 45 children with solid soft-tissue tumors for the following reasons:

1. To determine whether pediatric soft-tissue solid tumors were thallium-avid.
2. To compare the ^{201}Tl uptake sites with other radionuclides (^{67}Ga, [^{131}I]MIBG) and other imaging modalities.
3. To compare ^{201}Tl uptake, clinical grade and tumor histology.
4. To make a preliminary assessment of the application of ^{201}Tl in patient management.

METHODS

Patients

Forty-five children and infants (aged 18 mo to 16 yr; mean 7.3 yr) were studied over 2 yr. There were 25 boys and 20 girls. Lymphoma [5 with Hodgkin's disease, 12 with non-Hodgkin's lymphoma (NHL)], rhabdomyosarcoma (14 patients) and neuroblastoma (6 patients) were the major tumor groups studied. Three patients with Wilms' tumor, three with histocytosis, one with primitive neuroectodermal tumor of the thorax (PNET) and one patient with neurofibrosarcoma were also studied. Thallium-201 scans were incorporated into the staging protocols for all new solid-tumor patients after informed consent was obtained from parents or guardians. All patients had ^{201}Tl and ^{67}Ga total-body imaging as part of the initial staging protocol. The scan results were correlated with clinical findings, CT, plain radiographs, ultrasound and histopathology of the primary tumor and bone marrow examination.

Imaging Procedure

A scalp vein cannula was placed intravenously in the patients, which was left in situ until ^{67}Ga injection. Thallium-201 in doses based on body weight, 50 MBq (minimum) and 150 MBq (maximum) was given intravenously and imaging began within 30 min. A low-energy high-resolution parallel-hole collimator was used and imaging was performed with a GE Starcam 400 AC camera (Milwaukee, WI) initially and more recently by a GE 400011 XCT (Milwaukee, WI). Two-minute static images with a 20% window over the 72 keV energy peak and a 10% window over 166 keV energy peak were collected to cover the whole body. After ^{201}Tl study was completed, a total-body bone scan was obtained. At the

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TABLE 1
Scintigraphic Results for Lymphoma

Patient no.	Age (mo/yr)	Sex	^{201}Tl	^{67}Ga	Diagnosis		Stage
					Hodgkin's disease	NHL	
1	11	F	pos	pos	Nodular sclerosing		4
2	8	M	pos	pos	Nodular sclerosing		2
3	8	M	pos	pos	Nodular sclerosing		2
4	12	M	pos	pos	Lymphocyte depleted		4
5	10	F	pos	pos	Mixed cellularity		2
6	2	F	neg	pos		Malignant large cell	1
7	4	F	pos	neg		Malignant small cell	1
8	14	F	pos	pos		T-cell	2
9	3	M	pos	pos		T-cell	3
10	11	M	pos/neg*	pos		T-cell	3
11	5	M	pos	pos/neg*		T-cell	4
12	4	M	pos	pos		B-cell highly malignant	3
13	4	M	neg	pos		B-cell	3
14	13	M	pos	pos		B-cell	3
15	6	M	neg	pos		B-cell	3
16	14	M	pos	pos		B-cell	1
17	4	M	pos	pos		B-cell	3

*These sites were positive and the other sites were negative. pos = positive; neg = negative; NHL = non-Hodgkin's lymphoma.

completion of the bone scan, ^{67}Ga in doses based on body weight, 20 MBq (minimum) and 185 MBq (maximum), was given intravenously. Scans were performed at 48 hr, and in some patients at 72 hr using a medium-energy parallel-hole collimator. Two-minute images with a 20% window over the 93-, 184- and 296-keV energy peaks were collected to cover the whole body. Patients with neuroblastoma received a 25-MBq of [^{131}I]MIBG. Images were obtained at 48 hr and occasionally 72 hr postinjection. Twenty-minute or 100K spot views were collected to cover the whole body. A high-energy collimator and a 12% window over the 364 keV energy peak were used. Children receiving ^{131}I-MIBG were premedicated with Lugol's iodine prior to MIBG administration to block thyroid uptake. Two observers reviewed the images. Tumor histology was determined by hematoxylin and eosin staining supplemented by appropriate immunohistochemical stains, immunophenotyping and electron microscopy.

RESULTS

Lymphoma

The stage, histopathology and positivity of ^{201}Tl and ^{67}Ga uptake in five patients with Hodgkin's disease and 12 patients with NHL is shown in Table 1. All five patients with Hodgkin's disease showed increased tracer uptake on ^{201}Tl and ^{67}Ga (Fig. 1A) with a sensitivity of 100% for both tracers. The six patients with B-cell NHL had positive uptake on the ^{67}Ga images, but two had negative ^{201}Tl images. All patients with T-cell lymphoma had positive uptake on ^{201}Tl and ^{67}Ga images, but one child had several nodes on ^{201}Tl images that were not detected on ^{67}Ga images (Fig. 1B). Another patient had focal involvement in the kidneys not detected on the ^{201}Tl study that were avid on the ^{67}Ga image. A patient with malignant large-cell NHL had negative ^{201}Tl images, but positive ^{67}Ga images. Another patient with small-cell NHL had positive uptake on ^{201}Tl images but no uptake on ^{67}Ga. In the NHL group, there was sensitivity of 69% for ^{201}Tl and 85% for ^{67}Ga scintigraphy.

Rhabdomyosarcoma

Table 2 details the stage, histopathology and positivity of the tumors. Ten patients had positive uptake on both ^{201}Tl and ^{67}Ga images (Fig. 2). Three patients had negative uptake on both studies and one had a negative ^{201}Tl study but a positive ^{67}Ga study. No sites were detected on ^{201}Tl that were not detected on ^{67}Ga. Overall sensitivity for ^{201}Tl was 71% and 79% for ^{67}Ga. In four patients with pulmonary metastases on chest radiographs or CT scans, no detectable uptake of ^{201}Tl or ^{67}Ga was seen. No other metastases were detected by other modalities that were not detected by ^{201}Tl and ^{67}Ga.

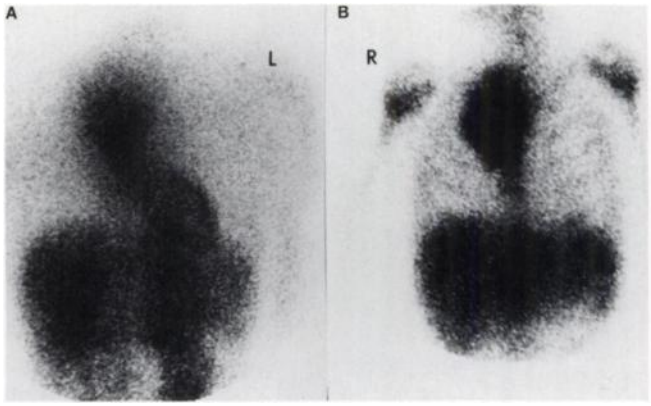

FIGURE 1. Hodgkin's disease in a 9-yr-old boy. (A) Thallium-201 chest scan shows tracer uptake in the upper mediastinum. (B) Gallium-67 scan shows tracer uptake in the mediastinal mass which appears to extend more superiorly and inferiorly than on the thallium study.

TABLE 2
Scintigraphic Results for Rhabdomyosarcoma

Patient no.	Age (yr)	Sex	^{201}Tl	^{67}Ga	Diagnosis	Stage
1	6	F	pos	pos	Alveolar	LOC
2	2	M	neg	neg	Alveolar	4
3	2	M	pos	pos	Alveolar	LOC
4	4	M	pos	pos	Embryonal	LOC
5	5	F	neg	neg	Embryonal	LOC
6	7	F	pos	pos	Embryonal	LOC
7	10	F	neg	pos	Embryonal	4
8	1	M	pos	pos	Undifferentiated	LOC
9	9	F	pos	pos	Undifferentiated	4
10	3	F	pos	pos	Undifferentiated	LOC
11	14	M	pos	pos	Poorly differentiated	4
12	5	F	pos	pos	Poorly differentiated	4
13	5	F	pos	pos	Poorly differentiated	LOC
14	11	M	neg	neg	Spindle cell	LOC

LOC = localized disease.

Neuroblastoma

All six neuroblastoma patients showed avid MIBG uptake (Table 3). Three children had negative ^{201}Tl studies and two had negative ^{67}Ga studies. The avidity of MIBG was much greater, however, and showed more tumor sites than either ^{201}Tl or ^{67}Ga.

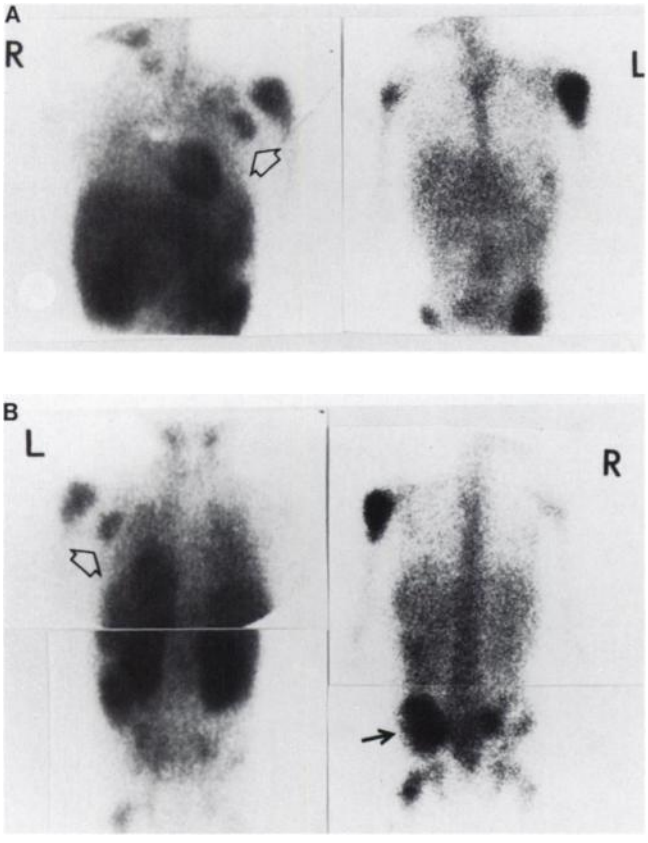

FIGURE 2. Non-Hodgkin's disease (T cell) in a 2-yr-old boy. (A) Anterior view and (B) posterior view. Thallium-201 scan (left) and ^{67}Ga scan (right). Multiple areas of tracer uptake are seen in the bones. More intense uptake in the bones is seen on the gallium study than on the thallium scan (arrow). The focal area of increased uptake within the nodes in the left axilla is more clearly seen on the thallium scan (open arrow) than on the gallium scan.

Wilms' Tumor and Other Tumors

The ^{201}Tl scans of two patients showed no significant uptake and mild uptake in one patient. These patients all showed ^{67}Ga uptake in the primary tumor, although the uptake was very mild in two patients. The histologic results for all three tumors were favorable.

Three patients with Langerhan's cell histocytosis had positive ^{67}Ga scans, but only one patient had mild uptake on the ^{201}Tl image. One patient with a neurofibrosarcoma had negative ^{201}Tl and ^{67}Ga scans. One child with primitive neuroectodermal tumor of the thorax showed avid accumulation of both ^{201}Tl and ^{67}Ga.

DISCUSSION

Thallium-201 has been widely used as a tumor imaging agent in adults (*1,2,5,13*). Its clinical application in primary bone tumors has been to determine the extent of primary tumor as a baseline for treatment response and to assess residual disease and recurrence. Ramanna et al. (*3*) compared histology graded before and after chemotherapy based on tumor necrosis histologically. Thallium-201 correlated better than bone and ^{67}Ga scans with the percentage of necrosis in the tumor. Stoller et al. (*8*) also compared ^{201}Tl with ^{67}Ga and MRI in primary bone tumors. Thallium-201 reflects residual disease and early recurrence more accurately than bone and ^{67}Ga scans, which may show significant uptake due to normal bone healing response. Thallium-201 was found to be the most accurate radionuclide for determining extent of the tumor and was useful in following tumor response to chemotherapy.

The mechanism for ^{201}Tl accumulation in tumors is unclear. Thallium-201 is considered to behave like potassium biologically and resembles alkali metals (e.g., cesium) which concentrate in tumors. Thallium-201 concentration in tumors is multifactorial, including blood flow, tumor

TABLE 3
Scintigraphic Results for Neuroblastoma

Patient no.	Age (yr)	Sex	^{201}Tl	^{67}Ga	MIBG	Diagnosis	Stage
1	6	F	pos	pos	pos	Moderate differentiation	3
2	2	F	neg	neg	pos	Moderate differentiation	3
3	2	M	neg	neg	pos	Moderate differentiation	4
4	2	F	neg	neg	pos	Neuroblastoma	3
5	2	F	pos	pos	pos	Neuroblastoma	4
6	5	F	pos	pos	pos	Poorly differentiated	4

viability, tumor type, sodium-potassium pump, cotransport system, calcium-ion exchange, vascular immaturity with leakage and increased cell membrane permeability (*17*).

Lymphoma

Lymphoma is one of the largest tumor groups studied by ^{201}Tl in adults (*2,4,10,11*). Waxman et al. (*2*) evaluated the utility of ^{201}Tl scintigraphy in Hodgkin's and NHL. Their study demonstrated ^{201}Tl accumulation to be greatest in low-grade lymphoma as compared to intermediate or high-grade disease. Gallium-67 studies generally had a lower sensitivity in the low-grade group and was highest in the intermediate and high-grade tumors. There is no clear trend between the ^{67}Ga and ^{201}Tl studies in patients with Hodgkin's lymphoma. Kaplan et al. (*4*) also had similar findings and suggest that the combination of ^{201}Tl for low-grade tumors and ^{67}Ga for intermediate and high-grade tumors allows a full spectrum for detection of NHL tumors. In this report, all the children with Hodgkin's disease had positive uptake on ^{201}Tl and ^{67}Ga studies. There was no difference in tracer uptake between histological type or disease stage. The children with the NHL group were considered to have high-grade tumors. The majority of these tumors, however, were ^{201}Tl-avid in contrast to the high-grade tumors in adults reported by Waxman et al. (*2*) and Kaplan et al. (*4*) which tended to have less ^{201}Tl uptake than the low-grade lymphomas. In this report, the histology of NHL was classified as B-cell, T-cell or undifferentiated (malignant small or large cells) disease. We did not see any significant difference in tracer uptake between histological groups or disease grading. Because the majority of the lymphoma patients showed avidity for ^{201}Tl, the data would suggest that more long-term studies are warranted to assess the accuracy of these radionuclides as a baseline for treatment response, detection of residual disease or recurrence and to define more clearly the clinical role of these radionuclides in patient management.

Rhabdomyosarcoma

There are few data on ^{201}Tl scintigraphy in soft-tissue sarcomas. Menendez et al. (*7*) reported good correlation of ^{201}Tl uptake with tumor necrosis after treatment in 16 patients with high-grade sarcoma of the bone and soft tissues. They also described five of eight patients with malignant fibrous histocytoma and a fibrosarcoma which all showed ^{201}Tl uptake. Thallium-201 uptake was visualized in a rhabdomyosarcoma of the occipital region (*18*) and a leimyosarcoma of the chest wall (*19*). Recent data from Ramanna et al. (*20*) indicate a sensitivity of 100% for ^{201}Tl uptake in 58 soft-tissue sarcomas. Cogswell et al. (*20*) documented the clinical application of ^{67}Ga in rhabdomyosarcoma in childhood and the specific use of ^{67}Ga in patient management and assessing response to therapy. For the 14 children with a primary tumor in this report, the sensitivity was lower for ^{201}Tl (71%) and ^{67}Ga (79%). Lung metastases were not detected by either ^{201}Tl or ^{67}Ga in four patients. There was no correlation of tracer uptake with histopathology or disease stage (Fig. 3). More patients need to be examined to determine whether ^{201}Tl is the most useful tracer for determining the extent of primary tumor as a baseline examination prior to therapy.

Neuroblastoma

There was overall poor ^{201}Tl uptake in the neuroblastoma patients. MIBG studies showed avid uptake in all patients. MIBG in combination with radionuclide bone scans are the investigations of choice. In neuroblastoma, ^{67}Ga has no prognostic benefit or role in the patient management (*21*). Our results find no role for ^{201}Tl scintigraphy in neuroblastoma.

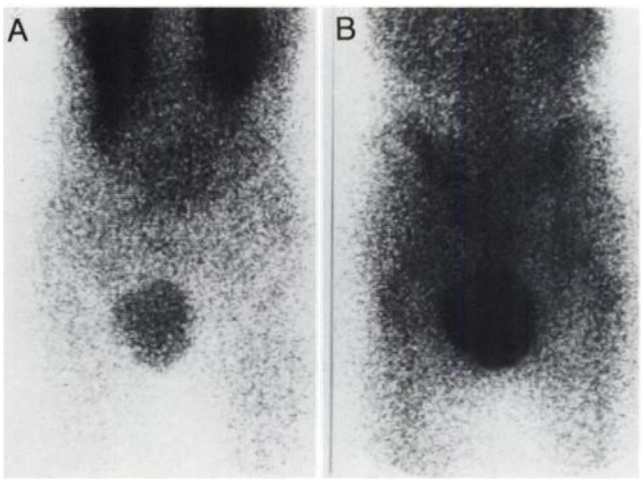

FIGURE 3. Rhabdomyosarcoma (undifferentiated) of the buttock in a 7-yr-old girl. (A) Thallium-201 scan and (B) ^{67}Ga scan. Both studies show avid accumulation within the tumor.

Wilms' Tumor and Other Tumors

Because there was no significant uptake of ^{201}Tl in Wilms' tumor, it has no clinical role in patient management.

Also, there was no significant uptake of ^{201}Tl in histiocytosis, suggesting no role in the management of this disorder.

Limitations of Thallium-201 Imaging

Gallium-67, more than ^{201}Tl, is likely to have a larger component of nonspecific uptake, which is probably related to an inflammatory reaction of the surrounding tissues to the tumor. Thallium-201 appears to more accurately reflect tumor activity. There are, however, several limitations of ^{201}Tl scintigraphy which relate to imaging capabilities. First, there is soft-tissue uptake, particularly in the muscles and splanchnic tissue, the latter causing considerable difficulty in interpretation of tracer distribution in the abdomen. The target-to-background ratio is less than that for ^{67}Ga studies. The physical and biological properties of ^{201}Tl (i.e., low photon energy, long half-life and low injected dose) are also limitations to imaging. These physical properties, however, allow ^{201}Tl studies to be performed earlier after injection at 30 min, whereas ^{67}Ga requires 48–72 hr. Sequential studies of ^{201}Tl followed by ^{99m}Tc bone scans can be performed on the same day. The optimal time after tracer injection for ^{201}Tl has yet to be defined. We imaged patients within 30 min of injection. Recent data (*22,23*) suggest better uptake if imaging is delayed for several hours. Also, the dynamics of tracer accumulation or washout rates may assist in determining grades of malignancy. The protocol in our institution now incorporates delayed imaging to determine these factors and the optimal intensity for lesion detection with ^{201}Tl is being assessed.

CONCLUSION

These preliminary data indicate that several major pediatric solid tumors show an avid accumulation of ^{201}Tl. Most of the tumor groups studied showed uptake on both ^{67}Ga and ^{201}Tl scintigraphy and only a small number showed a discrepancy in tracer accumulation. Whether both radionuclides should be used in this patient population has not been determined. Our data indicate that further assessment of these tumors is required to determine:

1. Whether both ^{201}Tl and ^{67}Ga studies are required in all patients or if one or the other radionuclides is preferable in different tumors.
2. Assessment of ^{201}Tl as an indicator of tumor response to therapy.
3. The optimal time and imaging characteristics for ^{201}Tl imaging in pediatric solid tumors.

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