Ga-67 Citrate Imaging in Tumors of the Genito-Urinary Tract: Report of Cooperative Study

Bertram J. L. Sauerbrunn, Gould A. Andrews, and Karl F. Hübner

Veterans Administration Hospital, Washington, D.C. and Oak Ridge Associated Universities, Oak Ridge, Tennessee

Whole-body imaging with Ga-67 citrate in 127 tumors of the genito-urinary tract has been evaluated by a cooperative group using a uniform protocol. Primary sites of tumor were not detectable by imaging, except for one bladder and one kidney tumor. Proven and apparent metastases yielded positive scans, however, in 51% of prostatic, 50% of bladder, 72% of kidney, and 53% of testicular neoplasms. In bladder and kidneys metastases, if bone sites are excluded, detection of soft tissue metastases was 61% and 75%, respectively. In embryonal-cell carcinoma of the testicle, 74% of metastatic foci were detected.

J Nucl Med 19: 470–475, 1978

This study is an interinstitutional evaluation of the use of Ga-67 citrate scanning in genito-urinary tract tumors by a cooperative group using a generally accepted protocol. The organization and background of the Cooperative Group to study Localization of Radiopharmaceuticals is detailed elsewhere (*1,2*) and in Group reports of Ga-67 citrate imaging studies in cases of untreated Hodgkin's disease, untreated malignant lymphoma, and untreated lung cancer (*3–5*).

Using the same uniform protocol and computer handling of data, we have systematically evaluated total-body Ga-67 citrate scanning in 127 patients, involving 43 testicular, 26 prostatic, 37 kidney and 21 bladder malignancies.

METHODS

Patients were referred for gallium scanning to the various nuclear medicine departments primarily to establish the extent of existing disease. No known bias was involved in the selection of patients. The various categories of the clinical status of the patients before scanning are defined as follows: *untreated*—patients who were scanned before any type of primary or secondary therapy; *early follow-up*—patients scanned within 60 days following primary surgery and/or radiation therapy; *later follow-up (symptomatic)*—patients scanned 60 days or more after initial treatment who had some new evidence of clinical disease; *later follow-up (asymptomatic)*—patients scanned 60 days or more after initial treatment who had no evident disease; *midst of therapy*—patients undergoing active therapy at the time of scan. In the latter category, all instances refer to chemotherapy with the exception of the prostate group in which both endocrine and chemotherapy were used.

Carrier-free Ga-67 citrate was administered intravenously, 0.045 mCi/kg of body weight, as a single dose. Total-body scanning was done 48 hr post-injection after suitable laxatives and enemas were given to remove gallium excreted into the bowel. Delayed scans at times were obtained. The spectrometer window covered the 184-keV and 296-keV peaks of Ga-67.

A computer recording system was devised so that the scan results could be compared with anatomic areas of disease detected by other means, and the evidence for or against malignancy at each site of interest was classified in several ways. For this re-

Received July 25, 1977; revision accepted Dec. 8, 1977.

For reprints contact: Medical and Health Sciences Div., Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37830.

port, the most important categories are:

1. Proven—histologic proof by biopsy, surgery, or autopsy;
2. Apparent—radiographic, directly visualized at surgery or endoscopy, palpation of superficial lesion;
3. Suspected—palpation of deep tissues or suspected radiographic lesion;
4. No confirmation of tumor—sites recorded because they were clinically suspected or because the positive scan called attention to them;
5. Benign—a nonmalignant lesion demonstrated at the site.

In turn, the scan results for each site were reported as positive, negative, or equivocal. In the tables, those categorized as suspected are listed, but in the following "Results" section of this paper, only proven or apparent sites of disease are used in determining the relative success of the scan procedure.

TABLE 1. Ga-67 SCAN RESULTS VS. OTHER EVIDENCE OF DISEASE IN PROSTATIC TUMORS

	Adenocarcinoma and carcinoma nos.		
No. of cases		25	
Scan results	Pos.	Neg.	Eqv.
Evidence of disease at sites			
proven	3	8	1
apparent	18	16	1
suspected	6	1	0
Totals	27	25	2
No evidence of tumor	5	7	1
Clinical status of cases	Untreated (6)		
	Treated (19)		

TABLE 2. Ga-67 SCAN RESULTS VS. OTHER EVIDENCE OF DISEASE IN BLADDER TUMORS

	Carcinomas*	
No. of cases	19	
Scan results	Pos.	Neg.
Evidence of disease at sites		
proven	5	6
apparent	4	4
suspected	3	0
Totals	12	13
No evidence of tumor	1	0
Benign lesions	2	0
Clinical status of cases	Untreated (3)	
	Treated (16)	

* Carcinomas include transitional-cell (13), adenocarcinoma (2), papillary (1), and transitional-cell-papillary (3). No equivocal scans were recorded. Two sarcomas, not shown on this table, are reported in text.

RESULTS

The overall results are given in Tables 1–4. "NOS" indicates "not otherwise stated;" "No." indicates "number of." Individual lesions may be multiple in one patient; they are described on the basis of scanning as positive (Pos), negative (Neg), or equivocal (Eqv).

The detailed results are related to the clinical status of the patients are given in Tables 5 and 6.

Tumors of the prostate. The scan results for 25 cases of prostatic tumor are given in Table 1. Of these cases, 18 were specifically listed as adenocarcinomas and the other seven, showing no difference in results, were not classified but are presumed to be adenocarcinomas. One case of transitional-cell carcinoma, not included in the table, had two proven lesions; one was positive and one negative on scan. For the entire group, 22 of 49 proven or apparent sites gave positive scans for a detection rate of 44%, all of the positives being at metastatic rather than primary sites. There were five positive scans obtained over bone and joint sites in which no other evidence for tumor was detected.

Tumors of the bladder. For bladder carcinoma, the results of scanning contrasted with other evidence of disease are shown in Table 2. In a total of 19 proven or apparent primary and metastatic tumor sites, there were nine positive scans for a detection rate of 47%. Two scans were recorded as positive over abdominal areas thought to be nodal metastases but later proven not to represent malignant tumor. Not shown in Table 2 is one leimyosarcoma, which was studied during therapy, showing a negative scan at its single proven site, and one treated rhabdomyosarcoma that had seven positive areas on scan, not confirmed as lesions.

Tumors of the kidney. The gallium-67 scan results for the different histologic types of kidney tumor, as compared with other evidence of disease, are shown in Table 3. The scans were positive in 27 instances of 44 proven or apparent primary and metastatic sites, resulting in an overall 61% scan detection rate. If only metastatic sites are considered, the rate is somewhat higher (26 of 36 sites, or 72%). Two scans were positive for sites in which a benign lesion was demonstrated.

Tumors of the testicle. Table 4 shows the scan results for the testicular tumors compared with other evidence of disease. For all histologic types, there were 30 positive scans in 62 proven or apparent primary or metastatic sites, for a detection rate of 48%. Referring to metastatic sites alone, there were 30 positive scans in 56 proven or apparent metastases, for a detection rate of 53%.

Scan results as related to clinical status. Tables 5

TABLE 3. Ga-67 SCAN RESULTS BY HISTOLOGIC TYPE VS. OTHER EVIDENCE OF DISEASE IN KIDNEY TUMORS

	Histologic type							
	Carcinomas		Wilms' Tumor		Squamous-cell		Transitional cell	
No. of cases studied	30*		3		2		2	
Scan results	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Evidence of disease at sites	11	6	2	1	0	0	1	0
proven	8	8	2	0	1	2	2	0
apparent	1	3	0	0	0	0	2	0
suspected	20	17	4	1	1	2	5	0
Totals	3	0	0	0	0	0	0	0
No evidence of tumor	2	0	0	0	0	0	0	0
Benign lesion	Untreated (7)		Untreated (1)		Untreated (0)		Untreated (0)	
Clinical status of cases	Treated (23)		Treated (2)		Treated (2)		Treated (2)	

* Carcinoma includes clear-cell (27), adenocarcinoma (2), and carcinoma NOS (1). Only one equivocal scan was reported; this was in an apparent lesion in a patient with carcinoma.

and 6 show the Ga-67 scan results compared with the combined proven and apparent disease sites as related to the various clinical status categories of the patients.

Prostate tumors (Table 5). In clinical status A, all primary tumors were negative and five bone sites were missed on scan. Five of seven proven or apparent abdominal nodal sites, however, were detected in Categories B and C. All other positive scans listed for all categories were in skeletal metastases of which 47% were detected. Overall detection of metastases was 22 of 43 (51%). The same percentage of positive scans in bone lesions was noted in Category E patients undergoing endocrine and chemotherapy.

Bladder tumors (Table 5). In the untreated group of three primary bladder tumors, only one (5 cm × 5 cm) lesion was positive on scan. All other positive scans were seen in Category C. In all, eight of 16 metastatic sites were detected (50%). Detection of soft-tissue metastases averaged 61% and included three of four abdominal nodal sites, one of two mediastinal sites, one of one liver site, and a negative scan in one lung site. Only three of eight bone sites were detected (37%).

Kidney tumors (Table 5). In eight untreated cases, only one primary kidney tumor (clear cell Ca) was detected but three of five metastatic sites were shown. It is interesting that three of three positive sites were detected in Category B (one lung lesion and two abdominal nodes). Two of three sites (66%) were detected in patients undergoing chemotherapy (cyclophosphamide, bleomycin, and doxorubicin).

The detection of soft-tissues metastases averaged 75% with the following distribution: 12 of 17 abdominal sites, two of three mediastinal sites, two of two peripheral node sites, five of five lung sites, and

TABLE 4. Ga-67 SCAN RESULTS BY HISTOLOGIC TYPE VS. OTHER EVIDENCE OF DISEASE IN TESTICULAR TUMORS

	Histologic type																	
	Malignancy (nos.)			Stromal			Seminoma			Embryonal			Teratoma*			Chorio-carcinoma		
No. of cases studied	3			3			11			13			11			2		
Scan results	Pos.	Neg.	Eqv.	Pos.	Neg.	Eqv.	Pos.	Neg.	Eqv.	Pos.	Neg.	Eqv.	Pos.	Neg.	Eqv.	Pos.	Neg.	Eqv.
Evidence of disease at sites	0	1	0	0	2	0	1	2	0	1	1	1	1	2	0	0	0	0
proven (Surg-Biopsy)	3	0	0	1	0	0	3	2	0	16	5	1	3	12	0	1	3	0
apparent	0	1	0	0	1	0	0	1	0	1	0	0	0	1	0	0	2	0
suspected	3	2	0	1	3	0	4	5	0	18	6	2	4	15	0	1	5	0
Totals	3	0	0	1	1	0	0	3	0	0	4	0	3	0	0	0	0	0
No evidence of tumor	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Benign lesion	Untreated (0)			Untreated (2)			Untreated (1)			Untreated (2)			Untreated (2)			Untreated (0)		
Clinical status of cases	Treated (3)			Treated (1)			Treated (10)			Treated (11)			Treated (9)			Treated (2)		

* Teratoma includes nine cases of malignant teratoma and two cases of teratoma NOS.

TABLE 5. Ga-67 SCAN RESULTS IN PROVEN OR APPARENT DISEASE SITES RELATED TO CLINICAL STATUS IN TUMORS OF PROSTATE, BLADDER, AND KIDNEY

	Prostate				Bladder				Kidney			
		Scan results				Scan results				Scan results		
Clinical status*	No. of Pts.	Pos.	Neg.	Eqv.	No. of Pts.	Pos.	Neg.	Eqv.	No. of Pts.	Pos.	Neg.	Eqv.
A	6	0	11	1	3	1	2	0	8	4	9	0
B	3	2	3	0	1	0	0	0	8	3	0	0
C	6	12	2	2	14	8	8	0	16	18	6	0
D	3	0	0	0	1	0	0	0	2	0	1	0
E	7	7	8	0	0	0	0	0	3	2	1	0

* A = Untreated; B = Early Follow-Up; C = Later Follow-Up (symptomatic); D = Later Follow-Up (asymptomatic); E = Midst of Therapy.

four of six liver sites. Bone detection, however, included only one positive scan in three bone sites (33%).

Testicular tumors (Table 6). Because of the variety of tumor types, the testicular tumors are grouped into the three major types and a fourth incidental category, so that roughly equal numbers in each group are compared. In Category A (untreated), primary testicular tumors were not detected, except for one equivocally positive scan. Six of six metastatic sites were detected, however, in embryonal-cell carcinoma, including mediastinal nodes (*2*), lung (*2*), pelvic nodes (*1*), and peripheral node (*1*). In one of two cases of untreated teratoma, two lung metastases and a mediastinal mass were detected, but two other sites were missed—a large 8 cm × 8 cm abdominal nodal mass and a 10 cm × 6 cm liver metastasis.

The sensitivity for detection of metastases varied considerably in the four groups of tumors, being very low in teratomas (four of 16 sites, or 25%), medium in seminomas (four of seven sites, or 57%), relatively high in embryonal-cell carcinoma (17 of 23 sites, or 74%), and four of eight in the odd group (50%).

The distribution of metastases in the largest groups included the following: embryonal cell (five of eight abdominal nodes, four of six mediastinal nodes, two of two peripheral nodes, and six of seven lung metastases); teratomas (one of nine abdominal nodes, one of one mediastinal nodes, 0/1 liver metastases and two of seven lung metastases); and seminoma (three of five abdominal nodes, one of two lung metastases).

In those patients undergoing active chemotherapy, a single patient with seminoma had a positive scan over one proven metastatic site, but a negative scan over a second proven site. A similar finding was seen in one of the cases of teratoma. There was a marked difference noted in embryonal-cell carcinoma and teratoma. In the former, positive scans were recorded in five of six metastases, but only one of six sites of disease were detected in the teratoma group.

DISCUSSION

This particular protocol of study was designed to determine the extent and avidity of gallium tracer uptake in a large series of histologically proven genito-urinary tract tumors. Heretofore, only limited information has been available on the subject.

TABLE 6. Ga-67 SCAN RESULTS IN PROVEN OR APPARENT DISEASE SITES IN TESTICULAR TUMORS AS RELATED TO CLINICAL STATUS

	Scan results															
		Seminoma				Embryonal				Teratoma				Other†		
Clinical status*	No. of cases	Pos.	Neg.	Eqv.	No. of cases	Pos.	Neg.	Eqv.	No. of cases	Pos.	Neg.	Eqv.	No. of cases	Pos.	Neg.	Eqv.
A	1	1	1	0	2	6	1	1	2	3	7	0	2	1	2	0
B	4	0	0	0	1	0	2	0	2	0	0	0	2	0	0	0
C	2	2	1	0	4	6	2	0	2	0	2	0	1	3	1	0
D	3	0	1	0	3	0	0	1	1	0	0	0	1	0	0	0
E	1	1	1	0	3	5	1	0	4	1	5	0	2	1	3	0

* A = Untreated; B = Early Follow-Up; C = Later Follow-Up (symptomatic); D = Later Follow-Up (asymptomatic); E = Midst of Therapy.

† Other tumors include two cases of choriocarcinoma, three of stromal, and three of malignancy unspecified.

With respect to prostatic carcinoma, our principal findings were mainly related to bone metastases, in which we observed a relatively low sensitivity of detection, as compared to other methods (bone scan, roentgenograph, biopsy). The inferiority of gallium compared to Tc-99m phosphate preparations as a bone scanning agent has been observed by others (*6*). Thus, the latter would be a preferable screening agent in preoperative evaluation of patients for whom radical prostatectomy is contemplated. Similarly, in bladder tumors only 37% of bone metastases were detected, although 61% of soft-tissue metastases were found. Thus, in general, it appears that gallium scans have little clinical use in staging or following up patients with these tumors.

The degree of localization in kidney carcinoma was somewhat more fruitful, except for the detection of bone metastases. Excluding bone lesions, soft-tissue metastases was detected in 75% of sites. Thus, gallium scanning may be of somewhat greater clinical use in kidney tumors for the detection of soft tissue metastases, especially in the clinical followup of cases in which lymphangiography may be contraindicated, not available, or unsatisfactory.

Similarly, certain testicular tumors (embryonal-cell carcinoma) have a surprising affinity for gallium—100% of metastases were imaged in untreated cases and 74% of metastases for the entire group. Bailey cites positive gallium findings in metastases correlating with positive evaluations using other methods in five patients with embryonal-cell carcinoma, four patients with choriocarcinoma, and two patients with teratoma (*7*). Mukerjee found gallium scanning of no value in the preoperative staging of 15 cases of testicular carcinoma (*8*). (In this latter series cell types were not specified.) Jackson reports five of six confirmed abdominal-nodal sites were detected by gallium scan, as well as a mediastinal and a lung metastasis (*9*). He does not specify cell types, although in two case summaries, illustrating positive gallium scans, one patient had pure embryonal-cell carcinoma and the other had a mixed embryonal-cell —terato-carcinoma. Patterson reports that gallium scans were positive in 13 of 15 patients in all disease sites showing evidence of disseminated seminoma; however, only two of 11 patients with proven disseminated teratoma had positive findings by scan (*10*).

Our own results, along with the foregoing reports from the literature, suggest a considerable variability in gallium uptake in testicular metastases. Of the three major groups, it appears that metastatic tumor of the embryonal-cell and seminoma type, in contrast to teratoma, are more readily detectable by gallium scanning.

Our scan findings relative to clinical status (Tables 5 and 6) are of some interest, although there are only a few cases in several categories. In untreated cases, a surprising number of positive scans was noted in proven or apparent sites of metastases in all groups, except prostate, bladder, and teratoma. This serves as a potential guide in clinical usage in untreated cases. One may also expect a greater yield of positive results in patients in whom clinical suspicion of disease is evident (Category C). In those patients who were scanned in the midst of chemotherapy (Category E), a considerable number of positive scans were obtained in some groups. Others have pointed out that positive gallium scan uptake in patients undergoing chemotherapy or at the completion of chemotherapy may be an early indication of therapy failure (*11*). Although our study was not designed to perform followup scans in the same patient, chemotherapy failure may have accounted for some of the positive scan findings in Category E.

A general observation in genito-urinary tumors was poor concentration of gallium in primary sites, as contrasted with relatively greater uptake in metastases. The location of primary prostate and bladder tumors in the pelvic area sometimes caused difficulty in scan interpretation because of overlying background activity in bowel or bone. Testicular tumors may have gone undetected because of the small size of the primary lesion, technical difficulties in scanning the area, or because of overlying activity in the penis, which may sometimes be seen normally. The normal uptake of gallium by the liver superimposes considerable background activity on the right kidney region. Thus, a number of factors may account for a relatively low tumor-to-background ratio in primary sites. Literature on gallium scanning of kidney tumors is sparse. Langhammer makes a brief reference to detection of only one of seven genito-urinary tract tumors with this radiotracer, but he does not report tumor types except to state that five were histologically verified (*12*). In a case report, two patients with renal-cell carcinoma were scanned with gallium, with positive uptake noted over a primary site in one (*13*). Negative scans have been reported in two children with Wilms' tumor (*14*).

Several factors may account for higher tumor-to-background ratios for gallium in metastases, resulting in better detection. Location may be important, since an implant in the lung or in certain nodal area may yield a positive scan because of the very low gallium background activity surrounding the sites. Additionally, there is some evidence that the proliferation ratio of some metastases may be greater than that of the primary tumor. Willis states that hepatic metastases, for example, usually exceed the mitotic

rate of the primary tumor or of other metastases by several fold (*15*). In his review on tumor imaging with radiopharmaceuticals, Patterson notes that gallium appears to localize best in the most undifferentiated tumors; he also cites evidence suggesting that the rate of proliferation may be one of the factors responsible for the degree of gallium uptake by tumors (*16*). Sometimes the clustering of metastases produces a visible focus when no one component would do so.

ACKNOWLEDGMENTS

Active members participating in the Protocols (in addition to the authors of this paper) are: Richard S. Benua, Memorial Sloan-Kettering Cancer Ctr., New York, N.Y.; Charles Boyd, University of Arkansas School of Medicine, Little Rock, Ark.; Bertrand Brill, Vanderbilt University School of Medicine, Nashville, Tenn.; Frank DeLand, University of Florida College of Medicine, Gainesville, Fla. (present address: University of Kentucky School of Medicine, Lexington, Kent.); C. Lowell Edwards, ORAU Medical Division, Oak Ridge, Tenn. (present address: Rockford School of Medicine, Rockford, Ill.); Ben I. Friedman, University of Tennessee College of Medicine, Memphis, Tenn.; Mohammed Moinuddin, University of Tennessee College of Medicine, Memphis, Tenn. (present address: Baptist Memorial Hospital, Memphis, Tennessee); Robert H. Greenlaw, Marshfield Clinic, Marshfield, Wisc.; Thomas P. Haynie, M. D. Anderson Hospital and Tumor Institute, Houston, Tex.; Gerald Johnston, NIH Clinical Ctr., Bethesda, Md.; David Preston, University of Kentucky School of Medicine, Lexington, Kent. (present address: University of Kansas Medical Center, Kansas City, Kan.); Charles David Teates, University of Virginia School of Medicine, Charlottesville, Va.; Robert H. Wilkinson, Duke University Medical Center, Durham, N.C.; and Joseph B. Workman, University of Maryland Hospital, Baltimore, Md. (present address: Duke University Medical Ctr., Durham, N.C.).

Much of the early work in organizing the group and the protocols was done by Ralph Kniseley, ORAU Medical Division, Oak Ridge, Tenn. (present address: 1024 E. Locust, Emmett, Id.); computer assistance is gratefully acknowledged from Martha Hansard, Howard Harmon, and Tom Akin.

This work was supported by the Energy Research and Development Administration and Joint AEC-NIH Interagency Agreement No. 40-266-71 and American Cancer Society Grant No. CI-54.

REFERENCES

1. KNISELEY RM: A cooperative group to study localization of radiopharmaceuticals. USAEC Report ORAU-118, Oak Ridge Associated Universities, 1973

2. KNISELEY RM: A coding index for tumor scanning in the cooperative group to study localization of radiopharmaceuticals. USAEC Report ORAU 119, Oak Ridge Associated Universities, 1973

3. JOHNSTON G, BENUA RS, TEATES CD, et al: ^{67}Ga-citrate imaging in untreated Hodgkin's disease: Preliminary report of cooperative group. *J Nucl Med* 15: 399–403, 1974

4. GREENLAW RH, WEINSTEIN MB, BRILL AB, et al: ^{67}Ga-citrate imaging in untreated malignant lymphoma: Preliminary report of cooperative group. *J Nucl Med* 15: 404–407, 1974

5. DELAND FH, SAUERBRUNN BJL, BOYD C, et al: ^{67}Ga-citrate imaging in untreated primary lung cancer: Preliminary report of cooperative group. *J Nucl Med* 15: 408–411, 1974

6. JOHNSON GS, JONES AE, MILDER MS, et al: The gallium-67 scan in clinical assessment of cancer. *J Surg Oncol* 5: 529–538, 1973

7. BAILEY TB, PINSKY SM, MITTEMEYER BT, et al: A new adjuvant in testis tumor staging: Gallium-67 citrate. *J Urology* 110: 307–310, 1973

8. MUKERJEE MG, MITTEMEYER BT: Experience in staging testis tumors with bleomycin 57 cobalt and present role of 67 gallium scan. *J Urology* 116: 467–468, 1976

9. JACKSON FI, DIERICH HC, LENTLE BC: Gallium-67 citrate scintiscanning in testicular neoplasia. *J Canadian Assoc Radiol* 27: 84–88, 1976

10. PATERSON AHG, PECKHAM MJ, MCCREADY VR: Value of gallium scanning in seminoma of the testes. *Br Med J* 1: 1118–1121, 1976

11. ANDREWS GA, EDWARDS CL: Tumor scanning with gallium 67. *JAMA* 223-10: 1100–1103, 1975

12. LANGHAMMER H, GLAUBITT G, GREBE SF, et al: ^{67}Ga for tumor scanning. *J Nucl Med* 13: 25–30, 1972

13. ANTONIADES J, HONDA T, CROLL MN, et al: Gallium-67 scanning in renal cell carcinoma. *J Urology* 109: 564–568, 1973

14. LEPANTO PB, ROSENSTOCK J, LITTMAN P, et al: Gallium-67 scans in children with solid tumors. *Amer J Roentgenology* 126: 179–186, 1976

15. WILLIS RA: Pathology of Tumors. 4th Ed. New York, Appleton-Century-Crofts, 1967, pp 175

16. PATTERSON AHG, MCCREADY VR: Review article: Tumor imaging radiopharmaceuticals. *British J Radiology* 48: 520–531, 1975