Gallium-67-Citrate Imaging in Extragonadal and Gonadal Seminomas: Relationship to Radiologic Findings

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Methods: The results and analysis of baseline and follow-up ^{67}Ga imaging in three patients with extragonadal seminoma were compared to those of nine patients with primary and metastatic gonadal seminomas. Gallium-67 tumor avidity was scored (0–6) relative to accumulation in the sternum and the liver. Response time to systemic therapy for ^{67}Ga imaging compared to other radiological examinations was also measured. **Results:** Prior to therapy, ^{67}Ga scan sensitivity was 100%, (3/3) in patients with extragonadal seminomas and 90%, (9/10) for primary and radiologically evident metastatic sites in patients with gonadal seminomas. The combined sensitivity was 92%, (12/13) with the smallest ^{67}Ga scan detecting a mass 1.5 cm in diameter. There was no significant difference in ^{67}Ga avidity or sensitivity between extragonadal and gonadal sites. Following chemotherapy, CT scanning demonstrated residual radiologic abnormalities in all three extragonadal seminoma tumor sites and 5/8 metastatic gonadal seminoma tumor sites. However, the ^{67}Ga scan was normal in 10/11 sites at the first radionuclide examination after systemic therapy, indicating no active tumor, an observation supported by clinical follow-up from 6 to 72 mo. **Conclusion:** Gallium-67 scanning appears useful in the management of patients with both extragonadal and gonadal seminoma and may be useful in differentiating active disease from fibrosis in the treated patient with a post-therapy residual radiologic mass.

Key Words: gallium-67-citrate imaging; CT scan; seminoma; extragonadal seminoma

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Germ-cell tumors most commonly arise from the testes but may be of extragonadal origin, i.e., originating in the mediastinum, retroperitoneum, sacrococcygeal region or pineal gland; the mediastinum represents the most common extragonadal site. These extragonadal germ-cell tumors are presumed to arise from either sites of aberrant germinal cell migration during embryogenesis or, alternatively, from a common precursor stem cell line that gives rise to germinal cells, the thymus and the pineal gland. Males and females are equally affected, and patients tend to present with metastatic disease (*1–3*).

Data exists to suggest that ^{67}Ga-citrate imaging may be helpful in the management of primary testicular seminomas, both for determining the extent of disease at initial presentation and for evaluation after treatment. Paterson reported that ^{67}Ga scan sensitivity reached 93% (*4*). Willan et al. reported a ^{67}Ga sensitivity of 83% and specificity of 95% in the staging of this tumor (*5*).

Because extragonadal seminoma (ES) is a rare malignancy, only limited information exists in the published literature regarding ^{67}Ga imaging of patients with this entity (*6,7*). In this study, we report our experiences with ^{67}Ga imaging of three patients with ES and provide a contrast of ^{67}Ga imaging results from nine patients with primary and metastatic gonadal seminoma (GS). The response time to systemic therapy for ^{67}Ga imaging compared to other radiological examinations was analyzed. This included, when appropriate, CT scans, chest radiographs and MRI.

MATERIALS AND METHODS

Patients

Between 1987 and 1993, 12 male patients with either ES or GS were evaluated, treated and subsequently followed-up by ^{67}Ga imaging at the Dana-Farber Cancer Institute. Their ages ranged from 23 to 47 yr (mean = 35.8, median = 34 yr).

Three of the patients had ES, two with mediastinal tumor with lymph nodal involvement and one with a retroperitoneal primary tumor site. The diagnosis of ES in these patients was based upon biopsy material demonstrating pure seminoma, an absence of elevated serum levels of alpha-fetoprotein at the time of initial presentation, and normal testes by physical and ultrasonographic examinations.

Nine patients were found to have GS as demonstrated by pathological review following either orchiectomy, resection of an undescended intra-abdominal testicular tumor or biopsy of a metastatic site. Patient 4 (Table 1) presented with Stage I primary testicular seminoma during routine follow-up of a complete remission from treated, Stage IV non-Hodgkin's lymphoma of the nodular poorly differentiated lymphocytic type. Eight patients had metastatic or relapsed GS. One of these eight (Patient 5) had

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metastases in two different sites, i.e., mediastinal and retroperitoneal aggregated mass, on the same occasion. A second patient, (Patient 6) relapsed in two different tumor sites, i.e., bilateral lung and mediastinum, on two separate occasions. Thus, two sites were indicated in this patient. Six other metastatic or relapsed locations included one mediastinal site, one pleura, one soft tissues of the shoulder and three retroperitoneal sites, resulting in nine sites of metastatic GS at the time of initial presentation or at the time of relapse in eight patients. In total there were ten sites of primary or metastatic GS in nine patients.

These patients had a follow-up period ranging from 6 to 72 mo (mean = 26.6, median = 22 mo).

Therapeutic Regimen

All three patients with ES and six patients with metastatic GS, including Patient 6, were treated with cisplatin-based combination chemotherapy. Patient 4, with Stage I primary testicular seminoma, was treated with infradiaphragmatic radiation therapy following orchiectomy. Patient 9, with relapse in the soft tissue of the right shoulder, was treated with cisplatin-based combination chemotherapy and adjuvant radiation therapy. Patient 11, who had a metastatic site in a left renal hilar node, was treated with infradiaphragmatic radiation therapy.

Gallium-67 Imaging

All 12 patients had a baseline ^{67}Ga scan; 10 patients had at least one follow-up ^{67}Ga study post-therapy. A total of 31 ^{67}Ga studies were obtained in the 12 patients. SPECT studies were performed for thoracic lesions. All ^{67}Ga studies were reread by two nuclear medicine physicians without knowledge of the clinical history, physical findings, original report or other radiological findings.

Patients were intravenously injected with 336.7–392.2 MBq (9.1–10.6 mCi) of ^{67}Ga-citrate and initial imaging was performed at 72 hr, using a gamma camera fitted with a medium-energy collimator. Depending upon the specific camera utilized, pulse-height analyzers were set on the 93- and 184-keV photopeaks or the 93-, 184- and 296-keV photopeaks.

One million count views were obtained of the anterior thorax, with 500k count views collected of the posterior thorax, anterior and posterior abdomen and pelvis. Paired views of the lateral head and neck and axillae were obtained for 300k, with the second image of the pair obtained for time.

Gallium-67 Avidity Scores

Gallium-67 tumor avidity was scored (0–6) relative to accumulation in the sternum on the anterior view of the thorax and the liver on the anterior view of the abdomen (Table 2); a score of 0 was equivalent to background accumulation, a score of 1 was defined as faint accumulation perceptibly greater than background, 2 was equivalent to ^{67}Ga avidity less than that of the sternum on the anterior thorax view, 3 was equivalent to ^{67}Ga avidity equal to that of the sternum on the anterior view, 4 was ^{67}Ga intensity greater than the sternum but less than the liver, a score of 5 was ^{67}Ga uptake equal to that of the liver, and a score of 6 was ^{67}Ga uptake greater than that in the liver. Scoring was performed on planar images. For thoracic tumors, scoring was performed following identification of the correct finding, i.e., existence, location, relation to the organs on SPECT studies. We excluded the finding of the effect of therapy or inflammatory disease.

Radiologic Staging and Follow-up

CT scans were performed at the time of original diagnosis and at 2- to 3-mo follow-up intervals during the first year, at 6-mo intervals for the next year and annually thereafter. Chest radiographs were performed monthly over the first 18 mo of follow-up. MRI examinations were performed in two patients.

RESULTS

Sensitivity of Gallium-67 Imaging

For baseline ^{67}Ga imaging, the sensitivity for ES was 100% (3/3). Gallium-67 sensitivity for GS was 90% (9/10); the combined sensitivity was 92% (12/13). The smallest lesion detected by ^{67}Ga imaging was a 1.5-cm lymph node in the left renal hilum which was also noted on CT scan (Patient 11).

Gallium-67 Avidity of Extragonadal Seminoma

Baseline studies of ES revealed ^{67}Ga avidity scores ranging from 3 to 6, with primary mediastinal sites showing the most intense uptake, scored as 6. Uptake of ^{67}Ga in lymph nodes at cervical, supraclavicular, pericardial and retroclavicular locations surrounding primary mediastinal tumors had avidity scores ranging from 4 to 5; ^{67}Ga avidity of a primary retroperitoneal tumor was 3 (Table 3).

The mean score of ^{67}Ga avidity in ES was 4.9. Following chemotherapy, all sites showed scores of 0 on the first follow-up ^{67}Ga scan.

Gallium-67 Avidity of Gonadal Seminomas

Nine out of ten disease sites of primary, metastatic and relapsed GS revealed ^{67}Ga avidity within mass lesions at the time of initial presentation; scores ranged from 3 to 6 (Table 3). Patient 4, followed for previously treated non-Hodgkin's lymphoma in complete remission, showed ^{67}Ga avidity scores of 2 and then 5 in a new primary site within the right testicle on two sequential scans.

With respect to other patient scan results, two mediastinal and one soft-tissue site involving the right shoulder were scored as 6, two retroperitoneal tumors and one pleural-based tumor showed scores of 5 and one patient with bilateral lung lesions showed scores of 4. One mediastinal tumor and one lymph node in the left renal hilum were scored as 3. The mean score of ^{67}Ga avidity in GS lesions was 4.8.

There was no significant difference between the ^{67}Ga avidity scores for sites of ES or GS. Four out of five mediastinal tumors of both ES and GS showed intense uptake, scored as 6.

Gallium-67 Avidity in Follow-up

One patient, who had a persistently positive ^{67}Ga image of a tumor focus in the soft tissues of the right shoulder and axillary lymph node (Patient 9) was scored as 2; all others were scored as 0 on the first follow-up study, indicating no scintigraphic evidence of active tumor.

Scintigraphic Versus Radiologic Assessment of Response

The response time to systemic therapy for ^{67}Ga imaging was compared to other radiological examinations. This included CT scans, chest radiographs and MRI. The assessment compared the time to reach ^{67}Ga negative status

TABLE 1
Scintigraphic and Radiologic Assessment of Response to Therapy

Patient no.	Tumor	RX	From end of RX to exam (days)	Image results		F/U (mo)	Clinical status
				Ga scan	Radiology		
1	Mediastinal seminoma	ICE	Baseline	Pos.	Pos.		
			+34	Neg.	Dec.	7	NEAD
2	Mediastinal seminoma	BEP	Baseline	Pos.	Pos.		
			+24	Neg.	Dec.		
			+189	Neg.	Dec.		NEAD
			+284		Inc.	26	Thymoma
3	Retroperitoneal seminoma	CEB	Baseline	Pos.	Pos.		
			+18	Neg.	Dec.		
			+245		Dec.		
			+357		Neg.	35	NEAD
4	Primary testicular seminoma	Orch. & XRT	Baseline	Pos.	Neg.	6	NEAD
5	Metastasis in mediastinum and retroperitoneum	VIP	Baseline	Pos.	Pos.		
			+24	Neg.	Dec.		
			+377		Dec.	16	NEAD
6	Relapse in lung	VIP	Baseline	Pos.	Pos.		
			+36	Neg.	Dec.		
			+64	Neg.	Dec.		
			+77		Dec.		
			+116		Neg.		
	Relapse in mediastinum	VIP	Baseline	Pos.	Pos.		
			+34	Neg.	Neg.	42	NEAD
7	Relapse in supraclavicular and mediastinal nodes	CEB	Baseline	Pos.	Pos.		
			+2	Neg.	Dec.		
			+64		Dec.	6	NEAD
8	Relapse in pleura	CEB	Baseline	Pos.	Pos.		
			+17	Neg.	Neg.	10	NEAD
9	Relapse in shoulder	BEP	Baseline	Pos.	Pos.		
			+19*	Pos.	Dec.		
		XRT	+21†	Neg.	Dec.		
			+127†		Dec.		
			+149†		Neg.		
			+232†	Neg.	Neg.		
			+421†	Neg.	Neg.		
			+588†	Neg.	Neg.		
			+776†	Neg.	Neg.	50	NEAD
10	Metastasis in retroperitoneum	BEP	Baseline	Pos.	Pos.		
			+21	Neg.	Dec.		
			+150		Neg.	32	NEAD
11	Metastasis in left renal hilar node	XRT	Baseline	Pos.	Pos.		
			+21	Neg.	Neg.	72	NEAD
12	Metastasis in retroperitoneum	CEB	Baseline	Neg.	Pos.		
			+106		Dec.		
			+204		Neg.	17	NEAD

*Following chemotherapy.
†Following adjuvant radiation therapy.
RX = treatment; F/U = follow-up; Pos. = positive result; Neg. = negative result; Dec. = decrease in size; Inc. = increase in size; NEAD = no evidence of active disease; Orch. = orchiectomy; XRT = radiation therapy; ICE = ifosfamide, carboplatin, etoposide; BEP = bleomycin, etoposide, cisplatin; CEB = carboplatin, etoposide, bleomycin; and VIP = vinblastine, ifosfamide, cisplatin.

to radiologic complete remission (Table 1). The results of radiologic findings included change in the size of mass following systemic therapy (decrease, increase) and time to reach complete remission.

Gallium-67 images returned to normal in 10 of the 11 tumors with positive scintigraphic baseline and follow-up studies at the first examination after treatment. This occurred from 2 to 36 days following the completion of ther-

TABLE 2
Gallium-67 Avidity Scoring

0 = background accumulation
1 = faint accumulation
2 < sternal uptake
3 = sternal uptake
4 > sternal uptake, < liver uptake
5 = liver uptake
6 > liver uptake

TABLE 3
Gallium-67 Scan Avidity by Site for 12 Patients with Extragonadal and Gonadal Seminoma

Extragonadal seminomas			Gonadal seminomas		
Patient no.	Site	Avidity score	Patient no.	Site	Avidity score
1	Mediastinum	6	4	Right testicle	5
	Cervical LN	5			
	Supraclavicular LN	5	5	Mediastinum	6
	Pericardial LN	5		retroperitoneum*	5
2	Neck and mediastinum	6	6	Relapse #1 bilateral lung	4
	Retroclavicular LN	4		Relapse #2 mediastinum	3
3	Retroperitoneum	3	7	Mediastinum	6
			8	Pleura	5
			9	Right shoulder	6
			10	Retroperitoneum*	5
			11	Left renal LN	3
			12	Retroperitoneum	0
	Mean avidity score	4.9		Mean avidity score	4.8

*Aggregated mass, not separable into discrete foci.
LN = lymph node.

apy. Adjuvant therapy was not given to any of the nine patients (ten total tumor sites) in whom ^{67}Ga images returned to normal.

On the other hand, nonscintigraphic radiologic examinations revealed residual masses in 3/3 ES sites and 5/8 GS sites from 24 to 377 days following completion of systemic therapy; all of these 11 sites were ^{67}Ga negative. Two patients with mediastinal ES demonstrated a decrease in size of mediastinal mass and resolution of lymph node involvement on the first follow-up CT scan after chemotherapy. The residual masses had been seen in the mediastinum 34 and 189 days following completion of chemotherapy. One patient with metastatic GS in the mediastinum and retroperitoneum (Patient 5) (Fig. 1) demonstrated an improvement of mediastinal mass and a decrease in size of retroperitoneal masses on the first follow-up CT scan after chemotherapy. The residual masses with stippled calcification remained by 377 days following completion of chemotherapy. Radiologic examinations revealed complete resolution in 3/8 GS sites at the first examination after treatment. This occurred from 6 to 37 days following the completion of therapy (Fig. 2).

In one case (Patient 9) with clinical relapse of GS in the soft tissue of the right shoulder, ^{67}Ga imaging identified active residual disease both within the right shoulder and right axilla. Adjuvant radiation therapy administered to this site resulted in a subsequently negative ^{67}Ga scan and freedom from active tumor over a 50-mo follow-up period.

Follow-up

There was no evidence of recurrent tumor in any treated ^{67}Ga negative sites during a follow-up period ranging from 6 to 72 mo (mean = 26.6, median = 22 mo). One patient with a mediastinal ES, (Patient 2) developed a new mass within the previously treated area which on repeat follow-up imaging was ^{67}Ga negative. Mediastinoscopy with biopsy demonstrated thymoma.

DISCUSSION

The degree of ^{67}Ga uptake in metastatic testicular carcinomas has been reported to vary according to cell type (*4,8,9*). Gallium-67 scan sensitivity results ranged from 93% for seminomas (*4*) to 74% for metastatic embryonal-cell carcinomas and only 25% for teratomas (*9*).

In our present study, ^{67}Ga imaging results for seminoma were similar to those reported by Paterson et al. (*4*) showing a combined sensitivity for both ES and GS of 92%. Indeed, we noted particularly intense ^{67}Ga avidity in the two patients with mediastinal ES and high ^{67}Ga avidity for metastatic GS sites, a potentially important issue if asked to scintigraphically identify additional sites of tumor.

There were only two instances of minimal ^{67}Ga uptake in our series; a retrospectively identified early primary testicular seminoma, and a postchemotherapy study in relapsed seminoma. Other baseline and follow-up ^{67}Ga images showed high ^{67}Ga avidity (score $\geq$3). Therefore it would appear that ^{67}Ga avidity is in part, a function of the amount or volume of viable tumor cells.

Current treatment of ES or GS includes radiation therapy, chemotherapy or a combination of both. In patients with advanced disease, significant improvement in treatment results have been achieved with the use of cisplatin-based chemotherapy regimens (*10,11*). Patients with ES appear to have a prognosis comparable to GS as in distinction to extragonadal nonseminomatous germ cell tumors (*1*). Our limited dataset showed a favorable prognosis in ES.

Following therapy, residual masses are commonly noted in patients with seminoma. It is important to note, how-

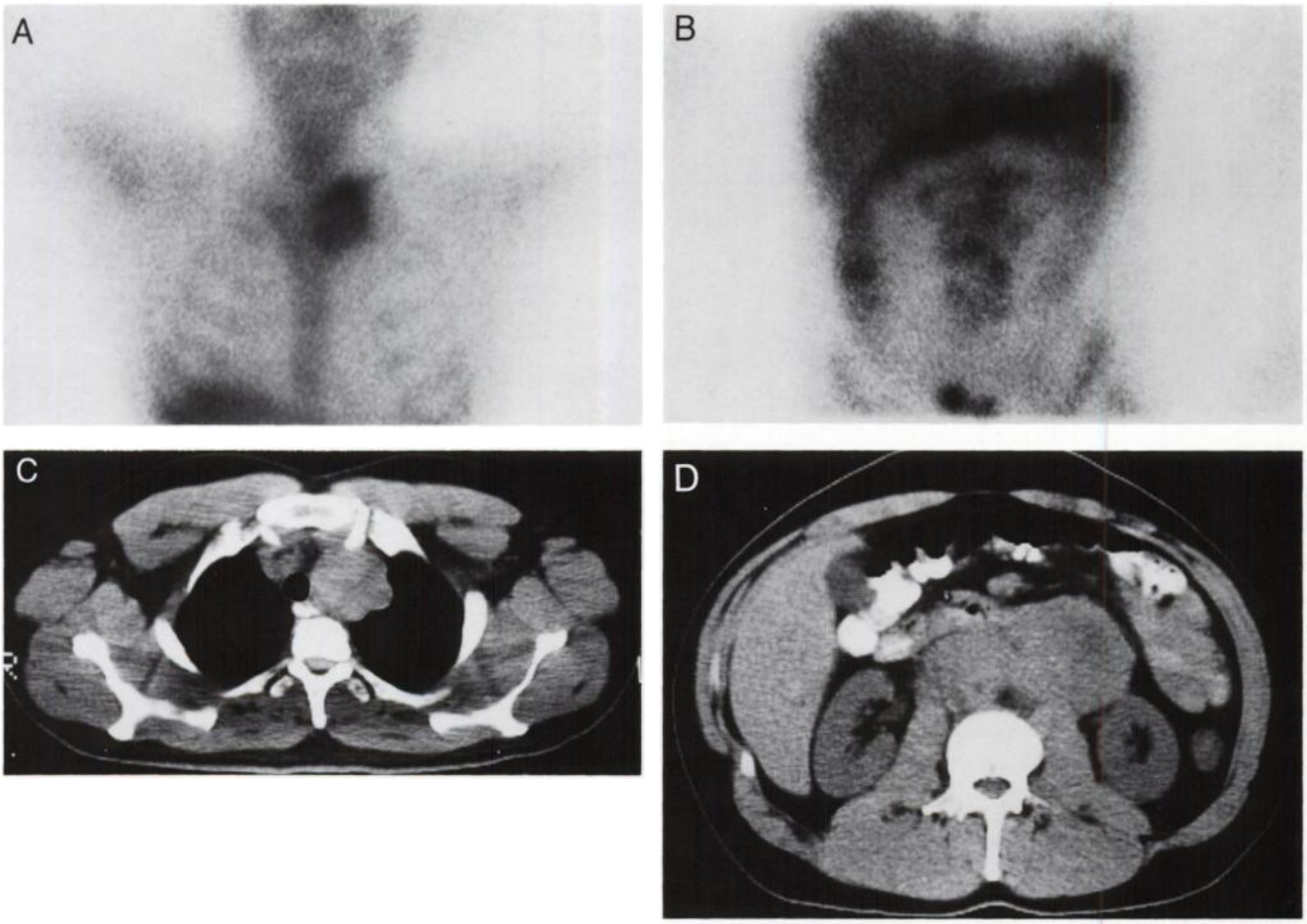

FIGURE 1. (A–D) Baseline studies of Patient 5, a 36-yr-old man with gonadal seminoma. (A) Gallium-67 imaging of the anterior thorax. Gallium-avid tumor was seen in left supraclavicular and mediastinal region, scored as 6. (B) Gallium-67 imaging of the anterior abdomen. Gallium-avid aggregated tumors were seen in para-aortic region, scored as 5. The uptake in the pelvis disappeared with imaging 144 hr postinjection. (C) CT scan shows a soft-tissue density mass in left supraclavicular and mediastinal region. (D) Huge retroperitoneal masses extended from the level of upper pole of right kidney to the level of bifurcation which surrounded and were inseparable from the vena cava and surrounded the aorta.

ever, that these masses infrequently represent sites of active tumor (*12,13*). Stomper et al. reported their experience with CT scanning in 18 patients treated with chemotherapy for abdominal, pelvic and mediastinal seminomatous disease. Residual masses were demonstrated in 13 successfully treated patients (*14*). Similarly, Williams et al. reported on serial CT scans in 33 patients with advanced seminoma (*15*). Although the immediate postchemotherapy CT examination showed marked regression, some radiographic evidence of a residual mass was noted in 29 patients. Complete radiographic resolution was seen in only four patients. Continued CT follow-up at 1 and 2 yr revealed further regression of the residual masses without additional treatment. For this reason surgery is now considered unnecessary for the majority of such patients (*12,13*).

It has been also reported in other tumor types that the presence of a residual mass after treatment may not always indicate residual disease (*16–18*). Iosilevsky et al. showed in a tumor model, using methyl cholanthrene-induced fibrosarcoma, that ^{67}Ga was an indicator of tumor viability (*19*). Kostakoglu concluded about residual Hodgkin's disease in the mediastinum, that ^{67}Ga SPECT was a useful noninvasive modality in differentiating recurrence/residual disease from fibrosis in the mediastinum when a CT scan was nonconclusive in terms of disease activity (*20*). Front et al. compared the negative predictive value (PV−) and positive predictive value (PV+) of ^{67}Ga scintigraphy and CT after treatment in 111 patients with lymphoma. They showed the low PV+ of CT after treatment and the high PV+ of ^{67}Ga studies and that the differences in disease-free survival between patients with negative and positive ^{67}Ga studies were significant, but the differences were not significant for CT (*21*). They reported further that ^{67}Ga scintigraphy may diagnose a recurrence of lymphoma even before clinical symptoms or other diagnostic tests, i.e., clinical examination or abnormality on CT or chest radiograph (*22*).

In our patients, the postsystemic therapy CT examination showed residual masses in 3/3 ES sites, and in 5/8 GS

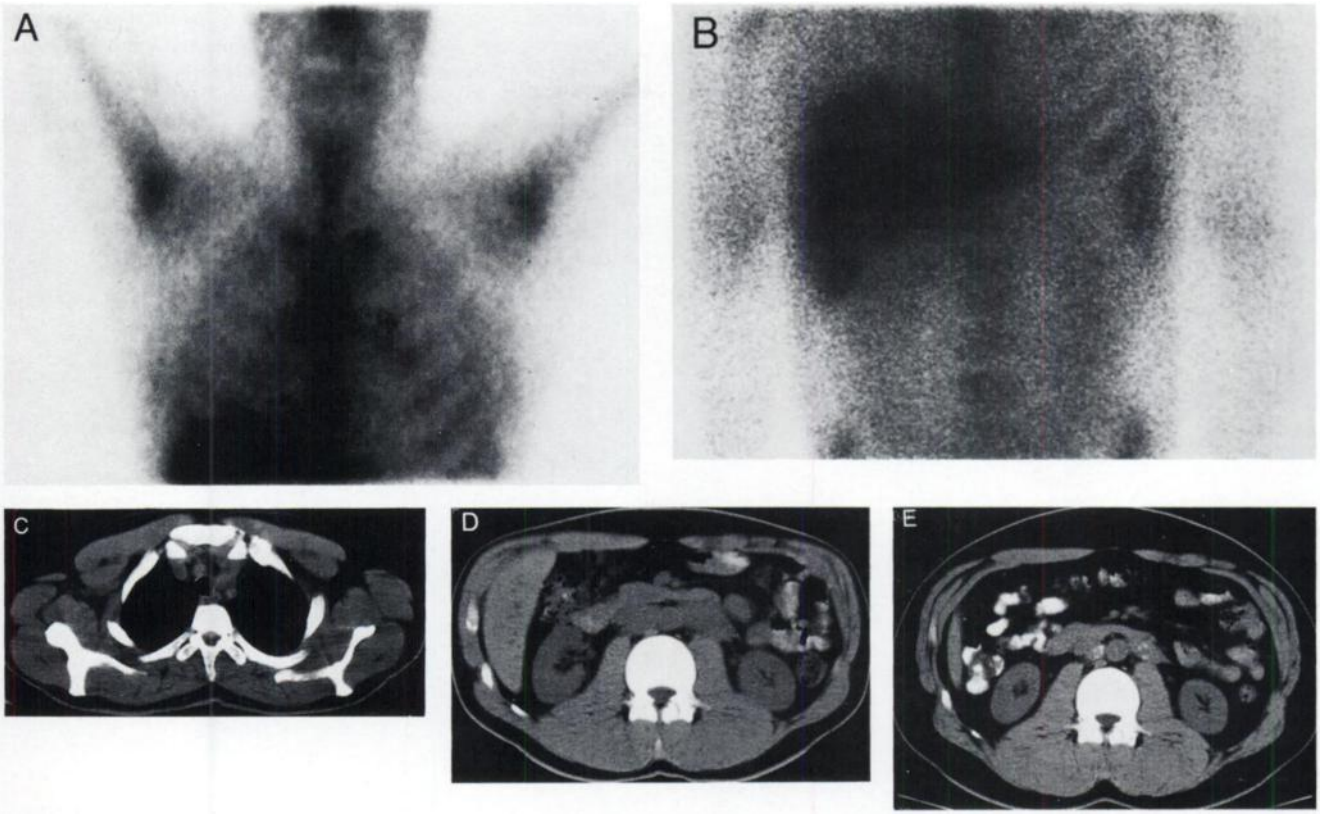

FIGURE 2. Gallium-67 and CT scans 24 days following completion of chemotherapy. (A, B) There is no evidence of residual gallium avid tumor. Faint bihilar uptake was considered response to treatment. (C) CT scan demonstrates improvement of left supraclavicular and mediastinal mass. There was no evidence of abnormal density area in bihilar region. (D) CT scan shows decreased in size of retroperitoneal masses with calcification. These masses extended from the level of the renal hila to approximately the level of bifurcation. (E) CT scan 377 days following completion of therapy. The confluent soft tissue with stippled calcification remained in para-aortic region.

sites. However ^{67}Ga imaging returned to normal immediately in 10/11 indicating an absence of active tumor, an observation supported by clinical follow-up ranging from 6 to 72 mo. One patient who maintained a positive ^{67}Ga scan after chemotherapy, received adjuvant radiation therapy and subsequently remained disease free. Gallium-67 imaging may be useful in confirming the absence of active tumor in patients with residual radiologic masses after treatment.

Gallium-67 imaging provides an effective means of whole-body screening in the management of patients with seminoma. The radionuclide appears equally avid and sensitive for both ES and GS in both primary and metastatic disease sites. In addition, ^{67}Ga may be capable of differentiating active disease from fibrosis in the treated patient with a post-therapy residual radiologic mass.

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