COBALT-LABELED BLEOMYCIN—A NEW RADIOPHARMACEUTICAL FOR TUMOR LOCALIZATION. A COMPARATIVE CLINICAL EVALUATION WITH GALLIUM CITRATE

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The efficacy of ^{57}Co-labeled bleomycin as a tumor-scanning agent was evaluated in 50 patients with malignant tumor. In terms of sensitivity, labeled bleomycin was found to be a superior agent for malignant tumor detection when compared with ^{67}Ga-citrate ($p \leq 0.005$). Maximum sensitivity (96%) was found in epidermoid carcinomas. Because of rapid blood clearance and rapid excretion by the kidneys, interpretation of ^{57}Co-bleomycin scans is facilitated.

Bleomycin has undergone extensive investigation as a cancer chemotherapeutic agent. These studies revealed that this drug produced good therapeutic results in squamous cell tumors, lymphomas, sarcomas, and testicular tumors (*1*). The use of ^{57}Co-labeled bleomycin as a tumor-scanning agent was initially reported from France and Japan (*2,3*). This work prompted us to carry out a comparative study of the potential value of ^{57}Co-bleomycin as a tumor-scanning agent. Bleomycin labeled with either ^{111}In or ^{99m}Tc has also been used as a tumor-scanning agent (*4,5*). Initial experiments in mice showed that ^{67}Ga-citrate and ^{111}In-labeled bleomycin did not clear as rapidly from the blood as did ^{57}Co-labeled bleomycin (*6*) which made the tumor-to-nontumor ratio for ^{57}Co-labeled bleomycin superior to that for ^{67}Ga-citrate and ^{111}In-labeled bleomycin. This study is a continuation of the preliminary work (*7*).

MATERIALS AND METHODS

All patients included in this review were referred to our department for scanning with the provisional diagnosis of a malignant tumor. The protocol and the technical details were as described in a previous report (*7*). Consent was obtained from each patient after the nature of the procedure had been fully explained. The ^{57}Co-bleomycin study was done before the ^{67}Ga-citrate study (*7*). The resultant images were interpreted independently by three observers and a semiquantitative grading (positive, negative, and equivocal) of the visualization of each lesion in the two studies was made. Those scans interpreted as demonstrating equivocal concentration (a suspicious area of increased activity) were considered negative. Only those patients in whom a histologic diagnosis was obtained were included in this report.

RESULTS

Fifty patients were studied. The histologic diagnosis and the scan findings are listed in Table 1. Cobalt-57 bleomycin scans were done in 50 patients and ^{67}Ga-citrate in 44 patients.

Cobalt-labeled bleomycin scans were unequivocally positive in 84% of patients with malignant tumors while ^{67}Ga-citrate scans yielded positive results in only 57% of the patients ($p \leq 0.005$) (Fig. 1). Of the various histologic types of tumors, maximum sensitivity for ^{57}Co-bleomycin was in epidermoid carcinomas (96%) while ^{67}Ga-citrate sensitivity was only 64% in these tumors ($p \leq 0.01$) (Table 2).

DISCUSSION

Considering the physical half-life, bleomycin labeled with ^{99m}Tc or ^{111}In would be preferable to ^{57}Co. However, our initial studies revealed many disadvantages of ^{111}In (*6,7*). Accumulation in the liver, spleen, and bone marrow was found in patients scanned after ^{111}In-bleomycin, strongly suggesting

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TABLE 1. SCAN RESULTS

Type of tumor	^{57}Co-bleomycin		^{67}Ga-citrate	
	No. of patients scanned	Positive no. of patients	No. of patients scanned	Positive no. of patients
Epidermoid carcinoma				
Lung	13	12	13	10
Head and neck	8	8	7	3
Metastatic	2	1	2	1
Adenocarcinoma				
Breast	2	1	1	0
Lung	2	2	1	1
Metastatic	10	8	8	4
Other types of carcinoma				
Undifferentiated lung	5	5	4	4
Melanoma (primary and metastatic)	3	2	3	1
Miscellaneous*	5	2	5	1

* This includes hepatoma, Ca kidney, mucoid Ca stomach.

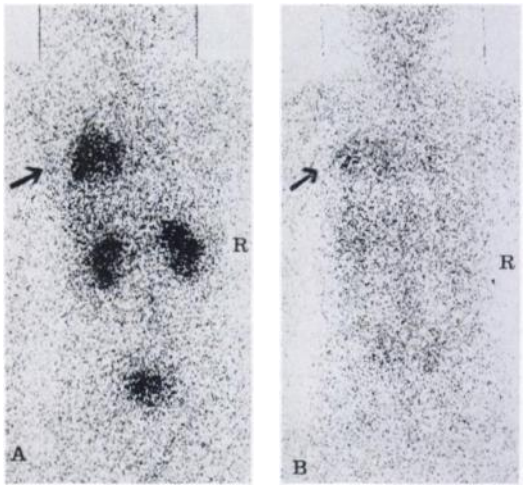

FIG. 1. Scans in 59-year-old man with large cell anaplastic carcinoma, lower lobe, left lung. (A) Posterior view scan 24 hr after injection of 600 μCi of ^{57}Co-bleomycin. (B) Same view 48 hr after injection of 3 mCi of ^{67}Ga-citrate.

TABLE 2. COMPARATIVE SENSITIVITY OF THE VARIOUS AGENTS

Type of tumor	^{57}Co-Bleo (%)	^{67}Ga-citrate (%)	^{57}Co and ^{67}Ga (P value)
Epidermoid carcinoma (primary and metastatic)	96	64	≤ 0.01
Adenocarcinoma (primary and metastatic)	78	50	≤ 0.15
All malignant tumors	84	57	≤ 0.005

that ^{111}In in some way either alters the bleomycin molecule or that it forms a much weaker chelate with bleomycin than does cobalt. We also found that indium-labeled bleomycin was not as sensitive as cobalt-labeled bleomycin in malignant tumors (*7*).

Technetium-labeled bleomycin was successfully prepared (*5*) and evaluated in many patients (*8*). The sensitivity was reported to be as high as 85% in malignant tumors with ^{99m}Tc-labeled bleomycin. However, technetium was released from the complex and bound to serum albumin "in vivo" resulting in delayed clearance from blood, which was even slower than ^{111}In-bleomycin (*4*). Technetium-99m-bleomycin prepared by Lin, et al was insensitive for small lesions. They were able to visualize only relatively large or superficially located tumors (*9*).

Gallium-67-citrate normally accumulates in the liver, spleen, and bone marrow and is excreted into the bowel, making scan interpretation difficult. Moreover, ^{67}Ga accumulation is nonspecific and can be seen in both malignant and benign lesions including cerebral infarction (*10–13*). It is necessary to wait 72 hr after injection for the scanning procedure because of the slow clearance of gallium from nontarget tissues.

Our study clearly shows that ^{57}Co-bleomycin is superior to ^{67}Ga-citrate in malignant tumor detection ($p \leq 0.005$). Cobalt-57-labeled bleomycin was found to be unequivocally positive in 96% of patients with epidermoid carcinomas and 78% of patients with adenocarcinomas. The respective figures for ^{67}Ga-citrate were only 64% and 50%. In epidermoid carcinoma, the difference in sensitivity between ^{57}Co-bleomycin and ^{67}Ga-citrate is statistically significant ($p \leq 0.01$). However, the difference in adenocarcinoma is not significant ($p \leq 0.15$). The overall sensitivity of ^{57}Co-labeled bleomycin in carcinomas of the lung reported by other investigators is about 75% (*14*) while in this study it was 95%.

Although bleomycin is sensitive toward malignant tumors, it also accumulates in benign lesions such as abscesses, tuberculosis and other granulomas, and in benign tumors such as meningioma (*15*).

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