Arterial Perfusion with Tc-99m Macroaggregated Albumin (MAAAP) in Monitoring Intra-Arterial Chemotherapy of Sarcomas

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Thirty infusion studies with Tc-99m-labeled macroaggregated albumin were carried out in 21 patients who had histologically proven peripheral tumors. Three patterns of tumor perfusion were noted: increased central radioactivity in 13 patients, decreased central radioactivity with or without increased peripheral radioactivity in four, and absence of radioactivity in four. In the last category, all four patients had no evidence of tumor neovascularity by contrast angiography. In all 21 patients the intraneoplastic patterns showed very good correlation between contrast angiography and radionuclide angiography. Pulmonary tracer uptake was documented in all 14 patients who had counts performed over the lungs; one had no evidence of tumor neovascularity by either angiographic study, and only 8 of the 13 remaining (61%) showed evidence of appreciable tumor arteriovenous shunting by contrast angiography. Decreased tumor perfusion, presumably due to vessel spasm, was found in one patient.

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Intra-arterial chemotherapy was introduced more than two decades ago for the treatment of neoplasms (*1*,*2*). It has a definite role in the management of hepatic tumors, and is used in melanomas, sarcomas, and neoplasms of the breast, head, neck, and pelvis (*1–6*) whenever technically and anatomically feasible. It has definite advantages over systemic chemotherapy, as maximum therapeutic concentrations are achieved locally on first pass with no added systemic toxicity (*7*). Maximal tumor perfusion by chemotherapy is an essential factor in response to treatment. Conventional contrast angiography is excellent for the evaluation of a tumor's vascular anatomy, but as demonstrated by Kaplan et al. (*8*), this method does not reproduce functional vascular perfusion of the tumor or the distribution of chemotherapeutic agents, both flowing at slower rates. Arterial perfusion with Tc-99m-labeled macroaggregated albumin (MAAAP) is used in various regional blood-flow studies (*8–12*). The particles, ranging in size from 15 to 90 μm, are trapped in the capillary bed and allow good appreciation of tumor shape, size, and vascularity. Also, the slow infusion rate of the procedure allows good evaluation of the first-pass perfusion pattern by chemotherapy. This report describes our experience with MAAAP in peripheral tumors, patterns of tumor uptake, correlation with contrast angiography, recognition of catheter misplacement, and the phenomenon of radioactive pulmonary uptake.

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MATERIALS AND METHODS

Twenty-one patients with pathologically proven peripheral tumors were selected for this study. Their characteristics are detailed in Table 1. Eighteen tumors were located in the extremities, one in the mandible, one in a paravertebral area, and one in the pelvis. Regional chemotherapy was indicated and feasible in all.

With a femoral approach, all patients had arterial catheter placement in the accessible artery closest to the

TABLE 1. CLINICAL CHARACTERISTICS OF THE 21 PATIENTS ANALYZED IN THE Tc-99m MAA INFUSION STUDY

Number of patients	21
Age, median (range) in years	35 (17–65)
Male/female	14/7
Diagnosis	
Soft-tissue sarcoma	6
Osteogenic sarcoma	6
Giant-cell tumor	3
Neurofibrosarcoma	2
Malignant fibrous histiocytoma	2
Ewing's sarcoma	1
Melanoma	1

tumor. Contrast angiograms were obtained before each chemotherapeutic course (a total of 30) followed within 3 hr by MAAAP (a total of 30) to evaluate tumor anatomy, catheter placement, and tumor perfusion. Arteriography was performed by injecting contrast medium at flow rates averaging 4 ml/sec for a total of 40 ml. Radiotracer perfusion studies were performed using 2 to 5 mCi of Tc-99m-labeled macroaggregated albumin (MAA)* in a 0.5-ml solution infused by mechanical pump during 45 sec. Appropriate views (usually anterior and lateral) were obtained with a scintillation camera while the radiotracer was in the catheter and after complete clearance of tracer from it. Evaluation of the distribution of radioactivity was made by visual inspection of the radiographic films and Polaroid scintigrams.

In the initial 11 studies, the phenomenon of pulmonary uptake of radiotracer was not appreciated and no scintigrams were made of the lungs. Assessment of radionuclide pulmonary uptake in 19 studies on 14 patients was judged by the radiographic films and Polaroid scintigrams of the lungs.

RESULTS

Tumor perfusion patterns. The following tumor perfusion patterns were identified (Table 2):

1. Increased central radioactivity pattern (13 patients), indicating excessive tumor perfusion with increased trapping of Tc-99m MAA in the tumor bed (Fig. 1).

2. A decreased central radioactivity pattern (four patients), with or without trapping of the radiotracer at the periphery of the tumor. This, when correlated with the contrast angiogram, indicated a central avascular area, presumably necrotic, and a degree of peripheral radiotracer trapping corresponding with the degree of peripheral hypervascularity in the rest of the tumor bed.

TABLE 2. TUMOR PERFUSION PATTERNS BY Tc-99m MAA INFUSION

Pattern of radiotracer uptake	Number	(Percent)
Increased central radioactivity	13	(62)
Decreased central radioactivity	4	(19)
No radioactivity	4	(19)
Total	21	

3. Absence of radioactivity from the tumor bed (four patients). Angiograms also indicated no tumor vascularization in three patients: one with a paravertebral neurofibrosarcoma, one with synovial sarcoma of the pelvis documented by a TCT and ultrasound of the abdomen, and one with an angiosarcoma of the upper extremity documented clinically and by biopsy. One tumor was avascular, with a mass effect by contrast and radiotracer angiography (fibrosarcoma of the lower extremity).

Correlation of radionuclide angiography with contrast angiography patterns. Table 3 summarizes the findings. In general there was a good correlation between the vascularity pattern within the tumor and the corresponding radionuclide pattern in the same area: hypervascular areas by contrast angiography showed as areas of increased radioactivity, indicating increased radiotracer trapping in the corresponding capillary bed; conversely, hypo- or avascular areas by contrast angiography showed as decreased areas of tracer uptake because of decreased radiotracer trapping.

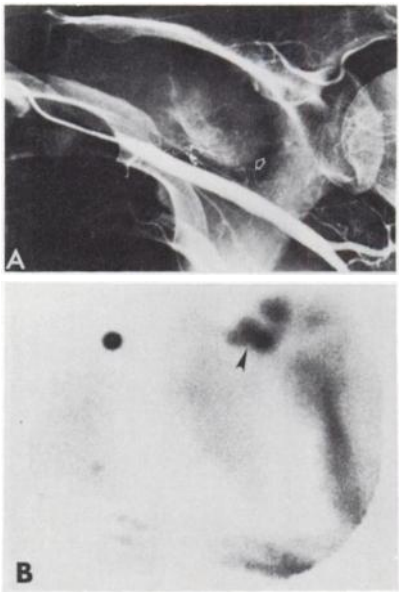

FIG. 1(A). Soft-tissue sarcoma of subclavian fossa, showing tumor neovascularity by contrast angiography (arrow). Arterial infusion with Tc-99m-labeled MAA, showing increased central radioactivity in neoplastic tissue (arrow). Pulmonary uptake is also noted.

TABLE 3. COMPARISON OF TUMOR PATTERNS BY CONTRAST AND RADIOTRACER ANGIOGRAPHY Tc-99m MAA INFUSION

Contrast angiography	Increased central radioactivity	Decreased central radioactivity	Absence of radioactivity
Hypervascular tumor	13		
Hypovascular tumor ± peripheral neovascularity		4	
Normal angiography			3
Avascular tumor (mass effect)			1

Lung shunting phenomenon. The lung shunting phenomenon with pulmonary uptake of MAA has been described previously (*9,10*). The MAA particles, measuring between 15 and 90 μm in diameter, are usually trapped in the first capillary bed, giving a good idea of the flow distribution within the perfused tissue. With tumor neovascularization, arteriovenous shunts with diameters larger than the microspheres allow escape of the radioactive material into the venous system and thence to the pulmonary capillary bed. Counts over the lungs measured pulmonary uptake in 14 patients (19 of 30 studies).

Correlation between pulmonary uptake and angiographic findings. There were 13 patients with evidence of tumor neovascularity and lung uptake. Only 8 of 13 patients showed evidence of significant tumor arteriovenous shunting by contrast angiography. An additional patient (angiosarcoma of the upper extremity) with normal contrast and radioactive angiograms had evidence of pulmonary uptake.

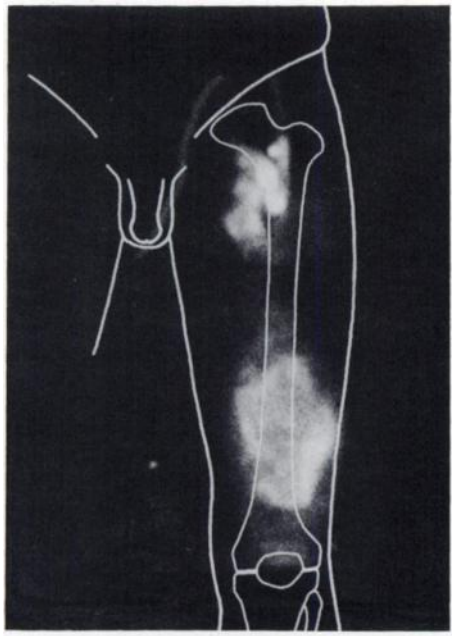

FIG. 2. Multifocal osteogenic sarcoma, with lesions in distal and proximal femur. Distal lesion shows decreased central uptake, increased peripheral uptake, and peripheral neovascularity agreeing with contrast angiogram.

Catheter displacement and probable vascular spasm. In one patient with sarcoma of the upper extremity, improper catheter placement was detected, with excessive perfusion in the normal tissues outside the tumor (Fig. 3). Better tumor perfusion was achieved after catheter repositioning. In another patient with Ewing's sarcoma of the ulna, poor tumor perfusion was attributed to probable arterial spasm distal to the catheter tip. Chemotherapy was delayed for 24 hr until improved tumor perfusion was observed.

DISCUSSION

Intra-arterial regional chemotherapy is gradually gaining wider acceptance in the management of cancers that respond poorly to systemic chemotherapy, such as sarcomas, melanomas, and tumors of the liver, pelvis, head, neck, and breast (*1-6*). The theoretical concept is that higher drug concentrations delivered to the neoplastic bed will result in higher response rates. Direction of maximal chemotherapy into the tumor tissues, therefore, becomes an important factor to evaluate. Kaplan et al. (*8*) demonstrated, using intra-arterial injection of Tc-99m-labeled sulfur colloid, that radionuclide localization depends to a great extent on the flow rate of the infusions. MAAAP studies, using slow infusion rates, are therefore becoming useful procedures ancillary to contrast angiography in the evaluation of tumor perfusion with drugs. They have been used to determine arterial blood flow in peripheral vascular disease (*10*) as well as hepatic (*9,11*) and pelvic neoplasms (*12*). Kaplan et al. (*13*) were able to predict response to chemotherapy based upon the tumor perfusion pattern by MAAAP. Bledin et al. (*9*) demonstrated the value of MAAAP in catheter placement and in prediction of gastrointestinal complications.

In this study we reviewed the value of MAAAP in peripheral tumors. Three patterns of tumor uptake were identified: central radioactivity was increased in 62%, decreased in 19%, and absent in 19%. In the last situation (four patients), there was an explanation for the lack of

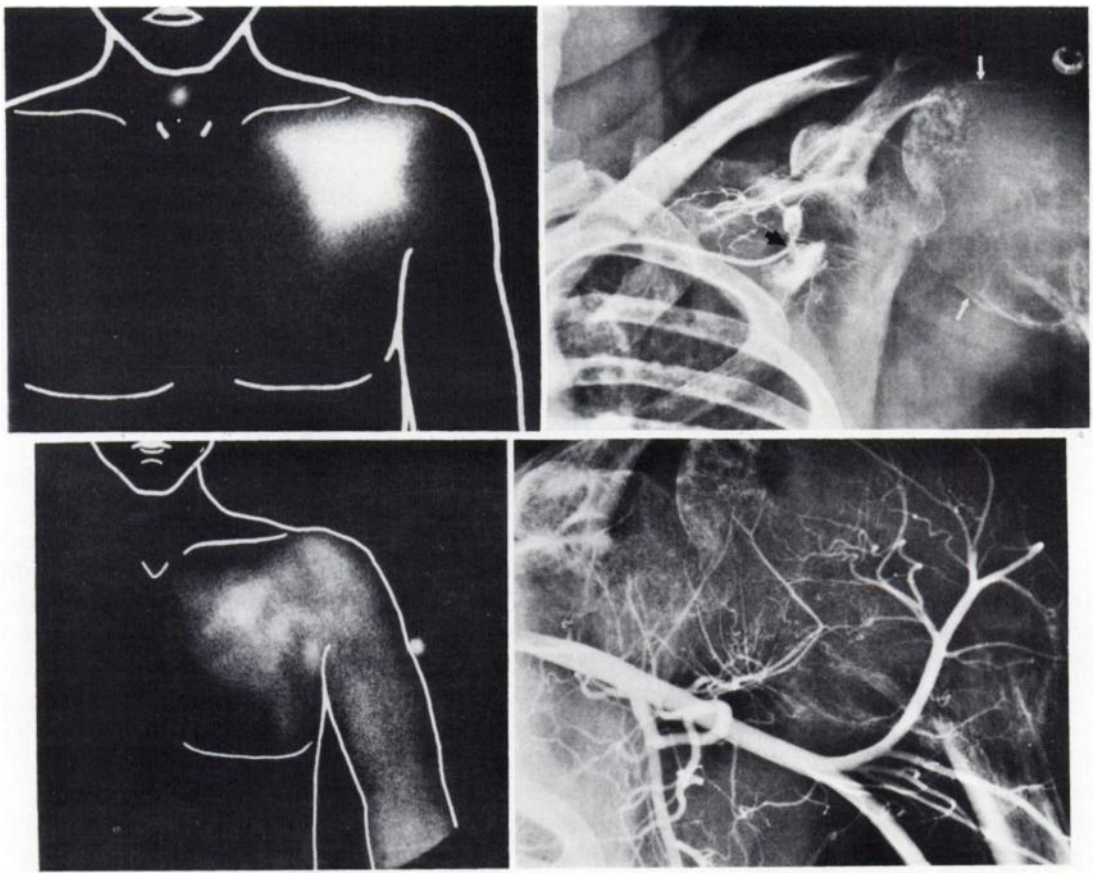

FIG. 3. Misplaced catheter giving radioactive uptake in Pectoralis major muscle (upper left), with no tracer detected in region of tumor. Corresponding contrast angiography (upper right) shows misplaced catheter (black arrow) and large expansile lytic lesion in proximal humerus (white arrow). Better perfusion of tumor is noted with proper catheter positioning (lower left), and corresponding contrast angiogram shows catheter in subclavian artery (lower right).

uptake in each case (avascular tumor in one, and normal contrast angiography in three). There was a very good correlation between the neoplastic pattern of vascularity by contrast angiography and the degree of radioactive uptake by radionuclide angiography in the same area.

The association of arteriovenous shunting with lung uptake of tracer has been described previously for the lower extremities (*10–14*) and in radiotracer studies of patients with hepatic tumors (*9*), where 38% of them showed such shunting. It is thought to result from the escape of Tc-99m-labeled microspheres through physiologic or neoplastic arteriovenous shunts into the venous circulation, where they lodge in the pulmonary capillaries. This occurred in 100% of the patients with peripheral tumors. Only 61% of those patients showed evidence of appreciable arteriovenous shunts in the tumor by contrast angiography; One patient with no evidence of tumor neovascularity by contrast angiography demonstrated lung uptake. However, in a small series of six patients undergoing adjuvant chemotherapy to the liver, no lung shunting was demonstrated. Rhodes et al. (*14*) found a 2–4% physiologic shunting of tracer when injected into a limb. This may mean that arteriovenous shunting could occur as a normal phenomenon in tissues of certain organs (e.g., muscle), while not occurring in others (e.g., liver). Interpretations concerning the phenomenon of lung uptake should be cautious until more data accumulate about its occurrence in patients undergoing radioactive angiography for non-neoplastic conditions or for adjuvant chemotherapy.

MAAAP studies were also helpful in detecting catheter malpositioning and arterial spasm (*15*), leading to better tissue perfusion.

The various patterns of MAA uptake by peripheral tumors, and its change with response to chemotherapy are currently being correlated. The number of followup studies is still too small for any conclusions.

In summary, we conclude that radionuclide MAAAP is a helpful ancillary procedure to contrast angiography in the evaluation of arterial chemotherapy to a peripheral tumor. It shows a good correlation with contrast angiography patterns, provides evidence of maximal tumor perfusion by chemotherapy, and helps in evaluating proper catheter positioning and arterial spasm. The phenomenon of pulmonary radioactive uptake was demonstrated in a high proportion of patients. Its significance, implications, and usefulness are yet to be determined.

FOOTNOTE

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