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HM-PAO Assessment of Human Tumour Perfusion

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Abstract—*Technetium-99m-labelled hexamethylpropylene amine oxime (HM-PAO) has been used to investigate tumour perfusion in 11 tumour sites in 8 patients with a variety of histologies. In 8 out of 11 instances single photon emission tomography clearly distinguished between tumour and normal tissues; in 7 cases due to increased HM-PAO uptake and in 1 due to reduced tumour uptake compared with hepatobiliary excretion of HM-PAO in adjacent normal liver. Heterogeneous uptake within individual tumour masses was observed in 3 cases. In 2 where a correlation between the pathology of excised tumour and the scan findings could be made, the findings were consistent with HM-PAO uptake in well-perfused tissue. These preliminary observations suggest that Technetium-99m-HM-PAO may be a valuable clinical technique for displaying patterns of tumour perfusion.*

INTRODUCTION

TUMOUR blood flow is considered to be critically important in the evolution and treatment of human tumours influencing the pharmakokinetics of cytotoxic drugs and the metabolic status of tumour cells with consequent modification of the sensitivity to radiation and chemotherapy. In hyperthermia, blood flow also influences the rate of heat decay from tumour in relation to heat dissipation from normal tissues resulting in selective tumour heating.

Total tumour blood flow describes the entire input and output irrespective of the size and functions of the transmitting vessels. Capillary blood flow, more specifically, refers to perfusion or nutritional flow. Perfusion has been measured by a number of radioactive tracer methods in experimental animals including Rubidium uptake [1] and distribution of radioactive microspheres [2] but neither technique is applicable to clinical studies. Attempts to measure human tumour perfusion have been less satisfactory but some information has been gained from xenon clearance [3] and positron emission tomography [4]. A technique using biodegradable human serum albumen microspheres has recently been devised for estimating the fractional distribution of cardiac output to organs in non-cancer patients [5].

Technetium-99m-HM-PAO is a recently-introduced radiopharmaceutical agent currently being used to investigate cerebral blood flow in patients with dementia, epilepsy, migraine, stroke and tumour [6]. The possibility of using this agent to measure extra-cerebral normal tissue and tumour blood flow has been explored in an animal model by comparing HM-PAO uptake with that of Rubidium^{86}, an established method for quantifying blood flow [7]. Good correlation between uptake of these 2 agents was demonstrated in muscle, spleen and subcutaneously-implanted sarcoma. This paper describes the use of Technetium-99m-HM-PAO, for the detection and *in vivo* imaging of human tumour perfusion. To our knowledge, HM-PAO has not been employed previously for this purpose.

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PATIENTS AND METHODS

Nine patients were included in the study. The histological diagnoses were as follows: adenocarcinoma (3), non-Hodgkin's lymphoma (2), Hodgkin's disease (1), carcinosarcoma (1), melanoma (1) and liposarcoma (1). One tumour site was investigated in each of 7 patients and 2 sites were studied in a further 2 patients. The estimated dimensions of the tumour at each site are shown in Table 1. Three patients (3, 5 and 8) were studied prior to treatment, the remaining patients had recurrent disease although none had received radiation in the field under observation. Technetium-99m-HM-PAO was prepared by adding 1GBq, in 5 ml, of freshly-eluted Technetium-99m pertechnetate to a vial containing predispersed, sterile non-pyrogenic freeze-dried HM-PAO (Ceretec Amersham International). 3.7 ml of solution containing 750 MBq of Technetium-99m was administered intravenously as a bolus injection within 15 min of preparation. Single photon emission tomography (SPECT) was performed within 60 min of injection, 64 × 20 sec

Table 1. Tumour characteristics and HM-PAO activity

Patient	Tumour site	Maximum dimension of tumour (cm)	Histology	Level of HM-PAO activity	Distribution of HM-PAO activity
1	Groin	13	Melanoma	+	Het
2	Mediastinum liver		Adenocarcinoma	±	Hom
3	Tonsil/ neck	7	T-cell lymphoma	+	Hom
4	Paraaortic	6	Carcinosarcoma	0	
5	Lung	7	Adenocarcinoma	+	Het
6	Chest wall	6	Myoxoid liposarcoma	+	Het
7	Pelvis	7	Adenocarcinoma	0	
8	Neck	6	Hodgkin's	0	
	mediastinum	8		+	Hom
9	Neck	4	Non-Hodgkin lymphoma	+	Hom

+: Increase.
−: Decrease.
0: Not defined.
Het: Heterogeneous (peripheral ring of high activity).
Hom: Homogeneous.

views being collected during a 360° rotation using a low-energy high-resolution collimator. The 64 views were pre-smoothed with a Hanning filter using a 0.83 cm^{-1} frequency cut-off. Tomograms were reconstructed with a simple ramp frequency filter. Trans-axial slices 0.6 cm thick were obtained encompassing the area of interest.

RESULTS

Uptake of Tc-99m-HM-PAO was observed in brain, myocardium, liver and kidney with lung and soft tissues generally showing a lower level of activity. The pattern of organ distribution was relatively constant in the 9 patients studied.

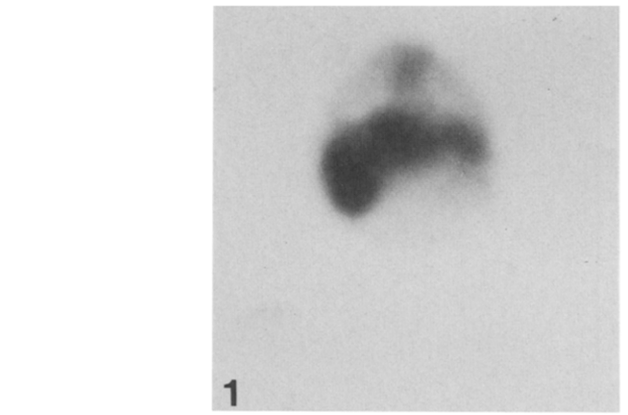
As shown in Table 1, 8 of the 11 tumour sites could be readily differentiated from surrounding normal tissue by an increased uptake of isotope in 7 patients and a decreased uptake in the 1 patient with liver metastases. Figure 1 shows uptake of HM-PAO in right cervical nodes involved by T-cell lymphoma. Figure 2 shows high uptake in mediastinal nodes involved by adenocarcinoma. In Fig. 2(a) the mass is seen on a chest radiograph and in Fig. 2(b) well-defined activity is identified in the same position on trans-axial emission tomographic section. The axillary veins on the side of the injection are also observed. Scanning of the liver in the same patient shows a lower uptake of HM-PAO compared with normal tissue (Fig. 3).

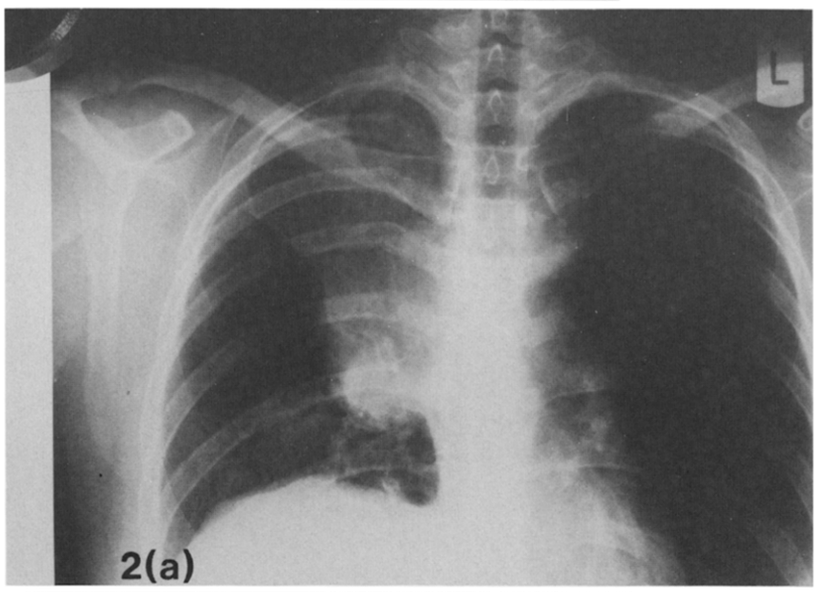
Heterogeneous uptake of HM-PAO within the tumour was observed in 3 patients. In each case a peripheral ring of increased activity surrounded an area of lower uptake (Fig. 4). Central necrotic tissue was documented macroscopically and microscopically in the 2 masses that were excised (Fig. 5).

In 3 of the 11 tumour sites HM-PAO was poorly-defined. In 2 cases tumours were present in the lower abdomen and pelvis and in the third, uptake of HM-PAO was clearly defined in a mediastinal mass of Hodgkin's disease but not in cervical nodes.

DISCUSSION

Tc-99m-HM-PAO is currently being evaluated as an agent for measuring cerebral blood flow in patients with dementia, epilepsy, migraine, stroke and tumour [6]. Being uncharged, lipophilic and of low molecular weight HM-PAO crosses the blood–brain barrier and is fixed within the brain for sufficient time to permit a SPECT study. To assess the possible value of HM-PAO in the investigation of extra-cerebral normal tissue and tumour blood flow a comparative study with Rubidium 86, an established method for measuring blood flow [1], has been carried out in an animal model [7]. Good correlation between uptake of these 2 agents was demonstrated in muscle, spleen and subcutaneously implanted sarcoma. In addition, propranolol-induced changes in tumour perfusion relative to normal tissue were comparable for both techniques suggesting that HM-PAO may be useful for investigating tumour perfusion. Although the correlation with Rubidium provides valuable support for HM-PAO as a tumour perfusion agent, precise uptake kinetics in normal and diseased tissues must be





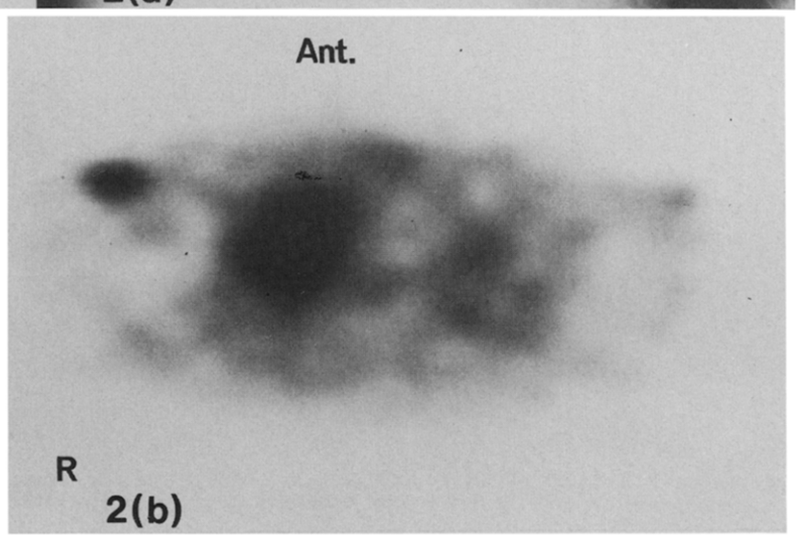
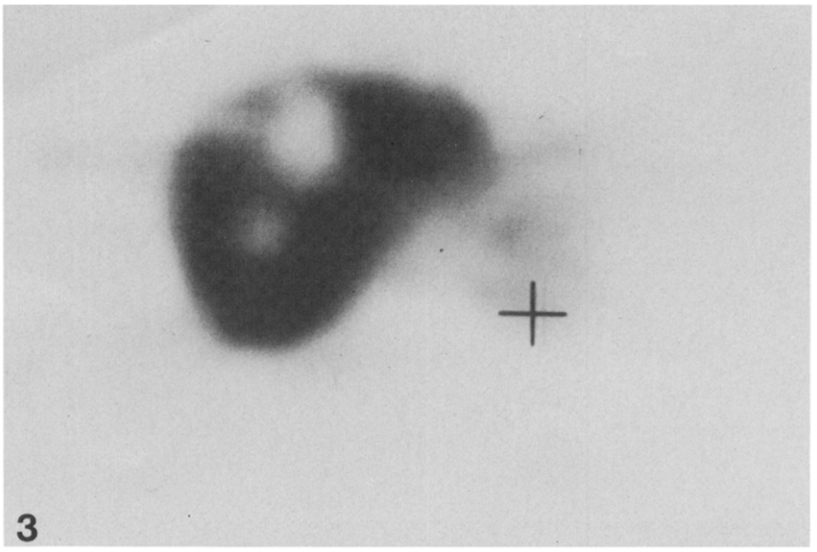
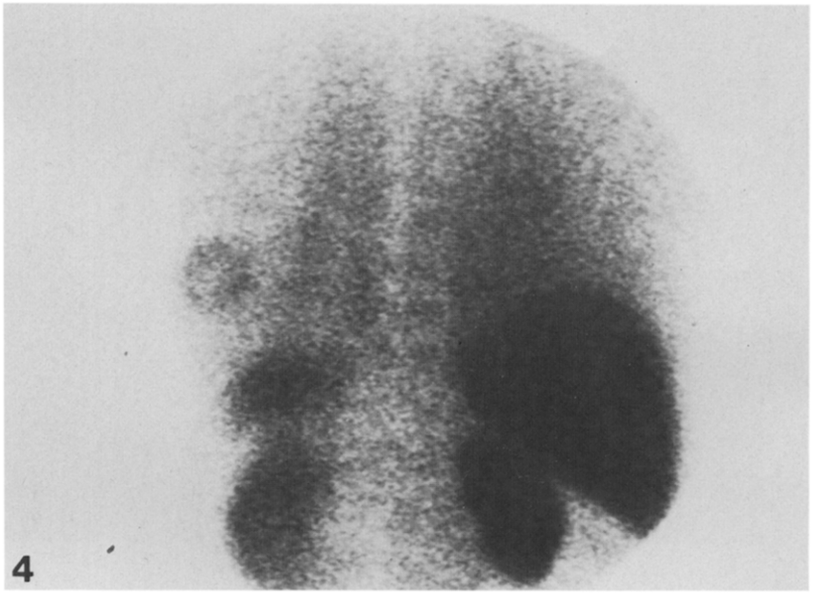


Fig. 1. *Trans-axial emission tomogram of the cervical region of the neck showing high and well-defined uptake of Tc-99m-HM-PAO in lymph nodes in a patient with a T-cell lymphoma.*

Fig. 2(*a*). *Plain PA chest* x-*ray of a patient with adenocarcinoma of unknown origin involving the right paramediastinum.* (*b*) *The trans-axial emission tomogram through the mass shows high well-defined uptake of HM-PAO in the right lung with a smaller area of activity in the axillary vein.*





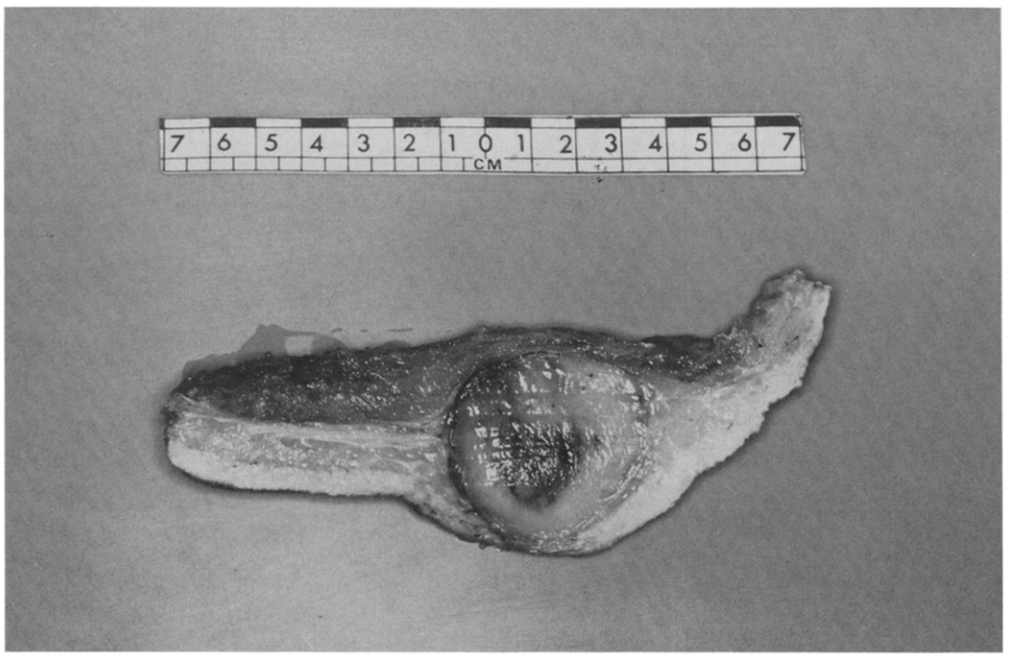


Fig. 3. Trans-axial tomogram of the liver of a patient with metastatic disease. The tumours are seen as areas of reduced activity in relation to the uptake and excretion of the HM-PAO by the liver parenchyma.

Fig. 4. Planar view of the posterior aspect of the chest and abdomen of a patient with a soft tissue sarcoma involving the left posterior chest wall. The tumour can be seen as a ring of high activity surrounding a photon-deficient centre.

Fig. 5. Macroscopic appearance of the excised soft tissue sarcoma shown in Fig. 4. A central necrotic core surounded by a rim of viable tumour.

determined. Until such information is available, the physiological implications of HM-PAO uptake remain speculative.

In the present preliminary clinical study tumour could be distinguished from normal tissue in 8 of 11 instances, a degree of activity comparable to conventional radioisotope tumour-localising techniques such as Gallium^{67} [8] and labelled antibodies [9]. The sensitivity of HM-PAO tumour localisation is likely to be influenced by tumour site. Thus, tumours were clearly visualised in the thorax, whereas a large pelvic adenocarcinoma ($7 \times 6 \times 3$ cm) could not be detected. Activity in kidney, bladder and bowel due to excretion of the agent is likely to reduce the usefulness of the technique in abdominal and pelvic tumours. HM-PAO is concentrated and excreted by the liver which shows high activity on scintigraphy. In 1 patient liver metastases were visualised as discrete photon-deficient areas indicating that uptake due to perfusion was low in relation to concentration and excretion by the liver. The observation that comparably-sized cervical and mediastinal nodes involved by Hodgkin's lymphoma showed dissimilar results with no uptake in the neck but a clearly visualised mass in the chest, suggests that there may be perfusion differences between metastases at different sites. HM-PAO uptake within individual tumour masses was heterogeneous in 3 patients and homogeneous in 4. Heterogeneity was taken to indicate the difference between well-perfused tumour tissue and poorly-perfused necrotic tissue, an interpretation supported by comparison of the scan appearance with macroscopic and microscopic pathological features in 2 masses which were subsequently excised.

If these preliminary observations are confirmed by more intensive studies HM-PAO may provide a useful clinical technique for investigating tumour perfusion. Since tumour perfusion is considered to be a significant factor in radiotherapy by influencing the oxygenation status of tumour cells and is also likely to be an important influence on the pharmacokinetics of chemotherapeutic agents, a method which enables tumour perfusion to be related to therapeutic response would clearly be of interest. In addition, HM-PAO scanning may provide a method for investigating the contention that the successful application of hyperthermia may depend on differential tumour heating due to less efficient heat dissipation from poorly-perfused tumour tissue. Finally, HM-PAO uptake could provide an important tool for developing and applying techniques for pharmacological manipulation of tumour blood flow as a basis for improved treatment.

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