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DETECTION OF VX2 CARCINOMA IN RABBITS BY PASSIVE MICROWAVE RADIOMETRY

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Abstract

VX2 cancers were grown at various anatomic sites in the New Zealand rabbit. Thermometric detection of these tumors was attempted by microwave radiometry as well as by contact thermometry using thermocouple and thermistor probes. Tumors, irrespective of site, could not be reliably detected by surface thermometry. Tumors growing subcutaneously in the ear could be detected early (diameter = 5mm) by microwave radiometry. Detection by microwave radiometry of tumors grown subcutaneously or intramuscularly in the hind limb was much less reliable. Blood flow rates in the tumor and surrounding tissues could not explain these site-related differences in tumor detectability by microwave radiometry.

Introduction

Our laboratory has been investigating the utility of passive microwave radiometry in the detection of cancer. Central to the success of this technique is the premise that malignant neoplasia are hotter than surrounding normal tissues. It has been well documented that many breast cancers are hotter by about 1°C than normal breast tissues[1], but little is known of the thermogenic properties of cancers in other anatomic sites. The role of tumor metabolic rate and blood flow in the elevation of tumor temperature is an open question.[2]

This paper reports on the thermal detectability of the VX2 carcinoma as a function of tumor volume in three different sites in the New Zealand white rabbits. In addition, blood flow rates were determined in conscious animals at both tumor-bearing and normal tissue sites in an attempt to correlate microwave thermography with tumor volume and rate of blood flow.

Materials and Methods

The VX2 carcinoma in the New Zealand rabbit was selected as the tumor model because this is a reasonably large animal in which tumors can be grown subcutaneously, intramuscularly, as well as intrahepatically for possible detection of deeply-seated tumors.[3] The tumor was obtained from Mason Research Institute, Worcester, Massachusetts. Tumor in ocula were injected subcutaneously in the left ear, the left hind limb, or intramuscularly in the left hind limb. Rabbits were checked daily for evidence of tumor "take." When subcutaneous tumors became palpable, volumes were calculated as $(\pi/6)\ d_1 \times d_2 \times d_3$ where d_1, d_2, and d_3 were caliper-measured diameters in three orthogonal planes. Volumes of intramuscular tumors were estimated as $(\pi/6)\ d^3$ where d was the difference in diameter between the right and left limb.

Prior to tumor inoculation and several times per week thereafter, thermal measurements were made at the site of tumor inoculation using the contralateral (right) site as a reference. Surface measurements were made by placing a thermistor probe (Narda Model 8011, Temperature Model Monitor) or a thermocouple probe (Keithley Model 870, Digital Thermometer) in contact with the left (tumor) or right (normal) area. Readings were recorded following 30 seconds of contact. Triplicate alternating (right and left) determinations were done at each site.

Radiometric measurements were made by placing the receiver antenna over the site and, following stabilization, recording five voltage readings at 5-second intervals. Again, triplicate alternating determinations were made at each site.

For measurements on the hind limb, the radiometer antenna was adjusted to 35.8°C to minimize thermal drift between the rabbit and the antenna.[4] For ear measurements, the antenna was adjusted to 33.6°C. Also, a piece of sponge rubber 2x3x3/8" wrapped in aluminum foil was used to position the ear against the antenna.

The microwave thermography system itself has been described in greater detail elsewhere.[5] Briefly, the unit is a Dicke-switched radiometer operating at 4.75 GHz with a dielectrically-loaded C-band antenna whose aperture dimensions are 0.8 x 1.6cm.

Tissue blood flow measurements were made using the radio-labeled microsphere method. Briefly, this procedure involves computing the number of milliliters of arterial blood of known radioactivity required to pass through each grain of tissue to account for the radioactivity measured in that tissue. Twenty-four hours prior to attaining measurements, the animals were anesthetized and indwelling polyethylene cannulas positioned in the thoracic aorta via the right femoral artery and the left ventricle via the right carotid artery. Introduction of the cannulas into the right femoral and right carotid arteries precluded further comparative radiometric observation since the cannulas substantially reduced blood flow to the reference right leg and right ear.

Results

The surface temperature obtained with thermistor and thermocouple probes were extremely variable. It was not uncommon to have more than 1°C variation on three successive readings at the same site in a given rabbit. No correlations could be made between the surface temperature difference (tumor minus normal) and tumor volume for any of the three tumor sites.

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Microwave thermal differences, on the other hand, could be correlated with tumor volume for those tumors in the ear. The tumor grown at this site had a volume doubling time of about 2-3 days. When the tumor volume reached about 0.07cm^3 (diameter = 0.5cm), tumors generally became warmer than the tumor-free reference ear. In Figure 1, 50 such ΔT determinations were made on ear tumors of various volumes in 11 rabbits.

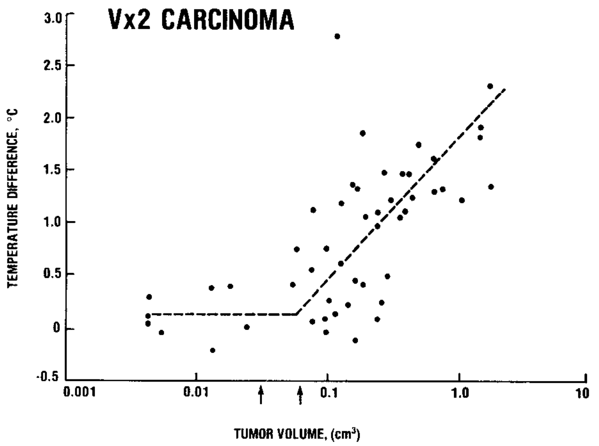

Figure 1

Subcutaneous and intramuscular tumors of the VX2 carcinoma in the left hind leg did not appear hot by microwave radiometry. In many cases (see Figure 2), as the tumor volume approached 1cm^3 at about 16 days following tumor cell inoculation, the tumor became significantly colder (about 0.02°C) than the reference right leg. The temperature difference between right and left legs (ΔT) prior to inoculation was 0.0 ± 0.1°C based on three determinations. As the tumor became palpable and followed a Gompertzian-type growth curve (Figure 2), the ΔT did not differ significantly compared with pre-inoculation values until about 16 days, whereupon the tumor began to exhibit colder ΔT values. This phenomenon was seen in rabbits with both subcutaneous and intramuscular tumors on the hind leg. The doubling times were about 1.6 days for the subcutaneous tumors and about 3 days for the intramuscular tumors.

In one rabbit with a subcutaneous tumor which spontaneously regressed, the microwave thermal pattern generally followed the growth of the tumor, i.e., that tumor became hotter as it grew larger, then became colder as it regressed.

Blood flow rates in ml of blood/min/g of tissue are listed in **Table I.** Means ± standard deviations are given for three determinations in one tumor-free rabbit, three rabbits bearing ear tumors, and three bearing leg tumors.

Discussion

There are two major conclusions to be drawn from these data. The first is that the VX2 carcinoma in the ear becomes thermogenic to the extent that it permits detection by microwave radiometry at a very early stage -- about 0.07cm^3, or about 5mm diameter. This compares quite favorably with other modalities, such as radiographic methods, where the lower limit for detection is generally thought to be about 10mm in diameter. It must be pointed out, however, that it simply is not known how rabbit ear or hind leg data would extrapolate to the clinical situation.

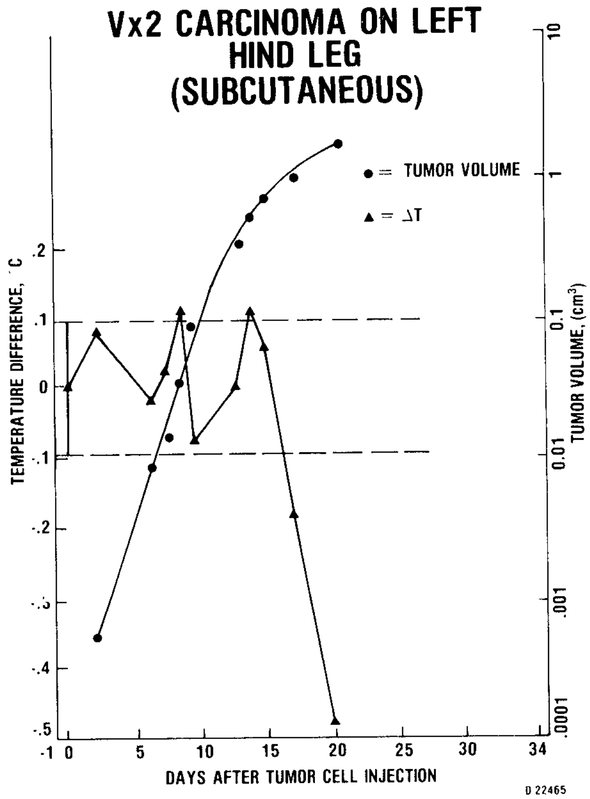

Figure 2

TABLE 1 - BLOOD FLOW RATES IN RABBITS

	RABBIT WITH NO TUMOR	RABBITS WITH EAR TUMOR	RABBITS WITH LEG TUMOR
MUSCLE	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.02
SKIN	0.28 ± 0.02	0.27 ± 0.18	0.19 ± 0.06
EAR	0.15 ± 0.06	-	0.05 ± 0.02
HEART	4.04 ± 0.70	5.04 ± 0.50	3.79 ± 1.79
KIDNEY	5.62 ± 0.60	4.74 ± 1.46	4.87 ± 1.03
LIVER	0.06 ± 0.03	0.41 ± 0.22	0.39 ± 0.22
TUMOR	-	1.10 ± 1.11	0.43 ± 0.18

The second major observation is that the thermogenic properties of tumors may be site-dependent. Whereas a tumor of a given volume may be detectable at one location, such as the ear, it may not be detectable at a different location, such as the leg. The appearance of a detectable thermal difference in a tumor most probably depends on the tumor vascular supply being sufficient to provide for an increased metabolism in the tumor and the ability of the surrounding normal tissue to deal with the excess heat. In the case of the ear, which has a relatively small normal tissue mass, the excess heat produced by the tumor cannot be effectively "sinked" by the surrounding ear tissues and consequently the tumor becomes detectable. The same tumor in the leg, however, may not be perceived as hot because the larger mass of normal tissue in the leg can "sink" the excess heat of the tumor more effectively. The results of the blood flow studies show that the tumor blood flows, 0.43 and 1.10 ml/min/g for the leg and ear tumors respectively, are considerably greater than blood flow rates in surrounding normal tissues, skin, muscle and ear. It is tempting to speculate, therefore, that the tumor has an ample blood supply irrespective of site of implantation and the ability to detect this tumor by microwave radiometry reflects the relative ability of surrounding normal tissues to carry off excess heat generated by the tumor.

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