THE FUNDAMENTAL AND EXPERIMENTAL STUDY OF THE MALIGNANT TUMOR SCANNING WITH RISA

TAKAMICHI YOSHIDA

*Department of Radiology, Kurume University School of Medicine,
Kurume, 830, Japan*

(Received for publication July 13, 1976)

I studied that the distribution of RISA in various tissues and tumor in NF sarcoma bearing mouse and tumor scanning in rabbit implanted Brown-Pearce tumor, Myxoma virus tumor and Fibroma virus tumor.

It was found from the results of the distribution study and experimental tumor scanning that the tumor scanning should be performed after 48 hours of admission of RISA when the activity in tumor went over that in blood. I thought that RISA has the possibility to be tumor scanning material.

INTRODUCTION

We with Department of Radiology have investigated the malignant tumor detection using various nuclear labelled compounds, like as some tumor affinity substances, including ^{131}I -diiodofluorescein (DIF), ^{131}I -labelled human serum albumin (RISA), ^{131}I -fibrinogen, ^{131}I -fibrinogen antibody, ^{131}I -fibrin, and ^{131}I -fibrin antibody. I have studied about RISA as a part of these series.

RISA is one of the most common radiopharmaceutical and use in clinical for brain tumor scanning, the measurement of cardia put out volume and blood circulation time.

Above all, RISA used for the brain tumor scanning showed the successful results. So I thought that RISA might be used for the tumor scanning other than brain tumor. However, the situation of the incorporation of RISA into a tissue and tumor is not necessary solved enough.

Then I have first studied the distribution of RISA in various tissues and tumor of the tumor bearing mouse. Moreover, I had a tumor scanning with RISA in the tumor bearing rabbit.

METHODS

The report consists of two parts, one is the distribution of RISA into mouse tissues, the other is the tumor scanning in tumor bearing rabbit.

1) *The distribution of RISA in mouse tissues and tumor*

ddN mouse, 2 months old, 18 g. of average body weight, was feeded by a trade solid feed and water, and used as a material.

The experimental tumor was NF sarcoma, which was implanted into axillar subcutane of ddN mouse.

0.5 $\mu\text{Ci/g}$ of RISA was injected into a tail vein of the mouse and sacrificed at the following time, 6, 12, 18, 36, 48, and

72 hours after injection. And various tissues except blood were extracted and washed out with physiologic saline and homogenized by dilute sulfuric acid and then they were counted the activity of RISA by the well type counter. The counts (CPM) was converted into per gram of tissue.

2) *The tumor scanning in the tumor bearing rabbit*

The rabbit, 2 kg of body weight, white, was used as a subjects. The experimental tumors were Brown-Pearce tumor (BP), Myxoma virus tumor (MxV) and Fibroma virus tumor (FbV), the former two are malignant tumor, the latter is benign tumor, which was used as a control to malignant tumor.

BP was implanted into the left thigh of the rabbit. The rabbit implanted MxV singly has so short survival period that FbV was first implanted into the right thigh and then MxV was implanted into the left thigh when FbV raised enough. It was reported (Kohi, 1963) that even if FbV was implanted before MxV, the immunity wasn't change in rabbit. So I made the implantation of FbV before MxV. Moreover, FbV was singly implanted into the right thigh of rabbits. 100 μ Ci/kg of RISA were injected into the ear vein of each rabbits in 5 days after the implantation of these tumors. The scintiscanning was made every 24 hours till 96 hours, more under certain cases.

The instrument was scintiscanner, Shimazu SCC-5 (2 inches) with cylindrical collimeter (12 mm). The scintigram was color scintigram by multi-scintigram system that was first developed by Dr. Prof. M. Ozeki et al. (1964).

RESULTS

1) *The distribution of RISA within the mouse tissues*

The distribution of RISA in NF sarcoma bearing mouse was shown in Table 1 and Fig. 1, which showed counts/min/g, from 6 hours to 72 hours. The concentration of RISA was higher in blood, tumor, lung and kidney, and lower in brain, and muscle. As a whole, the activity in various tissues gradually dropped down with the lapse of time together.

The concentration ratio of the tissue to blood in NF sarcoma bearing mouse was showed in Table 2 and Fig. 2. The concentration ratio of the tumor to blood was increased with lapse of time and went over the concentration of blood 48 hours after injection, it was important.

Scintigram is performed on the time of the lower back ground, which means usually a dominated activity of blood, because the delineation of the target organ is difficult in the occasion of a high activity of blood. The fact that the concentration of tumor went over that of blood, suggested that the tumor scanning should be performed after 48 hours of injection. The concentration of RISA in another tissues other than tumor were decreased with the lapse of time and never exceed that of blood.

2) *The tumor scanning in the tumor bearing rabbit*

a) Brown- Pearce Tumor

The scintigram of BP at 24, 48, 72, and 96 hours were showed in Fig. 3 a. The scintigram at 24 hours showed a diffuse distribution in the lower half body and not clearly the delineation of the tumor. It seemed to be by reason of the high concentration of RISA in

blood at this time. In the scintigram after 48 hours, the tumor was delineated clearly. In 96 hours after, the density of the dot, as a whole, was decreased, but the localization of tumor was still distinct.

b) Myxoma Virus Tumor

As described, MxV was implanted in the left leg of rabbit when FbV in the right leg raised enough.

The scintigram of MxV at 24, 48, 72 and 96 hours were showed in Fig. 3 b. The scintigram at 24 hours showed the localization in both thigh and the concentration in MxV was more than that in FbV. The concentration in MxV and FbV varied with the lapse of time. In the scintigram at 72 hours, the concentration in FbV was almost disappeared, but MxV was still delineated clearly, and at 96 hours, MxV was delineated yet.

c) Fibroma Virus Tumor

The scintigram at 24, 48, 72, and 96 hours showed in Fig. 3 c. In the scintigram at 24 hours and 48 hours, the concentration in FbV was very low and indistinct. In the scintigram at 72 hours, the concentration in FbV was almost disappeared. Thus, the activity of RISA in FbV, benign tumor, was lower and disappeared at early time.

DISCUSSION

Since the earliest day of scanning, people working in this field have hoped that malignant tumor could be found with some radioactive labelled compounds (Susuki, 1960 ; Schmidt et al, 1961 ; Charkes et al, 1965 ; Hirra et al, 1965 ; Sodee et al, 1965 ; Cavalieri et al, 1966).

In our laboratory, Dr. Prof. M. Ozeki

(1962) firstly reported a clear scintigram on the experimental tumor with ^{131}I -fibrinogen, that is, Yoshida sarcoma in rat, Brown-Pearce and MxV tumor in rabbit. After that, ^{131}I -fibrin antibody by Kohi (1963) and anti-fowl-rabbit-fibrinogen antibody and anti-human-rabbit-fibrinogen antibody by Takaki (1966) were investigated to the experimental tumor scanning resulting successful. However, clinical application of the antibody of fibrinogen or fibrin have many problems, for example of their refining and so on.

RISA is a common radiopharmaceutical and used for brain tumor scanning as usual. Bonte et al. (1965) reported on the mechanism of incorporation of RISA into the experimental tumor (V2 rabbit carcinoma). According to it, RISA injected into blood circulation rapidly comes to relatively uniform dilution within the subject's plasma protein. Within few hours after injection, the tumor was visualized as the blood pool, and RISA entered into the plasma pool in the tumor center space such as central necrosis (by radioautography). The fact was suggested that the second mechanism connected tumor cell and serum protein might be existed. When the tumor scanning was performed within a few hours after injection, the blood pool of tumor was visualized, and at 24 hours after of injection the tumor delineation was clearly, because that much of the difference in counting rate between tumor and surrounding tissues existed.

In this report, the concentration of all tissues including blood and tumor were decreased with the lapse of time as shown in Table 1 and Fig. 1. But the decrease rate of activity of RISA in tumor was lower than in blood, and 48 hours after injection, the activity in the tumor went over that in blood as shown in Table 1 and Fig. 2. At that

time, if one performed the tumor scanning, the tumor delineation ought to make a clear image. As a fact, in my tumor scanning of rabbit, tumor scanning at 48 hours obtained a clear image of tumor as shown in Fig. 3.

The concentration ratio of the tumor to blood was gradually increased with the lapse of time, in spite of the absolute value or counting rate was decreased. The concentration ratio of tumor to blood was about 1.00 during preferable scanning time that was not so different in both. Thus, the possibility of tumor delineation reflected the value of RISA in blood and tumor in the area be scanned.

The incorporation of RISA in various tissues of mouse were gradually decreased together and didn't remained in some organs and its excretion was relatively rapid. As described, tumor scanning at 48 hours in rabbit showed a clear tumor image. So I think that RISA has the possibility to be used as tumor scanning material.

ACKNOWLEDGEMENT

I wish to express my thanks to Dr. Prof. M. Ozeki for his guidance and encouragement, to Lecturer Y. Furukawa for his technical assistance and to Drs. K. Yano and T. Kohi for their helps.

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TABLE 1

Distribution of RISA in the tumor bearing mice (N. F. Sarcoma)

Elapsed time Organs	6 hr	12 hr	18 hr	24 hr	36 hr	48 hr	72 hr
Blood	18122	15214	12678	10867	8056	5745	3953
Tumor	8964	9780	8696	8331	6882	5433	4645
Brain	1298	976	756	684	573	461	186
Lung	10867	10342	9056	5433	2535	1811	1629
Heart	7245	6904	5796	3877	2896	2295	1203
Liver	3622	5433	3835	3586	2173	1593	832
Spleen	5429	4989	3042	2389	1991	1883	724
Kidney	14535	7245	5796	3677	2715	2317	1194
Muscle	3589	2535	2027	1739	1086	940	717

Fig. 1 RISA retention curve in the tumor bearing mice (N. F. Sarcoma).

TABLE 2
*Concentration ratio of the organs to blood
 in tumor bearing mice (N. F. Sarcoma)*

Elapsed time Organs	6 hr	12 hr	18 hr	24 hr	36 hr	48 hr	72 hr
Blood	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Tumor	0.494	0.642	0.685	0.766	0.854	0.945	1.175
Brain	0.072	0.064	0.060	0.063	0.071	0.080	0.047
Lung	0.600	0.680	0.714	0.500	0.315	0.315	0.412
Heart	0.400	0.454	0.457	0.357	0.359	0.399	0.304
Liver	0.199	0.359	0.302	0.329	0.269	0.277	0.210
Spleen	0.300	0.328	0.240	0.220	0.247	0.328	0.183
Kidney	0.802	0.476	0.457	0.338	0.337	0.403	0.302
Muscle	0.198	0.166	0.159	0.160	0.134	0.163	0.181

(Blood = 1.000)

Fig. 2 RISA in the tumor bearing mice (N. F. Sarcoma).
 Comparison of concentration ratio between blood and organs
 (---- Blood = 1.00).

▲——▲ Tumor ●——● Brain ○——○ Lung ●——● Heart
 ○——○ Liver △——△ Spleen ×——× Kidney ×——× Muscle

Fig. 3 Tumor scanning of tumor bearing rabbits in the lapse time.
 (a) Brown-Pearce (b) Myxoma Virus Tumor (c) Fibroma Virus Tumor

The original pictures were color scintigram but the insert picture became monochrome for the convenience of the print. The color arrangement was in the order of black, green, red, and violet from the side of the low activity.