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Preliminary study of metabolic radiotherapy with ^{188}Re via small animal imaging

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^{188}Re is a β^- (Emax = 2.12 MeV) and γ (155 keV) emitter. Since its chemistry is similar to that of the largely employed tracer, ^{99m}Tc, molecules of hyaluronic acid (HA) have been labelled with ^{188}Re to produce a target specific radiopharmaceutical. The radiolabeled compound, i.v. injected in healthy mice, is able to accumulate into the liver after a few minutes. To study the effect of metabolic radiotherapy in mice, we have built a small gamma camera based on a matrix of YAP:Ce crystals, with 0.6×0.6×10 mm^3 pixels, read out by a R2486 Hamamatsu PSPMT. A high-sensitivity 20 mm thick lead parallel-hole collimator, with hole diameter 1.5 mm and septa of 0.18 mm, is placed in front of the YAP matrix. Preliminary results obtained with various phantoms containing a solution of ^{188}Re and with C57 black mice injected with the ^{188}Re-HA solution are presented. To increase the space resolution and to obtain two orthogonal projections simultaneously we are building in parallel two new cameras to be positioned at 90 degrees. They use a CsI(Tl) matrix with 1×1×5 mm^3 pixels read out by H8500 Hamamatsu Flat panel PMT.

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1. INTRODUCTION

^{188}Re is an attractive therapeutic radioisotope with broad clinical applications. Oncology applications range from palliation of metastatic bone pain to bone marrow ablation and in general to the use of ^{188}Re labelled therapeutic agents to target specific cancerous tissues (see for instance reference [1]). Other therapeutic applications comprise the inihibition of restenosis after Percutanueous Transluminal Coronary Angioplasty (PTCA), radiation synovectomy, and intravasal brachytherapy. In the field of metabolic radiotherapy ^{188}Re shows several favourable characteristics. It can be produced carrier free using a W-Re generator (see for instance reference [2]) and its chemistry is similar to that of ^{99m}Tc which is the most used radioisotope in nuclear medicine (medical imaging). The ^{188}W parent has a 69 d half-life, which permits to use the generator for a relatively long period, the equilibrium between parent and daughter setting up within about two days. ^{188}Re decays to ^{188}Os* in about 0.7 days via the emission of a β-ray with a maximum energy of 2.12 MeV (0.78 MeV average energy), which can be used for destroying cancerous cells. In addition ^{188}Os* emits promptly (0.69 ns) a 155 keV γ-ray (15%), which can be used for imaging. Given the chemical similarity with ^{99m}Tc, it can be linked to molecules of hyaluronic acid (HA) which have the function of carrying it to specific sites in the body, e.g. with the production of an accumulation and retention of the drug in the liver [3]. Hence the potential interest for treating liver cancers. On the other hand the β radiation could interfere with the labelling process and destroy the molecule used to carry the radioisotope in the body to the target organ, thus reducing the therapeutic effect. Two additional points have to do with the relatively long lifetime and with the rich photon spectrum of ^{188}Re, which extends to high energy, compared to the single 140 keV photon emitted by ^{99m}Tc with a half-life of about 6 h. Taking into account the branching ratios (BR) and the lifetimes, the relative ^{188}Re/^{99m}Tc counting rate, for an equal number of μ-moles, is about 9%. This implies that photon detectors developed for imaging with ^{99m}Tc are not necessarily sensitive enough. The usual thickness of a low-energy Pb collimator, say 20 mm, will be almost transparent to ^{188}Re photon lines at 300 keV or higher energies, even with BRs depressed by a factor of ten or more, producing background counts which blur the image and worsen the spatial resolution. To study the effect of metabolic radiotherapy in mice, we have therefore built a new small high-sensitivity γ-camera, following the experience with the YAP-camera [4][5][6], which is used routinely to image small animals (mice) with ^{99m}Tc-HA at the Laboratori Nazionali di Legnaro, Italy (e.g. [7][8]).

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2. THE GAMMA CAMERA

The gamma camera is based on a matrix of yttrium aluminium perovskite doped with cerium (YAP:Ce or $YAlO_3$:Ce) crystals [9], with friendly mechanical properties (no igroscopicity), fast response (∼25 ns decay time), high density (5.37 g/cm^3) and good X- and γ-ray absorption. There are 66×66 pixels, each 0.6×0.6×10 mm^3, covering a field-of-view (FOV) of 40×40 mm^2. The pixels are covered laterally by a special 5 μm thick reflective coating which provides also the optical separation between neighboring elements. The scintillator is read out by a R2486 Hamamatsu PositionSensitivePMT [10] with a 76 mm diameter photocathode. The anode consists of 16 plus 16 wires crossing at 90^o and connected by two resistive chains, defining the x and y directions. The wires define an active area with a diameter of about 50 mm. A 20 mm thick lead parallel hexagonal-hole collimator [11], with hole diameter 1.5 mm and septa of 0.18 mm, is placed in front of the YAP matrix. The detector is triggered using the last dynode and the ends of the x and y resistive chains (x_1, x_2, y_1, y_2) are amplified, stretched and read out by a PC using a PCI 6023E card [12]. The coordinates of the photon impact point are then reconstructed by charge division,

$$x = (x_1 - x_2)/(x_1 + x_2) \quad (1)$$

and similarly for y.

3. CALIBRATIONS

The energy response of the detector to a spatially uniform source (flat field) of ^{99m}Tc 140 keV photons prior to energy equalization has been determined using a solution containing ^{99m}Tc which covered the whole FOV and was located a few centimeters in front of the collimator surface. The xy has been arbitrarily divided in pixels and the average energy computed in each pixel. The corrections to the measured energy extracted from this calibration are shown in Fig. 1 and have been used in the following. As shown below with the ^{188}Re spectrum, these corrections improve the energy resolution of the detector. Apart from the energy equalization, no other correction has been applied. With ^{99m}Tc the sensitivity of the gamma camera is found to be $\sim 2\times10^{-4}$ or $\sim 7\times10^{3}$ cps/mCi, which agrees roughly with calculations.

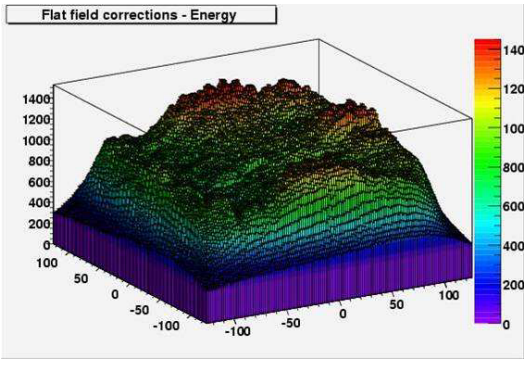

Figure 1. Flat field calibration with ^{99m}Tc.

Pointlike ^{241}Am (60 keV photons), ^{57}Co ($\sim$122 keV photons) and ^{137}Cs (660 keV) sources located in different positions a few millimeters distant from the collimator have been used both to simulate the ^{188}Re energy spectrum and to evaluate the spatial resolution of the detector. In addition ^{241}Am and ^{57}Co, together with ^{99m}Tc photons, permit the calibration of energy scale. The overall energy spectrum is presented in Fig. 2 and the cumulative image of the sources is visible in Fig. 3. The 60 keV is well prominent and a 122 keV shoulder is also visible; ^{137}Cs instead produces a broad shoulder at about half of the photon energy. Using appropriate energy cuts the three images can be separated. The intrinsic spatial resolution of the system is quite good, since individual collimator holes can be clearly seen in Fig. 3. The resolution however is worsened in practice by the small thickness of the septa relative to the hole diameter of the present collimators, making them partially transparent to radiation, so the actual effective resolution is $\Delta x \sim 3$ mm FWHM at 122 keV.

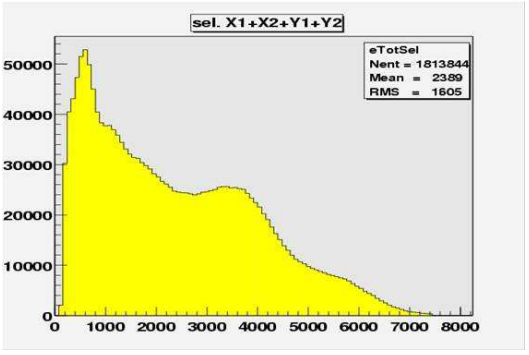

Figure 2. ^{241}Am, ^{57}Co and ^{137}Cs superimposed spectra measured with the YAP camera.

The ^{188}Re photon spectrum measured with a Ge detector is shown in Fig. 4. The 155 keV line is prominent, but many more lines are present at higher energy, in some cases, e.g. at $\sim$300 keV, with BRs only a factor of ten lower, or at 800-1200 keV with intensities lower only by a factor of 100 [13].

The ^{188}Re spectrum measured with the YAP camera during the imaging of a C57 mouse (see next section) is shown in Fig. 5. The spectrum is shown before and after applying the corrections for energy non-uniformity, and a clear improvement is observed with the shrinking of the 155 keV peak. After the corrections, the energy resolution is ΔE/E $\sim$ 33% @ 155 keV.

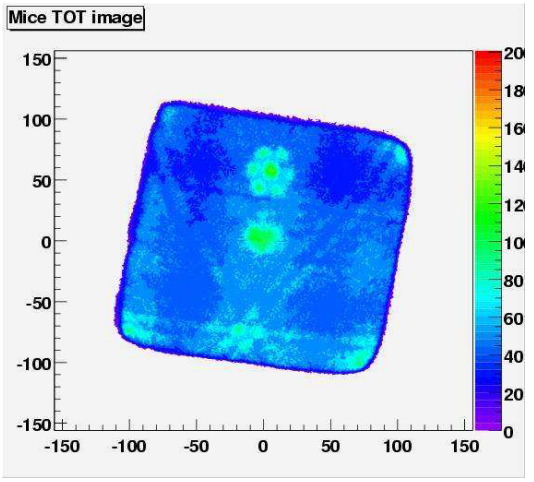

Figure 3. ^{241}Am (center), ^{57}Co (top) and ^{137}Cs (bottom) images measured with the YAP camera.

4. FIRST MEASUREMENTS WITH ^{188}Re

The labelling reaction of HA using ^{188}Re was carried out with good yields (65-70%). The radiolabelled compound was purified with a size exclusion chromatographic method before being used for biodistribution studies. Stability studies in rat serum confirmed the maintaining of the Re linked to the polymer and there was no evidence of radio-decomposition after a few hours.

The radiotoxicity of ^{188}Re has been tested "in vitro" and compared with ^{99m}Tc, with which no effect is expected. Cells of the M5076 tumor line have been treated with ^{188}Re and ^{99m}Tc solutions, and irradiated with X-rays. The number of binucleate cells and of micronuclei in the cells is then counted. Activities of 150-300 μCi of ^{99m}Tc show no effect, but ^{188}Re β-rays seem to be quite efficient [14].

To test the full chain, from the radiolabelling to to the imaging "in vivo", a C57 black mouse (healthy, female) has been injected with ^{188}Re-HA. After general anesthesia, the solution with an activity of about 250 μCi was injected in the caudal vein. The mouse was positioned along the diagonal of the FOV, with the locus of injection outside it, and was monitored for about three

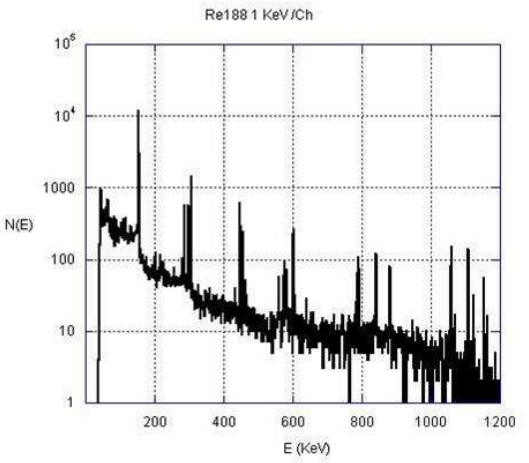

Figure 4. ^{188}Re spectrum measured with a Ge detector.

hours. The image collected in the first five minutes shows a large spot close to the locus of injection in the tail (Fig. 6). After 5 mins the activity concentrates roughly in the centre of the body, in a volume which contains the liver (Fig. 7). The activity is slowly decreasing during the 3 h of the measurement. After 3 h the mouse was sacrificed, and the organs were extracted and measured with a microcurimeter (Fig. 8). The liver contains 60% of the residual activity and close by organs another 20%, in agreement with the scintigrafic image (Fig. 7), where individual organs are not resolved. even with limited resolution the test shows that it is possible to monitor the biodistribution of ^{188}Re in mice, with a potential saving in the number of animals needed for testing the ^{188}Re therapy.

5. CONCLUSIONS

Preliminary results obtained using a new YAP camera in imaging ^{188}Re sources and C57 black mice injected with a ^{188}Re-HA solution have been presented. To increase the space resolution without losing sensitivity, and to obtain different projections simultaneously, we are building two new

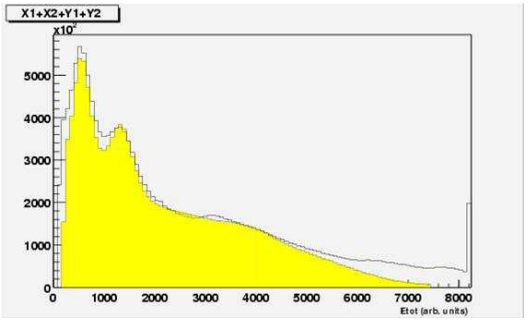

Figure 5. ^{188}Re spectrum measured with the YAP camera: the shaded spectrum has been corrected for energy non-uniformity.

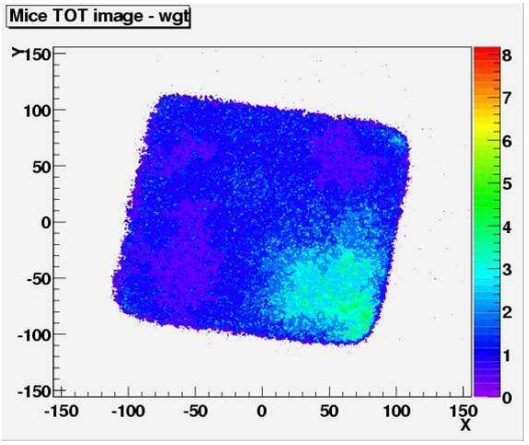

Figure 6. The image of the C57 mouse integrated for the first 5 minutes after the injection of ^{188}Re-HA in the caudal vein.

cameras to be positioned at 90 degrees around the animal. They use a CsI(Tl) matrix with 1×1×5 mm^3 pixels read out by H8500 Hamamatsu Flat panel PMT [10]. Parallel-hole Pb collimators 20 mm thick, with 1 mm diameter hexagonal holes and 0.2 mm thick septa, will be mounted in front of the scintillators. Also specially made collimators with thicker septa and/or different absorber material will be used. The front-end electronics for the 64 channels of the H8500 has been designed using MPX-08 chips [15]. The system will be mounted on a rotating support in order to produce tomographic images.

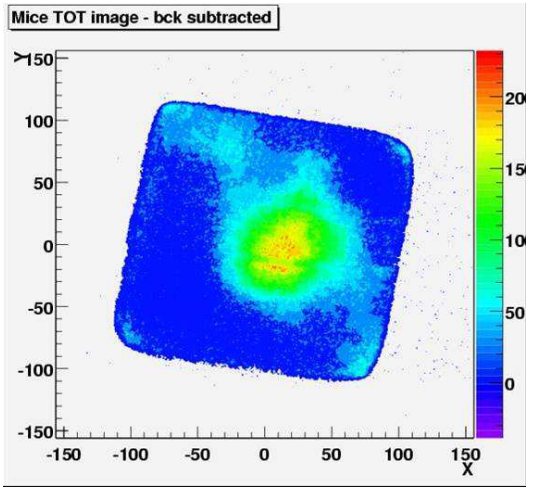

Figure 7. The image of the C57 mouse integrated between 5 and 185 minutes after the injection of ^{188}Re-HA in the caudal vein. The volume of large activity corresponds to the liver.

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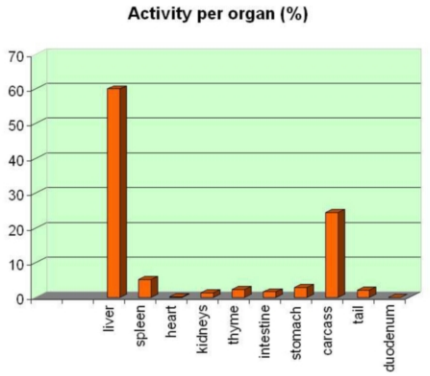

Figure 8. Activity of various organs "*post mortem*".

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