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POSITRON EMISSION TOMOGRAPHY OF MONOCLONAL ANTIBODIES

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A review on the use of monoclonal antibodies labeled with positron emitting nuclides is presented. Potential radionuclides for labeling are e.g. ^{18}F, ^{55}Co, ^{64}Cu, ^{66}Ga, ^{68}Ga, ^{76}Br, ^{89}Zr and ^{124}I. Radionuclides with short half-lives may be utilized especially by pretargeting approaches. Gallium-isotopes have also been coupled to antibodies, using chelation methods. One promising nuclide for antibody labeling seems to be ^{124}I ($t_{1/2} = 4.2$ d) as radioiodination of antibodies is a well-characterized procedure. Some of our own studies using ^{124}I labeled monoclonal antibodies in a nude mouse and rat human ovarian cancer xenograft are reported.

Review of the literature

Positron emission tomography (PET) is superior to SPECT in resolution, quantification possibilities and sensitivity (1), its disadvantages being only of economic nature. Monoclonal antibodies can be labeled for PET with either long-lived or short-lived positron emitting radionuclides (2). Possible radionulcides for PET are listed in the Table.

Short-lived radionuclides. Fluorine-18, gallium-68, and possibly iodine-122 and carbon-11, may be used clinically after two- or three-step pretargeting using labeled biotin or biotinylated antibodies with avidin-biotin amplification system (4, 5). In the literature no images have been shown so far with ^{18}F or ^{68}Ga. Fluorine-18 has been studied in a mouse human glioma xenograft model where an uptake of 18.7% ID/g tumor at 4 h with ^{18}F-labeled Mel-14 M-Ab was obtained (6). It has also been studied in a canine myocardial infarct model using fluorinated antimyosin (7). Several methods for fluorination have been described (8–11). Antibodies can also be labeled with β^+-emitting gallium isotopes (12–18). Gallium-68 is generator-produced (with an approximate generator half-life of 275 days) and therefore easily available. In mice bearing colon carcinoma approximately 50% ID/g tumor at 24 h using an anti-CEA MAB 35 was achieved, when it was labeled with the γ-emitting gallium-67 (13). The same anti-CEA antibody labeled with ^{67}Ga (specific binding of 64.2% vs. 67.7% with ^{125}I) showed improved localization ability in colon carcinoma patients (12). Tumor uptake (18.7% ID/g at 96 h) was also obtained in a study with M.2.9.4 anti-melanoma MAb labeled with ^{67}Ga by the use of P-ED-DHA chelation (14). Experimental studies using ^{66}Ga or ^{68}Ga have been reported. The utilization of a bispecific antibody labeled with ^{68}Ga hexadentate octahedral gallium

Table

Characteristics of selected positron emitters for antibody labeling (properties collected from (3))

Radionuclide	$t_{1/2}$	β^+_{max} (MeV)	β^+ abund.	main γ (keV)
Fluorine-18	109.7 min	0.635	97%	
Iron-52	8.2 h	0.80	56%	165 (100%)
Cobalt-55	18.2 h	1.50	81%	930 (80%)
Copper-64	12.8	0.656	19%	1340 (0.5%)
Gallium-66	9.45 h	4.15	57%	1039 (37%), 2748 (25%)
Gallium-68	68.3 min	1.90	90%	1078 (3.5%)
Arsenic-72	26.0 h	2.50	17%	835 (78%)
Bromine-76	16.1 h	3.6	62%	559 (63%)
Zirconium-89	78.4 h	0.90	22%	910 (99%)
Iodine-122	3.5 min	3.1	100%	
Iodine-124	4.15 d	2.14	26%	605 (67%)

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chelate (Ga-HBED-CC) for rapid pretargeting: an uptake 3.9% ID/g tumor at 48 h was obtained in a melanoma mouse model using preinjected MAb 3A10, ^{131}I-anti-chelate MAb and anti-enantiomeric ^{67}Ga-HBED-CC, whereas without preinjection it was 0.13% ID/g tumor (15). All the mentioned gallium isotope applications may be used for PET. A direct PET application has been reported in two dogs, imaged for myocardial damage using ^{66}Ga labeled transcomplexated DTPA-antimyosin MAb (16). Short-lived radionuclides for PET were labeled with parathyroid specific MAb BB5-G1 and specific uptake in xenografted parathyroid was obtained in a mouse model both with ^{68}Ga and ^{18}F label (17). Suitable positron emitters for very rapid targeting are carbon-11 and iodine-122, which have not yet been used in experimental studies. Carbon-11 can be coupled to proteins (19); for iodine-122 no applications have yet been reported but there are good possibilities for radioiodination of proteins (20).

Long-lived isotopes—Experimental studies. Cobalt-55 is also a possible positron emitter for antibody labeling; for convenience, cobalt-57 has been used in experiments. In a nude mouse model with xenografted colon carcinoma 17-1A MAb labeled with ^{57}Co by use of different chelates some differential tumor uptakes were observed at 24 h: EDTA 3.4, CDTA 11.6, DTPA 5.6, and CDTPA 6.4% ID/g tumor (21). Our group studied several MAbs labeled with ^{57}Co (22) using CDPTA chelation; an approximate uptake of 12% ID/g tumor was obtained using OC 125 MAb in a nude mouse bearing ovarian carcinoma xenograft. Copper-64 is also an interesting label. High specific uptakes have been demonstrated in a hamster model for colorectal carcinoma using ^{64}Cu-labeled intact MAb and F(ab')$_2$ fragments with bifunctional chelate Br-benzyl-TETA; at 24 h the uptake was 10.1% ID/g tumor (23). In another study ^{67}Cu benzyl-TETA-Lym-1 was localized at 27 h up to 14.3% ID/g tumor in a mouse (24). Zirconium-89 has also been evaluated (25). Bromine-76 can be used for protein labeling in the same way as ^{77}Br (26). However, ^{124}I has been the most widely used positron emitter for antibody PET, in spite of its limited availability and some difficulties with antibody labeling (27–29). In nude mice bearing Hep2 tumor xenografts studied with ^{124}I labeled anti-placental alkaline phosphatase (PLAP), 4.3% ID/g tumor at 48 h was obtained (30). Nude rats have recently been used for animal PET scanning studies: the first model was a neuroblastoma with a highly specific GD$_2$-ganglioside MAb 3 F 8 (31). Also uterine and ovarian cancer xenografts in rats have been studied with high resolution PET (32–33), and some of these data will be discussed later on. One reason for ^{124}I PET may be quantification for radioimmunotherapy (27, 28, 34), and it has been demonstrated both by phantom measurements (27) and by animal experiments (34) that ^{124}I PET has this potential. In a recent study, a monoclonal antibody, recognizing the external domain of the human c-erb B2 proto-oncogene product, was labeled with ^{124}I, and an uptake up to 12% ID/g human breast carcinoma xenograft in athymic mice was measured (35). This opens new aspects in radioimmunoimaging, since it might be possible to quantitate the overexpression of this oncogene product in breast cancer patients. It is still unknown, however, whether or not this can be applied in clinical work (36).

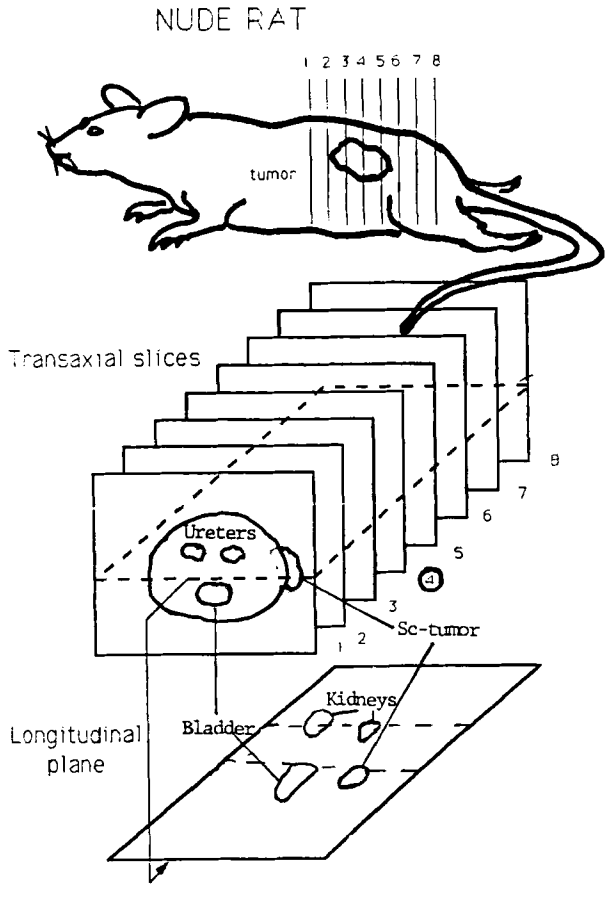
Clinical studies. Clinical PET studies (37, 38), have demonstrated that ^{124}I labeled MAbs can be used for predicting the absorbed radiation dose, obtained by a subsequent therapeutic activity (e.g. with ^{131}I-labeled MAb). Larson et al. (37) have also shown that these dosimetry calculations are consistent with measurements made by different PET scanners, which was demonstrated in a child with neuroblastoma using 3F8 MAb. Wilson et al. (38) studied 7 breast cancer patients with HMFG1 MAb and 2 patients with non-specific MAb: uptake was up to 7.7×10^{-3}% ID/g tumor. The highest uptake in the neuroblastoma study was 59×10^{-3}% ID/g tumor (37).

Our own experience

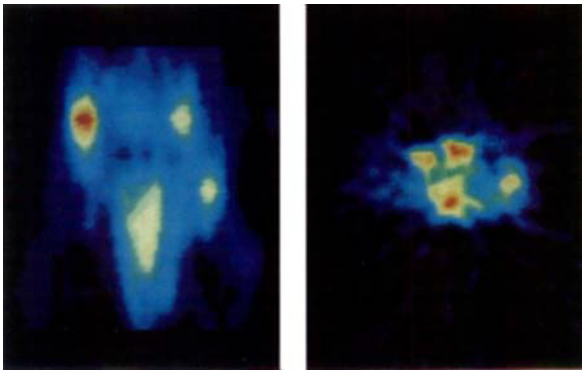
Radioantibodies and animal models. Female nu/nu rats (Taconic Farms, NY, NY, USA) and balb/c nude mice (Memorial Sloan-Kettering Cancer Center (MSKCC), NY, NY, USA) were used for animal models. For PET studies, altogether 24 nude rats were used. Human ovarian cancer cell lines SK-OV-3 and SK-OV-7 (33) were used as target cell lines and SK-Mel-30 cells as xenografted in animals were kept as controls. Murine monoclonal antibodies (MAbs) MX35 and MH99 (39, 40) were produced and characterized at MSKCC. MX35 is an IgG$_1$ subclass antibody which recognizes an antigen expressed in 90% of human epithelial ovarian cancers and, in lower concentrations, in several normal tissues as lung, fallopian tube, pancreas, endocervix, endometrial glands, and thymus. MH99 was developed following immunization with the SK-UT-1 (MSKCC) uterine cancer cell line. It is an IgG$_1$ subclass antibody, detecting 38 kD glycoprotein related to the 17.1 A antigen. The antigen is expressed an all normal epithelia, as well as in virtually all human epithelial ovarian cancers. Radiolabeling of MH99 and MX35 with ^{131}I and ^{124}I was performed using the chloramine-T method as described elsewhere (33). Labeling efficiency was determined using trichloroacetic acid precipitation assay (33) and the immunoreactivity was calculated using an absorption assay on cell line SK-OV 7.

Instrumentation. PET scanning was performed at Massachusetts General Hospital in Boston, using high resolution PET scanner for animals (41). The spatial resolution (FWHM) of this 1-ring system camera was 4.5 mm. Imaging was performed at 0–6 days after i.v. injections. In two animals also dynamical data were collected for 2 h.

Imaging findings and tissue data. Specific localization of ^{124}I-labeled monoclonal antibodies MX35 and MH99 was



a)



b) c)

Fig. 1. Schematic illustration of a rat with subcutaneous ovarian cancer xenograft and PET images 5 days after i.v. injection of ^{124}I-MX35. a) (upper panel) demonstrates the possibility to reconstruct a longitudinal slice from transaxial slices. b) (left lower). A transaxial slice (thickness 5 mm) is presented where rat ureters (∅ 1–2 mm), urinary bladder and subcutaneous 2 gr tumor (SK-OV-3) are seen. c) (right lower). In the longitudinal plane (thickness 5 mm) pelvices of rat kidneys, bladder and the same subcutaneous tumor are visualized.

demonstrated by PET scanning. With ^{124}I-labeled monoclonal antibodies the ROIs on the PET images were as follows: ^{124}I-MX35 6.4 ± 1.2 (SK-OV-3), 6.8 ± 1.7 (SK-OV-7), and 1.1 ± 0.1 (SK-Mel-30); ^{124}I-MH99 4.8 ± 1.0 (SK-OV-3), and 4.4 ± 0.8 (SK-OV-7). These scannings were performed 5 days after injection in rats bearing subcutaneous xenografts. Fig. 1a demonstrates the possibility to reconstruct from transaxial PET slices a longitudinal slice. In Fig. 1b a transaxial slice (thickness 5 mm) is presented where rat ureters (∅ 1–2 mm), urinary bladder, and subcutaneous 2 g tumor (SK-OV-3) are seen. In the longitudinal plane (thickness 5 mm) in Fig. 1c pelvices of rat kidneys, bladder and the same subcutaneous tumor are visualized. Corresponding tumor-to-blood ratios in tissues on the 6th day were as follows: ^{124}I-MX35 3.4 (SK-OV-3), 3.6 (SK-OV-7), and 0.9 (SK-Mel-30); ^{124}I-MH99 2.6 (SK-OV-3), and 2.8 (SK-OV-7). In tissue sampling the tumor-to-blood ratios increased as function of time up to 6 days in these nude rats. The maximum uptake at 6 days was 2.2% ID/g tumor in a rat model (using ^{124}I-MX35), whereas it was 12.3% ID/g tumor in a mouse model (using ^{131}I-MX35). A dynamic study revealed that the tumor-to-blood ratio was >1:1 at 54 min in an intraperitoneal xenograft model as presented in Fig. 2. A partial volume effect may interfere with interpretation of data, since the blood curve was drawn using rat abdominal aorta, and its diameter is smaller in size than one pixel in a PET image. In PET images the tumors were clearly visualized, including intraperitoneal tumors corresponding to the lesions seen in MRI or CT images.

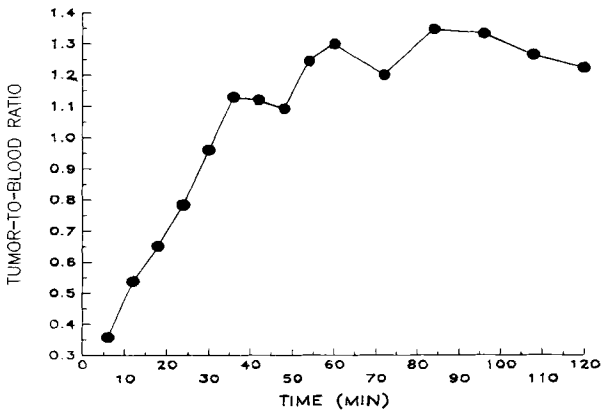


Fig. 2. Dynamic study with PET using ^{124}I-MX35 by collecting 10 × 6 min and 5 × 12 min frames in a nude rat bearing intraperitoneal ovarian cancer xenograft. The tumor-to-blood ratio was calculated as ROI ratios at the tumor site and at abdominal aorta (1 pixel).

Discussion and Conclusions

In experiments on nude rats it was clearly demonstrated that PET could accurately locate tumors in 3 dimensions (32). The images can be used for quantitative interpretation, and the resolution with this PET camera was <5 mm. More accurate experimental images in animal studies have been described using pinhole SPECT (42)

where a resolution of 2.5 mm was achiever in rats, but a quantitative interpretation of the images is probably not possible. In the presently reported nude rat study also organs, such as liver, spleen, and kidney pelvices were clearly visualized. Intraperitoneal tumors were visualized as good as in the corresponding MRI images. The dynamic study (Fig. 2) showed that the antibody accumulation is a quite fast process; this is probably mainly depending on the second fast exponential component of antibody kinetics (in 2–3 exponential models) (43, 44). The weakness in this study was quantification of the blood component, as it was impossible to define a region of interest for the rat abdominal aorta without including adjacent structures because of the small diameter of the vessels. The blood volume is also too small for collection of adequate samples. Anyhow, PET opens new perspectives of 3-D dynamic imaging of in vivo antibody kinetics.

Clinical PET studies (37, 38) have demonstrated the value of ^{124}I PET as a guidance for subsequent radioimmunotherapy with radioiodinated antibodies, allowing in vivo estimation of absorbed radiation doses. An alternative or a supplement to PET for assessment of absorbed radiation doses in radioimmunotherapy could be direct measurements using a beta-probe. The antibodies MX35 and MH99, labeled with ^{124}I are suitable for targeting studies, as shown by PET studies. Some animals have also been studied for positron labeled antibody targeting using a beta-probe (45, 46). The advantage of the beta-probe is its close vicinity to tissue containing the β-emitting nuclide.

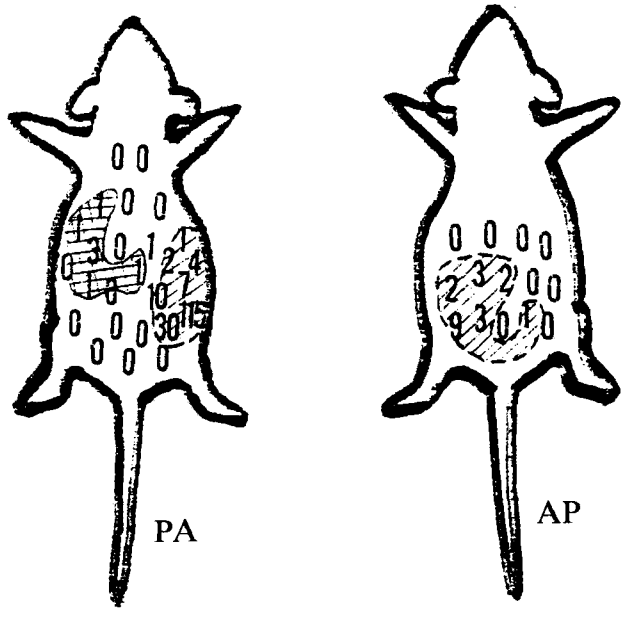


Fig. 3. A beta-probe study of a nude mouse with intraperitoneal and subcutaneous SK-OV-7 ovarian cancer after injecting ^{131}I-MX35. The probe counts (10 s/point) were measured 2 days after i.v. injection and were in good agreement with tumor sites (shaded areas).

Even though good results have been reported also with gamma probes (47–50), the influence of distant background adtivity remains a problem. In an intraperitoneal mouse tumor model radionuclide measurements using the β-probe were in concordance with gamma camera imaging and the radioantibody localization was similar to cancer tissue distribution confirmed by surgery (Fig. 3).

This beta probe (51, 52) can also be constructed for intraluminal or endoscopic surgical purposes opening up a wide scale of applications e.g. probe studies inside a bowel (colorectal carcinoma) and during less radical operations, such as laparoscopies. Fortunately, positron emission detection with X-Y coordinates for microdosimetric purposes is also possible using the beta camera (53).

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