Arronax and Nuclear Medicine
Innovations in molecular imaging and targeted radionuclide therapy

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Radioactivity?


154

MÉTHOD

THO-RA

EMBELLISSANTE PARCE QUE

4°

DENTIFRICE
THO-RADIA

A BASE DE SELS DE THORIUM

FORMULE
du Docteur Alfred CURIE

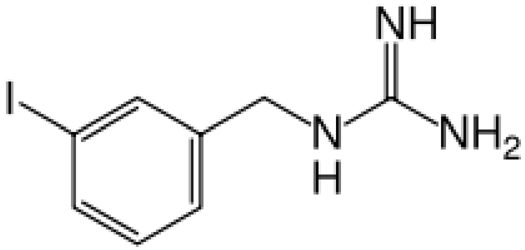
Le grand tube : 6 francs

Astringent et bactéricide, il stérilise la cavité buccale, évite et combat les gingivites, prévient la carie et les pyorrhées alvéolaires. Il assainit les dents, laisse dans la bouche une délicieuse impression de fraîcheur, conserve l'éclat, la blancheur et l'intégrité de la dentition.

Pas de joli sourire sans de jolies dents

CHEZ LES PHARMACIENS EXCLUSIVEMENT

A Nuclear Medicine Pioneer



William H. Beierwaltes (1917 – 2005), Nuclear Medicine pioneer with the use of iodine-131 invented meta-iodo-benzyl-guanidine (MIBG) and was the first to administer antibodies (polyclonal) labeled with iodine-131 to a melanoma patient in 1951.

Srivastava SC, Buraggi GL. NATO Advanced Study Institute on "radiolabeled monoclonal antibodies for imaging and therapy--potential, problems, and prospects". Int J Biol Markers. 1987;2:43-8.

Nuclear Medicine

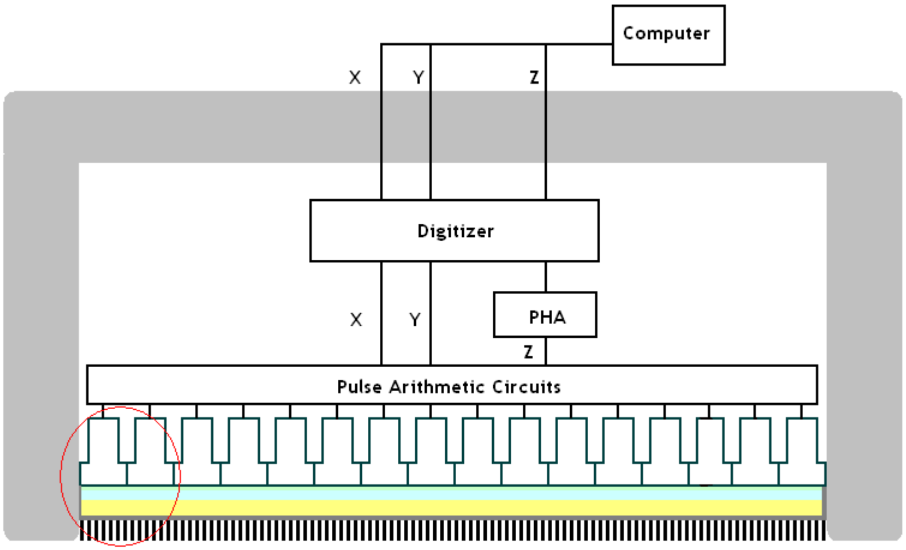
Use of radioactive drugs (radiopharmaceuticals) to:

- Visualize lesions or measure physiological functions
  - by single photon imaging with gamma emitting radionuclides
    - scintigraphy
    - whole bod scans
    - Single Photon Emission Tomography (SPET or SPECT)
  - by Positron Emission Tomography (PET) with positron emitting radionuclides
- Kill cancer cells with electron or alpha-particle emitting radionuclides
  - by brachytherapy
  - by targeted radionuclide therapy

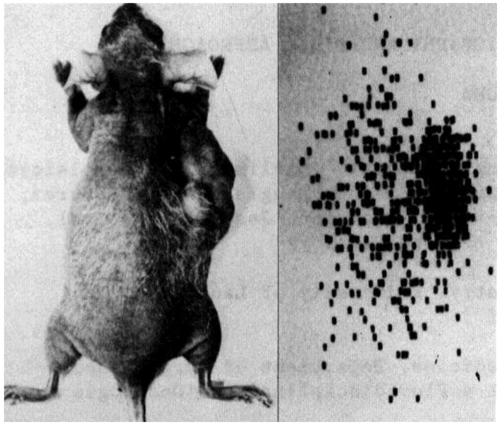
Nuclear Medicine deals with all medical domains, particularly oncology, neurology and cardiology. This presentation will be limited to Nuclear Oncology

SINGLE PHOTON IMAGING

Single photon imaging



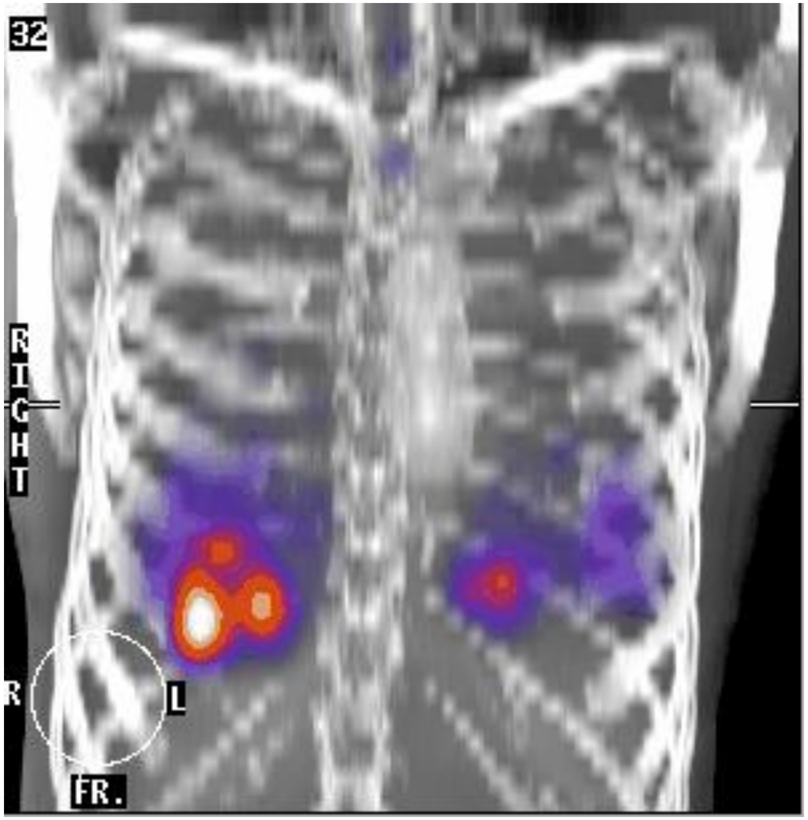
Anger camera



Gamma imaging: planar imaging, whole body imaging and single photon emission tomography (SPECT)

Radionuclides: iodine-131, iodine-123, technetium-99m, indium-111…

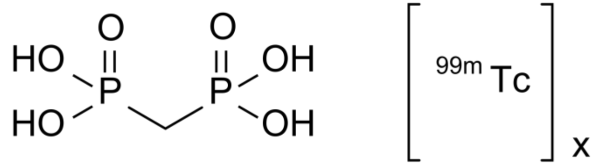
Specific delivery of radionuclides to tumors

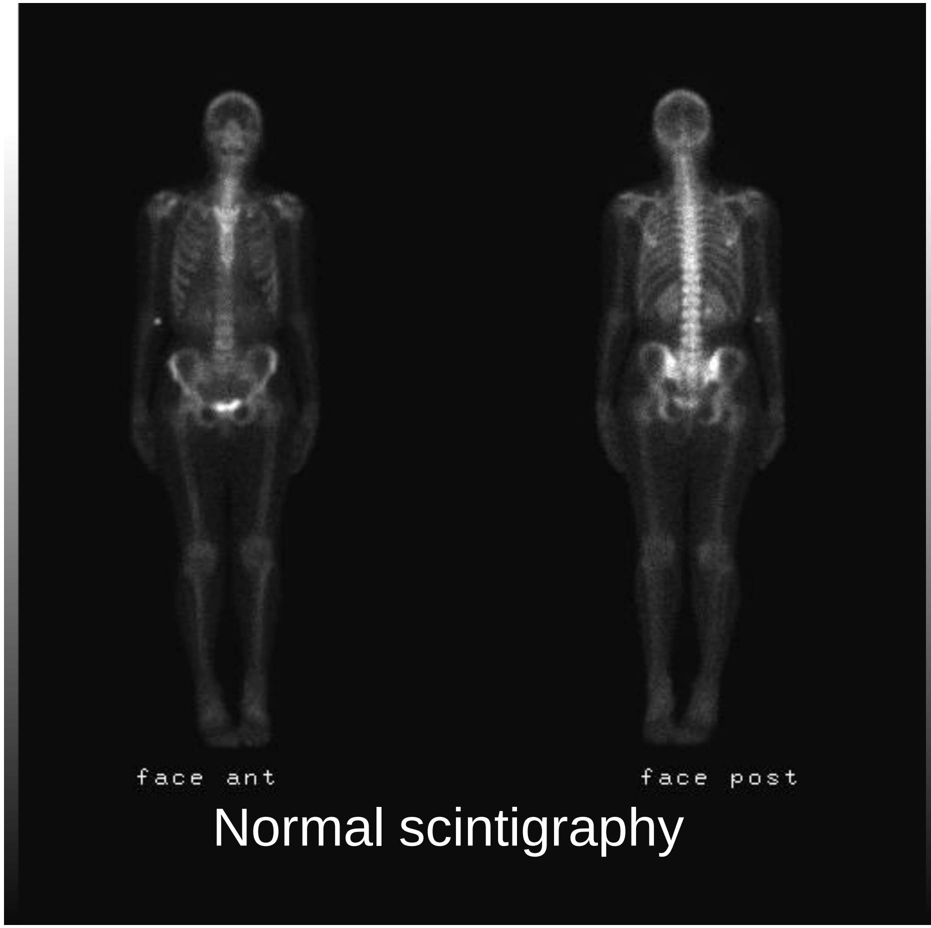


Lung metastases from thyroid carcinoma

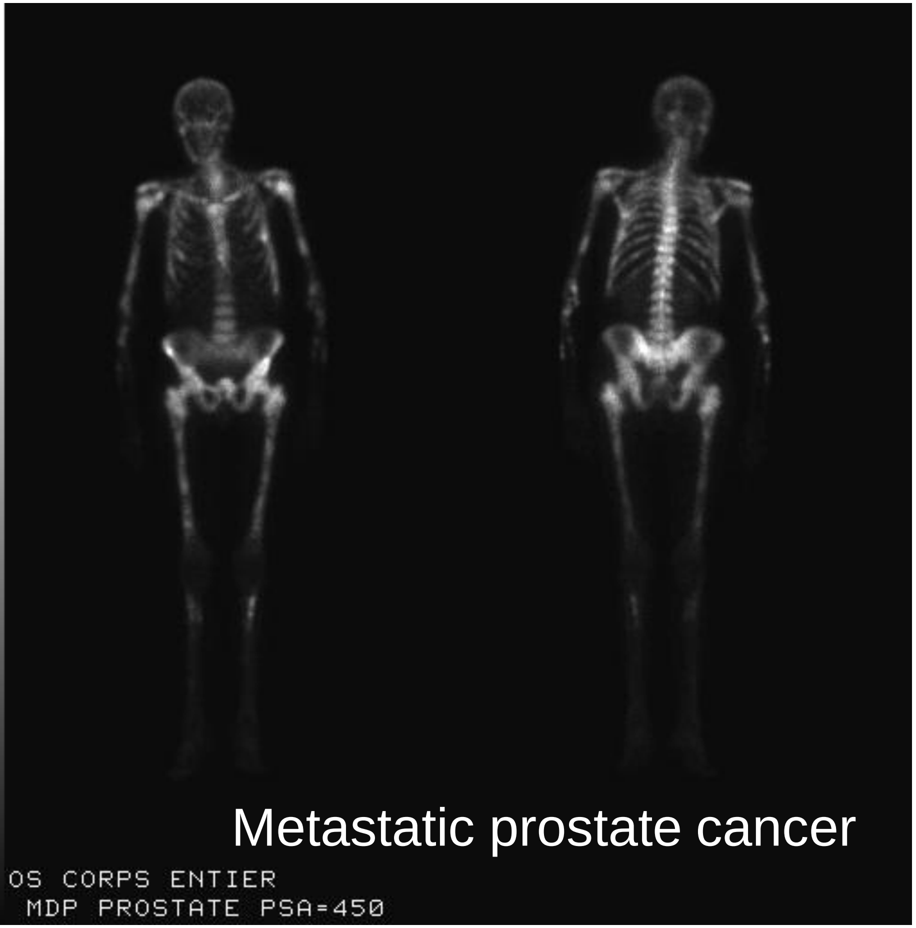
Images: courtesy of Dr Glenn Flux, The Royal Marsden, London, UK

Bone scintigraphy



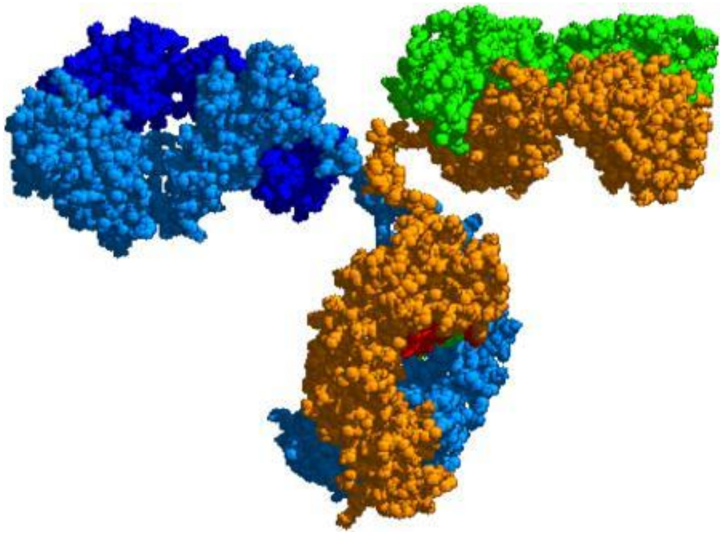


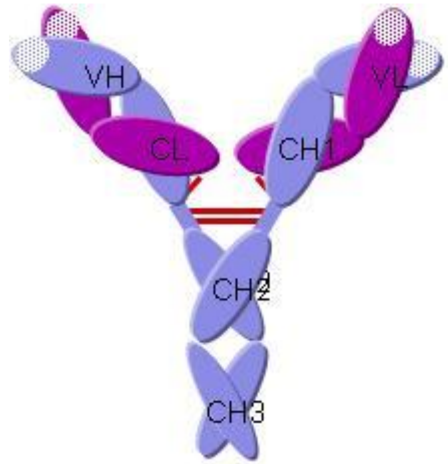
Normal scintigraphy

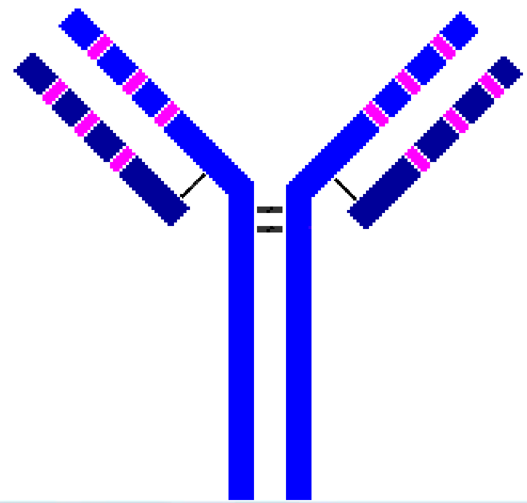


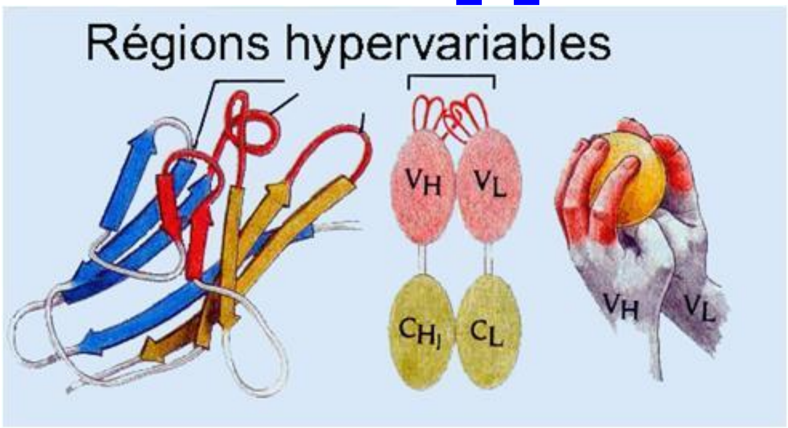
Metastatic prostate cancer

Antibodies



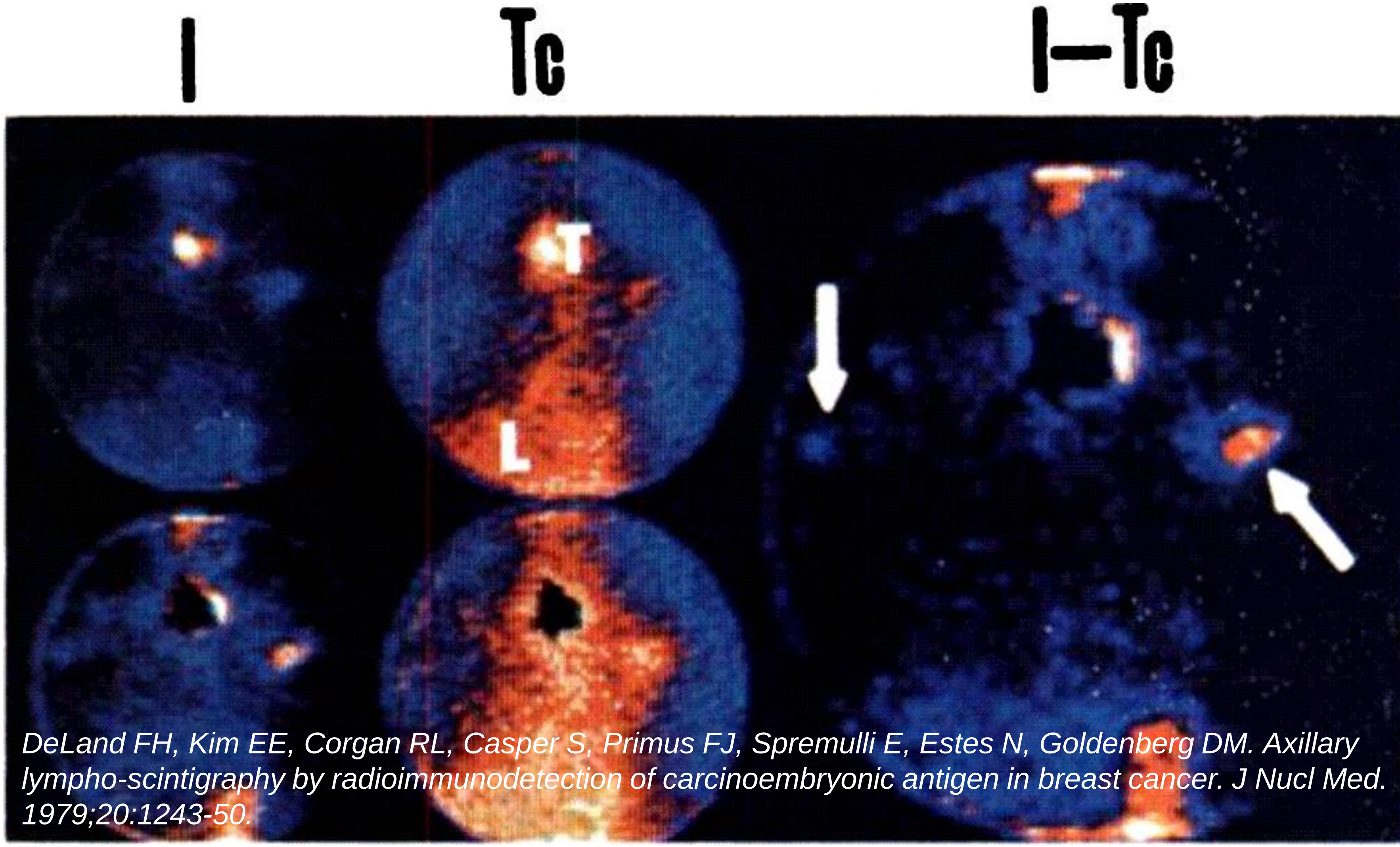






Hunter WM, Greenwood FC. Preparation of iodine-131 labelled human growth hormone of high specific activity. Nature. 1962; 194: 495-6.

Immunoscintigraphy with an iodine-131-labeled anti-CEA antibody



DeLand FH, Kim EE, Corgan RL, Casper S, Primus FJ, Spremulli E, Estes N, Goldenberg DM. Axillary lympho-scintigraphy by radioimmunodetection of carcinoembryonic antigen in breast cancer. J Nucl Med. 1979;20:1243-50.

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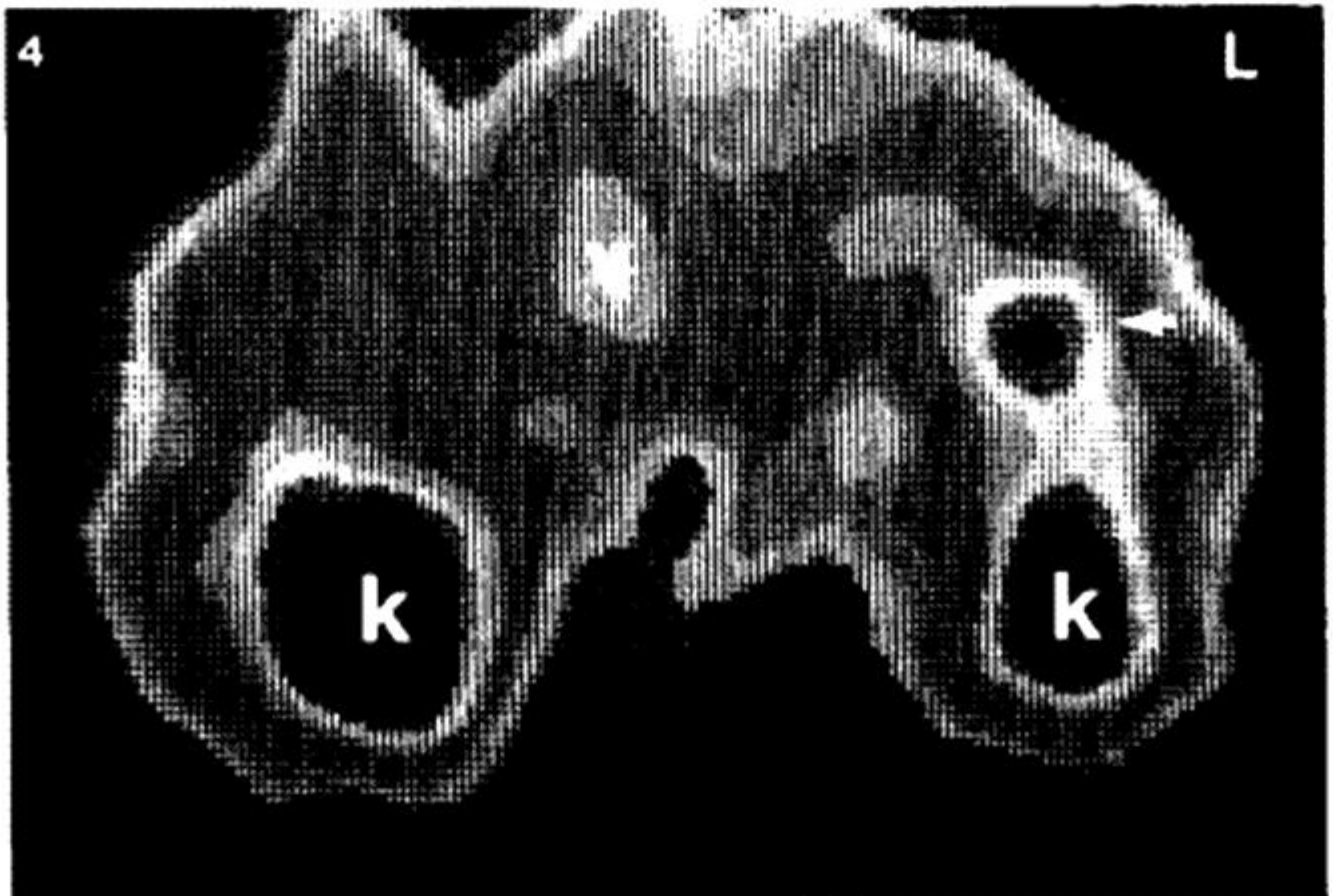
Immunoscintigraphy with an iodine-123-labeled anti-CEA F(ab')$_2$ fragment



Delaloye B, Bischof-Delaloye A, Buchegger F, von Fliedner V, Grob JP, Volant JC, Pettavel J, Mach JP. Detection of colorectal carcinoma by emission-computerized tomography after injection of ^{123}I-labeled Fab or F(ab')$_2$ fragments from monoclonal anti-carcinoembryonic antigen antibodies. J Clin Invest. 1986;77:301-11.

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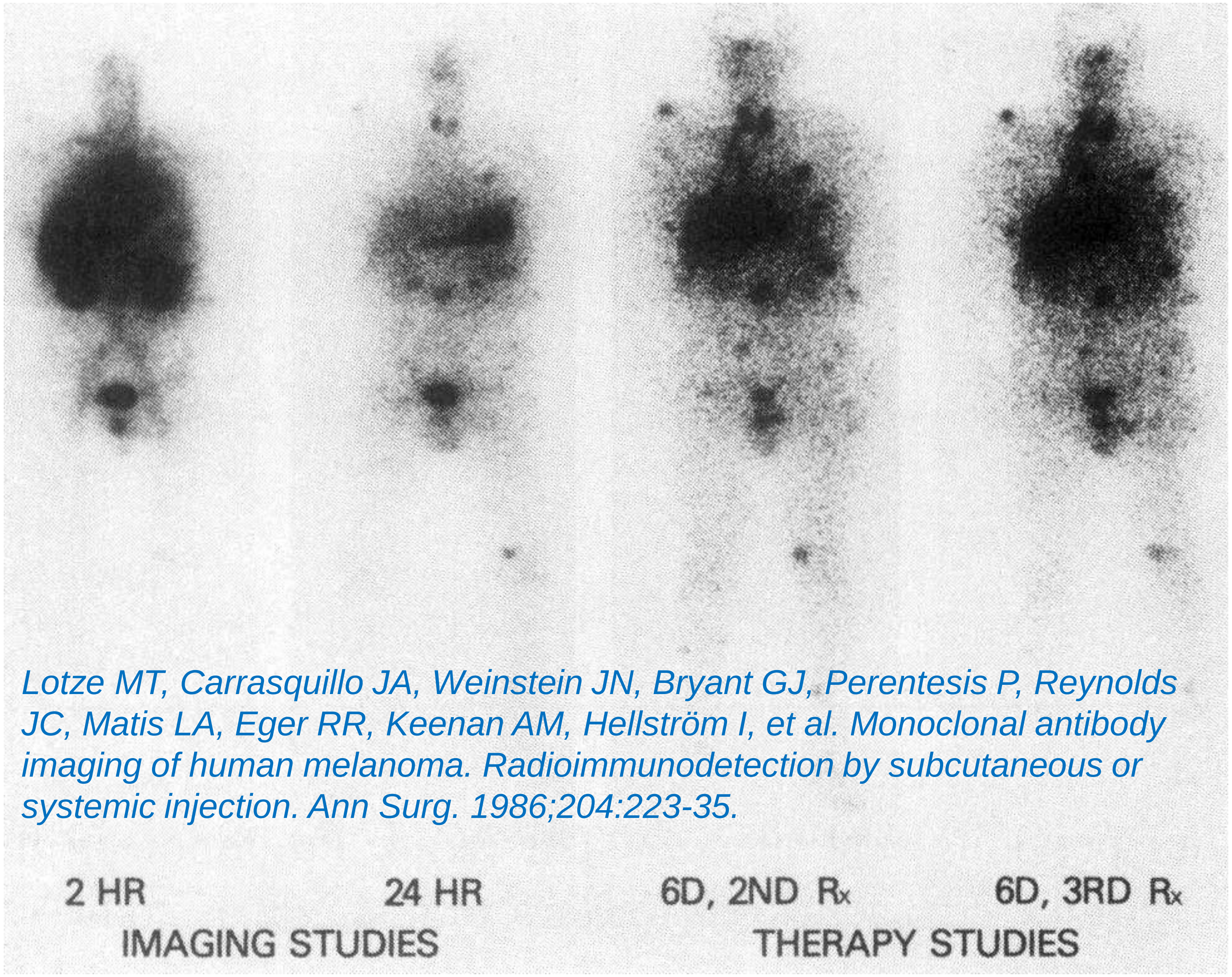
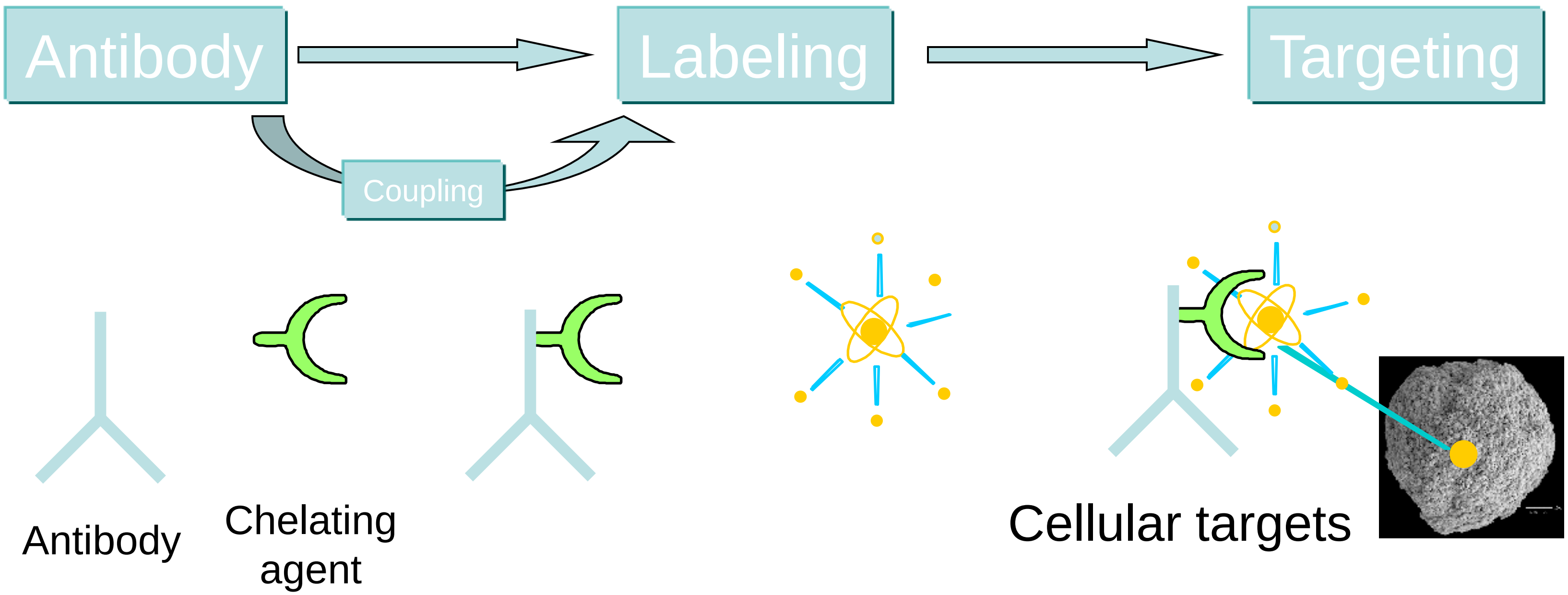
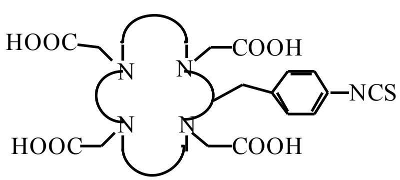
Melanoma imaging with an anti-p97 Fab labeled with iodine-131



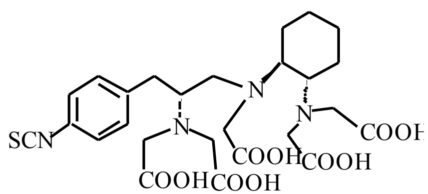
Lotze MT, Carrasquillo JA, Weinstein JN, Bryant GJ, Perentesis P, Reynolds JC, Matis LA, Eger RR, Keenan AM, Hellström I, et al. Monoclonal antibody imaging of human melanoma. Radioimmunodetection by subcutaneous or systemic injection. Ann Surg. 1986;204:223-35.

Bifunctional chelating agents

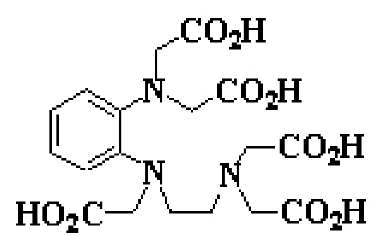




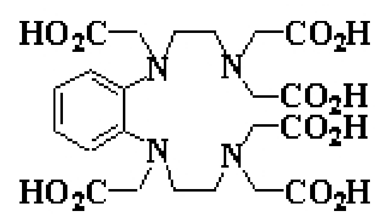
DOTA



CHX-DTPA



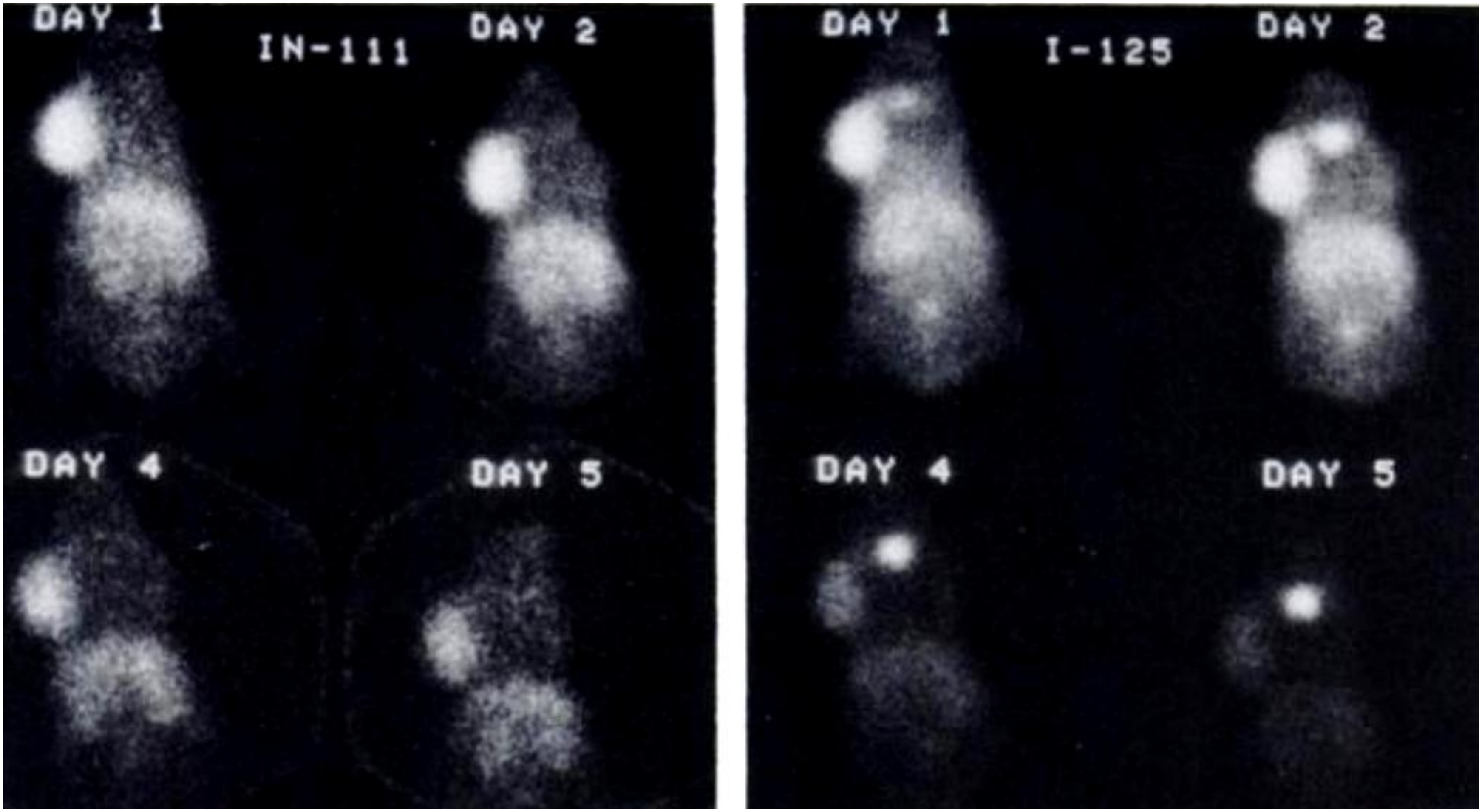
Ph-DTPA



Ph-TTHA

Subramanian R, Meares CF. Bifunctional chelating agents for radiometal-labeled monoclonal antibodies. Cancer Treat Res. 1990;51:183-99.

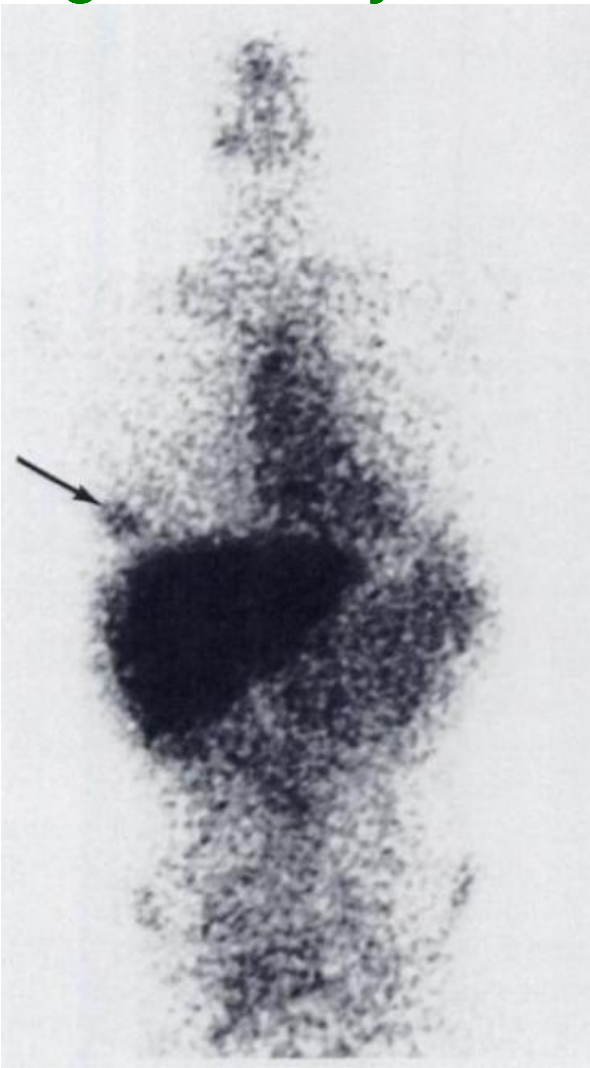
Antibody internalization and catabolism of labeled antibodies



Khaw BA, Cooney J, Edgington T, Strauss HW. Differences in experimental tumor localization of dual-labeled monoclonal antibody. J Nucl Med. 1986;27:1293-9.

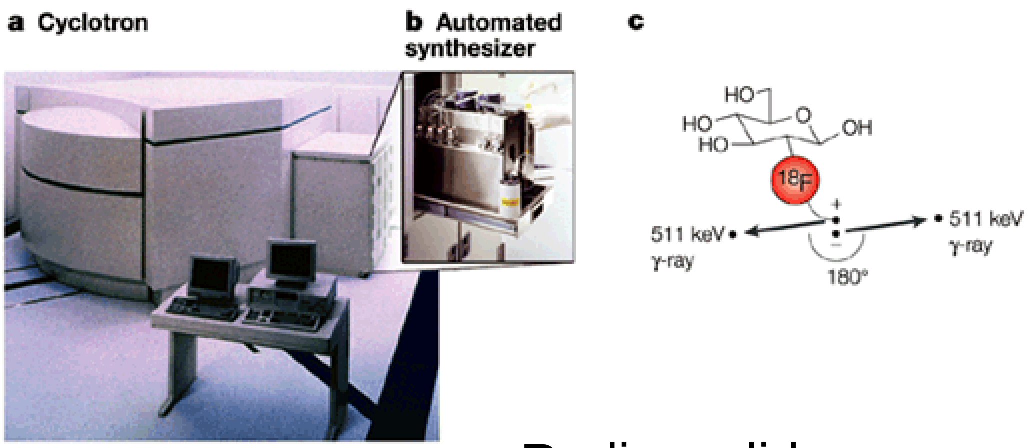
Melanoma imaging with an indium-111-labeled internalizing antibody

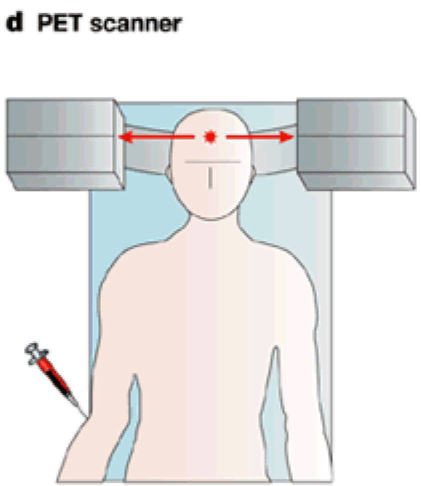
Murray JL, Rosenblum MG, Sobol RE, Bartholomew RM, Plager CE, Haynie TP, Jahns MF, Glenn HJ, Lamki L, Benjamin RS, et al. Radioimmunoimaging in malignant melanoma with ^{111}In-labeled monoclonal antibody 96.5. Cancer Res. 1985;45:2376-81.



POSITRON EMISSION TOMOGRAPHY (PET)

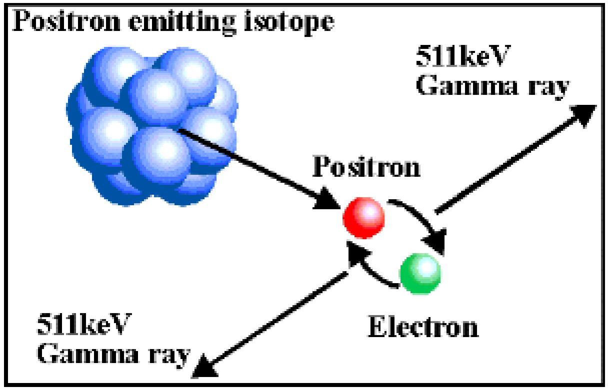
Principle of PET-Scan

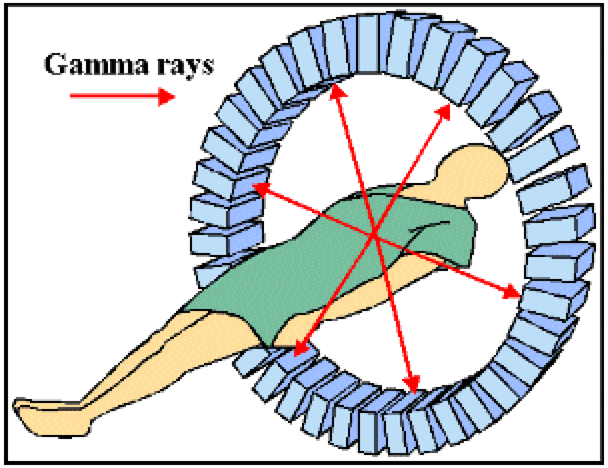




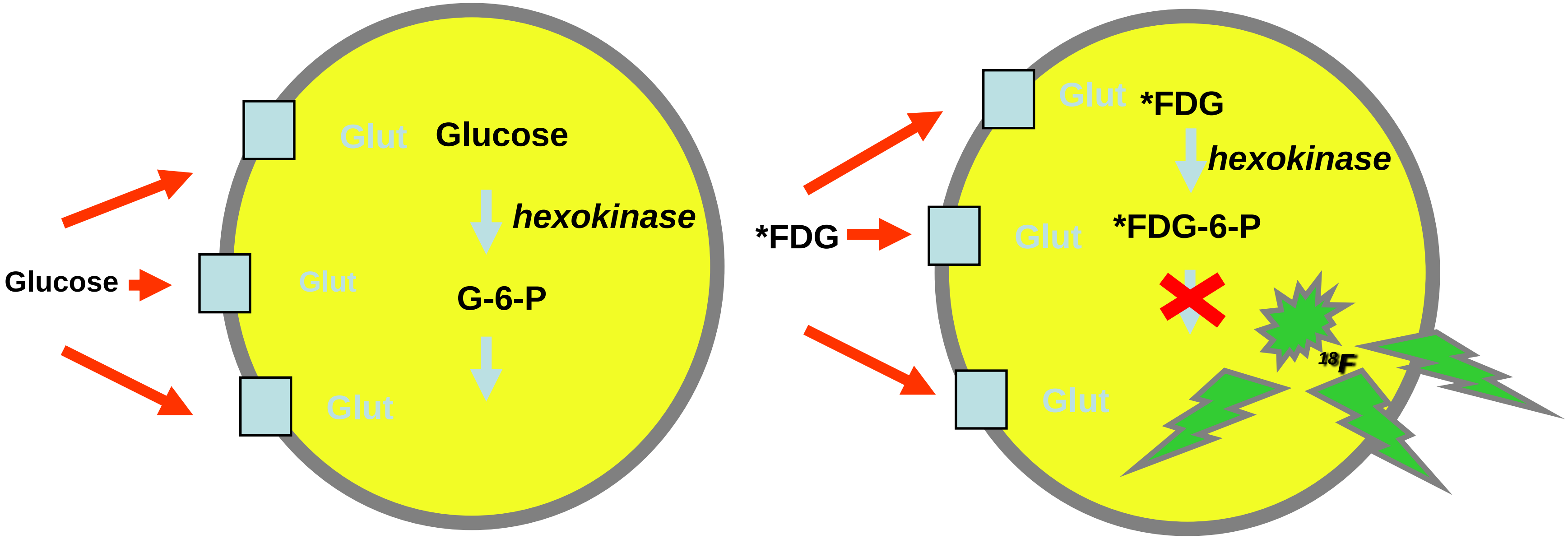
Radionuclides:

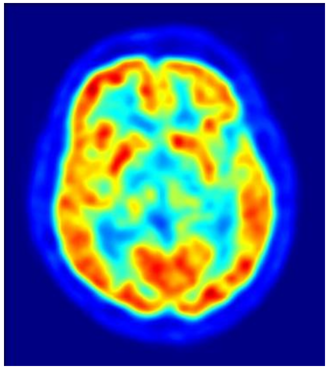
- carbon-11
- fluorine-18
- gallium-68
- copper-64
- iodine-124
- zirconium-89





FDG: imaging of GLUT's

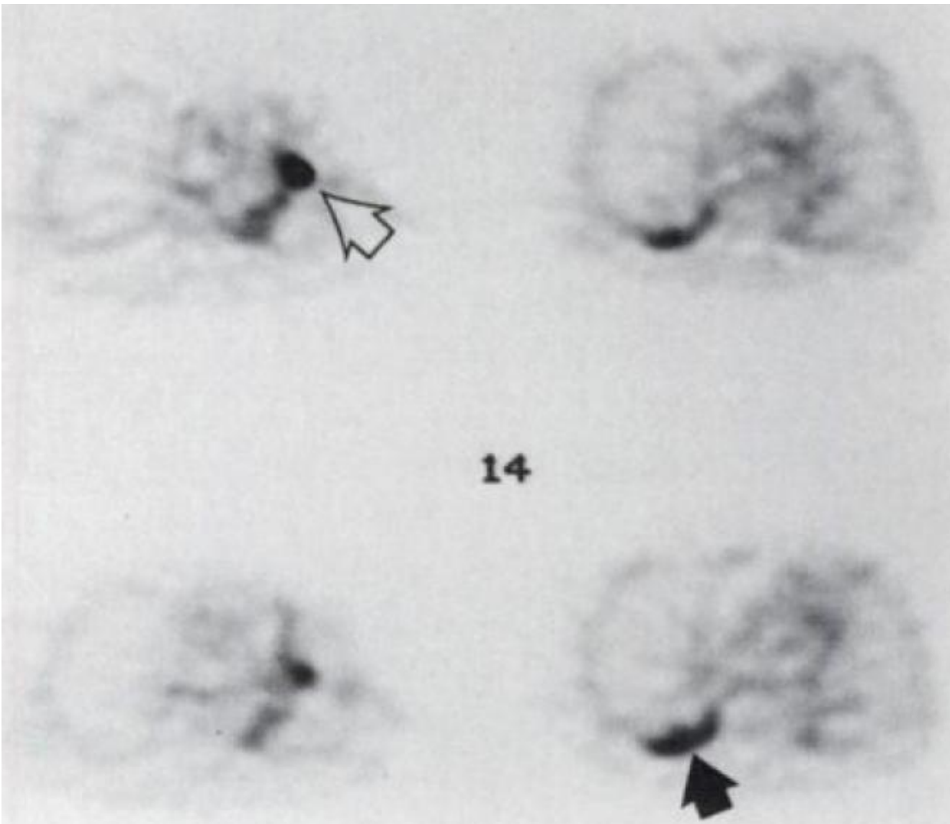


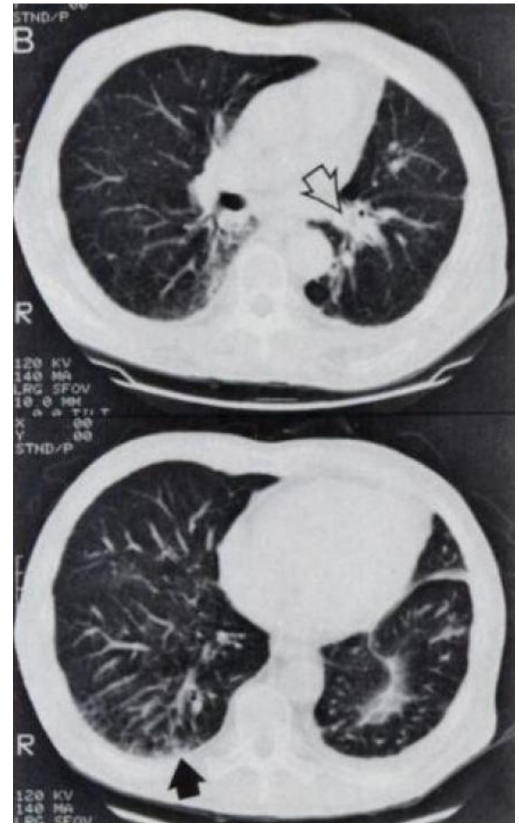


Metabolically active cells:

- brain cells
- heart muscle cells (decreased at rest)
- tumor cells
- inflammation cells

PET imaging with ^{18}F-FDG



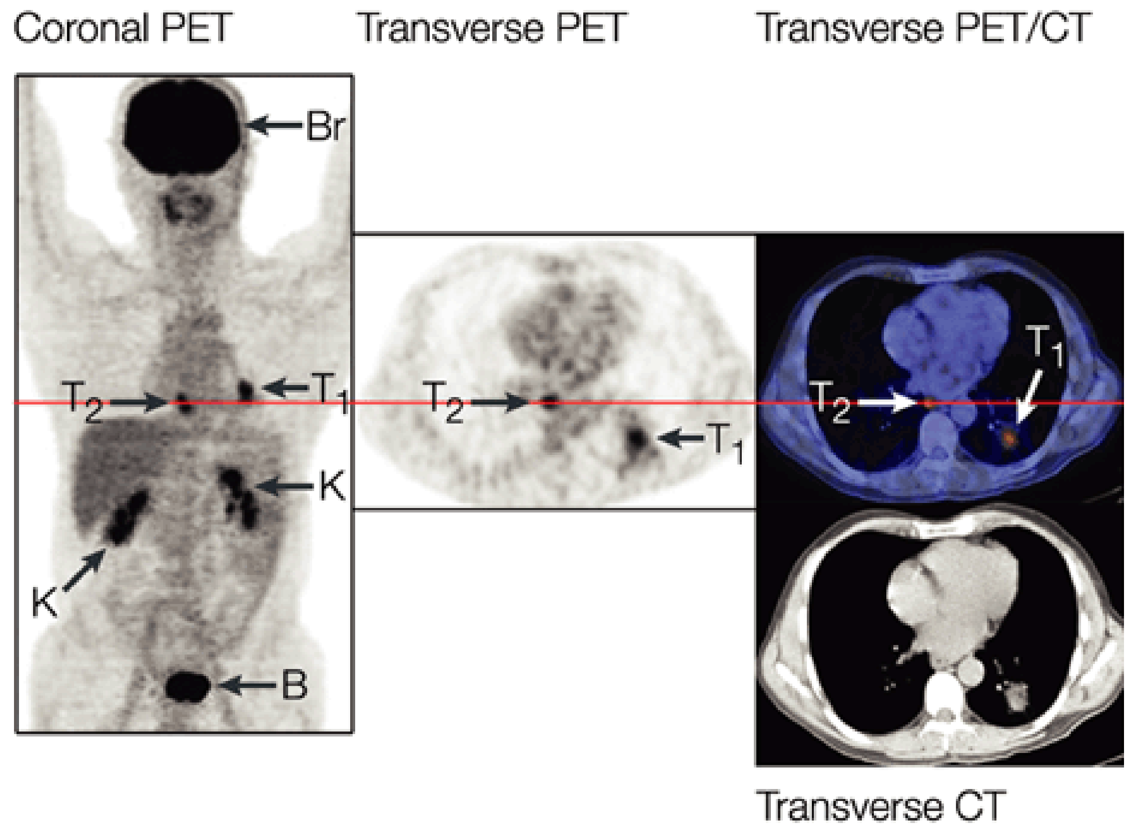


Yonekura Y, Benua RS, Brill AB, Som P, Yeh SD, Kemeny NE, Fowler JS, MacGregor RR, Stamm R, Christman DR, Wolf AP. Increased accumulation of 2-deoxy-2-[18F]Fluoro-D-glucose in liver metastases from colon carcinoma. J Nucl Med. 1982;23:1133-7.

Inoue T, Kim EE, Komaki R, Wong FC, Bassa P, Wong WH, Yang DJ, Endo K, Podoloff DA. Detecting recurrent or residual lung cancer with FDG-PET. J Nucl Med. 1995;36:788-93.

PET-Scan: image fusion

PET-CT



FDG-PET imaging of tumors

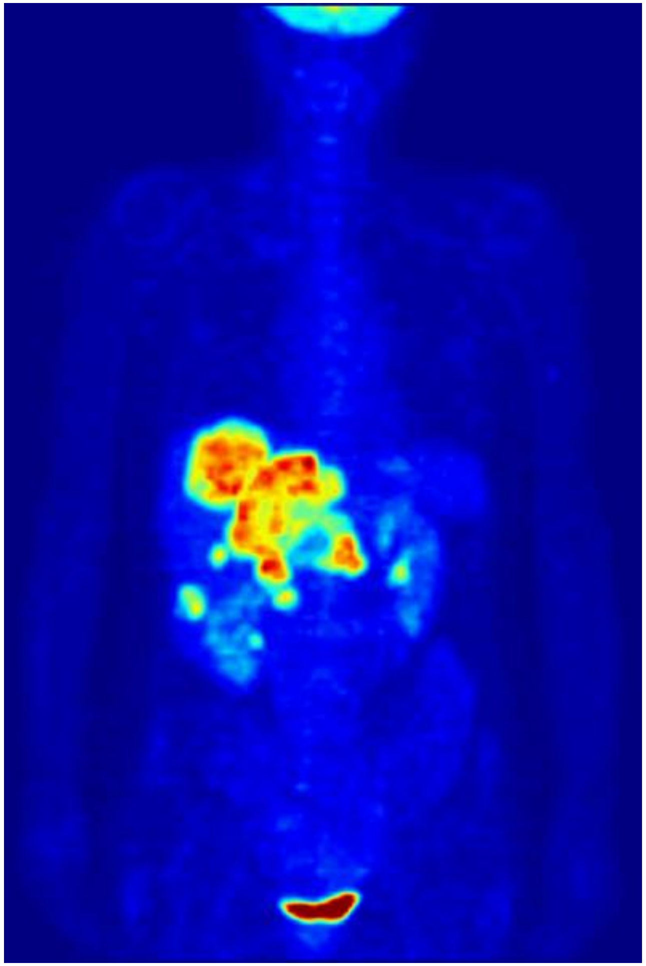
FDG-PET is higly effective at detecting a variety of tumors:

- lung cancer
- Hodgkin's lymphoma
- non-Hodgkin's lymphoma
- colorectal cancer
- breast cancer
- …

Not so good in:

- brain tumors
- prostate cancer

Inflammation as possible false positive



Ell PJ. The contribution of PET/CT to improved patient management. Br J Radiol. 2006;79:32-6. Review.

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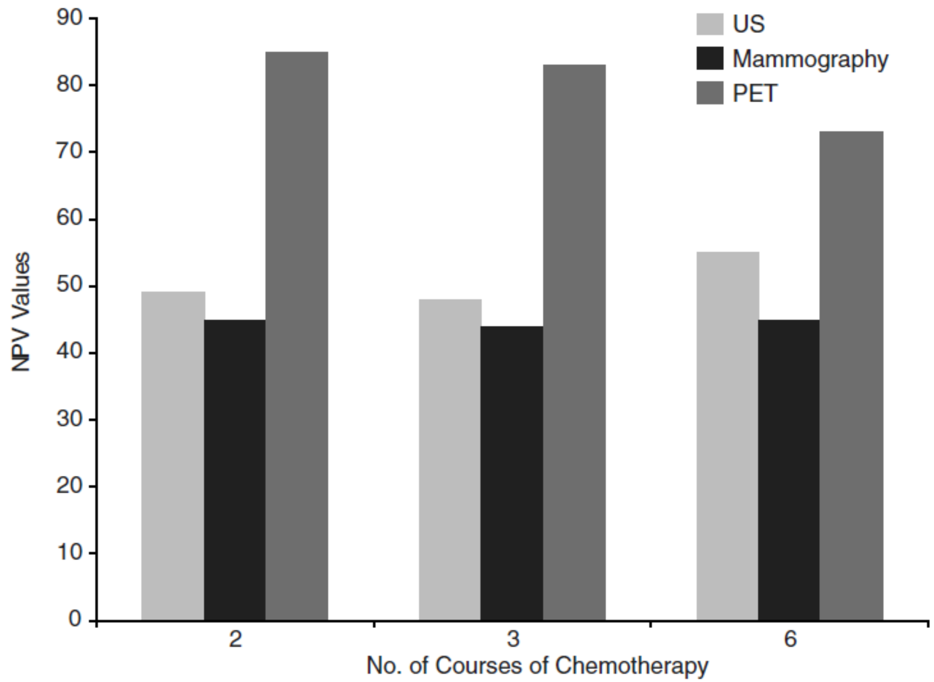
Response to chemotherapy in breast cancer

Table 3. Relative Changes of FDG Uptake (SUV_{max}) During Neoadjuvant Chemotherapy

	Baseline		After Course 1		After Course 2		After Course 3		After Course 6	
Group	No.	%	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)
Group A	10	100	−59.6	12.6	−78.7	11.4	−86.3	15.8	−90.2	21.7
Group B	25	100	−35.6	16.2	−47.9	18.7	−61.3	26.0	−74.8	30.7
Groups C + D	28	100	−16.3	20.9	−22.6	21.8	−35.6	21.4	−53.2	23.8

Abbreviations: FDG, [^{18}F]fluorodeoxyglucose; SUV_{max}, maximum standard uptake value; SD, standard deviation.



Rousseau C, Devillers A, Sagan C, Ferrer L, Bridji B, Campion L, Ricaud M, Bourbouloux E, Doutriaux I, Clouet M, Berton-Rigaud D, Bouriel C, Delecroix V, Garin E, Rouquette S, Resche I, Kerbrat P, Chatal JF, Campone M. Monitoring of early response to neoadjuvant chemotherapy in stage II and III breast cancer by [^{18}F]fluorodeoxyglucose positron emission tomography. J Clin Oncol. 2006;24:5366-72

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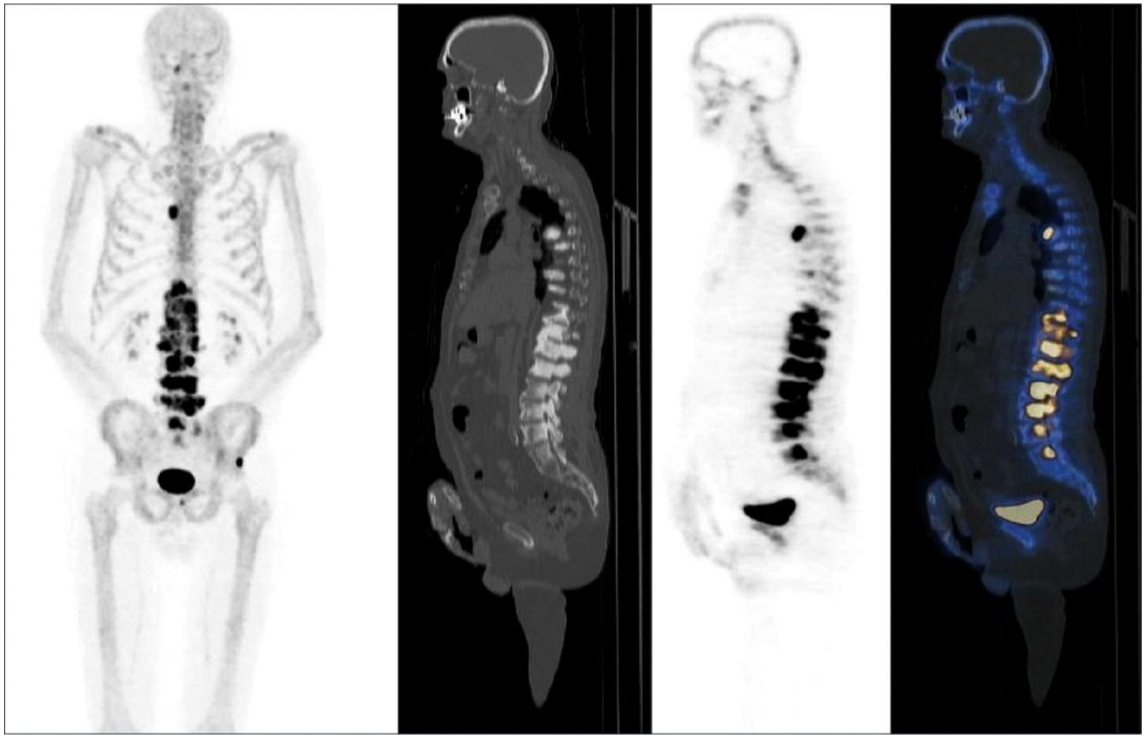
Bone scintigraphy with ^{18}F-fluoride

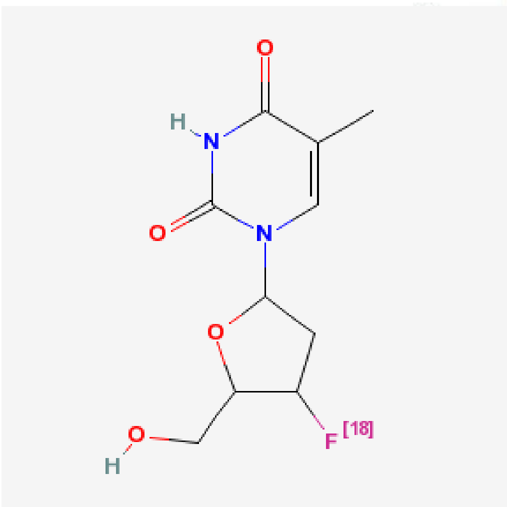


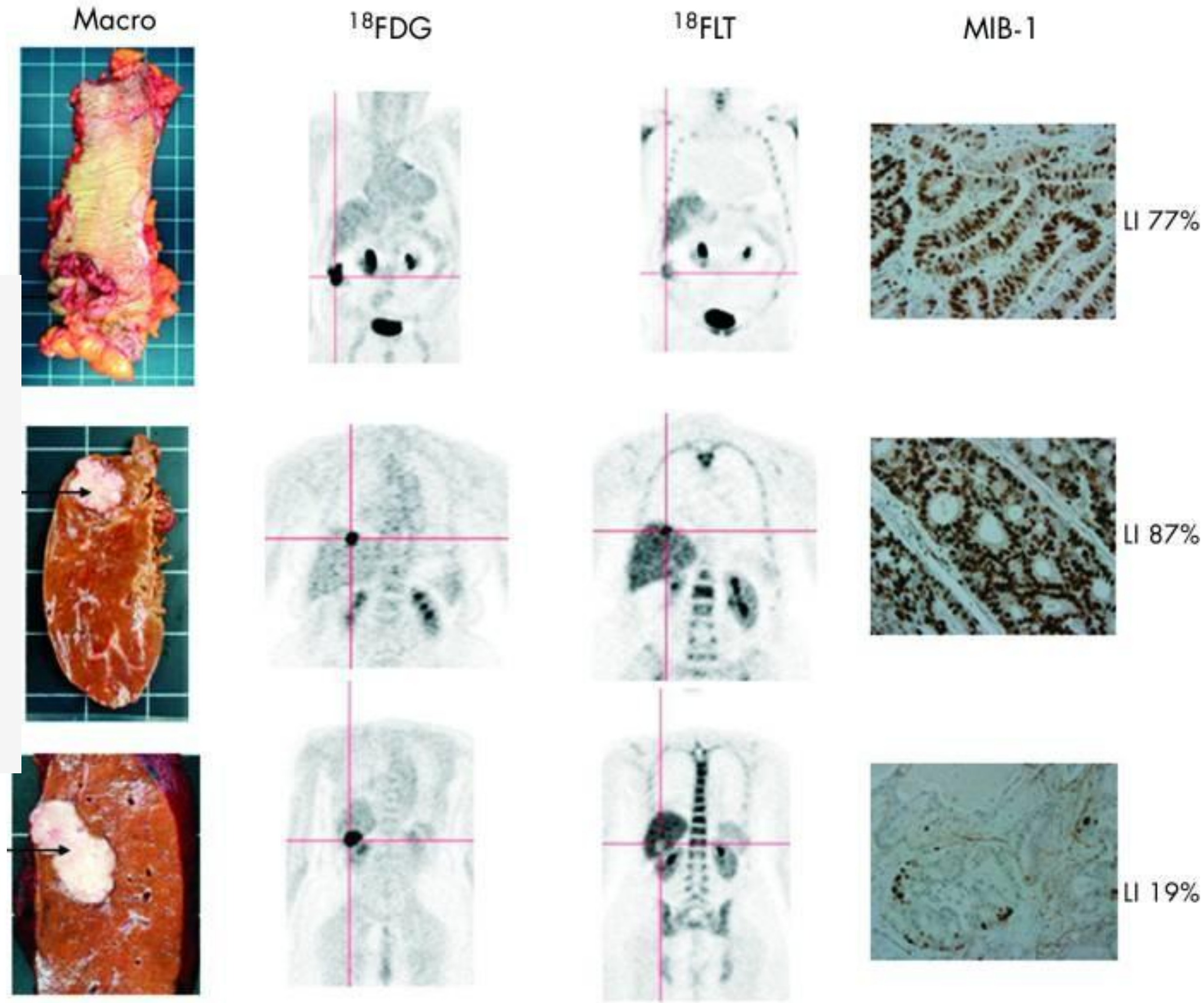
Imaging bone metastases of lung, prostate, breast cancers

Not tumor specific: marker of osteoblast metabolism

Groves AM, Win T, Haim SB, Ell PJ. Non-[^{18}F]FDG PET in clinical oncology. Lancet Oncol. 2007;8:822-30. Review.

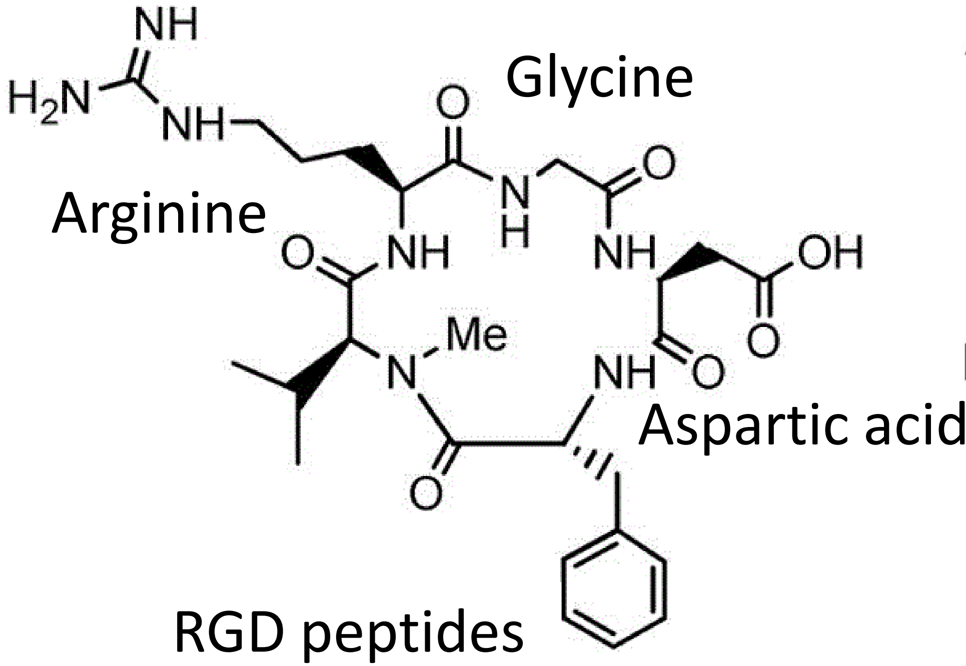
Imaging tumor proliferation with ^{18}F-FLT

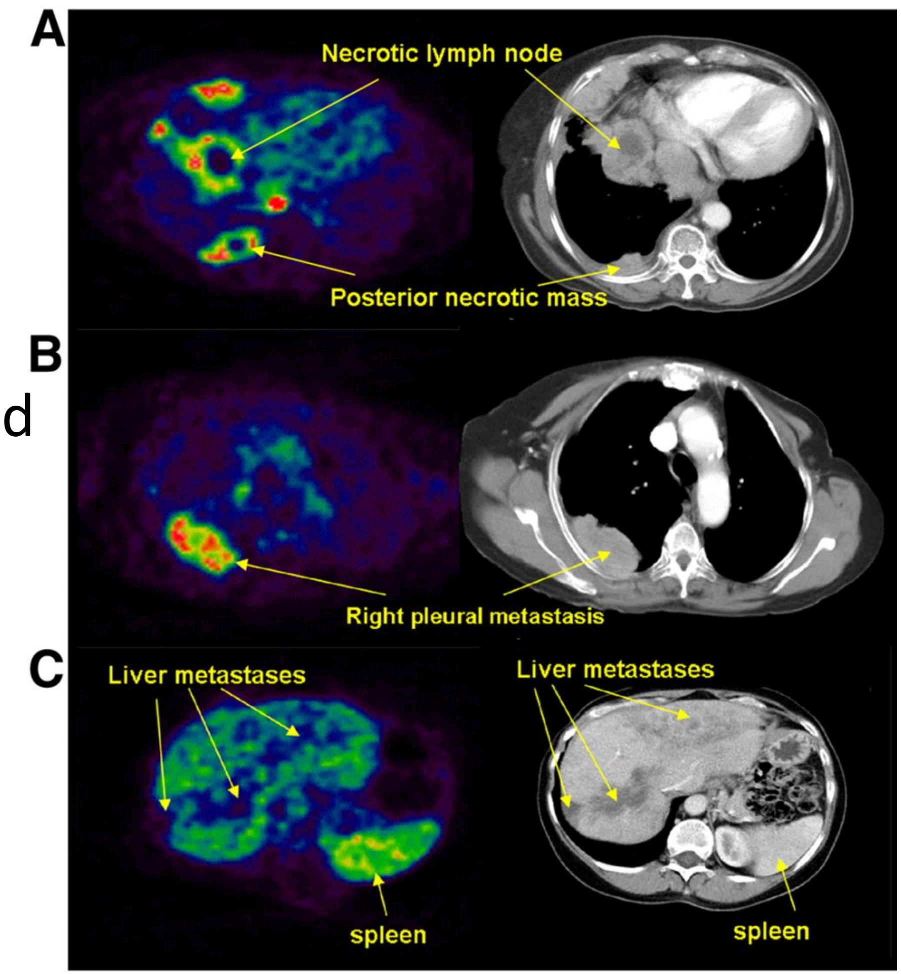




Francis DL, Freeman A, Visvikis D, Costa DC, Luthra SK, Novelli M, Taylor I, Ell PJ. In vivo imaging of cellular proliferation in colorectal cancer using positron emission tomography. Gut. 2003;52:1602-6.

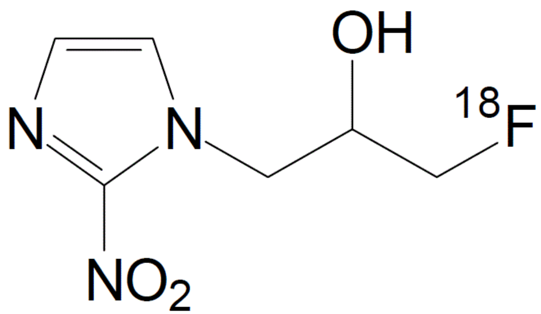
PET imaging of tumor angiogenesis

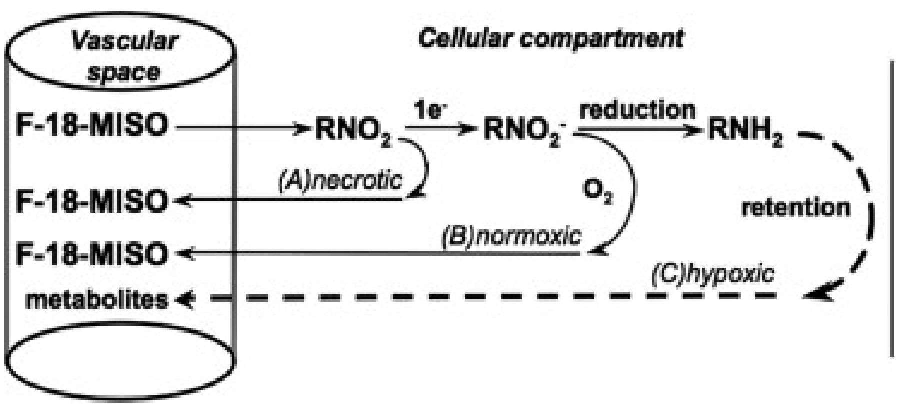




Kenny LM, Coombes RC, Oulie I, Contractor KB, Miller M, Spinks TJ, McParland B, Cohen PS, Hui AM, Palmieri C, Osman S, Glaser M, Turton D, Al-Nahhas A, Aboagye EO. Phase I trial of the positron-emitting Arg-Gly-Asp (RGD) peptide radioligand ^{18}F-AH111585 in breast cancer patients. J Nucl Med. 2008;49:879-86.

Normal scintigraphy with F-18-Fluoromisonidazole (FMISO)



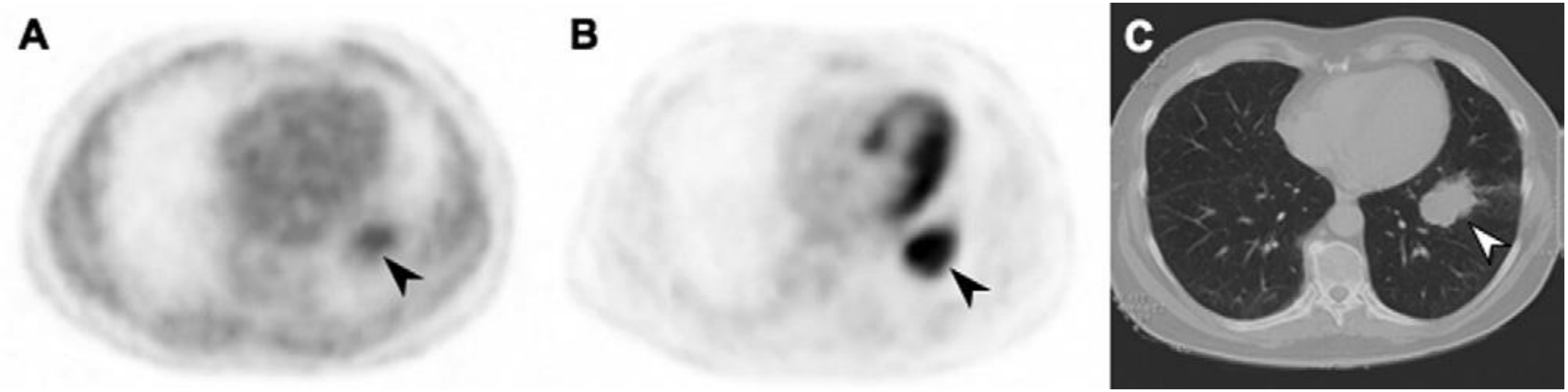


Lee ST, Scott AM. Hypoxia positron emission tomography imaging with ^{18}F-fluoromisonidazole. Semin Nucl Med. 2007;37:451-61. Review.

FDG-FMISO comparison

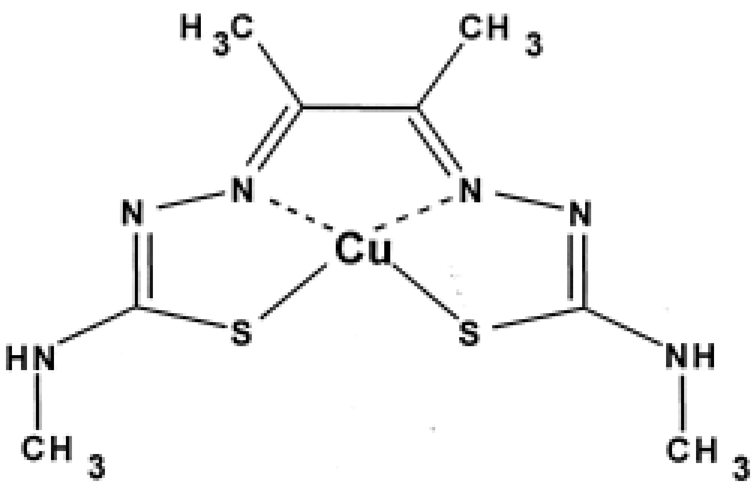
Non-small cell lung cancer

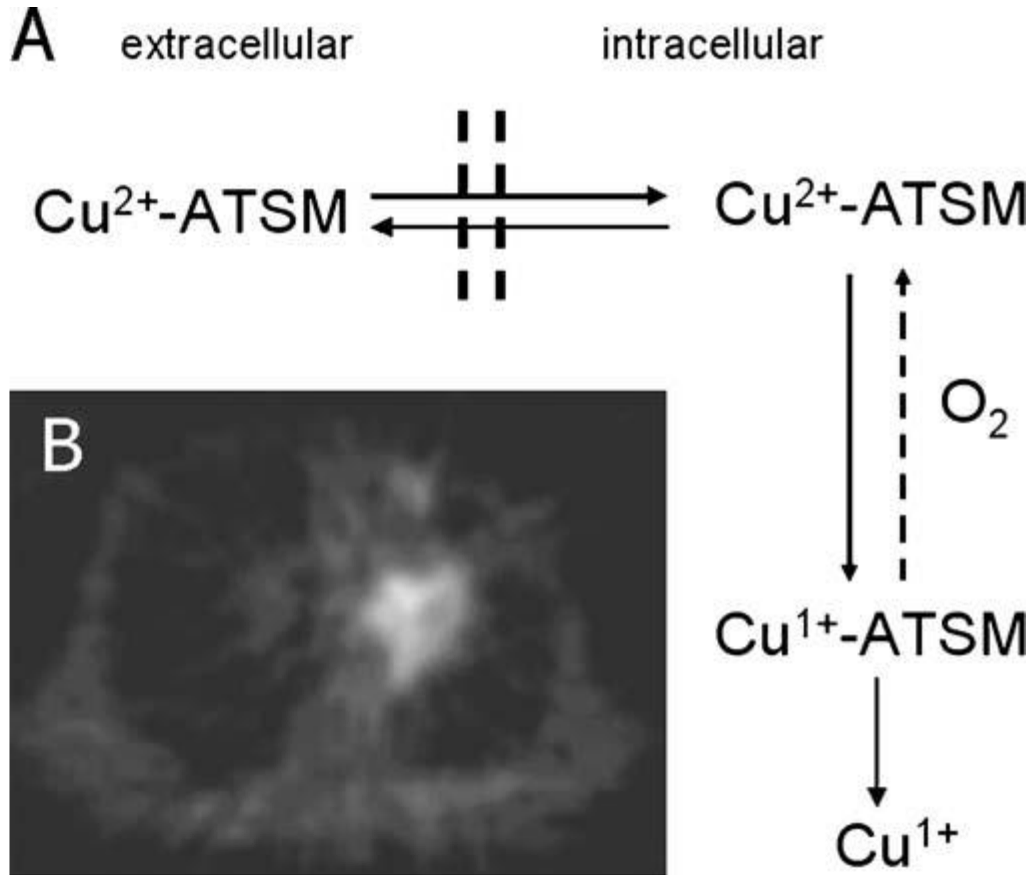
FMISO FDG



Lee ST, Scott AM. Hypoxia positron emission tomography imaging with ^{18}F-fluoromisonidazole. Semin Nucl Med. 2007;37:451-61. Review.

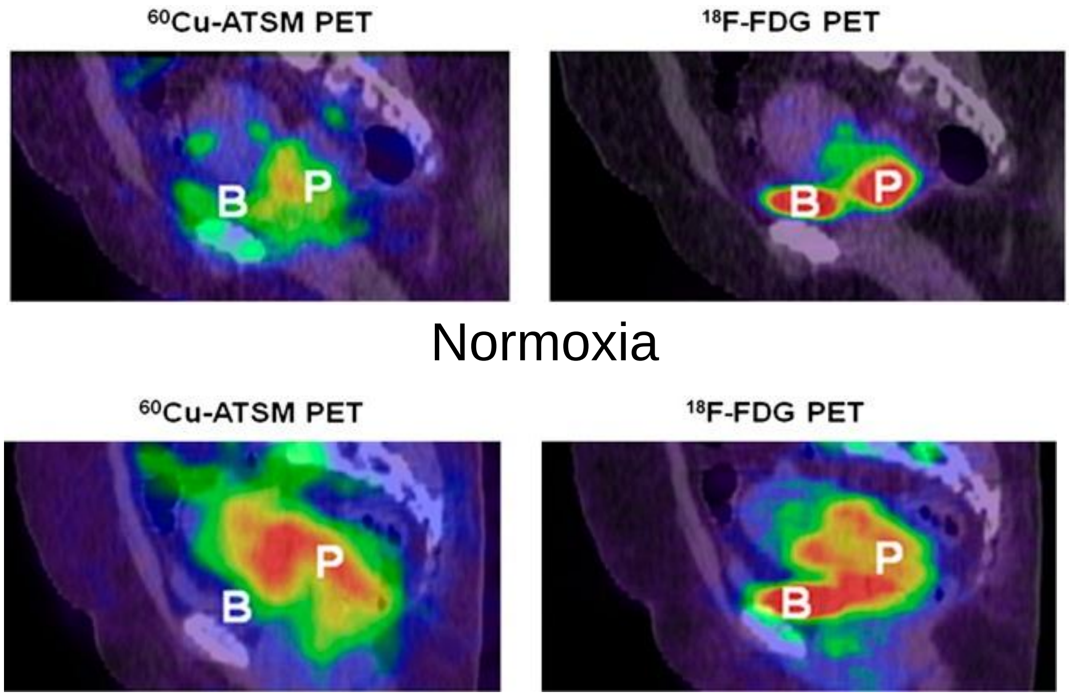
Cu-ATSM

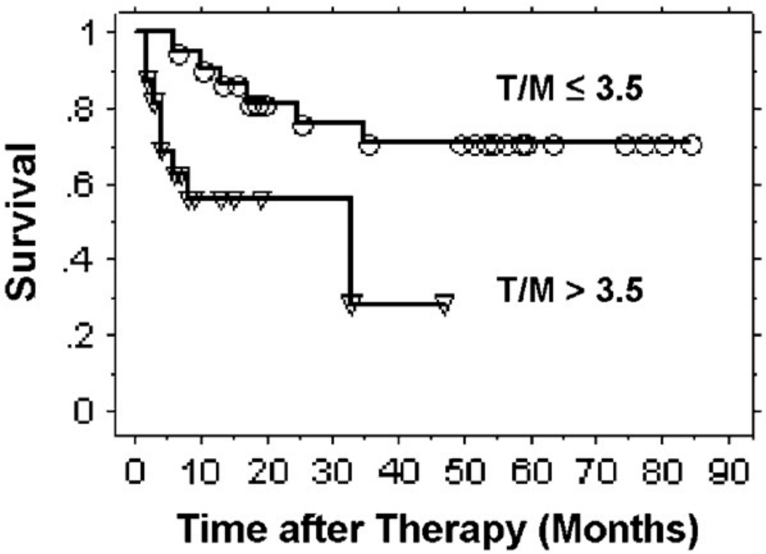




Padhani AR, Krohn KA, Lewis JS, Alber M. Imaging oxygenation of human tumours. Eur Radiol. 2007;17:861-72. Review.

Tumor hypoxia assessment using Cu-ATSM in cervical cancer





Hypoxia

B = Bladder P = Primary Tumor

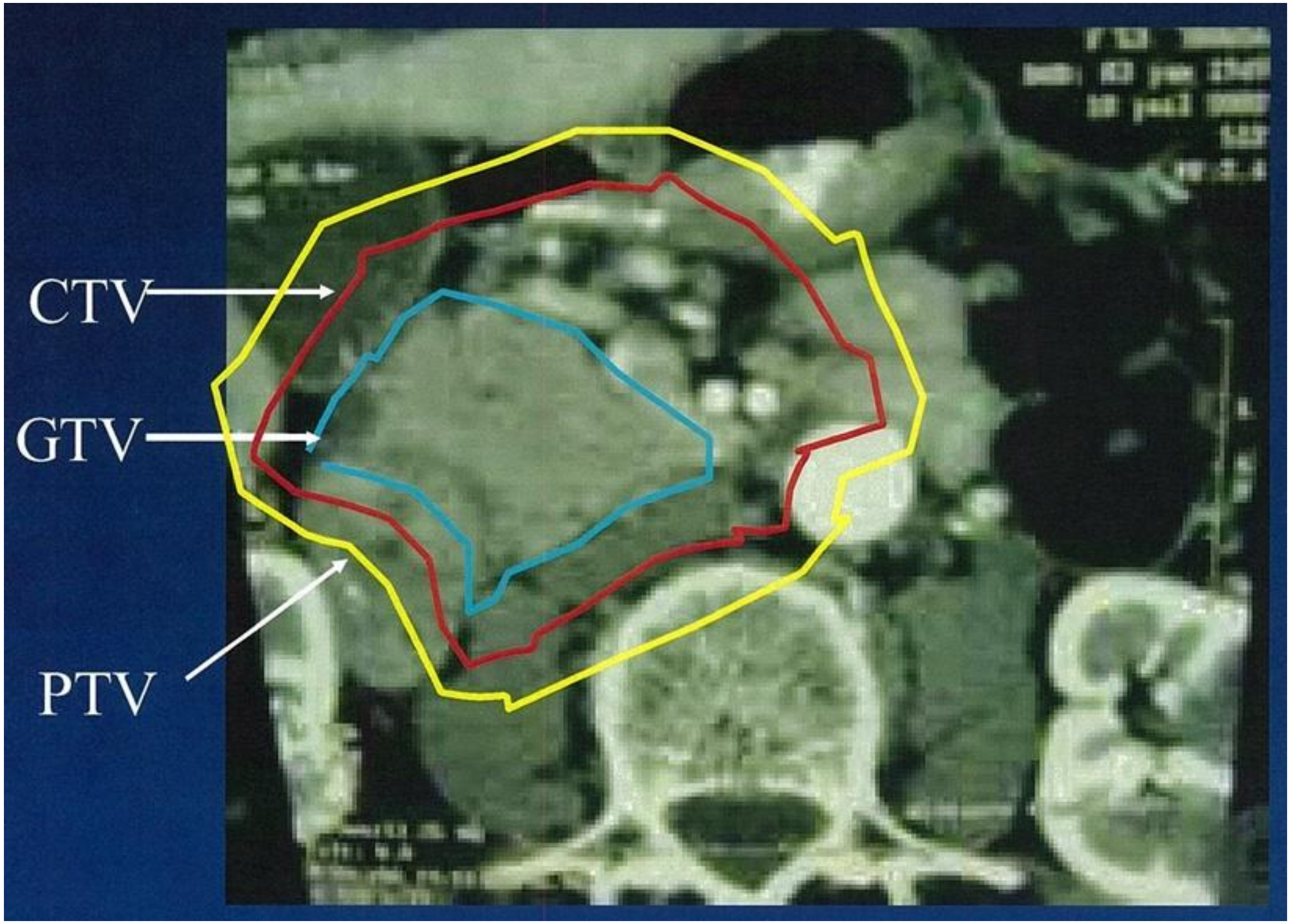
Dehdashti F, Grigsby PW, Lewis JS, Laforest R, Siegel BA, Welch MJ. Assessing tumor hypoxia in cervical cancer by PET with ^{60}Cu-labeled diacetyl-bis(N4-methylthiosemicarbazone). J Nucl Med. 2008;49:201-5

Target volume in external beam radiotherapy

GTV: gross tumor volume

CTV: clinical target volume

PTV: planned target volume



Somatostatin analogues

Targeting neuroendocrine tumors that over-express somatostatin receptors

Ala-Gly-Cys-Lys-Asn-Phe-**Phe-Trp**

Cys- Ser-Thr-Phe-**Thr- Lys**

Somatostatine 14

DPhe-Cys-**Phe-DTrp**

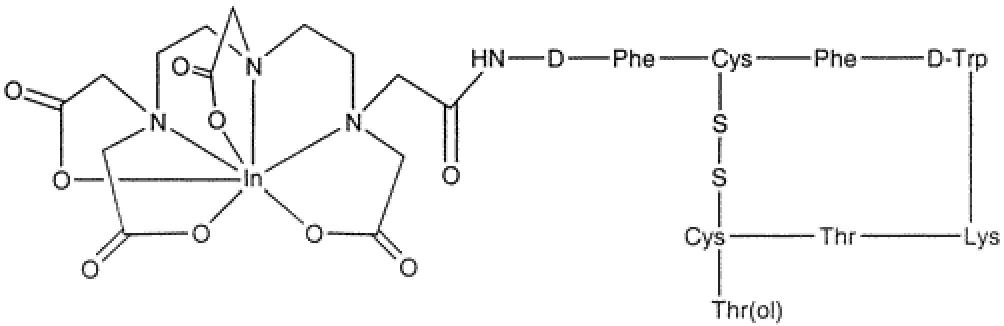
Thr(ol)-Cys-**Thr-Lys**

Octreotide

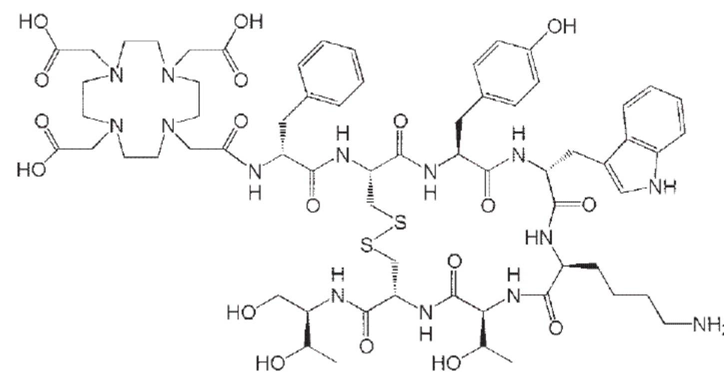
DOTA-DPhe-Cys-**Phe-DTrp**

Thr(ol)-Cys-**Thr-Lys**

[DOTA^0]octreotide (DOTAOC)



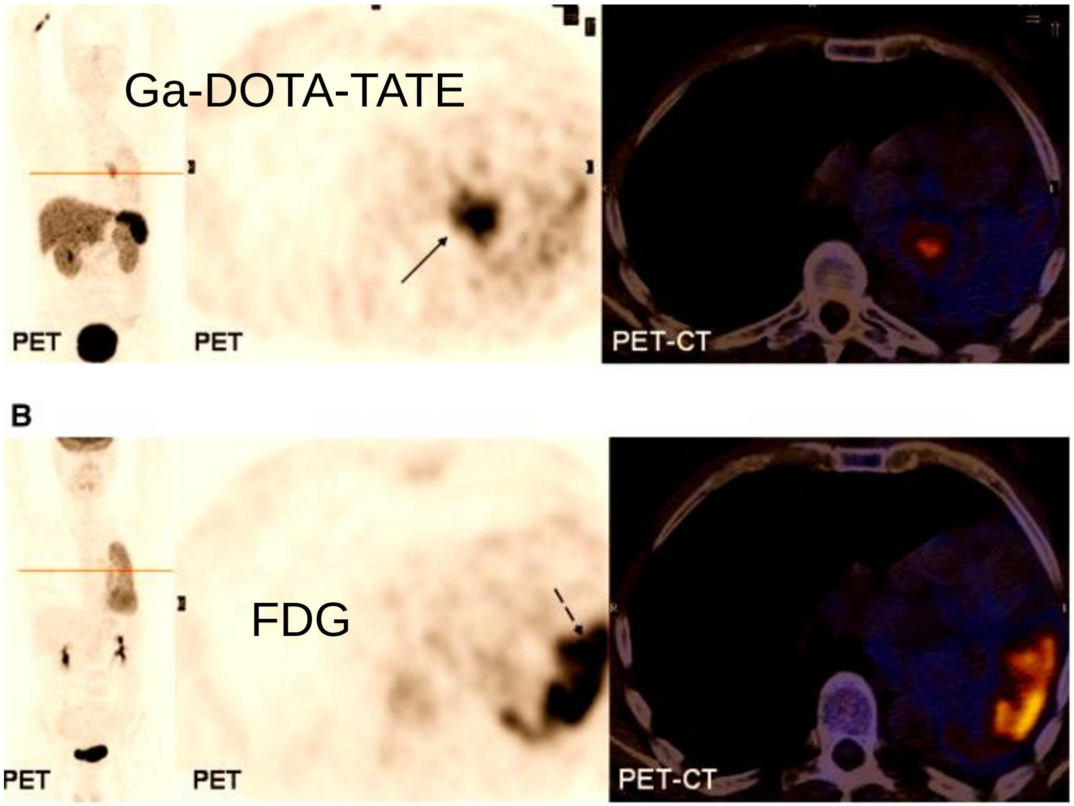
^{111}In-DTPA-Octreotide (OctreoScan®)



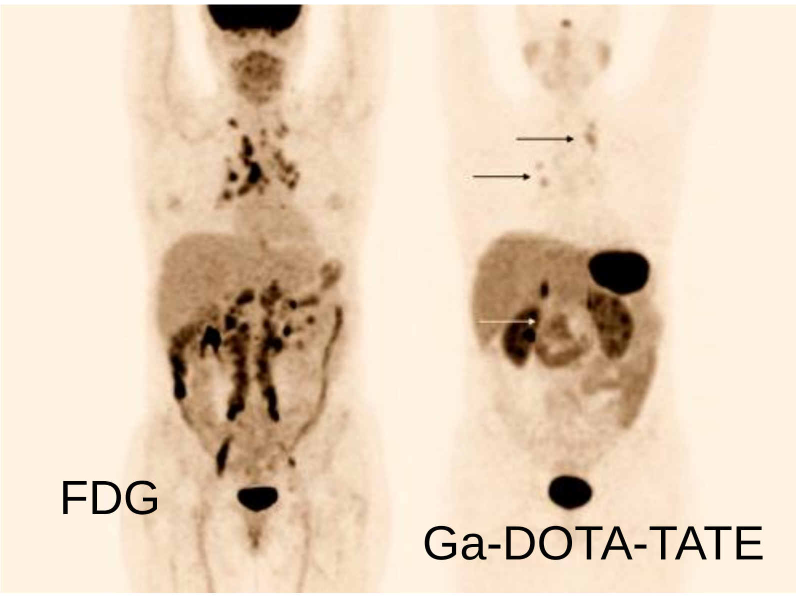
[Tyr^3]octreotide D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr(ol)

[Tyr^3]octreotate D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr

^{68}Ga-PET (DOTA-octreotate)
PET imaging of neuroendocrine tumors



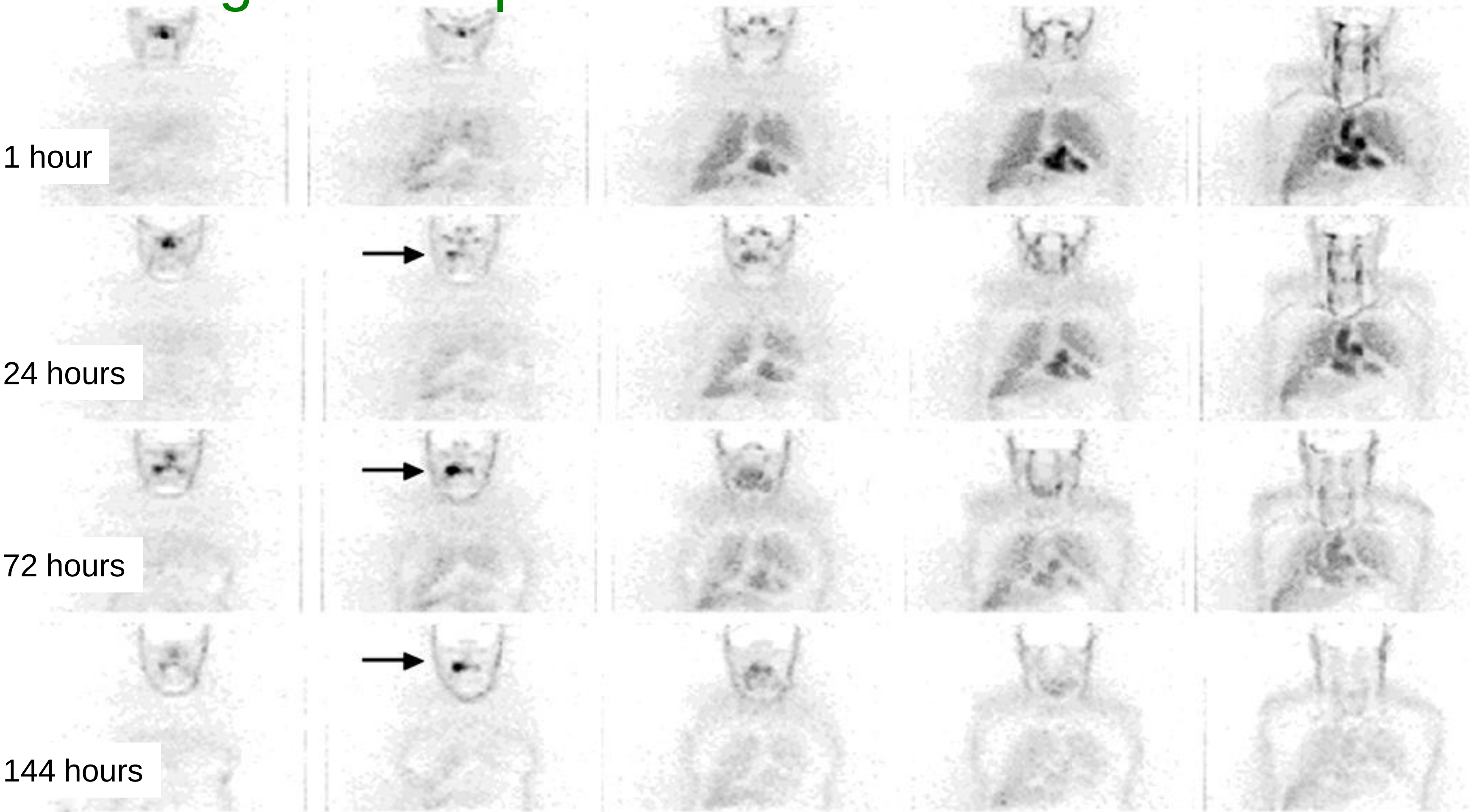
Non-specific uptake of FDG



Tumor lesions negative for ^{68}Ga-DOTA-TATE: contraindication for treatment with ^{177}Lu-DOTA-TATE

Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, Dickson J, Caplin M, Ell PJ. Functional imaging of neuroendocrine tumors with combined PET/CT using ^{68}Ga-DOTATATE (DOTA-DPhe^1,Tyr^3-octreotate) and ^{18}F-FDG. Cancer. 2008;112:2447-55.

Long half-life positron emitters: zirconium-89



Börjesson PK, Jauw YW, Boellaard R, de Bree R, Comans EF, Roos JC, Castelijns JA, Vosjan MJ, Kummer JA, Leemans CR, Lammertsma AA, van Dongen GA. Performance of immuno-positron emission tomography with zirconium-89-labeled chimeric monoclonal antibody U36 in the detection of lymph node metastases in head and neck cancer patients. Clin Cancer Res. 2006;12:2133-40.

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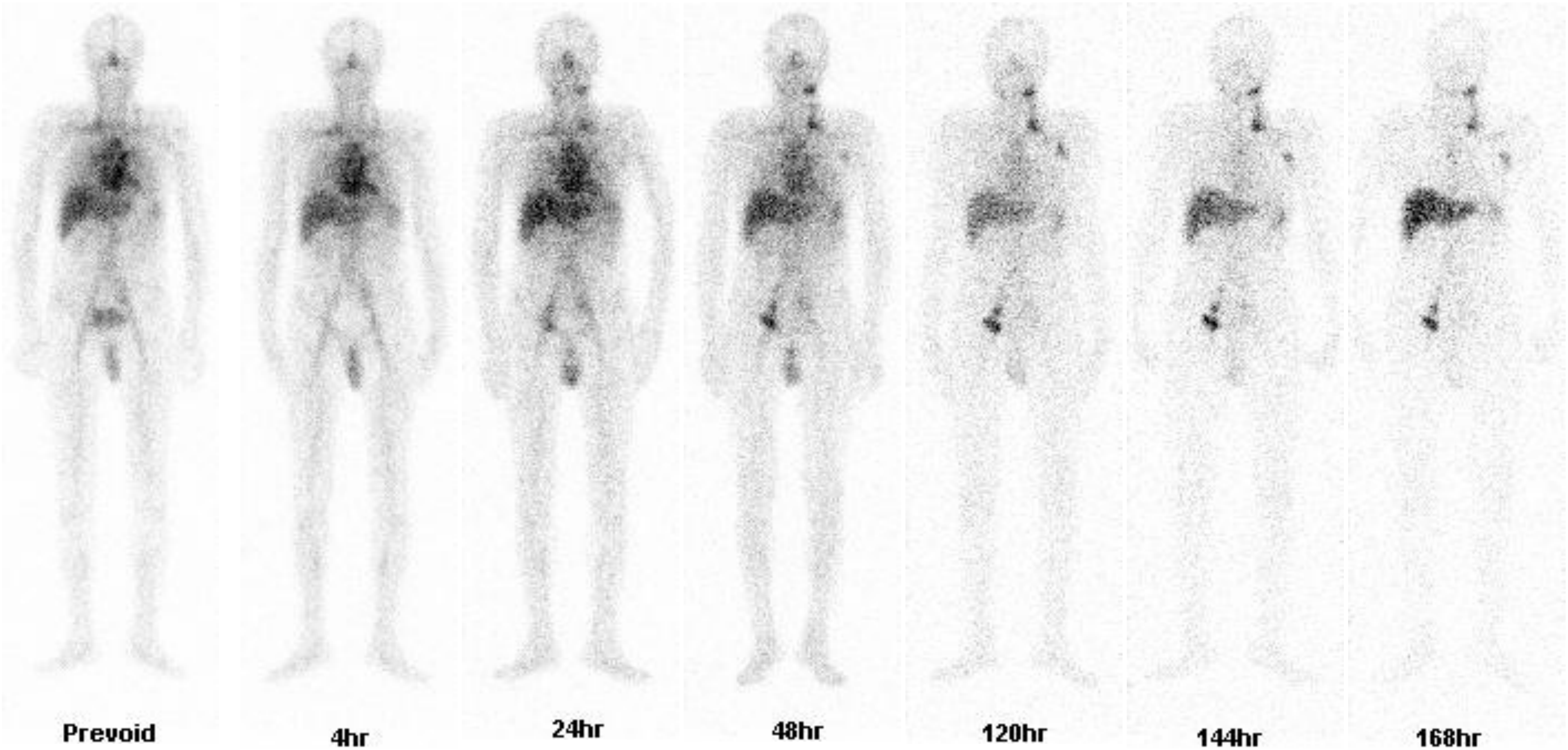
TARGETED RADIONUCLIDE THERAPY

Magic bullets have nothing magic



Biodistribution of indium-111-labeled epratuzumab (anti-CD22, Immunomedics)

Sharkey RM, Brenner A, Burton J, Hajjar G, Toder SP, Alavi A, Matthies A, Tsai DE, Schuster SJ, Stadtmauer EA, Czuczman MS, Lamonica D, Kraeber-Bodere F, Mahe B, Chatal JF, Rogatko A, Mardirrosian G, Goldenberg DM. Radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-DOTA humanized anti-CD22 IgG (^{90}Y-Epratuzumab): do tumor targeting and dosimetry predict therapeutic response? J Nucl Med. 2003;44:2000-18.

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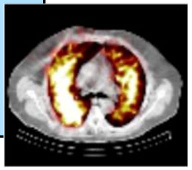
Patient specific Monte-Carlo dosimetry

SPECT

CT

d_0, d_1, d_3, ...

- Corrections:
  - dead time
  - attenuation
  - scatter
- Registration
- Calculation of $\tilde{A}$ map at the voxel level



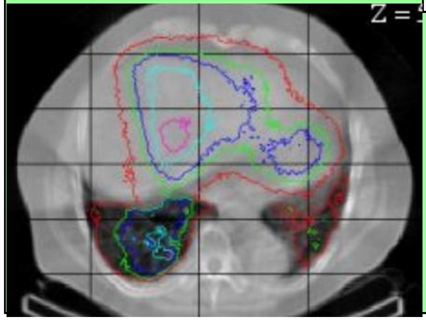
MCNPX

OEDIPE software

- Specific voxel-based geometry

- Automatic segmentation (lungs, bone, soft tissue and air)

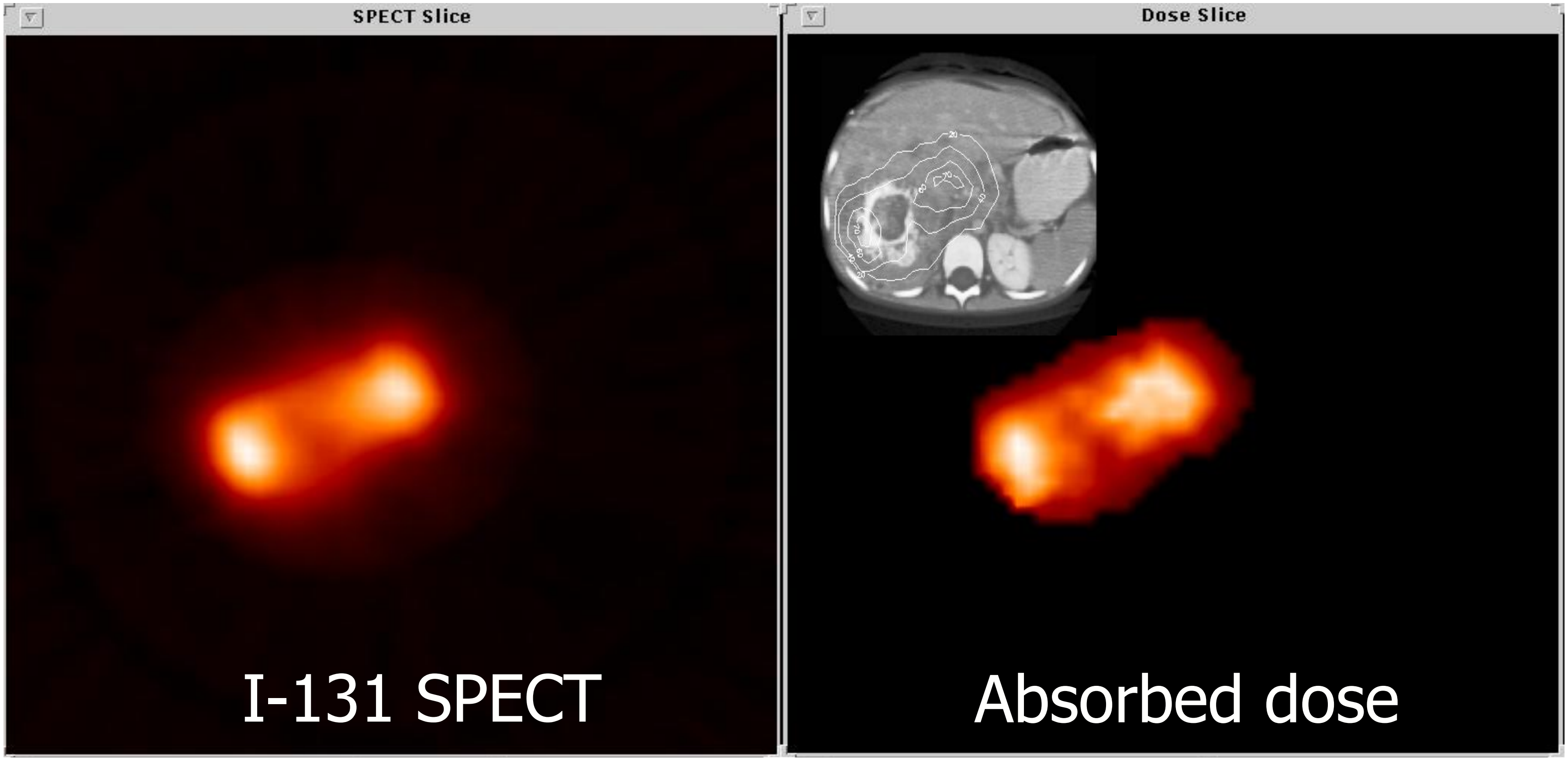
- Manual segmentation



Chiavassa S, Aubineau-Lanièce I, Bitar A, Lisbona A, Barbet J, Franck D, Jourdain JR, Bardiès M. Validation of a personalized dosimetric evaluation tool (Oedipe) for targeted radiotherapy based on the Monte Carlo MCNPX code. Phys Med Biol. 2006;51:601-16.

Dosimetry

Radionuclide therapy is the only treatment modality that allows the agent delivering treatment to be directly imaged



Images: courtesy of Dr Glenn Flux, The Royal Marsden, London, UK

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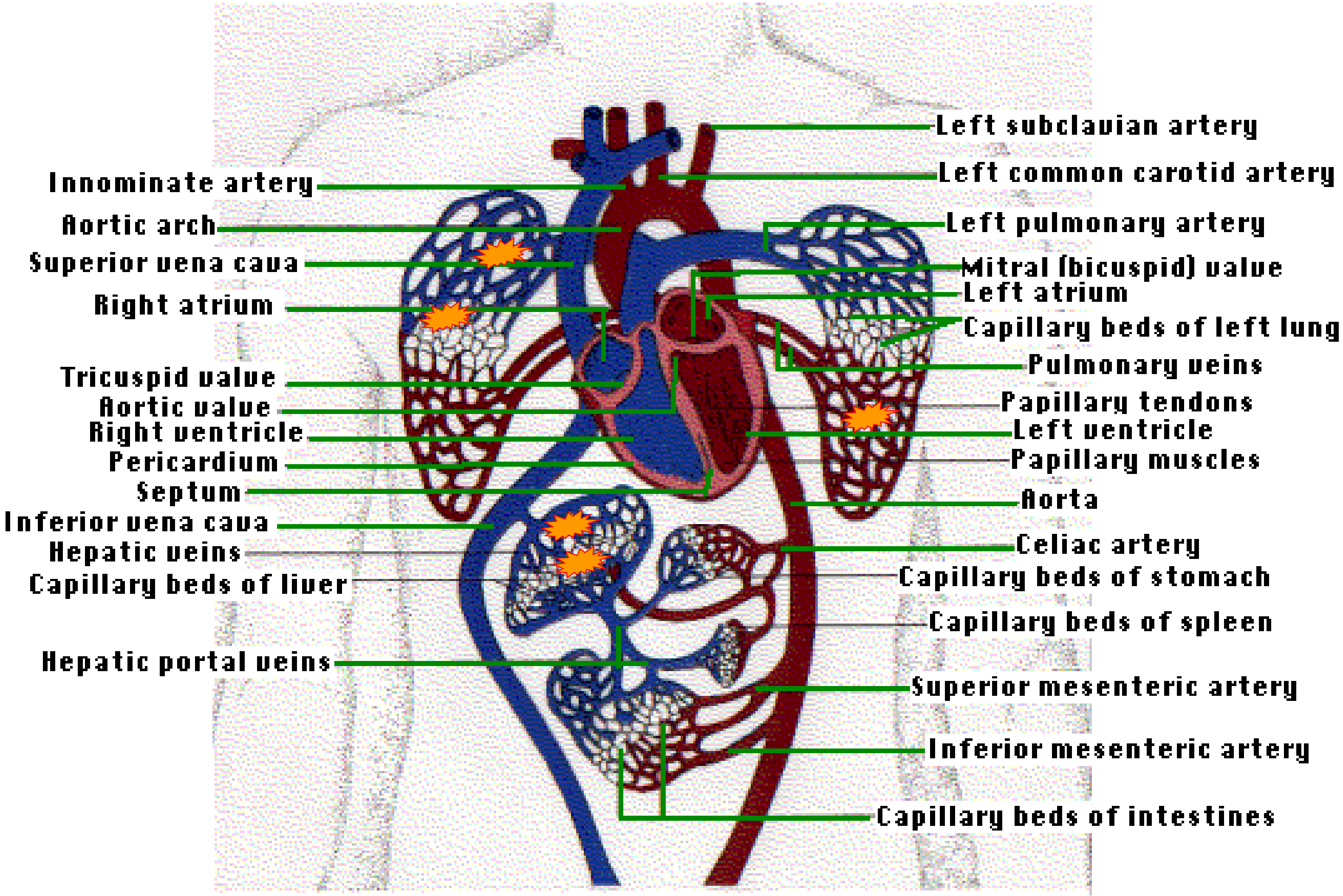
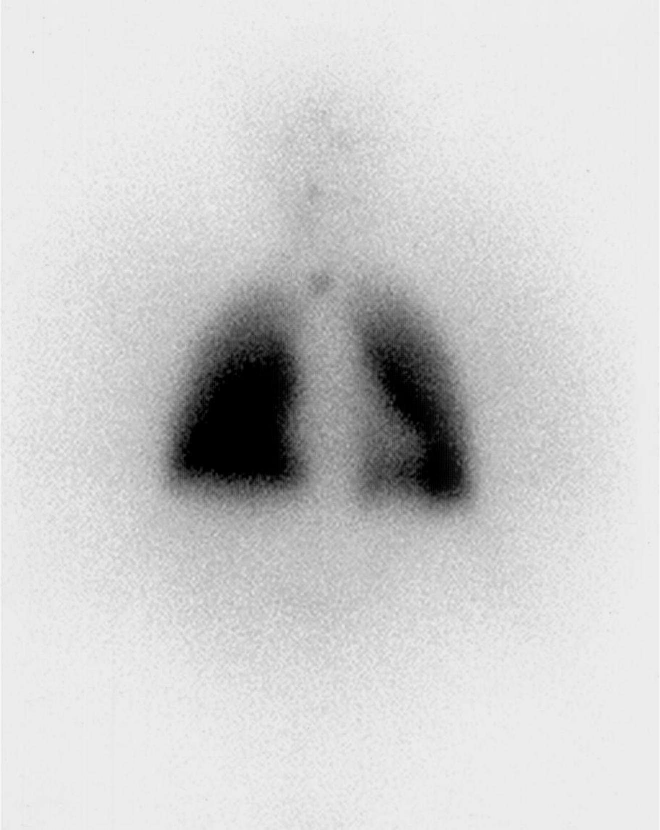
Targeted radionuclide therapy: coping with disseminated diseases



Radiotherapy of metastatic thyroid cancer with ^{131}I-iodide

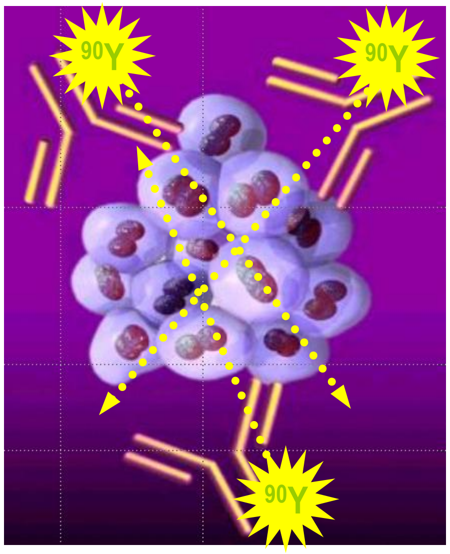


Lung metastases	Response rate	10-year survival
Microscopic (normal CT)	83 %	91 %
Microscopic (abnormal CT)	53 %	63 %
Macroscopic	14 %	11 %

Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, Francese C, Fontaine F, Ricard M, Parmentier C. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. J Nucl Med. 1996;37:598-605.

Radioimmunotherapy

- Radioimmunotherapy (RIT) has been developed for more than 20 years
- With important improvements: new stable chelates, humanized antibodies and pretargeting methods
- Effects of RIT result from both radiobiological and immunological mechanisms (ADCC, CDC, Apoptosis)
- RIT may destroy tumour cells that do not bind by the drug through a cross-fire effect



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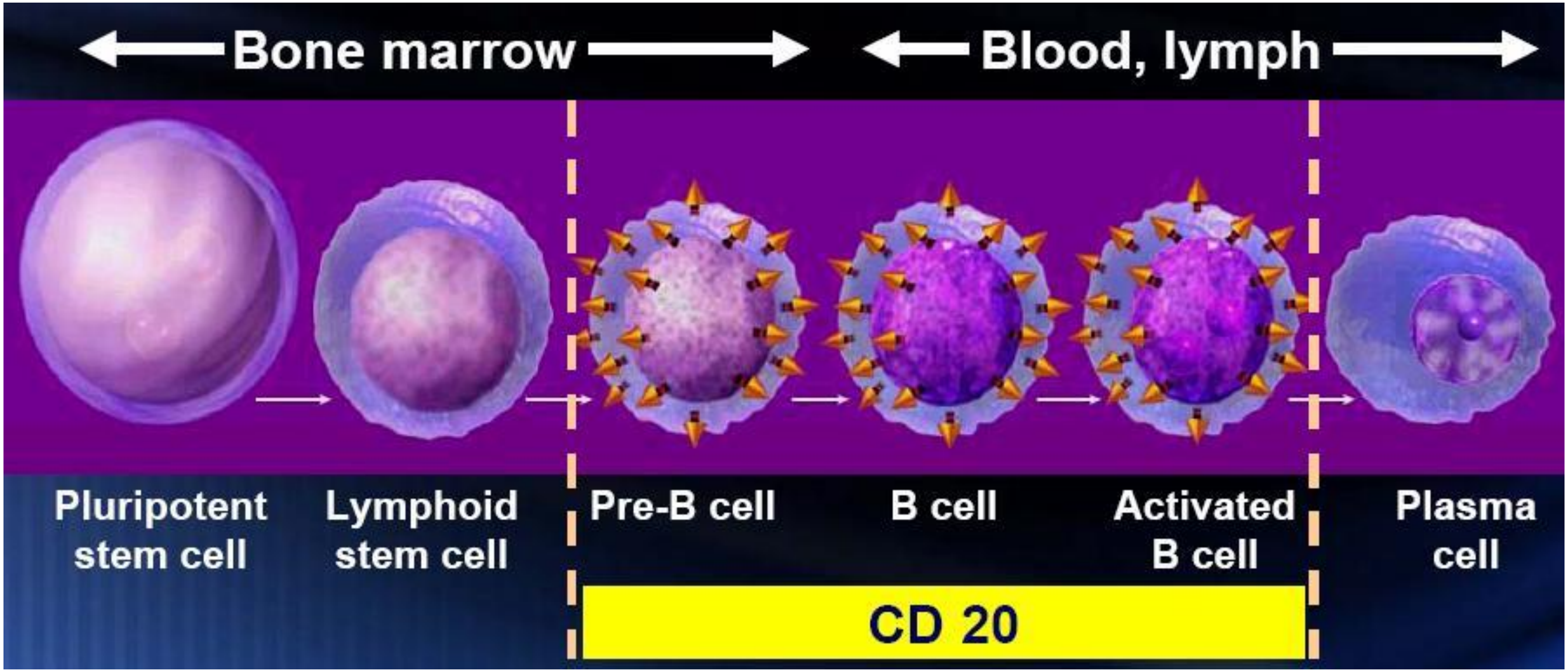
Expression of the CD20 antigen

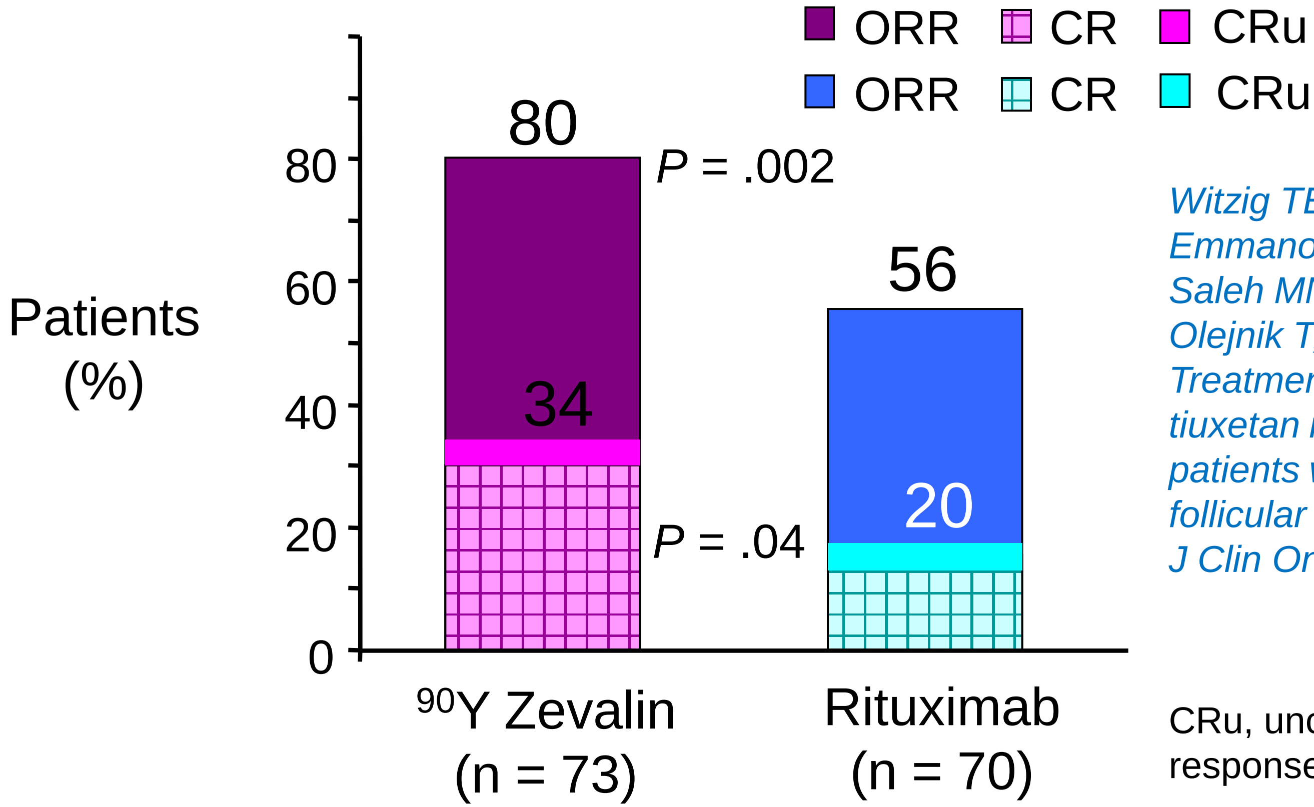


Rituximab (Rituxan®), chimeric
Tositumomab (Bexxar®), ^{131}I-Murine
Ibritumomab (Zevalin®), ^{90}Y-Murine

Press. Semin Oncol.1999;26 (Suppl14):58.

Zevalin® vs Rituximab in non-Hodgkin's malignant lymphoma

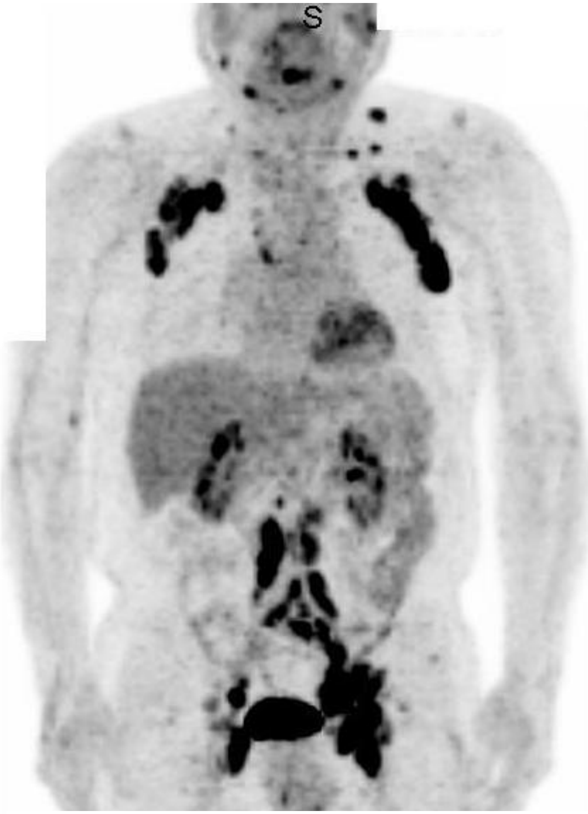
Zevalin: yttrium-90-labeled anti-CD20 antibody
Rituximab: unlabeled anti-CD20 antibody



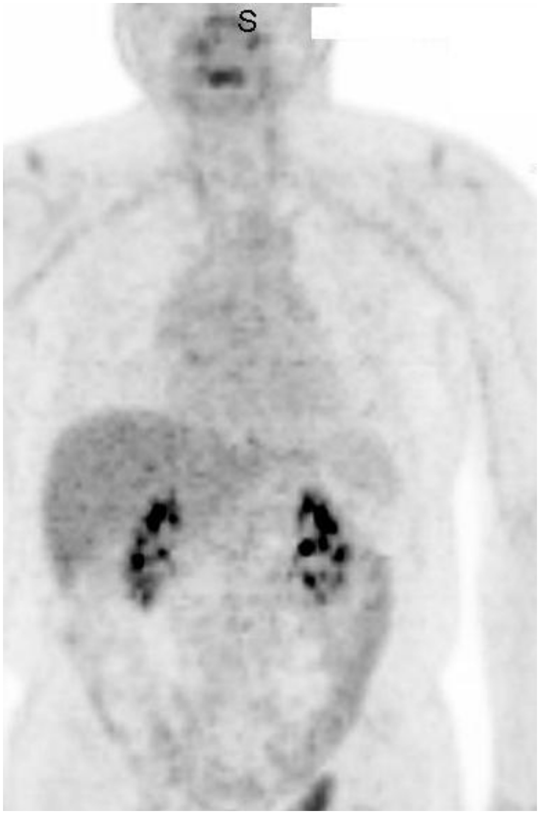
Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, Cripe L, Wiseman G, Olejnik T, Multani PS, White CA. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol. 2002;20:3262-9.

CRu, unconfirmed complete response

^{18}F-FDG imaging in Zevalin therapy (^{90}Y-labeled anti-CD20 antibody)



Pre-RIT

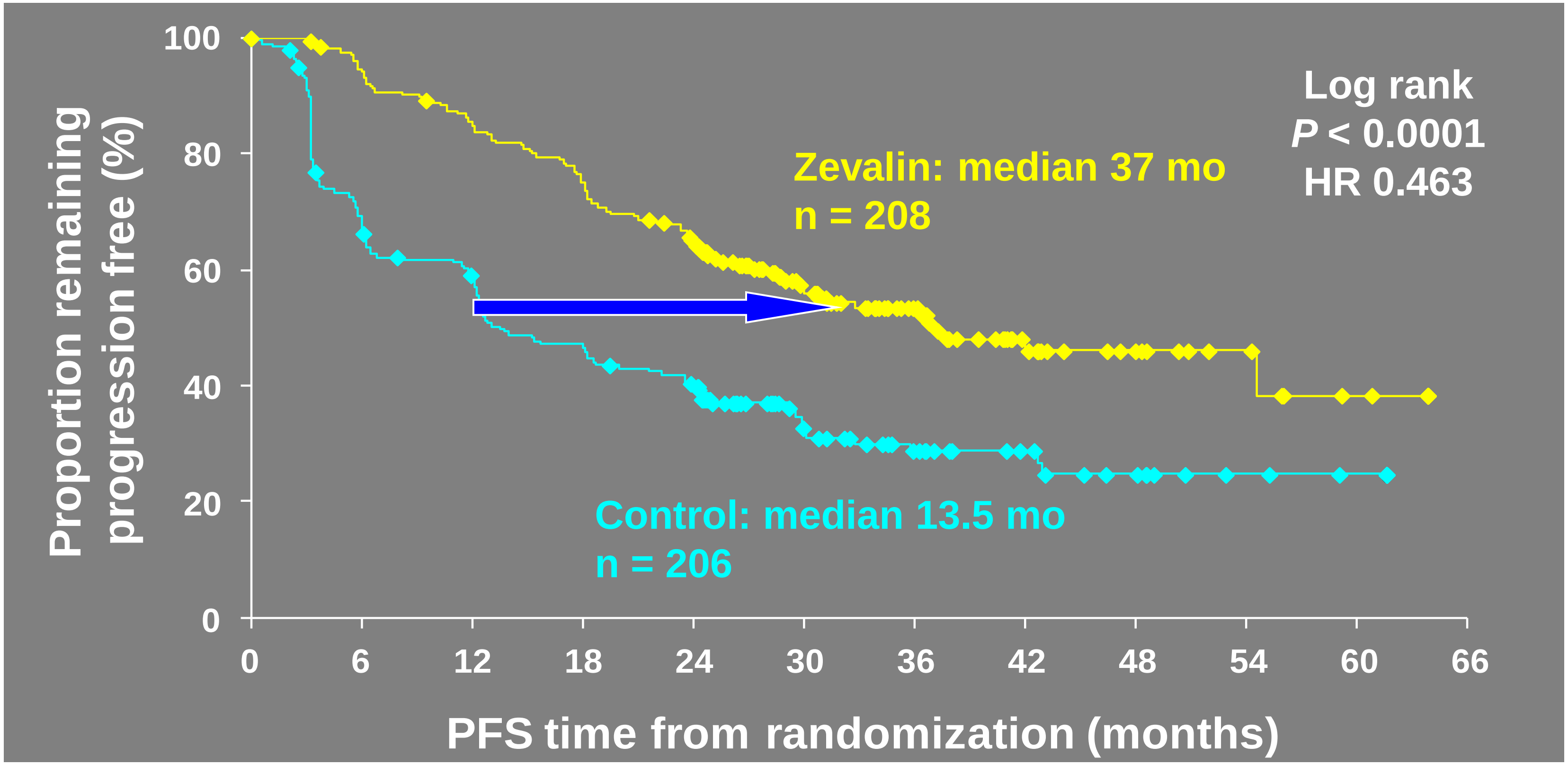


After 1 injection of Zevalin

Courtesy of Françoise Kraeber-Bodéré, Médecine Nucléaire, CHU de Nantes

Ben-Haim S, Ell P. ^{18}F-FDG PET and PET/CT in the evaluation of cancer treatment response. J Nucl Med. 2009;50:88-99. Review

Consolidation radioimmunotherapy of follicular lymphoma



Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, Huijgens PC, Kolstad A, d'Amore F, Gonzalez Diaz M, Petrini M, Sebban C, Zinzani PL, van Oers MH, van Putten W, Bischof-Delaloye A, Rohatiner A, Salles G, Kuhlmann J, Hagenbeek A. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol. 2008;26:5156-64

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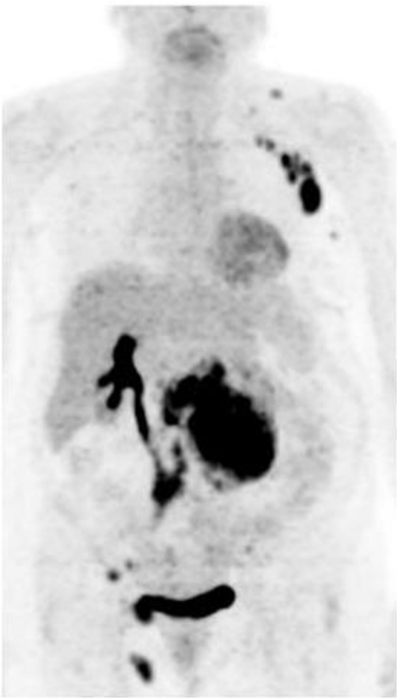
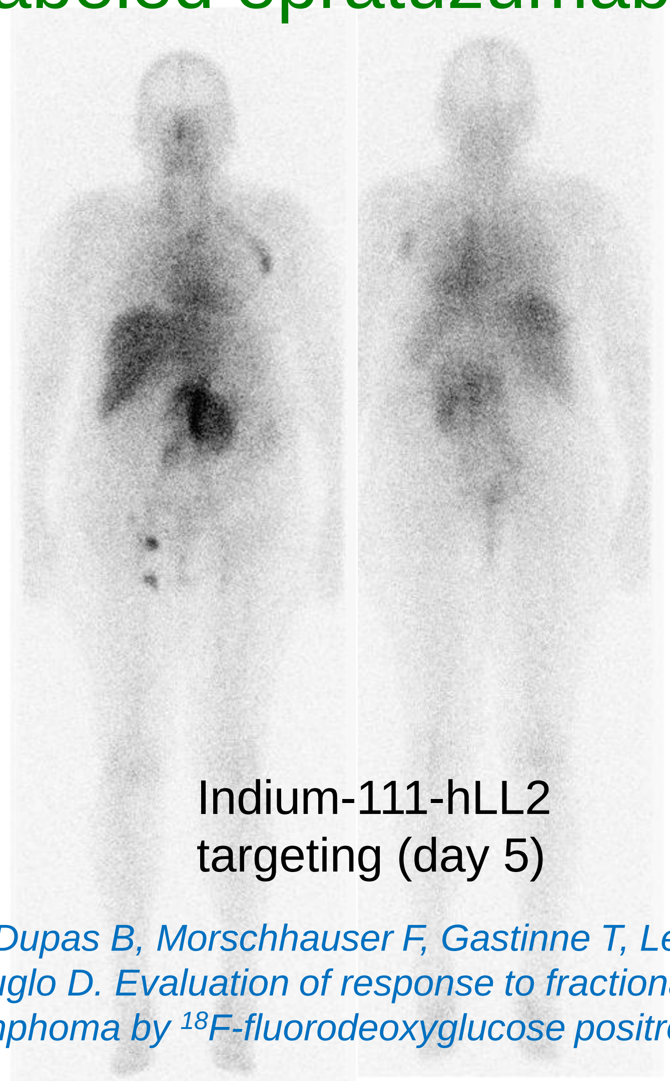
Targeting of other antigens than CD20: ^{90}Y-labeled epratuzumab (hLL2)



Baseline PET

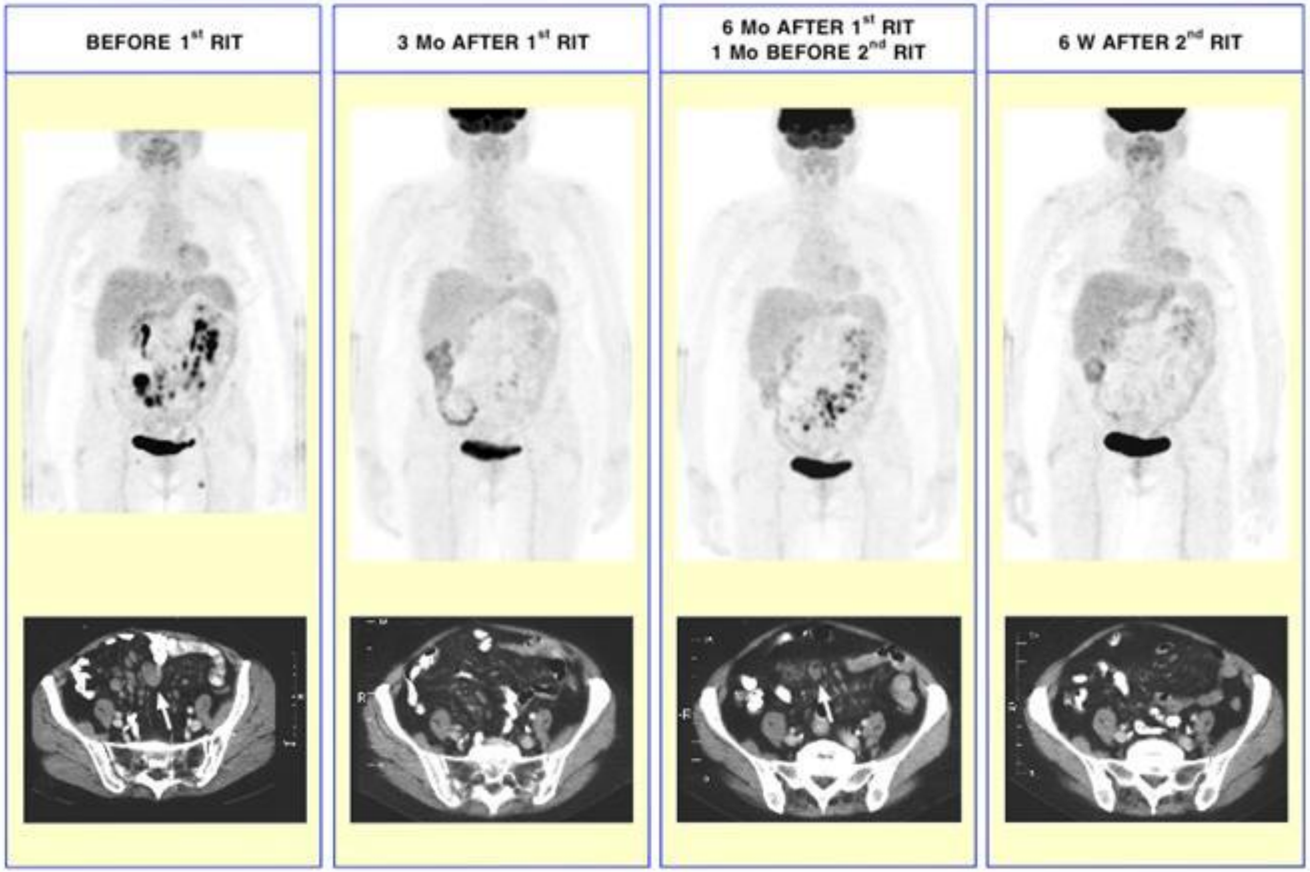


Indium-111-hLL2 targeting (day 5)

PET 6 weeks post RIT

Bodet-Milin C, Kraeber-Bodéré F, Dupas B, Morschhauser F, Gastinne T, Le Gouill S, Campion L, Harousseau JL, Wegener WA, Goldenberg DM, Huglo D. Evaluation of response to fractionated radioimmunotherapy with ^{90}Y-epratuzumab in non-Hodgkin's lymphoma by ^{18}F-fluorodeoxyglucose positron emission tomography. Haematologica. 2008;93:390-7.

Repeated injections of ^{90}Y-labeled epratuzumab

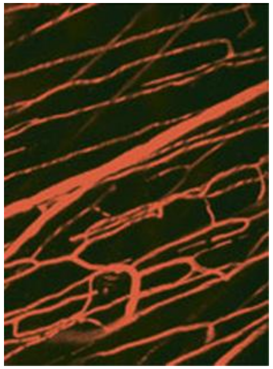


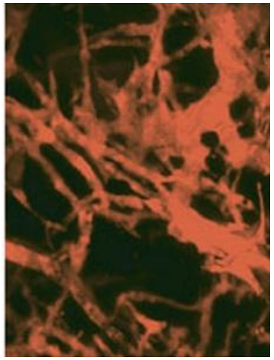
Bodet-Milin C, Kraeber-Bodéré F, Dupas B, Morschhauser F, Gastinne T, Le Gouill S, Campion L, Harousseau JL, Wegener WA, Goldenberg DM, Huglo D. Evaluation of response to fractionated radioimmunotherapy with ^{90}Y-epratuzumab in non-Hodgkin's lymphoma by ^{18}F-fluorodeoxyglucose positron emission tomography. Haematologica. 2008;93:390-7.

Solid tumors

- Example:
  - Lack of Efficacy of Two Consecutive Treatments of Radioimmunotherapy With 131I-cG250 in Patients With Metastasized Clear Cell Renal Cell Carcinoma. Brouwers AH, Mulders PF, de Mulder PH, van den Broek WJ, Buijs WC, Mala C, Joosten FB, Oosterwijk E, Boerman OC, Corstens FH, Oyen WJ. J Clin Oncol. 2005, 23:6540-8.
- However: 5 disease stabilizations for 29 treated patients

Capillaries in normal tissues are well-organized

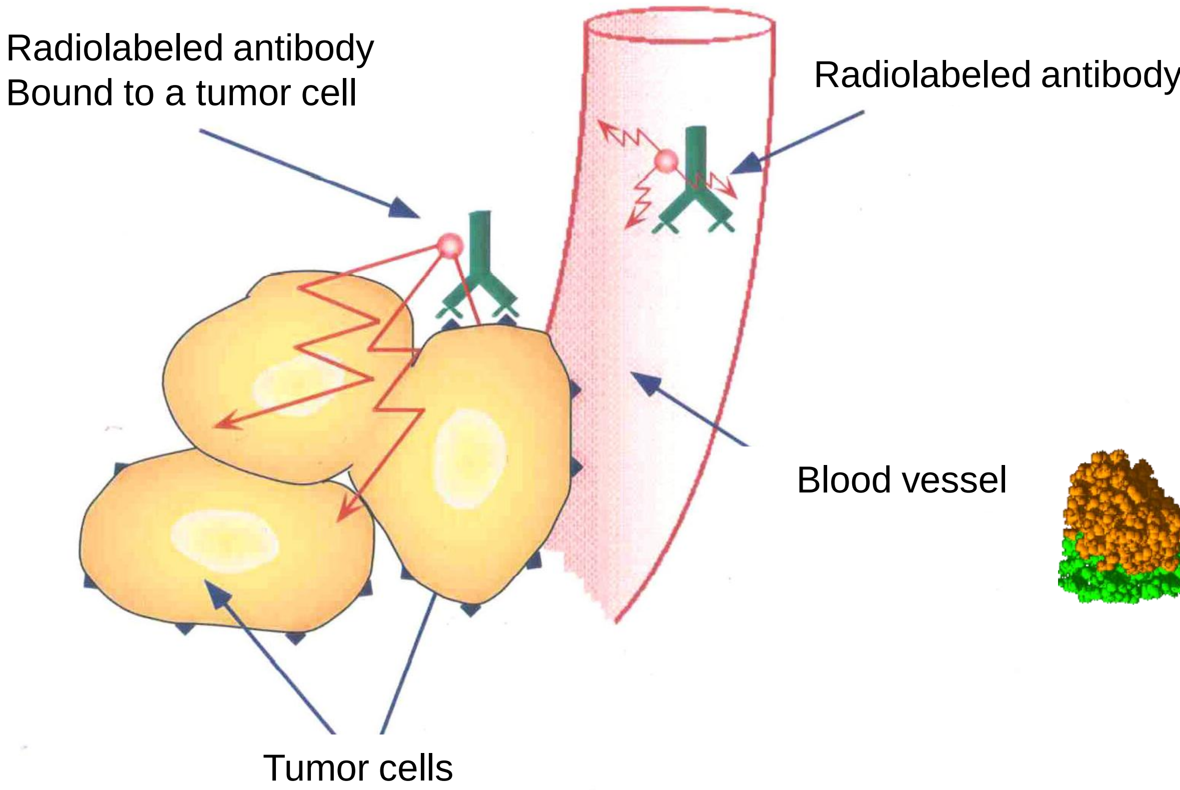


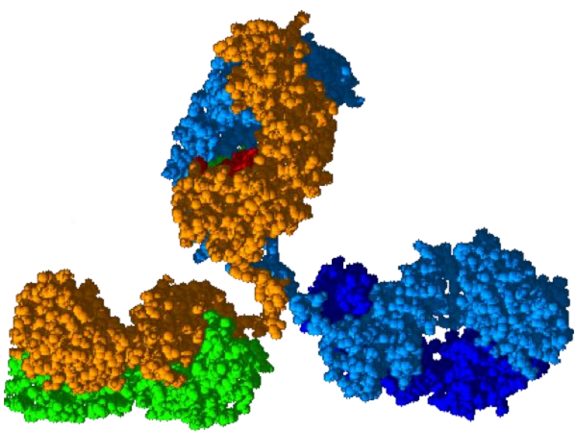


Capillaries in tumor are ill-organized: blood flow is slow and chaotic

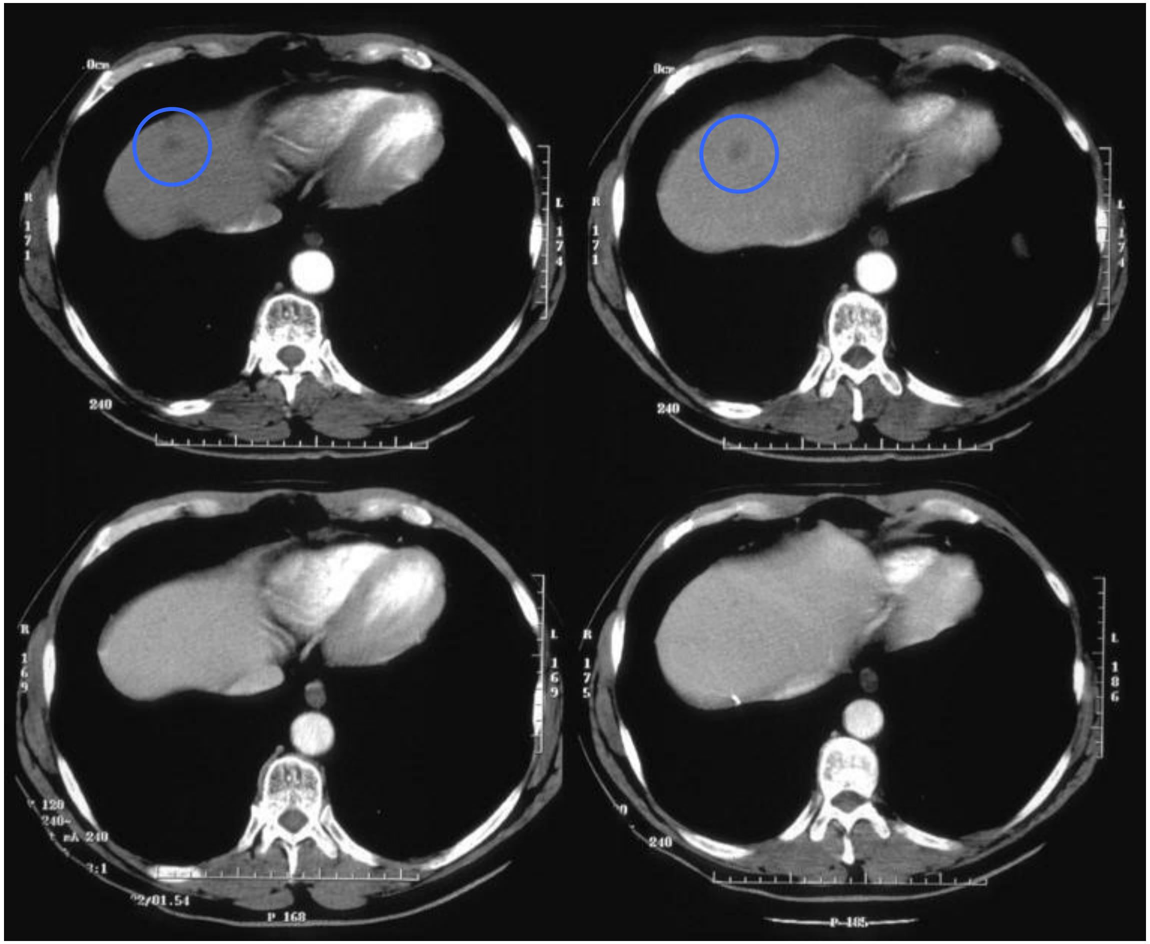
Chang YS, di Tomaso E, McDonald DM, Jones R, Jain RK, Munn LL. Mosaic blood vessels in tumors: frequency of cancer cells in contact with flowing blood. Proc Natl Acad Sci U S A. 2000;97:14608-13.

Physiological constraints: antibody extravasation



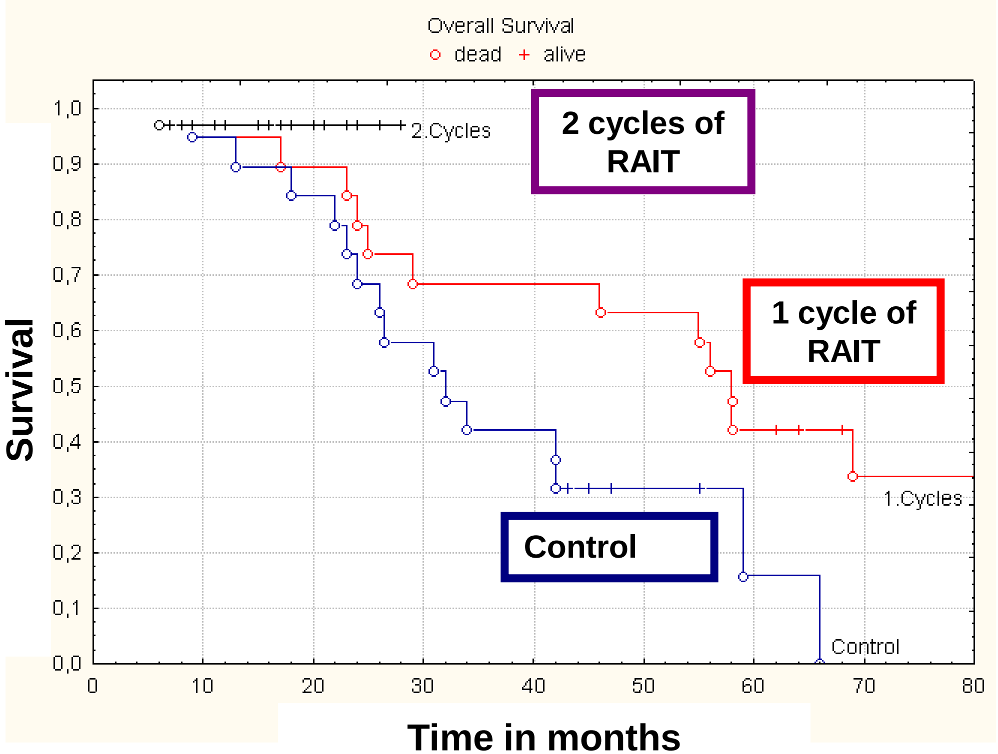


Small size tumor lesions



Behr TM, Salib AL, Liersch T, Béhé M, Angerstein C, Blumenthal RD, Fayyazi A, Sharkey RM, Ringe B, Becker H, Wörmann B, Hiddemann W, Goldenberg DM, Becker W. Radioimmunotherapy of small volume disease of colorectal cancer metastatic to the liver: preclinical evaluation in comparison to standard chemotherapy and initial results of a phase I clinical study. Clin Cancer Res. 1999;5(10 Suppl):3232s-3242s.

Radioimmunotherapy of residual disease in colon cancer



Liersch T, Meller J, Bittrich M, Kulle B, Becker H, Goldenberg DM. Update of carcinoembryonic antigen radioimmunotherapy with (131)I-labetuzumab after salvage resection of colorectal liver metastases: comparison of outcome to a contemporaneous control group. Ann Surg Oncol. 2007;14:2577-90

Liersch T, Meller J, Kulle B, Behr TM, Markus P, Langer C, Ghadimi BM, Wegener WA, Kovacs J, Horak ID, Becker H, Goldenberg DM. Phase II trial of carcinoembryonic antigen radioimmunotherapy with 131I-labetuzumab after salvage resection of colorectal metastases in the liver: five-year safety and efficacy results. J Clin Oncol. 2005;23:6763-70

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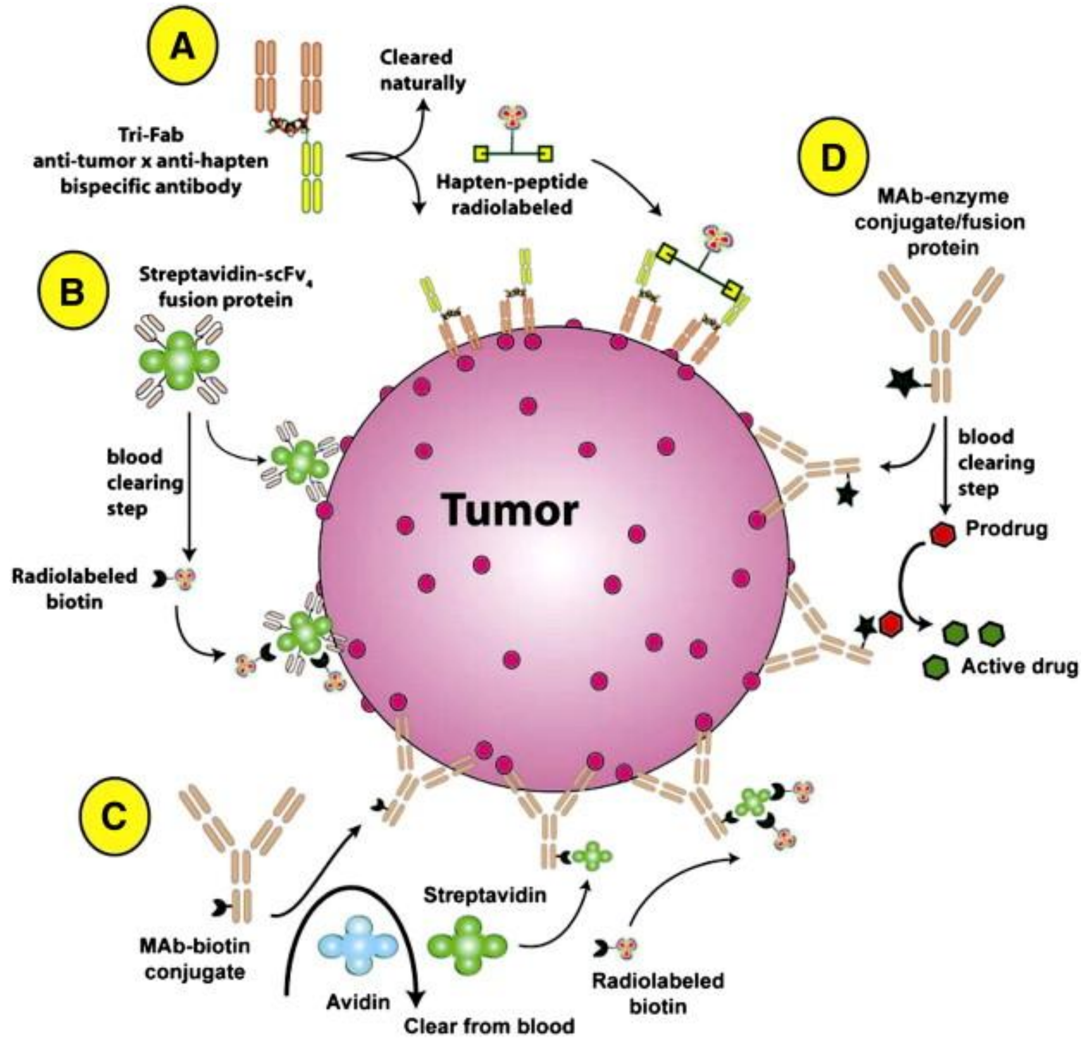
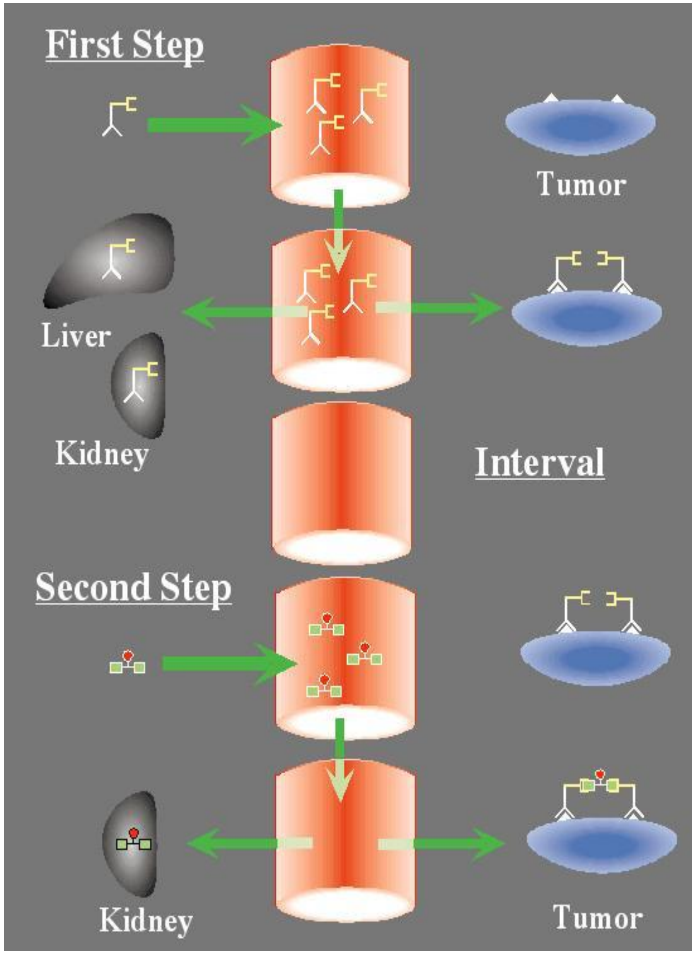
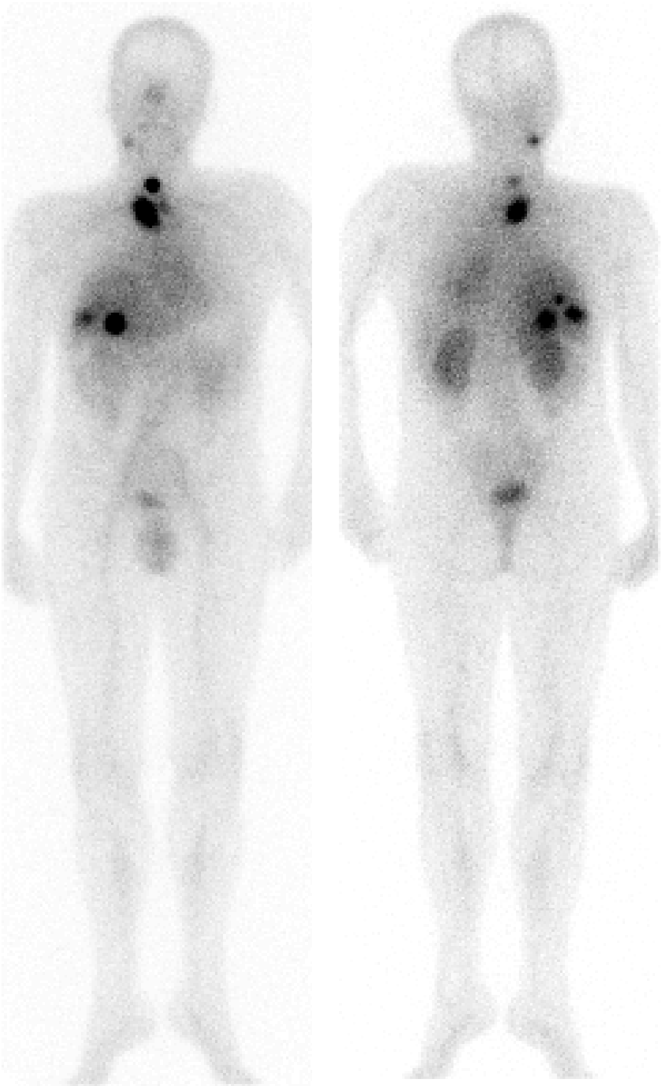
Examples of pretargeting methods



Sharkey RM, Goldenberg DM. Use of antibodies and immunoconjugates for the therapy of more accessible cancers. Adv Drug Deliv Rev. 2008; 60: 1407-20.

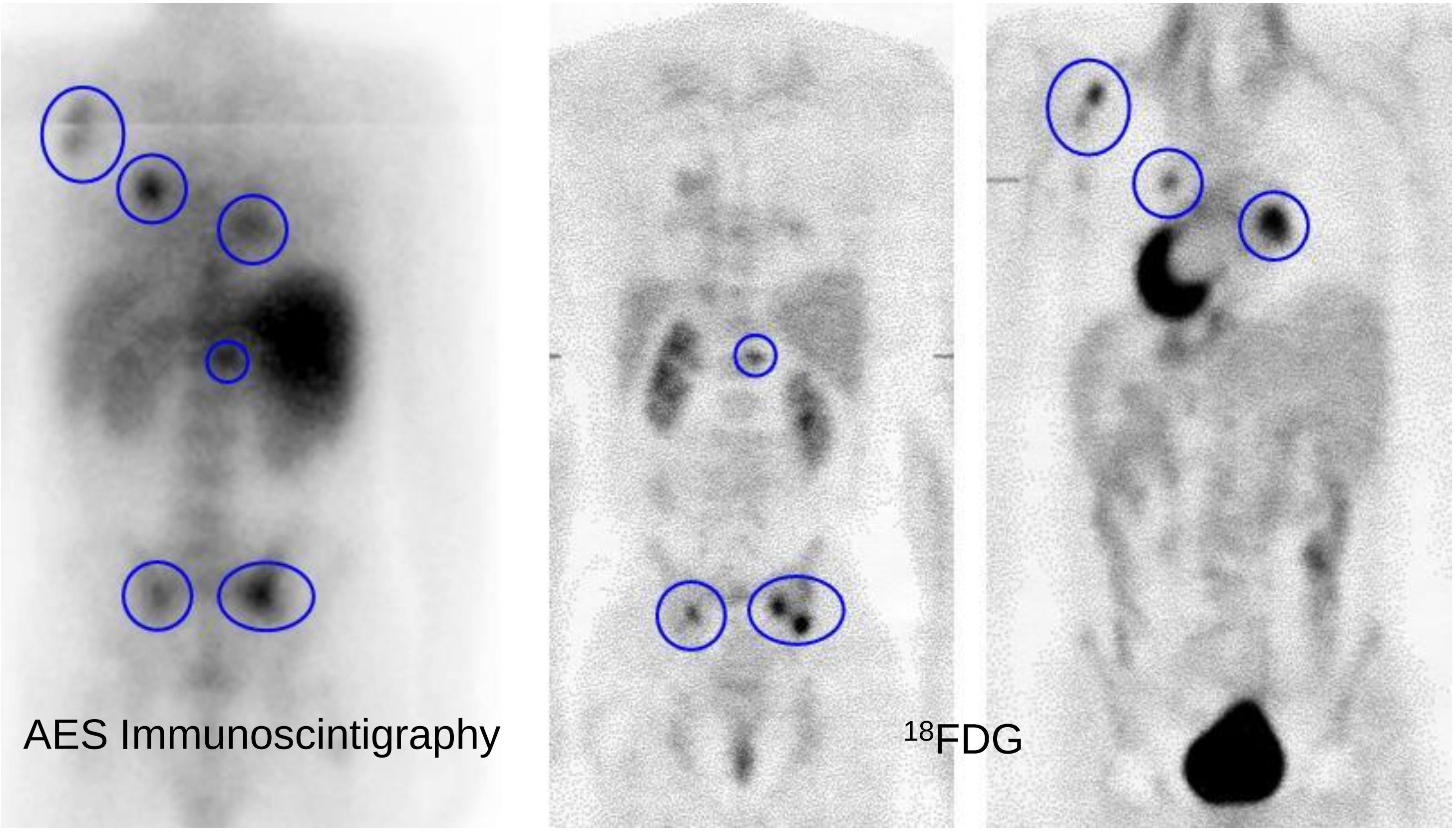
AES Pretargeting





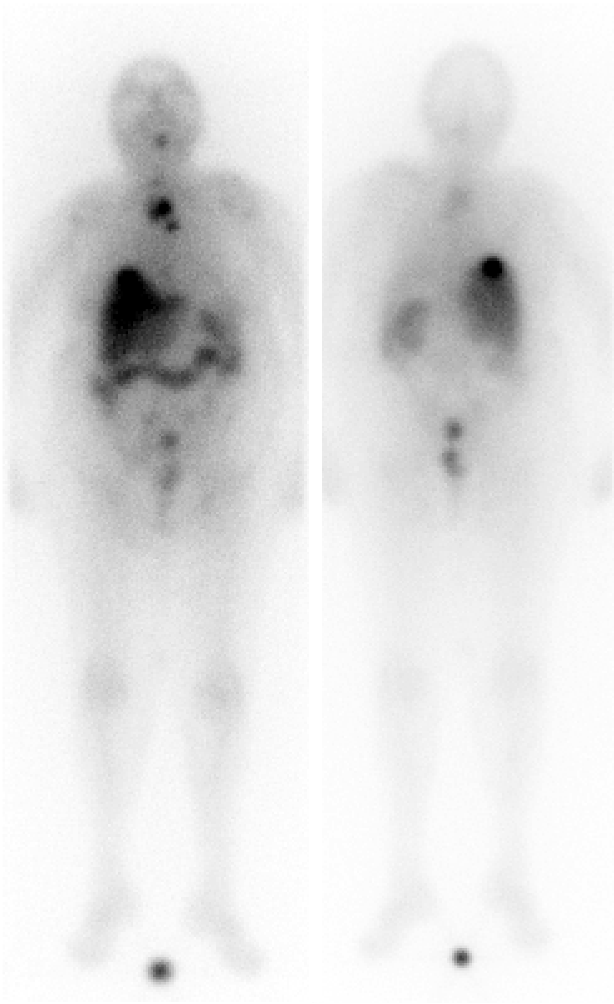
Barbet J, Peltier P, Bardet S, Vuillez JP, Bachelot I, Denet S, Olivier P, Leccia F, Corcuff B, Huglo D, Proye C, Rouvier E, Meyer P, Chatal JF. Radioimmunodetection of medullary thyroid carcinoma using indium-111 bivalent hapten and anti-CEA x anti-DTPA-indium bispecific antibody. J Nucl Med. 1998;39:1172-8.

Immunoscintigraphy versus TEP



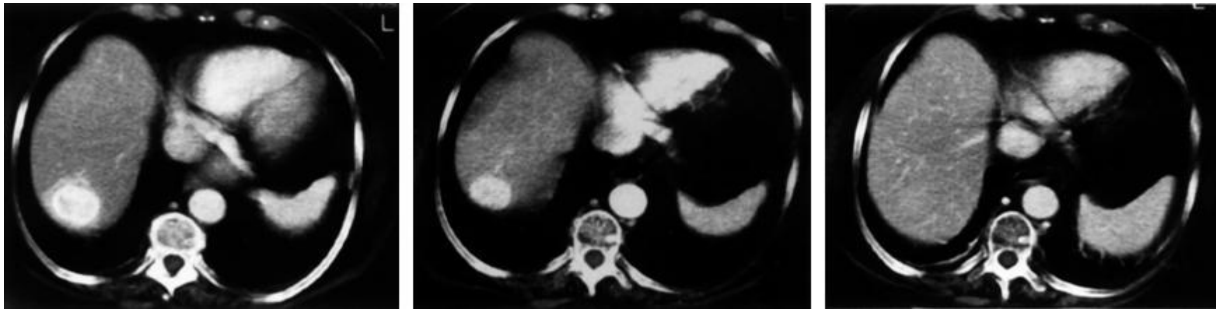
Kraeber-Bodéré F, Faivre-Chauvet A, Ferrer L, Vuillez JP, Brard PY, Rousseau C, Resche I, Devillers A, Laffont S, Bardiès M, Chang K, Sharkey RM, Goldenberg DM, Chatal JF, Barbet J. Pharmacokinetics and dosimetry studies for optimization of anti-carcinoembryonic antigen x anti-hapten bispecific antibody-mediated pretargeting of Iodine-131-labeled hapten in a phase I radioimmunotherapy trial. Clin Cancer Res. 2003;9:3973S-81S.

AES radioimmunotherapy of Medullary Thyroid Carcinoma



80 mCi of ^{131}I-hapten

Toxicity: grade 0 (WBC, PLT)



Before RIT **6 months** **12 months**

Kraeber-Bodéré F, Bardet S, Hoefnagel CA, Vieira MR, Vuillez JP, Murat A, Ferreira TC, Bardiès M, Ferrer L, Resche I, Gautherot E, Rouvier E, Barbet J, Chatal JF. Radioimmunotherapy in medullary thyroid cancer using bispecific antibody and iodine 131-labeled bivalent hapten: preliminary results of a phase I/II clinical trial. Clin Cancer Res. 1999;5:3190s-3198s.

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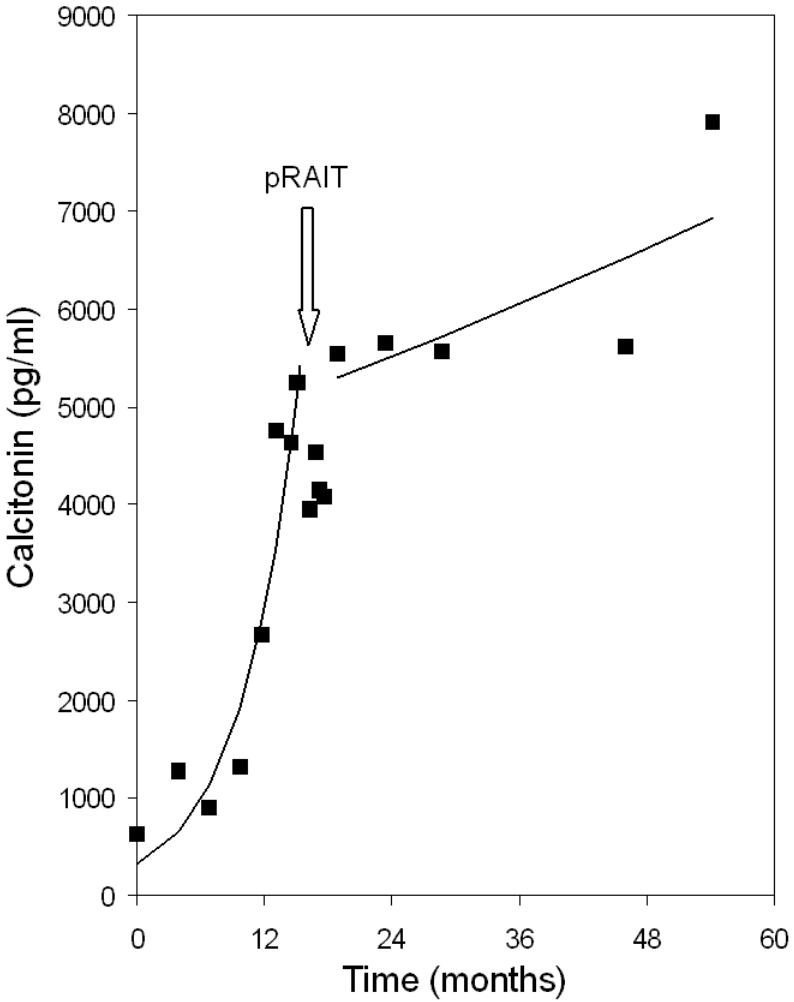
AES radioimmunotherapy of Medullary Thyroid Carcinoma

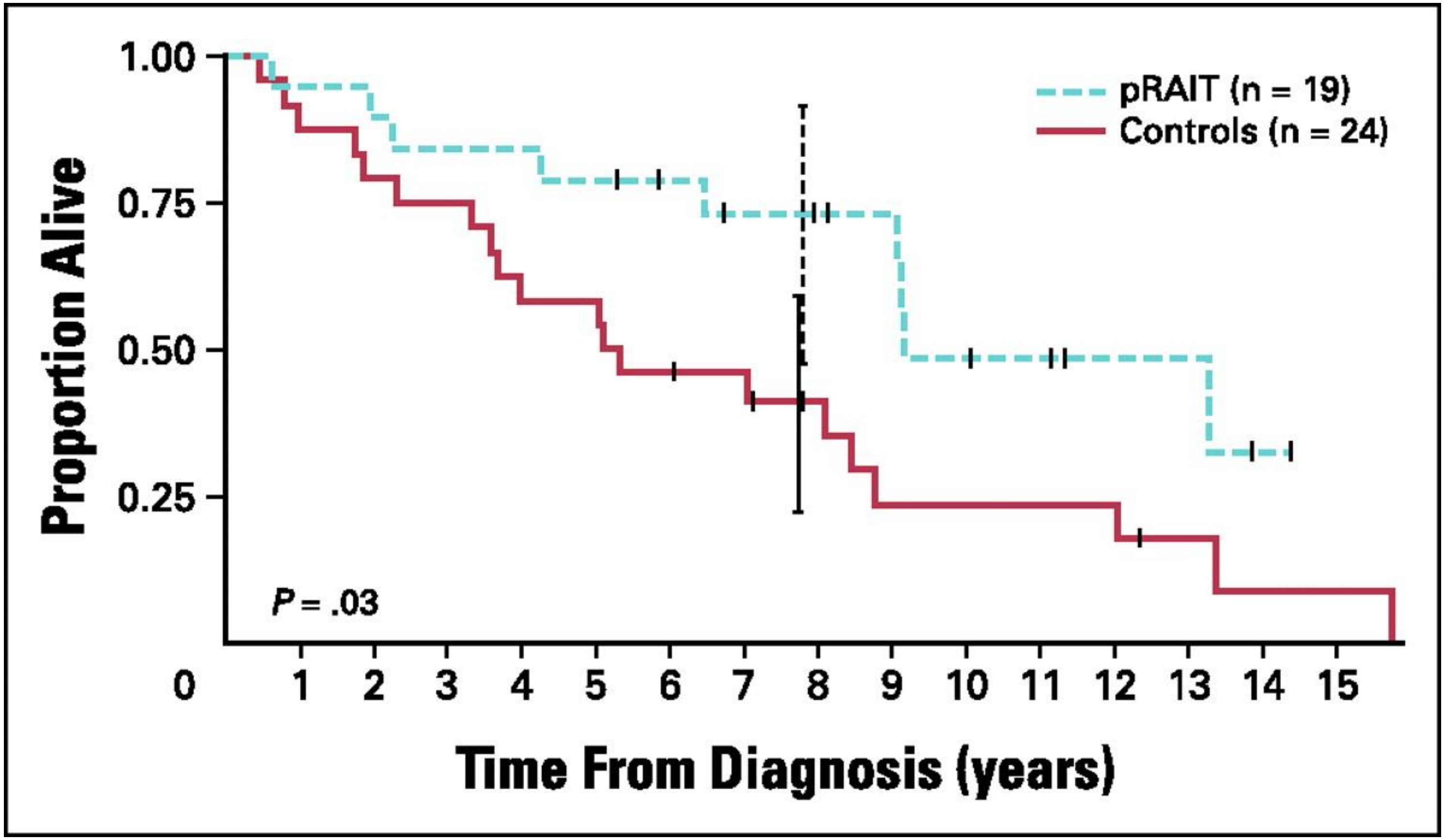


Disease stabilization

Beneficial to cancer patients ?

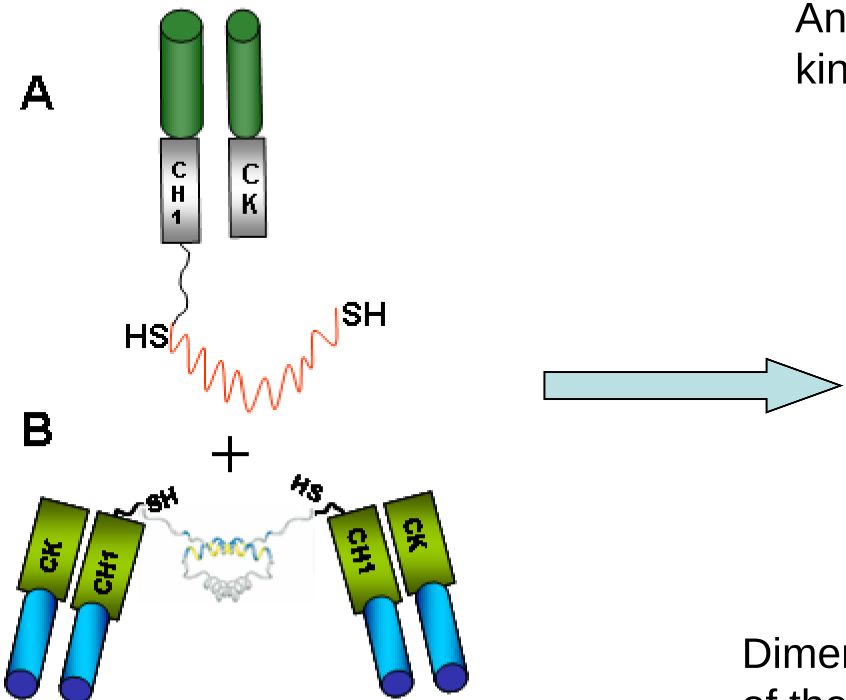
Kraeber-Bodéré F, Rousseau C, Bodet-Milin C, Ferrer L, Faivre-Chauvet A, Campion L, Vuillez JP, Devillers A, Chang CH, Goldenberg DM, Chatal JF, Barbet J. Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and 131I-labeled bivalent hapten in a phase I optimization clinical trial. J Nucl Med. 2006;47:247-55.

AES radioimmunotherapy of Medullary Thyroid Carcinoma

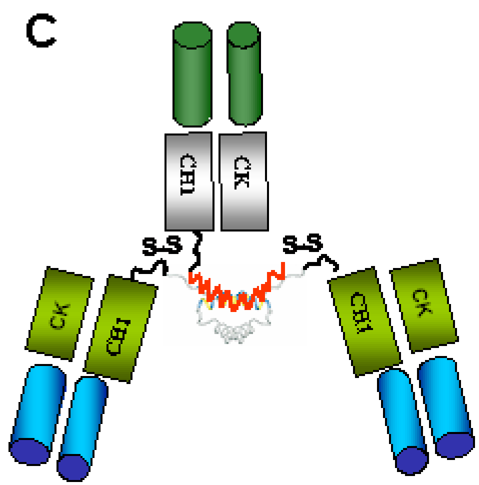


Chatal JF, Campion L, Kraeber-Bodéré F, Bardet S, Vuillez JP, Charbonnel B, Rohmer V, Chang CH, Sharkey RM, Goldenberg DM, Barbet J; French Endocrine Tumor Group. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group. J Clin Oncol. 2006;24:1705-11

The "Dock and Lock" system



Anchoring domains (AD) of A kinase anchor proteins (AKAPs)



Dimerization and docking domain (DDD) of the regulatory subunit of PKA

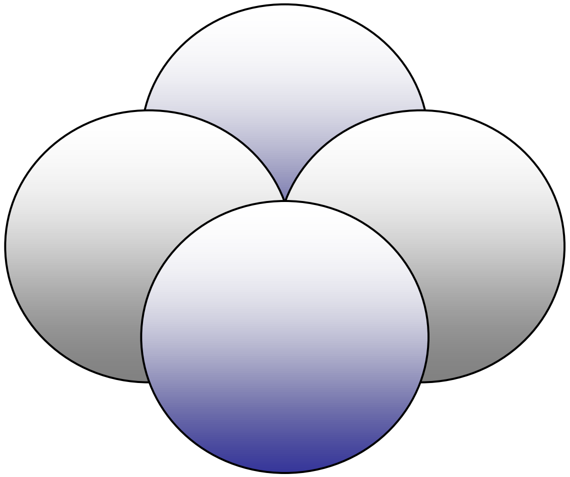
TF2: 157 kDa divalent x monovalent anti-CEA x anti-HSG

Rossi EA et al. Stably tethered multifunctional structures of defined composition made by the dock and lock method for use in cancer targeting. Proc Natl Acad Sci U S A. 2006, 103, 6841-6846.
Sharkey RM et al. Signal amplification in molecular imaging by pretargeting a multivalent, bispecific antibody. Nat Med. 2005, 11, 1250-1255.

Electrons and alpha particles

Positron , Electron

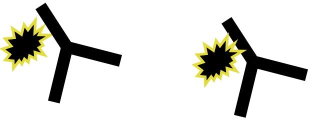
Helium nucleus



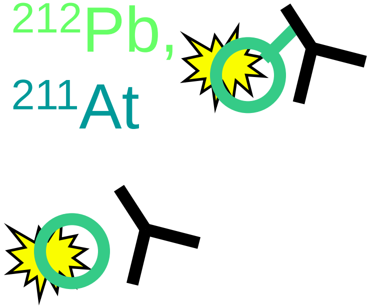
	iodine-131	bismuth-213
Mean range	360 µm	60 µm
Energy	0.182 MeV	5.9 MeV
LET	0.5 keV/µm	100 keV/µm
Half-life	8 days	46 min

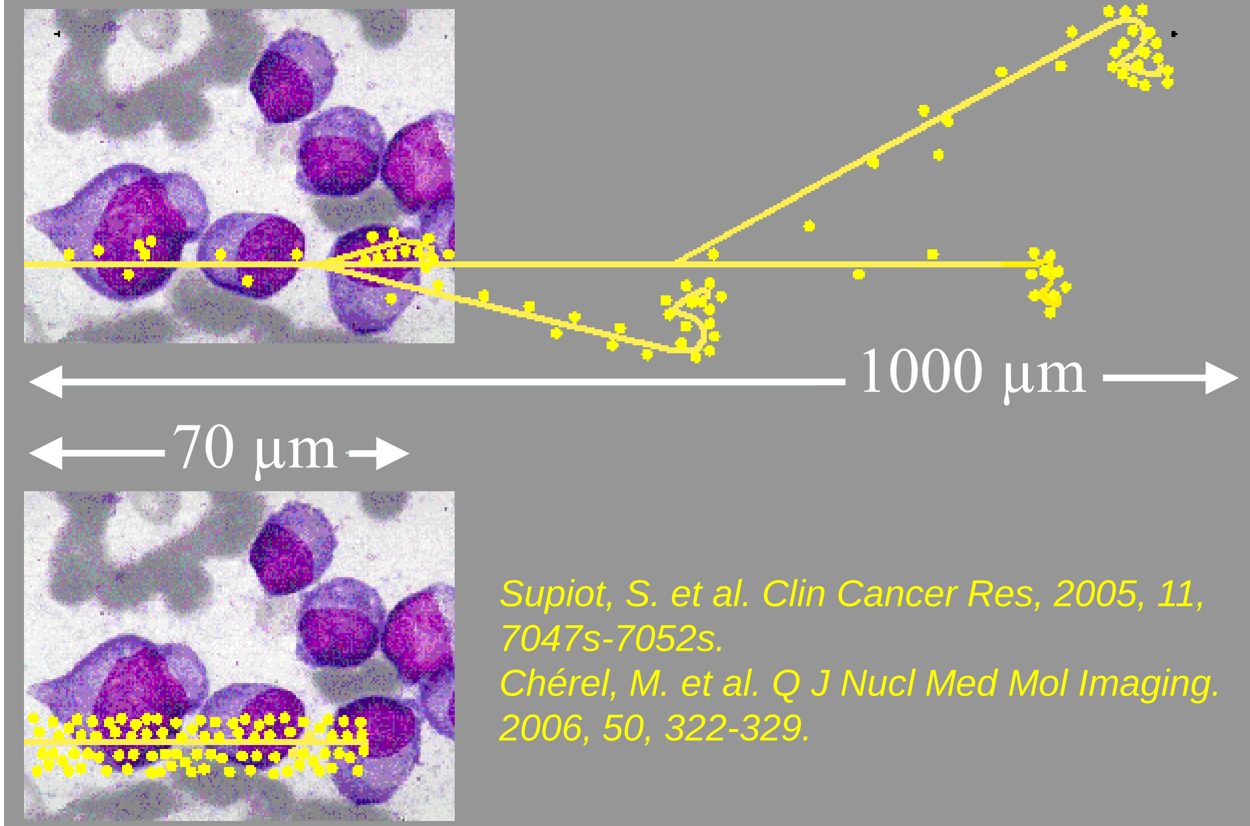
Alpha-immunotherapy

^{131}I, ^{90}Y,
^{177}Lu,
^{67}Cu, ^{47}Sc



^{213}Bi,
^{212}Bi,
^{212}Pb,
^{211}At





Supiot, S. et al. Clin Cancer Res, 2005, 11, 7047s-7052s.
Chérel, M. et al. Q J Nucl Med Mol Imaging. 2006, 50, 322-329.

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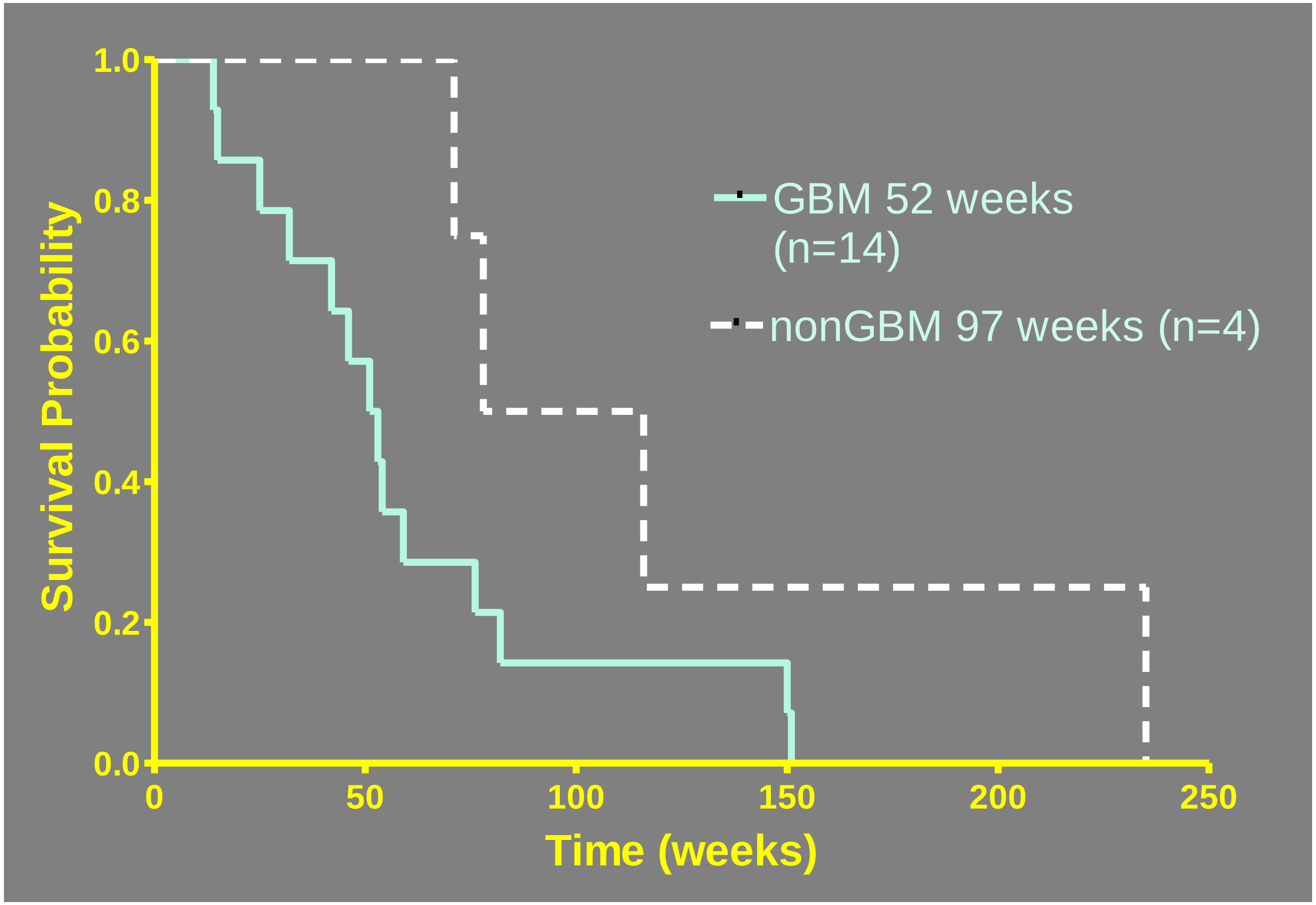
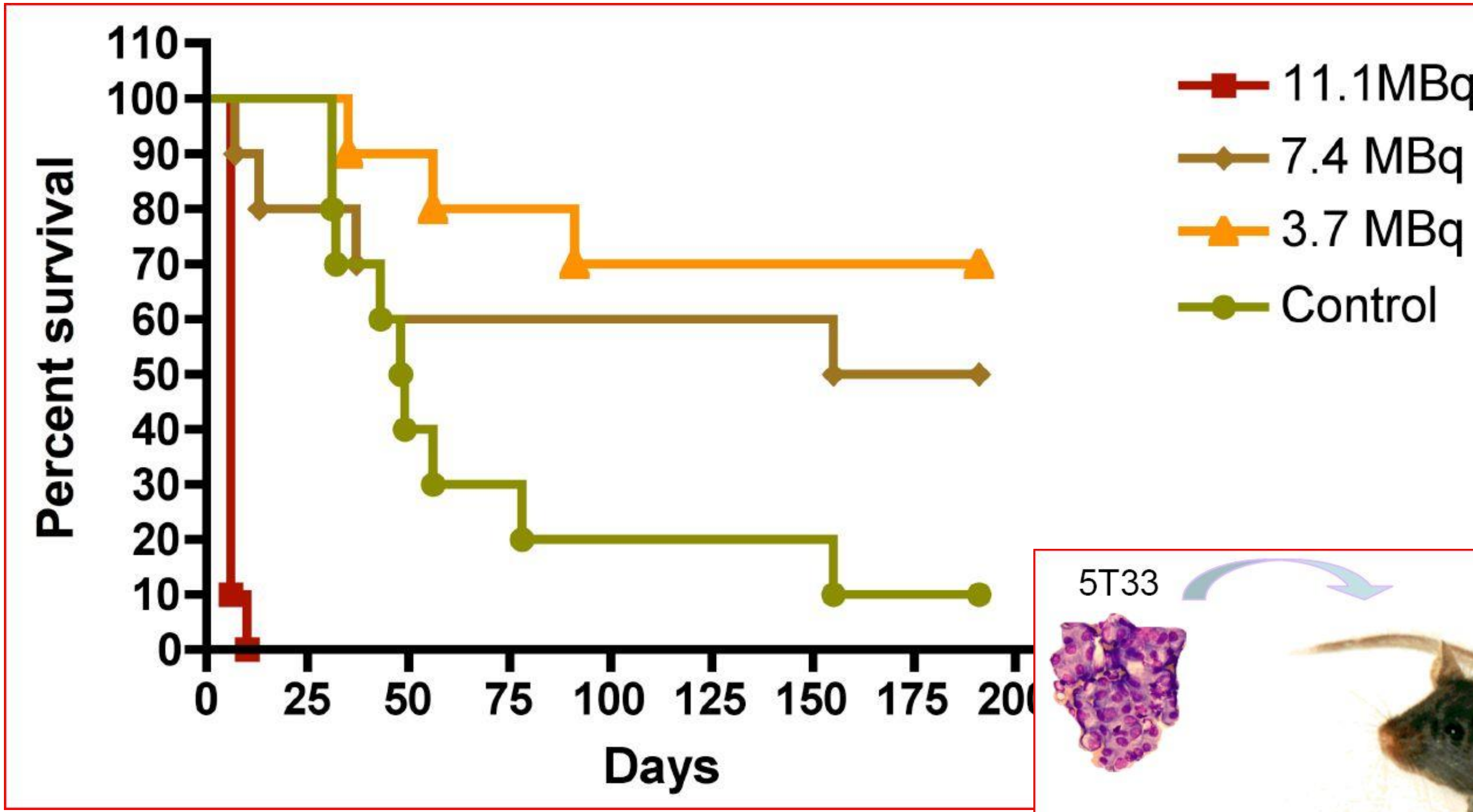
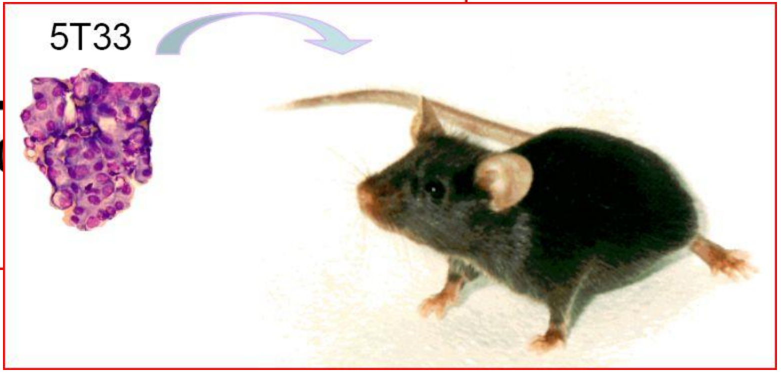
Phase 1 ^{211}At-labeled chimeric 81C6 in recurrent brain tumor patients



Historical Control: 23 weeks: Brem H et al., Lancet. 1995, 345, 1008-12.
Zalustky MR, Nuclear Medicine Tomorrow, 2008, Nantes, France

Alpha-immunotherapy of multiple myeloma





Courtesy of Michel Chérel and François Davodeau

C57 Bl/KaLwRij mice

Bismuth-213-labelled anti-CD138 injected i.v.

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Use	Radionuclide	T1/2 (hr)	Emission	Emax (keV)	Production
Gamma Imaging	Iodine-131	193	β^-, γ	610, 362	Reactor
	Iodine-123	13.3	γ	159	Cyclotron
	Technetium-99m	6.0	γ	141	Reactor (Generator)
	Indium-111	67	γ	171, 245	Cyclotron
	Gallium-67	78	β^-, γ	607-907, 93	Cyclotron
PET	Carbon-11	0.34	β^+	961	Cyclotron
	Fluorine-18	1.8	β^+	633	Cyclotron
	Scandium-44/44m	3.9/59	β^+	1474	Cyclotron (Generator)
	Gallium-68	1.1	β^+	1899	Cyclotron (Generator)
	Copper-64	12.7	β^+, β^-	653, 1675	Cyclotron
	Iodine-124	100.2	β^+	1535 and 2138	Cyclotron
	Zirconium-89	78.4	β^+, γ	897, 909	Cyclotron
Therapy	Iodine-131	193	β^-, γ	610, 362	Reactor
	Yttrium-90	64	β^-	2250	Reactor
	Rhenium-188	17	β^-, γ	2120, 155	Reactor (Generator)
	Lutetium-177	161	β^-, γ	498, 208	Reactor
	Copper-67	61.8	β^-, γ	392-577, 185	Cyclotron
	Scandium-47	80	β^-, γ	441, 159	Cyclotron
	Bismuth-213	0.76	α, γ	5869 and 8376	Nuclear waste (Generator)
	Astatine-211	7.2	α, X	5869 and 7450	Cyclotron

Région BRETAGNE

Région PAYS DE LA LOIRE

REGION Poitou Charentes la démocratie participative

UNIVERSITÉ DE NANTES

AGENCE NATIONALE DE LA RECHERCHE ANR

Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE

PREFECTURE DE LA REGION PAYS DE LA LOIRE

PREFECTURE DE LA LOIRE-ATLANTIQUE

angers loire métropole communauté d'agglomération

académie Nantes

MINISTÈRE DE L'ÉDUCATION NATIONALE

MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR ET DE LA RECHERCHE

Nantes Métropole COMMUNAUTÉ URBAINE

LOIRE ATLANTIQUE Conseil général

Anjou CONSEIL GÉNÉRAL DÉPARTEMENT DE MAINE-ET-LOIRE

cnrs dépasser les frontières

Inserm Institut national de la santé et de la recherche médicale

ECOLE DES MINES DE NANTES

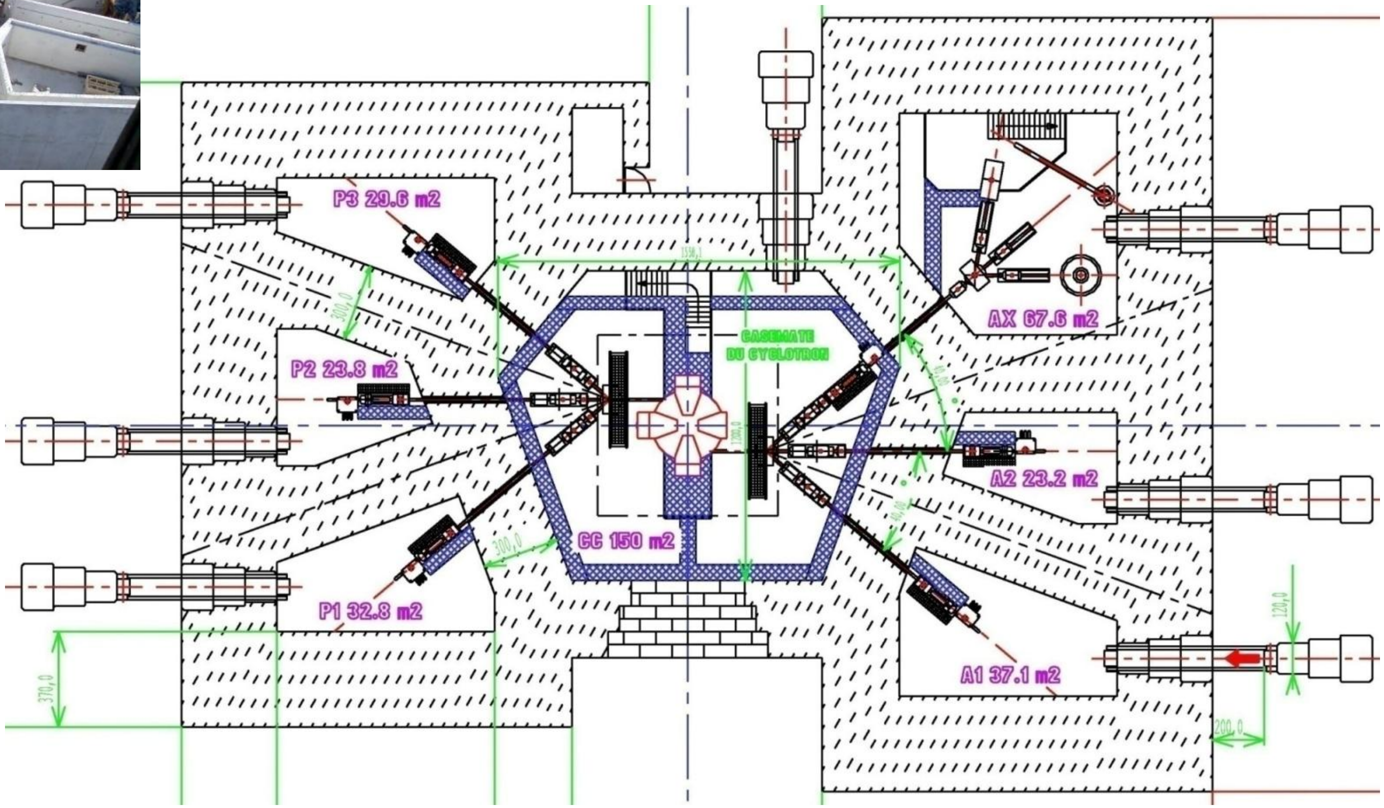
CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Centre René Gauducheau Centre de Lutte Contre le Cancer —Nantes Atlantique—

ARRONAX

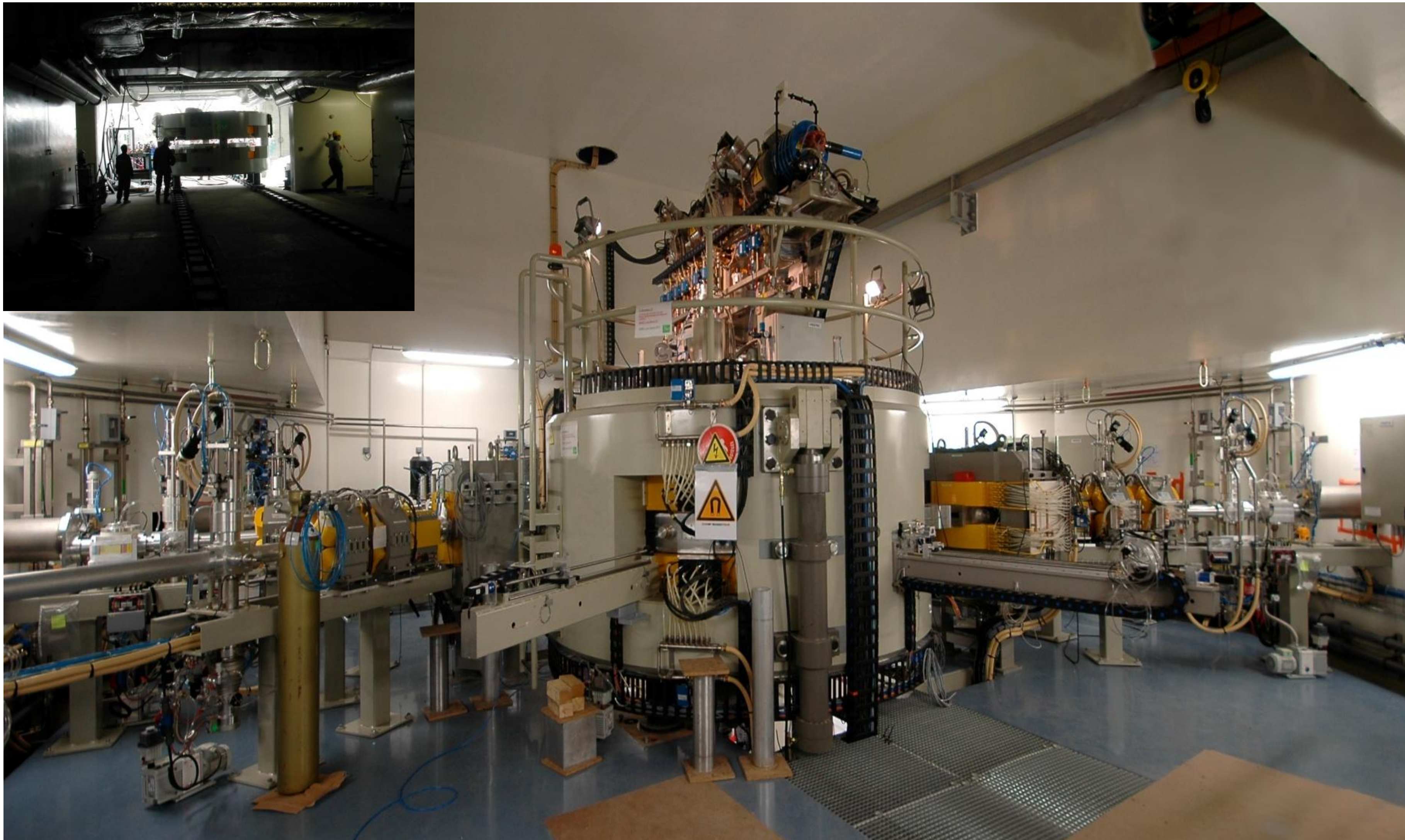
The Arronax building

Vaults and beam lines



ARRONAX

The cyclotron (Vault CC)

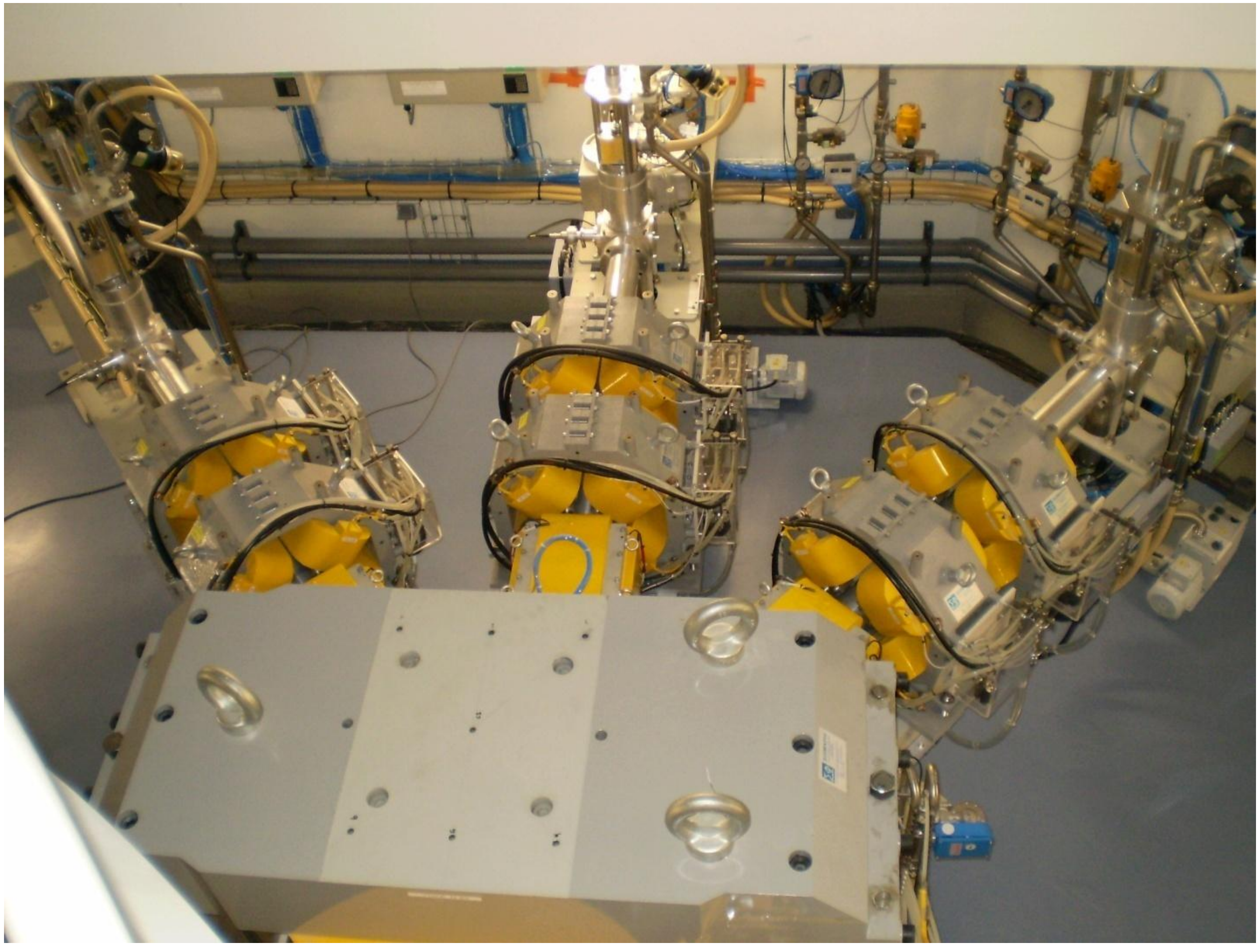


ARRONAX

Vault doors

Motorized door on rails (35 t)

Beam switches



AX Vault: radiolysis and radiobiology

ARRONAX

Radionuclide production beam line

Targetry system

Shielded hoods

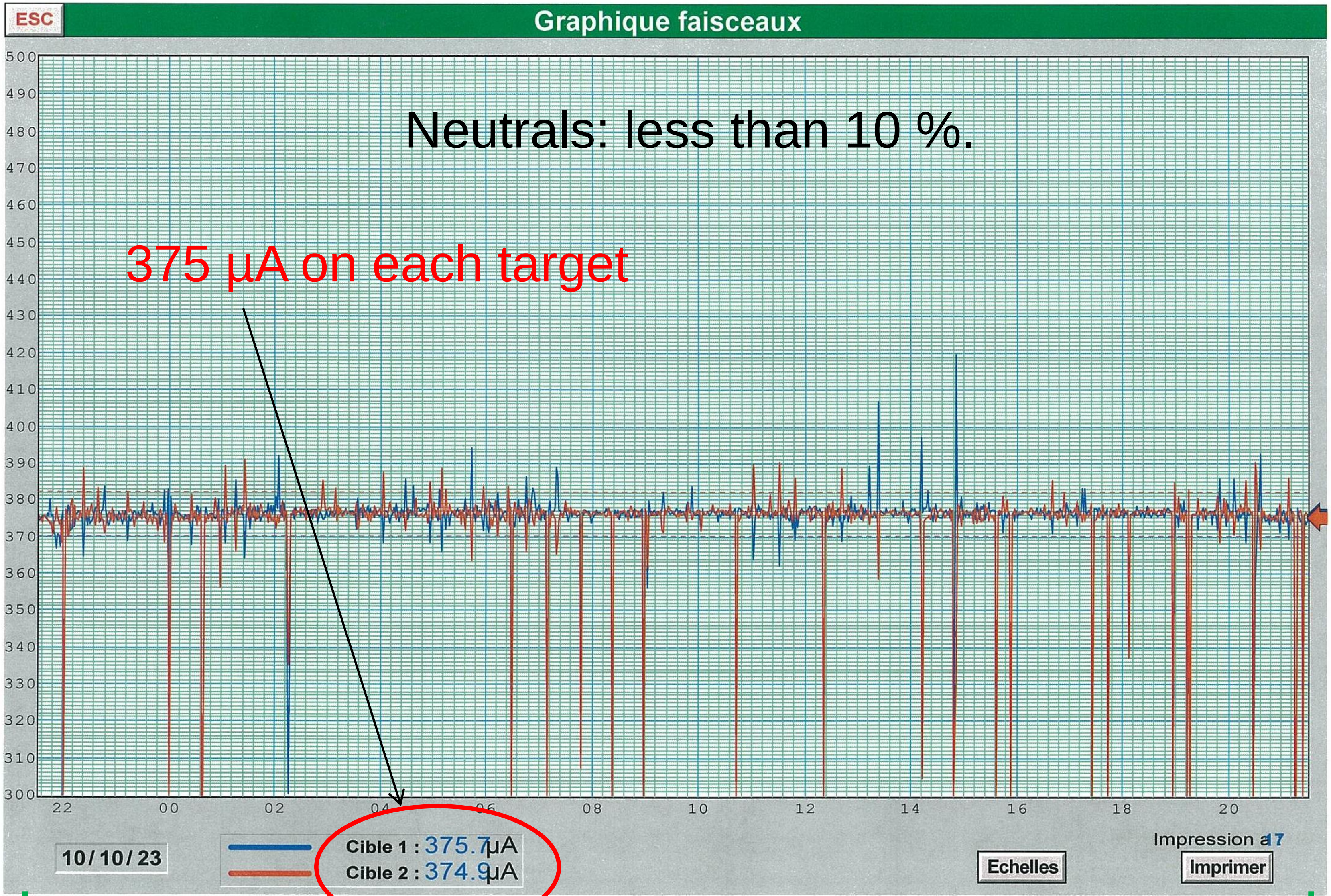
Main characteristics:
High energy - High intensity

Beam	Accelerated particles	Energy range (MeV)	Intensity (µA)	Dual beam
Proton	H^-	30-70	<375	Yes
	HH^+	17	<50	No
Deuteron	D^-	15-35	<50	Yes
Alpha	He^{++}	68	<70	No

Specifications have been achieved and the cyclotron is fully operational since January 2011

Neutrals: less than 10 %.

375 µA on each target



24 hours

Arronax missions

- To produce radionuclides for research purposes (Nuclear Medicine)
  - Not suitable to produce fluorine-18 or carbon-11. A priority list of radionuclides has been set.
- To serve as an irradiation facility for radiolysis and radiobiology research projects
  - Alpha particle pulsed beam, protons, gammas (cesium-137 source), even neutrons (Adiabatic Resonance Crossing system with AAA).
- To produce radionuclide for commercial purposes and help regional economy development
- To participate in student (University and Ecole des Mines) and professional training

Haddad F, Ferrer L, Guertin A, Carlier T, Michel N, Barbet J, Chatal JF. ARRONAX, a high-energy and high-intensity cyclotron for nuclear medicine. Eur J Nucl Med Mol Imaging. 2008;35:1377-87.

Major projects

- Alpha-immunotherapy (cooperation with the Oncology Research team of the Nantes-Angers Cancer Research Center, Chelatec and Atlab Pharma)
  - Production of astatine-211
  - Treatment of multiple myeloma and propstate cancer (AlphaRIT consortium)
- Brachytherapy (cooperation with AAA)
  - Neutron activation for the production of holmium-166
  - Treatment of liver cancer (Theranean consortium)
- Pairs of electron/positron emitters for targeted radionuclide therapy
  - Copper-67/copper-64
  - Scandium-47/scandium-44
- Studies of water radiolysis with the pulsed alpha-beam in the context of nuclear waste strorage
- Pulsed alpha-beam for radiobiology studies
- Industrial projects
  - Strontium-82 for strontium-82/rubidium-82 generators (TEP in cardiology)
  - Germanium-68 for germanium-68/gallium-68 generators (TEP in oncology)

Strontium-82 production: target

$^{85}Rb + p \rightarrow {}^{82}Sr + 4n$

- **Pressed** pellet of RbCl

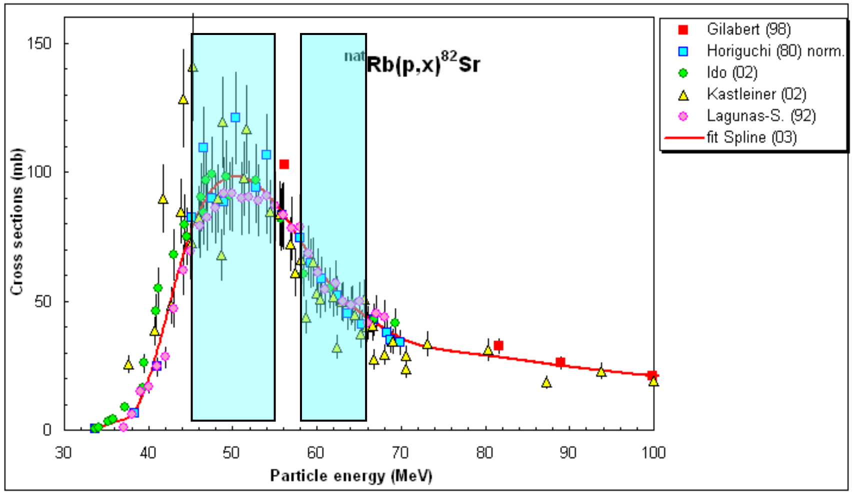
  Purity > 99.8%

  mass = 4.0 g

- **Encapsulated** in laser welded stainless steel

Encapsulation

- **Dual target**



Specifications of the final product

- **Total Radioactivity** at Calibration Time
- **Specific Activity*** ≥ 925MBq/mg (≥ 25mCi/mg)
- **Activity concentration*** ≥ 1850MBq/mL (≥ 50mCi/ml)
- **Radionuclide identity**
  Energy of major photoelectric peak having energy of 776.5keV via the Rb-82 daughter at the equilibrium
- **Radionuclide purity***
  ^{85}Sr ≤ 5 GBq/GBq^{82}Sr (≤ 5mCi ^{85}Sr/mCi ^{82}Sr)
  ^{83}Rb ≤ 0.0015 GBq/GBq^{82}Sr (≤ 0.0015 mCi ^{83}Rb/mCi ^{82}Sr)
  ^{84}Rb ≤ 0.0015 GBq/GBq ^{82}Sr (≤ 0.0015 mCi ^{84}Rb/mCi ^{82}Sr)
  ^{83}Sr ≤ 0.0015 GBq/GBq ^{82}Sr(≤ 0.0015 mCi ^{83}Sr/mCi ^{82}Sr)
  All other radiocontaminants ≤ 0.01 GBq/GBq ^{82}Sr (≤ 0.01 mCi/mCi ^{82}Sr)

- **Appearance:** Clear, colorless solution

***specifications** are given at the calibration time (7 days after ship date)

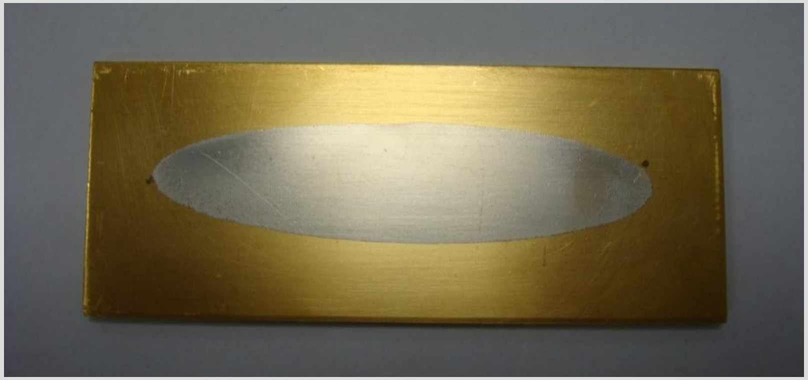
This radiochemical is not tested for sterility or pyrogenicity.

Copper-64 production

$^{64}Ni + p \rightarrow n + ^{64}Cu$

Target: electroplated nickel-64 on a gold support

Extraction yield: >90%
Radionuclide purity > 99.9%
Ni recovery >90%

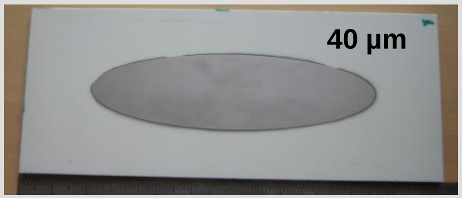


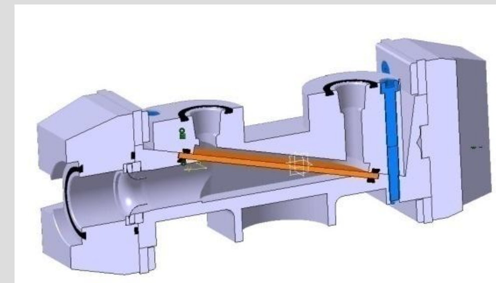
Production started at Arronax in September 2011

Astatine-211 production

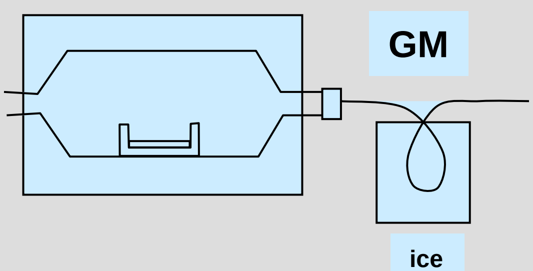
$^{209}Bi + alpha \rightarrow\ ^{211}At + 2n$

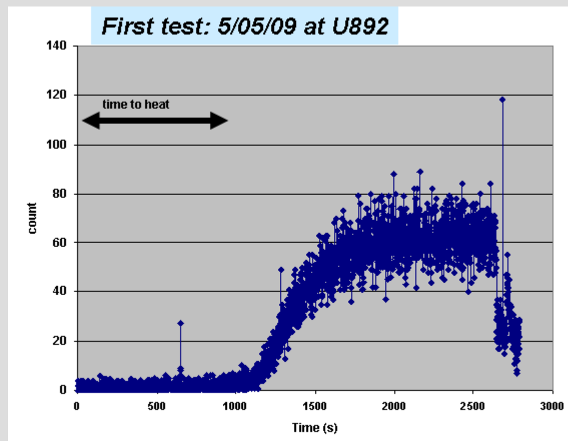
Bismuth deposited under vacuum on AlN





Extraction by distillation





Monitoring the extraction

Production: 200-300MBq /week at CEMHTI/CNRS (Orléans, France)
Yield: around 80%

Production is expected to start at Arronax 1^er semester of 2012

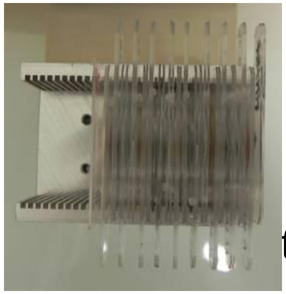
Optimisation of radionuclide production

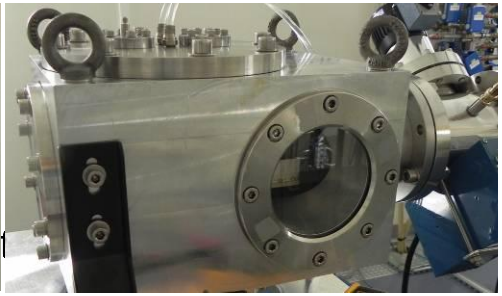
- To calculate expected activities
  - development of an analytical calculation code
  - use of Monte-Carlo codes

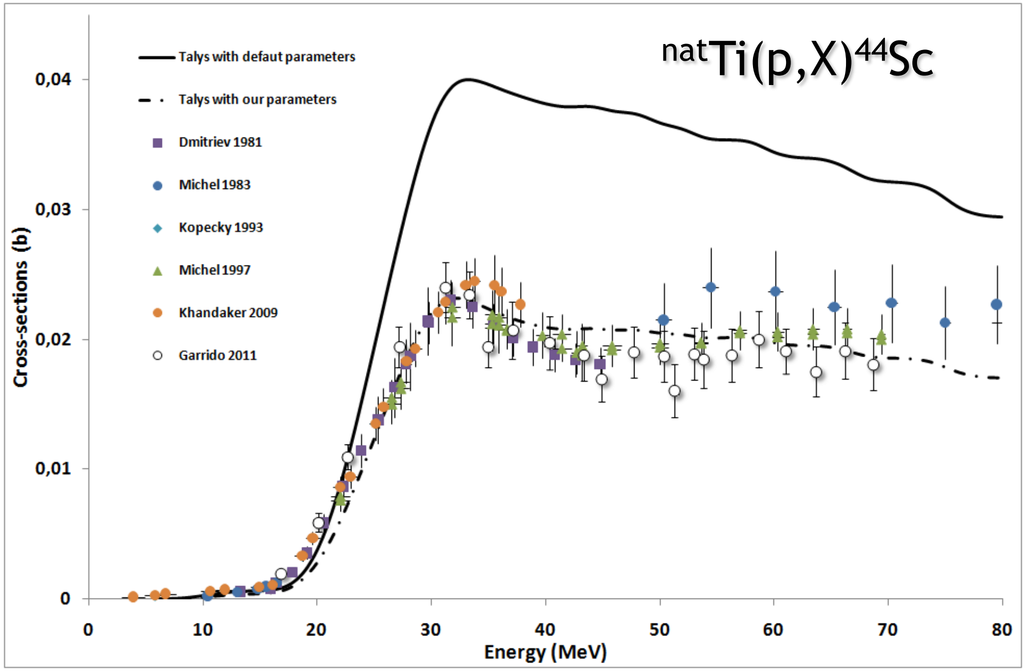
$$A_{ct} = \phi \, \frac{N_A . \rho}{A} \left(1 - e^{-\lambda t}\right) \int_{E_{min}}^{E_{max}} \frac{\sigma(E)}{dE/dx} \, dE$$

reaction cross section

- Measurement of production cross section
  - Development of an experimental device on ARRONAX (stacked foils)

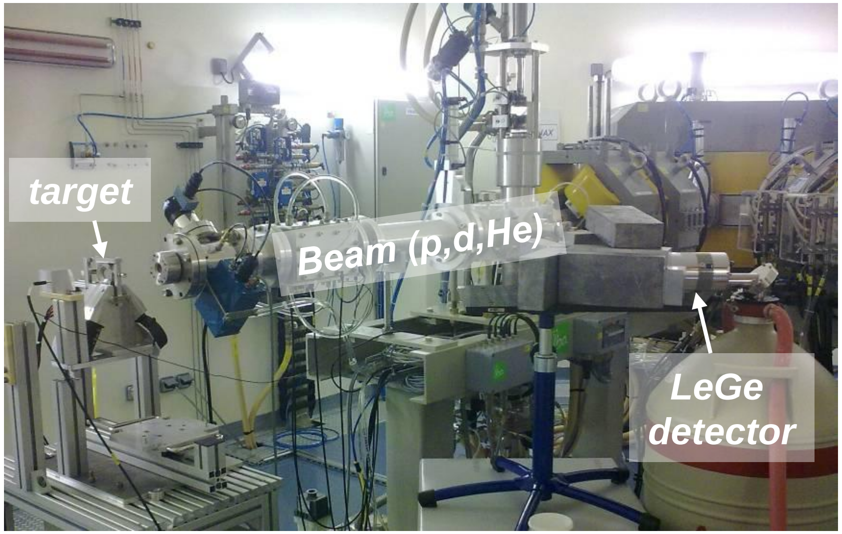


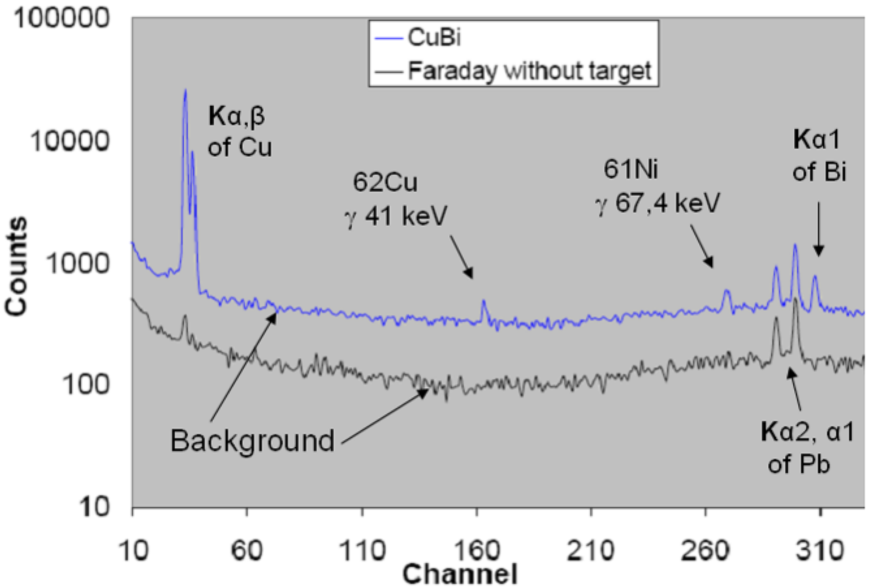




Proton Induced X-ray Emission at ARRONAX

- High energy PIXE at ARRONAX (up to 70MeV)
  - information deeper than the surface
  - multi layer analysis (RX and gamma information)
  - various type of incident particles (p, d, alpha)
- Feasibility studies in progress





Conclusion

- Nuclear Medicine is making progress in imaging (PET) and therapy (Targeted Radionuclide Therapy)
- Radionuclides other than the traditional ones are needed
- Arronax will supply some of these as it is a now running with the original specifications met
- Production of radionuclides and radiochemistry experiments have started
- We still need a few months to deliver radionuclides to research teams and industry
- One challenge will be for us to be capable of producing radionuclides such as strontium-82 or copper-67 at the very high intensities that the cyclotron can deliver
- Another challenge will be to meet GMP standards

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