INTEGRATED ACADEMIC STUDIES OF MEDICINE

IASM

FACULTY OF MEDICAL SCIENCES

IASM41

Radionuclide Therapy of Bone and Liver Metastases

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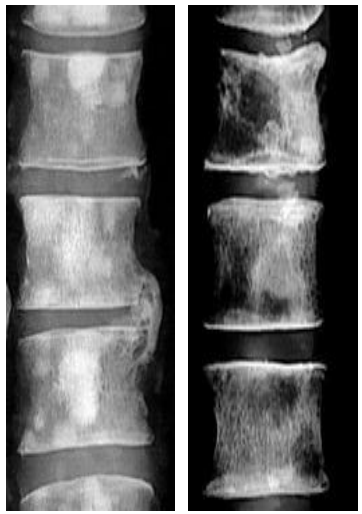
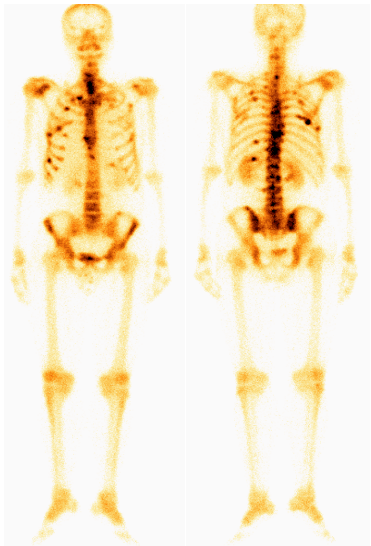
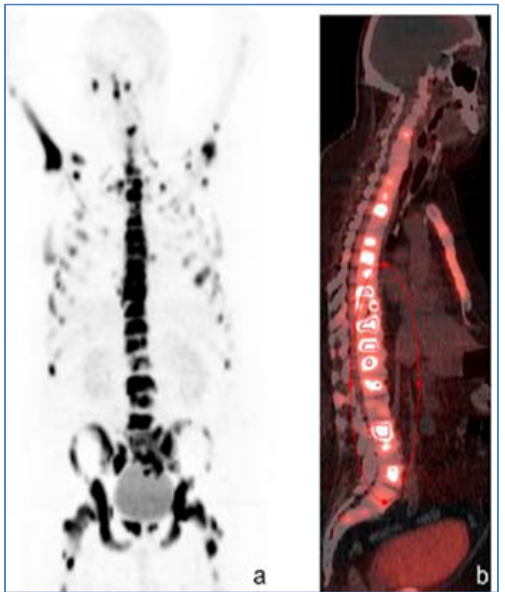
Assist. Prof.

Spectrum of Bone Disease in Cancer

Tumor	Mean frequency, %	Range, %
Breast	73	47–85
Prostate	68	33–85
Thyroid	42	28–85
Kidney	35	33–40
Lung	36	30–55
Esophagus	6	5–7
Gastrointestinal	5	3–11
Rectum	11	8–13





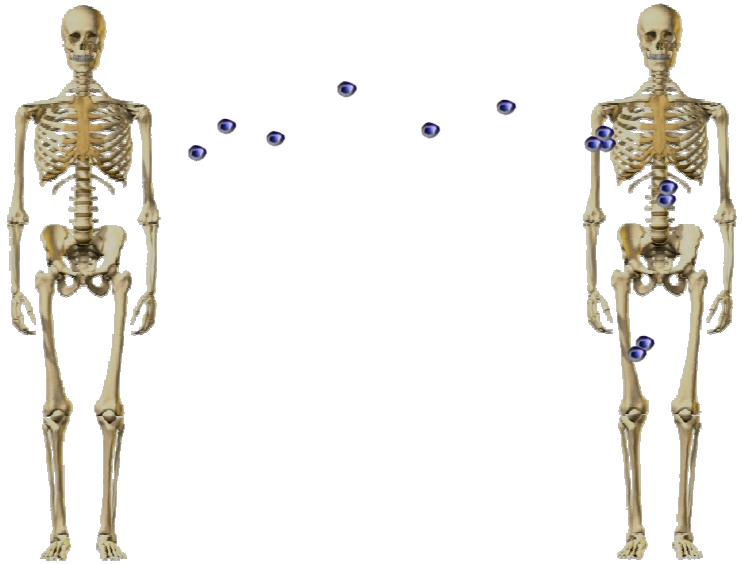


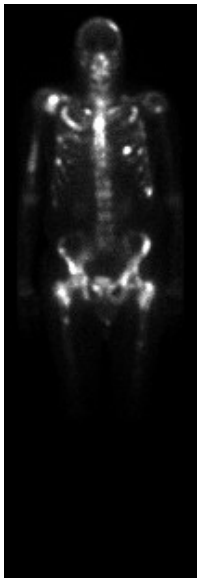
Spectrum of Bone Disease in Cancer

Treatment-Related Fractures

New Bone Metastases

Disease-Related Skeletal Complications



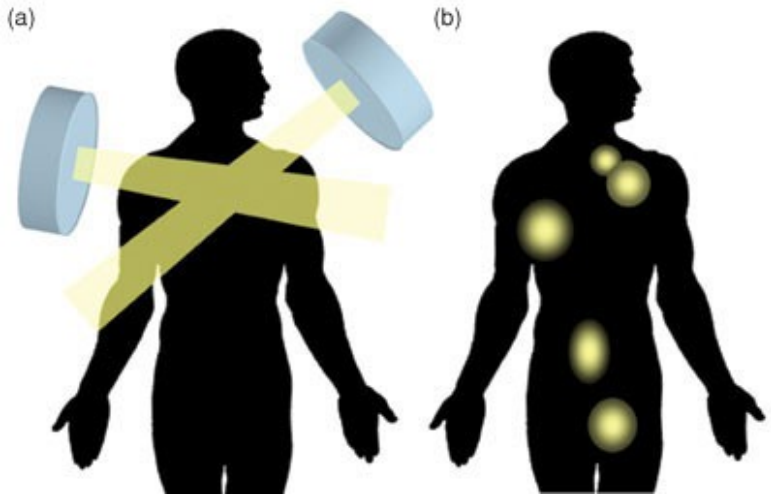


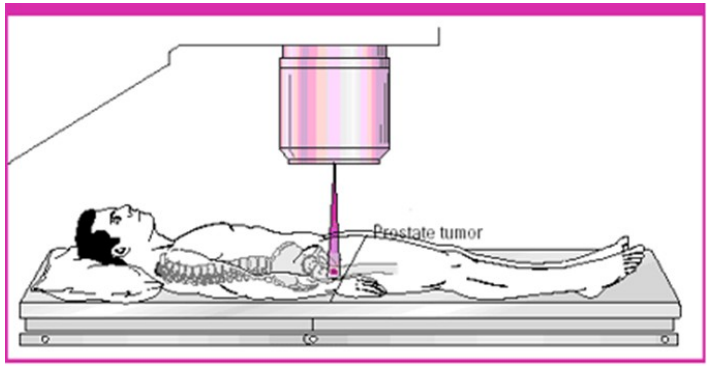
Targeted → Delivery of radiation to specific tissue

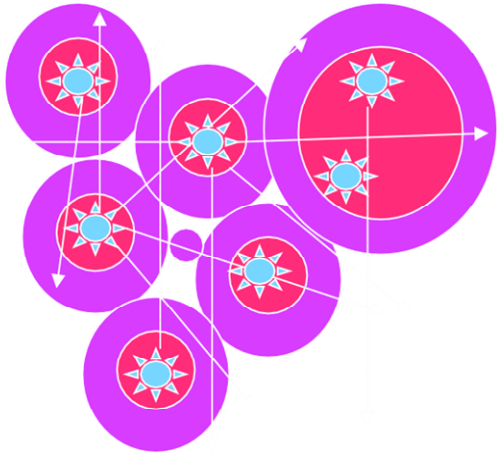
Radionuclide → Use of radiation to destroy lesions

Therapy → Treatment of benign or malignant lesions

Targeted Radionuclide Therapy







Spectrum of Bone Disease in Cancer

NCCN National Comprehensive Cancer Network®

NCCN Task Force Report: Bone Health in Cancer Care

American Cancer Society®

- Analgetics

I- aspirin, ibuprofen, naproxen; II- kodein; III- morfin

- Bifosfonats:

Alendronat, Risedronat, Ibandronate, Zoledronat

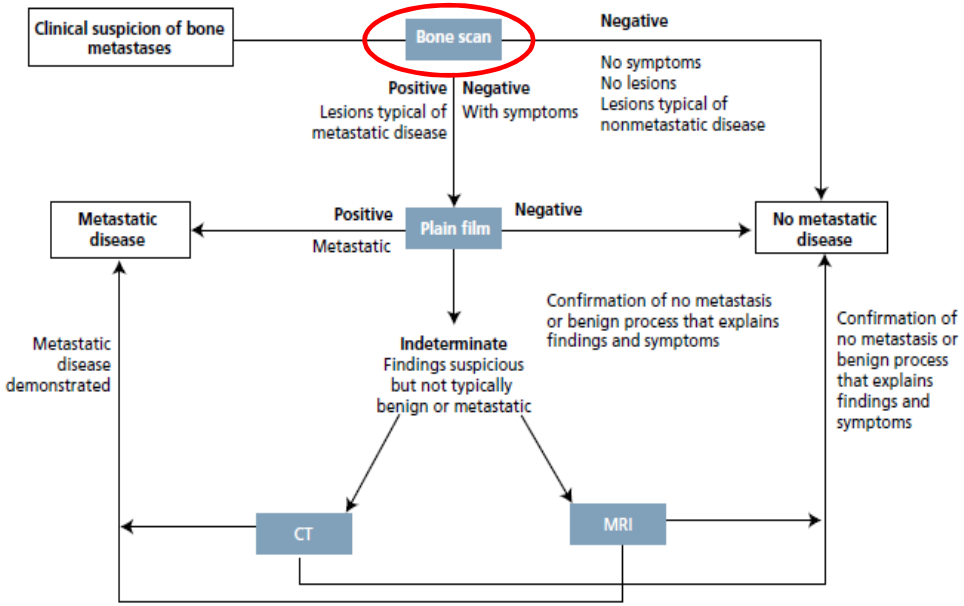
- Radiotherapy
- Chemotherapy:

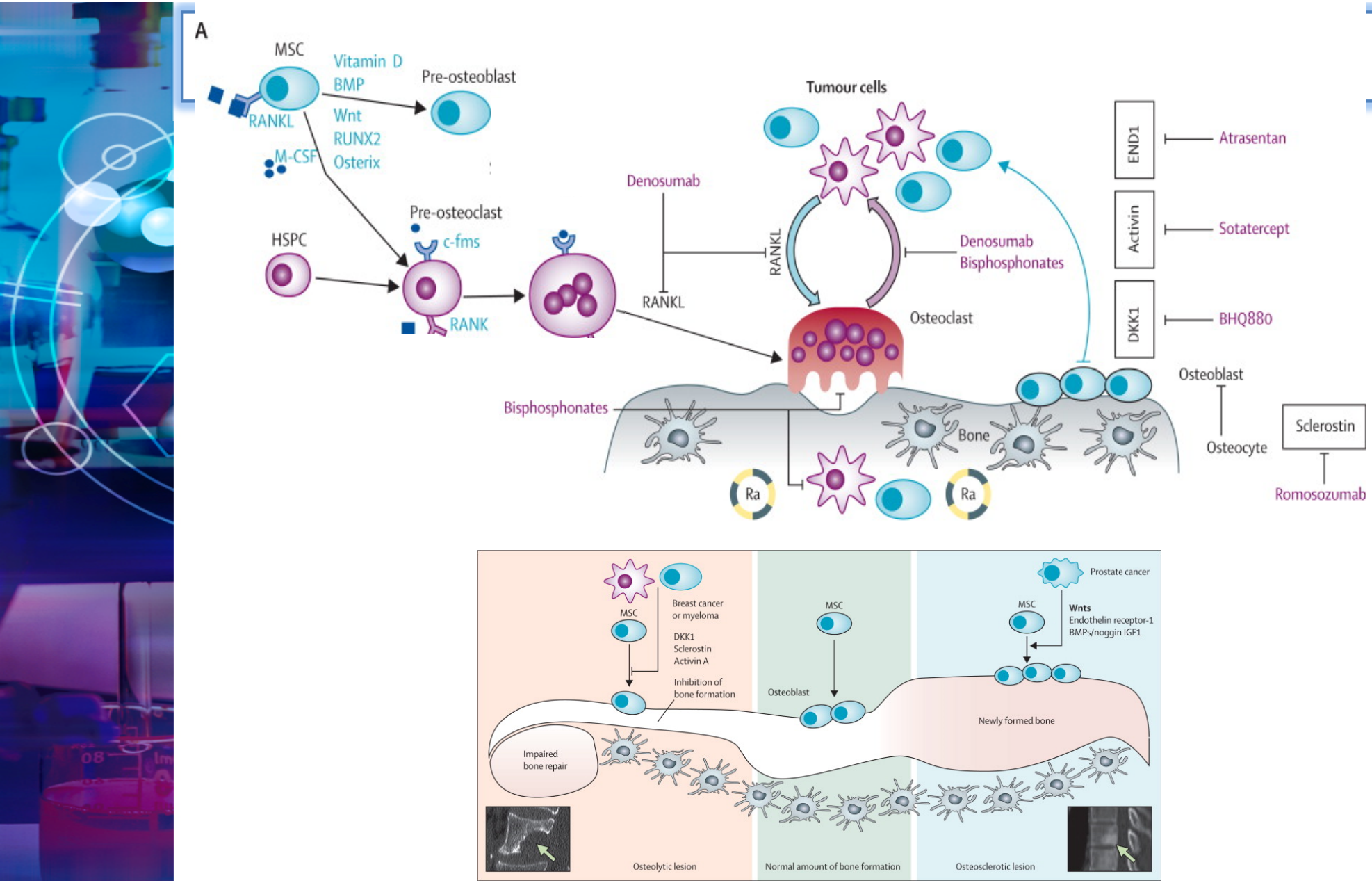
Tamoxifen, Aminoglutetimid

- Biologic therapy:

Denosumab

- Surgery
- Radionuclide therapy




A
MSC
Vitamin D
BMP
Wnt
RUNX2
Osterix
Pre-osteoblast
RANKL
M-CSF
HSPC
Pre-osteoclast
c-fms
RANK
Tumour cells
Denosumab
RANKL
RANKL
Denosumab
Bisphosphonates
Osteoclast
Bisphosphonates
Bone
Ra
Ra
END1
Atrasentan
Activin
Sotatercept
DKK1
BHQ880
Osteoblast
Osteocyte
Sclerostin
Romosozumab

MSC
Breast cancer
or myeloma
DKK1
Sclerostin
Activin A
Inhibition of
bone formation
MSC
Osteoblast
MSC
Prostate cancer
Wnts
Endothelin receptor-1
BMPs/noggin IGF1
Newly formed bone
Impaired
bone repair
Osteolytic lesion
Normal amount of bone formation
Osteosclerotic lesion

Targeted Radionuclide Therapy

The ideal agent for painful bone metastases:

- ✓More uptake in lesions than normal bone
- ✓Distribution predicted by Tc-99m MDP scan
- ✓Rapid clearance from remainder of body
- ✓Long half life
- ✓Beta energy >0.8 MeV - < 2.0 MeV
- ✓Easy to produce
- ✓Cost reasonable

Targeted Radionuclide Therapy

Radiopharmaceuticals

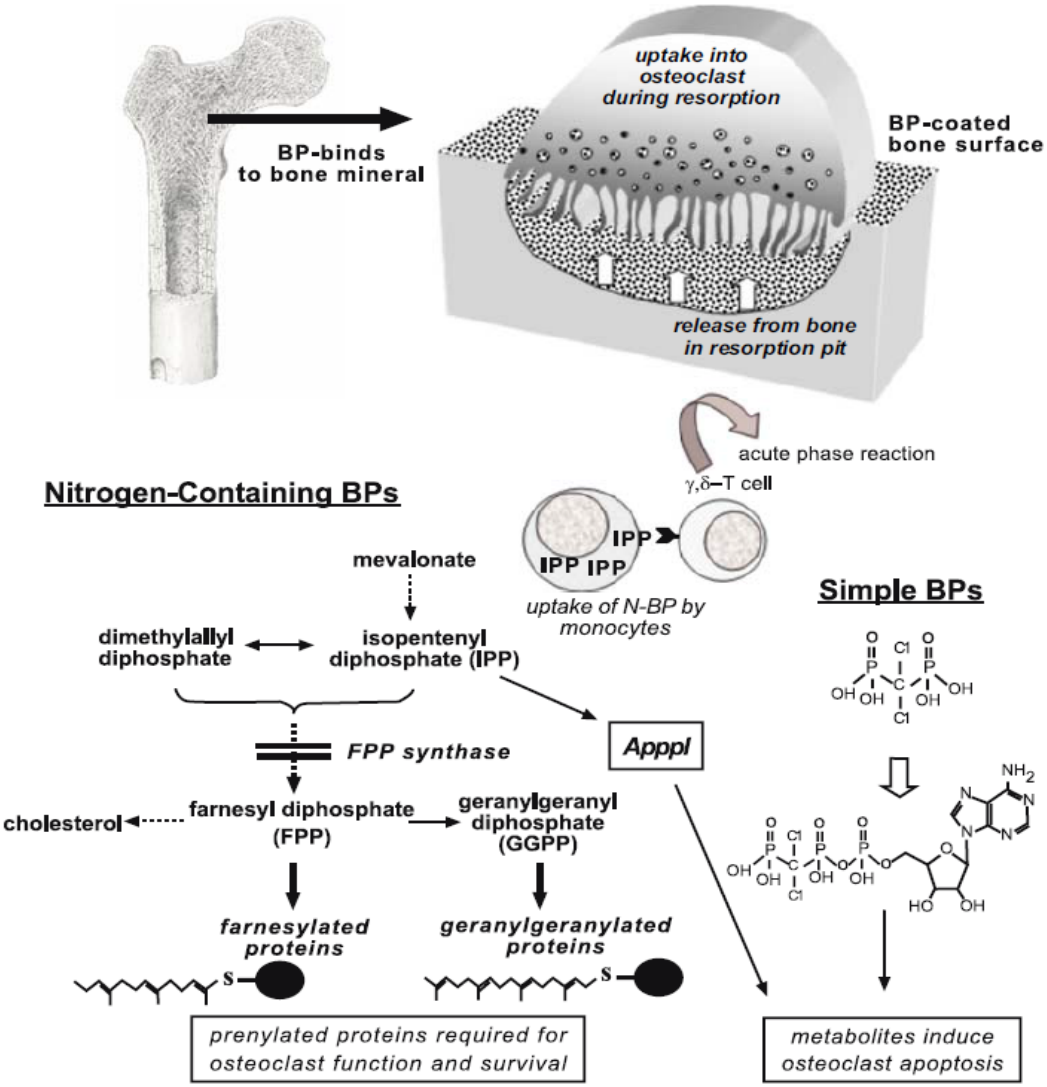
Radiopharmaceutical	Half-life (in days)	Beta-radiation (MeV)		Gamma-radiation		Range in soft tissue (max)
		max	mean	keV	%	mm
^{153}Sm-EDTMP	1.93	0.81	0.23	103	29	3.1
^{186}Re-HEDP	3.7	1.07	0.35	137	9	4.5
^{89}Sr-Chloride	50.5	1.46	0.58	910	0.01	6.6

EDTMP= etilen-diamino-tetrametilen-fosfat
HEDP= hidroksi-etlien-difosfonat

- ^{89}Sr=150 MBq, - **148 MBq**
- ^{153}Sm=37 MBq/kg, **37 MBq/kg**
- ^{186}Re=1,295 MBq **1,3-3 GBq**

i.v. + 0,9%NaCl

- Mechanism of action



Indications

Absolute

✓ Metastases on skeletal scintigraphy
✓ Failure of drug therapy
✓ Failure of other forms of therapy

Relative

✓ Asymptomatic metastases
✓ Less than 3 metastatic foci
✓ Osteolytic metastases
✓ Expected survival less than 60 days

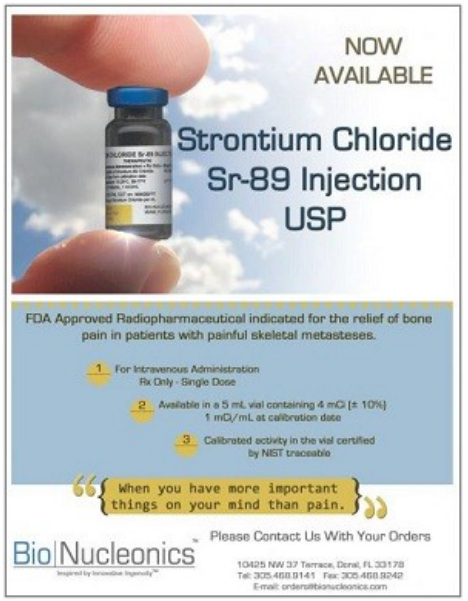
Contraindications

- Pathological fractures
- Hg < 90 gl^{-1},
- Le < 3.5×10^{9} l^{-1},
- Tr < 100×10^{9} l^{-1}
- Cre >180 µmol/l
- GFR <30 ml/min

^{89}Sr (Metastron®)

- 4 mCi fixed dose

GE Healthcare



- FDA-approved in Jun, 1993 for Amersham Health (now GE Healthcare)

^{153}Sm (Quadramet®)

- Complex decay
- Beta has maximum energy of 0.81 keV
- Half-life 1.95 days
- Gamma photon (103 keV) can be used for imaging
- Excretion mostly renal

Quadramet®
iba | Molecular

QUADRAMET®
(SAMARIUM SM 153 LEXIDRONAM INJECTION)
Jazz Pharmaceuticals

- 1 mCi/Kg
- FDA-approved in March 1997 for DuPont Merck
- Now marketed by Jazz Pharmaceuticals in the US and IBA worldwide

Present: ^{153}Sm (Quadramet®)

- 1 mCi/Kg

Quadramet®
iba | Molecular

QUADRAMET®
(SAMARIUM SM 153 LEXIDRONAM INJECTION)
Jazz Pharmaceuticals

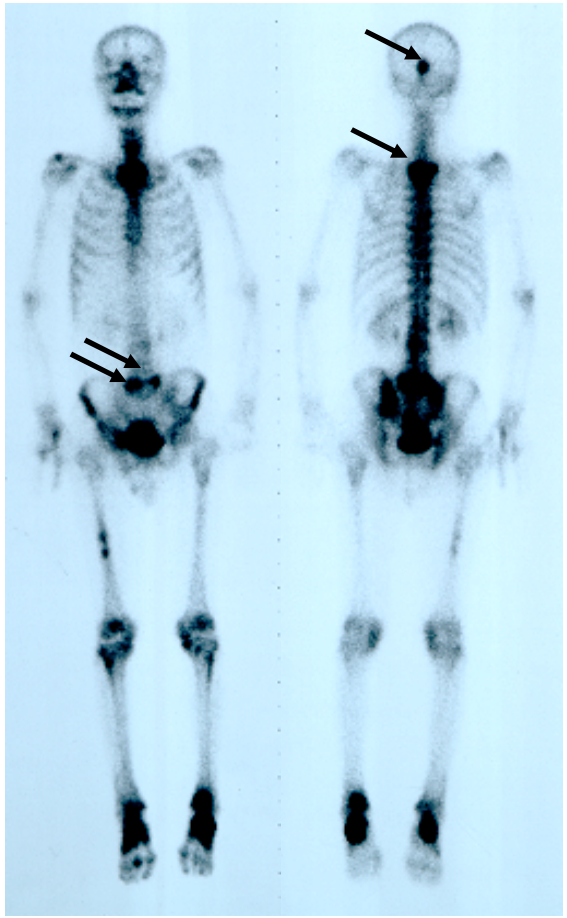
- FDA-approved in March 1997 for DuPont Merck
- Now marketed by Jazz Pharmaceuticals in the US and IBA worldwide

Check list:

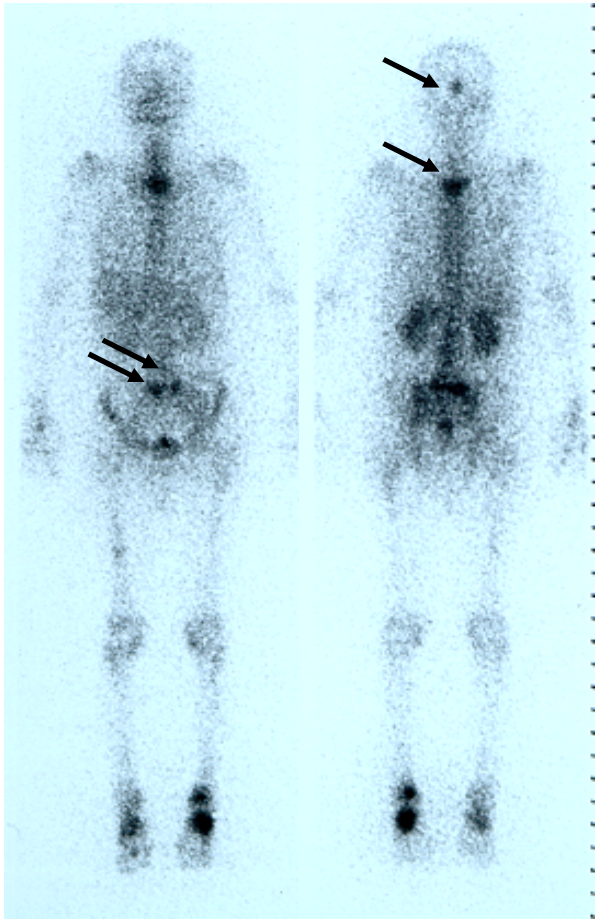
- Proven bone metastases
- Objective evidence of referral for therapy
- Complete blood count
- Recent bone scan
- Signed consent form
- Appropriate continuity of care, including blood counts

Targeted Radionuclide Therapy

^{99m}Tc-MDP

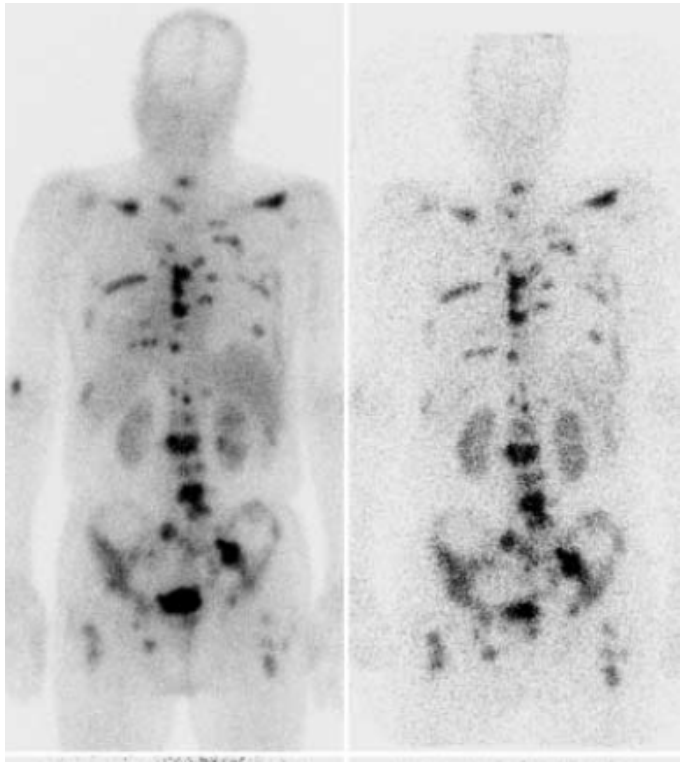


^{186}Re-HEDP

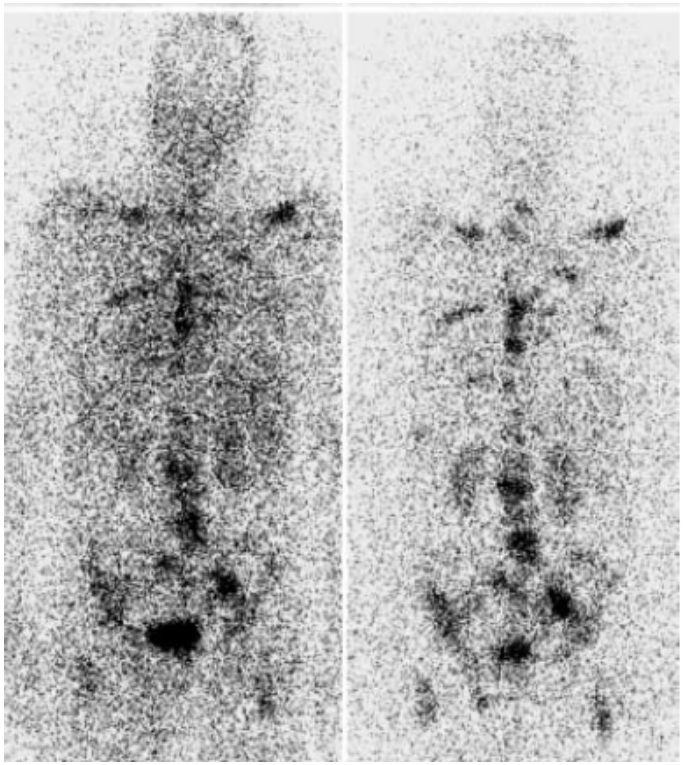


Targeted Radionuclide Therapy

^{99m}Tc-MDP



^{186}Re-HEDP



Targeted Radionuclide Therapy

^{166}Ho-DOTPM

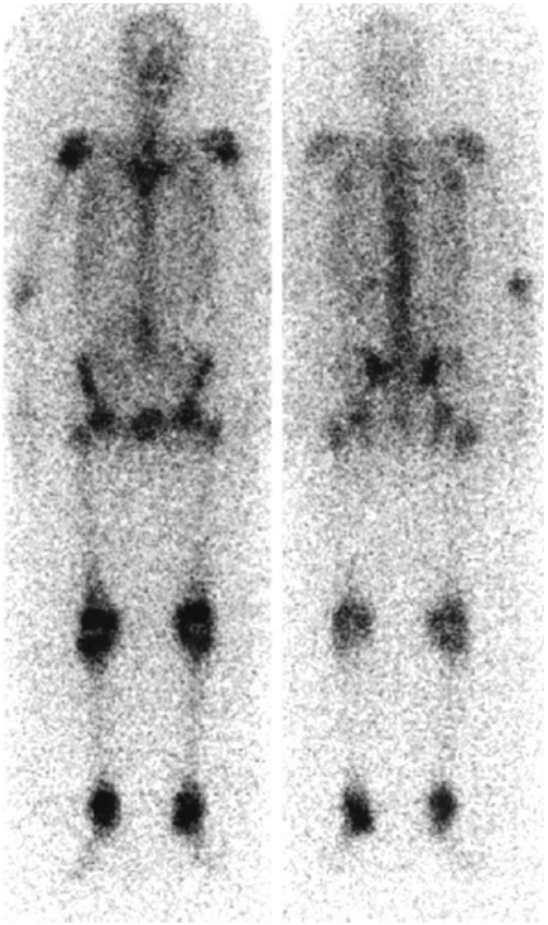
^{177}Lu-BPAMD

^{153}Sm-DOTMP

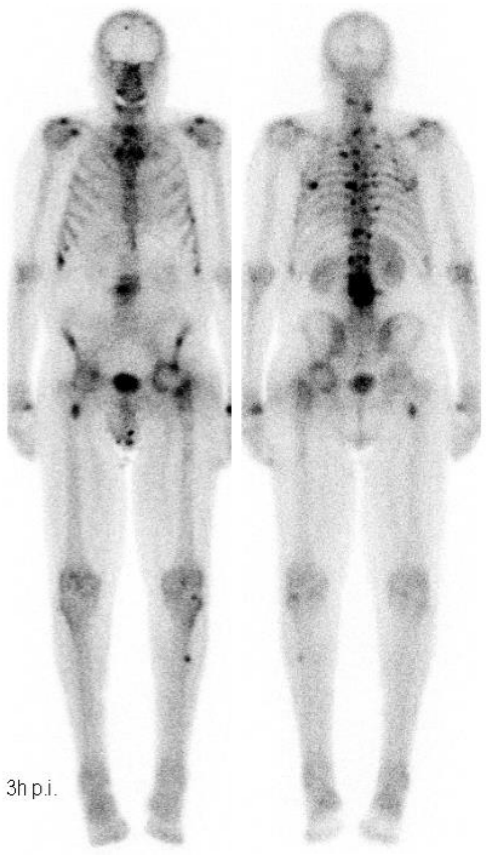
$^{186/188}$Re-CTMP

^{166}Ho-DOTPM

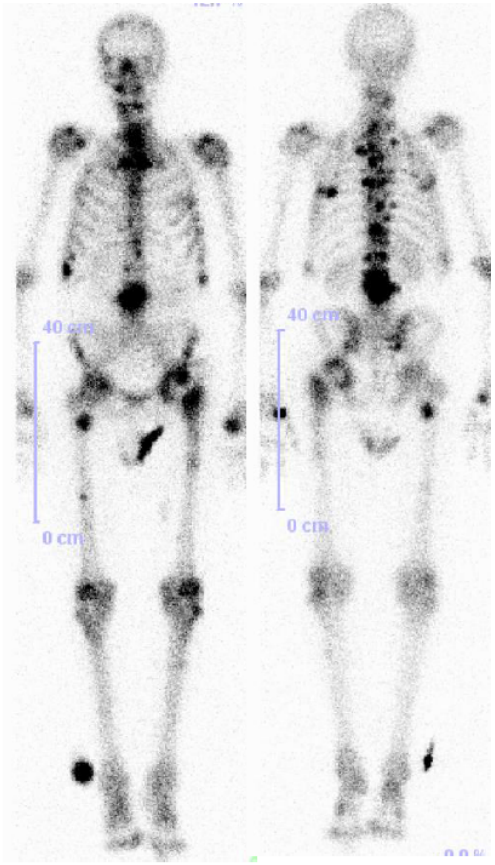
(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid)



Targeted Radionuclide Therapy



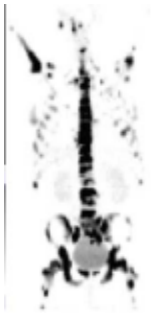
Tc-99m MDP

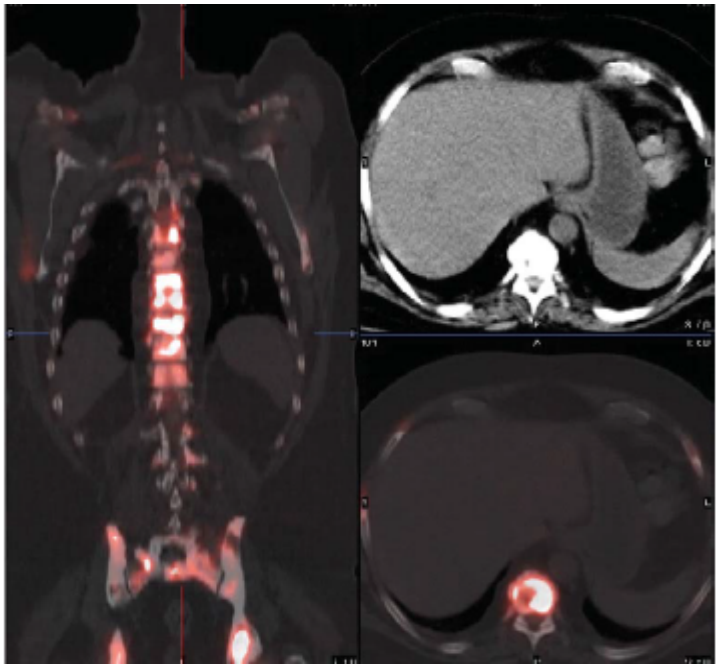


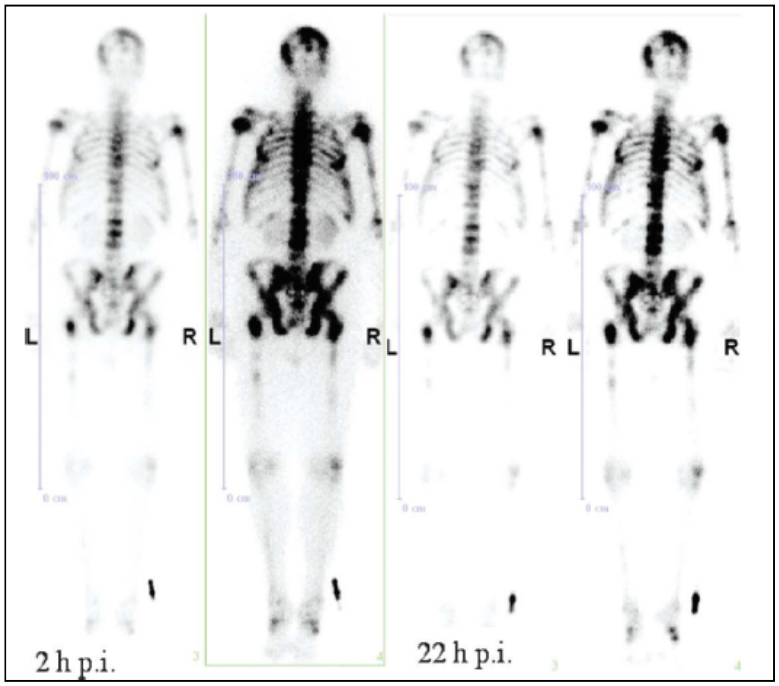
Lu-177 BPAMD

Targeted Radionuclide Therapy

BPAMD = (4-{[bis-(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)





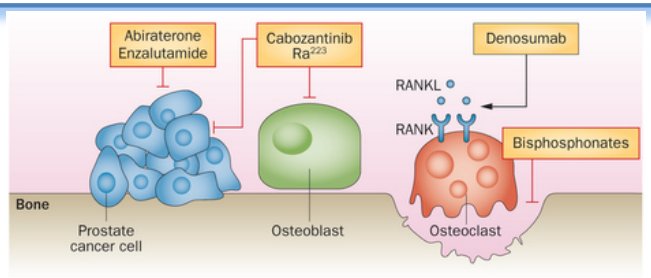


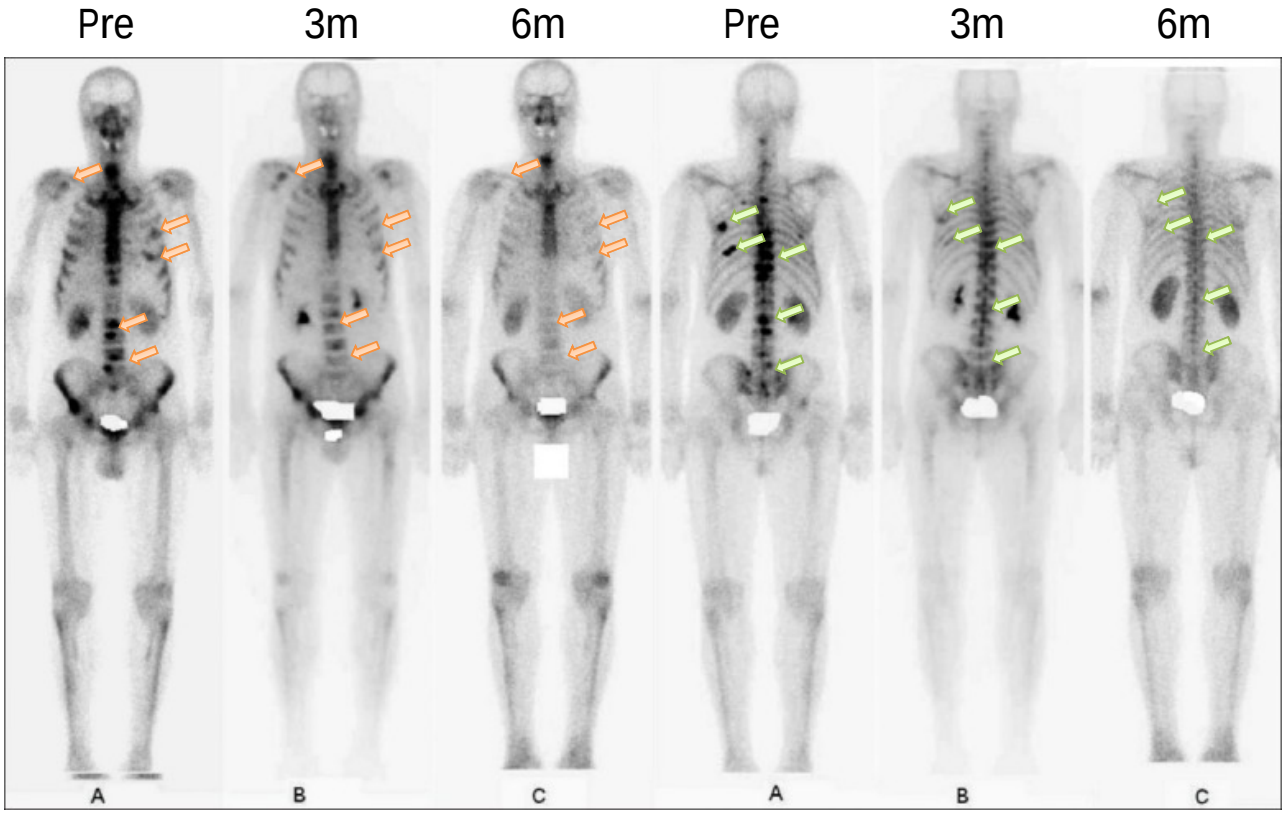
^{68}Ga-BPAMD PET/CT

^{177}Lu-BPAMD

Targeted Radionuclide Therapy

- ^{153}Sm + Denosumab





Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton

Vidya Soerdjbalie-Maikoe[1], Rob C.M. Pelger[1], Guus A.B. Lycklama à Nijeholt[1], Jan-Willem Arndt[2], Aeilko H. Zwinderman[3], Socrates E. Papapoulos[4], Neveen A.T. Hamdy[4]

Eur J Nucl Med (2002) 29:494–498

- Palliative treatment was given to 131 patients in the form of local radiotherapy (n=10), ^{89}Sr (n=46) or i.v. olpadronate (n=66)
- The incidence of SCC was 17% in the whole group, and highest in controls receiving no palliation (50%)
- None of the patients treated with local radiotherapy, only 4% of patients receiving ^{89}Sr and 21% of patients given olpadronate developed this complication

Clinical Role of Sm-153 EDTMP in the Treatment of Painful Bone Metastatic Disease

Clinical Nuclear Medicine • Volume 31, Number 10, October 2006

Mónica Coronado, Andrés Redondo,† Juan Coya,* Enrique Espinosa,† Rosa Mª Couto,* Pilar Zamora,† Mª Dolores Marin,* Beatriz Castelo,† Mª Eugenia Lillo,* Laura Frutos,* Manuel González Barón,† and Luis M. Martín Curto**

- 64 patients with painful bone metastases treated with ^{153}Sm were retrospectively evaluated
- The most common primaries were breast in 28 cases (44%) and prostate in 27 (41%)
- The response rate was 85% (21% complete, 40% moderate, and 24% minor)
- Onset of improvement took place a median of 7 days after ^{153}Sm administration, and pain relief persisted for a mean of 3 months
- Myelotoxicity appeared in 29% of the administrations

^{89}Sr versus ^{153}Sm-EDTMP: Comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma

Maciej Bączyk[a], Rafał Czepczyński[a], Piotr Milecki[b], Marlena Pisarek[a], Robert Oleksa[a] and Jerzy Sowiński[a]

Nuclear Medicine Communications 2007, **28**:245–250

- 60 male patients with advanced prostate carcinoma and 40 female patients with advanced breast carcinoma
- 30 men and 20 women were treated with ^{89}Sr
- 30 men and 20 women were treated with ^{153}Sm
- Complete pain relief was found in 40% of women and 40% of men treated using ^{153}Sm and in 25% of women and 33% of men treated with ^{89}Sr
- No analgesic effect occurred in 20% of patients
- A better analgesic effect was found in cases of osteoblastic metastases compared to mixed metastases

^{223}Ra (Alpharadin®)

- Complex decay scheme, including mostly alpha, but also beta and gamma
- Half life of 11.4 days
- Excretion mostly renal, but also through the GI tract
- Very short range and therefore causes less damage to surrounding tissues than other radiopharmaceuticals

ALGETA

- Developed in Norway by Algeta, approved in Europe
- Marketed by Bayer Healthcare

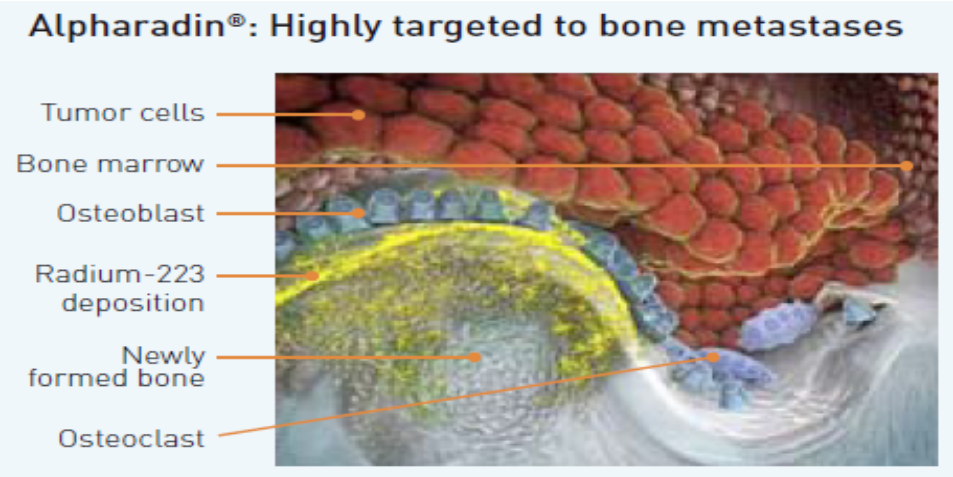
BAYER

^{223}Ra (Alpharadin®)

- ^{223}Radium hlorid –Ca analogue,
- 4h i.v.-77% in bone

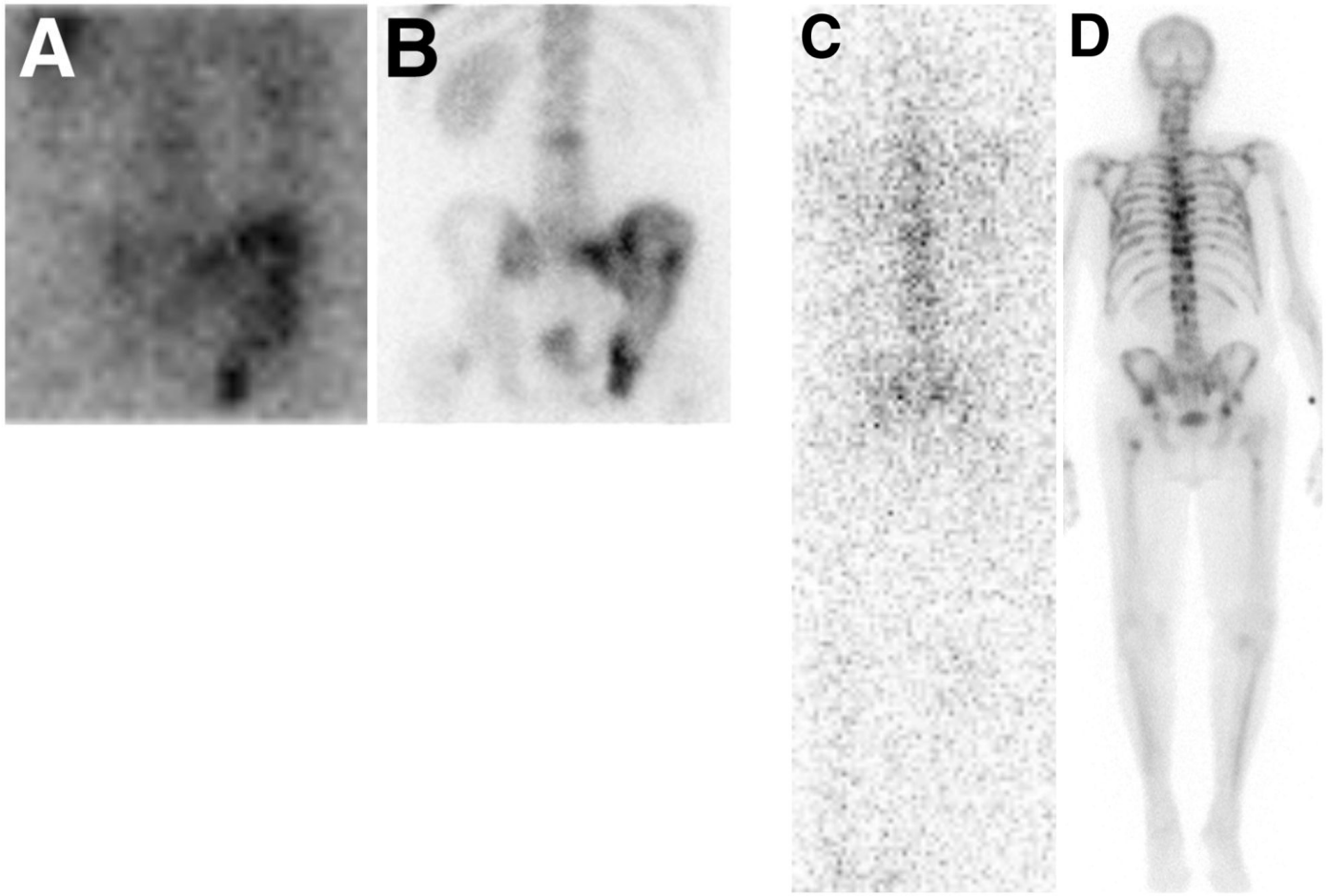
^{223} Radium	11.4 d	α 5.78 MeV	range in tissue : 2-10 cells 100um
		γ : 269 keV -13.6%	154 keV-6% 324 keV-4%

- 50 kBq / kg i.v.; every 4 weeks, 4-6 months



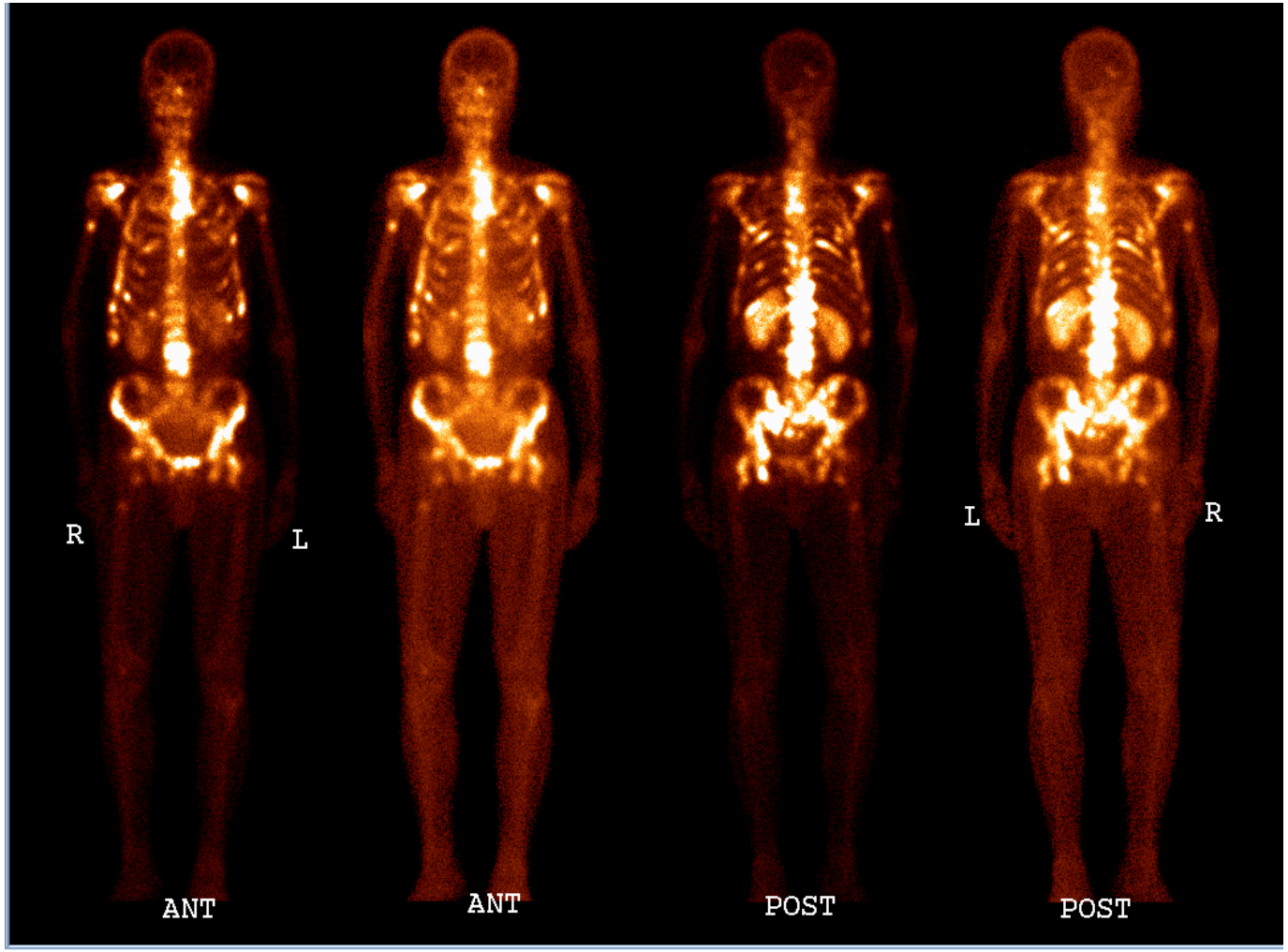
^{223}Ra (Alpharadin®)

^{223}Ra ^{99m}Tc-MDP ^{223}Ra ^{99m}Tc-MDP



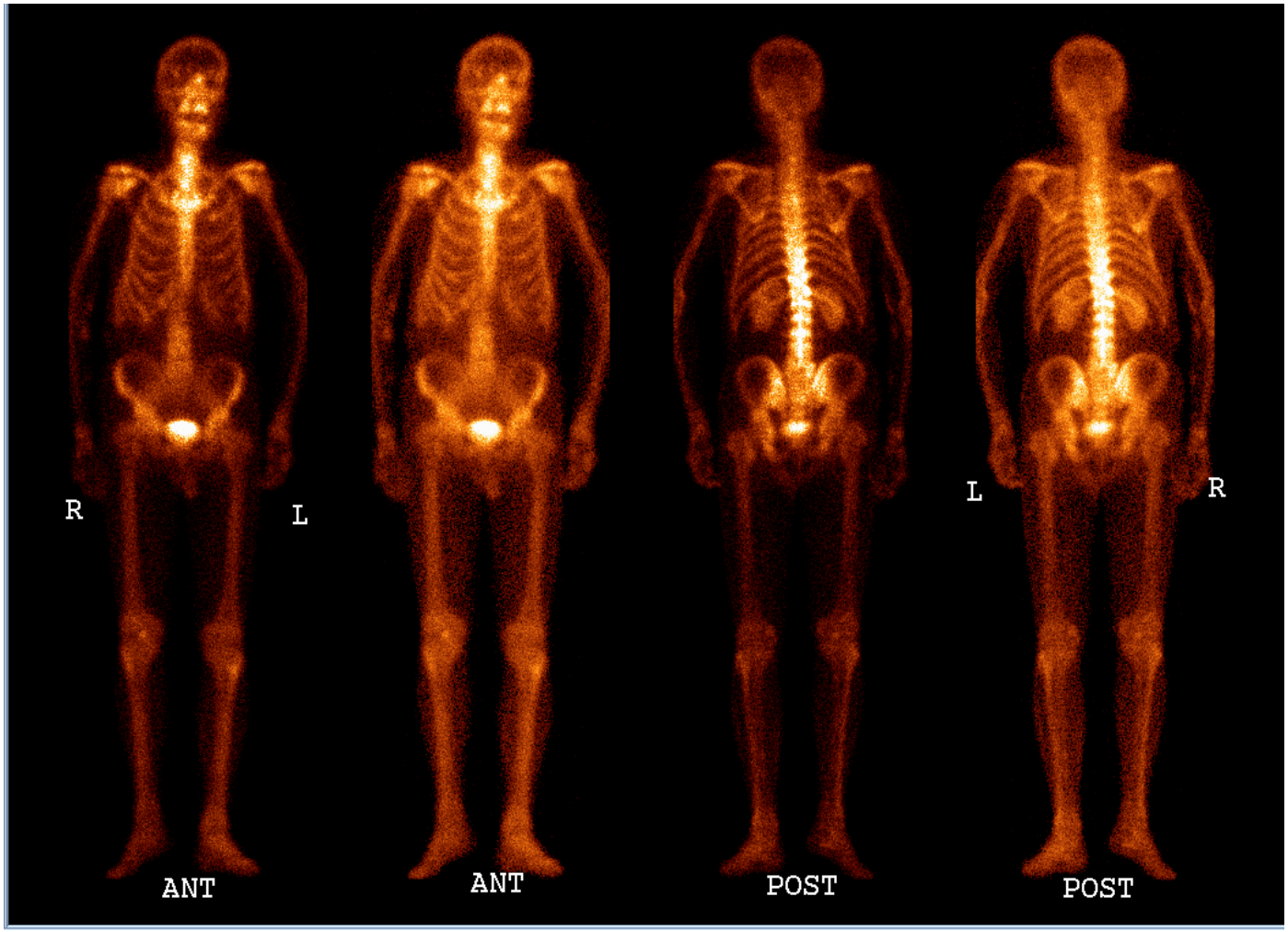
^{223}Ra (Alpharadin®)

- ^{99m}Tc-MDP pre before Alpharadin



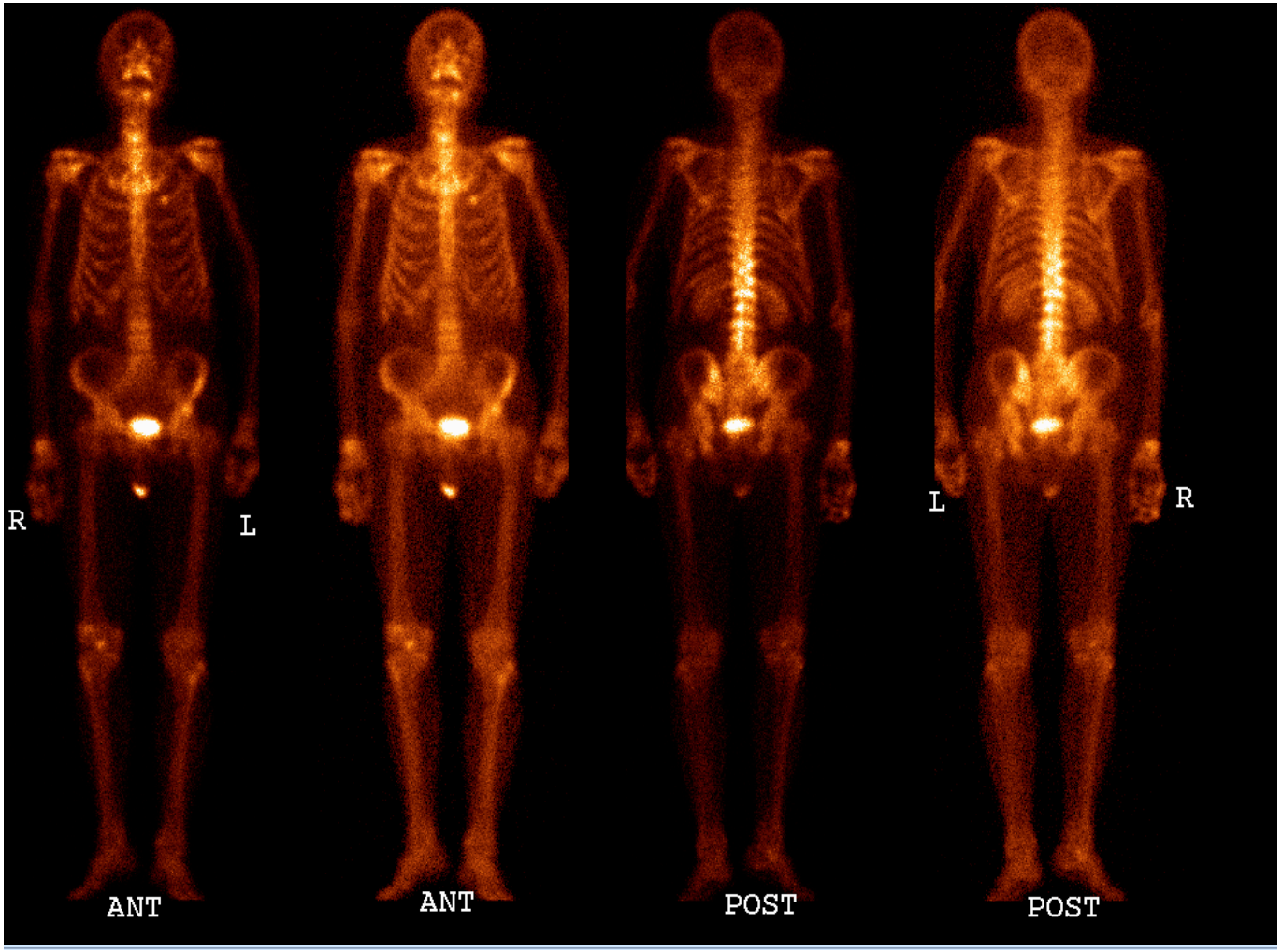
^{223}Ra (Alpharadin®)

- ^{99m}Tc-MDP 6 months after



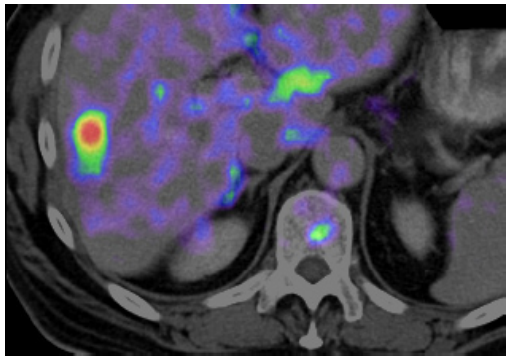
^{223}Ra (Alpharadin®)

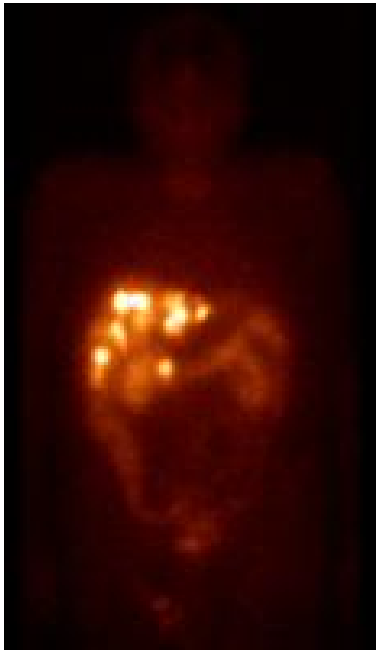
- ^{99m}Tc-MDP 9 months after



Liver tumors

- Primary – hepatocellular carcinoma, cholangioma, sarcoma, hepatoblastoma
- Secondary - TU of the digestive tract, lung, breast, melanoma,
- Small metastatic foci are difficult to visualize





SIRT

- Primary and secondary liver malignancies are common and associated with a poor prognosis. Surgical resection is the treatment of choice; however, many patients have unresectable disease. In these cases, several liver directed therapies are available, including SELECTIVE INTERNAL RADIATION THERAPY

- SIRT is a multidisciplinary treatment involving nuclear medicine, interventional radiology and oncology. High doses of localised internal radiation are selectively delivered to liver tumour tissues, with relative sparing of adjacent normal liver parenchyma. Side effects are minimal and radiation protection measures following treatment are straightforward

Liver tumors

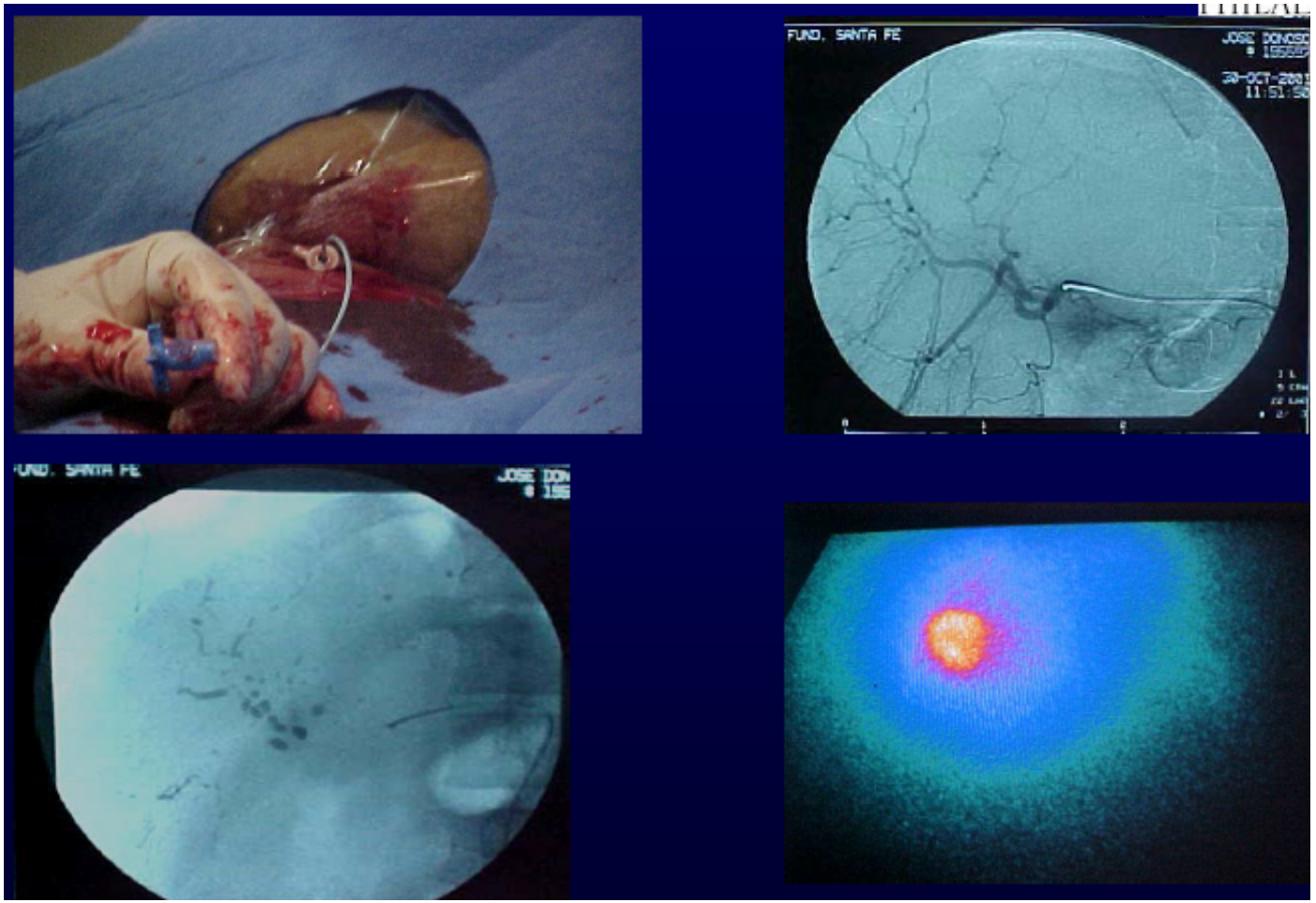
GUIDELINES

EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds

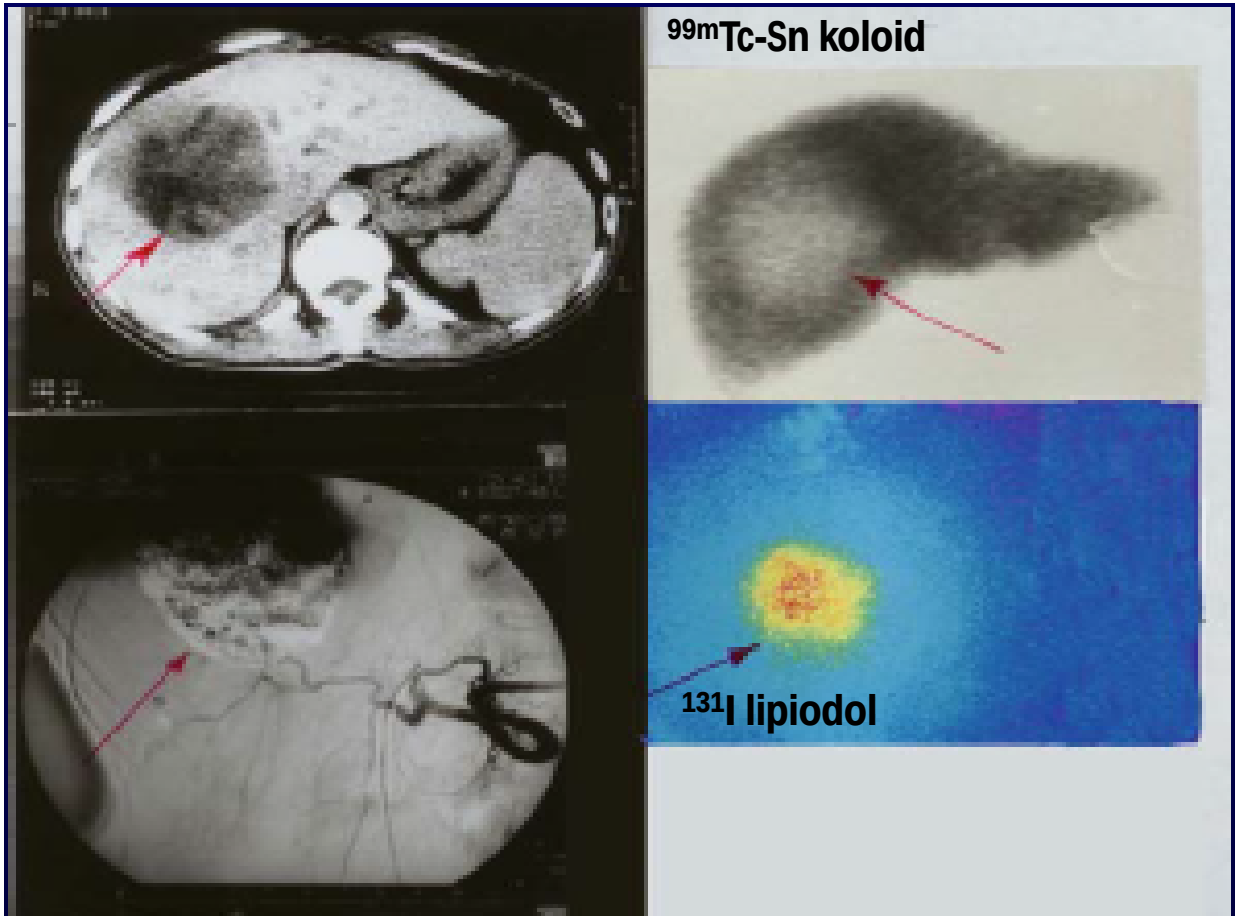
- HCC - greater density of arterioles, predominantly supplied by the hepatic artery 80%
- Lipiodol: 131I, (Japan 1984) 188Re (Lipiocis®)
- Fatty acid ethyl ester of iodinated opium oil
- Rapid diffusion into the tumor, slow clearance
- Protocol: 30 days; 2-3 months
- Lipiodol+chemotherapy 3-5x higher radiation tumor/surrounding tissue dose

Liver tumors

- Transarterial embolization a. hepatica

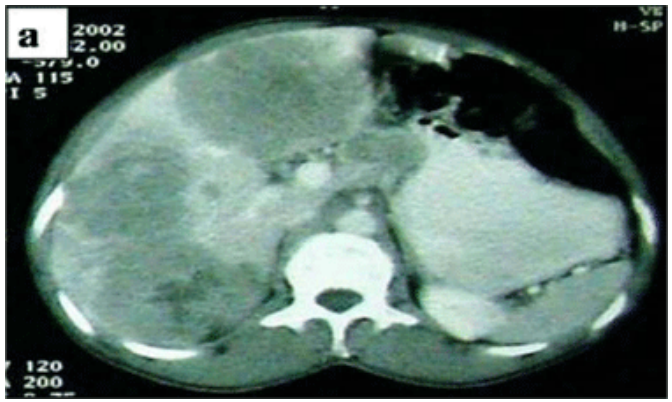


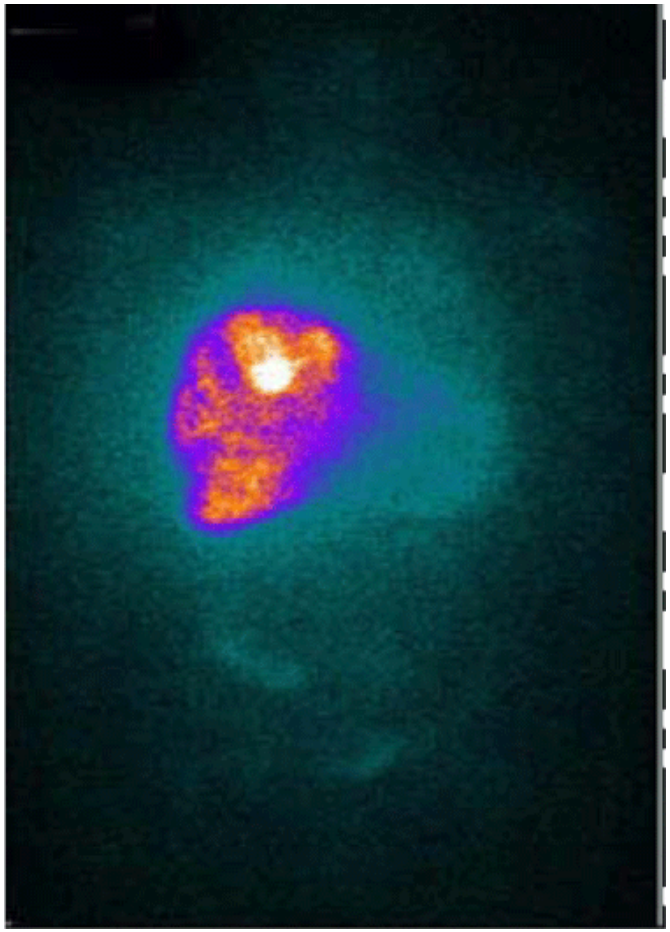
Liver tumors



Liver tumors

^{188}Re lipiodol





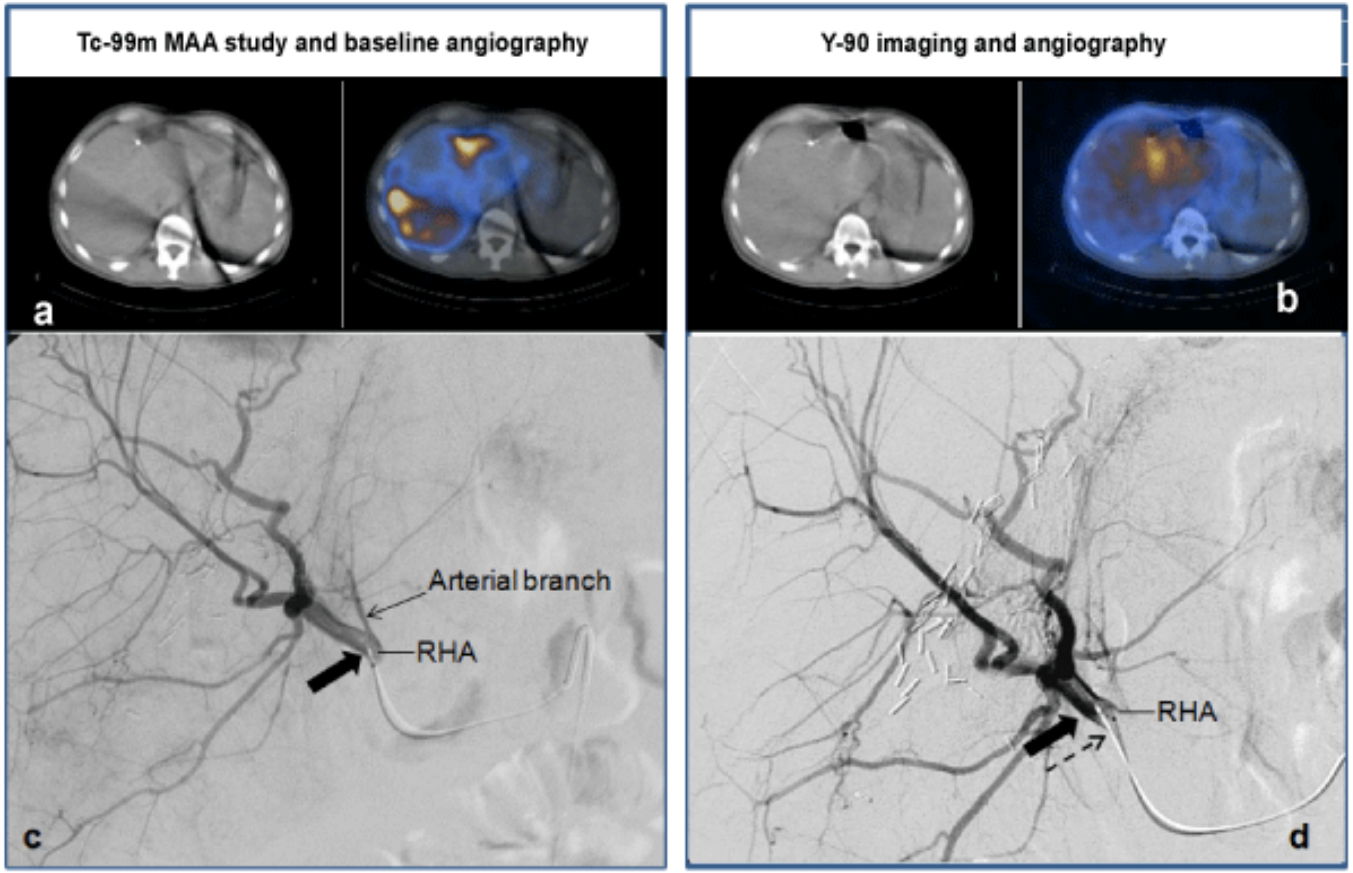
Liver tumors SIRT

- **^{90}Y-Microsfere (SIR-Spheres® TheraSphere®)**
- ^{188}Re-Microsfere (β- 2.12 MeV; γ-155 KeV)
- ^{166}Ho-Microsfere (β- 1.85 MeV)
- ^{165}Dy-Microsfere (β- 1.3 MeV)
- Radioembolizaton: iradiation (90%)+ishemia(10%)

Characteristics of Microspheres

Parameter	Resin	Glass
Trade name	SIR-Spheres	TheraSphere
Diameter	22 ± 10 µm	32 ± 10 µm
Specific gravity	1.6 g/dL	3.6 g/dL
Activity per particle	50 Bq	2500 Bq
Average number of microspheres per administered activity	40–80 million	1.2–8 million
Material	Resin with bound yttrium	Glass with yttrium in matrix

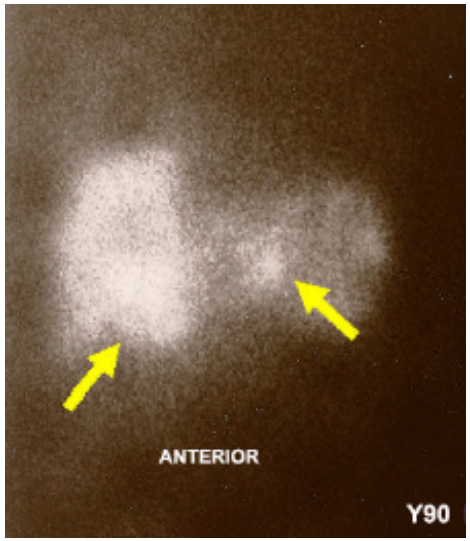
- ^{99m}Tc-MAA

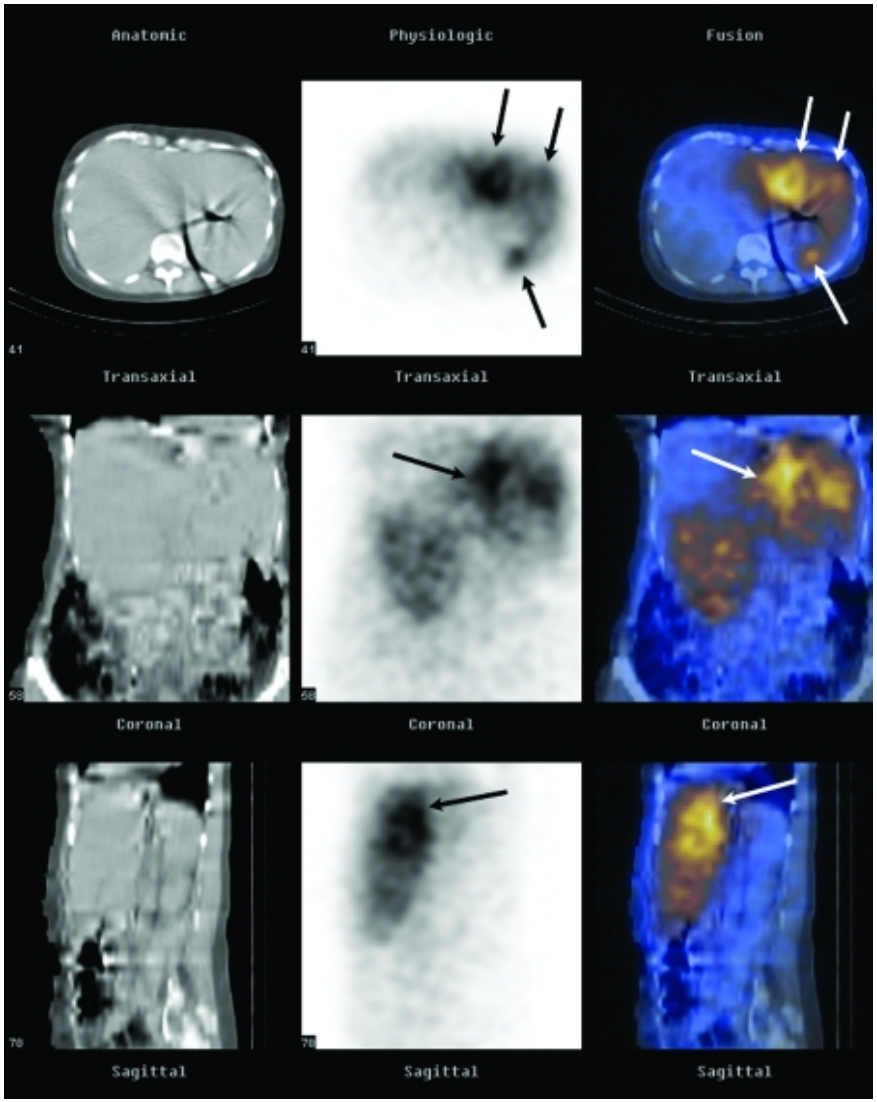

Tc-99m MAA study and baseline angiography
Y-90 imaging and angiography
a
b
Arterial branch
RHA
RHA
c
d

Liver tumors SIRT

^{90}Y- SIR-Spheres®

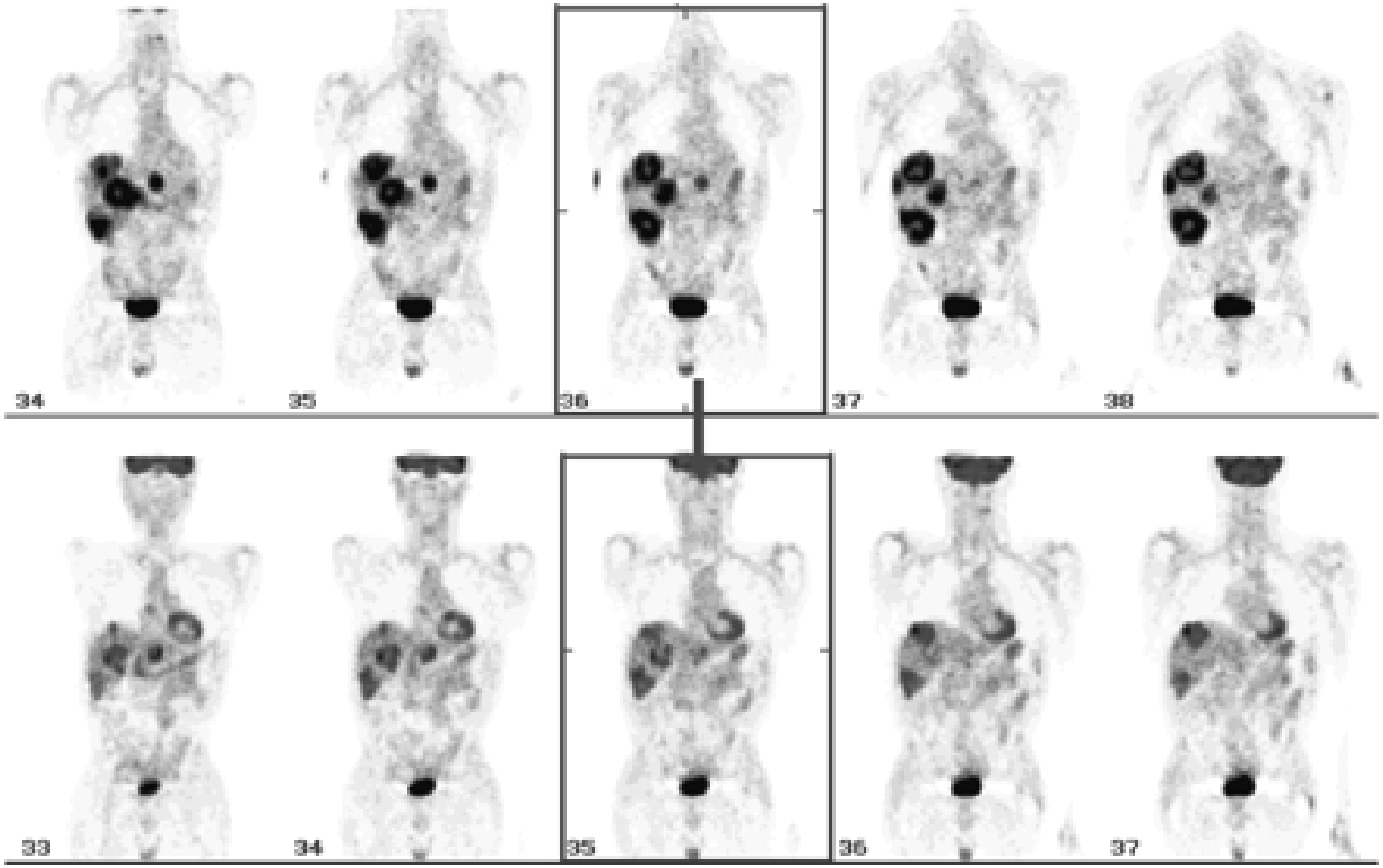
“Bremsstrahlung” imaging





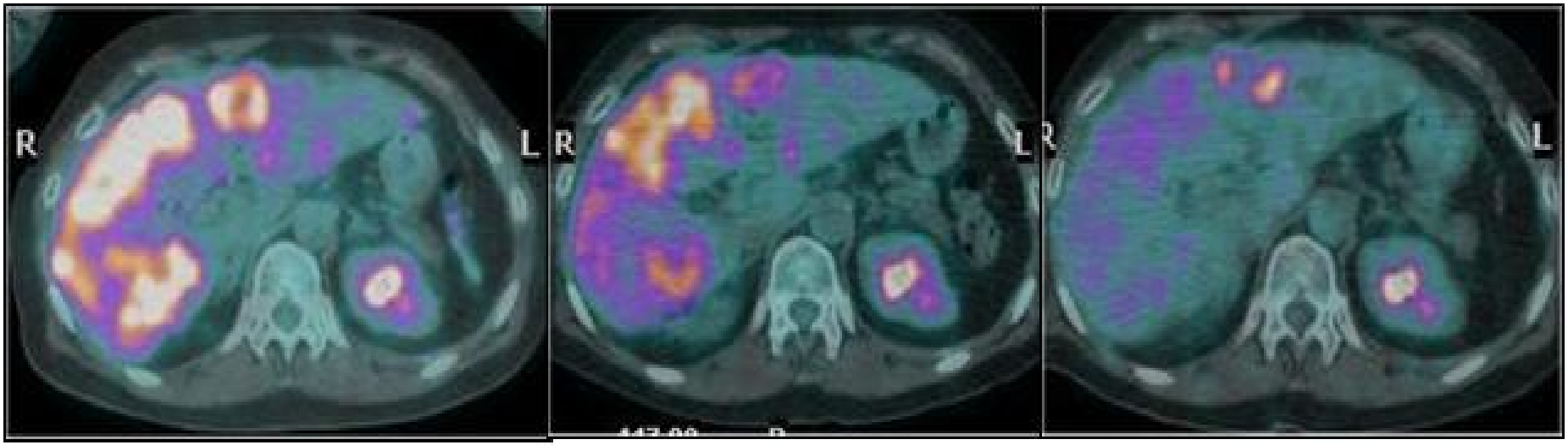
Liver tumors SIRT

^{18}FDG PET before (A) after (B) ^{90}Y- SIR-Spheres®



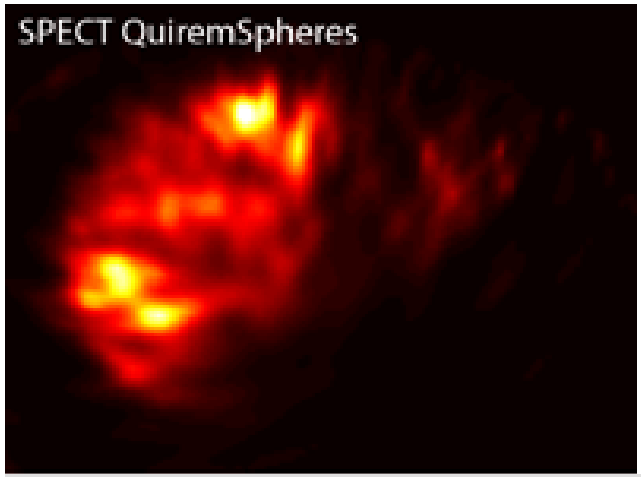
Liver tumors SIRT

^{188}Re-Microsfere (SIR-Spheres®)



Liver tumors SIRT

- ^{166}Ho-QuiremSpheres® Eβmax = 1.84 MeV, $T_{1/2}$ =26.8 hr



[^{166}Dy]/^{166}Ho generator

^{166}Dy – 81.5h

$^{166}HoCl_3$, y-80keV