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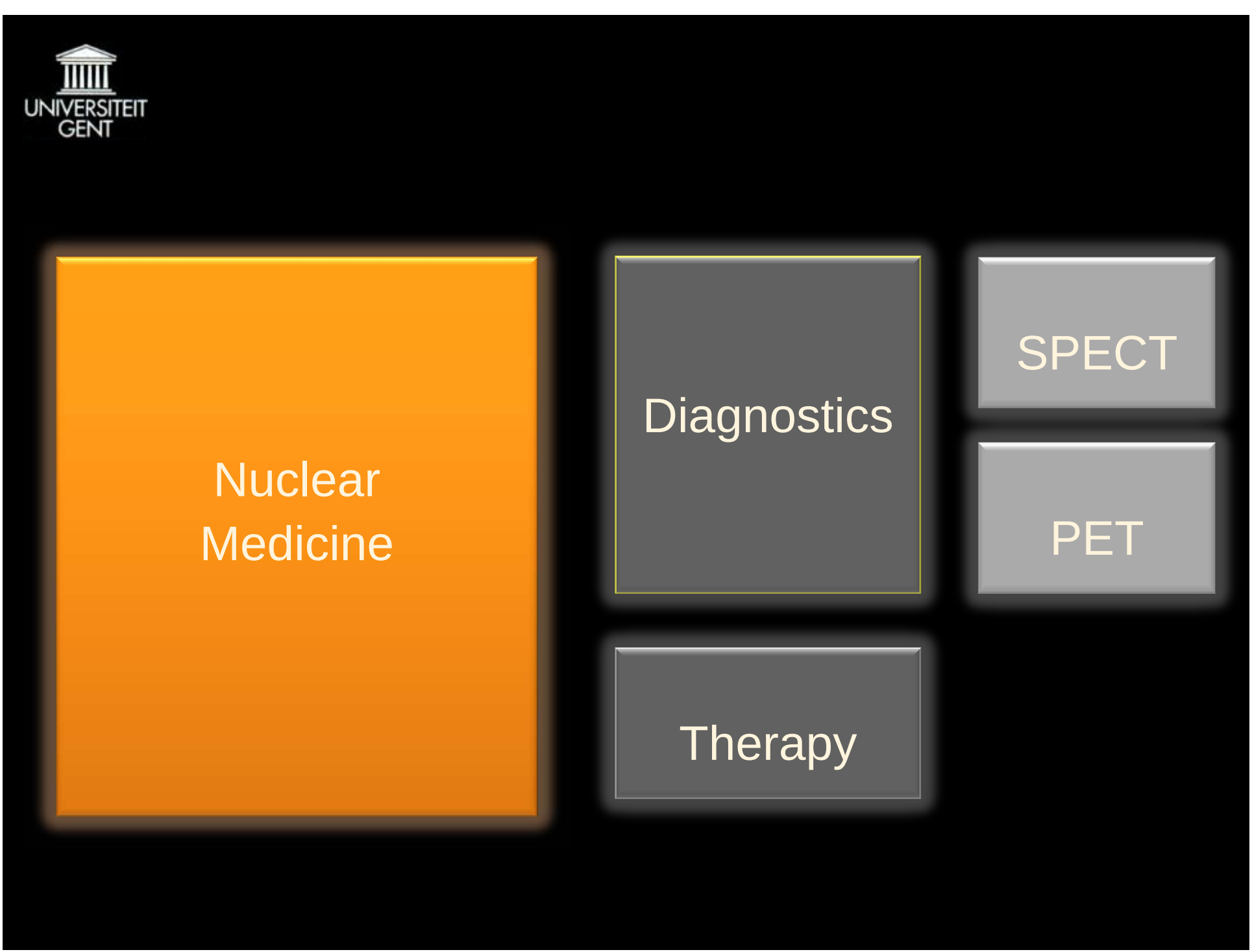
New radionuclides in metabolic therapy
medical aspects

Bieke Lambert Nucleaire Geneeskunde UZ Gent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Nuclear Medicine
Diagnostics
SPECT
PET
Therapy

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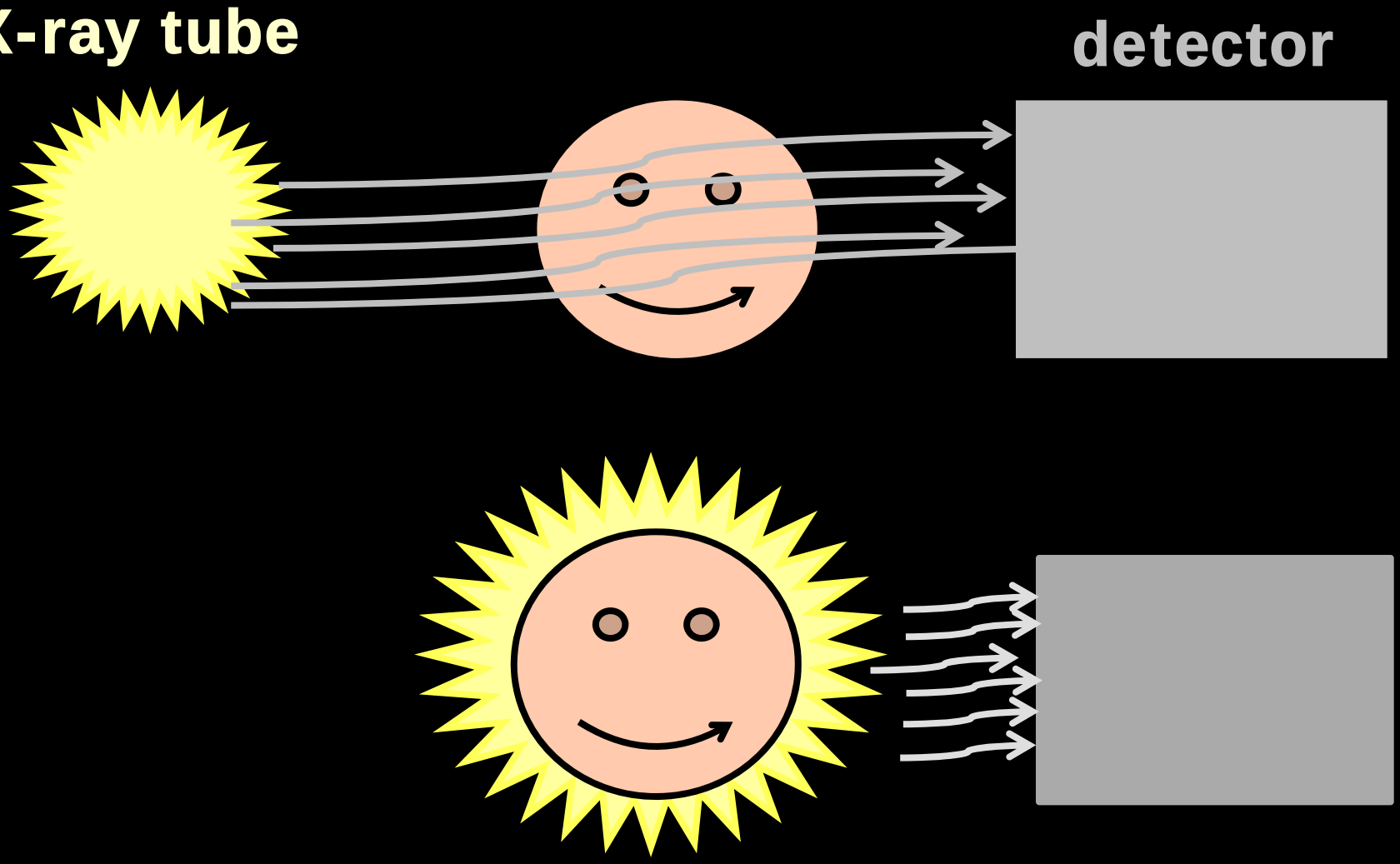

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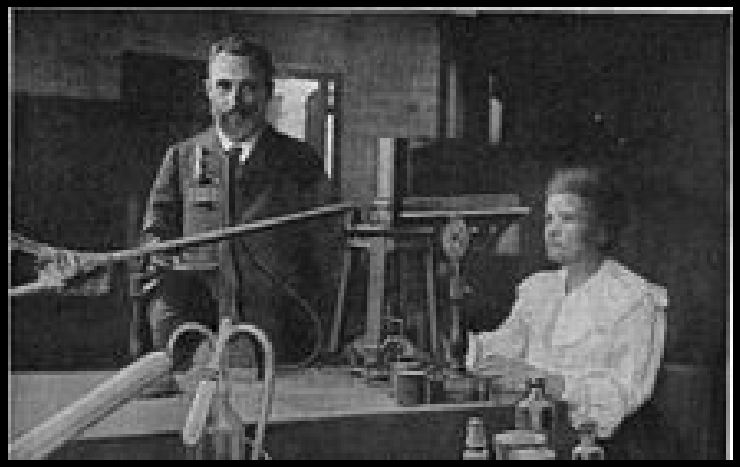
History

1896 Henri Becquerel
1897 Pierre and Marie Curie 'radio-activity'
1898 Pierre and Marie Curie 'Radium-226'



1901 Radium-226 for skin tuberculosis

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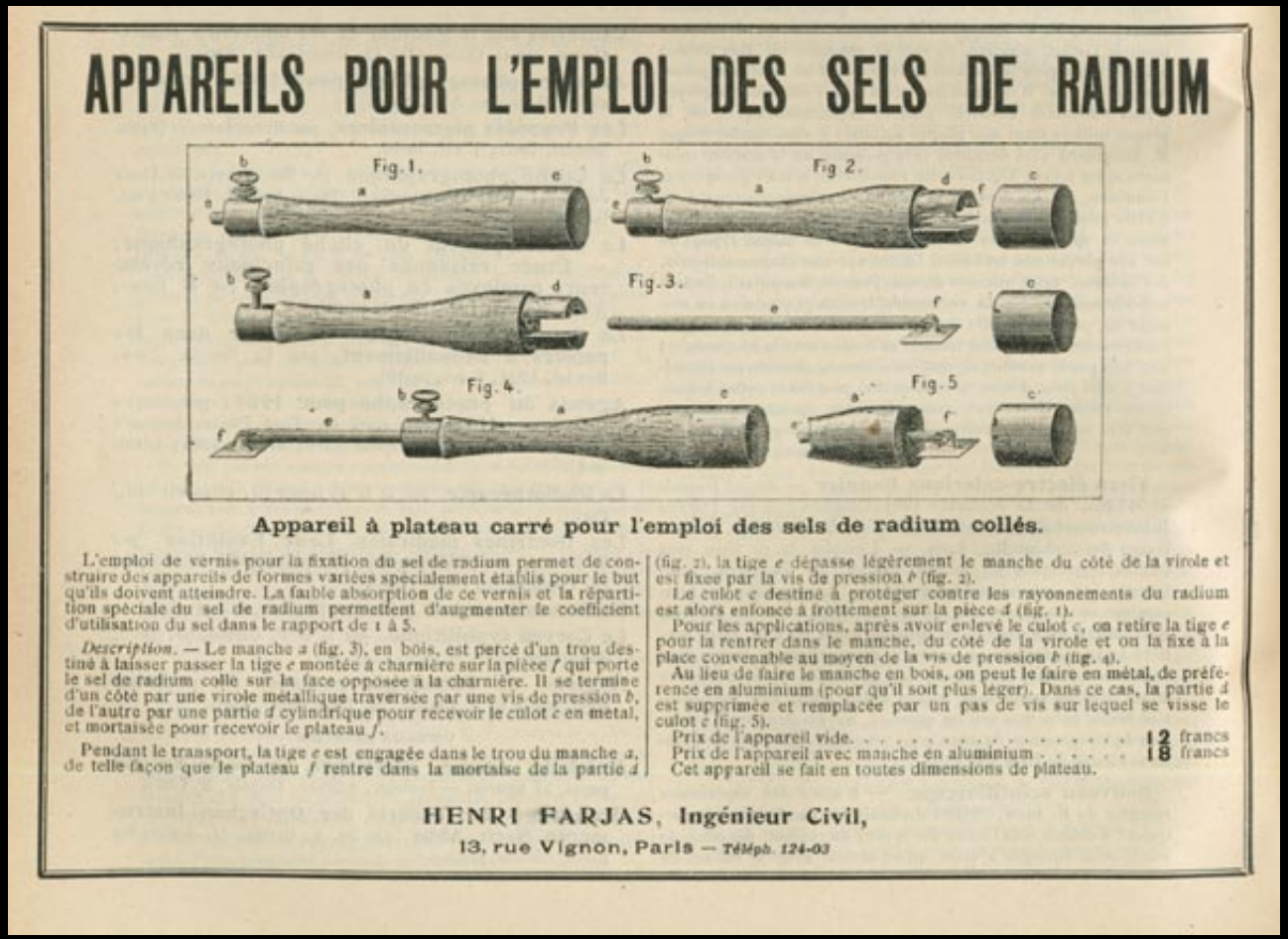

APPAREILS POUR L'EMPLOI DES SELS DE RADIUM

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5

Appareil à plateau carré pour l'emploi des sels de radium collés.

L'emploi de vernis pour la fixation du sel de radium permet de construire des appareils de formes variées spécialement établis pour le but qu'ils doivent atteindre. La faible absorption de ce vernis et la répartition spéciale du sel de radium permettent d'augmenter le coefficient d'utilisation du sel dans le rapport de 1 à 5.

Description. — Le manche *a* (fig. 3), en bois, est percé d'un trou destiné à laisser passer la tige *e* montée à charnière sur la pièce *f* qui porte le sel de radium collé sur la face opposée à la charnière. Il se termine d'un côté par une virole métallique traversée par une vis de pression *b*, de l'autre par une partie *d* cylindrique pour recevoir le culot *c* en métal, et mortaisée pour recevoir le plateau *f*.

Pendant le transport, la tige *e* est engagée dans le trou du manche *a*, de telle façon que le plateau *f* rentre dans la mortaise de la partie *d* (fig. 2), la tige *e* dépasse légèrement le manche du côté de la virole et est fixée par la vis de pression *b* (fig. 2).

Le culot *c* destiné à protéger contre les rayonnements du radium est alors enfoncé à frottement sur la pièce *d* (fig. 1).

Pour les applications, après avoir enlevé le culot *c*, on retire la tige *e* pour la rentrer dans le manche, du côté de la virole et on la fixe à la place convenable au moyen de la vis de pression *b* (fig. 4).

Au lieu de faire le manche en bois, on peut le faire en métal, de préférence en aluminium (pour qu'il soit plus léger). Dans ce cas, la partie *d* est supprimée et remplacée par un pas de vis sur lequel se visse le culot *c* (fig. 5).

Prix de l'appareil vide. . . . . 12 francs
Prix de l'appareil avec manche en aluminium . . . . . 18 francs
Cet appareil se fait en toutes dimensions de plateau.

HENRI FARJAS, Ingénieur Civil,
13, rue Vignon, Paris — *Téléph. 124-03*

...Radium-226 and Radon-222 for treatment of skin lesions (1915)

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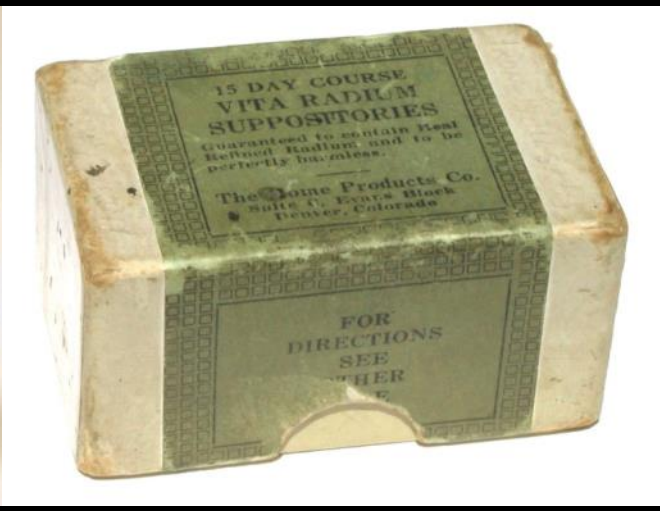

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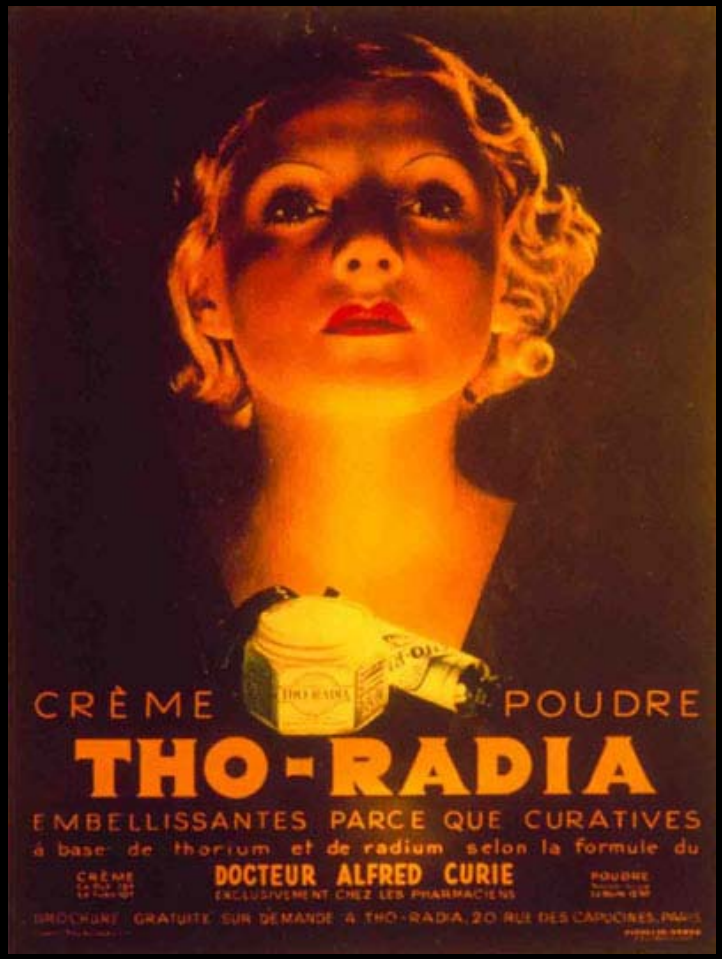

…1930: glow in the dark

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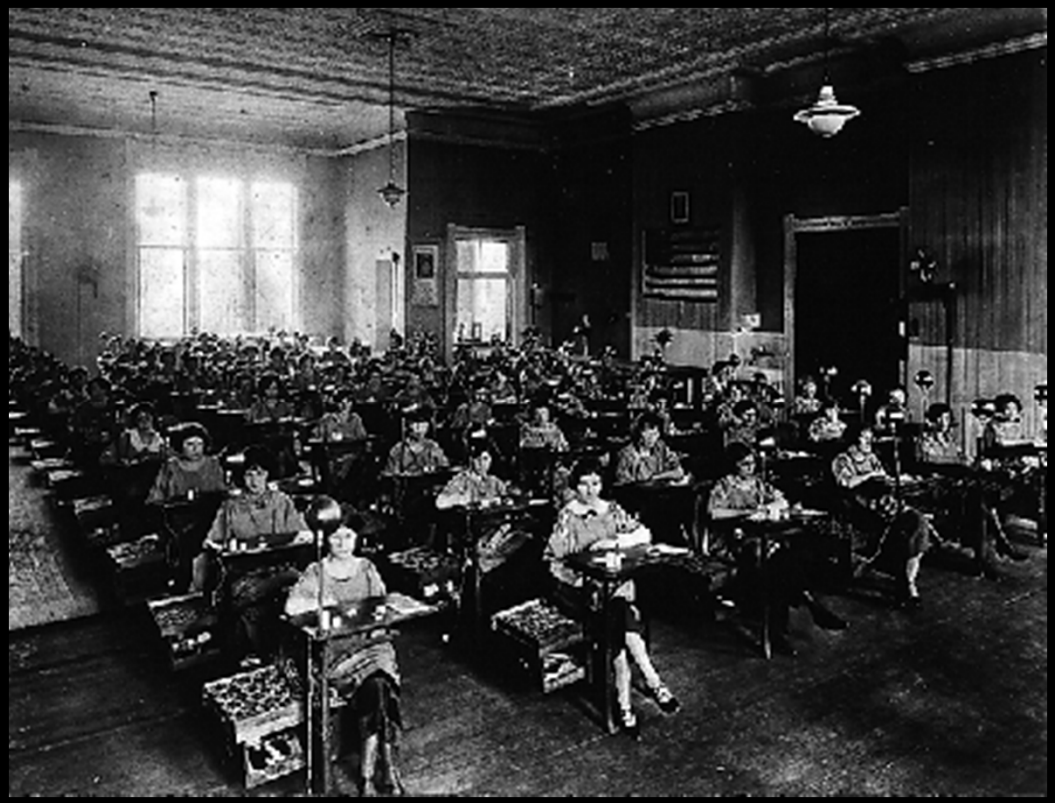

… Radium girls (1928)

History

1936 P32 as first systemic treatment for leukemia
1939 I131 treatment for Graves' disease

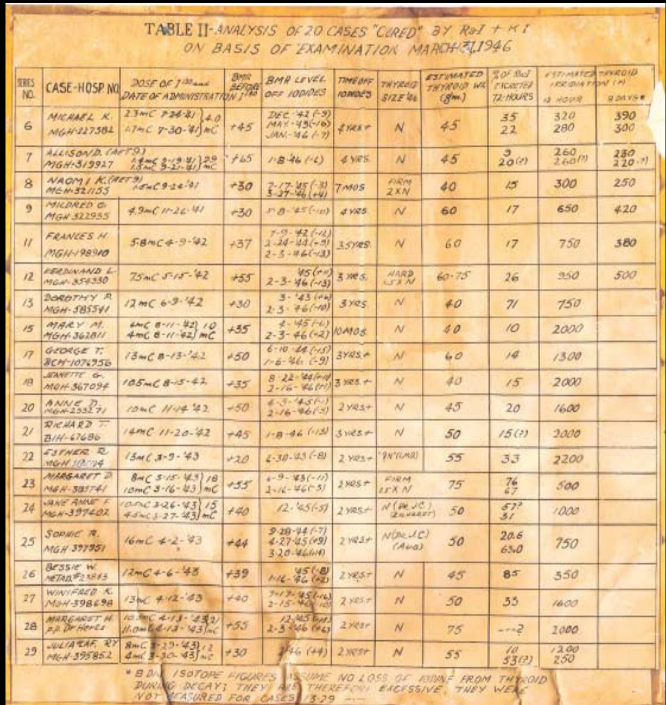

TABLE II-ANALYSIS OF 20 CASES "CURED" BY RaI + KI
ON BASIS OF EXAMINATION MARCH 31, 1946

SERIES NO.	CASE-HOSP NO	DOSE OF I131 and DATE OF ADMINISTRATION	BMR BEFORE I130	BMR LEVEL OFF IODIDES	TIME OFF IODIDES	THYROID SIZE	ESTIMATED THYROID WT (gm)	% OF RaI EXCRETED 72 HOURS	ESTIMATED THYROID IRRADIATION (r) 12 HOUR	8 DAYS*
6	MICHAEL K. MGH-227382	2.3mC 7-24-41, 1.7mC 7-30-41 } 4.0 mC	+45	DEC '42 (-9) MAY '45 (-16) JAN '46 (-7)	4 YRS +	N	45	35 22	320 280	390 300
7	ALLISON D. (AFT 9) MGH-319927	1.4mC 8-19-41, 1.5mC 9-2-41 } 2.9 mC	+65	1-8-'46 (-6)	4 YRS	N	45	9 20(?)	260 260(?)	280 220(?)
8	NAOMI K. (AFT 9) MGH-321155	1.5mC 9-24-'41	+30	7-17-'45 (-3) 3-27-'46 (+4)	7 MOS	FIRM 2XN	40	15	300	250
9	MILDRED G. MGH-322935	4.9mC 11-26-'41	+30	5-8-'45 (-10)	4 YRS	N	60	17	650	420
11	FRANCES H. MGH-198918	5.8mC 4-9-'42	+37	7-9-'42 (-12) 2-24-'44 (+5) 2-3-'46 (-13)	3.5 YRS	N	60	17	750	380
12	FERDINAND L. MGH-354330	7.5mC 5-15-'42	+55	'45 (+11) 2-3-'46 (-13)	3 YRS.	HARD 1.5XN	60-75	26	350	500
13	DOROTHY P. MGH-385541	12mC 6-9-'42	+30	3-'43 (+6) 2-3-'46 (-10)	3 YRS	N	40	71	750	
15	MARY M. MGH-362811	6mC 8-11-'42, 4mC 8-11-'42 } 10 mC	+35	4-'45 (-6) 2-3-'46 (+2)	10 MOS	N	40	10	2000	
17	GEORGE T. BCH-1076756	13mC 8-13-'42	+50	6-10-'44 (-15) 1-6-'46 (-9)	3 YRS +	N	60	14	1300	
18	JEANETTE G. MGH-367094	10.5mC 8-15-'42	+35	8-22-'44 (+4) 2-16-'46 (+1)	3 YRS +	N	40	15	2000	
20	ANNE D. MGH-233271	10mC 11-14-'42	+50	4-3-'45 (-) 2-16-'46 (-5)	2 YRS +	N	45	20	1600	
21	RICHARD T. BIH-67686	14mC 11-20-'42	+45	1-8-'46 (-13)	3 YRS +	N	50	15(?)	2000	
22	ESTHER R. MGH [illegible]	13mC 3-9-'43	+20	6-30-'45 (-8)	2 YRS +	"9N" (LMR)	55	33	2200	
23	MARGARET D. MGH-383741	8mC 3-15-'43, 10mC 3-16-'43 } 18 mC	+55	4-9-'43 (-11) 2-16-'46 (-5)	2 YRS +	FIRM 1.5XN	75	76 67	500	
24	JANE ANNE F. MGH-397402	10.5mC 3-26-'43, 4.5mC 3-27-'43 } 15 mC	+40	12-'45 (-5)	2 YRS +	N (Dr. J.C.) [illegible]	50	57? 31	1000	
25	SOPHIE R. MGH-397951	16mC 4-2-'43	+44	9-28-'44 (-7) 4-27-'45 (+9) 3-20-'46 (+4)	2 YRS +	N (Dr. J.C.) (Aug)	50	20.6 63.0	750	
26	BESSIE W. NETAB #23813	12mC 4-6-'43	+39	'45 (-8) 1-16-'46 (+2)	2 YRS +	N	45	85	350	
27	WINIFRED K. MGH-398698	13mC 4-12-'43	+40	7-17-'45 (-16) 2-15-'46 (-10)	2 YRS +	N	50	35	1600	
28	MARGARET H. P.P. Dr Hertz	10.5mC 4-13-'43, 11.0mC 4-13-'43 } 21 mC	+55	12-'45 (+12) 2-3-'46 (+6)	2 YRS +	N	75	---?	2000	
29	JULIA ZAF, RY MGH-395852	8mC 3-29-'43, 4mC 3-30-'43 } 12 mC	+30	[illegible]'46 (+4)	2 YRS +	N	55	10 53(?)	1200 250	

* 8 DAY ISOTOPE FIGURES ASSUME NO LOSS OF IODINE FROM THYROID DURING DECAY; THEY ARE THEREFORE EXCESSIVE. THEY WERE NOT MEASURED FOR CASES 13-29 —

Dr. Hertz document on
I131 for Graves' disease

1942 Sr89 for bone pain
1952 Radiosynovectomy

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Present

Thyroid
- benign
- malignant

→ I-131

Neuro-endocrine tumours → I-131 mIBG/ Radiolabelled somatostatine analogs

Liver tumours
- primary
- metastasis

→ Y-90 microspheres

Bone metastasis → Sm-153 EDTMP/ Sr-89/Ra223

Arthritis
Brain tumorus and cysts → Radiolabelled colloids

Lymphoma → Y-90 / I131 antibodies

Hematologic disorders → P-32

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In general

contra-indication for all RNT:
pregnancy or inadequate contraception.

recent FANC/AFCN guidelines on a vigilant time window between the RNT and death

Samarium-153: 13d

Yttrium-90: 15 d for Zevalin, 30 d for other treatments

Sr89: 303 d

Ra223: 60 d

I131: 18 d (Thyroid Ca) and 29d (benign)

I131-mIBG: 47d

Radionuclide Treatment of benign thyroid disorders

Iodine-131

- beta emitter (E max 606 keV)
- gamma emitter (364 keV)
- $T_{1/2}$ 8 d

Patient preparation

- Stop Strumazol/PTU/iodine containing medication etc
- Assess volume, uptake (and kinetics)
- Calculate the activity
  - > 14mCi hospital stay in radionuclide therapy ward
  - < 14 mCi ambulatory

Radionuclide Treatment of benign thyroid disorders

Indications

- Hyperthyroidism

  ✓Graves' disease
  ✓Toxic adenoma
  ✓Toxic struma

- Volume reduction of euthyroid struma

131I treatment of benign thyroid disorders

- Low cost
- effective
- Retreatment possible
- >> ambulatory

- Radioprotection
- Sialodenitis
- Evolution to hypothyroidism
- Excacerbation ophtalmopathy M Graves?
- Possibility of cancer induction

Treatment of Thyroid Cancer

Papillar **Follicular**	Well differentiated >> Iodine avid Good prognosis
Anaplastic	Very poorly differentiated Not Iodine avid >>FDG PET Rare Very bad prognosis
Medullar	Neuroendocrine tumour Rare Octreotide scan

Treatment of Thyroid Cancer

Differentiated Thyroid Cancer

Papillary
Follicular

THYROIDECTOMY

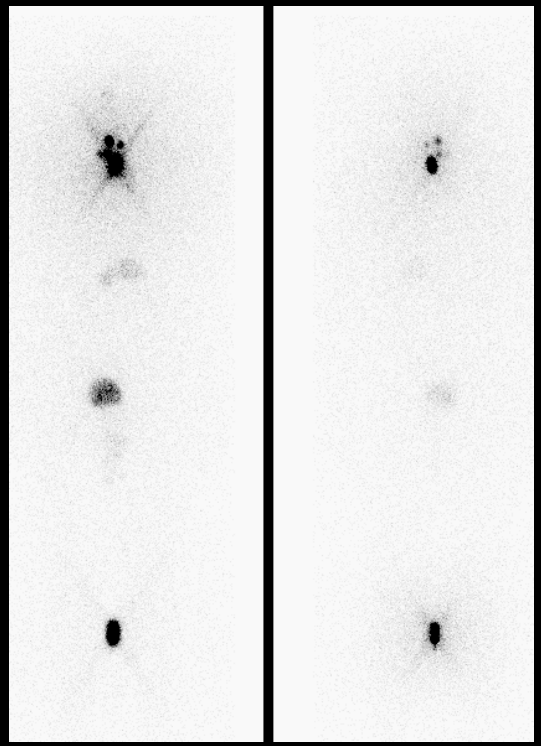
Thyroxine substitution
Suppress TSH stimulus

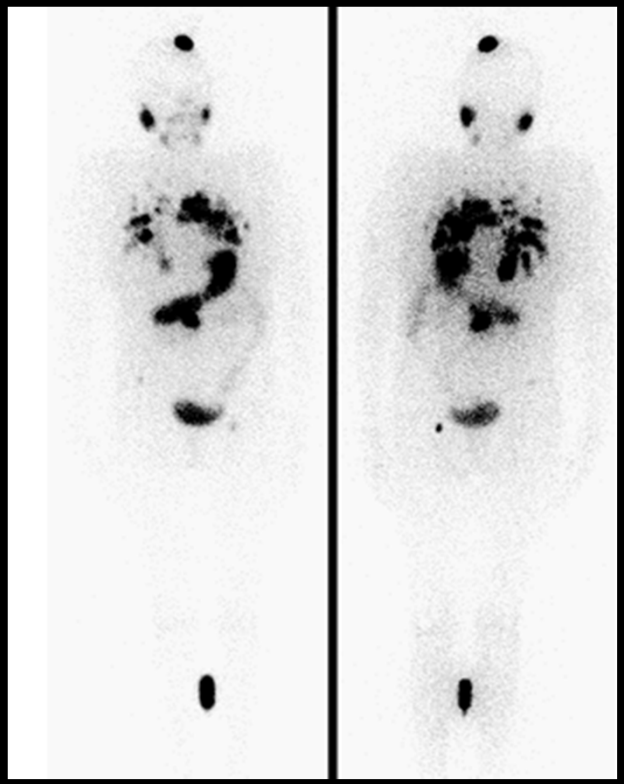
I131

Treatment of Thyroid Cancer

Role of I-123 scan?

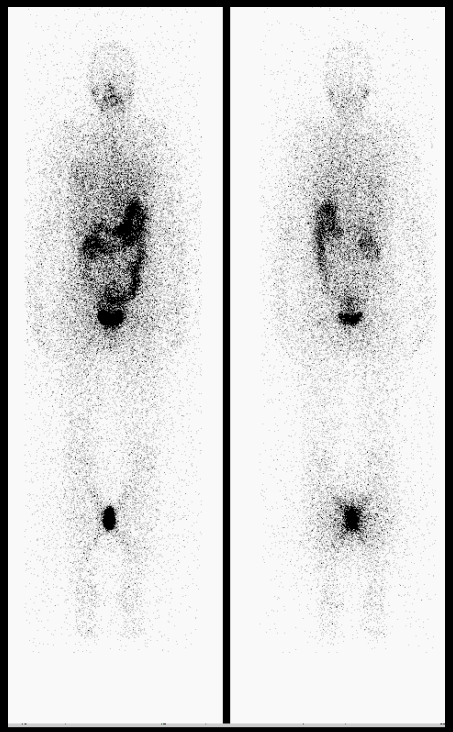
- Simulates treatment with I-131
- Follow up





Treatment of Thyroid Cancer

Follow up scan: normal findings
physiologic uptake in salivary glands, nasal and oral mucosa, stomach, intestines, bladder



Treatment of Thyroid Cancer

- Patient preparation:
  - provoke hypothyroidism/ TSH rise by withdrawing thyroid hormone substitution

  Or

  - recombinant TSH (Thyrogen) in order to avoid hypothyroidism

  - avoid exogenous iodine

- Always hospitalisation in radionuclide therapy ward and guidelines for radioprotection at home

- Post therapy scan

Treatment of Thyroid Cancer

Radioprotection

- Stay in radionuclide therapy ward
  24h-5 dd

- Radioprotective guidelines for 1-3 wks

  Sleep separately
  Toilet hygiene
  Depending on job, stop working for several wks
  No close (< 1m) contact for > 1h
  ...

Treatment of Thyroid Cancer

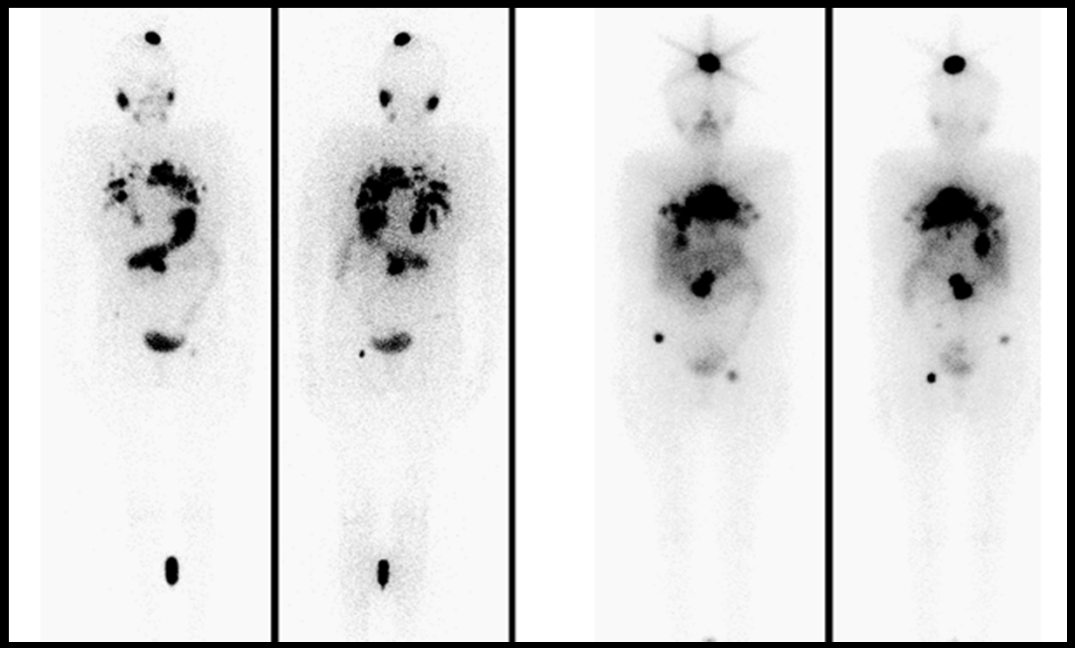
I131 treatment most often used:

- Ablation of residual normal thyroid tissue post-resection

Treatment of Thyroid Cancer

Besides treatment as adjuvant post thyroidectomy:

- Treatment of metastatic disease



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Radiosynoviorthesis

Based on radiolabelled colloid

Radionuclide
Energy beta emission
~
size joint

Colloid particles 2-5µ
Phagocytosis
by synoviocytes and macrophages

Y-90
t1/2 2.7 d
Eβmax 2.3 MeV
max range 11mm

Re-186
t1/2 3.7 d
Eβmax 1.1 MeV
max range 4mm

Er-169
t1/2 9.4 d
Eβmax 0.4 MeV
max range 1mm

Alternative P32

Radiosynoviorthesis

Indications ~ EANM guidelines

- Rheumatoid arthritis
- Spondylarthropathy (e.g. reactive or psoriatic arthritis)
- Other inflammatory joint diseases, e.g. Lyme disease, Behcet's disease
- Persistent synovial effusion
- Haemophilic arthritis
- Calcium pyrophosphate dihydrate (CPPD) arthritis
- Pigmented villonodular synovitis (PVNS)
- Persistent effusion after joint prosthesis
- Undifferentiated arthritis (where the arthritis is characterised by synovitis, synovial thickening or effusion)

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Radiosynoviorthesis

Contra-indications ~ EANM guidelines

1. Absolute
   - Pregnancy and breast-feeding
   - Local skin infection
   - Ruptured popliteal cyst (knee)
2. Relative
   - The radiopharmaceuticals should only be used in children and young patients (<20 years) if the benefit of treatment is likely to outweigh the potential

     hazards.
   - Extensive joint instability with bone destruction.
   - Evidence of significant cartilage loss within the joint.

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Radiosynoviorthesis

Practical aspects

Intra-articular injection

except for knee, under fluoroscopic guidance

Immobilisation 48-72h

Interval between surgery/arthroscopy/punction: 2-6 wks

No major radioprotective issues

Less invasive than surgical synoviorthesis

Less revalidation needed than arthroscopic synoviorthesis

Longer lasting effect than IA steroids and possible to combine

Can be repeated if needed (>6mths)

No systemic side effects

Very safe in experienced hands

Radiosynoviorthesis

Practical aspects

Safety depends on expertise operator
Rare leakage/skin tatoes /necrosis
It takes time to respond
~15% pain and swelling 6-48h

Radiosynoviorthesis

Efficacy

depends on which joint and which underlying disease

>>> retrospective data: suggest good and long lasting responses

<<< prospective randomized trials

Radiosynoviorthesis

Efficacy

summary prospective randomized trials

Göbel et al. Rheumatol Int 2007
79 joints
Re186 alone vs Re186+steroid vs steroid alone
In favour of combined treatment: success rate 82% at 3 y
Less joint destruction?

Van der Zant et al. Eur J Nucl Med 2007
44 pts, 68 joints
Er169/Re186+steroid vs steroid alone in upper extremity
69% response vs 32% at 12m

Jahangier et al. Arthritis Rheum 2005
97 pts, 50 knee joints, if 2 failed IA steroid injections in history
90Y +steroid vs steroid alone
Both groups only 48% response, no difference in response duration, negative effect
Y90 on joint destruction?

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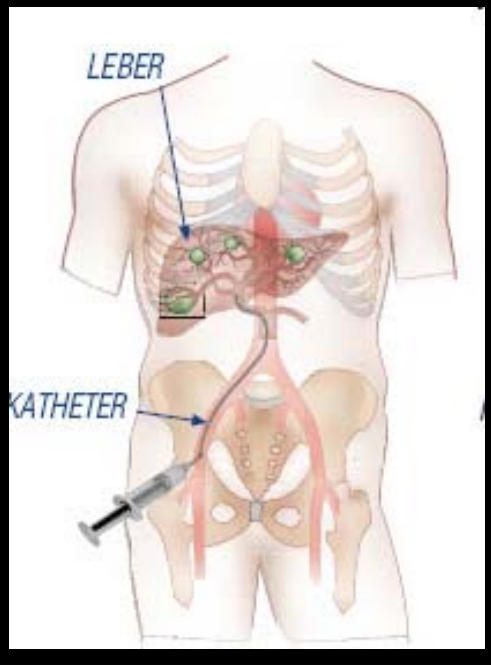
Liver Tumours

Intra-arterial administration

Tumour >>> Arteria hepatica
Liver parenchyma 75% Vena Porta

Already a tumour selective effect by delivering the radionuclide in the hepatic artery (or even superselective in the feeding artery)

No general anaesthesia needed



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How did it start?

Lipiodol

contrast material for the detection of HCC:

when injected into the hepatic artery
the oil is retained by HCCs for several weeks
to over a year, but it is cleared from
the normal liver parenchyma within 7 days

not suitable for systemic use
vehicle for anti-tumoral agents: chemo or Iodine-131

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^{131}I-Lipiodol

Indications

Palliative setting

Raoul et al. Hepatology 1997: Randomized trial ^{131}I-Lip vs TACE

Raoul et al. J Nucl Med 1994: Randomized trial ^{131}I-Lip vs no active treatment in patients with portal vein thrombosis

Post-resection

Lau et al. Lancet 1999: Controlled randomized trial:
Single administration ^{131}I-Lipiodol post-resection

While awaiting liver transplantation

Brans et al. Cancer Biother Radiopharm 2001

Lambert et al. Cancer Biother Radiopharm 2005

Raoul et al. Br J Surg 2003

^{131}I-Lipiodol : Tolerance

Adverse events

Early

- moderate pyrexia (29%)
- hepatic pain on injection (12.5%)
- self limiting respiratory symptoms (3%)
- acute pneumonitis (0.5%-2%)
- transient decrease liver function (20%)

Late

- leukopenia (7%)
- lung fibrosis

Despite good tolerance, no escalation in activity possible due to radioprotection concerns

www.eanm.org

Yttrium-90 microspheres

non biodegradable particles loaded with Yttrum-90, that are trapped in the end arterioles following IA administration

^{90}Y-glass microspheres

- Therasphere, Nordion, Canada
- No randomized data available
- Mainly applied for HCC

^{90}Y-resin microspheres

- SIRspheres, Sirtex, Australia
- Some randomized data available
- Mainly applied for colorectal liver mets and HCC

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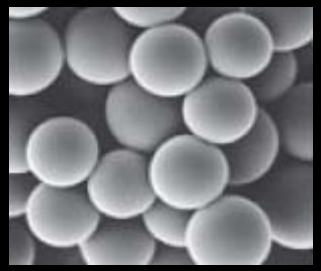
Y-90 microspheres



Radioprotection Y-90 microspheres

^{90}Yttrium

- Pure beta-emitter
- 11 mm path length (max) soft tissue
- Shield with plastic, not with lead

No major radioprotective issues for the patients

No need for isolation/hospitalisation

SPECIAL CONTRIBUTION

Posttherapy Radiation Safety Considerations in Radiomicrosphere Treatment with ^{90}Y-Microspheres

Seza A. Gulec[1] and Jeffry A. Siegel[1,2]

[1]Center for Cancer Care, Goshen Health System, Goshen, Indiana; and [2]Nuclear Physics Enterprises, Marlton, New Jersey

J Nucl Med 2007; 48:2080–2086

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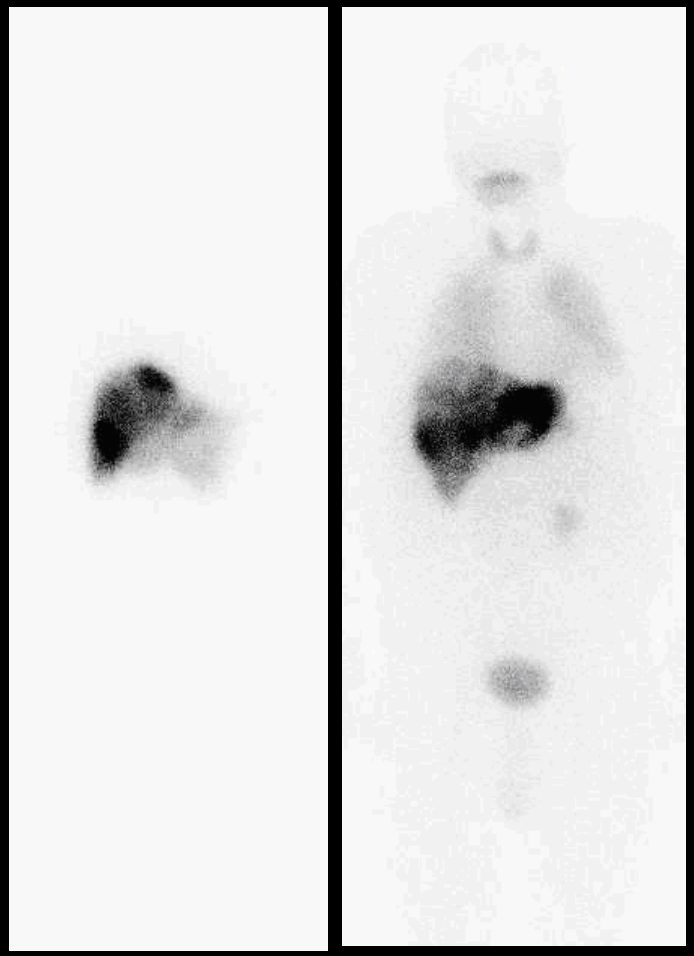
Procedure / Patient preparation / MAA

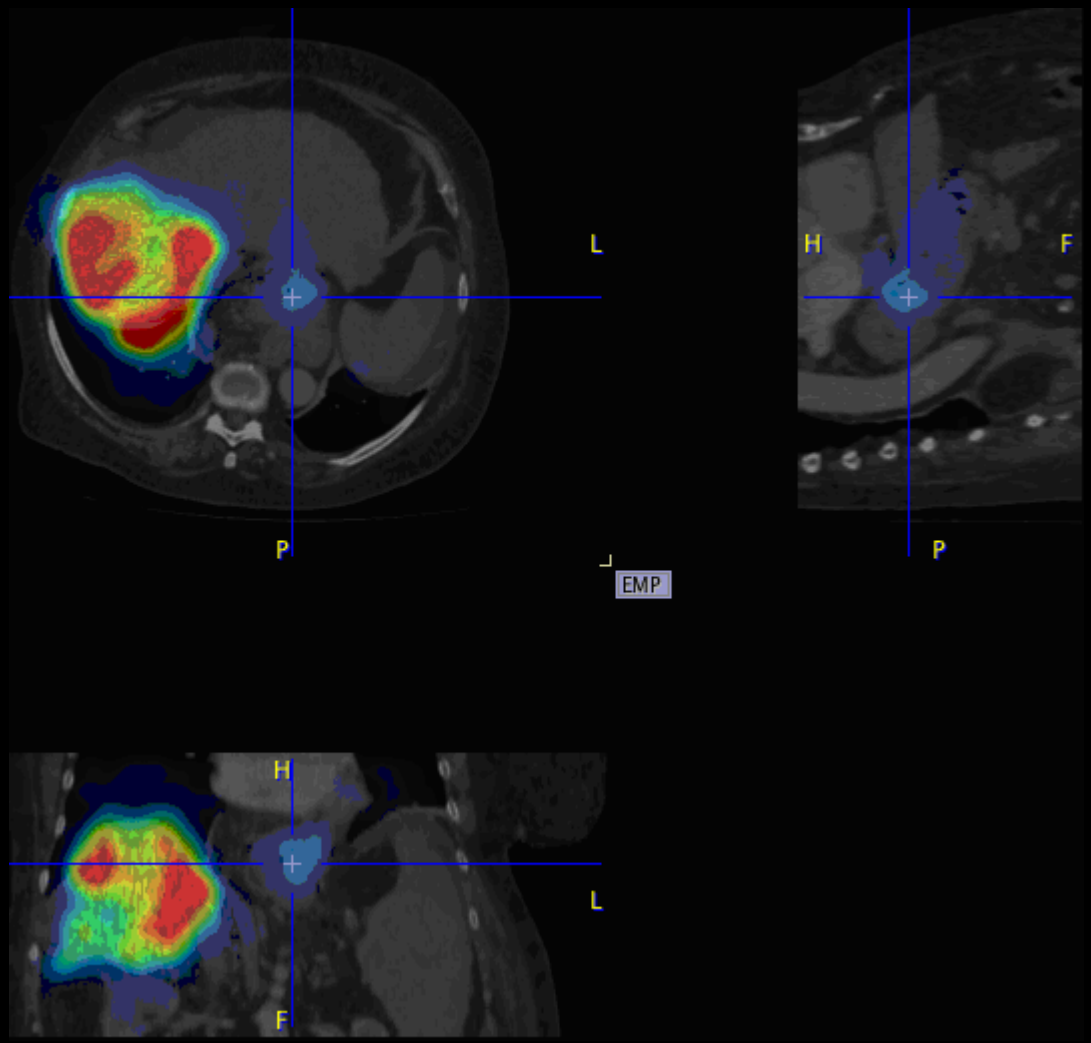
^{99m}Tc MAA-scan



Procedure / Patient preparation / MAA

MAA-scan

SPECT/CT or fusion



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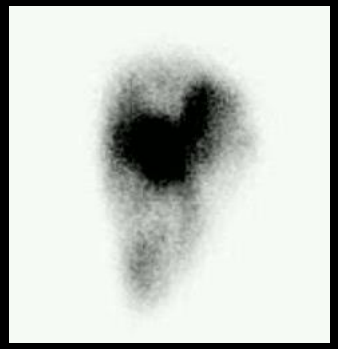
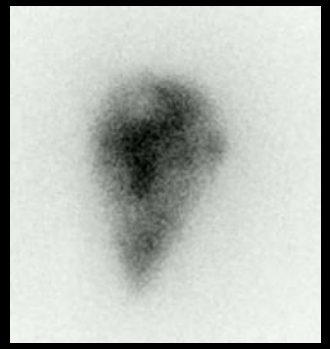
Procedure / Post therapy scan

Tc99-MAA



90-Yttrium



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Yttrium-90 microspheres/ Patient selection

Primary or secondary liver tumours
>>HCC
>>CRC
< mbreastCa, NET, CholangioCa, ...

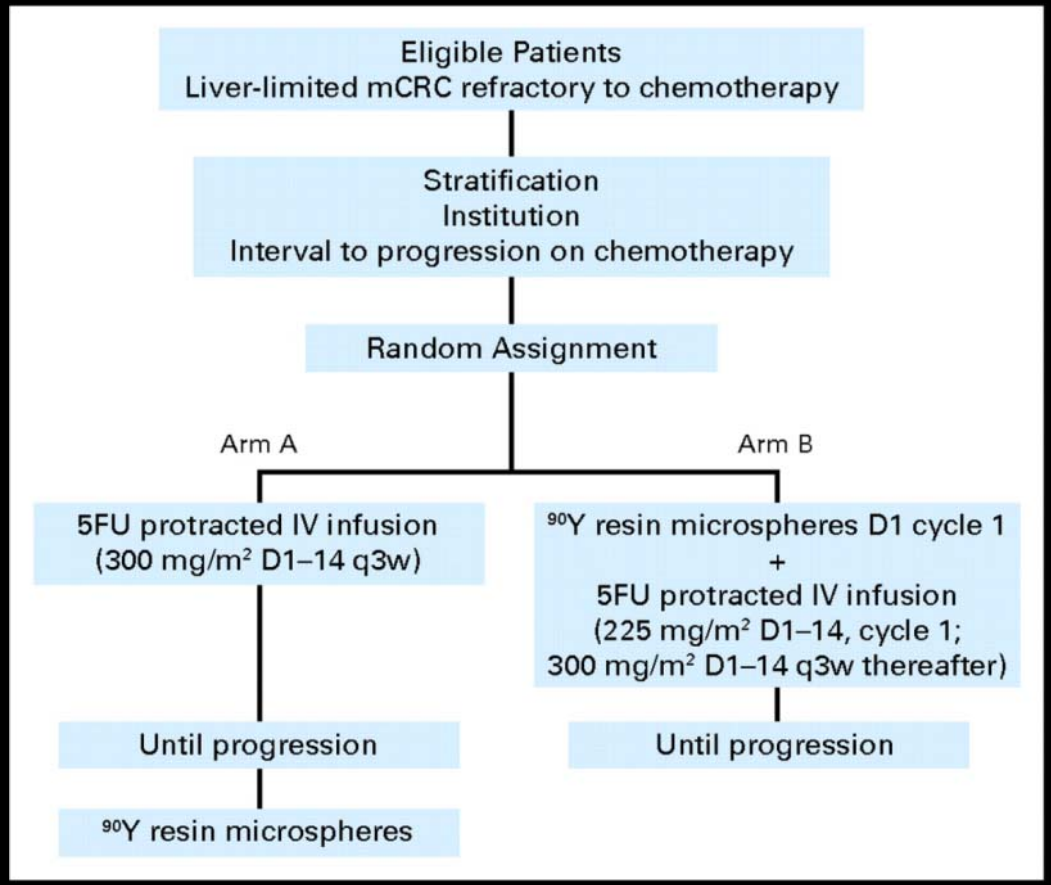
- Karnofsky at least 70%
- (No ascites)
- Bilirubine < 2mg/dL (3 mg/dL if a single segment is treated)
- Child-Pugh not exceeding B7
- No or minimal extrahepatic disease
- (No prior radiotherapy of the abdomen)

Portal vein thrombosis is NOT a contra-indication

Yttrium-90 microspheres

Colorectal liver metastasis

Hendlisz et al. JCO 2010



N=46
Chemorefractory CRC liver mets

Cross over possible to combined therapy arm

Significant difference in TTLP and TTP

Literature / clinical data / SIR-Spheres

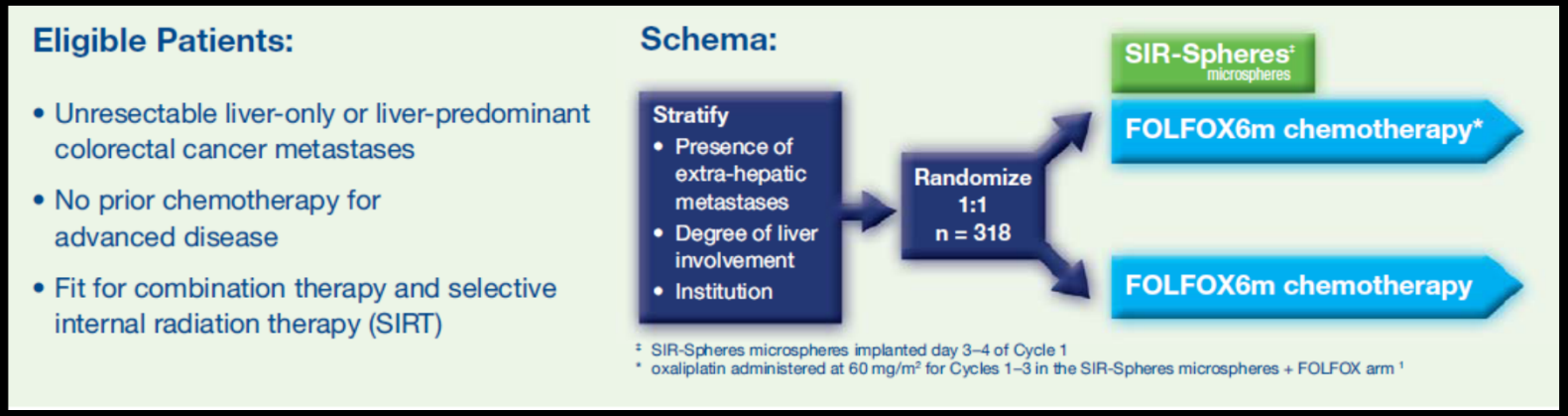
Colorectal liver metastasis

Future?

SIRFLOX/FOXFIRE study

FIRST LINE in CRC liver mets:

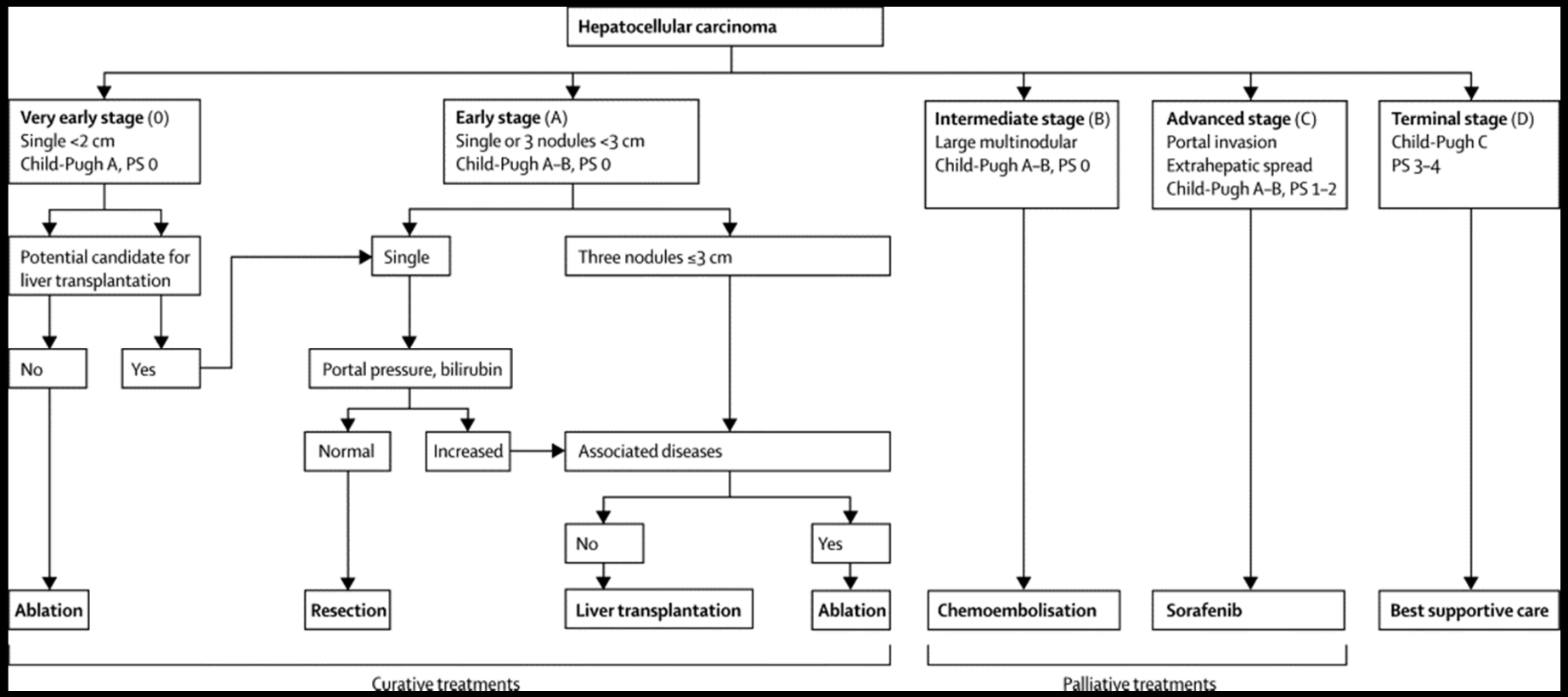
Randomized FOLFOX vs FOLFOX plus single session SIR-Spheres



Yttrium-90 microspheres

HCC

Barcelona Classification 'BCLC'

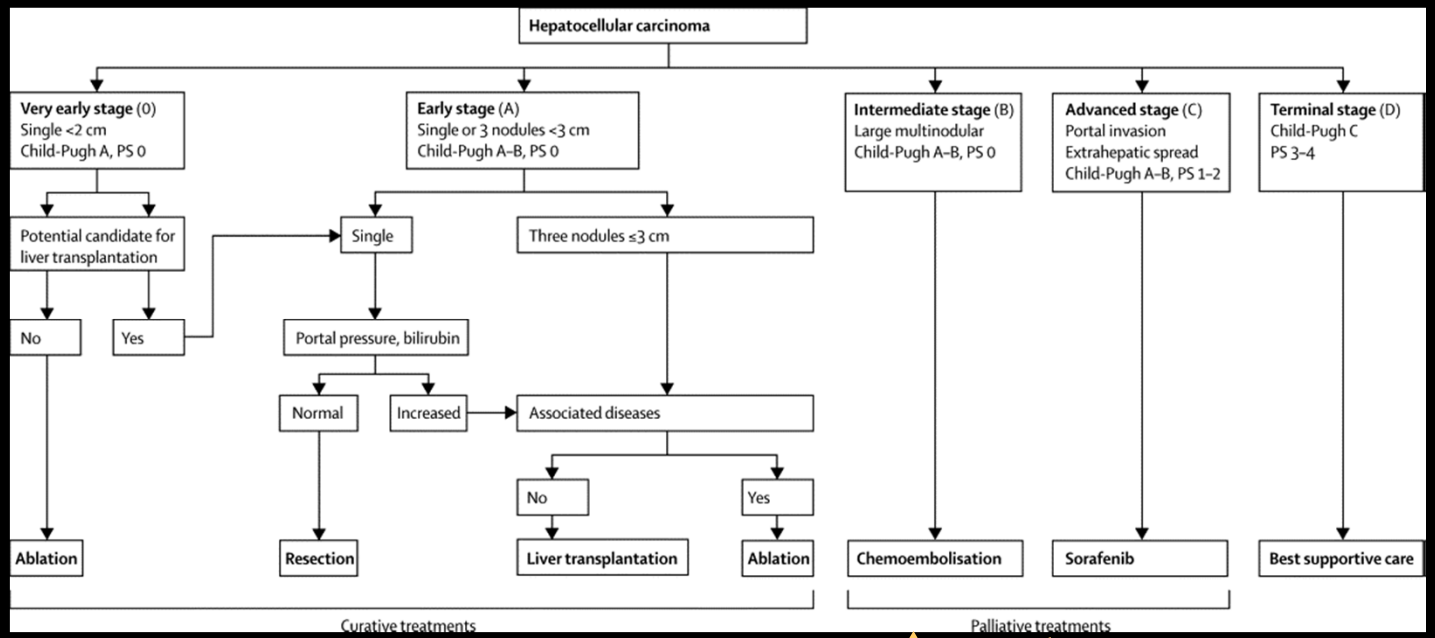


Forner, Bruix, Llovet. Lancet 2012

Yttrium-90 microspheres

HCC

Barcelona Classification 'BCLC'



'SIRT' for intermediate stage HCC
(not amenable to resection/RFA/Tx),
especially if portal vein thrombosis is present

Yttrium-90 microspheres

HCC

Lewandowski et al. Am J Transplant. 2009

"A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization."

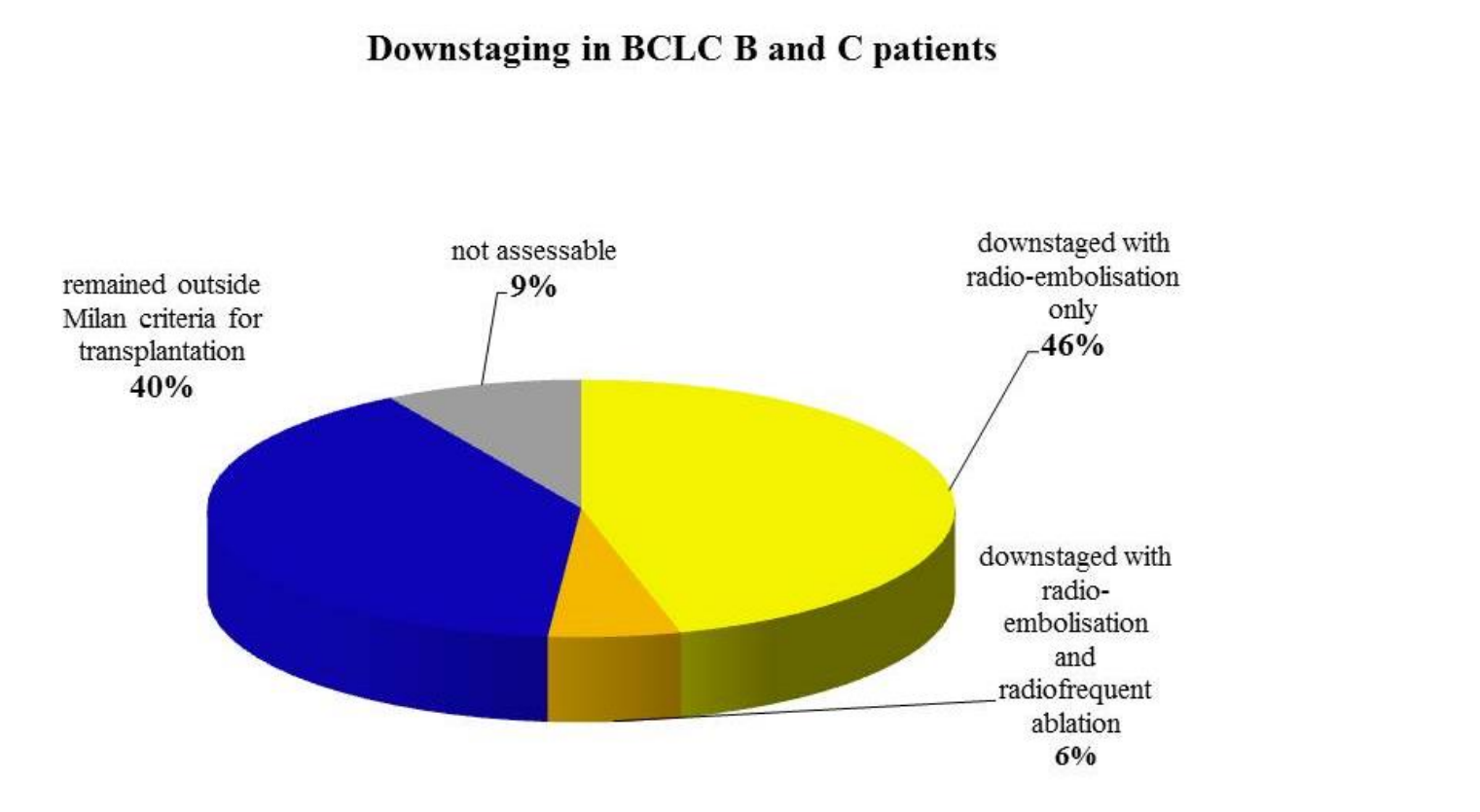
Cohort study comparing chemo-embolisation vs Yttrium-90 in 86 UNOS T3 HCC patients:

- more downstagings achieved with Yttrium-90
- better survival
- pitfall: different tumour biology?

Yttrium-90 microspheres

HCC

UZG results for downstaging HCC patients towards Tx



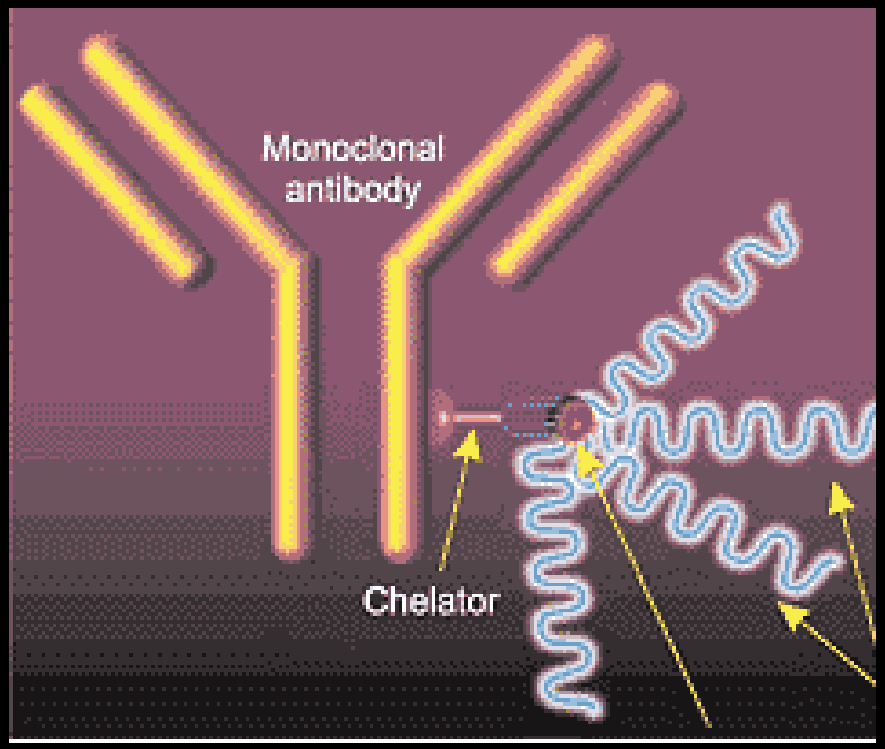
Yttrium-90 microspheres

HCC

Salem R. Gastroenterology 2009

"Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes."

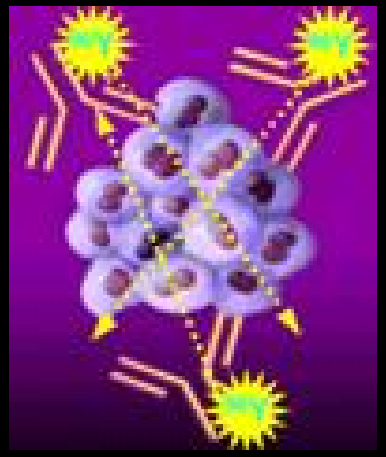
Single center prospective longitudinal study
n= 291 HCC patients; 526 treatments
Toxicity
Fatigue 57%, pain 23%, nausea/vomiting 20%, bilirubine gr III/IV 19%
Response
WHO 42%, EASL 57%
TTP 8 m
Survival



Drugs Fut 2002

Anti CD20 immunotherapy

Yttrium-90 labelled anti CD20 (Zevalin ™)
Iodine-131 labelled anti CD20 (Bexxar ™)



Anti CD20 immunotherapy

Yttrium-90 labelled anti CD20 (Zevalin ™)

CD20 is an antigen is expressed in a relatively high quantity by some lymphomas.

Rituximab is a chimeric anti CD20 antibody. Rituximab as a cold antibody is an established anti tumour therapy.

Ibritumomab is the murine variant of the anti CD20 antibody, it can be labelled with In111 (imaging) or Y90 (therapy) by the chelating agent tiuxetan.

Anti CD20 immunotherapy

« Zevalin »

Indications

>>> Follicular or transformed low grade non hodgkin lymphoma

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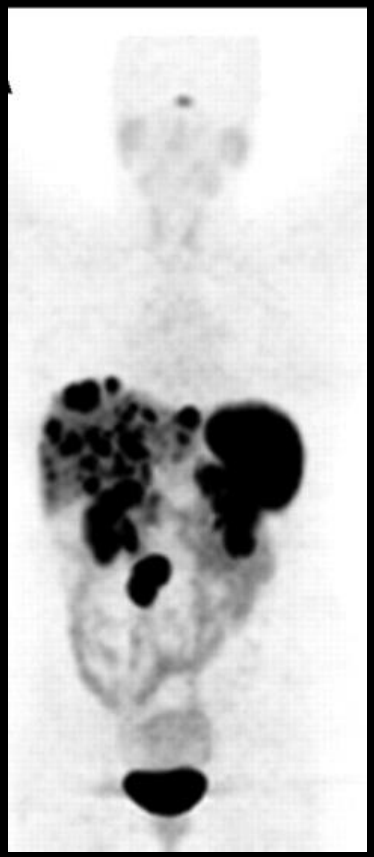
Neuro-endocrine tumours



Ga68-DOTATOC PET UZ Leuven

Somatostatin receptor overexpression

Octreotide as somatostin analogue
Various analogues ~ 5 receptor subtypes

Labelled with
Indium-111
Gallium-68
Yttrium-90
Luthetium-177

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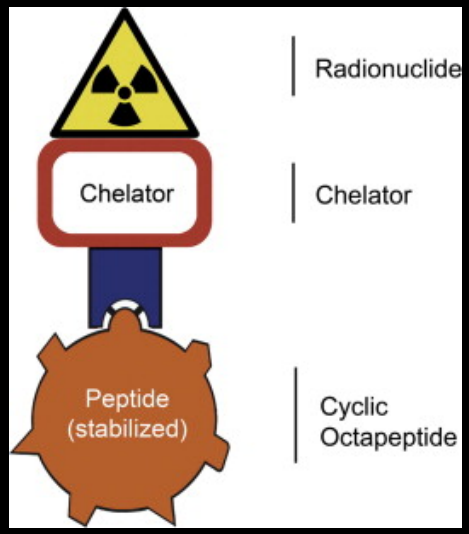
PRRT

Peptide Receptor Radionuclide Therapy



Radiolabelled somatostatin analogues

Octreotide/Pentreotide (Indium-111)
DOTATOC (Yttrium-90)
DOTATATE (Luthetium-177)
Lanreotide (Yttrium-90, Indium-111)

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PRRT

Peptide Receptor Radionuclide Therapy

Indications

Inoperable tumours from neuro-endocrine origine

Tumours should have an uptake on pretherapy scan (OctreoScan, OctreoPET) that exceeds normal liver uptake.

>> GEP-NET

gastro-entero-pancreatic neuro-endocrine tumours overexpressing somatostatin subtype receptor 2 and 5

Bergsma et al. Best Pract Res Clin Gastroenterol. 2012

PRRT

Peptide Receptor Radionuclide Therapy

90Y-DOTATOC and Lu177-DOTATE

Efficacy

No RCTs available

>> symptomatic responses

15-35% radiological PR (limited CR)

Responses ~ long term outcome

Adverse events

For 90Y rare renal impairment (preventive amino acids infusions and dosimetry needed)

Haematologic adverse events (>>>mild)

Bergsma et al. Best Pract Res Clin Gastroenterol. 2012

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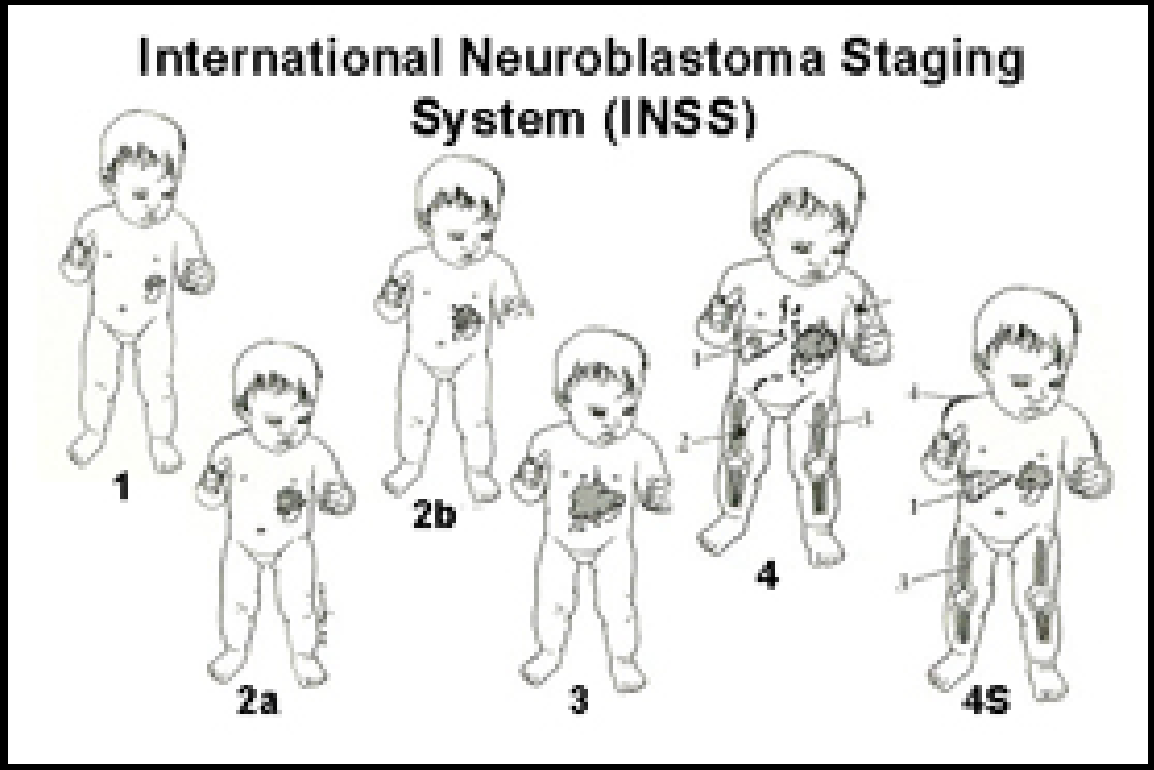
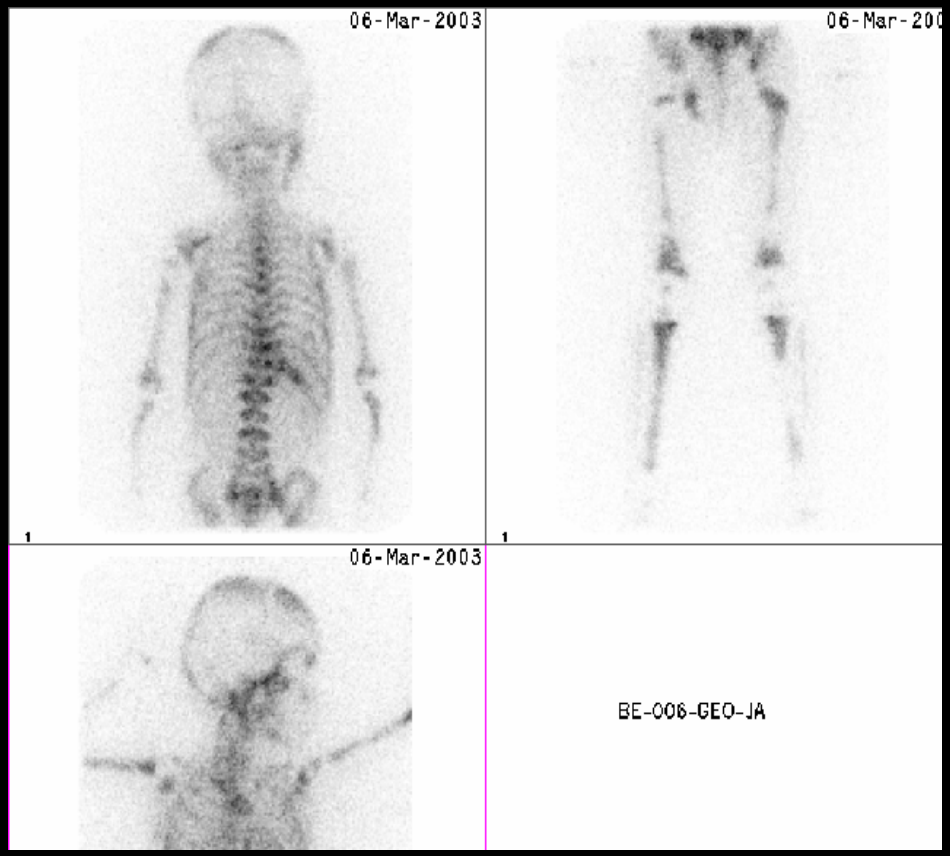


mIBG

Meta-Iodo-Benzyl-Guanidine



Iodine-123 scan of neuroblastoma with massive bone marrow invasion

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mIBG

Meta-Iodo-Benzyl-Guanidine

- Analogue of normetanephrine
- False neuro-transmitter
- Radiolabelled with

  Iodine-123 for imaging
  staging neuroblastoma
  diagnostic imaging of paraganglioma,
  medullary thyroid cancer, NET, ...

  Iodine-131 for therapy

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I-131 mIBG

Indications

Inoperable tumours from neuro-ectodermal origine

- Phaechromocytoma / Paraganglioma
- Carcinoid tumours (if no avidity for somatostatin analogues)
- Medullary thyroid carcinoma (if no avidity for somatostatin analogues)
- Neuroblastoma

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I-131 mIBG

Practical aspects

- Pretherapy imaging assessment: diagnostic scan with I123-mIBG
- If tumour uptake > liver: therapy can be considered
- Some centers use a fixed activity of I131-mIBG for therapy (between 100-300mCi)
- Some centers estimate the activity of I131-mIBG for therapy based on 3 time point analysis of pretherapy scans. Aimed WB dose of 2 Gy.

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I-131 mIBG

Practical aspects

- Administration of 131-mIBG
- hospital stay radionuclide therapy ward for at least 72h and subsequent radioprotective guidelines
- most activity is cleared renally within the first 5 days
- post therapy scan

I-131 mIBG

Future?

Use of I-131-MIBG therapy in case of neuroblastoma under investigation:

- High dose I-131-MIBG therapy as part of a myeloablative treatment

Klingebiel et al. Eur J Cancer 1998; 34: 1398-1402**.**

Yanik et al. Journal of Clinical Oncology 2002; 20: 2142-2149

- Treatment of residual disease

Garaventa et al. Br J Cancer 1999; 81: 1378-1384

- Combination with radiosensitizers and application of new radiosensitizers

Mastrangelo et al. Eur J Cancer 1995; 31A: 606-611

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Bone metastasis

Commonly available

^{89}Sr-Cl_2
^{153}Sm-lexidronam
^{186}Re-etidronate

} EANM guidelines

Research setting

^{188}Re-HEDP
^{117m}Sn-DTPA

^{223}Ra

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Radiopharmaceuticals

Radiopharmaceutical	half-life (days)	energy (MeV)	emission
Sr89-Cl	51	1.46	β
Sm153-EDTMP	1.9	0.71	β/γ
Re186-HEDP	3.8	1.07	β/γ
Re188-HEDP	0.7	2.02	β/γ
Sn117m-DTPA	13	CE	β/γ

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Indications

< EANM guidelines for bone pain palliation

bone metastasis

- osteoblastic: shown on scintigraphy not only on plane X-ray
- painful and multiple

Guidelines on a European, Belgian and Dutch level
are not exclusively designed for prostate cancer patients.
Most studies referred to also contain subsets of patients suffering breast cancer, lung cancer or bladder cancer.

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Contra-Indications

< EANM guidelines for bone pain palliation

1. Absolute
   Pregnancy, breastfeeding
2. Relative
   - Hb < 90 g/l
   - total white cell count < 4.0 x 10^9/l (Dutch: 3.0 x 10^9/l)
   - platelets < 100 x 10^9/l
   - rapidly deteriorating renal function – GFR < 30 ml/min
   - DIC: risk factor for severe thrombocytopenia
   - recent hemi-body external beam radiotherapy (3 m)
   - life expectancy of < 4 weeks. (Dutch: 12 weeks)

RNT has no place in the management of
acute/chronic spinal cord compression or pathological fracture.

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Patient preparation

- recent bone scintigraphy to confirm osteoblastic nature
- exclude other causes of increased uptake and pain (myelum compression)
- Lab test:
  - complete blood counts within 7 days prior to treatment (WBC > 3.0/4.0 x 10^9/l, platelets > 100 x 10^9/l)
  - exclude renal failure and DIC
- no recent other treatment with haematologic side effects
- Recent data suggest no interference of bisphosphonates

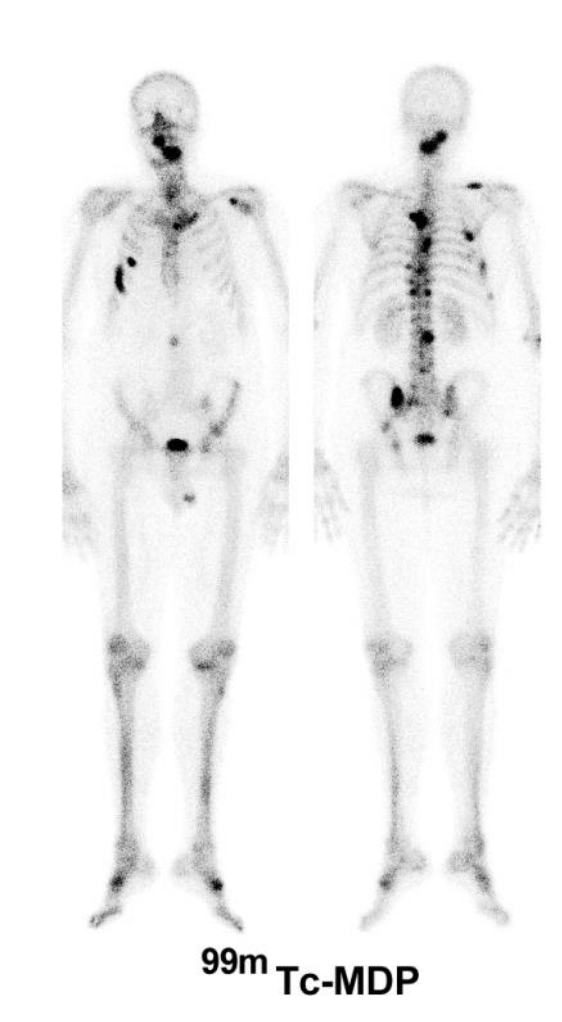
Practicalities

Administration and radioprotection

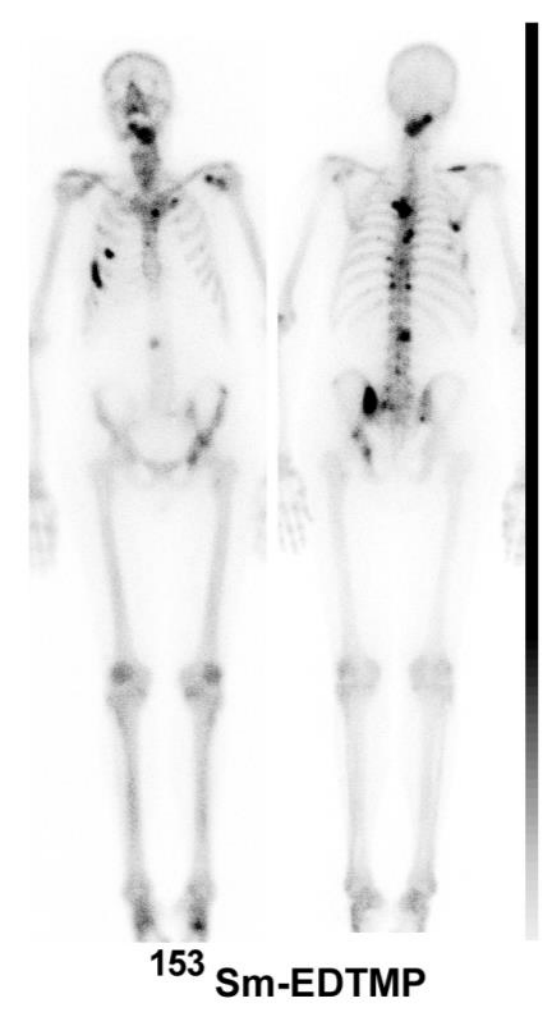
- slow IV infusion for Sr89, bolus injection for Sm153-EDTMP
- use perspex /lead shielding for vial and syringe
- single hospital visit (Sm153-EDTMP: 6 hours stay in Belgium): controlled area
- urine does contain radio-activity (place catheter in case of incontinence)
- FANC restrictions in case of early death post therapy

Practicalities

post therapy scan



^{99m}Tc-MDP



^{153}Sm-EDTMP

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Follow up

Toxicity

- "pain flare": adapt medication for 2-10 days
- haematological:
    - check blood week 3-8
    - decrease in platelets and WBC
    - nadir: about 4 weeks (Sm153), later for Sr89
    - but not grade IV and not requiring treatment
    - spontaneous recovery within 8-12 weeks

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Efficacy

Sr89 (Metastron) vs placebo

Response due to the ^{89}Sr (150 MBq) was shown in small double-blind RCT

1 study failed to show response compared to placebo, but: activity administered was probably too low: 3 x 75 MBq

However: the RCTs comparing ^{89}Sr to placebo have weak methodology!

Lewington et al. Eur J Cancer 1991
Finlay et al. Lancet Oncol 2005
Bauman et al. Radiother Oncol 2005

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Efficacy

Sr89 (Metastron)

A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer

Aikaterini Dafermou[1], Paolo Colamussi[1], Melchiore Giganti[1], Corrado Cittanti[1], Maurizio Bestagno[2], Adriano Piffanelli[1]

"Our results, in a total of 610 patients, all with prostate cancer and homogeneously evaluated, show that 60% of patients with diffuse skeletal metastases experience substantial pain relief or remain essentially pain-free (26%) for several months. If "mild" responses are also included, 81% of patients derive some benefit from the treatment….

Local radiotherapy has similar rates of success, but it is used only in patients with limited bone metastases and is not repeatable in the event of relapse of previously irradiated lesions."

European Journal of Nuclear Medicine Vol. 28, No. 7, July 2001

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Sr89 (Metastron) vs EBRT

Oosterhof et al. Eur Urol 2003

- randomisation local field RT versus 150 MBq Sr89
- n=203 hormone-refractory prostate cancer
- equal response (35%)
- survival slightly but statistically significant better for local field RT
- cost ^{89}Sr vs standard local field RT in the Netherlands: 25% higher for RNT!

Quilty et al. Radiother oncol 1994

- randomisation local field/hemibody RT versus 200 MBq Sr89
- n= 305 hormone-refractory prostate cancer
- responses *(66%)* and survival equal
- *significant less new pain sites in case of ^{89}Sr*

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EBRT vs EBRT+Sr89

Porter et al. Semin Oncol 1993

- randomisation EBRT plus placebo versus EBRT plus 400 MBq ^{89}Sr
- n=126 hormone-refractory prostate cancer
- significant more patients pain free and without analgetics at 3 m
- significant impact on daily activities
- less new pain sites, longer interval for next EBRT

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Efficacy

Sm153-EDTMP (Quadramet)

Samarium Sm-153 Lexidronam for the Palliation of Bone Pain Associated with Metastases

Double-blind placebo-controlled study (Serafini et al. J Clin Oncol 1998) :

- placebo versus 0.5 mCi/kg versus 1 mCi/kg group
- decline in VAS > placebo (p=0.034) at all weeks in 1 mCi/kg group
- decline in VAS > placebo (p=0.044) at week 1 in 0.5 mCi/kg group
- 1 mCi/kg group rapid onset of pain relief (< 1 week)
- pain relief up to 4 months after treatment

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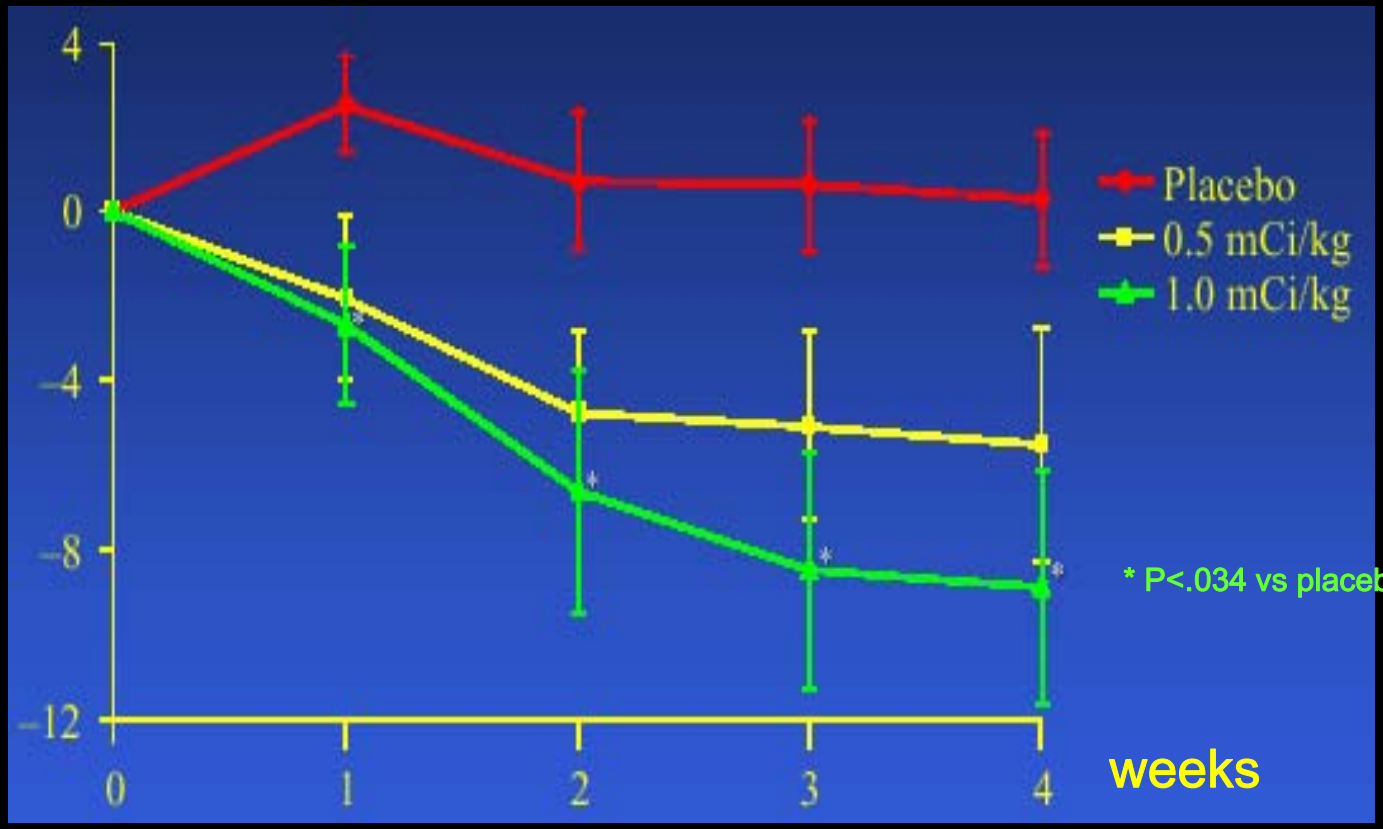
Efficacy

Sm153-EDTMP (Quadramet)



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Repeated treatment with Sm153-EDTMP

Safety and Efficacy of Repeat Administration of Samarium Sm-153 Lexidronam to Patients With Metastatic Bone Pain

Sartor et al. Cancer 2007

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Repeated treatment with Sm153-EDTMP

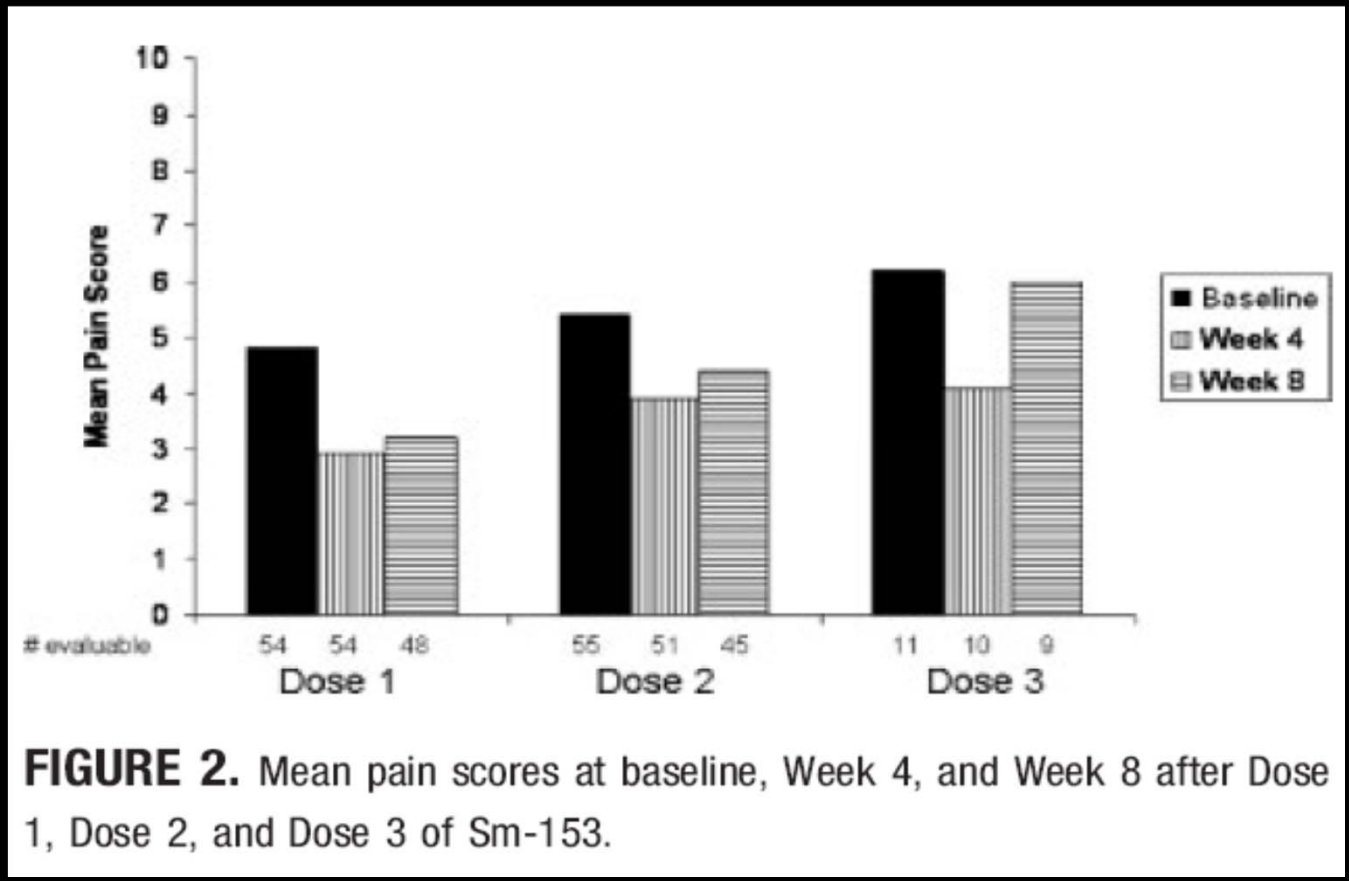

FIGURE 2. Mean pain scores at baseline, Week 4, and Week 8 after Dose 1, Dose 2, and Dose 3 of Sm-153.

Sartor et al. Cancer 2007

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Issues requiring further research

To combine with chemotherapy?

Effects of Low-Dose Cisplatin on ^{89}Sr Therapy for Painful Bone Metastases from Prostate Cancer: A Randomized Clinical Trial

Rosa Sciuto, MD; Anna Festa, MD; Sandra Rea, MD; Rosella Pasqualoni, MD; Serenella Bergomi, MD; Germana Petrilli, MD; and Carlo L. Maini, MD J Nucl Med 2002; 43:79–86

- double blind RCT, n= 70, ^{89}Sr+cisplatinum vs ^{89}Sr+placebo
- significant better (62 vs 92%) and longer response (60 vs 120 d)
- comparable toxicity

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VOLUME 27 · NUMBER 15 · MAY 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Consolidation Docetaxel and Samarium-153 in Patients With Bone Metastases From Castration-Resistant Prostate Cancer

Karim Fizazi, Philippe Beuzeboc, Jean Lumbroso, Vincent Haddad, Christophe Massard, Marine Gross-Goupil, Mario Di Palma, Bernard Escudier, Christine Theodore, Yohann Loriot, Elodie Tournay, Jeannine Bouzy, and Agnes Laplanche

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Issues requiring further research

Earlier use of RNT in the course of the disease?

Roberts et al: Int J Rad Oncol Biol Phys; 2002: 54: 193 (abstr)
"Can ^{89}Sr delay the onset of bone pain?"

^{89}Sr: median time to development of pain of 213 days,
with 33% free of pain at one year

Placebo: median time to development of pain of 168 days,
with 18 % free of pain at one year. (p=0.01)

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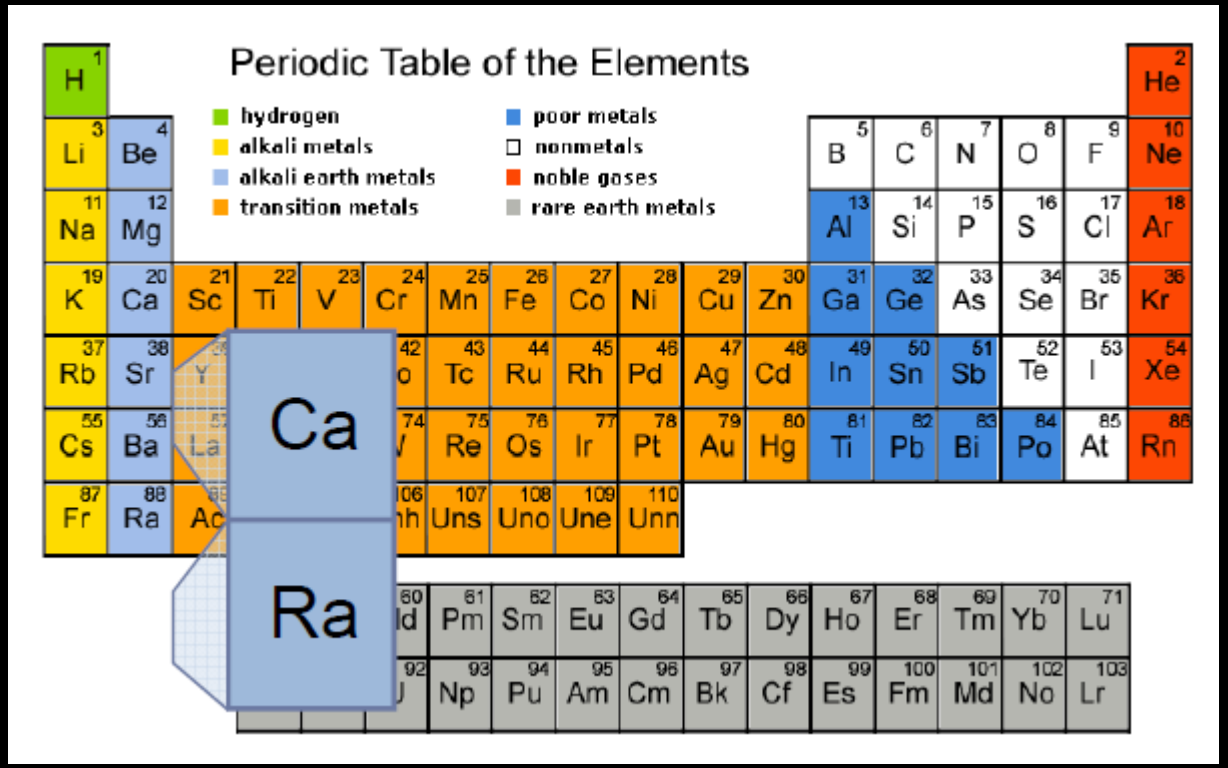
Ra223



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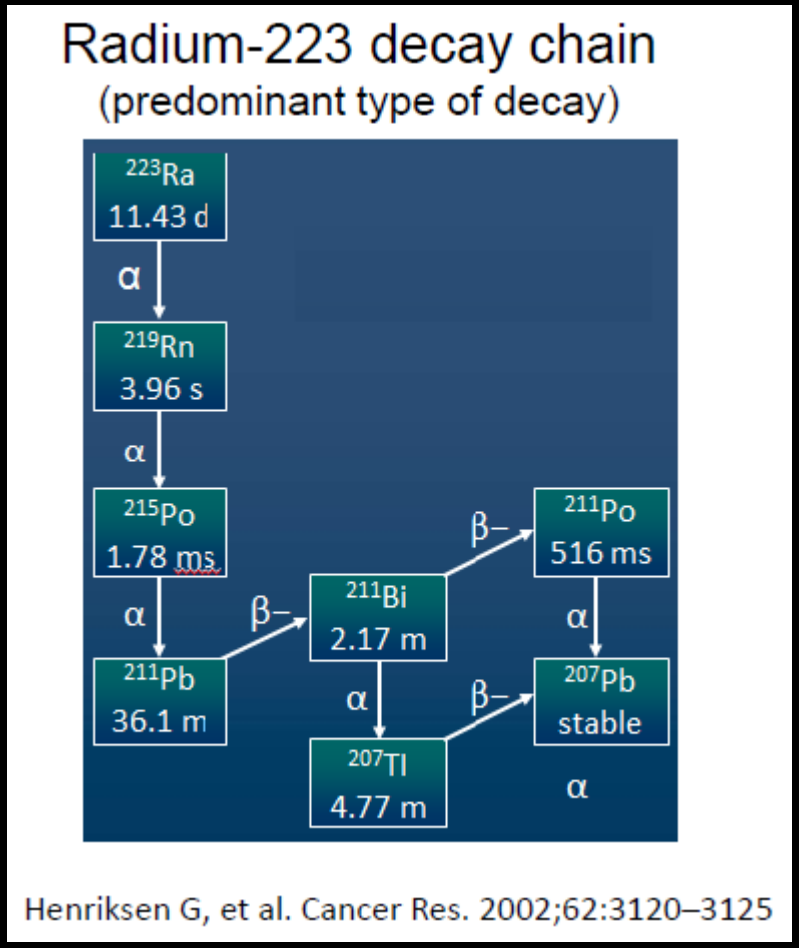

Ra223

AlphaRadin (Bayer Pharma AG)

$RaCl_2$	Calcium mimetic, built in bone with high turn over
Radium-223	t1/2 11,4 d
Alpha emitter	high LET: very short path length, double strand breaks

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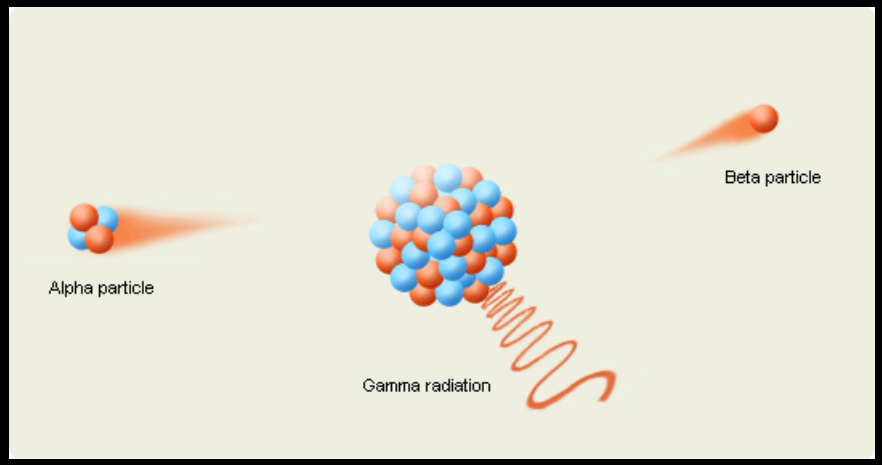
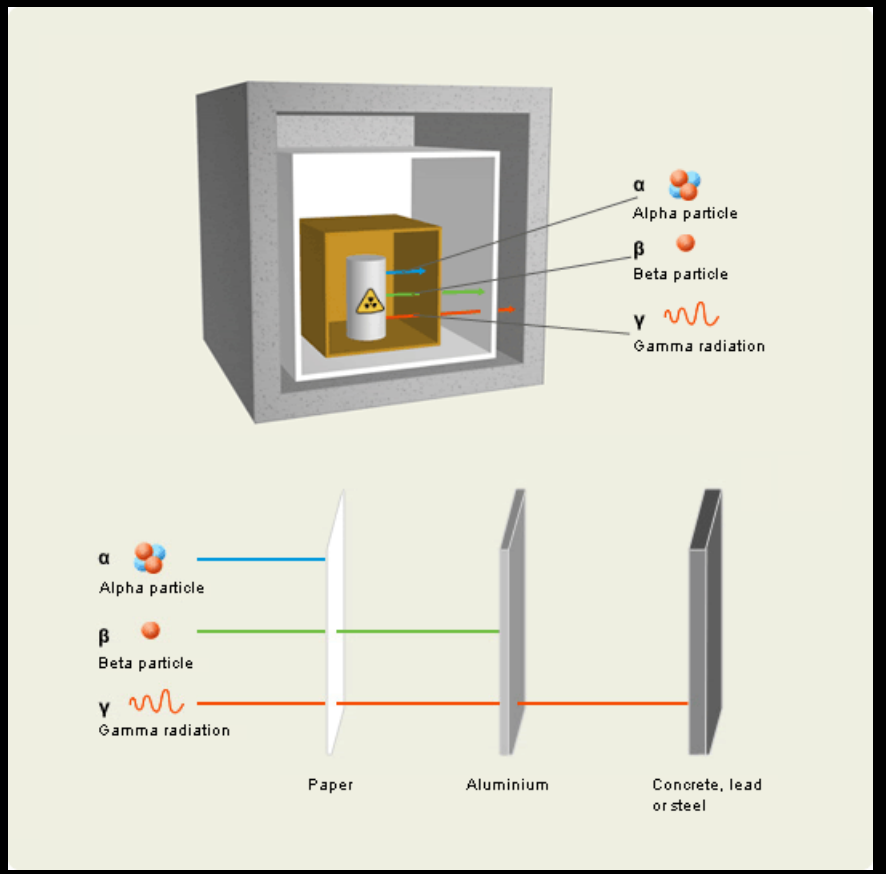
Ra223





www.vae.lt

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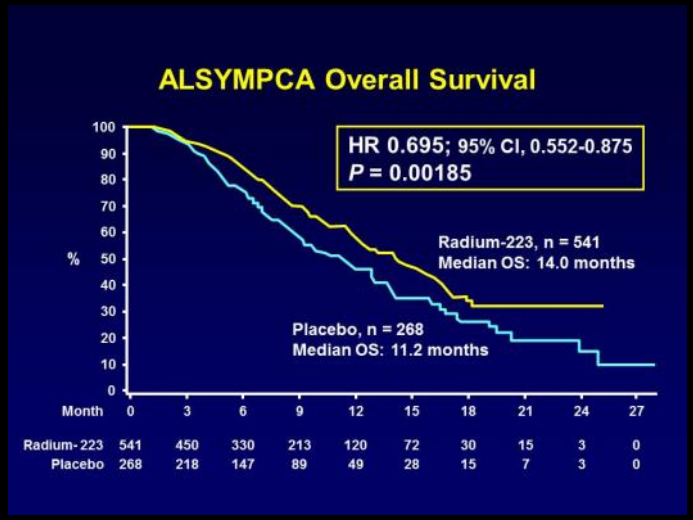
Ra223

ALSYMPCA Study
Large RCT
6xRa223 over 6m vs placebo

HRPC
Min. 2 bone mets, no visceral mets
Symptomatic
Progressive PSA post docetaxel
or docetaxel refused



Less adverse events recorded in Ra223 group compared to placebo

Parker C, and ALSYMPCA Investigators. N Engl J Med. 2013

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Ra223

ALSYMPCA Adverse Events of Interest Hematologic

	All Grades		Grades 3 or 4	
	Radium-223 (n = 509) n (%)	Placebo (n = 253) n (%)	Radium-223 (n = 509) n (%)	Placebo (n = 253) n (%)
Hematologic				
Anemia	136 (27)	69 (27)	**54 (11)**	**29 (12)**
Neutropenia	20 (4)	2 (1)	**9 (2)**	**2 (1)**
Thrombocytopenia	42 (8)	14 (6)	**22 (4)**	**4 (2)**

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Ra223

MSKCC Radiation Safety Precautions for Clinical Phase I Study Following Alpharadin, Radium-223, Injection

You will be given a card which informs people that you have received radioactive medicine, always carry this card with you.

There are NO restrictions regarding contact with other people after receiving the study drug.

During the first week after study drug injection there may be some radioactivity in your blood, urine, and stools, therefore you should take the following precautions:

- Use medical gloves when wiping up blood, urine, stools, or vomit, or when handling stained clothes.
- A normal toilet should be used in preference to a urinal. The sitting position should be used instead of the standing position.
- Wipe up any spilled urine or stool with a tissue and flush it away.
- If you are sick, wipe up spilled vomit with a tissue and flush it away.
- Ensure that you always thoroughly wash your hands after using the toilet or after wiping up spilled fluids.
- Wash any linen or clothes that become stained with urine, blood or stools separately from other clothes and rinse them thoroughly.
- If you are sexually active, the use of a condom is recommended during the first week after each study drug injection because there may be some slight radioactivity in the body fluids (but most in blood, urine and stools).
- If sampling of blood, urine or stools is necessary during the first week following study drug administration, please inform the personnel that you have been treated with radioactive Radium-223.
- If you need medical care such as an operation or hospital admission during the first week following administration, please inform the personnel that you have been treated with radioactive Radium-223.

Radiation Safety Considerations for the Use of 223RaCl2 DE in Men with Castration-resistant Prostate Cancer. Dauer, Lawrence et aL

Health Physics. 106(4):494-504, April 2014.
DOI: 10.1097/HP.0b013e3182a82b37

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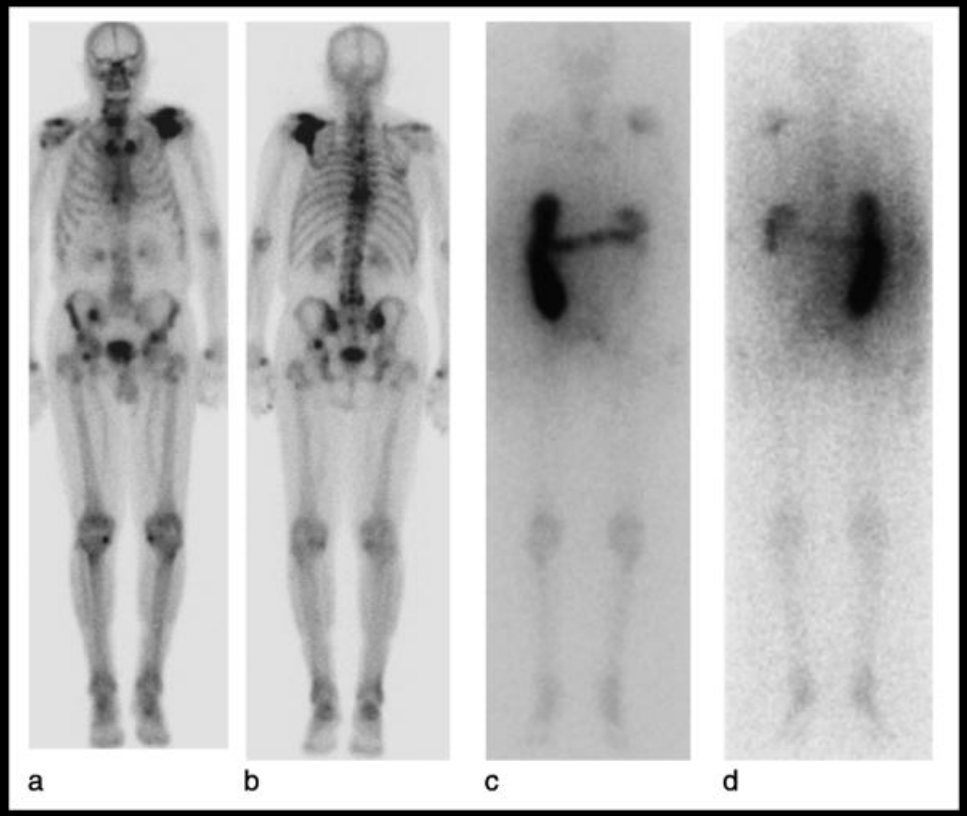
Ra223



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