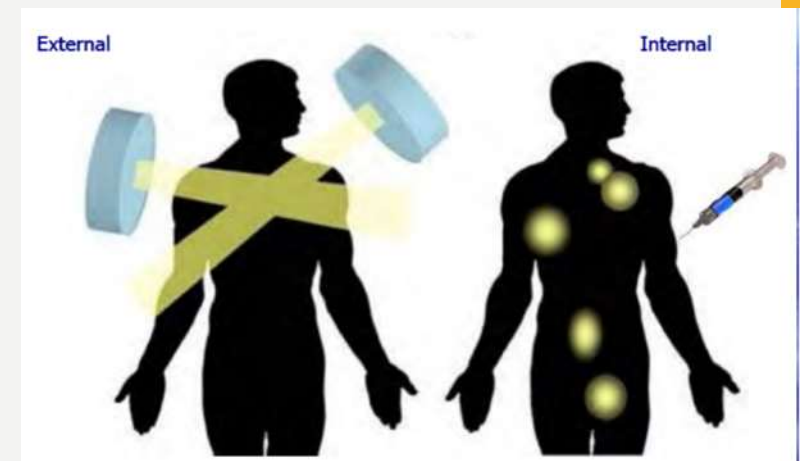
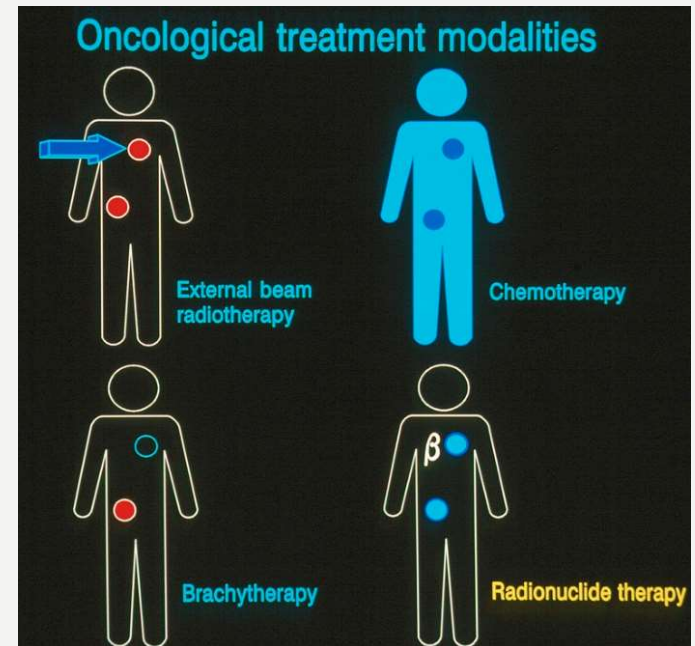




NUCLEAR MEDICINE THERAPY

- Radionuclide therapy has the advantage of delivering a highly concentrated absorbed dose to the targeted tumor while sparing the surrounding normal tissues. In addition, the selective ability of radionuclide therapy is advantageous in the treatment of systemic malignancy, such as in bone metastases, where whole body irradiation using external beam radiotherapy is impossible.
- The requirements for a therapeutic radionuclide may be divided into two categories physical and biochemical.



THE REQUIREMENTS FOR A THERAPEUTIC RADIONUCLIDE

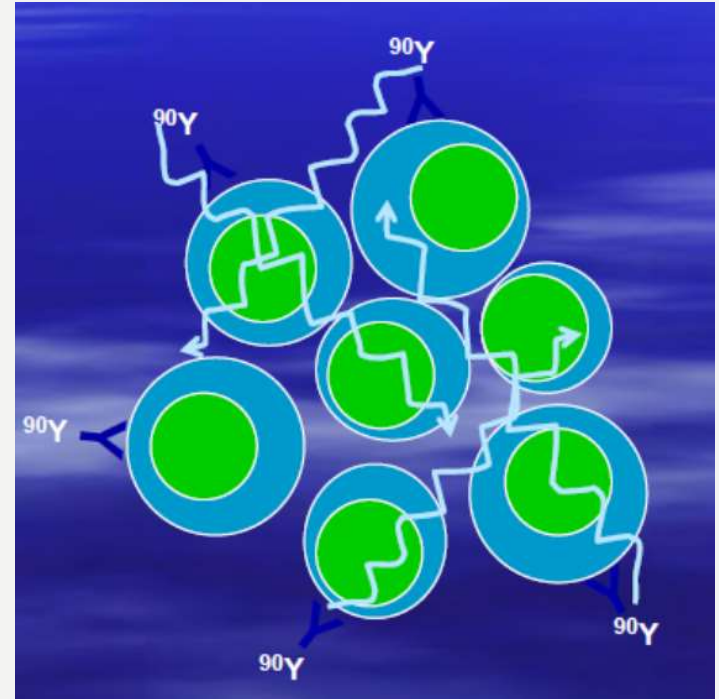
- **optimal effective half-life:** for an efficient radiation delivery, a balanced optimal biological and physical half-life should be chosen (5-20 days)
- **high-linear energy transfer (LET):** α - and β -particles, are preferable. Some β -emitting radionuclides also decay with γ -radiation (if the energy and intensity are within the diagnostic range, it provides the ability to visualize distribution of the radiopharmaceutical within the patient's body)
- An ideal radiopharmaceutical should be able **to decay into a stable daughter product** such as ^{153}Sm , which fully decays into stable ^{153}Eu .
- **High target-non target ratio:** selective concentrations and prolonged retention in the tumor, while maintaining minimum uptake in the normal tissue

Ionizing radiations interact with biological substrates through direct and indirect mechanisms.

Direct effects involve one-electron oxidation reactions, while indirect effects are mediated through water dissociation, leading to the production of reactive oxygen species

TRT can have direct cytotoxic effects as well as indirect or bystander effects.

Bystander effects occur in adjacent nonirradiated cells, that are similar to that observed in irradiated cells.



Bystander effect

RADIONUCLIDES FOR THERAPY

Radionuclide	Abbreviation	Emission	Half-Life	Energy _{max} (keV)	Travel Distance	Characteristics of Radiation Class
Actinium-225	²²⁵ Ac	Alpha/beta ⁻ /gamma	9.92 days	7.069	50–100 μm	+ Short range, high energy
Astatine-211	²¹¹ At	Alpha	7.20 h	5.867	50–100 μm	+ Double stranded DNA breakage
Bismuth-213	²¹³ Bi	Alpha/gamma	46 min	6.051	50–100 μm	+ Oxygen independent
Lead-212	²¹² Pb	Alpha/beta ⁻ /gamma	10.64 h	8.785	50–100 μm	– No crossfire
Iodine-131	¹³¹ I	Beta ⁻ /gamma	8.02 days	606	200 μm–1 mm	+ Crossfire effect
Lutetium-177	¹⁷⁷ Lu	Beta ⁻ /gamma	6.68 days	498	230 μm	– Oxygen dependent
Rhenium-188	¹⁸⁸ Re	Beta ⁻ /gamma	16.98 h	2.110	11 mm	– Long range, low energy
Yttrium-90	⁹⁰ Y	Beta ⁻	2.67 days	2.280	12 mm	– Single stranded DNA breakage
Indium-111	¹¹¹ In	Auger/gamma	2.8 days	245	4 nm	+ Very short range
Iodine-125	¹²⁵ I	Auger/gamma	59.49 days	35	2 nm	– Necessary to be internalized

I-131 is a gamma (0,364 MeV) and beta emitter (0,61 MeV) and most of the radiation is delivered by beta particles, a $T_{1/2}$ =8.02 days and a medium path length in tissue of about 0.4 mm. Gamma emission, allows imaging, (dosimetric calculations, posttherapeutic whole body scintigraphy). Disadvantages: additional unwanted whole body radiation to the patient and radiation protection problems for the staff.

RADIOIODINE THERAPY: MALIGNANT THYROID DISEASE

Thyroid gland

Follicular epithelial cells

C cells

Diferentiated
thyroid carcinoma (TC)

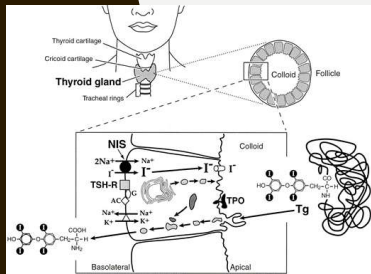
Undifferentiated
TC

Medullary
TC

Papillary TC

Follicular TC

Anaplastic
TC



- 1949. for the first time in Europe patient with metastasizing thyroid cancer was treated with I-131
- 1–2% of all malignancies,

**Total
thyroidectomy**
+/- lymph node
dissection



**Postoperative
patient evaluation**



**Radioiodine
therapy/
ablation**

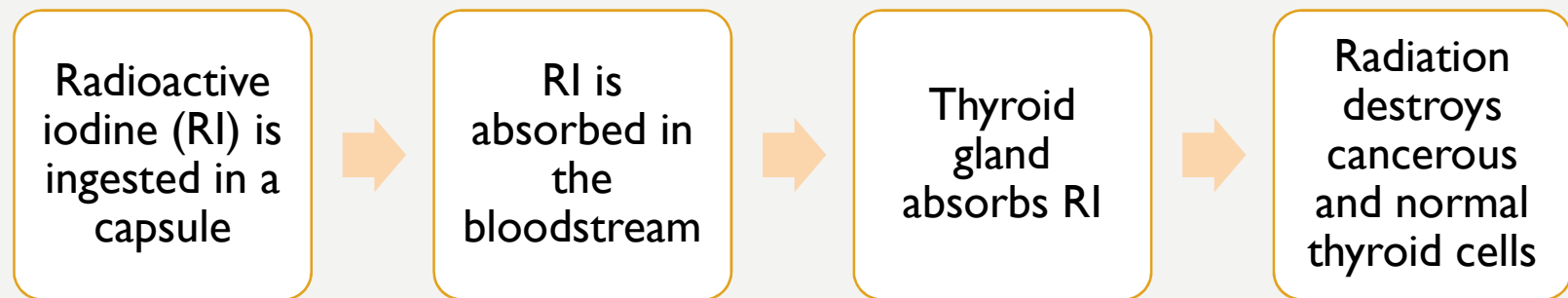
- Besides appropriate surgery, meaning (near) total thyroidectomy with staging lymphadenectomy, there is evidence that the additional use of radioiodine for remnant ablation reduces recurrent and metastatic disease
- With the exception of papillary thyroid cancer pT1a (TNM classification), which is treated only by surgery, the therapy of DTC includes total thyroidectomy, radioiodine remnant ablation and TSH suppressive thyroid hormone treatment
- the goal of thyroid surgery in DTC is the radical removal of the primary tumor and lymph node metastases in the neck

Iodine is taken up by thyrocytes via the NIS. This mechanism allows iodine to be concentrated within the thyroid gland. Promoted by TPO, iodine is then bound to thyroglobulin (iodination), and stored within the colloid of the follicles. The uptake mechanism of radioactive iodine does not differ from nutritional iodine uptake.

PATIENT PREPARATION

- Before administration of radioiodine it is necessary that TSH $>35\text{mU/l}$
- After (near) total thyroidectomy the patient should be without LT4 for at least 4–6 weeks or since recombinant human TSH (rhTSH) has been available intramuscular injection of 0.9 mg rhTSH on day 1 and 2; measurement of TSH on day 3; administration of the therapeutic dose in the case of TSH $>35\text{ mU/l}$
- The 7-10 days before RIT, a low iodine diet should be prescribed.
- At the time of RIT the patient should be well hydrated orally and the radiation of the salivary glands should be reduced by administration of vitamin C containing drops or chewing gum.
- For gastric protection H2-blockers or proton pump inhibitors, and in the case of larger remnants also corticosteroids, are administered.
- According to the activity administered and the national radiation regulations, the patient remains in the therapy ward for 3–7 days.

Contraindications: Absolute (Pregnancy, Breastfeeding) and Relative (Clinically relevant: bone marrow depression, pulmonary function restriction together with expected accumulation in lung metastases, salivary gland restriction)

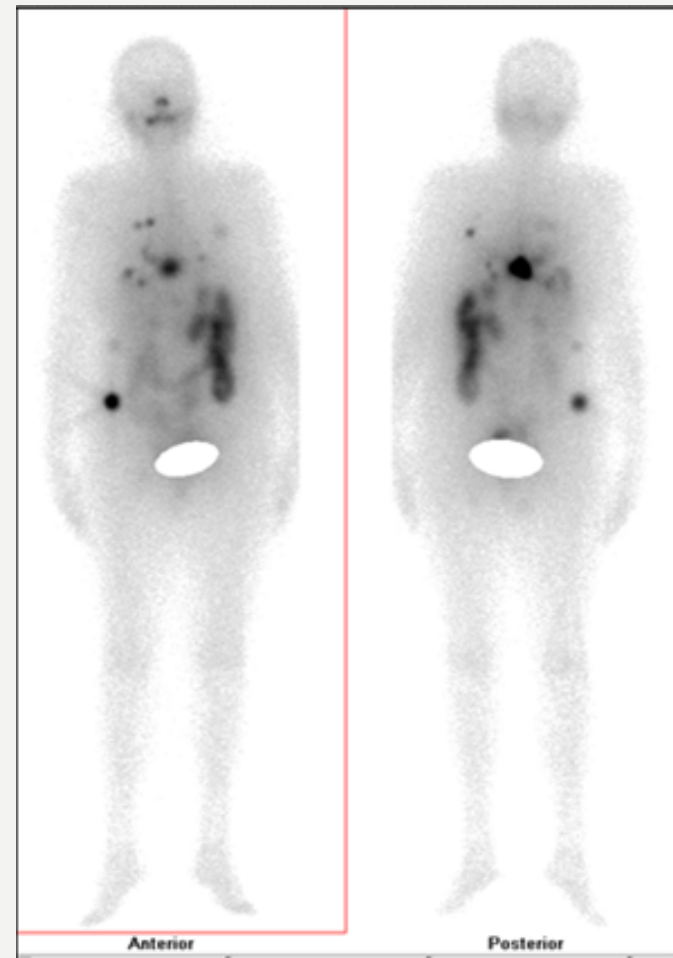
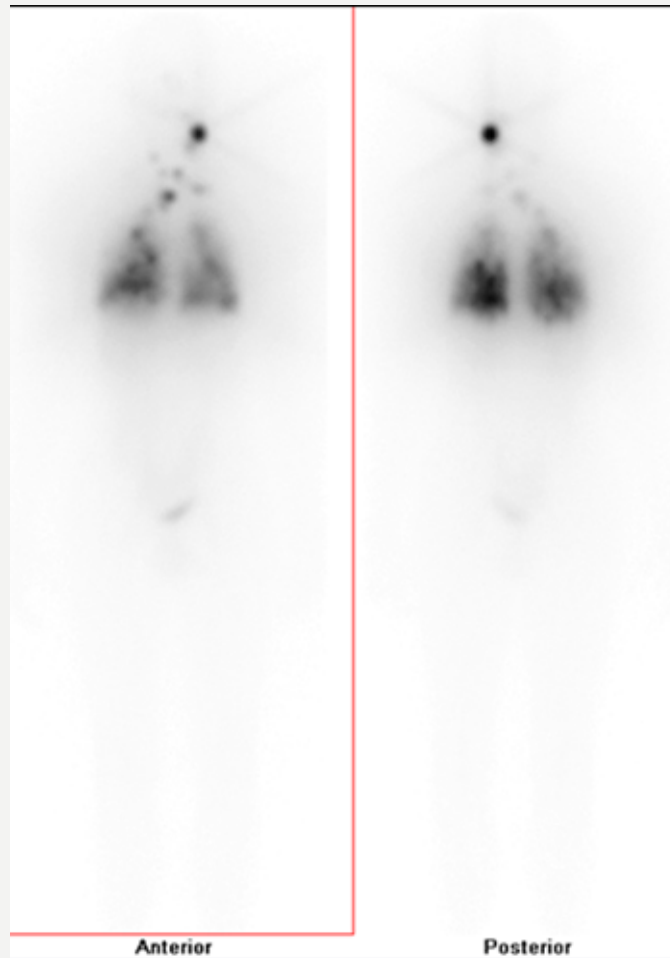


Compared to the benefits of RIT, the side effects are not serious. If surgery was not appropriate and a larger remnant has to be treated by radioiodine, thyroiditis is a common side effect. Administration of corticosteroids, however, can reduce local pain during the treatment period.

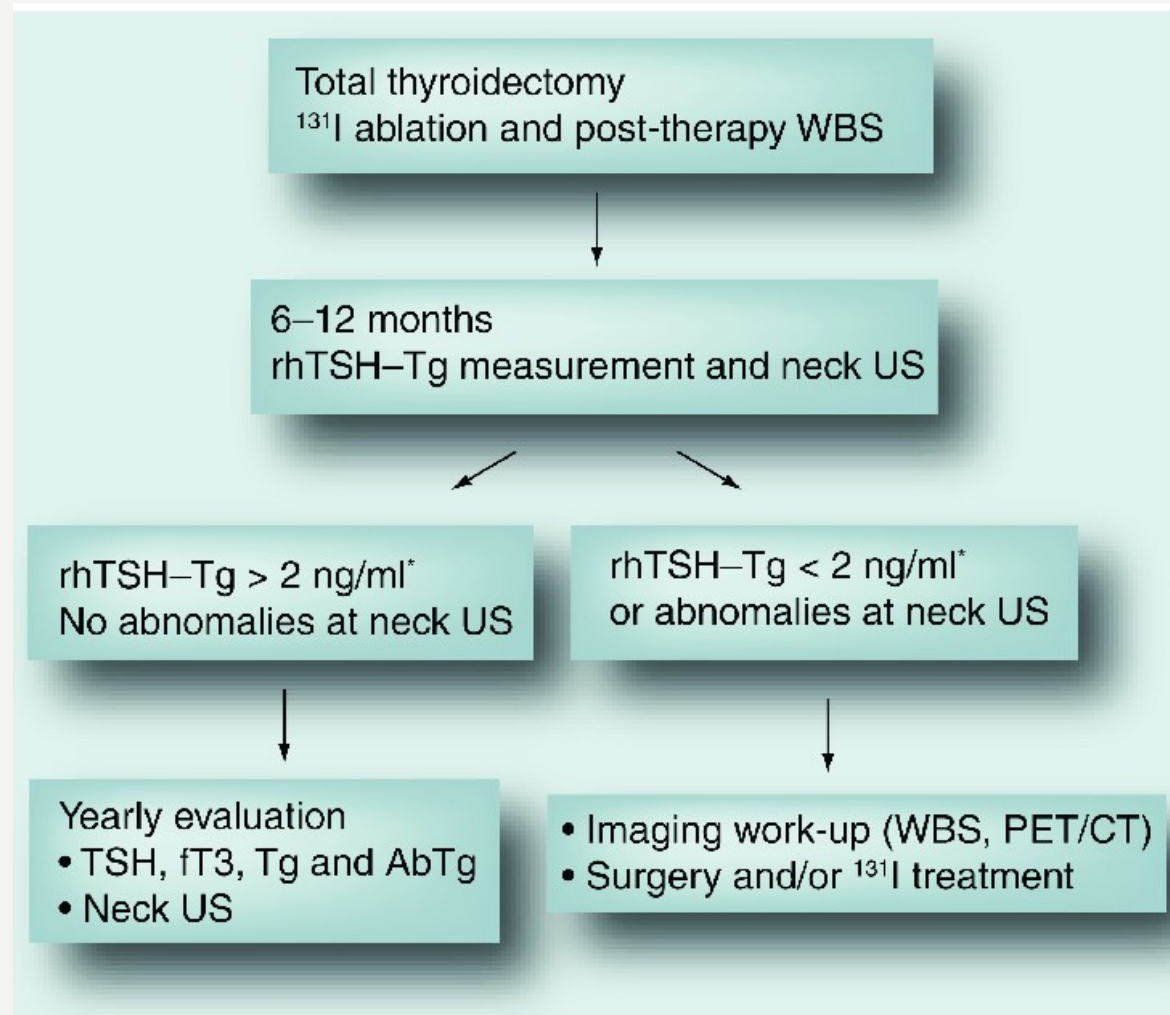
SIDE EFFECTS OF RIT

- Short-term side effects of RAI treatment may include: Neck tenderness and swelling. Nausea and vomiting. Swelling and tenderness of the salivary glands. In about 30% of cases acute swelling of the salivary gland can occur.
- After several courses of RIT a dry mouth may remain as a late complication.
- There is also evidence that after repeated RIT an impairment of the lacrimal glands may occur.
- In about 5% of patients thrombocytopenia and leukopenia develop depending on the cumulative dose administered.
- In the case of disseminated lung metastases and repeated RIT, fibrosis of the lung may occur.

POSTTHERAPY WHOLE BODY SCINTIGRAM



THE DTC FOLLOW-UP AFTER INITIAL TREATMENT (SURGERY AND RADIOIODINE ABLATION)





NEUROENDOCRINE TUMORS (NETS)

- are rare tumors characterized by the ability to synthesize, store, and secrete a variety of neuro-amines and peptides that can lead to secretory syndrome. NETs are mainly from the digestive tract and bronchopulmonary, and their incidence has been steadily increasing in the last three decades
- NETs are biological and clinically heterogeneous. The potential for metastatic evolution and the ability to generate a secretory syndrome vary considerably depending on the primary tumor location.
- More than 40% of patients have metastatic disease at the time of diagnosis, which justifies the importance of a good pre-therapeutic evaluation.
- incidence of NETs has increased more than 6-fold over the last 4 decades, with a predominant rise in localized tumors rather than metastatic tumors NETs are a heterogeneous group of malignancies that frequently overexpress somatostatin receptors (SSTRs)

Neuroendocrine neoplasm	Classification
Gastrointestinal and pancreatobiliary tract	
Well-differentiated neuroendocrine tumor (NET)	NET, grade 1
	NET, grade 2
	NET, grade 3
Poorly differentiated neuroendocrine carcinoma (NEC)	Small cell NEC
	Large cell NEC
Upper aerodigestive tract and salivary glands	
Well-differentiated neuroendocrine tumor (NET)	NET, grade 1
	NET, grade 2
	NET, grade 3
Poorly differentiated neuroendocrine carcinoma (NEC)	Small cell NEC
	Large cell NEC
Lung and thymus	
Well-differentiated neuroendocrine tumor (NET)	Typical carcinoid/NET, grade 1
	Atypical carcinoid/NET, grade 2
	Carcinoids/NETs with elevated mitotic counts and/or Ki67 proliferation index
Poorly-differentiated neuroendocrine carcinoma (NEC)	Small cell (lung) carcinoma
	Large cell NEC
Thyroid	
Medullary thyroid carcinomas (MTC)	Low-grade MTC
	High-grade MTC



FEATURES OF GEP-NET BY GRADE

Differentiation	Well Differentiated			Poorly Differentiated
Grade	G1	G2	G3	
Mitotic count	<2/10 hpf	2-20/10 hpf	>20/10 hpf	
Ki-67	<3%	3-20%	>20%	
Clinical course	Indolent	Intermediate	Intermediate	Rapid
Somatostatin receptor expression	Higher	Intermediate	Lower	
FDG-PET avid lesions	Lower	Intermediate	Higher	
Mutations	DAXX/ATRX, MEN-1, mTOR pathway (pNET) CDKN1B (SI-NET)			TP53, RB1

Tang et al, NANETS 2016

- **Functional NETs**-cause different symptoms, depending on their location and whether the tumor secretes hormones and which hormones
- **Nonfunctional NETs** do not secrete hormones



DIAGNOSTICS

- NETs are uncommon cancers that are commonly misdiagnosed as another condition causing delays in diagnosis and care. In fact, about half are not properly diagnosed until later stages, when the cancer has spread to other areas and is far more difficult to treat
- SSTR should be the preferred imaging modality for initial diagnosis, selection of patients for peptide receptor radionuclide therapy (PRRT), and localization of unknown primaries
- Biochemical testing NETs from different sites may differ in the tumor markers secreted. The traditional empiric measurement : serum chromogranin A and the 24-h urinary 5-HIAA remain of value;

SSTR EXPRESSION FOR PTS' SELECTION

Krenning Score

Grade 1: uptake < normal liver

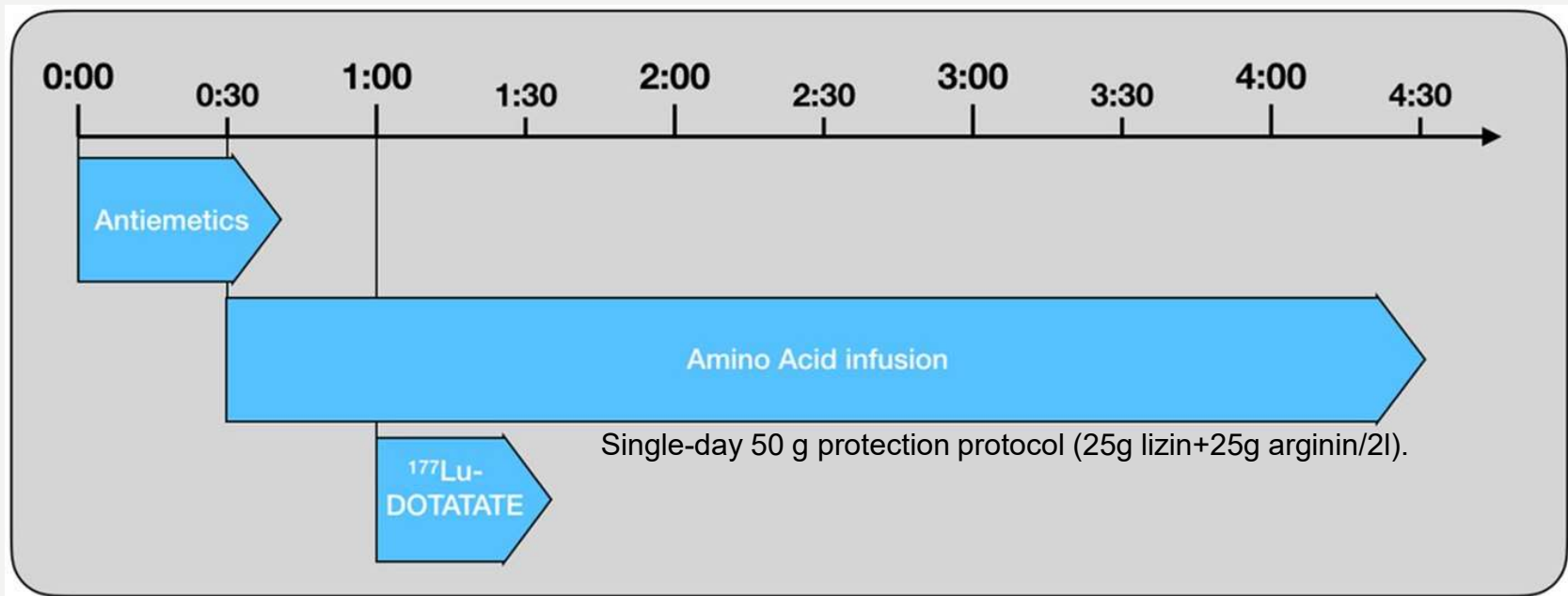
Grade 2: uptake = normal liver

Grade 3: uptake > normal liver

Grade 4: uptake > spleen or kidneys

- **^{99m}Tc -EDDA/HYNIC-TOC (Krenning score 2-4)**
- **^{111}In -pentetreotide: SSTR expression** greater than background hepatic uptake - eligibility requirement for PRRT.
- **^{68}Ga -based SSTR PET** : Necessary levels of SSTR expression have not been clearly defined, but lesion uptake should exceed background hepatic uptake
- **PET-CT lesions' detection is superior to SRS (especially for small lesions)**

RADIOPHARMACEUTICAL ADMINISTRATION



All SSTR-targeting radiopharmaceuticals described above and currently in clinical use are SSTR agonists, such as DOTATOC, DOTANOC, and DOTATATE labeled with ^{68}Ga , ^{90}Y , or ^{177}Lu .

Thomas A. NANETS/SNMMI Procedure Standard for Somatostatin Receptor–Based Peptide Receptor Radionuclide Therapy with ^{177}Lu -DOTATATE J Nucl Med 2019;60:937-943

SIDE EFFECTS OF PRRT

- **Acute side effects:** nausea (25%), vomiting (10%), fatigue and abdominal pain, carcinoid crisis (<1%)
- **Myelosuppression:** 4-6 weeks after PRRT, usually grade 1/2
- **Hematotoxic effects** grade 3 and 4 have been described in 13% and 10%
- **Nephrotoxicity-**Despite renal protection, the median decrease of the creatinine clearance 4% per year in patients treated with ¹⁷⁷Lu-DOTATATE.
The risk factors are DM, HTA.

PRRT TOXICITY: GENERALLY WELL TOLERATED

- NETTER I: Nephrotoxicity (Grade>3): 5.4% in the PRRT (3,6% in the controls) Haematological toxicity: 2% (myelodysplastic syndrome)

J. Strosberg et al. Lancet Oncol 2021

- 55 pts, 4-PRRT-cycles: No grade 3 or 4 liver and renal toxicity occurred. Patients presenting with impaired liver or renal function prior to PRRT, either improved or had stable findings. No deterioration was observed.
(Duan et al. The Oncologist 2022)

WHO IS A CANDIDATE FOR PRRT?

Inclusion

Sufficient tumor uptake on ^{111}In -octreotide scintigrams

Hematology

Hemoglobin ≥ 5.0 mmol/l

White blood cell count $\geq 2 - 3.5 \times 10^9/\text{l}$

Platelet count $\geq 75 - 100 \times 10^9/\text{l}$

Kidney function

Creatinine (serum) $\geq 150 \mu\text{mol/l}$ or creatinine clearance ≥ 40 ml/min

Karnofsky Performance Status ≥ 50

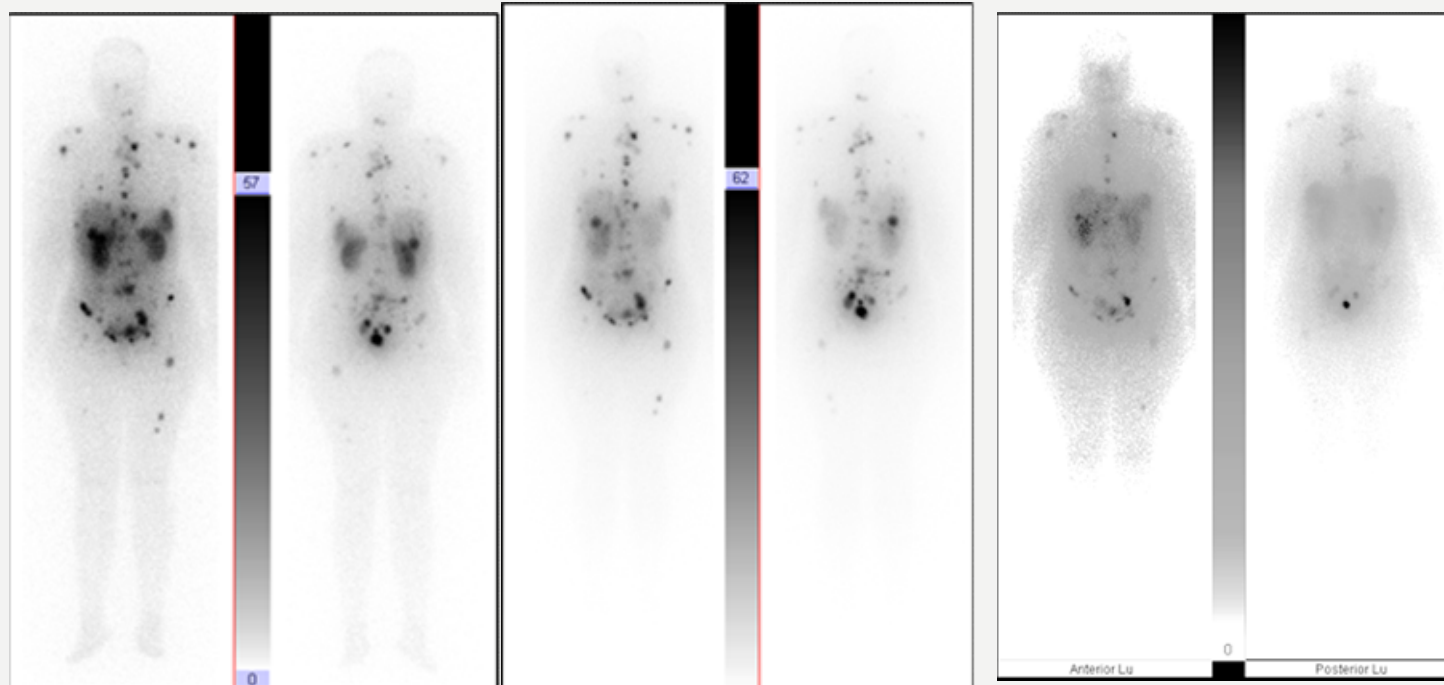
Life expectancy > 6 months

Exclusion

Chemotherapy within 6 weeks prior to treatment start

Pregnancy/lactation

¹⁷⁷Lu-DOTATATE WBS



22.4.2021.

24.7.2021.

30.10.2021.

37 years old women,

Tu regii pelvis C76.3; Meta in hepate C78.7, Meta in Igl pelvis C77.8, Meta in ossibus C79.5; St. post HT 5FU/DTIC No IV. St. post PRRT N0 III (22.04.2021. cum ¹⁷⁷Lu DOTATATE et 24.07.2021.; 30.10.2021. cum ¹⁷⁷Lu DOTATATE/⁹⁰Y DOTATATE). Somatuline Autogel in curso

THE MORE COMMON SIDE-EFFECTS ARE:

- Nausea
- Vomiting
- Abdominal discomfort or pain
- The Less Common Side-effects are: Subacute hematological toxicity, Temporary hair loss.
- In some cases there is delayed toxicity to the kidneys and renal insufficiency is experienced.
- Serious hematologic toxicity is rare.

ALPHA-PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

- Targeted α -particle therapy (TAT) offers a therapeutic option for patients resistant to β -irradiation treatments.
- ^{213}Bi or ^{225}Ac
- $\alpha = 8.32\text{MeV}$ ^{213}Bi
 27.5MeV ^{225}Ac ,
range 50–80 μm .
- high LET
- High efficacy

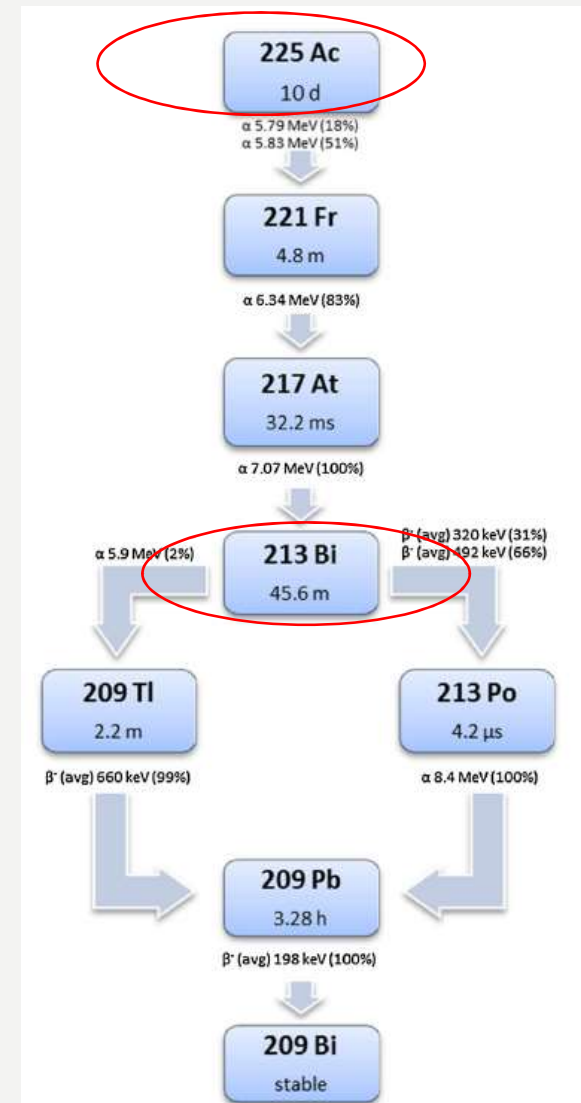
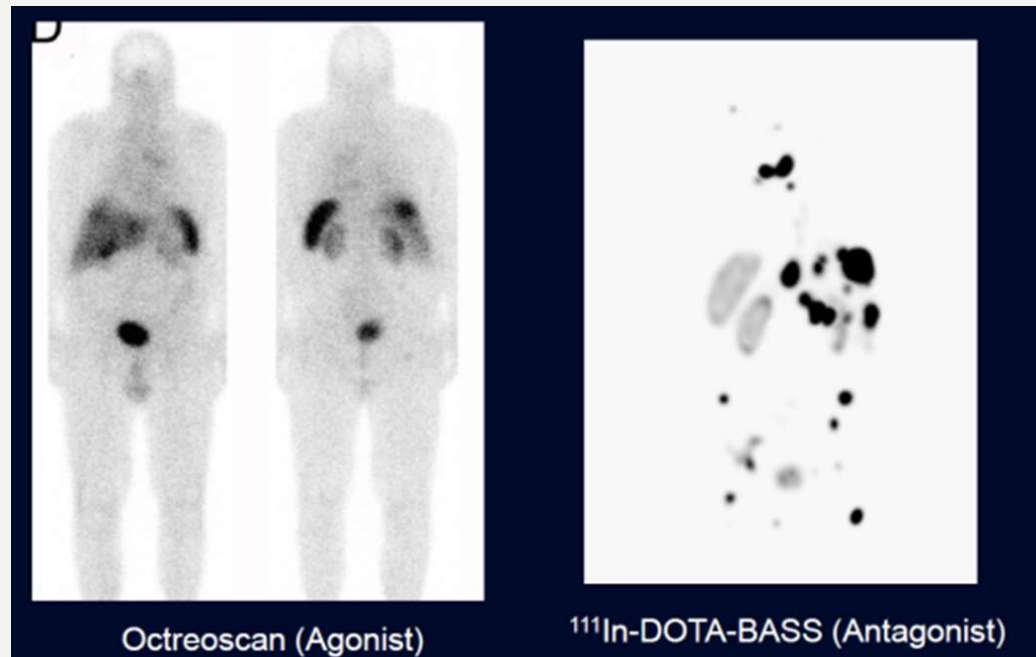
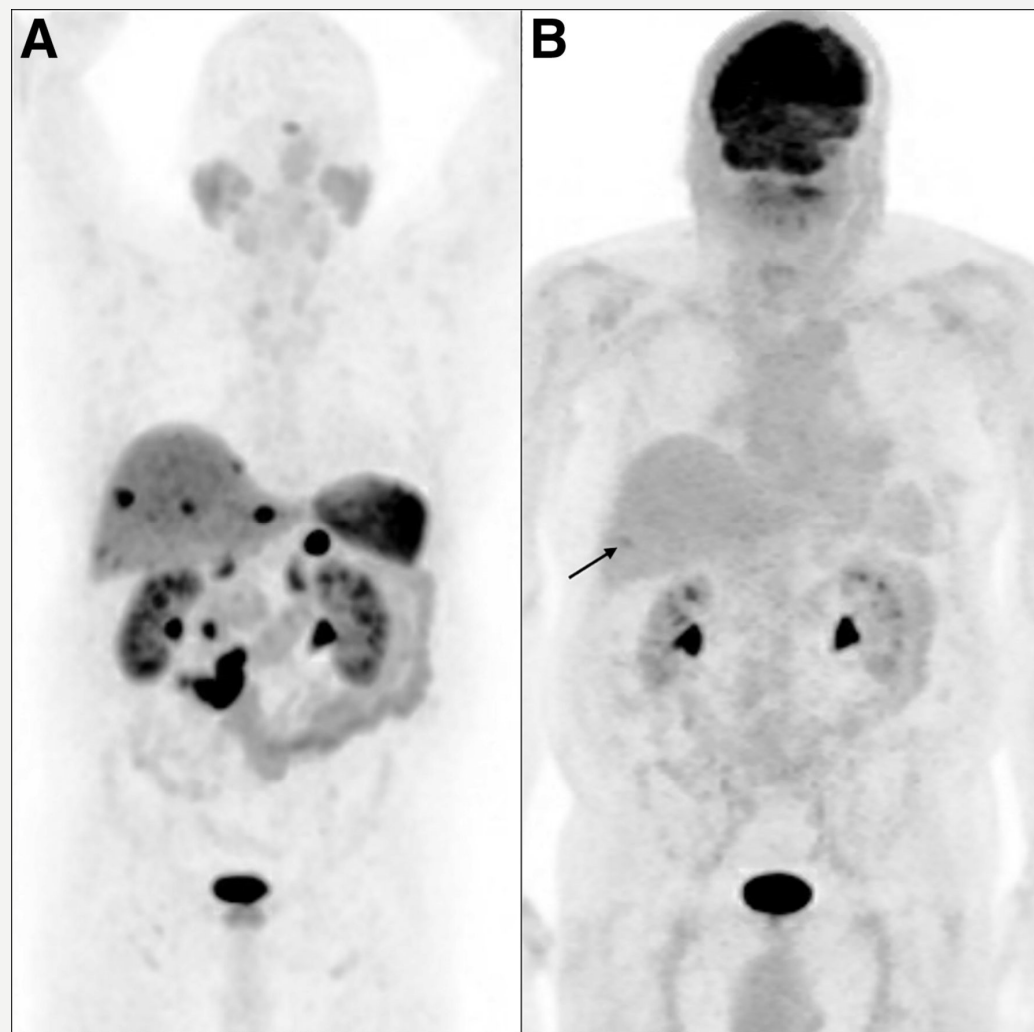


Fig. 1 Decay of ^{225}Ac ; four consecutive α -particle-emitting daughters are formed during decay (color figure online)

SST ANTAGONIST

- recent developments have indicated that potent SSTR antagonists known to poorly internalize into tumor cells may be as good as, or even superior to, agonists for such purposes
- in vitro and in vivo data demonstrated higher tumor uptake with a higher tumor-to-background ratio and longer tumor retention time than for agonists,
- 4-fold increase on average in tumor binding of the SSTR antagonist ^{177}Lu -DOTA-BASS as compared with the SSTR agonist ^{177}Lu -DOTATATE suggesting that this binding may increase not only localization accuracy for tumors but also the efficacy of radionuclide therapy with SSTR antagonists. (First-in-Humans Study of the SSTR Antagonist)

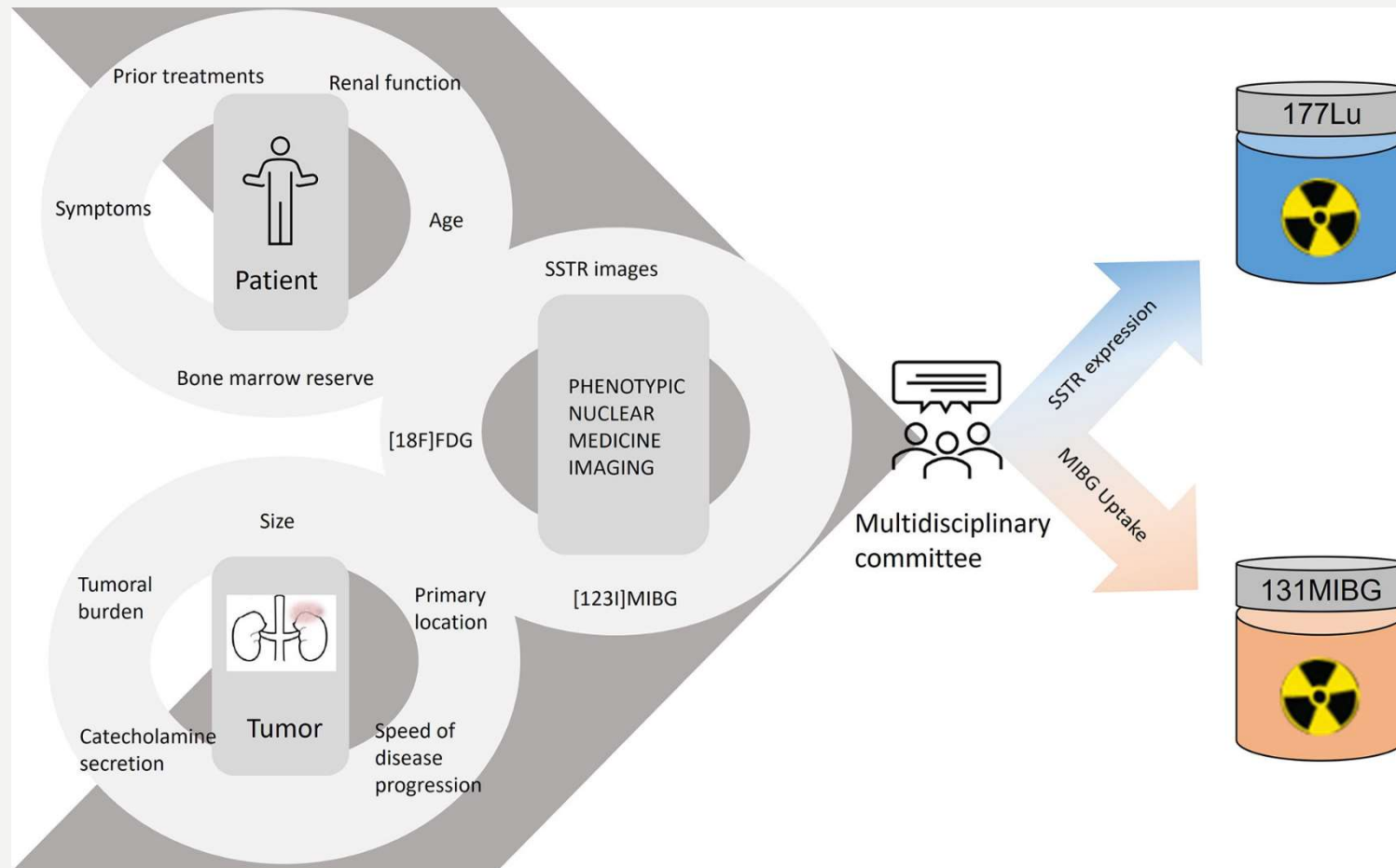




A) 68Ga-DOTATATE PET shows prominent uptake in primary tumor, lymphadenopathy, and liver metastases. (B) 18F-FDG PET shows no abnormal uptake

Maximum-intensity projection images of patient with metastatic grade 1 (Ki-67 < 2%) NEN from small-bowel primary. Sonya Park et al. J Nucl Med 2021;62:1323-1329

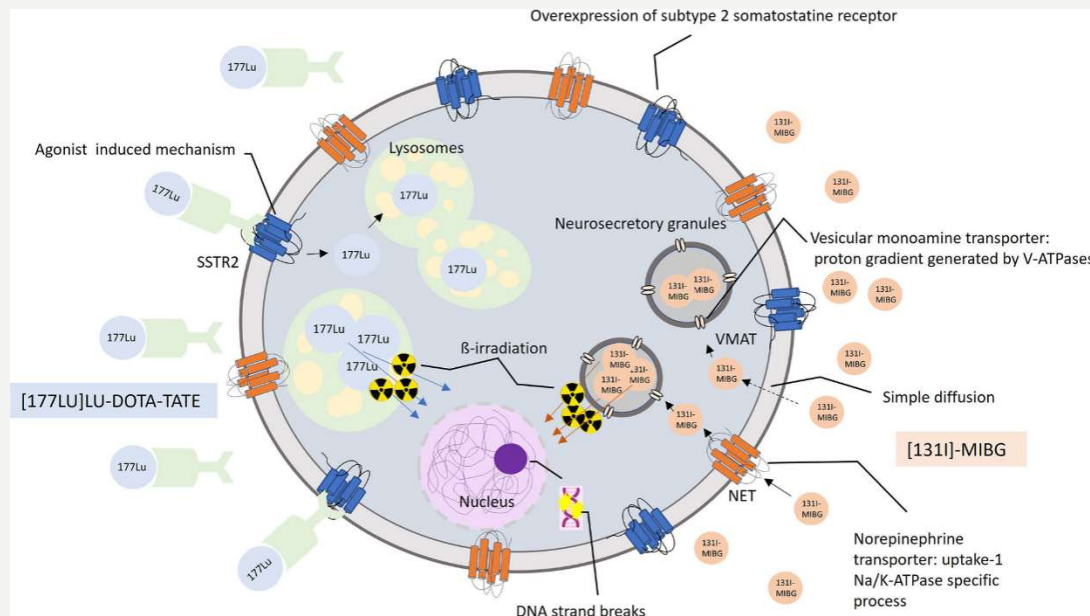
Copyright © Society of Nuclear Medicine and Molecular Imaging



To select whether to administer one or another radiolabeled treatment, the phenotypic nuclear medicine images signal the expression of the therapeutic targets. In addition to the phenotypic images, we must also assess the patient's profile (age, previous treatment, and bone marrow reserve) and the characteristics of the tumor (volume, location, hormonal secretion, and growth rate), so as to choose the best treatment option

NET-S ¹³¹I-MIBG THERAPY

- Metaiodobenzylguanidine (mIBG) shows a similar molecular structure to the adrenergic neurotransmitter norepinephrine (NE).
 - NE which is synthesized and stored in adrenergic granules, is then secreted and to some extent reassumed by the adrenergic cells. Through this re-uptake mechanism mIBG is transported into the chromaffin storage granules in adrenergic tissue as a false transmitter
- ¹³¹I-MIBG plays an important role in the therapy of neuroblastoma for recurrent or refractory stage 3-4



PATIENT PREPARATION

- Thyroid blocking is essential before administration of mIBG in order to prevent thyroid irradiation caused by the uptake of free I-131 which emerges from chemical instability and biologic decomposition of MIBG.
- For diagnostic applications of I-123-MIBG, 100 mg of potassium iodide or 23 mg/kg body weight of sodium perchlorate is given orally 20 min before up to 4 days after tracer injection.
- For MIBG therapy the thyroid should be blocked with 100 mg potassium iodide starting 1 day before tracer application and continued for at least 14 days
- Some medications have been shown to interfere with MIBG kinetics.

PATIENT PREPARATION

Mechanism of interaction	Medication	Suggested withdrawal
1. Inhibition of uptake-one	Tricyclic antidepressants	7 – 21 days
	Cocaine	7 – 14 days
	Labetalol	14 days
	α -Antagonists	7 – 14 days
	Antipsychotics	21 – 28 days
2. Inhibition of granular uptake	Reserpine, tetrabenazine	14 days
3. Competition for granular uptake	Sympathomimetics	7 – 14 days
4. Depletion of content from storage granules	Reserpine, tetrabenazine	14 days
	Labetalol	14 days
	Guanethidine	14 days
5. Calcium mediated	Calcium antagonist	14 days
6. Others	β -Adrenergic antagonists	7 – 14 days

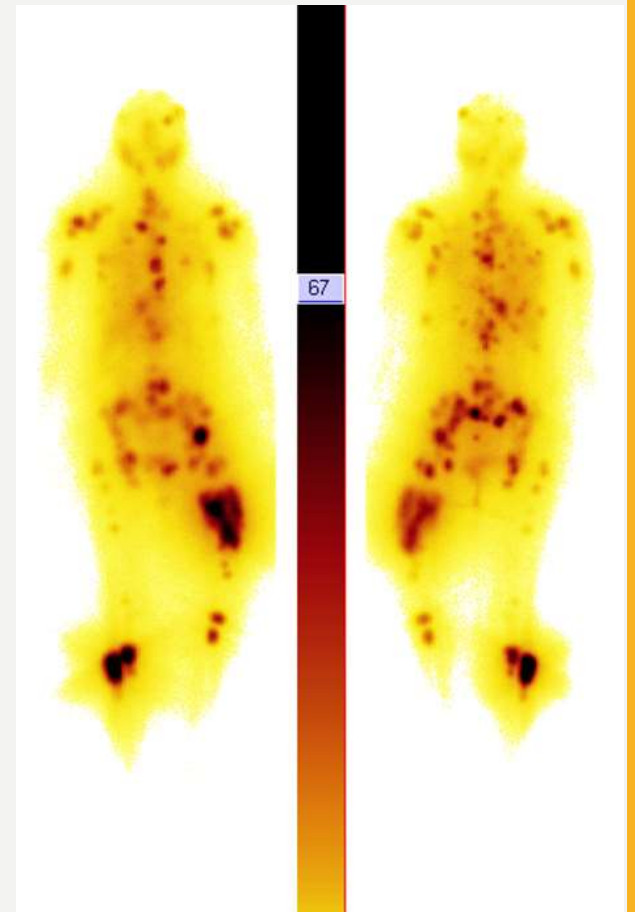
RADIONUCLIDE DOSAGE AND ADMINISTRATION

- According to the EANM procedure guidelines, 40–80 MBq (1.2–2.2 mCi) I-131-MIBG or 400 MBq (10.8 mCi) I-123-MIBG should be used for adults for diagnostic imaging. The appropriate dosage for children is weight adapted and can be calculated for therapeutic use reported doses vary 100-200 mCi
- A slow intravenous administration is essential to prevent release of norepinephrine from storage granules due to MIBG, which could result in a hypertensive crisis.
- After injection vital signs should be monitored. Additionally, an α -receptor blocker should be available.
- Most tumors are visible after 24 h. Due to a decline in liver activity over time, a better contrast may be achieved 48 -72 h after injection. Therefore, whole body images are recommended 24 and 48 h after injection. In addition, SPECT images should be performed.

^{131}I -MIBG

- For diagnosis with radioiodinated MIBG adverse effects are very rare. They are due to a release of catecholamines from storage granules and may occur after too rapid injection. Symptoms include tachycardia, hypertension, pallor, vomiting and abdominal pain .
- For the therapeutic use of ^{131}I -MIBG possible hematological side effects are predominant, especially if the bone marrow is affected by the tumor. This risk increases after chemotherapy

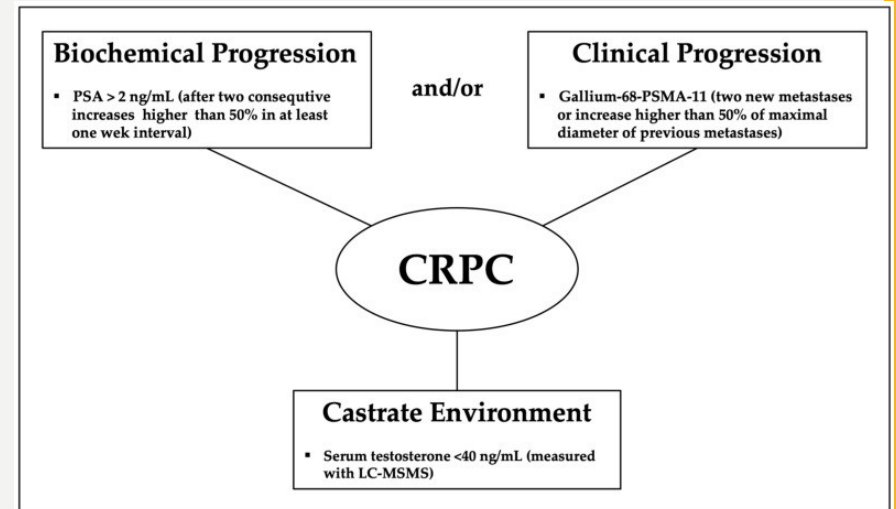
**Pheochromocytoma
metastaticum 5.55GBq ^{131}I -
MIBG**



PROSTATE CANCER

- Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020. Depending on each person's situation, treatment options for prostate cancer might include:

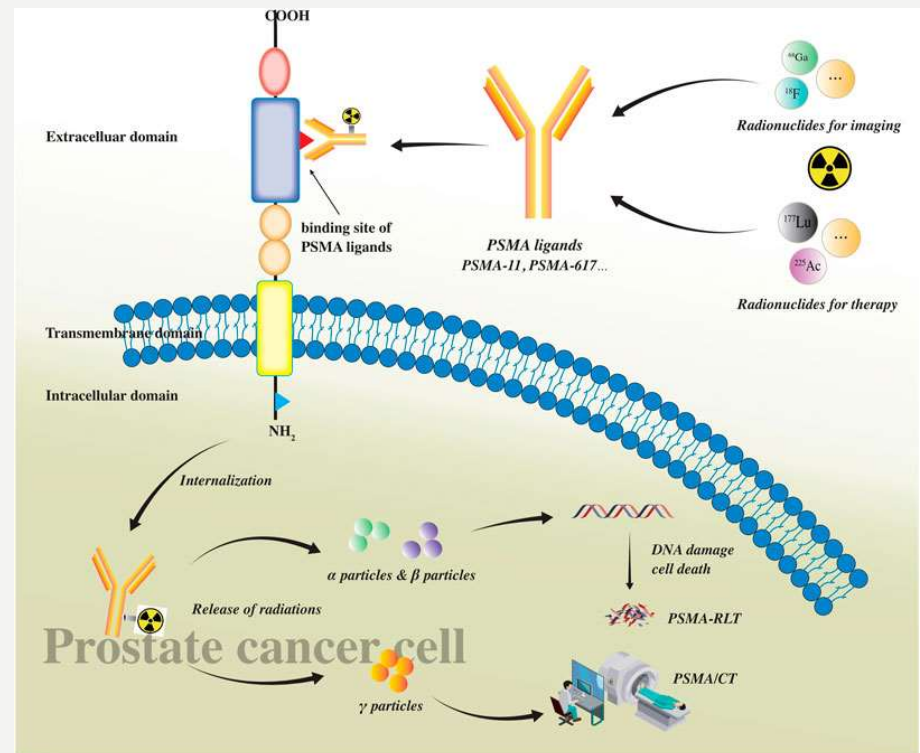
Observation or Active Surveillance for Prostate Cancer, Surgery , Radiation Therapy, Hormone Therapy, Chemotherapy for Prostate Cancer, Targeted Drug Therapy for Prostate Cancer, Treatments for Prostate Cancer Spread to Bones



About 10% to 20% of all prostate cancers are classified as castrate-resistant prostate cancer (CRPC).

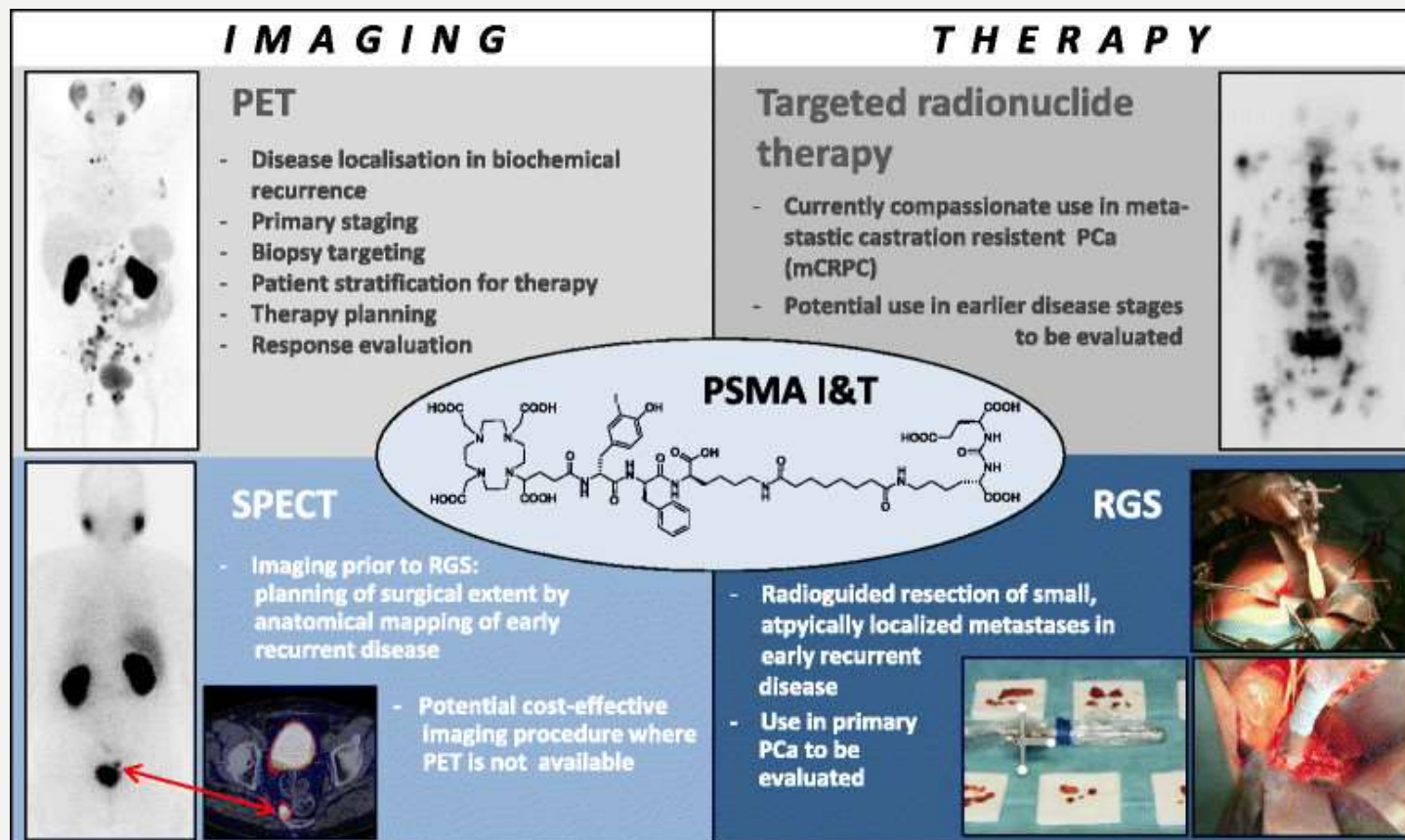
- Current guidelines for assessing metastasis recommend
- a) skeletal scintigraphy (bone scan) -has a sensitivity of 79% and a specificity of 82% for metastatic lesions
- b) abdominal and pelvic computed tomography (CT), although CT has a high sensitivity for metastases to cortical bone, it is limited in its sensitivity to tumors restricted to the marrow space. CT also has a low sensitivity when screening for lymphatic disease (42%) and is fairly poor in detecting smaller volume and size metastases .
- As such, there is a substantial need to improve detection of metastatic prostate cancer

- Prostate specific membrane antigen (PSMA) is a type II transmembrane antigen expressed in all forms of prostate tissue as well as other benign tissues such as salivary glands, duodenal mucosa, and neuroendocrine cells. PSMA expression in these benign tissues is significantly lower than in prostate cancer lesions where PSMA expression is notably increased. In healthy prostate cells, PSMA is localized to the cytoplasm and apical side of the epithelium. During malignant transformation, PSMA is transferred to the luminal surface of the prostate ducts and presents a large extracellular domain to ligands.



PSMA THERANOSTICS

- Patients with a positive ^{68}Ga -PSMA PET/CT are candidates for treatment with ^{177}Lu -PSMA radioligand therapy (RLT), which targets the lesions revealed by ^{68}Ga -PSMA PET/CT.



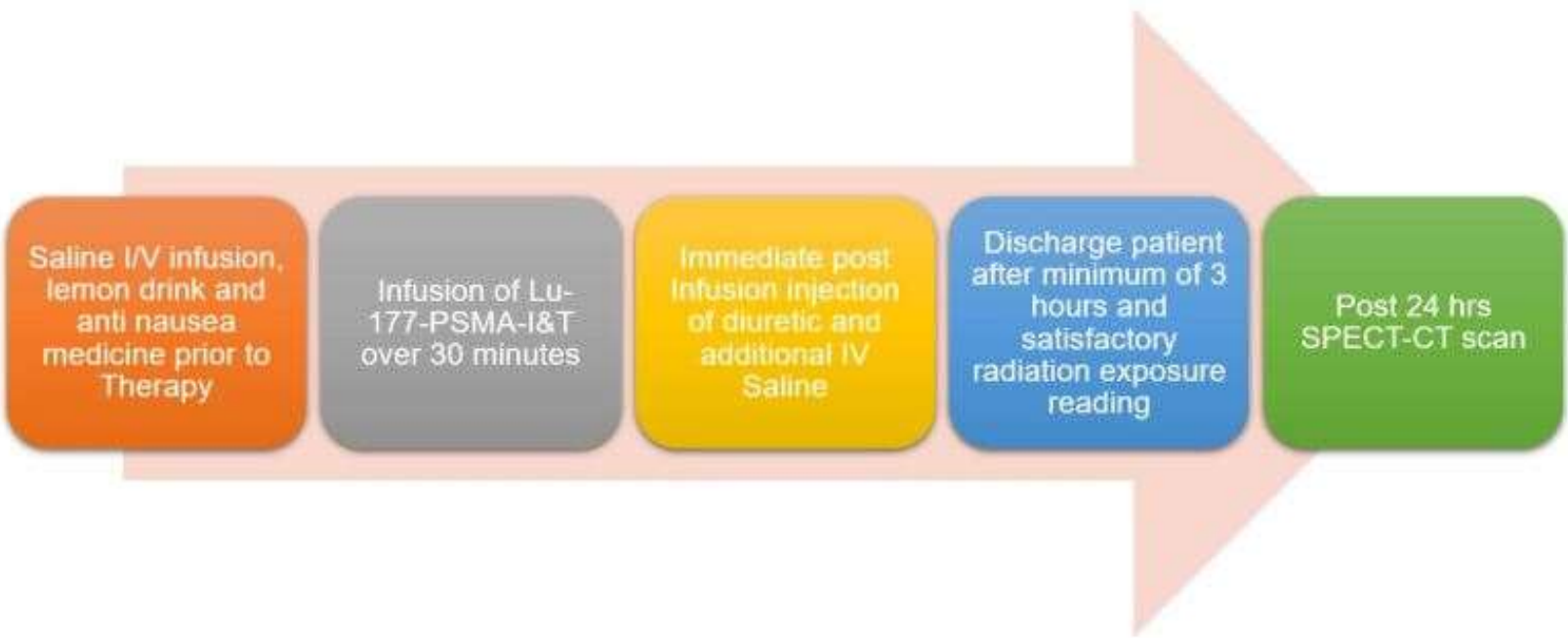
NUCLEAR MEDICINE APPLICATIONS IN PROSTATE CANCER

- **Tc-99m Diphosphonates (99mTc-MDP) Bone Scan / F-18-Sodium Fluoride Bone Scan** are designed to identify skeletal metastases in prostate cancer. The national comprehensive cancer network (NCCN) recommends an initial bone scan for patients at high risk for skeletal metastases (PSA equal or >20 ng/mL; clinical stage at least T2c; or Gleason 8, 9, or 10).
- Ga-68-PSMA PET/CT is currently the gold standard for PSMA imaging in prostate cancer, providing high sensitivity and specificity for detecting and staging the disease. However, Ga-68-PSMA PET/CT may be unavailable, particularly in resource-limited settings. In these situations, Tc-99m-PSMA single-photon emission computed tomography/computed tomography (SPECT/CT)

- **Current clinical indications** include metastatic, castrate-resistant, progressive prostate cancer following conventional systemic, taxane-based chemotherapy. (Patients who cannot take or tolerate the chemotherapy for any reason are also candidates.) The tumor must show adequate expression of PSMA on a baseline [Ga-68] Ga-PSMA PET/CT scan. In addition, patients should have a life expectancy of at least six months, adequate bone marrow and renal function without renal outflow obstruction, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less.
- Diffuse bone marrow disease with a high risk of marrow failure will exclude patients from therapy.

TREATMENT PROTOCOLS FOR LU-177-PSMA THERAPY

- Patients typically receive 4 to 6 treatment cycles at 6- to 8-week intervals. Administered doses may be scaled or adjusted due to disease burden, renal impairment, or after dosimetry testing, but a typical administration is 7.4 GBq (200 mCi).
- Patients usually fast before treatment but with oral hydration. They receive intravenous hydration and antiemetics in the treatment facility before therapy administration.
- Xerostomia due to physiologic PSMA expression by salivary glands and dry eyes due to PSMA expression by the lacrimal glands may occur and may be irreversible. Hematuria is occasionally reported. The most commonly reported adverse effects are fatigue (43%), dry mouth (39%), and anemia (32%).
- Following treatment, marrow suppression may occur, usually in patients with preceding marrow impairment, and should be carefully monitored. Renal function also requires monitoring, but renoprotective amino acid infusions are unnecessary for current PSMA therapies, unlike similar radioligand therapy with [Lu-177] Lu-dotatate, which is used for somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors.



```
graph LR; A[Saline I/V infusion, lemon drink and anti nausea medicine prior to Therapy] --> B[Infusion of Lu-177-PSMA-I&T over 30 minutes]; B --> C[Immediate post Infusion injection of diuretic and additional IV Saline]; C --> D[Discharge patient after minimum of 3 hours and satisfactory radiation exposure reading]; D --> E[Post 24 hrs SPECT-CT scan];
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Saline I/V infusion, lemon drink and anti nausea medicine prior to Therapy

Infusion of Lu-177-PSMA-I&T over 30 minutes

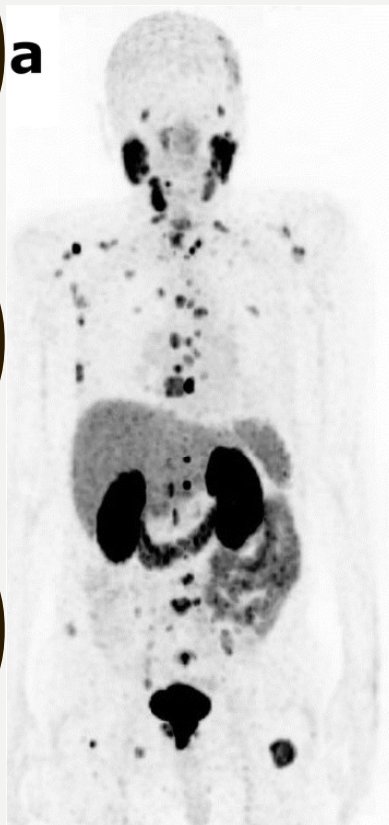
Immediate post Infusion injection of diuretic and additional IV Saline

Discharge patient after minimum of 3 hours and satisfactory radiation exposure reading

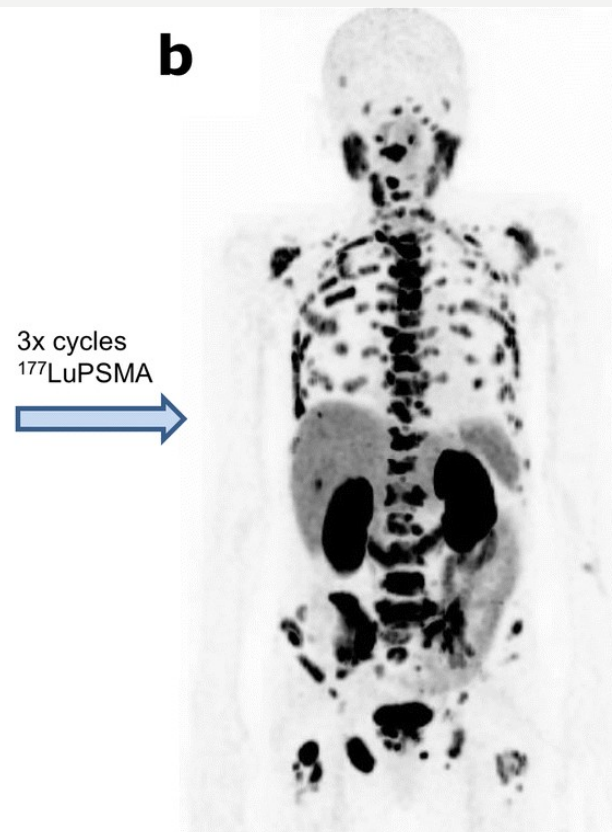
Post 24 hrs SPECT-CT scan

OTHER NUCLEAR MEDICINE THERAPIES IN PROSTATE CANCER

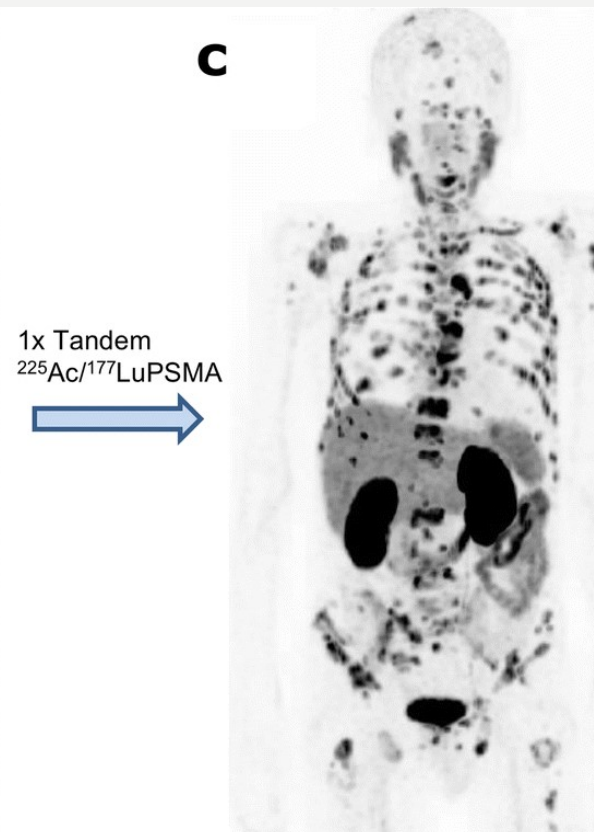
- Beta-emitting radioisotopes samarium-153 [Sm-153] and strontium-89 [Sr-89] are used to manage pain from bone metastases in prostate and other cancers.
- Sr-89 is administered as chloride salt and [Sm-153] as an EDTMP complex. Both bind to sites of osteogenesis, usually indicated by the uptake of other bone-seeking radiopharmaceuticals in imaging bone scans.
- Metastasis irradiation is an indirect effect of osteoblastic bone turnover rather than due to direct binding to tumor cells. Both agents have shown effective pain relief from bone metastases in clinical trials, but unfortunately, they provide no survival advantage.
- Radium-223 (Ra-223) is an alpha-emitting radioisotope given to people with osteoblastic metastases from prostate cancer.
- Radium-223 has not been shown to provide a survival benefit in patients with visceral metastases or bulky nodal disease ($>3\text{--}4\text{ cm}$).



05/2017
PSA=142 ng/ml



02/2018
PSA=486 ng/ml



05/2018
PSA=213 ng/ml

RADIONUCLIDE THERAPY OF BONE METASTASES

- Radionuclide therapy of bone metastases represents a systemic therapy with intravenous administration of radioactive agents. It is the aim to apply a maximal dose to the target – in this case bone metastases – and a minimal dose to the rest of the body. The dose to the rest of the body determines the frequency and intensity of side effects and limits treatment efficacy.
- Over 60% of all breast cancer patients develop osseous metastases of the osteolytic or combined osteolytic/osteoblastic type during the course of the disease. Half of prostate cancer will develop (predominantly osteoblastic) and a third of lung cancer patients will develop metastatic bone disease.

^{89}Sr is a calcium analog and is incorporated into the newly formed hydroxyapatite of the bone matrix.

^{153}Sm is radiolabeled to a bisphosphonate (EDTMP) and adsorbed onto the hydroxyapatite surface of metabolically active bone by the same mechanism as technetium $^{99\text{m}}\text{Tc}$ -labeled bisphosphonates used for diagnostic bone scintigraphy.

Selective uptake depends on the degree of the metabolic (i.e. osteoblastic) response of metastatic tissue. Increased bone turnover leads to enhanced incorporation of bone-seeking radiopharmaceuticals at metastatic sites, and can therefore deliver a high, targeted local radiation dose. The effective half life of ^{89}Sr in bone metastases is greater than 50 days, compared with 14 days in normal bone

Nuclide	Carrier
Strontium-89	Chloride
Samarium-153	EDTMP
Rhenium-186/188	HEDP
Yttrium-90	Citrate
Phosphorus-32	Orthophosphate

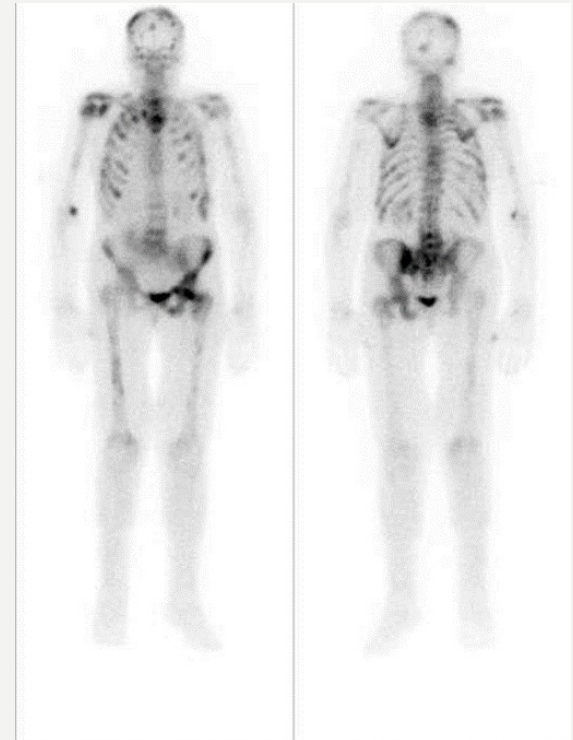
- the mechanism and radiobiology of pain reduction using unsealed source therapy is not yet fully understood. A direct radiation effect on neuronal tissue seems unlikely due to the well-known high radiation resistance of peripheral neurons. It is more conceivable that radiation to cells and tissues surrounding the metastasis promotes cell signaling changes, resulting in modulation of both pain reception and transmission.
- Due to the delay between treatment administration and onset of pain relief, which may take 1 week in case of ^{153}Sm -EDTMP and up to 4 weeks using ^{89}Sr , patients should have a life expectancy of at least 3 months.

INDICATIONS, CONTRAINDICATIONS AND PROCEDURE OF PAIN PALLIATION TREATMENT

- Surgical stabilization and/or external-beam radiation are the treatments of choice for the management of solitary, painful bone metastases, bones at high risk of pathological fracture, and in patients with impending spinal cord compression.
- Systemic radionuclide therapy is indicated to manage multifocal metastatic bone pain following failure of conventional analgesics and to palliate recurrent pain within a previously irradiated site. It is likewise indicated if the side effects of high-dose analgesics become intolerable and significantly compromise the quality of life, even if pain control is adequate.
- A prerequisite for radionuclide treatment of metastatic bone pain is the demonstration of multifocal abnormal skeletal uptake on conventional ^{99m}Tc phosphate bone scan, corresponding to known pain sites. Patients should have reasonable bone marrow reserves, as evidenced by (near) normal blood counts

RADIONUCLIDE THERAPY OF BONE METASTASES

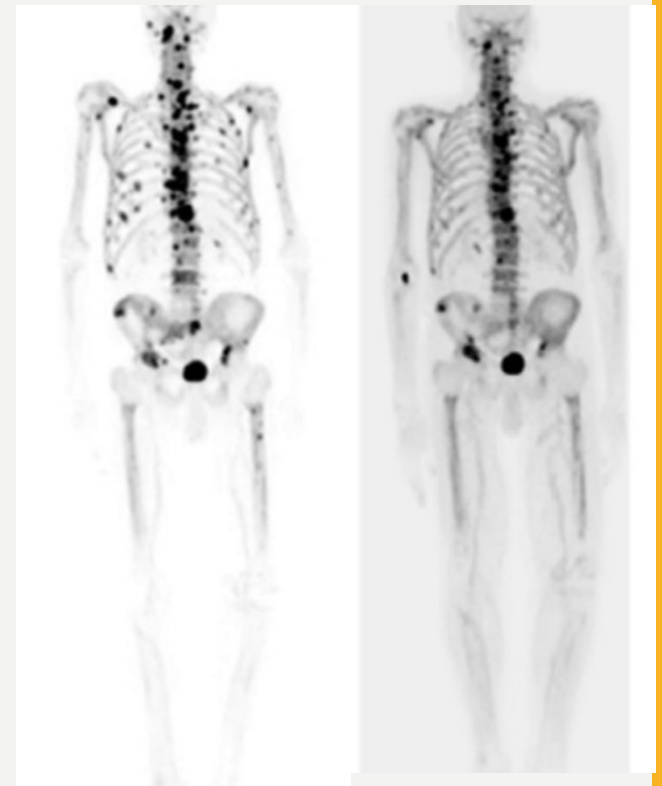
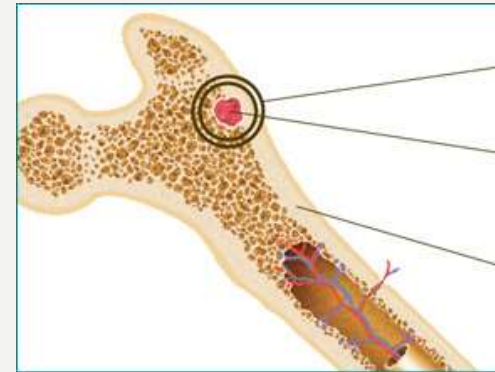
- The effect of Sr-89 treatment began 10–20 days postinjection and reached a maximum after 6 weeks. Pain improvement lasted for 6 months on average
- Following appropriate oral hydration, the bone-seeking radiopharmaceutical is administered intravenously via a peripheral cannula, usually in an outpatient setting, depending on local legislation. Prior to discharge, the uptake and distribution of the activity of ^{153}Sm -EDTMP can be documented by whole-body scanning



Carcinoma prostate
metastaticum in ossibus
 ^{153}Sm -EDTMP

RADIONUCLIDE THERAPY OF BONE METASTASES

- The bone-seeking alpha-particle emitter radium-223 is predicted to deliver a high absorbed radiation dose to the bone surface, with sparing of the bone marrow compartment.
- ^{223}Ra is a calcium mimetic isotope and deposits on hydroxyapatite .
- ^{223}Ra $T_{1/2} = 11.4$ days , 94% decay energy is released from α -particles.
- The approved injection dose is 1 every month for a total of 6 cycles. The excretion is mainly through gastrointestinal system, raising concern in the co-existence of constipation and inflammation in bowels



TREATMENT ANKYLOSING SPONDYLITIS

- Therapy with ^{224}Ra was considered to be indicated with radiologically proven early ankylosing of one or two parts of the spine with ongoing inflammation diagnosed by a value of the C-reactive protein (CRP) above 10 mg/l, clinical progression failing to respond to nonsteroidal anti-inflammatory drugs (NSAIDs), and/or if analgesic/anti-inflammatory drugs are contraindicated.
- Contraindications for this therapy were considered to be diseases of the blood formation system, recent fractures, severe liver damage, pregnancy and lactation, age of patient less than 21 years, and acute infection
- 80% of the patients experienced a reduction of pain, a reduction of analgesic medication and in 9 out of the 16 patients a improvement of mobility could be objectively evaluated

POLYCYTHEMIA VERA (VAQUEZ-OSLER DISEASE) – PCV

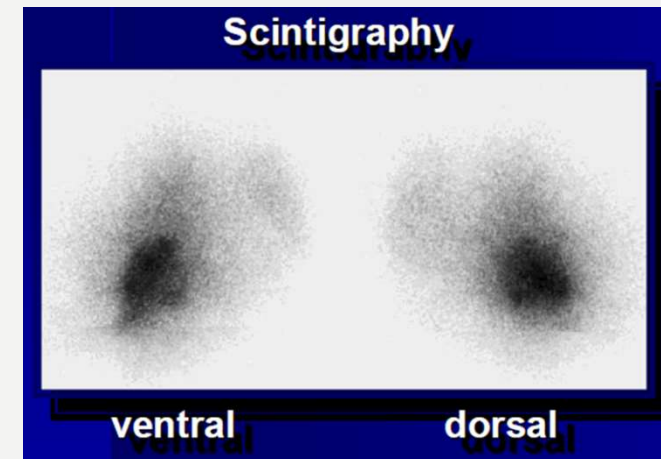
- was first described in the year 1892 . PCV is a clonal neoplastic disease with the proliferation of erythrocytes, it is included in the group of myeloproliferative diseases (MPD). All the bone marrow elements (erythrocytes, megacaryocytes, granulocytes, and fibroblasts) are involved in the hyperplasia but erythropoiesis is the dominant factor. Hypervolemia, increased cardiac output, hyperviscosity and the resultant impaired blood flow are the reasons for most clinical manifestations
- Phosphorus-32 is a pure β^- -emitter with a half-life of 14.3 days. The average energy of the emitted β^- -particles at 0.695 is relatively low, the maximum energy is 1.71 MeV and the average range in tissue is about 3 mm, with a maximum of 8 mm.
- Radiophosphorus for the therapy of PCV is used in the chemical form of sodium-hydrogen-phosphate

- The drugs of choice in the inhibition of cell proliferation are hydroxyurea derivatives, which are non-alkylation substrates that selectively inhibit cells in the Sphase of the cell cycle,
- Busulfan is another drug used and one study has reported a longer time period of remission,
- The indications for therapy with P-32: No or only minor effect of hydroxyurea, Age over 70 years and minor risk of secondary malignancies, Chemotherapy refused by the patient, Unwillingness to undergo frequent blood count, checks as is mandatory under chemotherapy

INTRA-ARTERIAL THERAPY OF HEPATOCELLULAR CARCINOMA

- The only really effective treatments for HCC are local surgery (resection, transplantation) and ablative techniques (alcoholization, cryotherapy, radiofrequency). However, such approaches can only be proposed for a small number of patients (15–25%)
Ethiodol or lipiodol is a secondarily iodized oil (38% by weight) extracted from poppy seeds.
- accumulation of lipiodol in the peritumoral sinusoids by a mechanism of embolization, The idea of using this agent as a therapeutic vector arose from the observation of a prolonged retention of lipiodol on the HCC several months after intra-arterial injection via the hepatic artery

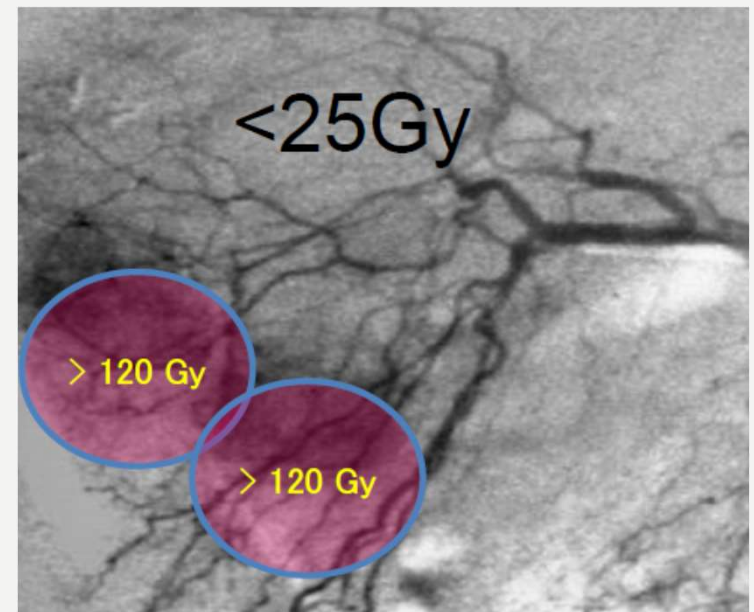
injected by intra-arterial administration, after arteriography, ^{131}I -lipiodol is fixed preferentially at the level of the liver, the tumours, and the lungs



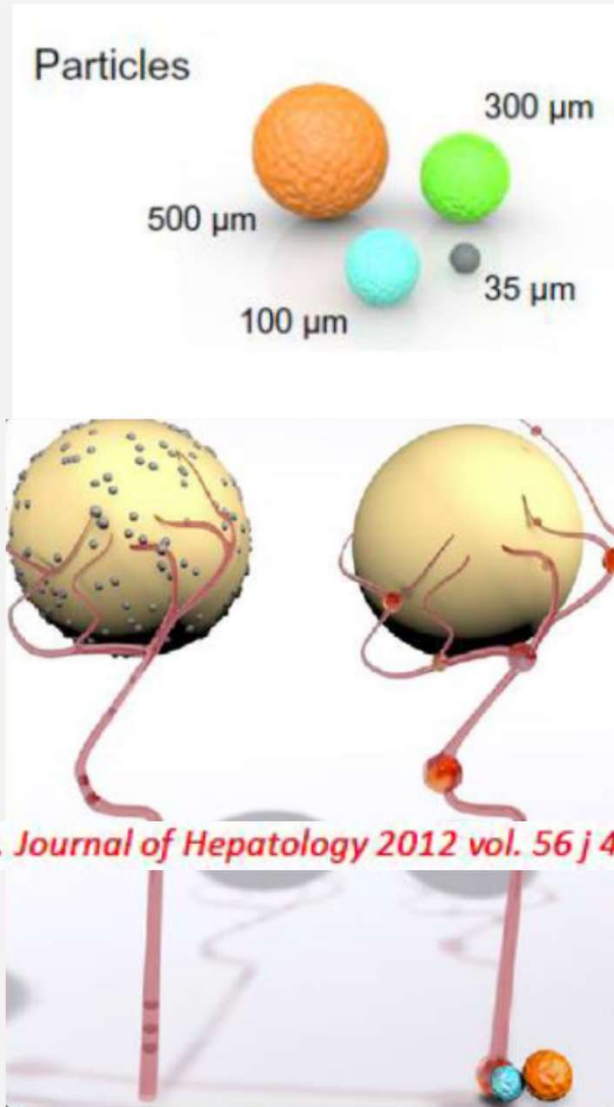
SELECTIVE INTERNAL RADIO-THERAPY (SIRT)

- Selective Internal Radiation Therapy (SIRT) is a treatment for primary liver cancer or metastases that cannot be removed by surgery,
- SIRT relies on the delivery of a radioactive substance into the tumour vascular supply via an intra-arterial catheter placed under radiological guidance. This exploits the fact that both primary and secondary liver tumours derive 80–100% of their blood supply from the hepatic artery, whereas the hepatic artery supplies only up to 30% of the normal liver parenchyma.

The aim is to deliver a tumouricidal dose of radiation (>100 Gy) to tumour tissues, with relative sparing of adjacent normal liver parenchyma. The most commonly used radionuclide is yttrium-90 (^{90}Y) labelled to resin microspheres (SIR-Spheres) or embedded in glass microspheres (TheraSpheres).



SELECTIVE INTERNAL RADIO-THERAPY (SIRT) TRANS-ARTERIAL RADIO-EMBOLIZATION (TARE)



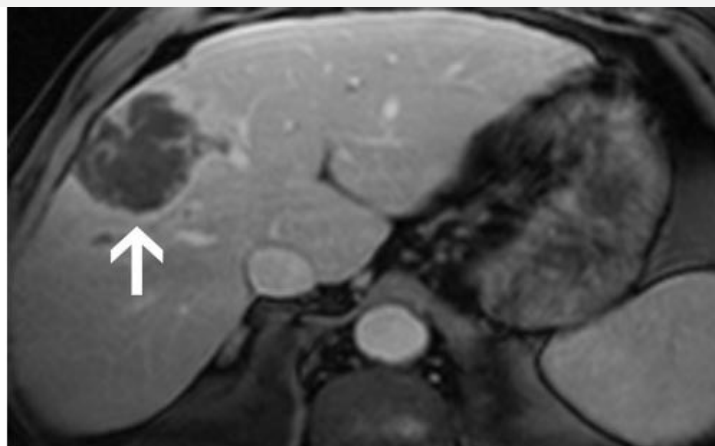
The microspheres size range (20–60 μm) allows optimal peri-tumoral vascular deposition and prevents passage into the venous circulation and bypassing the liver. They remain permanently implanted in the liver and are not metabolised or excreted. The ^{90}Y isotope is on the surface of resin microspheres and internally for glass microspheres.

BEFORE

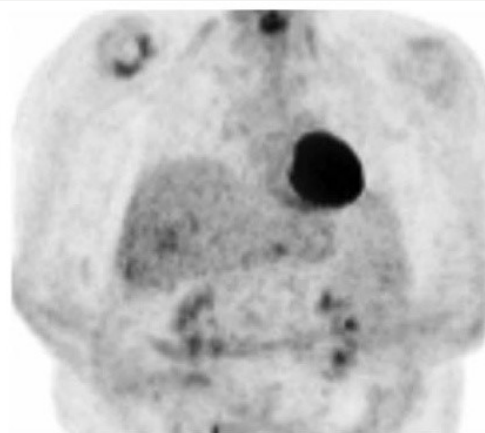
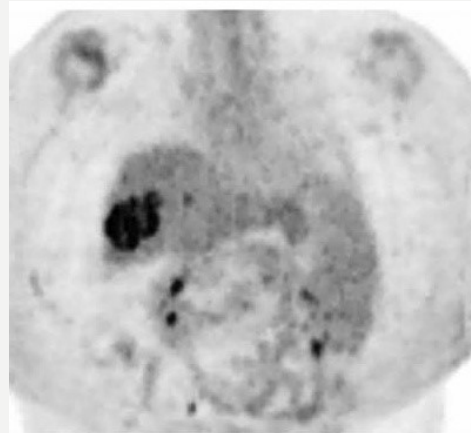


a.

AFTER SIRT



b.



c.

SELECTIVE INTERNAL RADIO-THERAPY (SIRT) TRANS-ARTERIAL RADIO-EMBOLIZATION (TARE)

FOXFIRE STUDY
Global

SIR-Spheres⁺
microspheres

FOLFOX6m* ± bevacizumab^{C4,C5}

FOLFOX6m* ± bevacizumab^{C1}

Clinical study demonstrated that SIRT could be added safely to oxaliplatin-based chemotherapy, with promising outcome data

significant increase of overall survival for FOLFOX/SIRT.

- FOLFOX 16 – 19 months
- SIRT/FOLFOX 29 – 38 months

PROCEDURE

- SIRT is a two-part procedure and a pre-therapy angiography is initially performed. Vessels feeding the tumour are assessed, usually the common hepatic artery, lobar arteries or smaller branches. To prevent potential extrahepatic retrograde flow of radioactive material into the stomach, duodenum and pancreas, the gastroduodenal, right gastric and left gastric arteries may be embolised. The catheter is then placed at the site(s) of subsequent treatment delivery and technetium-99m labelled macroaggregated albumin (^{99m}Tc -MAA) is administered. MAA is similar in size to microspheres and acts as a surrogate marker of its distribution.
- Following treatment, patients may have some liver pain and nausea, which can last for a few days.

RADIOSYNOVIORTHESIS (RADIATION SYNOVECTOMY)

- local treatment of chronic inflammatory joint diseases
Indications: Basically RSO is indicated for the local treatment of almost all kinds of chronic synovitis .The *main indications* for radiosynoviorthesis are
- Rheumatoid arthritis
- Seronegative spondyloarthropathy (i.e., reactive arthritis, psoriatic arthritis)
- Haemarthrosis in haemophiliacs
- Recurrent joint effusions (i.e., after arthroscopy)
- Pigmented villonodular synovitis (PVNS)) Osteoarthritis (activated arthrosis)
- Undifferentiated arthritis (where the arthritis is characterized by synovitis, synovial thickening or effusion)
- *Absolute contraindications:* Pregnancy, Breast feeding , Local skin infection, Acute rupture of popliteal cyst (Baker's cyst)
- *Relative contraindications:* Extensive joint instability with bone destruction , RSO should only be used in children and young patients (<20 years) if the benefit of treatment is likely to outweigh the potential hazards. But it is routinely applied in haemophilic children.

RADIOSYNOVIORTHESIS (RADIATION SYNOVECTOMY)

- After intra-articular administration the radioactive particles in colloidal form are taken up by phagocytosis in synovial macrophages. A particle size of about 5 ± 10 nm is essential to avoid leakage and provide homogenous distribution on the surface of the synovium. β -radiation leads to coagulation necrosis, sclerosis and fibrosis of the synovial tissue including vessels and pain receptors, resulting in reducing effusion, swelling and pain of the joint. Due to the fact that cartilage has no ability to phagocytose, this tissue is not a target for the radiation effects

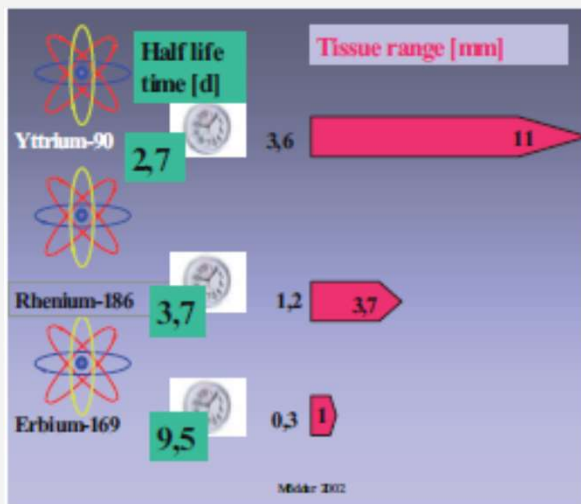


Fig. 29.1. Radioisotopes for radiosynoviorthesis



- *Rheumatic patients* need systemic treatment with antirheumatoid drugs because rheumatism is a systemic disease. If after at least 6 months a few joints do not show adequate improvement even after corticosteroid injections into the affected joints, these joints are selected for RSO, thus avoiding escalation of systemic therapy with its possible side effects



Fig. 29.3. The hands as the "visiting card" of the rheumatic patient. Soft tissue scintigram with ^{99m}Tc -MDP shows a typical

The hands of the rheumatic patient. Soft tissue scintigram with ^{99m}Tc -MDP shows a typical pattern in psoriatic arthritis

The most common and approved radiopharmaceuticals used for RSO are:

^{90}Y -yttrium citrate or silicate (^{90}Y colloid), only used for RSO of knee joints

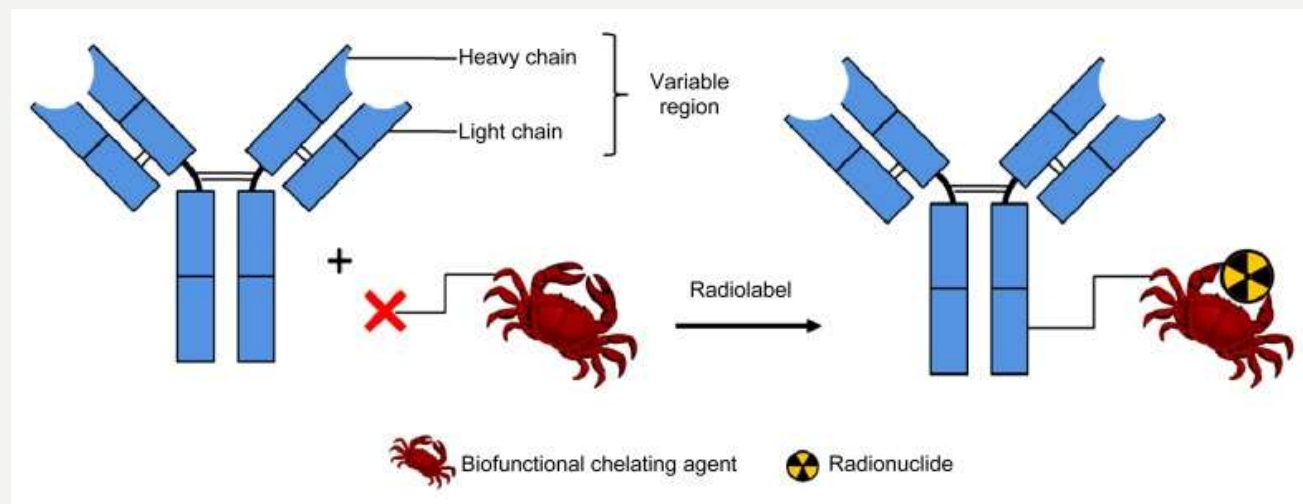
^{186}Re -rhenium sulphide (^{186}Re colloid), used for RSO of middle sized joints

^{169}Er -erbium citrate (^{169}Er colloid), used for RSO of small joints

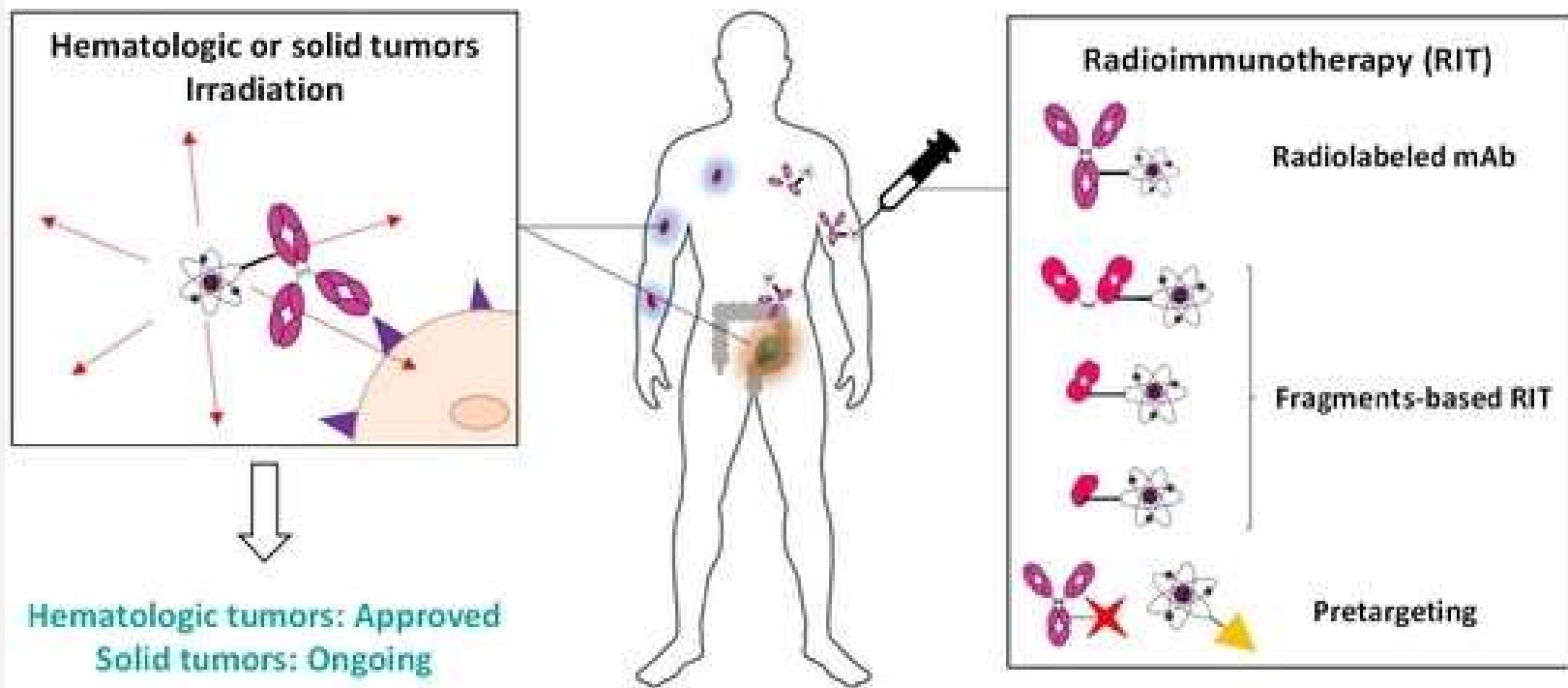
Parameter	Yttrium-90	Rhenium-186	Erbium-169
$T_{1/2}$ (days)	2.7	3.7	9.5
Energy (MeV)	2.26	0.98	0.34
Tissue penetration (mm)			
Max.	11.0	3.7	1.0
Mean	3.6	1.2	0.3
Joints	knee	shoulder, elbow, wrist, hip, ankle	small joints of hands and feet

RADIOIMMUNOTHERAPY (RIT)

- is a type of cancer cell targeting therapy which uses monoclonal antibodies (mAbs) labelled with a radionuclide directed against tumour-associated antigens.
- The ability for the antibody to specifically bind to a tumour-associated antigen increases the dose delivered to the tumour cells while decreasing the dose to normal tissues. By nature, the technique requires the tumour cells to express an antigen that is unique to the neoplasm or is inaccessible in normal cells.



RADIOIMMUNOTHERAPY (RIT)



- Over the decades, an increasing number of new antibodies have been studied in clinical trials and have shown positive evidence of efficacy, particularly in non-Hodgkin's lymphoma (NHL).
- The current US Food and Drug Administration (FDA)-approved radiopharmaceuticals for RIT include ibritumomabtiuxetan (Zevalin®, approved in 2002) and ¹³¹I-tositumomab regimen (Bexxar®, approved in 2003), both for the treatment of refractory NHL.
- Other potential applications of RIT include the treatment of breast, lung, pancreatic, stomach and ovarian carcinoma, neoplastic meningitis, leukemia, high-grade brain glioma, and metastatic colorectal cancer.

- ⁹⁰Y-ibritumomab tiuxetan (commonly known as Zevalin®) is a murine anti-CD20 antibody conjugated to linker-chelator tiuxetan. Zevalin® can be administered as outpatient therapy without significant patient restrictions.
- Zevalin® was registered for treating relapsed or refractory, low-grade, follicular lymphoma, and transformation B-cell NHL, including refractory NHL following rituximab treatment, and approved by the FDA in 2002. In 2008, Zevalin® was approved for consolidation therapy following partial response or complete response after frontline induction chemotherapy in patients with previously untreated follicular lymphoma in the European Union.
- ¹³¹I-Tositumomab (Bexxar®) is an mAb that is labelled with ¹³¹I. Bexxar® is used to treat certain types of NHL. In a clinical trial of 60 patients with previously untreated follicular lymphoma, Bexxar® provided a significant therapeutic efficacy compared with that provided by the last qualifying chemotherapy. Based on the promising outcomes, Bexxar® was approved by the FDA for clinical practice in patients with rituximab-relapsed or refractory, low-grade follicular lymphoma. One year later, the FDA approved Bexxar® for RIT in NHL patients without previous rituximab therapy.