Therapy with radionuclides

- Aim is to acheive interaction of radiotracer and tumor cells, with minimal iraddiation of surrounding tissue (absorbed dose „only” to tumor cells)

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Radionuclide therapy types

- Radionuclides in elementary form (I-131, P32; Sr 89)
- Metabolic agents: I-131- MIBG
- Antibodies
- Reducing agents
- Labeled cells
- Liposomes
- Microspheres- blockage of blood vessels
- Intracavitary aplication

Therapeutic radiotracers

- In-111, Y-90 i Lu-177 labeled somatosatin analogues

- In-111 (67 h, y-173, 247 keV; Auger and conversion electron, range <1um)

- Y-90 (64h, medium E β - 900 keV, range 5,3 mm)

- Lu-177 (6,7 days; medium E β -133 keV; y-208 keV, range < 1 mm)

Selection of radionuclide for therapeutical application

- α or ß emitter
- γ emitter (detection)
- Apropriate effective time of elimination
- Increased organ accumulaton, in regard to surrounding tissue
- Radionuclids that have performance of accumulation and retention in target organ

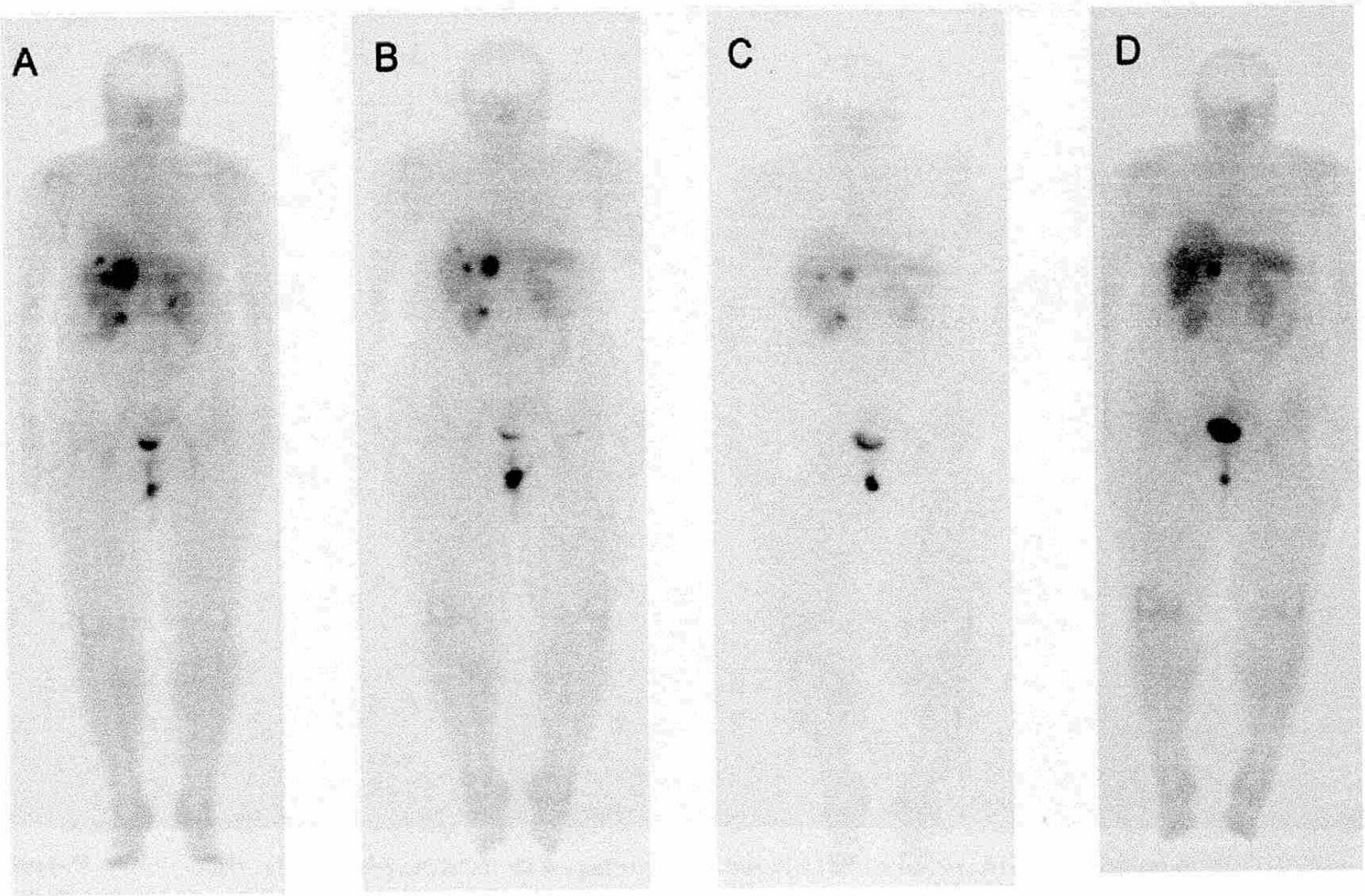

Figure 4 Liver metastases of a neuroendocrine pancreatic carcinoma (glucagonoma) before (A) and after (B-D) multiple peptide receptor radionuclide therapies using the somatostatin analog ^{90}Y-DOTA-TATE. Whole-body scans (anterior views) using ^{99m}Tc-EDDA-HYNIC-TOC show a continuous decrease of uptake and size of the liver lesions.

Radionuclide accumulation in tumor

It depends on:

- Blood supply
- Exstravascuar compartment
- Interstitial pressure and permeability

Tumor blood supply

- Decreases exponentially with mass
- Blood stasis leads to thrombosis and occlusion
- Tumor cells become hypoxic- NECROSIS

Tumor blood supply

- Decreased perfusion leads to reduced efficiency of radionuclide therapy:
  - Decreased amount of radionuclides in tumor
  - Hypoxic cells have lower requirements for metabolic substrates
  - Hypoxic cells are less sensitive to radiation

α emitters:

- Range: 50-90 μm (penetration of about 10 cellular diameters), have high LET –linear energy transver, 400x higher than ß emitters

- Disadvantages: all tumor cells must be irrardiated to achieve a therapeutic effect- increased absorbed dose on surrounding tissue- secondary tumor

ß emitters

- Short range (<200 μm): P-33; Sn-121
- Medium range (200 μm – 1mm): I-131; Sm-153; Te-161: Re-186
- Long range (> 1mm): P-23; Sr-89; Y-90; Re-188

Auger electrons

- Radionuclides that have radioactive decay in a form of electron capture or internal conversion
- They emit X rays or Auger electrons
- Very short range (< 1 μm)
- The radioacive source must be close to the cell nucleus

Radioimmunotherapy

- Radiotracer attached to anti-tumor antibody
- All tumor cells must express target antigen, with uniform distribution
- Prolems: antibodies- allergic reactions, the ratio of tumor-healthy tissue (desirable > 10:1), tumor heterogenity, suitable for small tumors
- Problem of bone marrow irradiation!

Palliative bone therapy

- Bone-seeking radiotracers , ß emitters
- Sr-89 chloride($t_{1/2}$=50 days;$ß^-$=1,71 MeV), Re-186 ($t_{1/2}$=3,7 days; $ß^-$ =0,98 MeV) HEDP; Sm-153 ($t_{1/2}$=1,9 days; $ß^-$ = 0,81 Mev)-EDTMP
- Bone scintigraphy 1-2 weeks before therapy
- Evaluation of therapy success- bone scintigraphy 2-3 months after therapy
- Positive effect in 90% of patients. Duration of treatment response is about 3-4 months

- Bone metastases are most common in breast, prostate and lung cancer
- Solitary or multiple

Palliative treatment of painful bone metastases

- External irradiation – in a case of localised pain. In 80% of patients the pain is being reduced, in about 30% pain completely disappears

- Radionuclide therapy – in a case of multiple painful metastases

Samarium-153 lexidronam treatment of painful bone metastases

Sm-153 lexidronam

Sm-153

- ß emitter – therapeutic application
- Range in the bone ~ 1,7 mm
- γ rays, energy of 103 keV – gama camera→ visualisation of radiotracer distribution
- t½ 46 hours

lexidronam = tetraphosphate

Mechanisam of accumulation is similar to MDP/ DPD

- Urinary excretion

Sm-153 lexidronam- indications

- Pain reduction (= palliative pain relasing therapy) in a case of multiple bone metastases

Sm-153 lexidronam therapy-contraindications

- Chemotherapy or extrernal radiotherapy over huge body surface within the last 6 weeks– bone marrow suppression

Patient preparation

- Tc-99m diphosphonate scintigraphy must be provided to confirm osteoblastic lesions
- Level of leukocytes and trombocytes in the blood: evaluation of bone marrow function
- Hydratation ~ 0,5 L of fluid before injecion to improve renal excretion of radionuclide

Sm-153 lexidronam application

- 1 mCi/kg of body weight
- intravenously

Sm-153 lexidronam- therapeutic effect

- Pain reduction starts within one weeak
- Pain reduction in 70% of patients
- In about 30% pain completely disappears
- Therapy response duration ~ 4 months

Bone marrow suppression

- Control of leukocyte and thrombocyte levels
- transient myelosuppression 3-4 weeks after Sm-153 lexidronam application
- Bone marrow recovery 2 weeks after

Therapy repeat

- Up to 4 applications of Sm-153 lexidronam, minimum 2 months interval between therapy
- Previously control of L and Trc

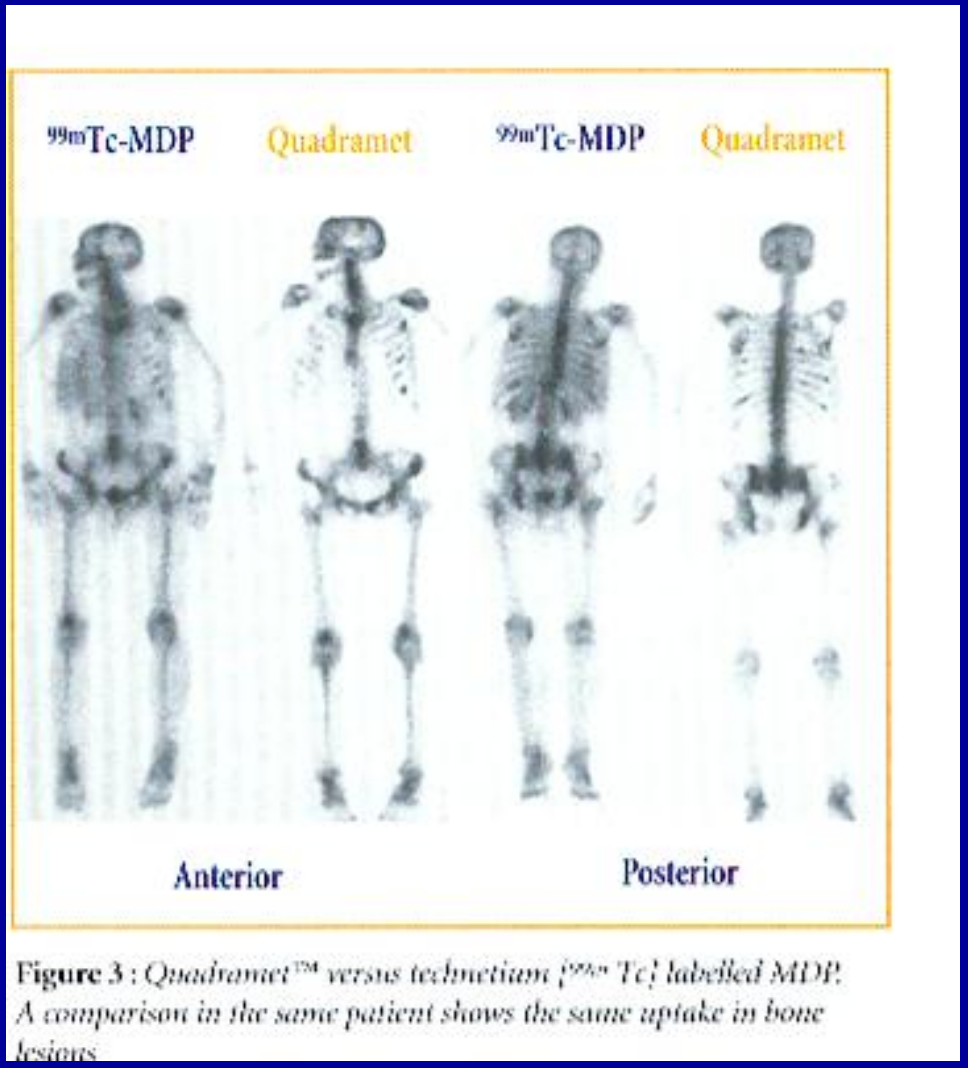

Figure 3 : *Quadramet™ versus technetium {99m Tc} labelled MDP. A comparison in the same patient shows the same uptake in bone lesions*

Comparison of Tc99m MDP bone scintigram before and after Sm-153 EDTMP

DOSIMETRY

- In calculation of tumor dose main limitation is maximal tolarable dose for surrounding tissue
- Dose limiting organ depends on applayng modality and radiotracer characteristic (half-life, ellimination, radiation)
- Bone marrow – systemic therapy
- Spinal cord – intrathecal application
- Bladder – kidney elimination

DOSIMETRY

- MIRD- **M**edical **I**nternal **R**adiation **D**ose committee, American Society of Nuclear Medicine:
- Absorbed dose calculation includes: target organ and/or tumor and its mass, dose limiting organ, average decay energy, absorbed fraction…
- These parameters can be measured by various diagnostic tools: scintigraphy, CT, MRI…

The end!