BELNUC
RADIOLIGAND THERAPY COURSE
30.11.2024, SHERATON BRUSSELS AIRPORT

Challenges and controversies in NET RLT: Interactive cases and pannel discussion

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Case 1

Dr Ioannis Karfis

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HEMODYNAMIC CHANGES AFTER PRRT: HYPERTENSIVE CRISIS

- 06/2007: 62y old female patient with malignant left pheochromocytoma with synchronous kidney and lymph node metastases

  > 06/2007: resection + left nephrectomy + lymph node dissection

  > 05/2009: new pulmonary and mediastinal lymph node metastases treated with 4c streptozotocin/5FU with morphological PR

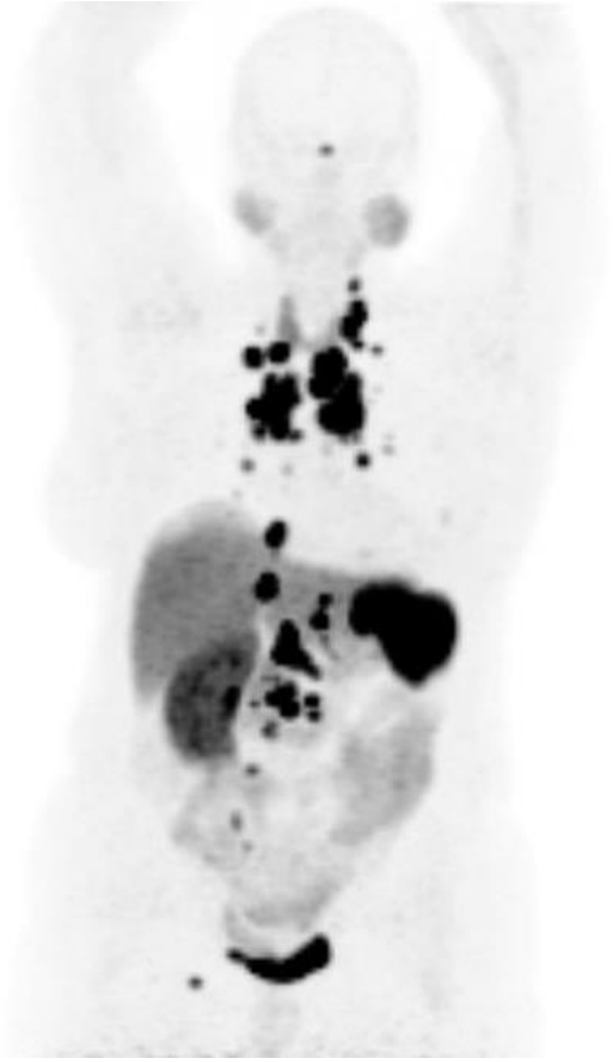
  > 04/2013: new progression (pulmonary/mediastinal lymph node) treated with sunitinib

  > 10/2014: further disease progression (clinical: paroxysmal hypertensive crises, on imaging with new liver and bone marrow lesions).
  ClCr: 41mL/min
  Urinary catecholamines/24h: 4-6x ULN (of low value)
  5 antihypertensive drugs (α-, β- blocker, iCa-channel, iACE, diuretic) with no results....

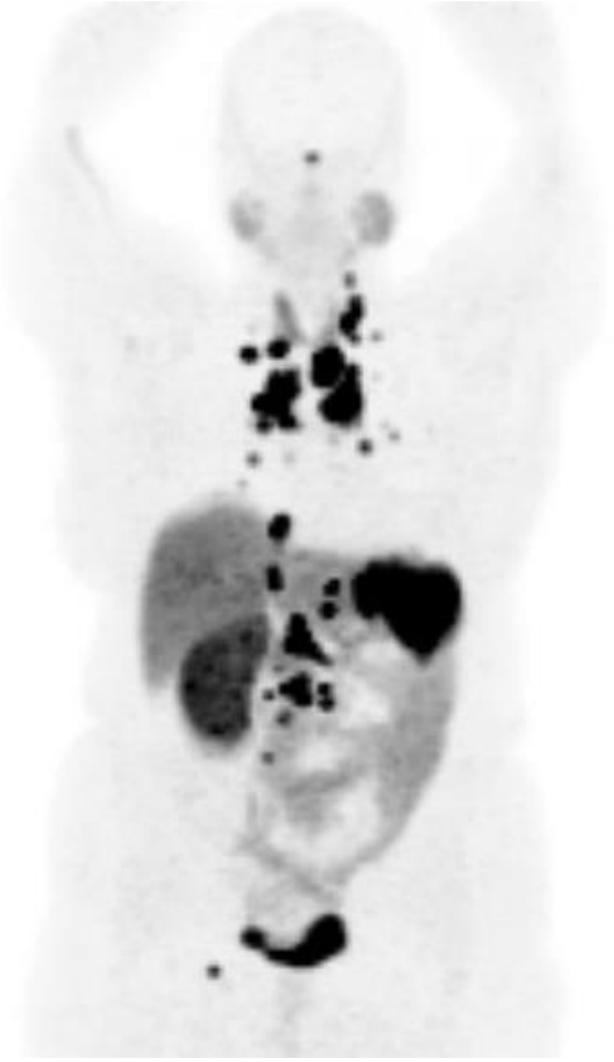
  > referral to our center: → PRRT (4c: 01/2015, 04/2015, 10/2015, 03/2016)
  → 1st cycle ended up with asymptomatic hypertensive crisis (>230-250/100-110mmHg) → nifedipine iv (ICU)
  → progressive normalisation of BP values, marked improvement of QoL (trekking, biking)
  → SD on DOTATATE PET/CT 1y after end of PRRT
  → persistance of elevated urinary catecholamines/24h: 3-4x ULN (of low value).

HEMODYNAMIC CHANGES AFTER PRRT: HYPERTENSIVE CRISIS

BASELINE PRRT DOTATATE PET 09/2014



post 4c PRRT DOTATATE PET 06/2016



HEMODYNAMIC CHANGES AFTER PRRT: HYPERTENSIVE CRISIS → THM

- Hypertensive crisis: paroxysmal sustained elevations in BP ≥180/120 mmHg due to catecholamine excess (1000x baseline)
  patients at risk: highly symptomatic (multiple anti antihypertensive drugs), high tumor load
  very rare AE with PRRT (anecdotal cases), occurrence: min or hours after PRRT.

- Tx (ICU): conventional approach: (α-blocking iv: phentolamine/clevidipine) vs alternative approach (nicardipine/verapamil).

- Prevention: α-blockers (terazocine in Belgium).

- Tips oh how to proceed:
  Know your patient. Inform your ICU/on call physician about the case days prior PRRT.
  Consult the institutionnal SOPs for hypertensive crisis. Consult the departmental SOP for transfert of radioactive patients to ICU.
  Prolong the injection duration (1-2h).
  Alternatevely decrease injected activity by 25 or 50%.

- Do not ever adminster metoclopramid to a patient with catecholamine-producing neoplasias.

Makis W et al: Nucl Med Mol Imaging 2015, Nazari MA et al: *Lancet Diabetes Endocrinol* 2023, Leonard Jb et al: *AJEM* 2018

Case 2

Prof. Dr Christophe Deroose

UZ Leuven / KU Leuven

Paravenous injection of [^{177}Lu]Lu-DOTATATE in NET patient: how do you react?

1. I run away screaming and pulling my hair.
2. Nothing special, we always inject [^{177}Lu]Lu-DOTATATE subcutaneously.
3. Perfom lipoaspiration and injection of corticosteroids.
4. Call plastic surgeon to shedule flap plasty in 4-6 weeks
5. Raise arm and give stressball to patient to promote lymphdrainage
6. Perform [^{177}Lu]Lu-DOTATATE SPECT/CT to localize the radiopharmaceutical and perform dosimetry.

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5. **Raise arm and give stressball to patient to promote lymphdrainage**
6. Perform [177Lu]Lu-DOTATATESPECT/CT to localize the radiopharmaceutical and perform dosimetry.

Extravasation of therapeutical radiopharmaceuticals

Figure 1. Image of the patient's antecubital fossa, showing wet desquamation at day 29.

Table 1. Timeline of Observations at Site of Extravasation (Days After Infusion)

Time (day[a])	*Observation*
1	At home, the patient's wife noted an area of erythema approximately 3–4 inches in diameter in the antecubital fossa; she noted this "receded in diameter" during the subsequent week. There was no skin breakdown.
7	2.5 × 3 inch erythematous area was noted (in clinic).
14	Tenderness at the site was noted (in clinic).
22	Enlarged 7 × 11 cm (2.8 × 4.3 inch) site was noted (in clinic) with no warmth, streaking, or skin breakdown.
26	The patient's wife, a health professional, noted a bulla and began treating the area with bacitracin gauze dressings.
29	The wound was characterized as a grade 3 dermatitis[b] associated with radiation, moist desquamation (Fig. 1). The site had begun to desquamate, leaving a denuded area with serous exudate. The family applied dry sterile dressings that were changed 3 times a day secondary to saturation. Consultations with dermatology and plastic surgery were arranged; plastic surgery recommended 1% sulfur sulfadiazine cream and gauze dressings.
34	The site was noted as "slightly smaller" 6 × 10.5 cm (2.4 × 4.1 inch) and draining serosanguineous fluid, and follow-up with plastic surgery was arranged for further evaluation of the wound and for possible skin grafting.

From Ref. 1.

^{90}Y-ibitumomab tiuxetan (Zevalin®)

Williams et al. Cancer Biother & Radiopharm. 2006; 21(2):101-5
Siebeneck, Clin J Oncol Nursing, 2008; 12(2):275-8

Extravasation of therapeutical radiopharmaceuticals

4 Weeks PI

Erythema
Desquamation

5 Weeks PI

Moist desquamation
Purulent drainage

20 Weeks PI

Persisent wound
Necrosis

Williams et al. Cancer Biother & Radiopharm. 2006; 21(2):101-5
Siebeneck, Clin J Oncol Nursing, 2008; 12(2):275-8

Extravasation of ^{90}Y-ibritumomab tiuxetan (Zevalin®)

CLINICAL CASE

Complex upper arm reconstruction using an antero-lateral thigh free flap after an extravasation of Yttrium-90-ibritumomab Tiuxetan: A case report and literature review

A. Baus [a,d,*], C. Keilani [a,d], C.-S. Bich [a], F. Entine [b], M. Brachet [a], P. Duhamel [a], J.-C. Amabile [b], J.V. Malfuson [c], E. Bey [a]

[a] *Plastic Surgery Unit, Percy Military Hospital, 92140 Clamart, France*
[b] *French Army Radiation Protection Unit, Percy Military Hospital, 92140 Clamart, France*
[c] *Hematology Unit, Percy Military Hospital, 92140 Clamart, France*
[d] *Faculty of medicine Pierre-et-Marie-Curie,75252 Paris cedex 05, France*

65 year old man
NHL
Myeloablative R/ 1200 MBq
20G catheter antecubital vein
End of flushing: extravasation needle puncture site (~1-2 mL; ~10% total activity)
Dose estimate: 50Gy

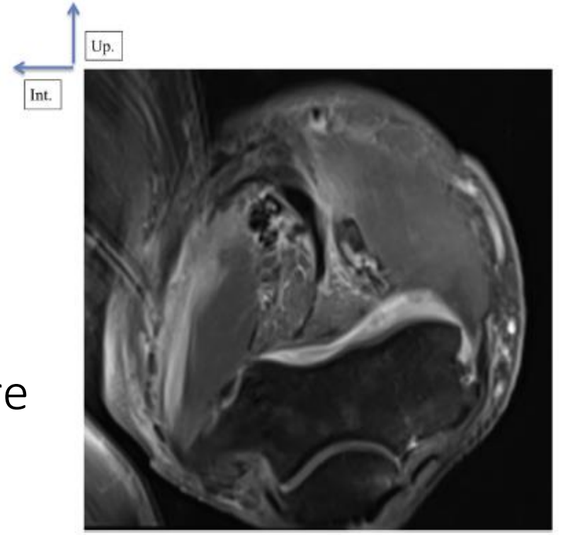

Figure 2 Left upper arm on MRI (T1 + Gadolinium-weighted): soft tissue infiltration, muscular inflammation and muscle signal abnormality (pronator teres, brachioradialis muscle, and brachialis muscle).

Irradiation dose	From 4 to 6 Grays (Gy)	6 to 12 Gy	12 to 15 Gy	15 to 25 Gy	> 25 Gy
					
Clinical response.	Transient depilation.	Cutaneous erythema (Sunburn).	Dry desquamation.	Wet desquamation with spontaneous healing.	Radionecrosis without spontaneous healing.

Pre-op

Necrosis

Restrictive range movement

Baus et al., Annales de Chirurg Plast Esthét 2018; 63:175-81

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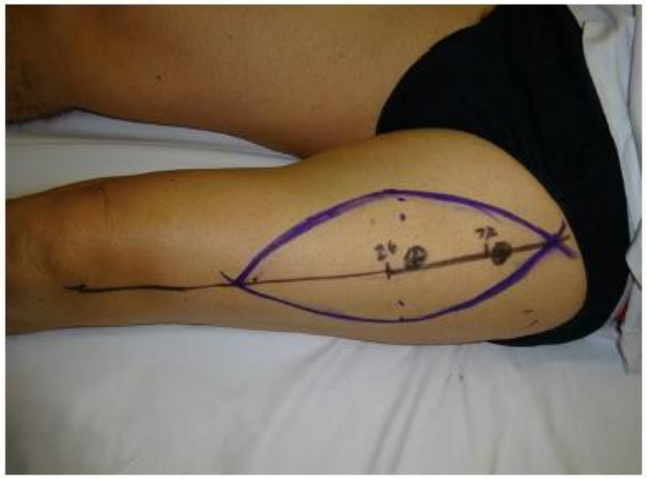


Marking flap (tigh)

Debridement necrosis

Covering cutaneous defect

Complete recovery

Baus et al., Annales de Chirurg Plast Esthét 2018; 63:175-81

Extravasation of ^{90}Y-DOTATOC

A 53-year old woman with a NET complained about pain in arm at the insertion site after administration of 3.5 GBq ^{90}Y-DOTATOC

Swollen arm at the catheter insertion site

=>suspicion of ^{90}Y-DOTATOC extravasation

Dose rate meter

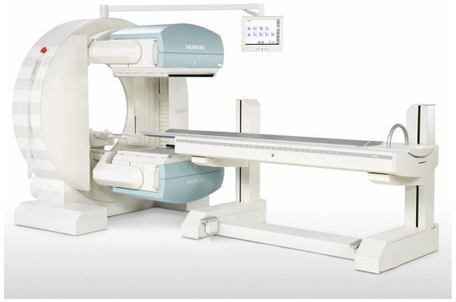
measure the dose rate at the insertion place at 1 cm from the insertion site

Image bremsstrahlung and monitor the fraction of extravasated β–activity

Extravasation of ^{90}Y-DOTATOC

Dose rate meter

Gamma-camera



1 hour post-infusion

75 mSv/h @ 1 cm

Dose to skin estimate:
Worst case (3.5 GBq ^{90}Y-DOTATOC / no reabsorption)

59 Gy

Actions :

Reduce the residence time, e.g.:

- local puncture (without results)
- local massage
- vertical and elevated arm position
- squeezing a stress ball to stimulate lymphatic drainage

Terwinghe, et al., Deroose C, Eur J Nucl Med Mol Imaging. 2012;39(S2): S205-S205 - OP267

Extravasation of ^{90}Y-DOTATOC

Dose rate meter

Gamma-camera

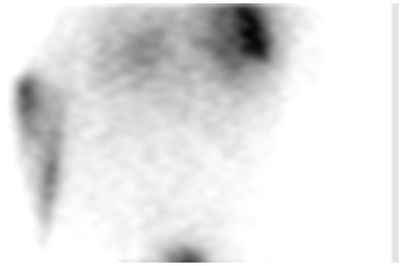
1 hour post-infusion

75 mSv/h @ 1 cm

18 hour post-infusion

<1 mSv/h @ 1 cm

-98%



-91%

Time-integrated activity coefficient: 4hrs

59 Gy **14 Gy** (Varskin) – **74 Gy** (Handbook)

Dose to skin estimate:
Worst case (3.5 GBq ^{90}Y-DOTATOC / no reabsorption)

Radionuclide and Radiation Protection Data Handbook 2002; D. Delacroix; Radiation Protection Dosimetry Vol 98 No 1, 2002. Published by Nuclear Technology Publishing

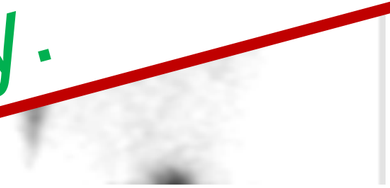
Extravasation of ^{90}Y-DOTATOC

Dose rate meter

1 hour post-infusion

75 mSv/h

Gamma-c



-91%

Dose to s

Worst case (-DOTATOC
/ no reabsorption)

Time-integrated activity coefficient: 4hrs

59 Gy **14 Gy** (Varskin) – **74 Gy** (Handbook)

No symptoms nor clinical signs (redness, desquamation, …) up to 2 months after the incident (death due to progression of Merckel cell carcinoma)

Real skin dose: lower than 10 Gy.

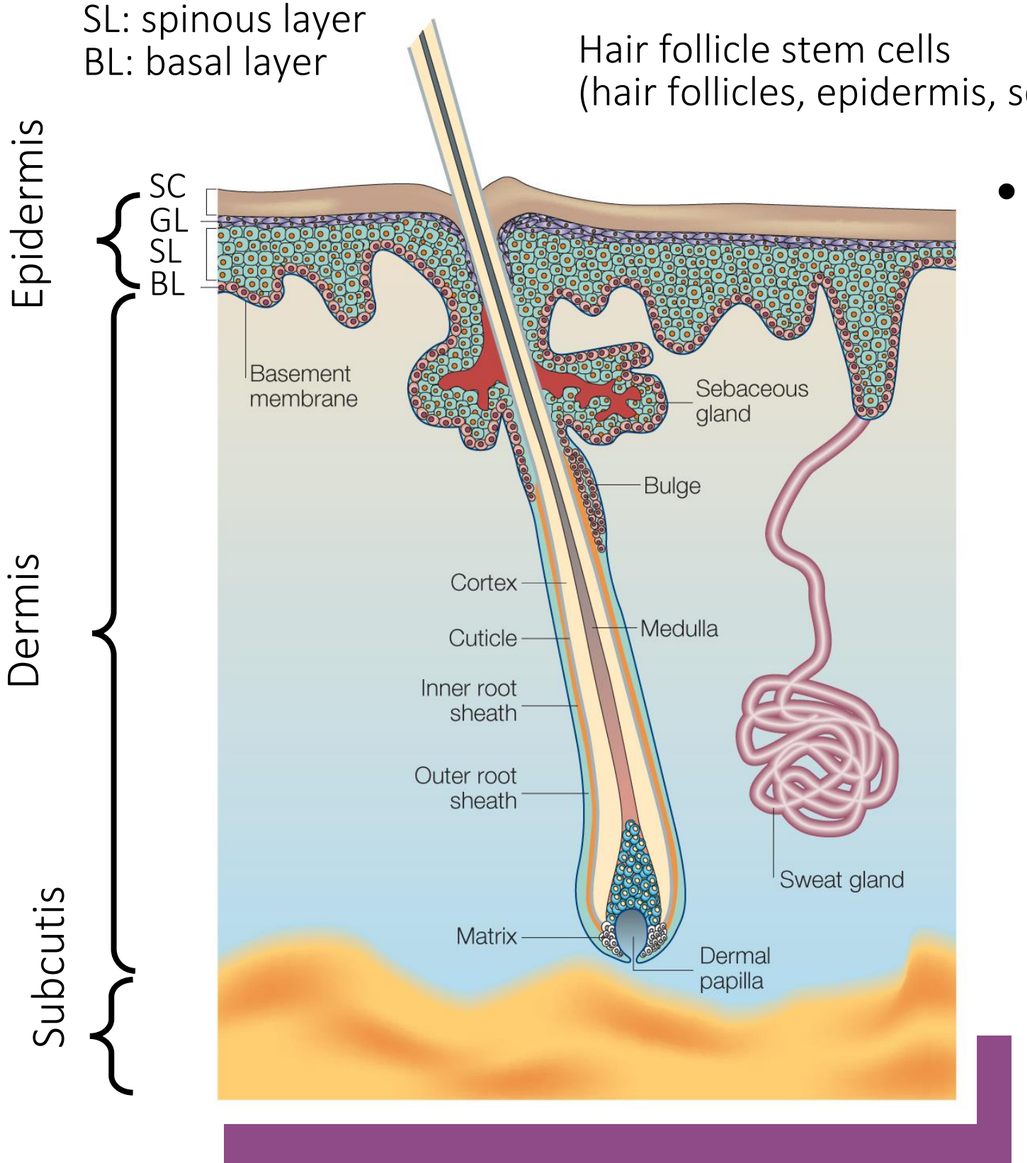
Radionuclide and Radiation Protection Data Handbook 2002; D. Delacroix; Radiation Protection Dosimetry Vol 98 No 1, 2002. Published by Nuclear Technology Publishing

Damage to skin stem cells

SC: stratum corneum
GL: granular layer
SL: spinous layer
BL: basal layer

Epidermal stem cells (BL)
Everday regeneration of different layers epidermis

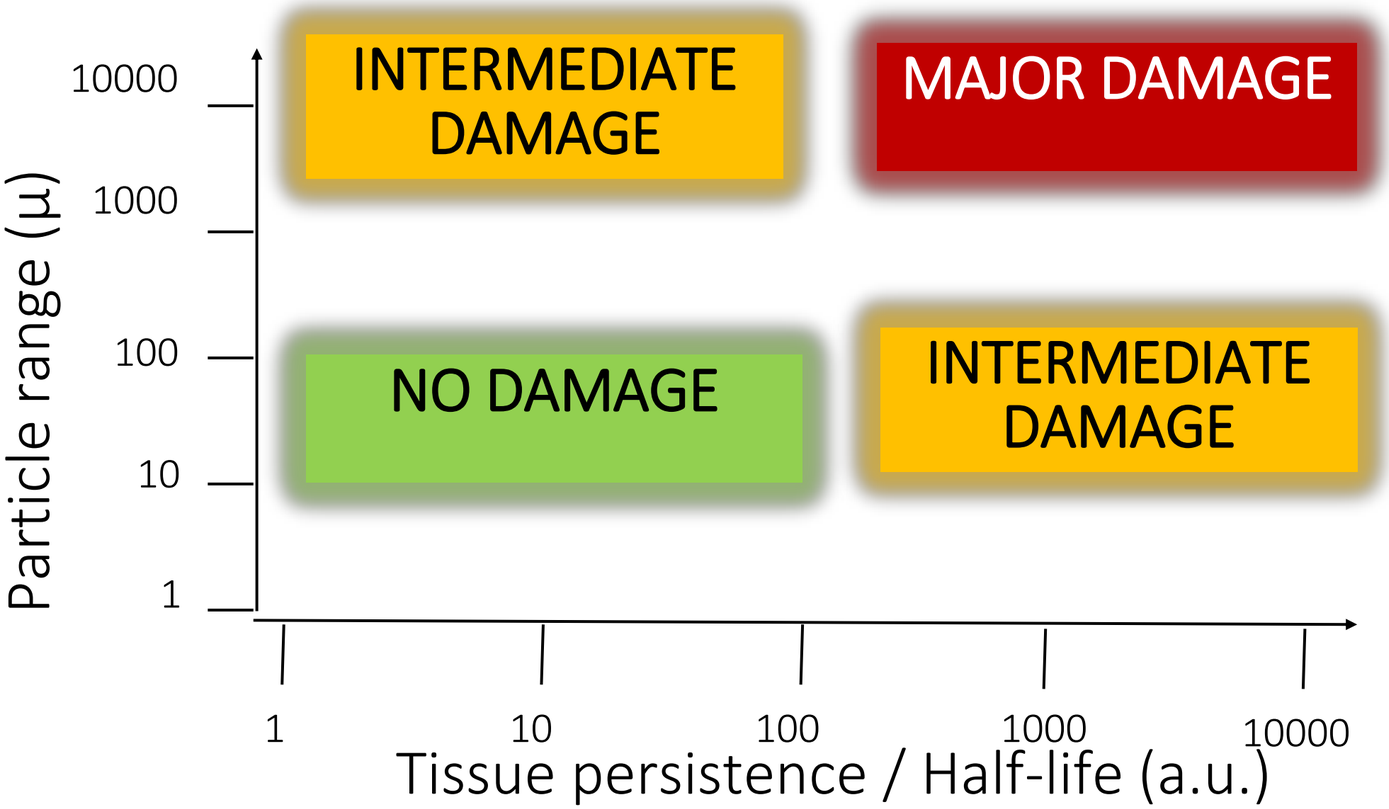
Hair follicle stem cells
(hair follicles, epidermis, sebaceous glands)

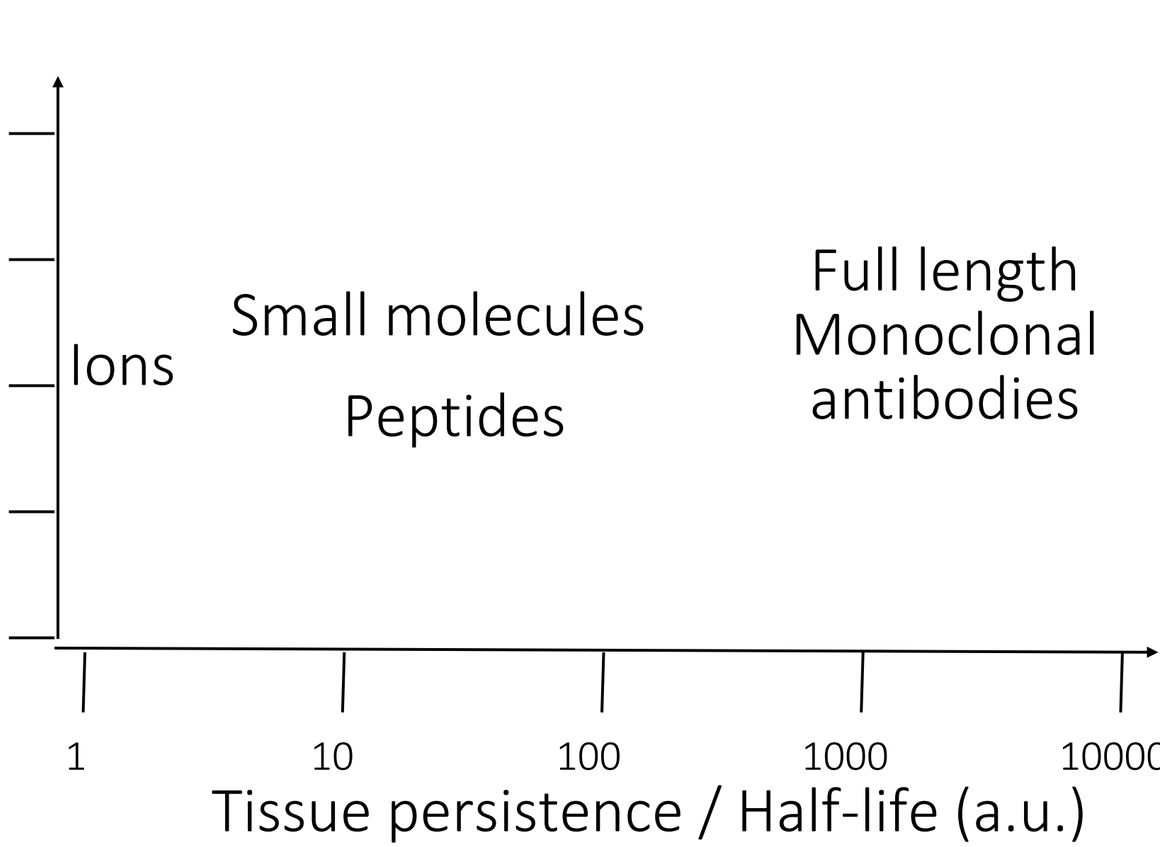


- Damage to stem cells depends on:
  - Radiopharmaceutical
    - Half-live
    - Tissue persistance (in function of half-live)
      - Very low (ions)
      - Very high (monoclonal antibody)
    - Radionuclide – range of ionizing radiation
      - Very short (α-emitters) ~50-80 µ
      - Very far (high energy β-emitters) ~12 mm
  - Amount of extravastion (measurements/imaging)

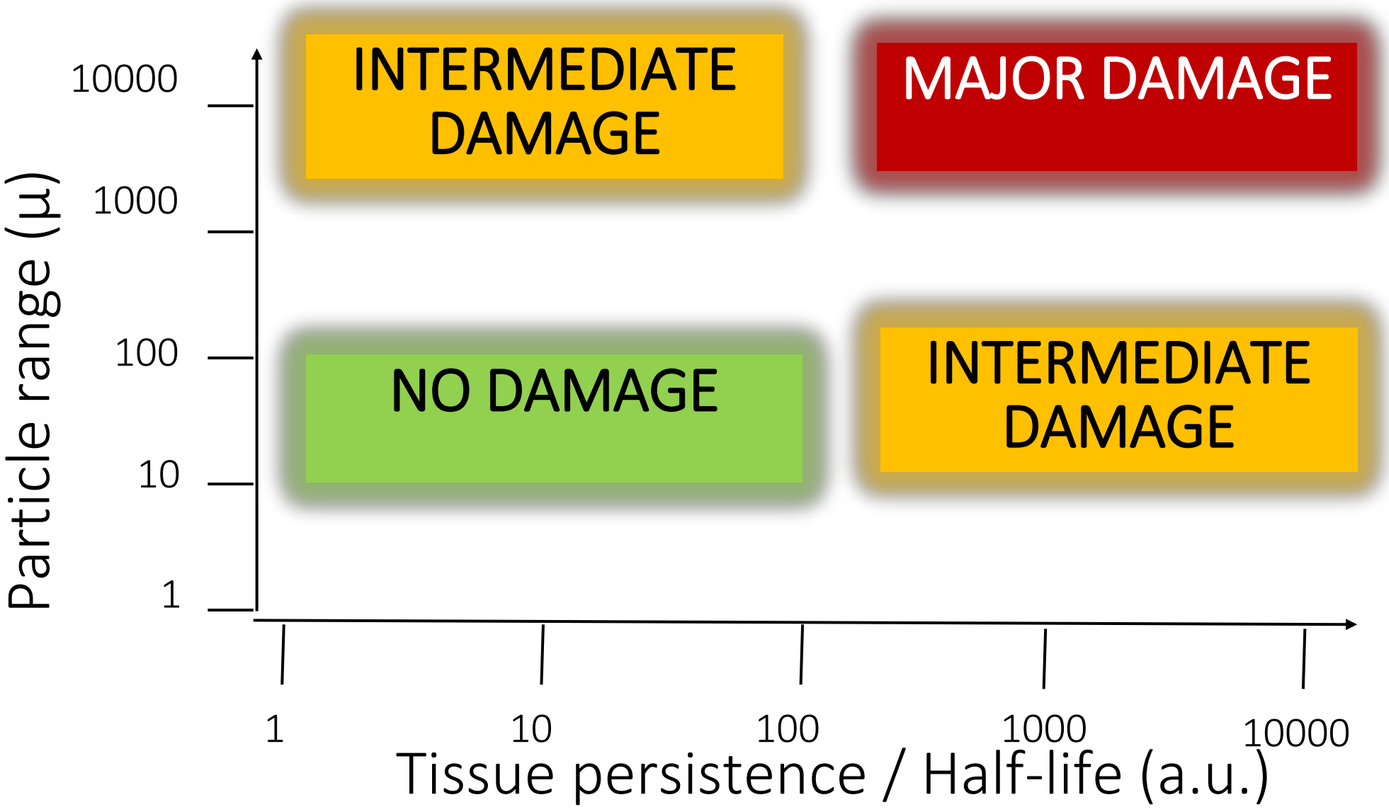
Adapted from Fuchs et al. Nature Rev Gen 2002; 3:199-209

Extravastion: assesment of potential for damage

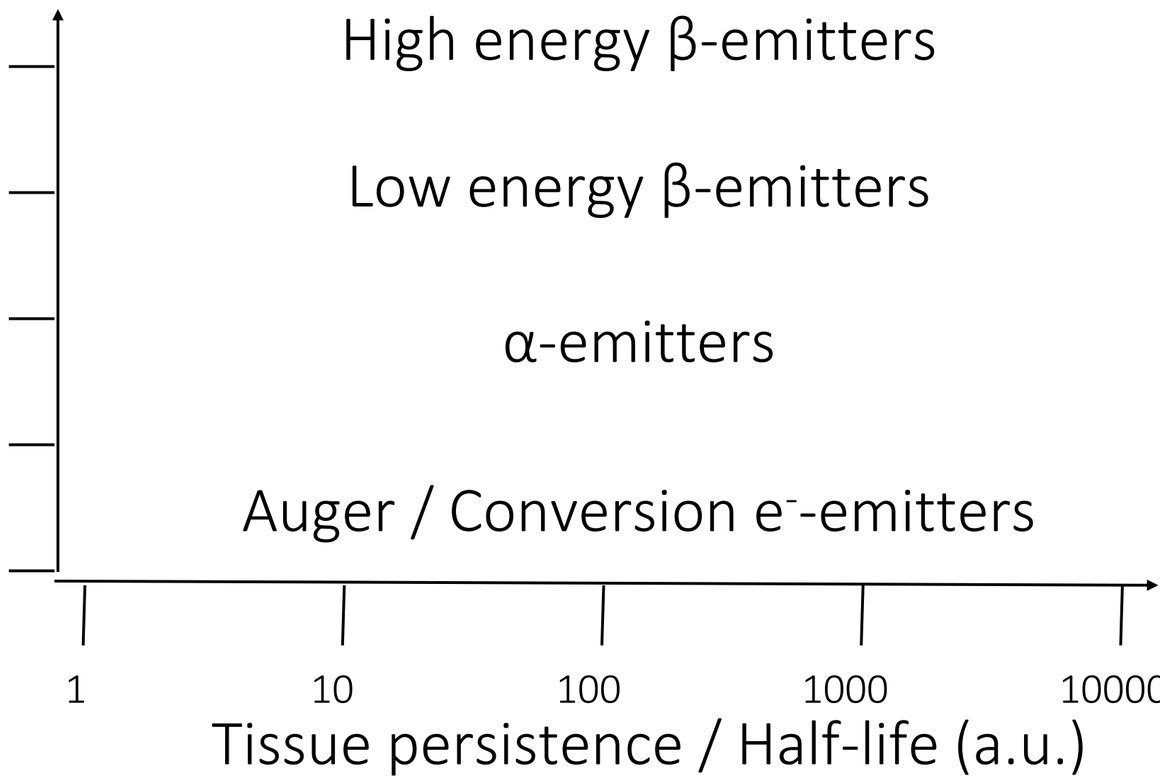




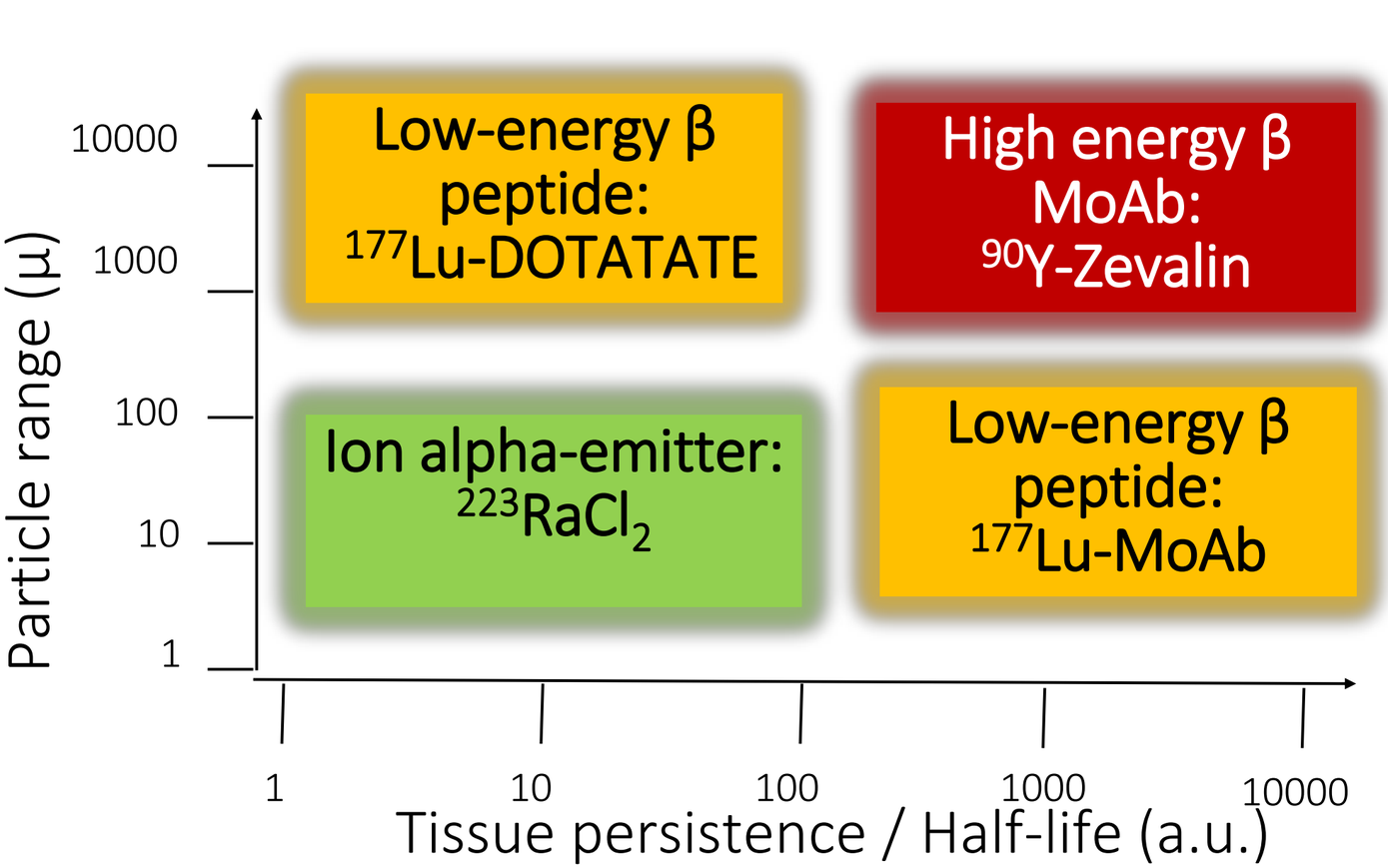
Extravastion: assesment of potential for damage

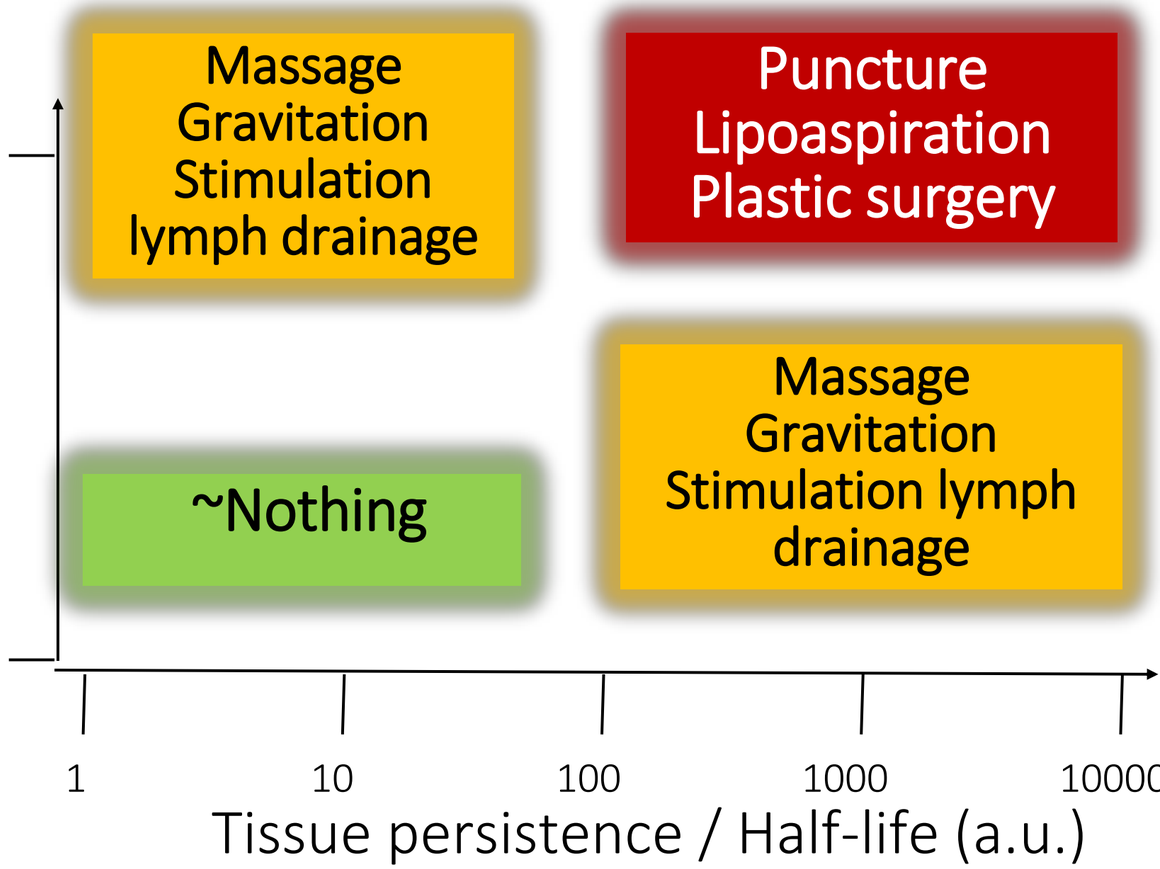


Therapeutic Radionuclide

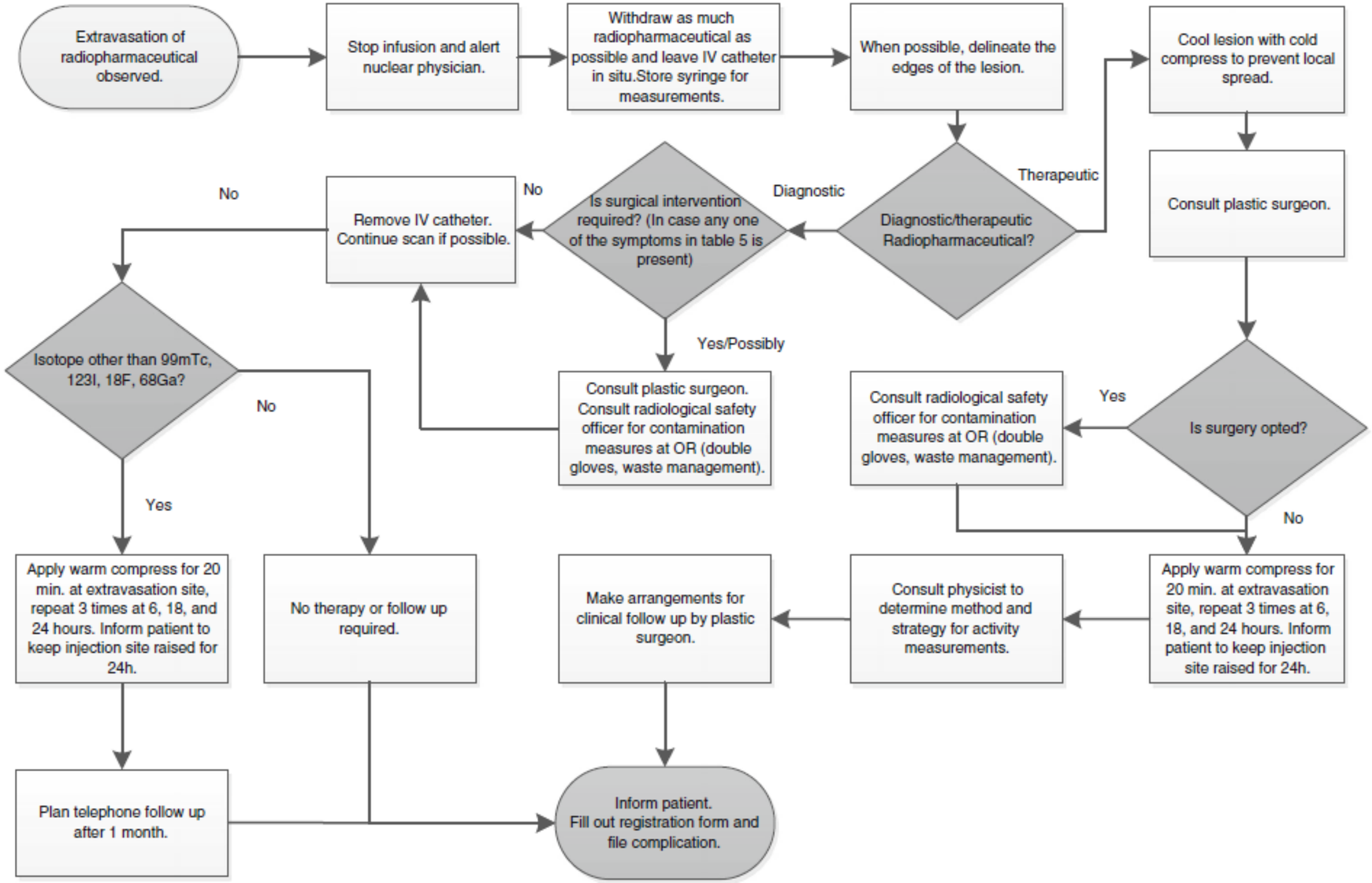


Extravastion: assesment of potential for damage





Extravasation management sheme

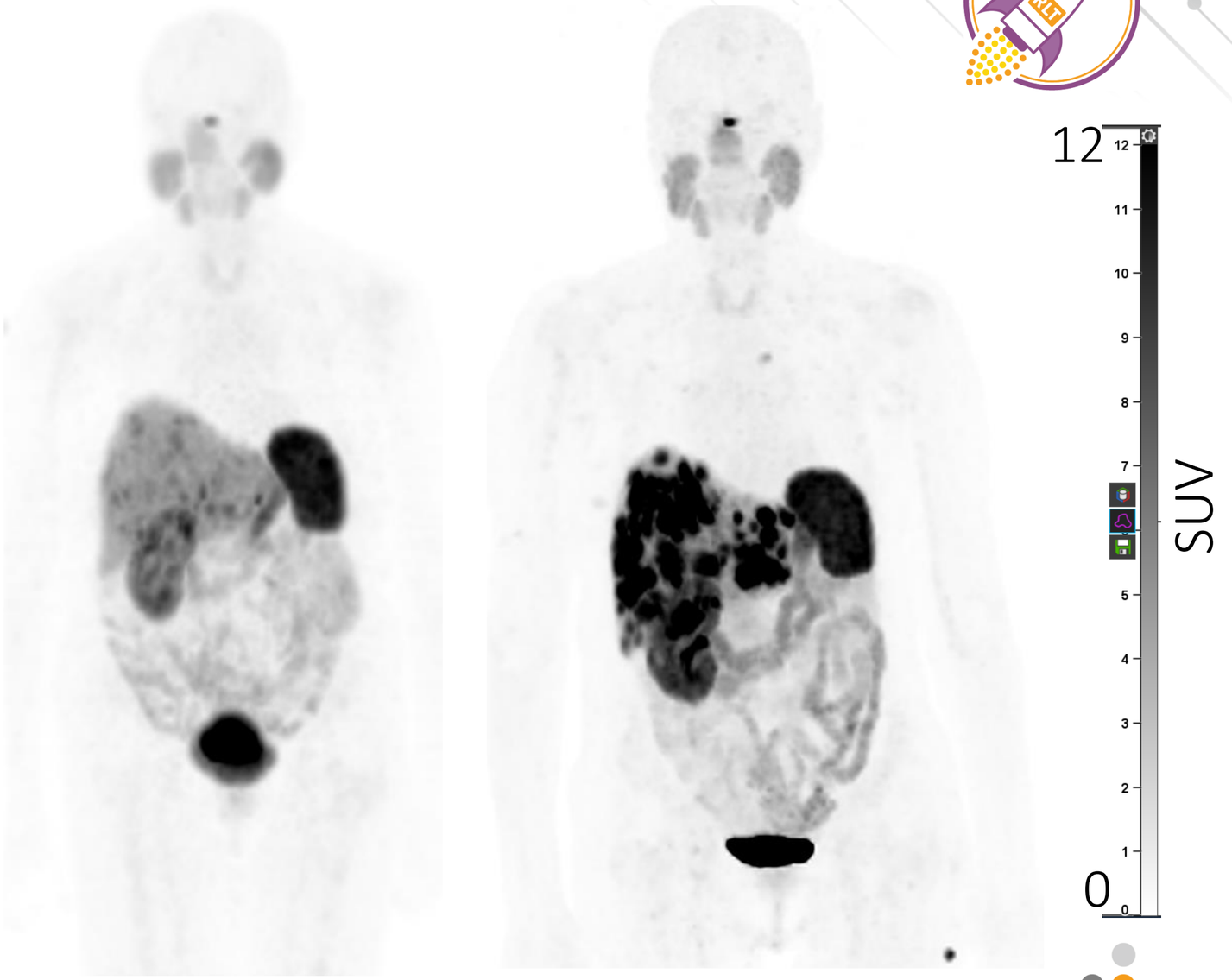


van der Pol et al. Eur J Nucl Med Mol Imag 2017(44):11234-43

Extravasation of [^{177}Lu]Lu-DOTATATE

- Woman, 74 y old
- History:
  - Nephrectomy for angiomylipoma
- Oncological history:

  - 6Y: pT3 N2 Mx. NET colon; Right hemicolectomie. G2 siNET
  - Referred for PRRT: progressive liver metastases after SSA and everolimus
  - Difficult veins: in theater peripheral catheter (anesthesiologists)



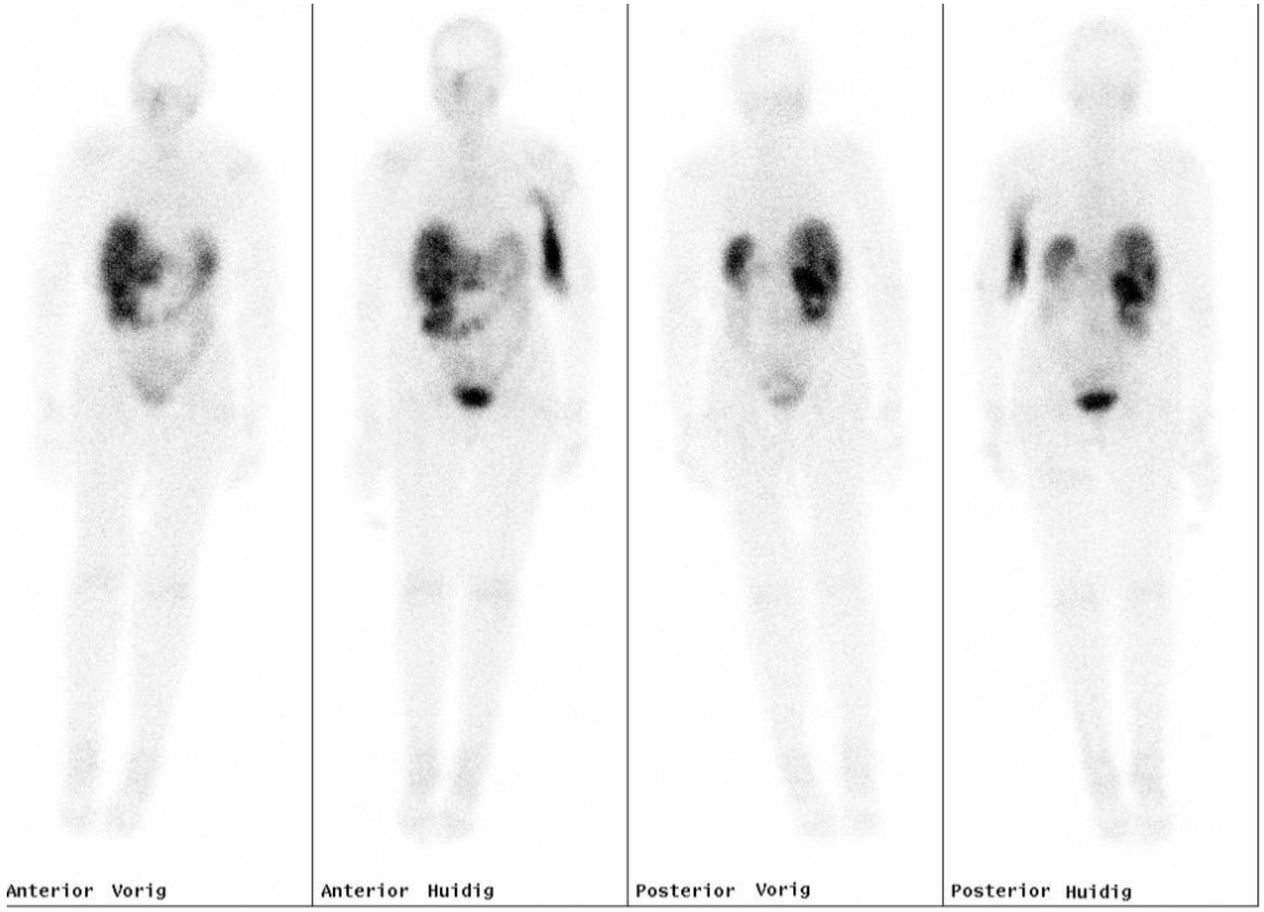
-4 Y

Current

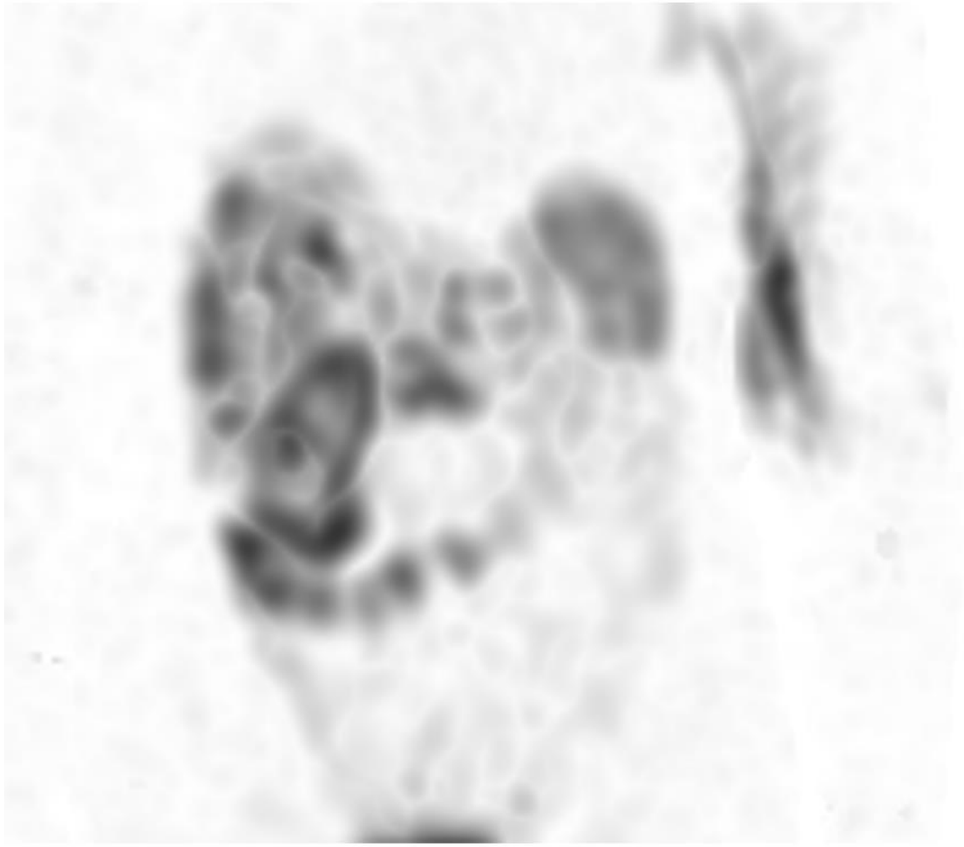
Extravasation of [^{177}Lu]Lu-DOTATATE

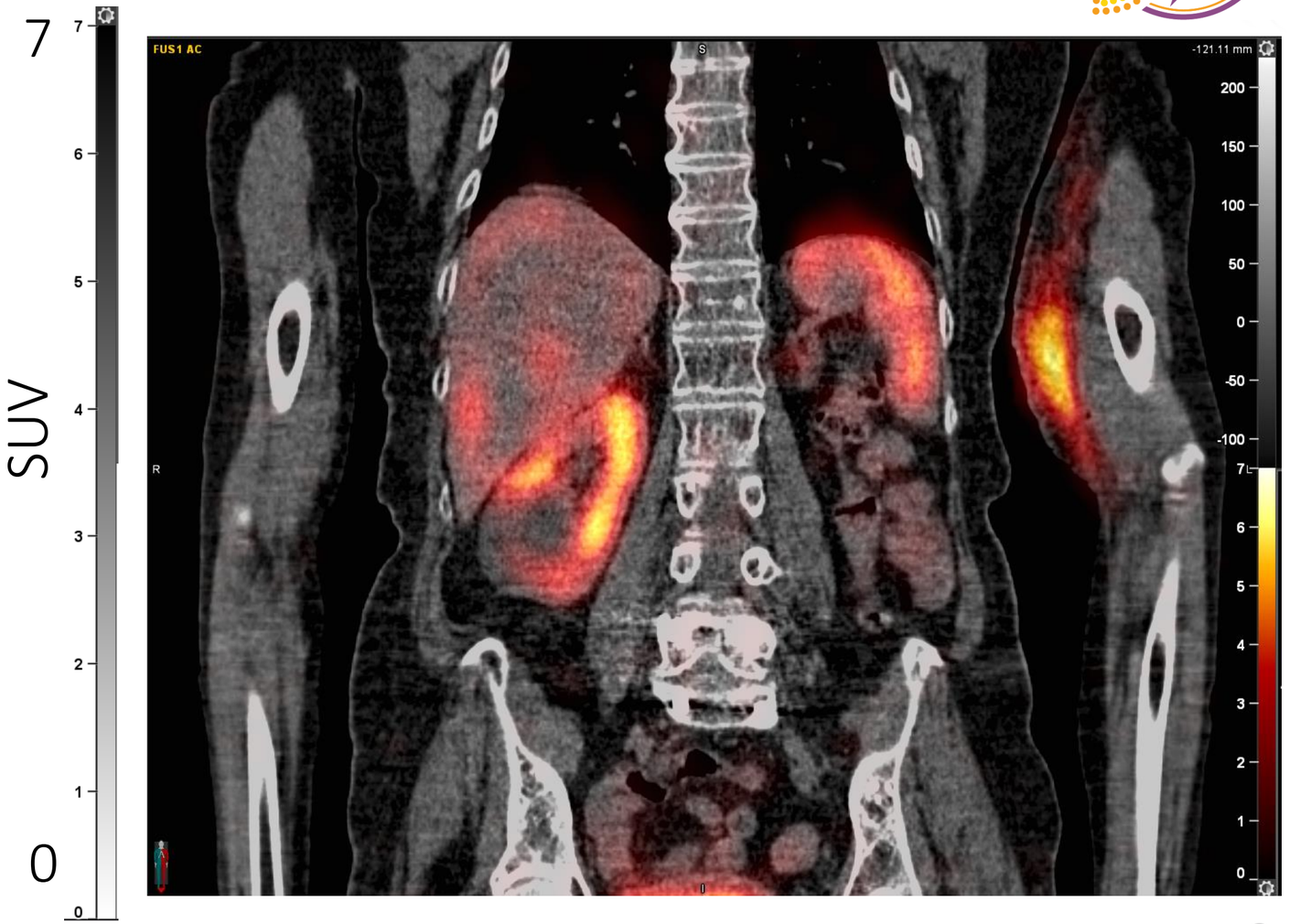
- Woman, 74 y old
- Bump in left ellbow report in evening
- R/
  - Ice application
  - Elevation arm

  ⟾ rapid regression of edema
- Post-therapy imaging morning

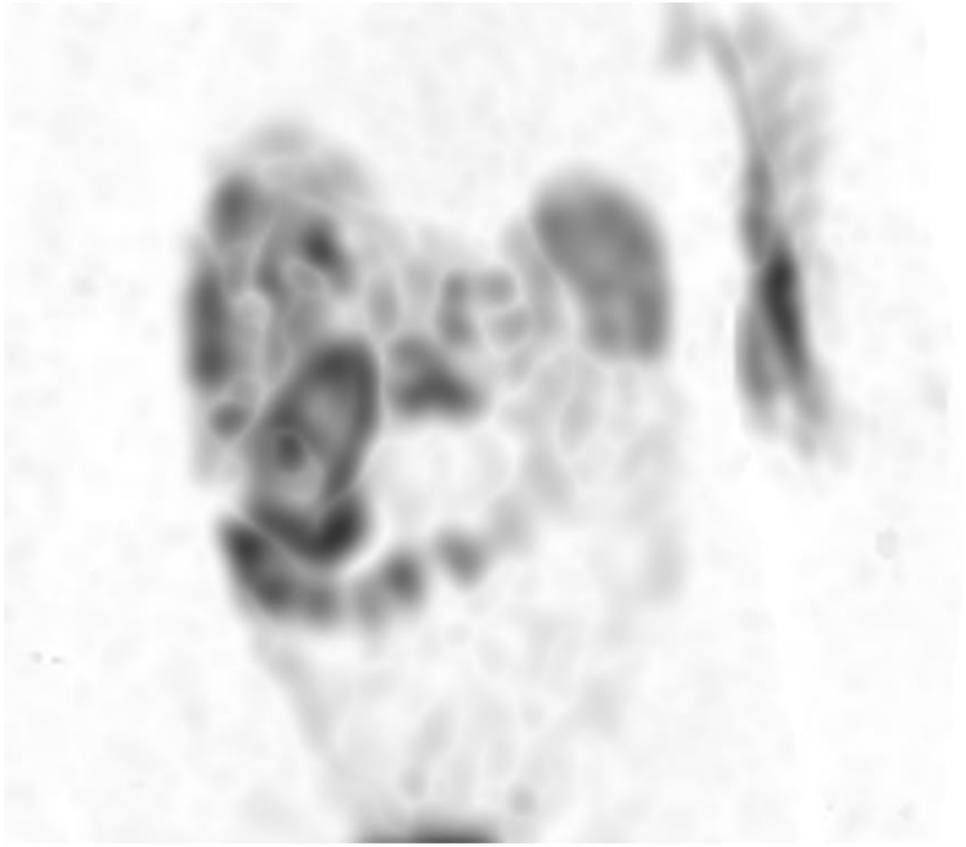


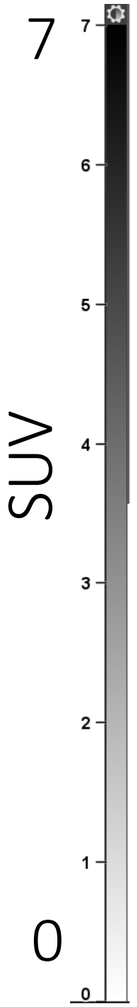
Extravasation of [^{177}Lu]Lu-DOTATATE

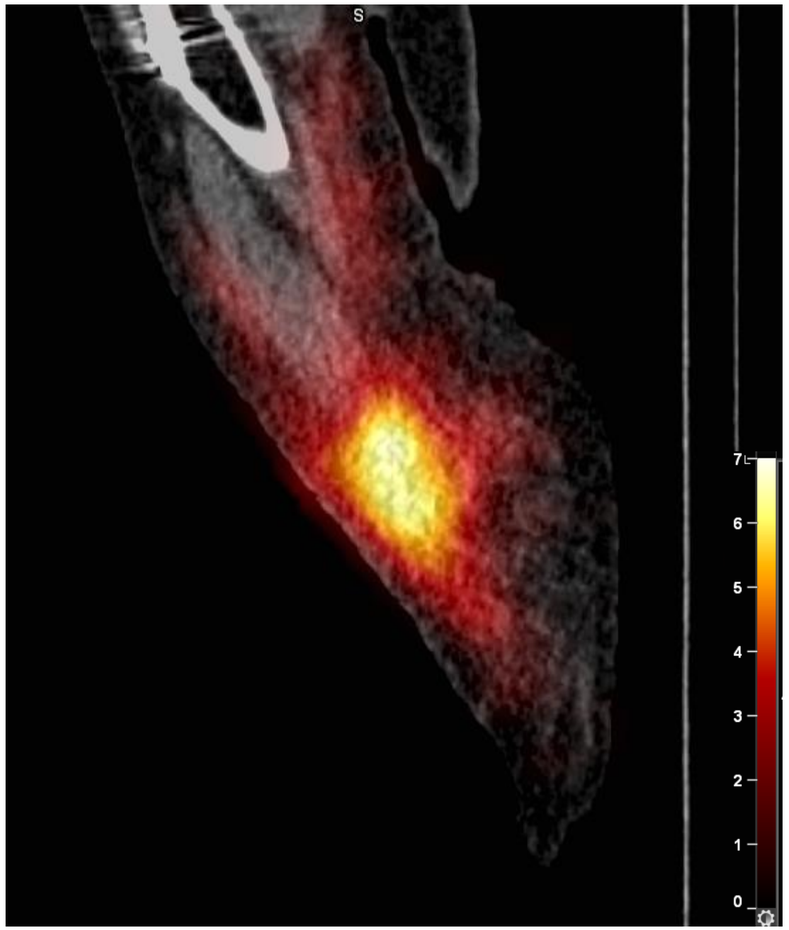




Extravasation of [^{177}Lu]Lu-DOTATATE

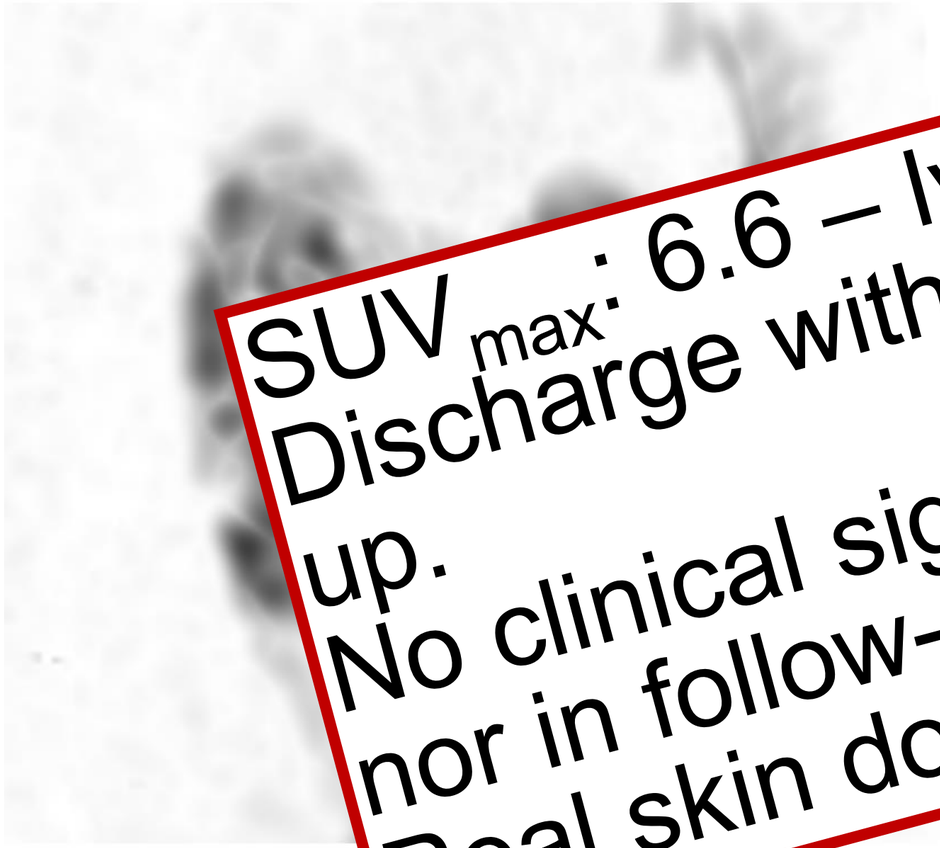


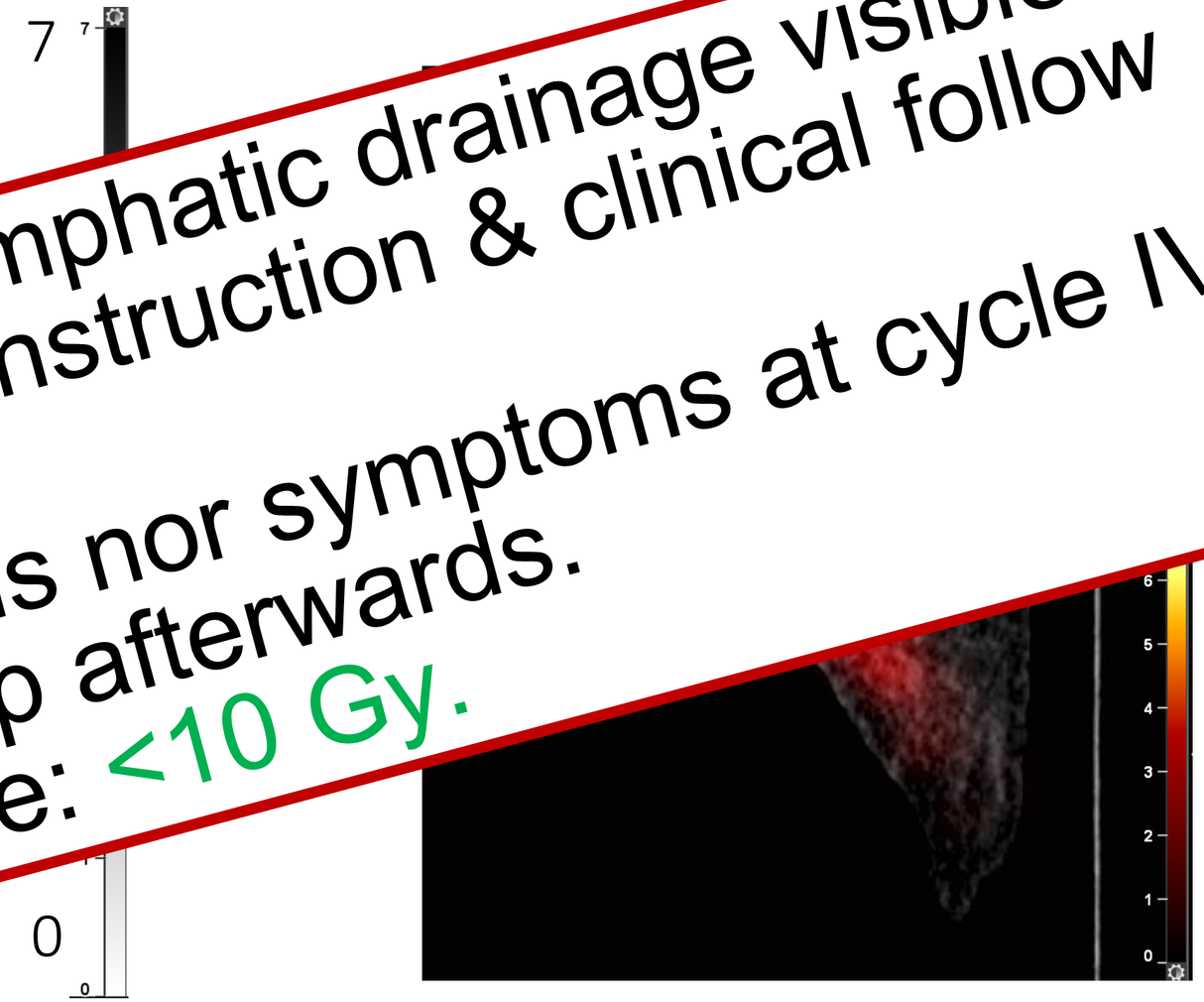




SUV_{max}: 6.6

Extravasation of [^{177}Lu]Lu-DOTATATE



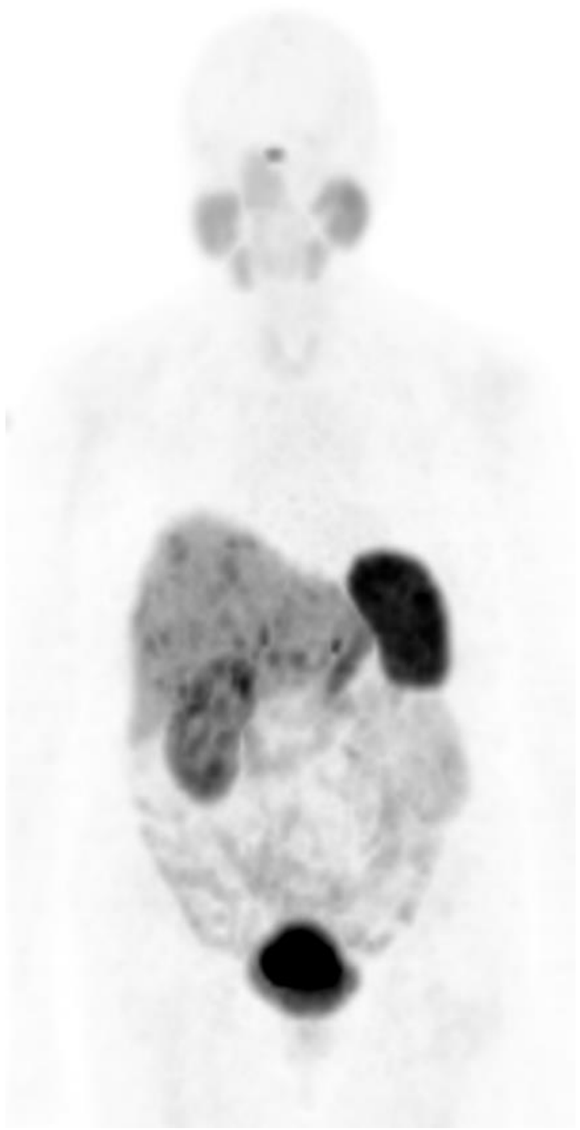


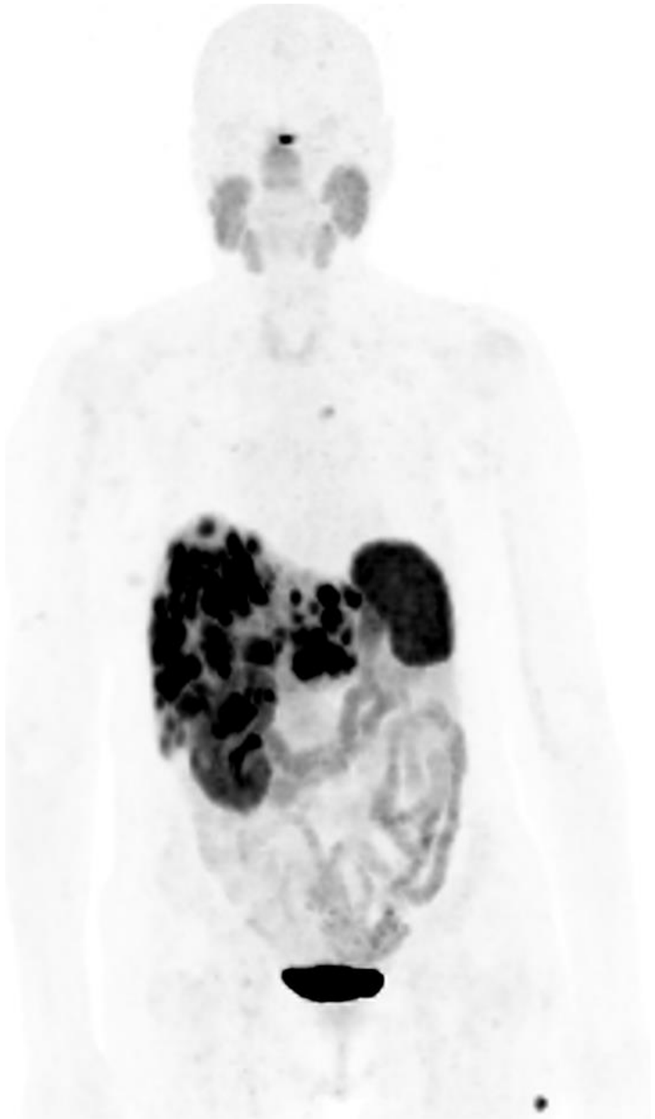
SUV_{max}: 6.6 – lymphatic drainage visible
Discharge with instruction & clinical follow up.
No clinical signs nor symptoms at cycle IV nor in follow-up afterwards.
Real skin dose: <10 Gy.

SUV_{max}: 6.6

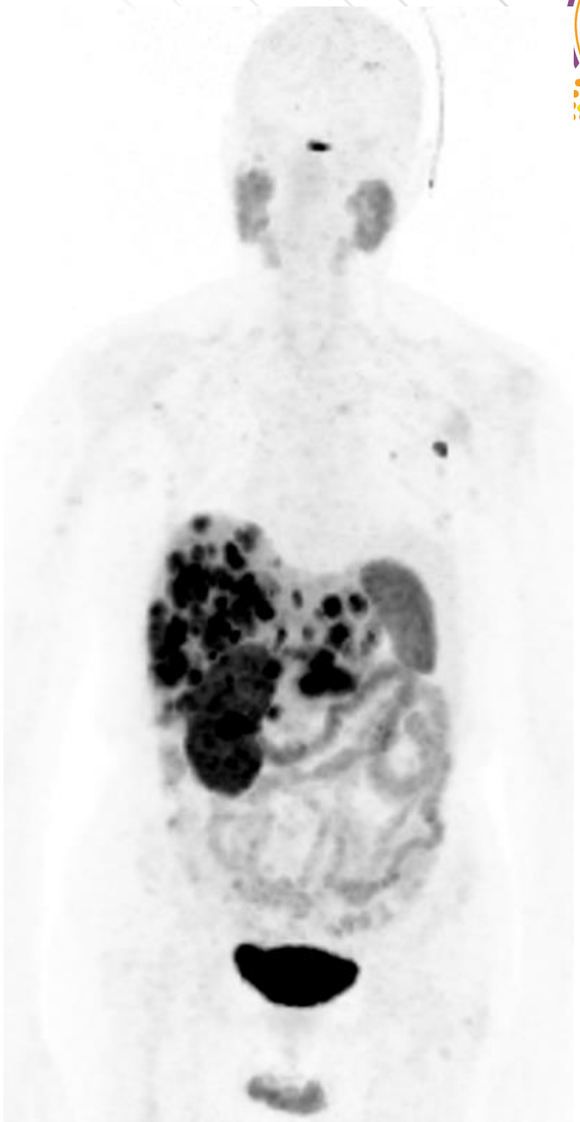
Extravasation of [^{177}Lu]Lu-DOTATATE

-4 Y

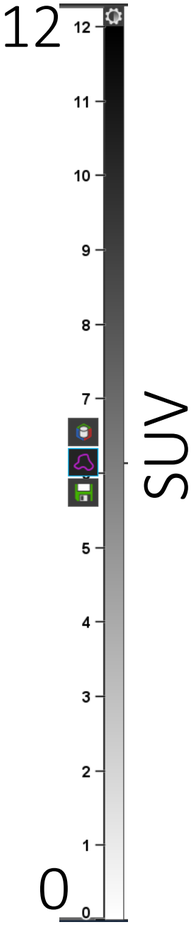




Baseline PRRT



11M after
PRRT C1



Case 3

Dr Ioannis Karfis

Institut Jules Bordet / HU Brussels

HORMONAL SYNDROMES: INSULINOMA

- 10/2015: 54y old female patient with malignant insulinoma (body of pancreas, low G2, Ki67: 4%) with synchronous hepatic and spleen metastases

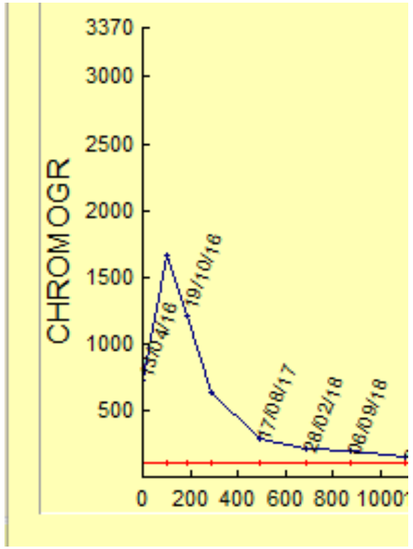
  > 10/2015: treated with somatostatin analogues, with rapid clinical deterioration / morphological liver progression

  > 12/2015: profound hypoglycemia crises → continuous perfusion with glucose G30/neuroglycopenic symptoms

  > 01-03/2016: 3c of capecitabine/temozolomide with SD

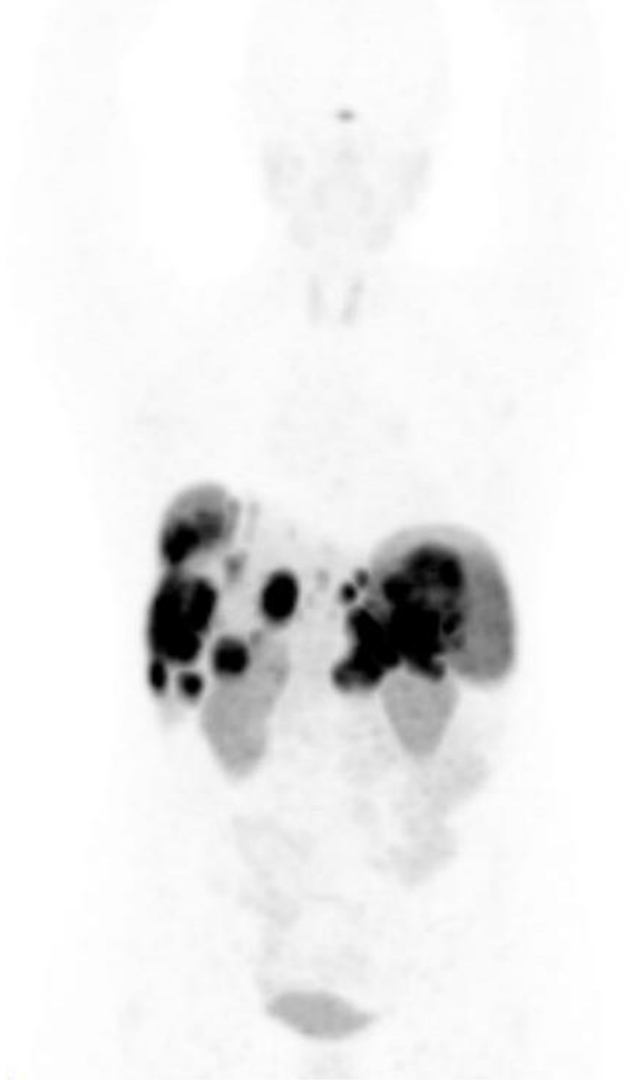
  > 03/2016: start diazoxide with some decrease of glucose perfusion needs

  referral to our center: → PRRT (4c: 04/2016, 07/2016, 11/2016 and 02/2017)
  → marked decrease of glucose perfusion needs after C1
  → diazoxide was completely stopped after 2c of PRRT upon continuous clinical improvement and rapid disappearance of hypoglycemic episodes
  → PR on MRI (best morphological response)
  → PR on DOTATATE PET/CT and further near-CR 20m after treatment compltetion
  → CgA evolution with PRRT
  → Baseline insuline and C-peptide values were not available
  → post-PRRT FU with MRI q3m and close monitoring of glycemias (diary).

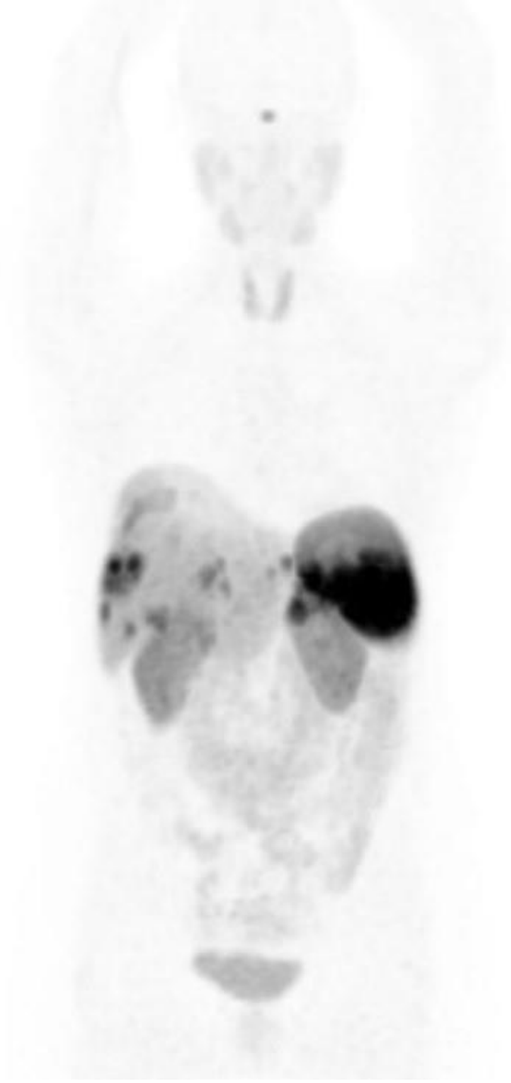


HORMONAL SYNDROMES: INSULINOMA

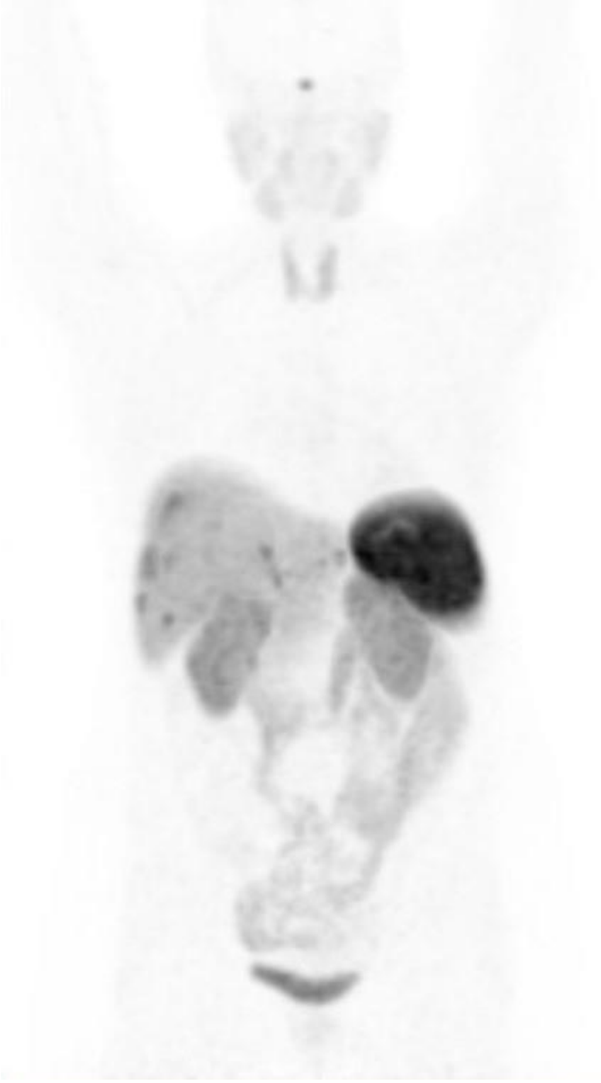
BASELINE PRRT1 DOTATATE PET 13/04/2016



post 4c PRRT1 DOTATATE PET 26/04/2017



20 months post PRRT1 DOTATATE PET 06/09/2018



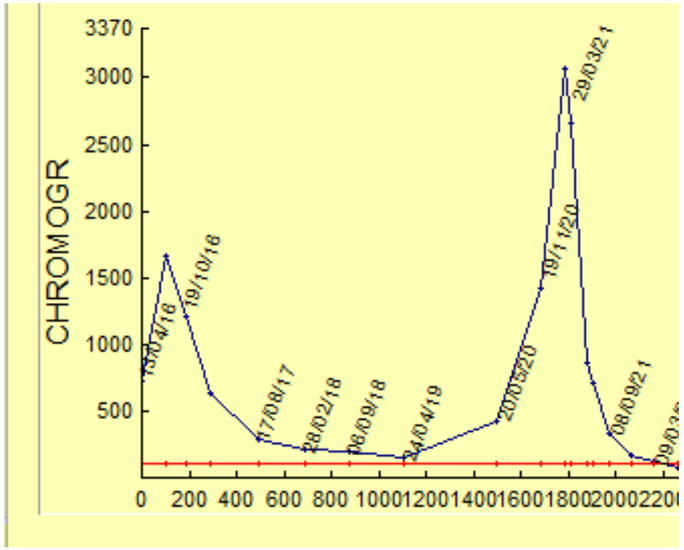
HORMONAL SYNDROMES: INSULINOMA

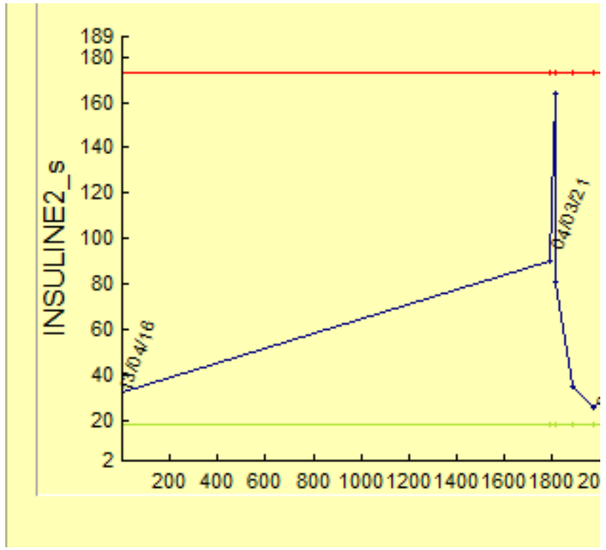
- 01/2021: reappearance of hypoglycemic episodes treated initially with snacks/sugar

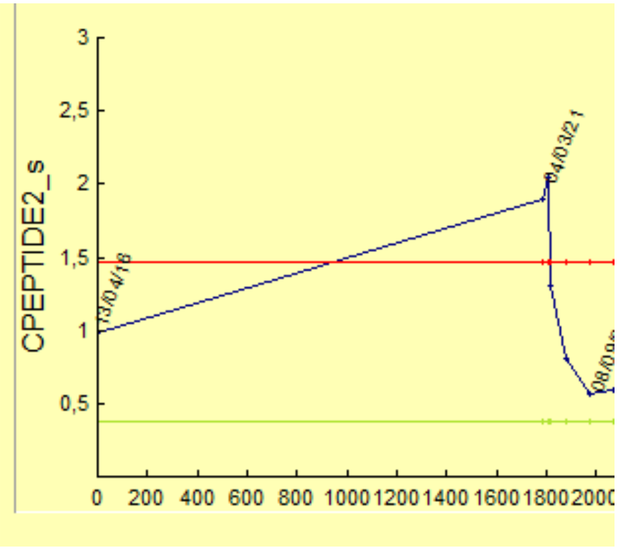
  > 02/2021: re-start diazoxide with initial response

  > 03/2021: MRI: SD, DOTATATE PET/CT: discreet increase of the SSTR-volume on pancreas and hepatic lesions.

  > 03/2021: → re-treatment with PRRT (03/2021, 06/2021)
  → complete clinical response
  → PR on MRI
  → PR on DOTATATE PET/CT
  → post-PRRT FU with MRI q3m and (again) close monitoring of glycemias (diary).
  → CgA evolution with PRRT2 Insuline and C-peptide evoliution with PRR2

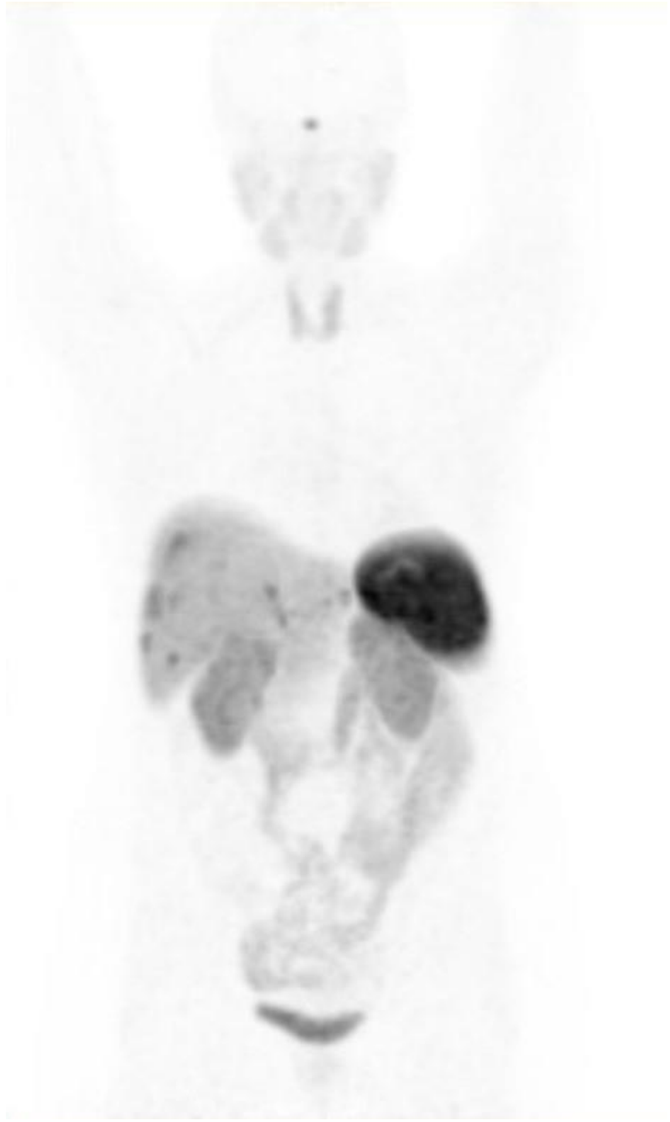




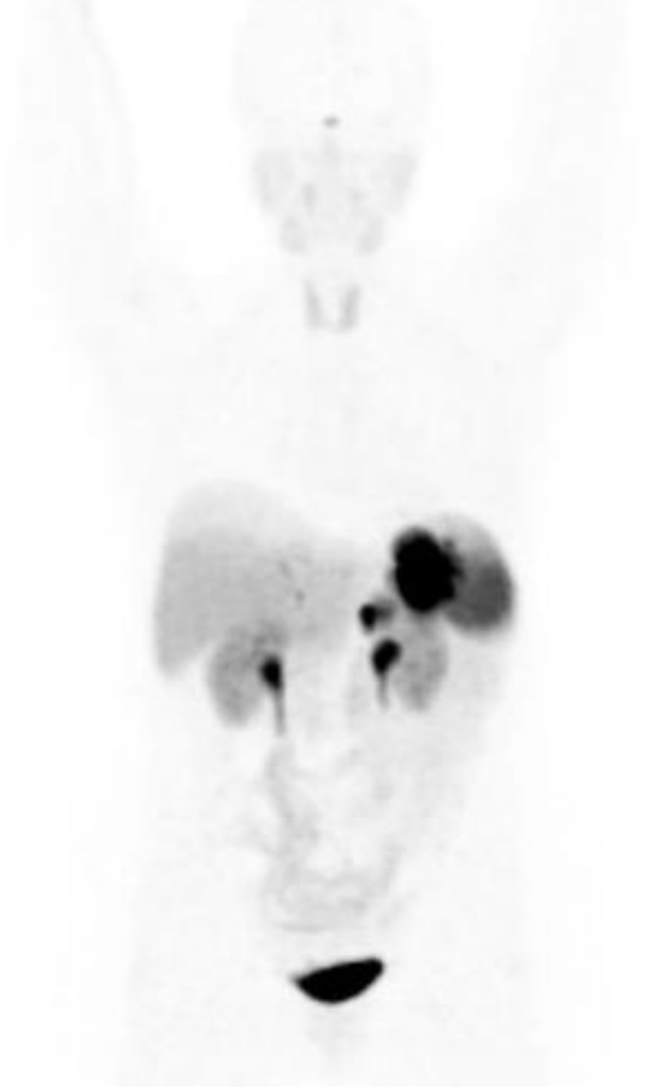


HORMONAL SYNDROMES: INSULINOMA

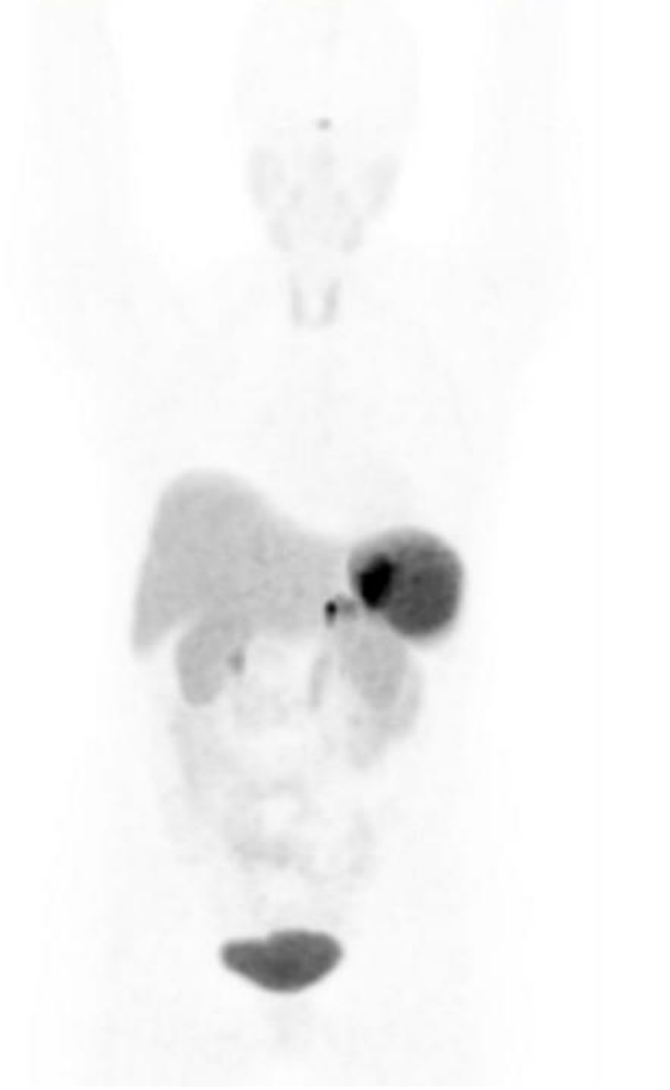
End of PRRT1 DOTATATE PET 2018



BASELINE PRRT2 DOTATATE PET 04/03/2021



post 2c PRRT2 DOTATATE PET 08/09/2021



HORMONAL SYNDROMES: INSULINOMA

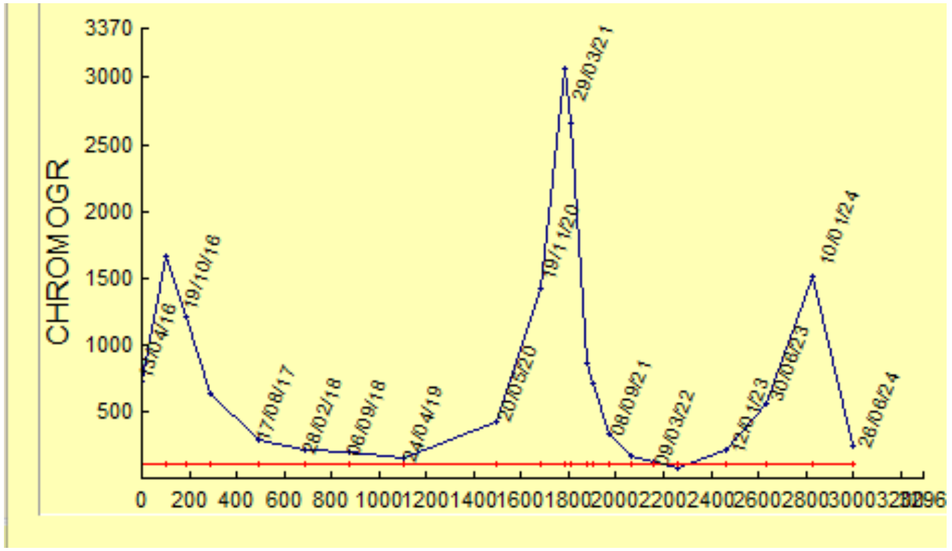
- 11/2023: reappearance of hypoglycemic episodes

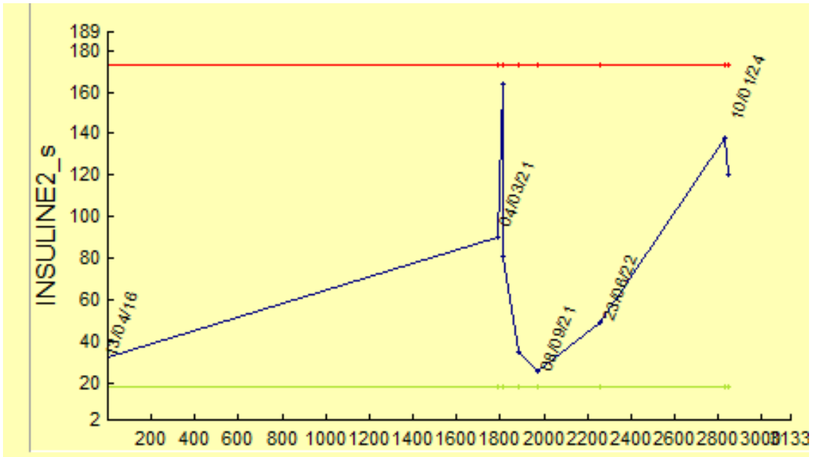
> 01/2024: MRI: increase of the volume of spleen lesion (SD elsewhere)
DOTATATE PET/CT: increase of the SSTR-volume on pancreas and spleen lesions.

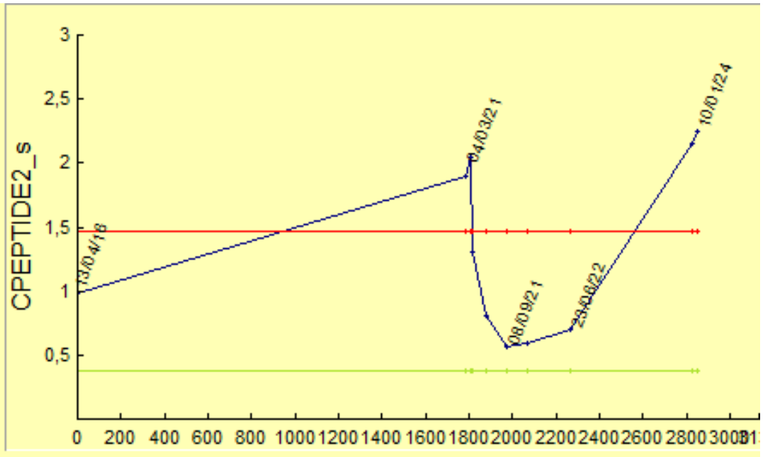
> 01/2024:
→ re-re-treatment with PRRT (01/2024 and 04/2024)
→ complete clinical response
→ PR on MRI
→ PR on DOTATATE PET/CT
→ CgA evolution with PRRT3

Insuline

and C-peptide evoliution with PRR3

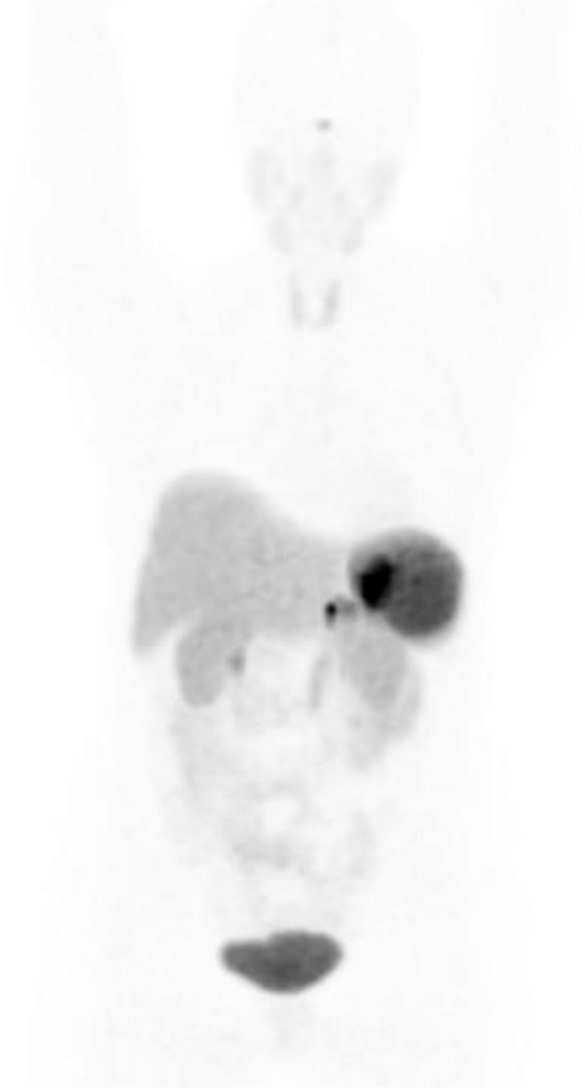






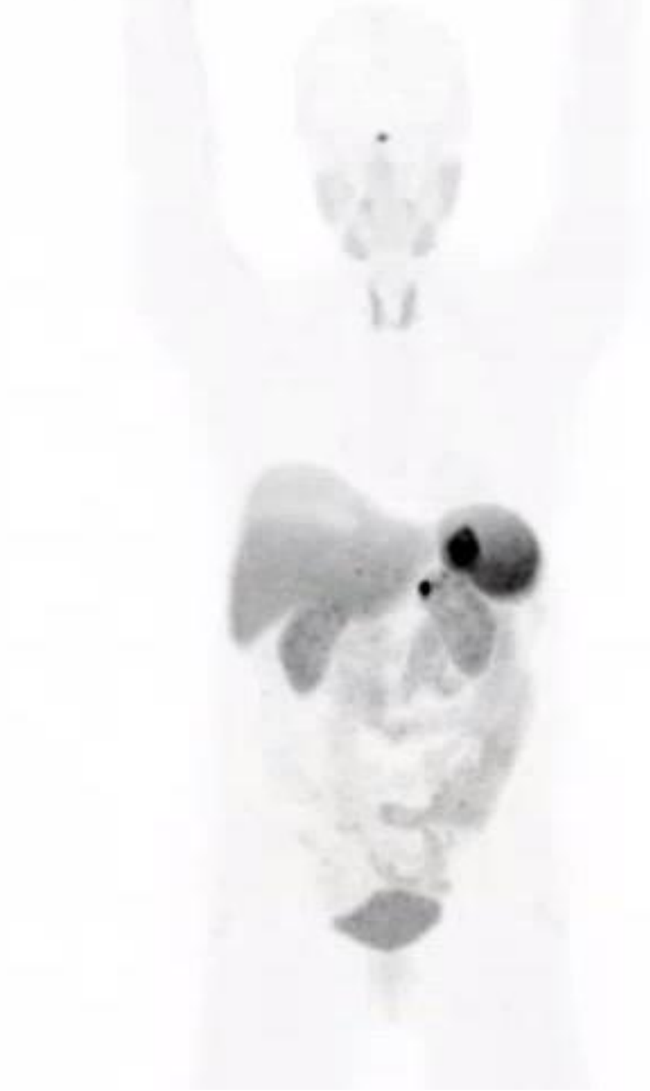
HORMONAL SYNDROMES: INSULINOMA

End of PRRT2 DOTATATE PET 08/09/2021



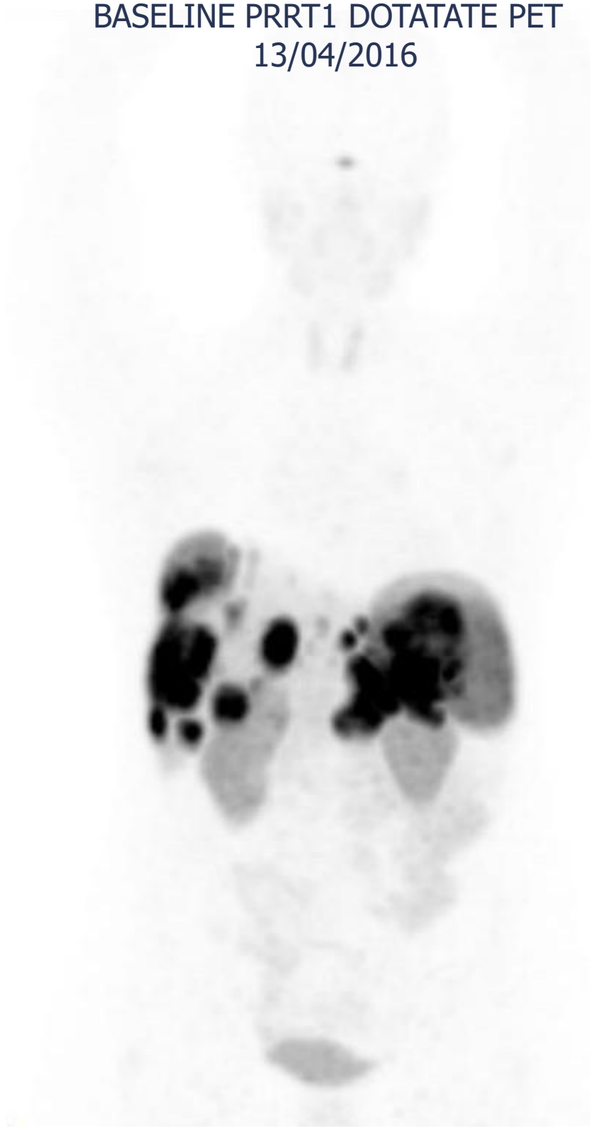
BASELINE PRRT3 DOTATATE PET 01/2024

post 2c PRRT3 DOTATATE PET 06/2024

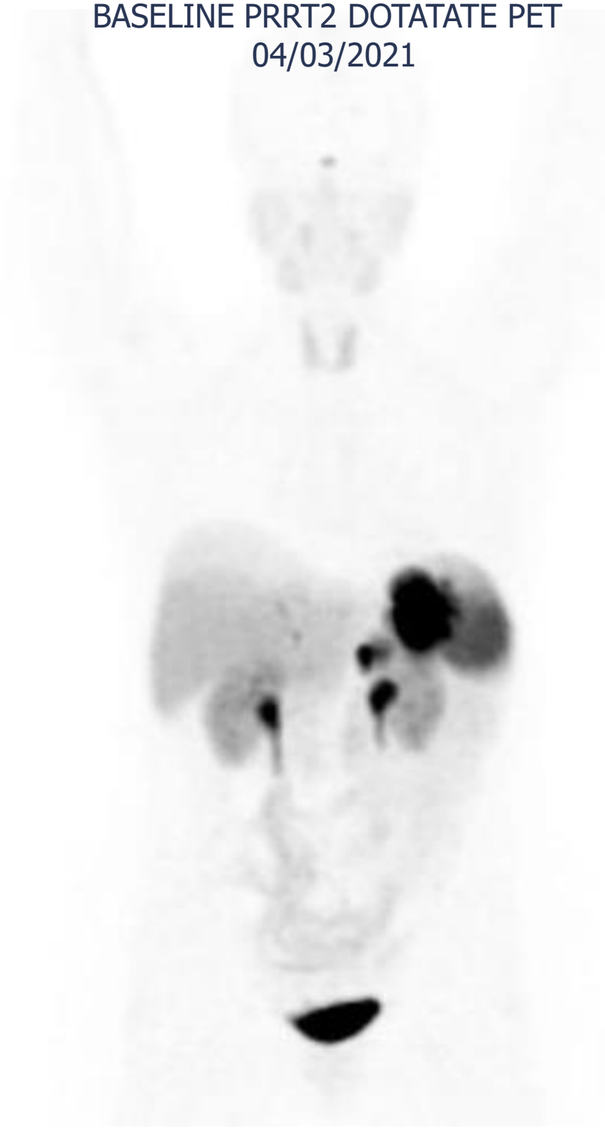


HORMONAL SYNDROMES: INSULINOMA

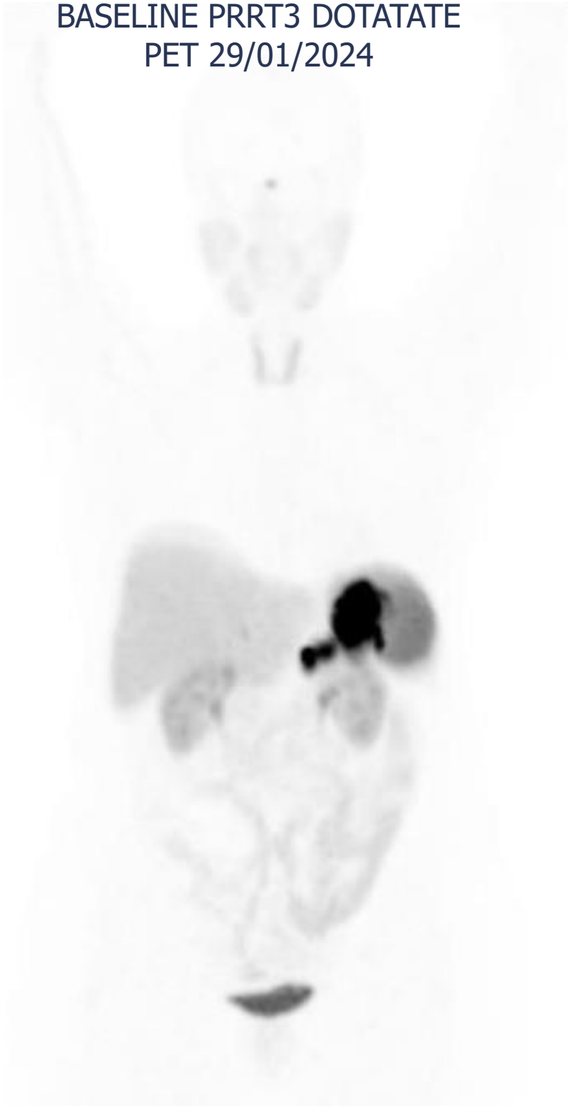
BASELINE PRRT1 DOTATATE PET
13/04/2016



BASELINE PRRT2 DOTATATE PET
04/03/2021



BASELINE PRRT3 DOTATATE
PET 29/01/2024



HORMONAL SYNDROMES: INSULINOMA → THM

- Insulinoma: the most common functional panNET → endogenous hyperinsulinemic hypoglycemia.
  PRRT: 85-95% symptom control (long-lasting), OS and PFS: probably lower than other NETs (associated hypoglycemia? tumor biology?).

- In progressive patients after an initial PRRT, re-treatment with ^{177}Lu-DOTATATE can be considered

*not PRRT continuation

- reTx data from meta analysis:
  → pooled mPFS: 13m, pooled DCR: 71%
  → survival benefit (mPFS rePRRT < mPFS initial PRRT)
  → safety profile: limited G3/4 tox, similar to initial PRRT.

- No prospective data so far, but 2 ongoing prospective trials (ReLUTH NCT04954820 and NET RETREAT NCT05773274).

Friebe l et al: *JNM* 2024, Veltroni A et al: *Eur J Endoc* 2020, Kos-Kudła B et al: *J Neuroendocrinology* 2023, Strosberg J et al: *Cancer Treat Rev* 2021