Evaluation of peptide receptor radionuclide therapy using ^{225}Ac-DOTATOC in a mouse model of liver metastases of pancreatic neuroendocrine tumor

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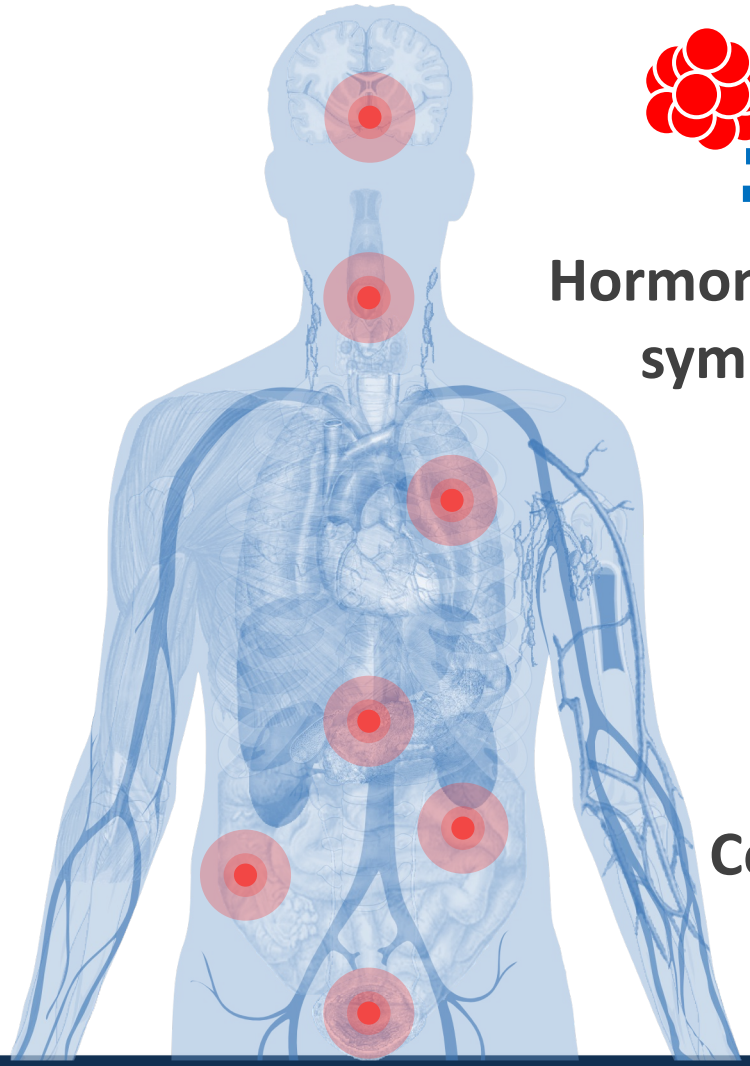
Introduction
Neuroendocrines tumors (NETs)

- Arising from cells of the neuroendocrine system
- Overexpressing somatostatin receptors
- More often located in the gastrointestinal tract or lungs
- Relatively indolent but heterogenous
- Can secrete hormones… or not



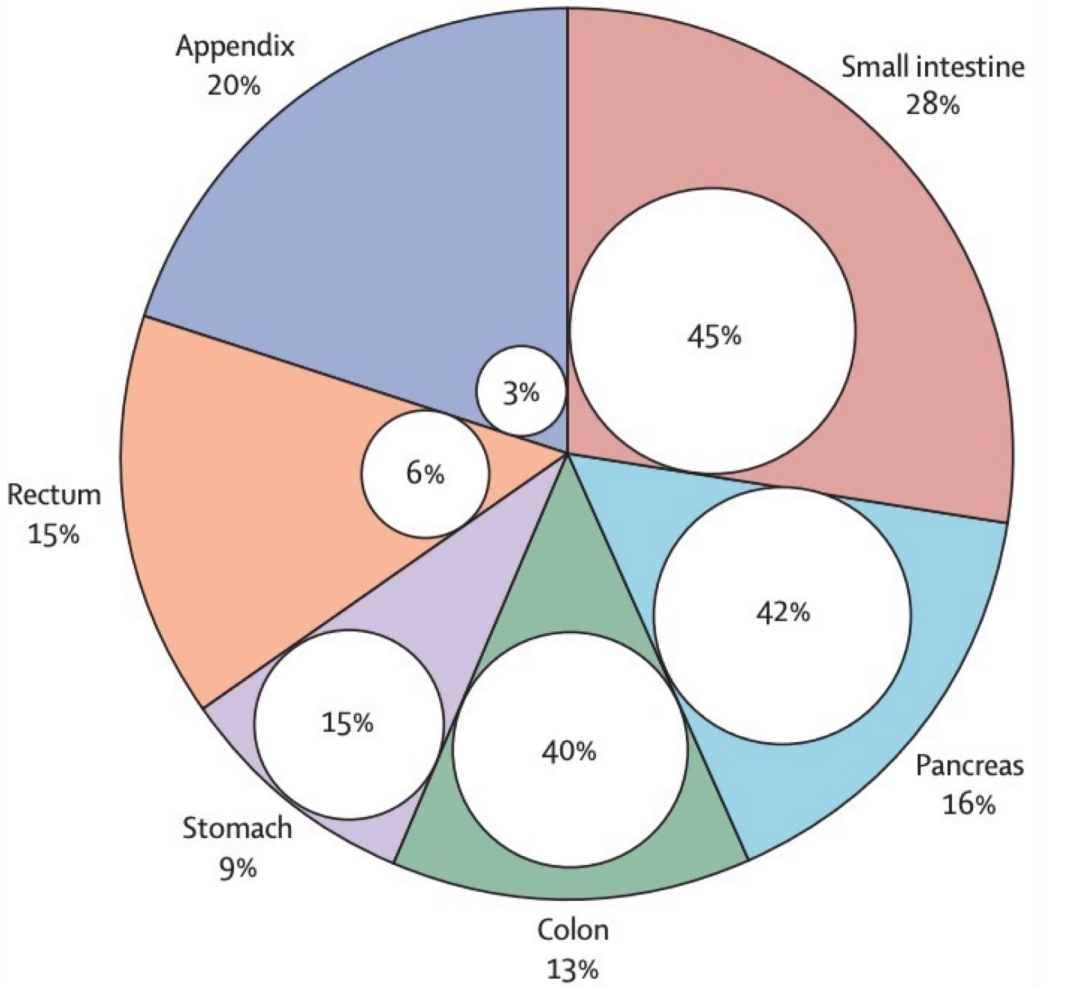
Hormone-related symptoms

Compressive symptoms

Modlin IM, et al. Evolution of the Diffuse Neuroendocrine System – Clear Cells and Cloudy Origins. Neuroendocrinology. 2006.
Dasari A, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017

Introduction
Neuroendocrines tumors (NETs)

- At diagnosis 65-95% of GEP NETs show liver metastasis
- Tumor burden in the liver : THE most crucial prognostic factor
- 5-year survival : 13-54% vs 75-99% without liver metastasis



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Introduction
Neuroendocrines tumors (NETs)

NETs overexpress SST receptor

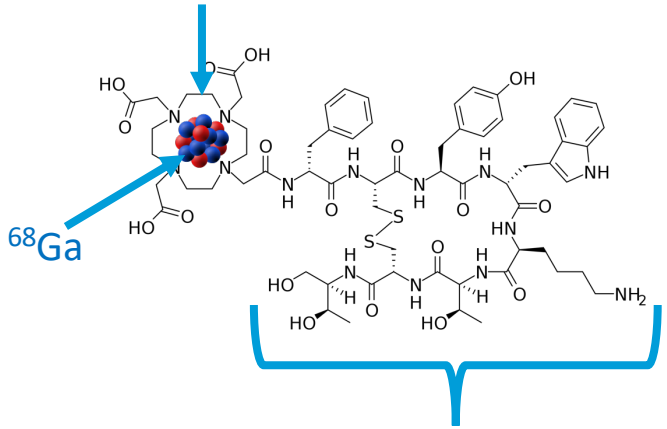
Molecular target : scintigraphy then PET/CT with ^{68}Ga-DOTATOC

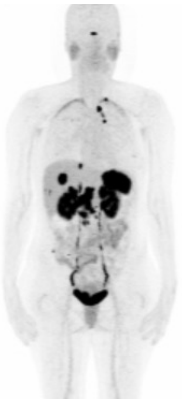
Development of a specific imaging :

- ✓ Confirm the well-differentiation
- ✓ Whole body imaging
- ✓ Prognosis
- ✓ Theranostic

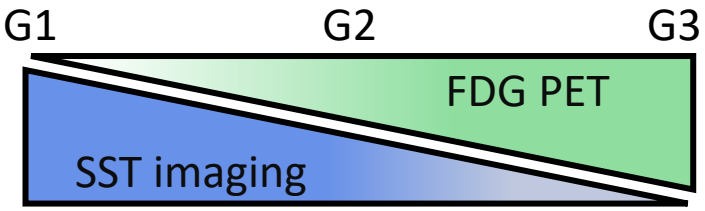
^{68}Ga-DOTATOC

Chelator : DOTA





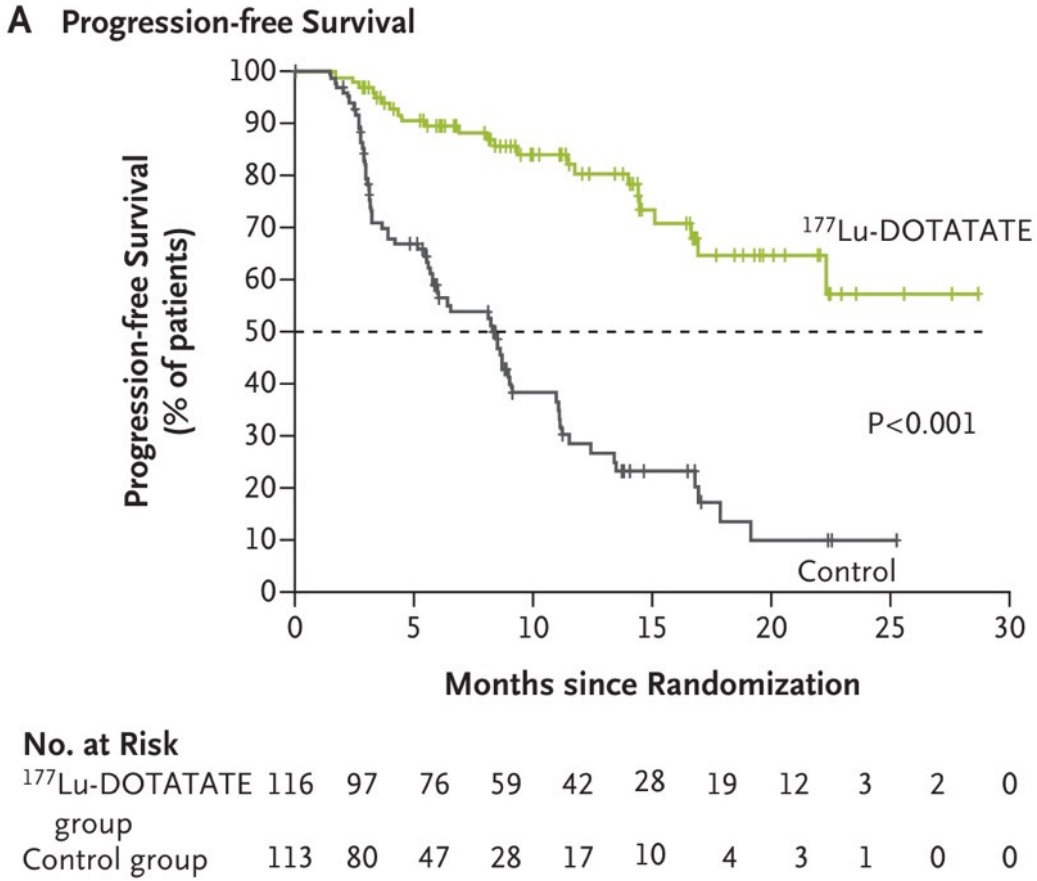
octreotide = TOC



Deppen SA, et al. J Nucl Med Off Publ Soc Nucl Med. 2016
Yang et al. Acta Radiol Stock Swed, 2014
Graham et al. J Nucl Med, 2017.

Introduction
Current therapy

- Wait and watch, SSA, TKI, chemotherapy
- ^{177}Lu Somatostatin analogues radiolabeled with β- emitters
- 2017 NETTER-1
- 2018 FDA and EMA approvals



Pavel M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2020.
Strosberg J, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017.

Introduction
PRRT

- Good clinical efficacy and improved quality of life
- Refractory to β- therapy
- Mainly achieved disease stability
- 3% Myelodysplastic syndromes / Leukemia

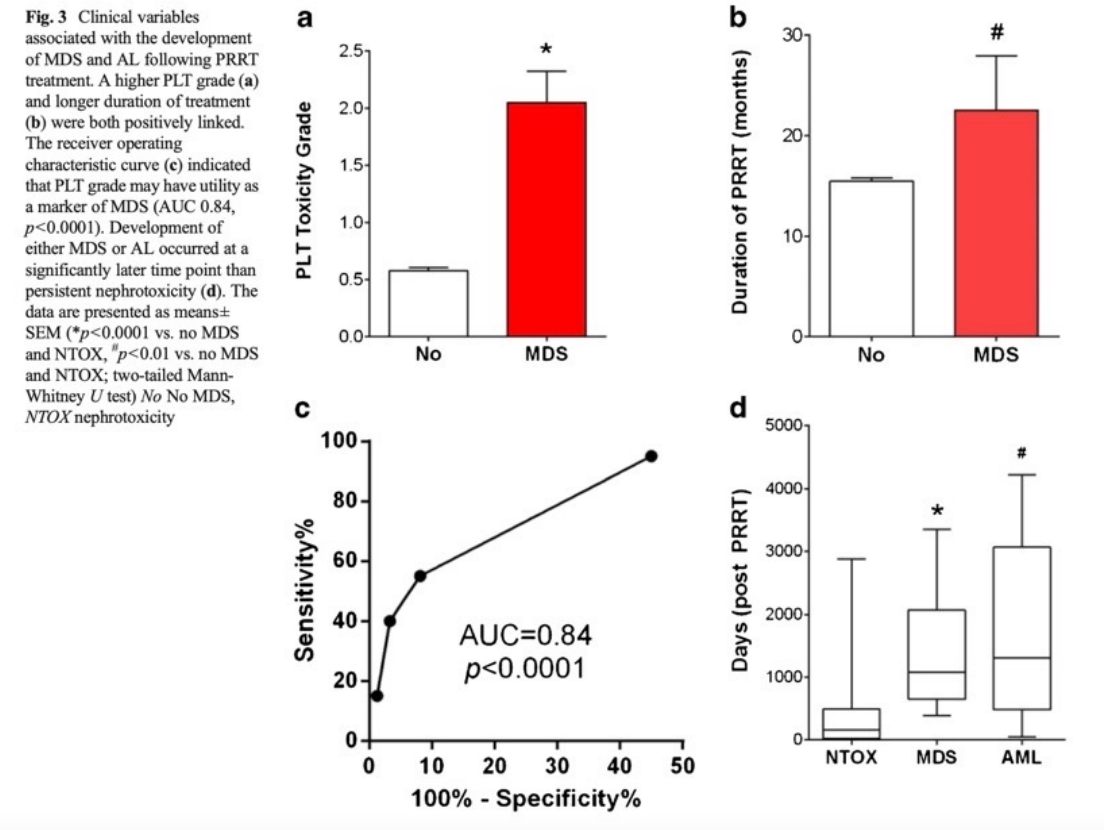
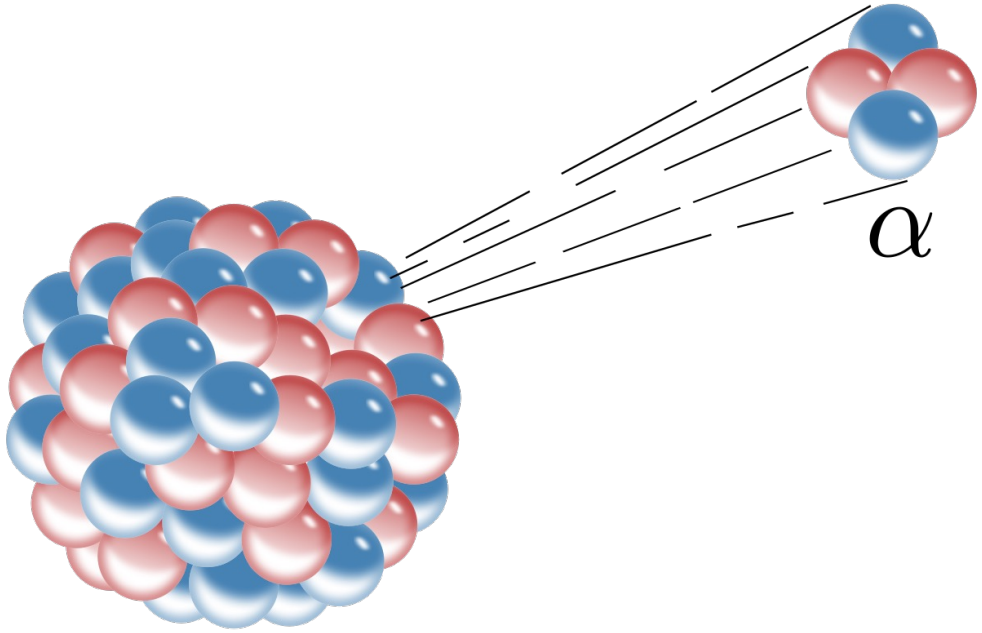


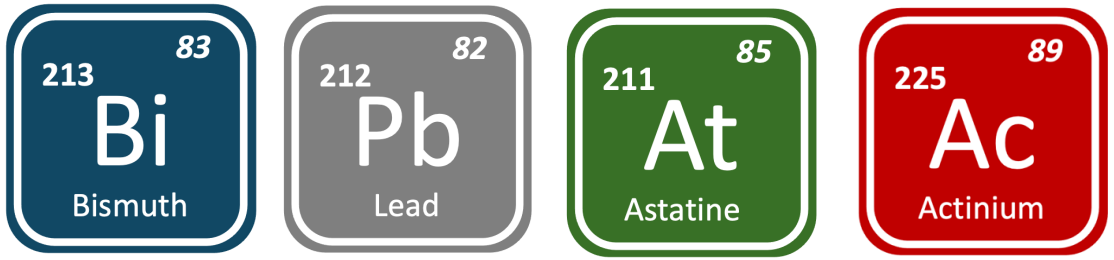
Fig. 3 Clinical variables associated with the development of MDS and AL following PRRT treatment. A higher PLT grade (**a**) and longer duration of treatment (**b**) were both positively linked. The receiver operating characteristic curve (**c**) indicated that PLT grade may have utility as a marker of MDS (AUC 0.84, $p<0.0001$). Development of either MDS or AL occurred at a significantly later time point than persistent nephrotoxicity (**d**). The data are presented as means± SEM (*$p<0.0001$ vs. no MDS and NTOX, $^{\#}p<0.01$ vs. no MDS and NTOX; two-tailed Mann-Whitney *U* test) *No* No MDS, *NTOX* nephrotoxicity

Camus B, et al. Indications of Peptide Receptor Radionuclide Therapy (PRRT) in Gastroenteropancreatic and Pulmonary Neuroendocrine Tumors. Clin Med. 2021

Bodei L, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015

Introduction
α-emitters





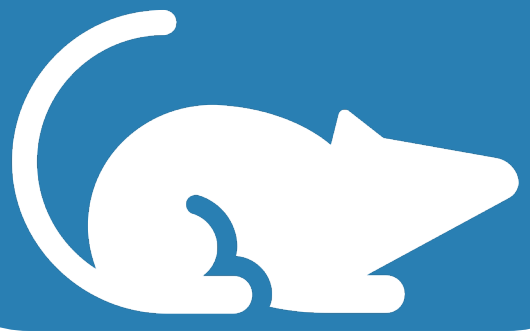
- Higher energy and short range in tissue
- Ionization and DNA double strain breaks
- Higher toxicity to tumoral cells
- Minimize damage to healthy tissue

Targeted Alpha Therapy Working Group, et al. (2018). JAMA Oncol. 4, 1765–1772
Makvandi M, Dupis E, Engle JW, et al. Alpha-Emitters and Targeted Alpha Therapy in Oncology: from Basic Science to Clinical Investigations. Target Oncol. 2018;13:189–203

Introduction
Objectives

1

To develop a mouse model of pNET liver metastases by intraportal injection of AR42J cells



2

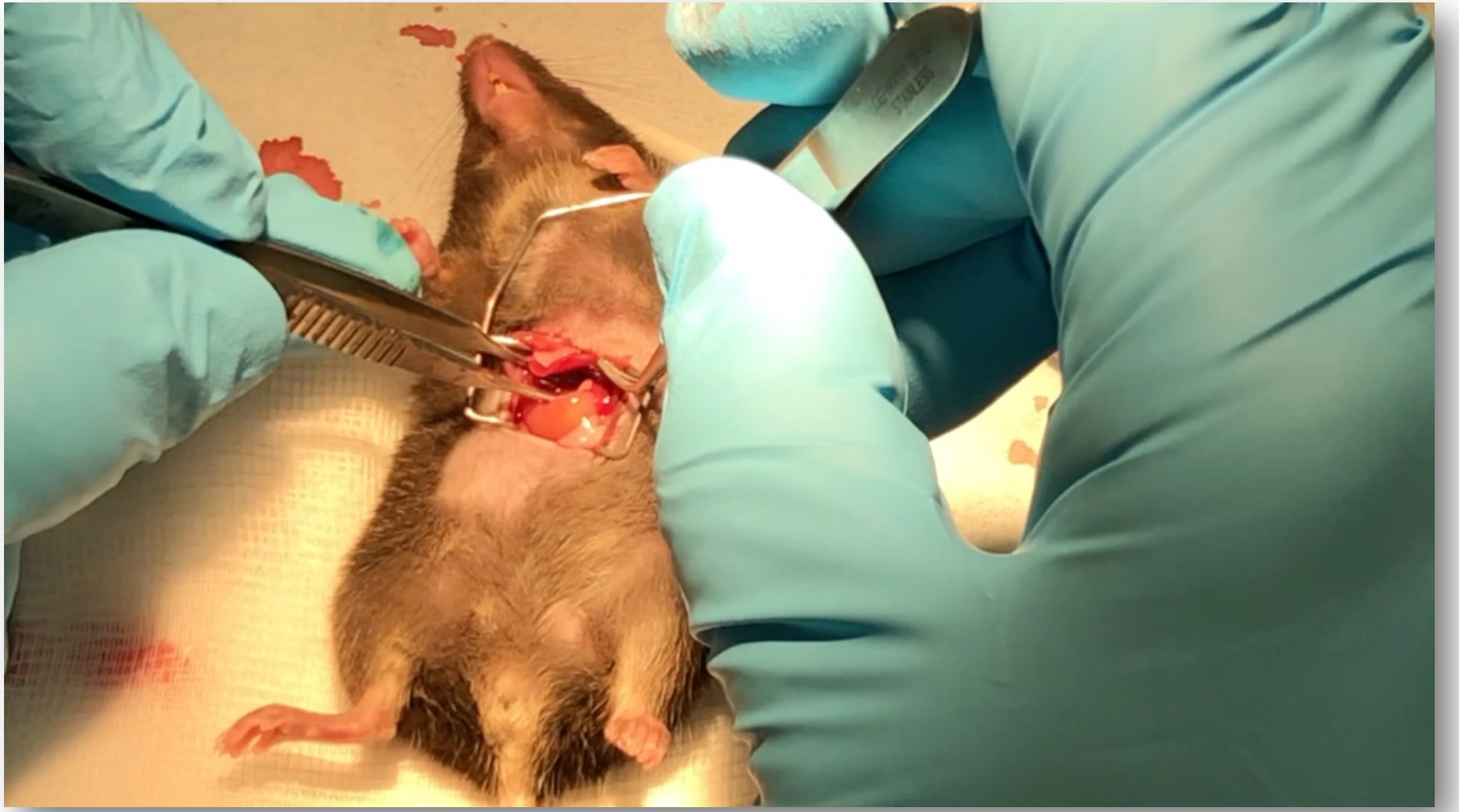
Phenotypic characterization with PET/MR and MRI follow-up

3

Treatment with ^{225}Ac-DOTATOC

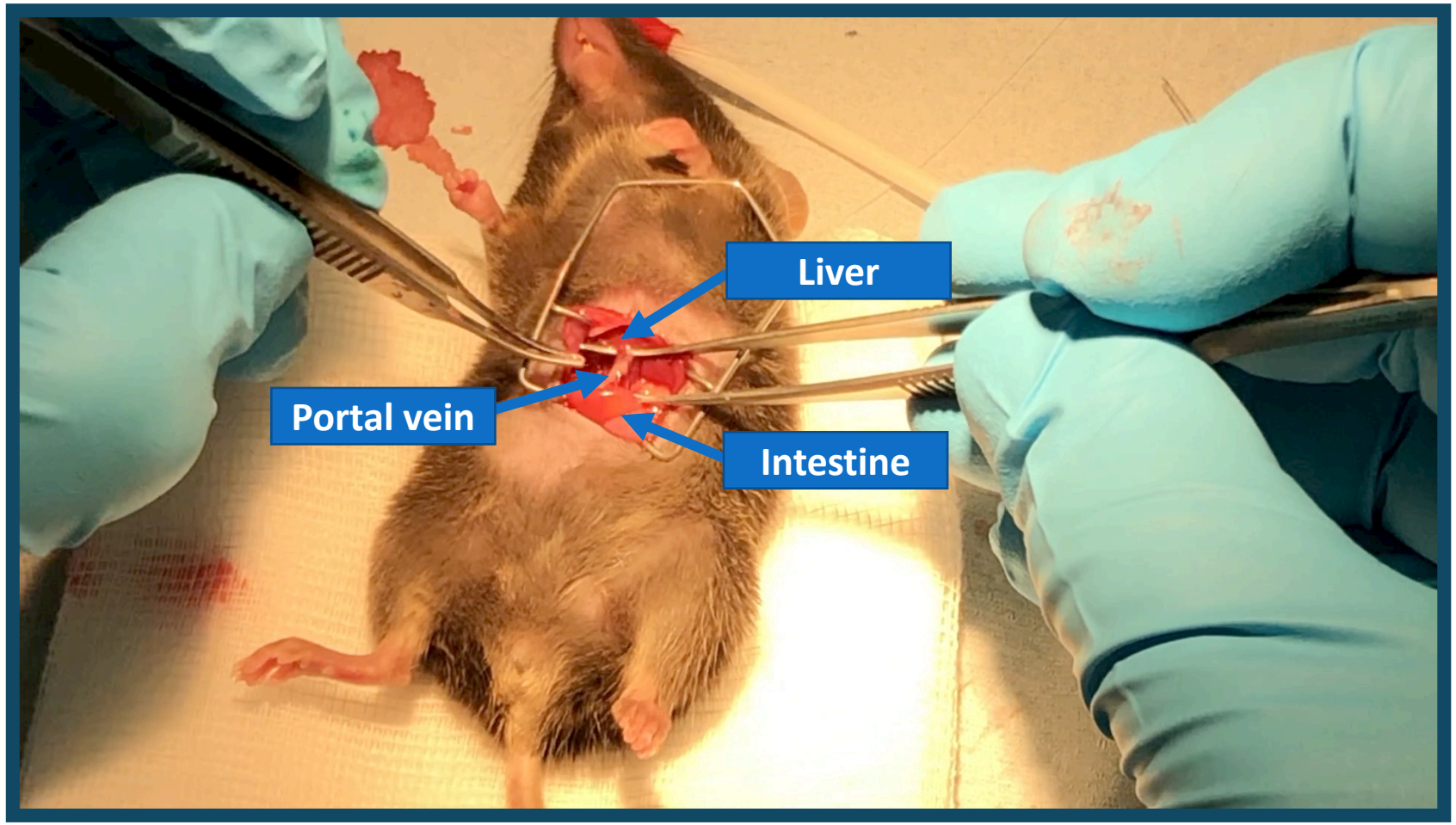
Methods

Surgical procedure

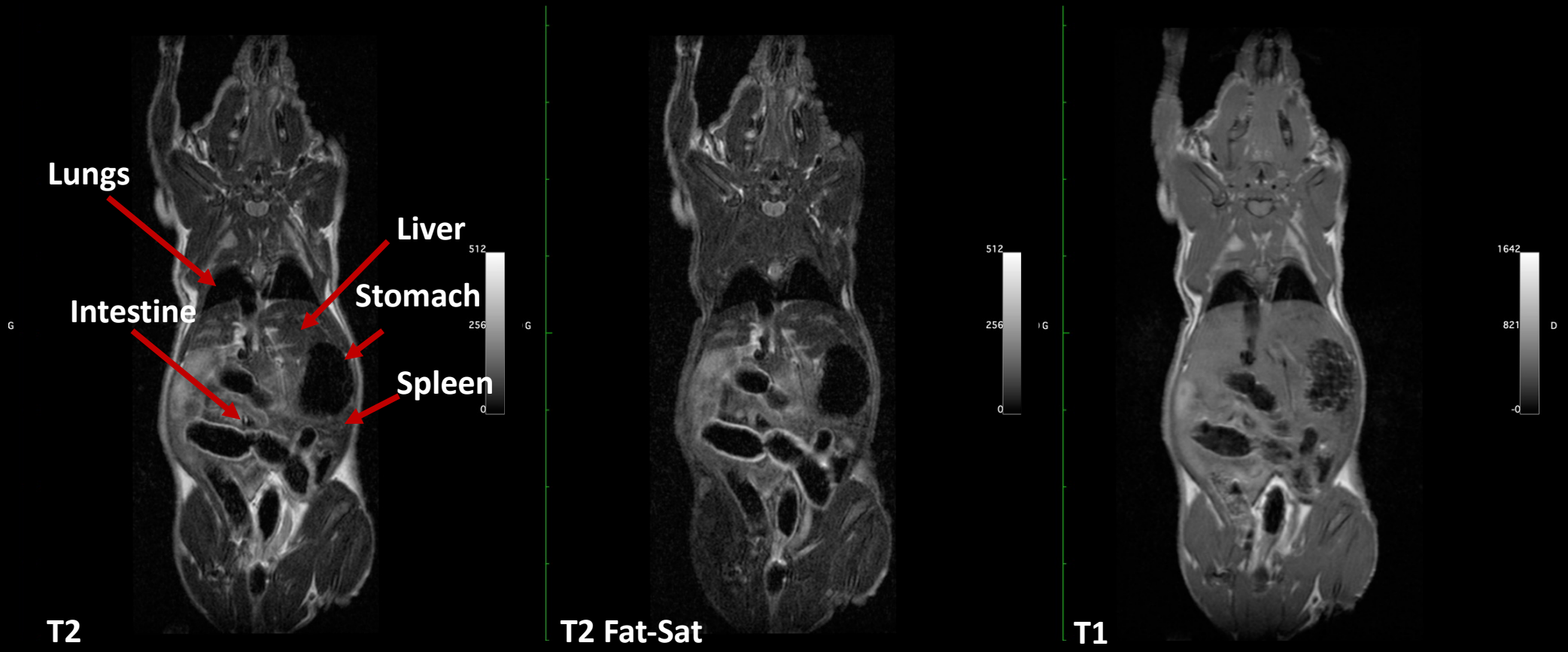


Methods

Surgical procedure



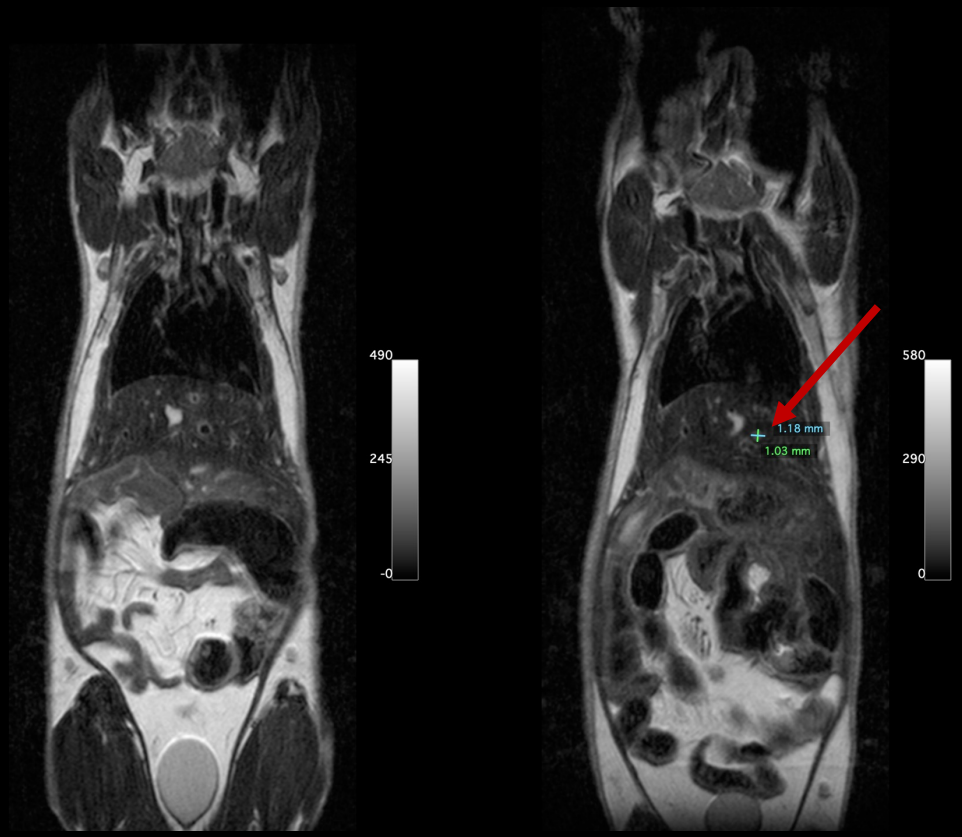
Results
MRI


Lungs
Liver
Intestine
Stomach
Spleen
512
256
0
T2
T2 Fat-Sat
512
256
0
T1
1642
821
-0

Results

MRI follow-up

D11 **D15**

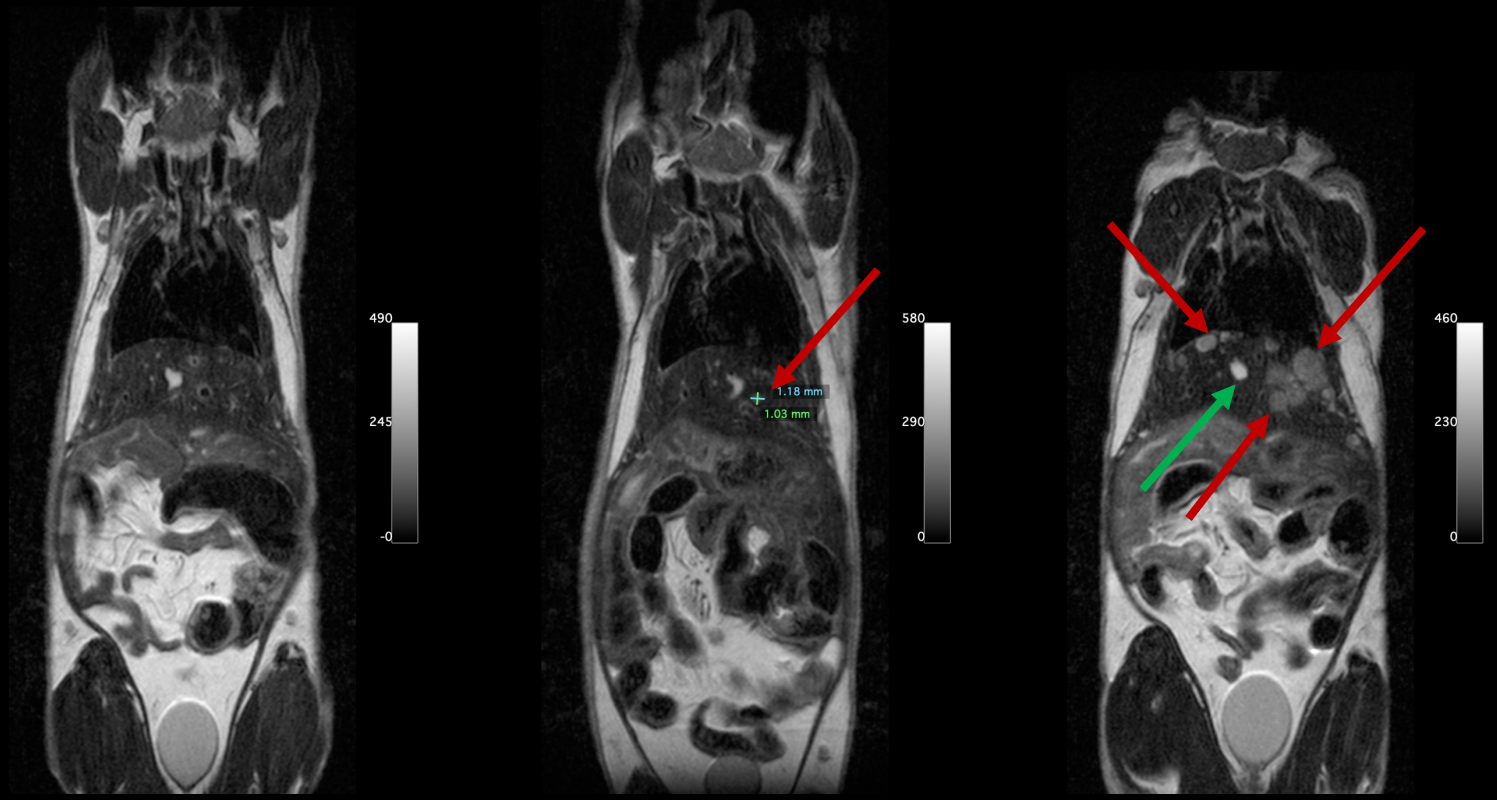


Lugat, A., et al. Survival impact of [225Ac]Ac-DOTATOC alpha-therapy in a preclinical model of pancreatic neuroendocrine tumor liver micrometastases. Eur J Nucl Med Mol Imaging (2024)

Results

MRI follow-up

D11 **D15** **D23**



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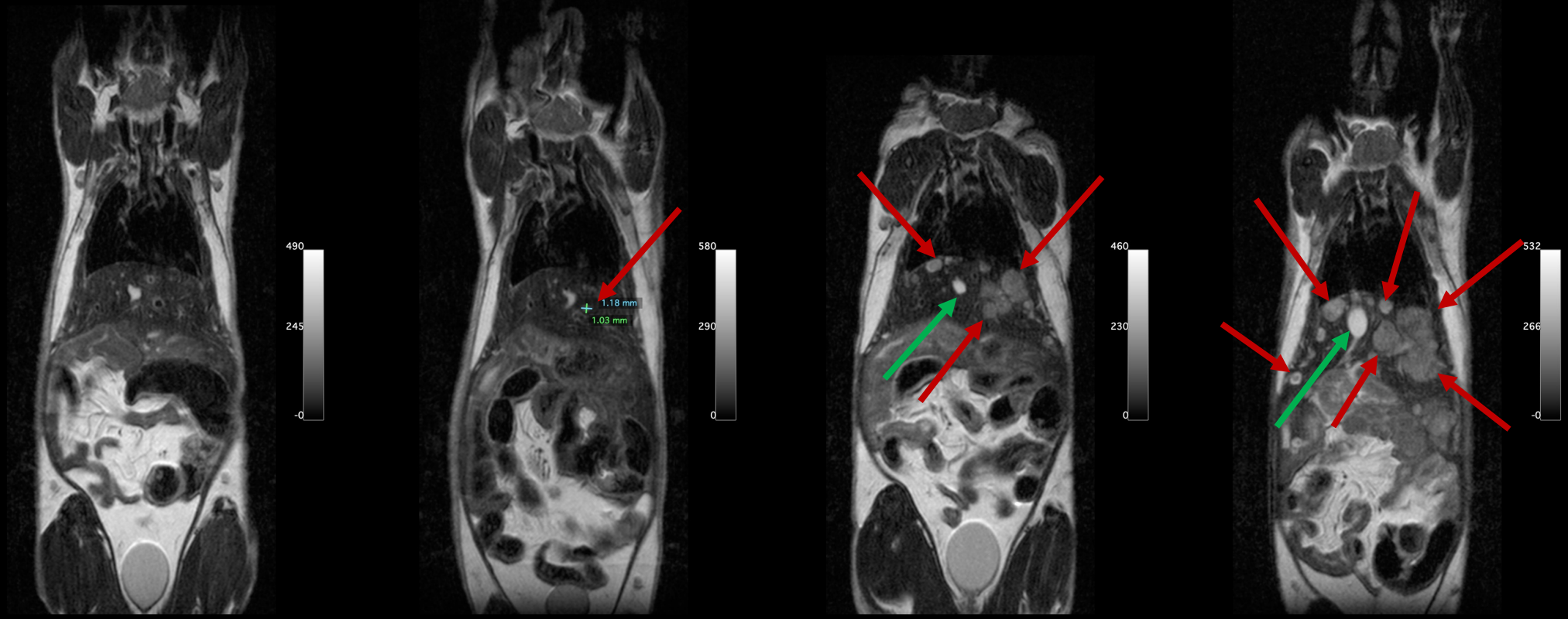
Results

MRI follow-up

D11 **D15** **D23** **D25**



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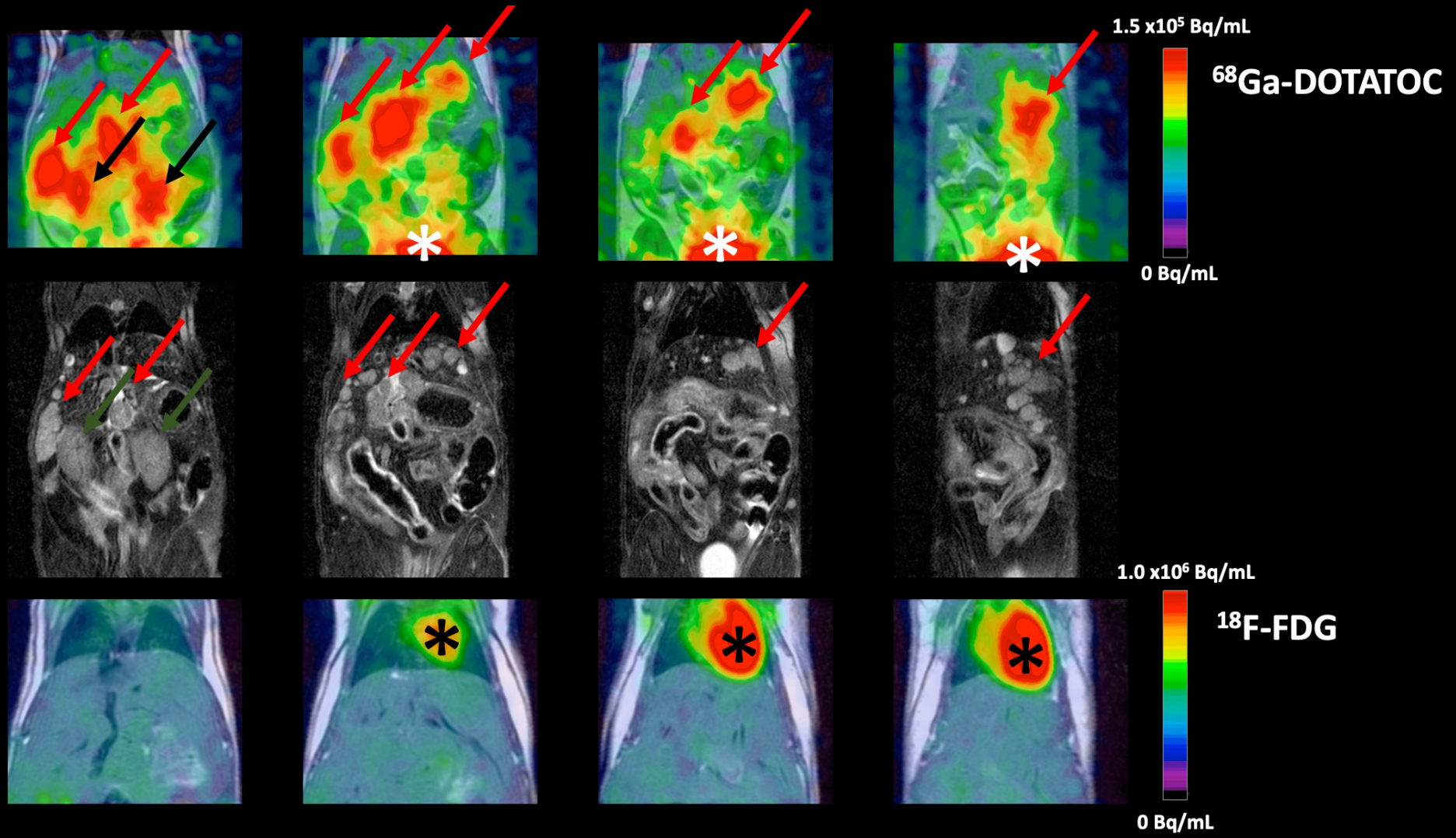
Results

Phenotypic characterization with PET/MR



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Methods

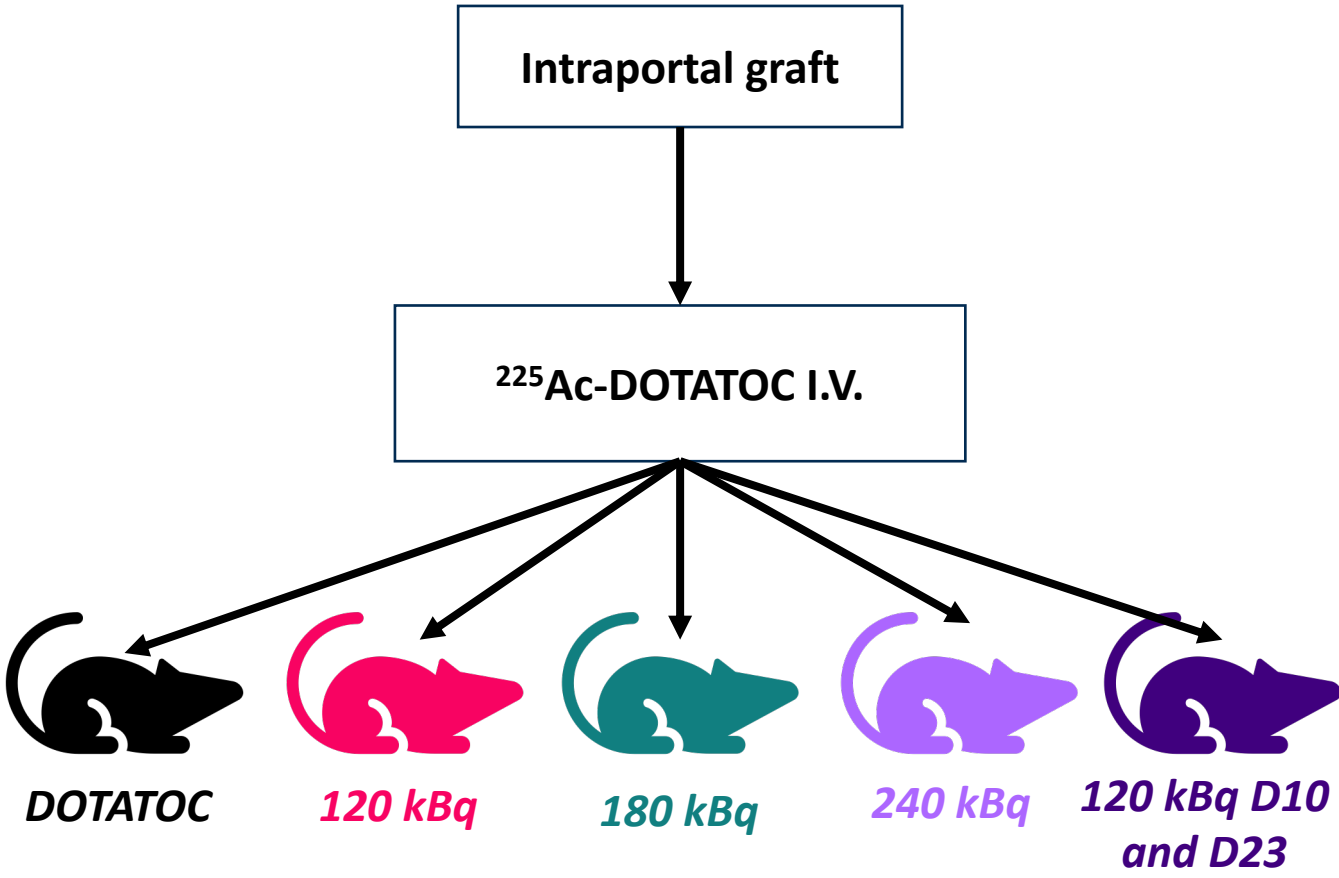
α-particle therapy with ^{225}Ac-DOTATOC

40 mice

DOTATOC, 120, 180, 240 kBq I.V. D10 et 120 kBq I.V. D10 and D23

Clinical and biological follow-up

MRI follow-up



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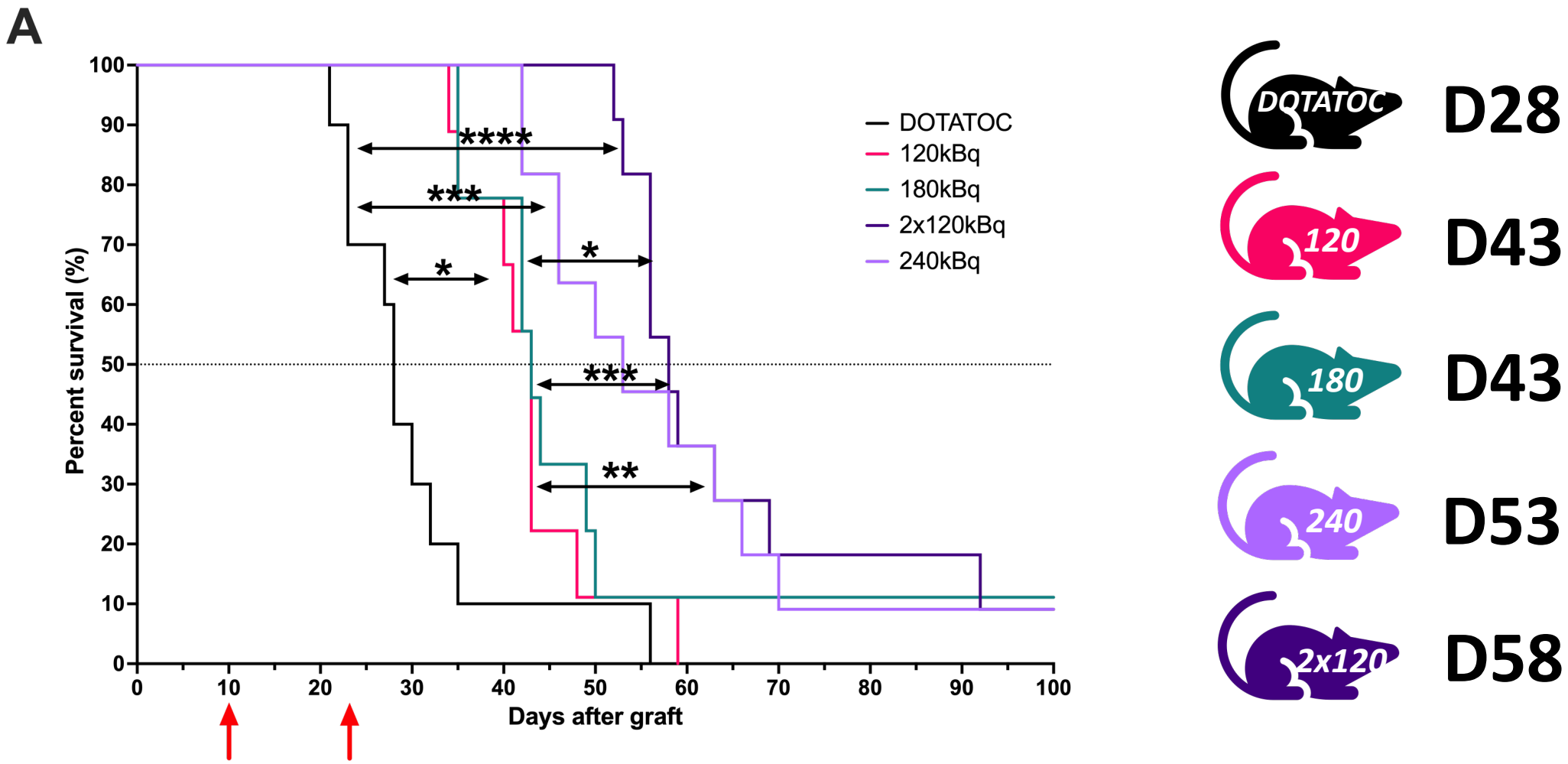
α-particle therapy with ^{225}Ac-DOTATOC

Overall survival



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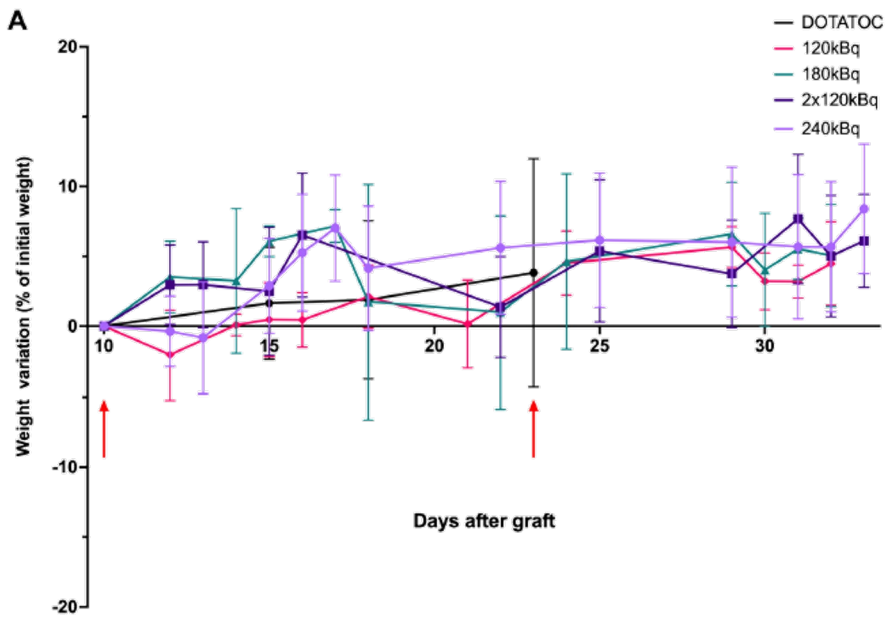
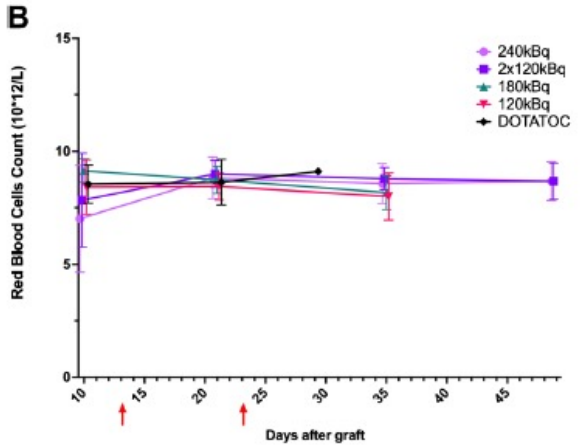
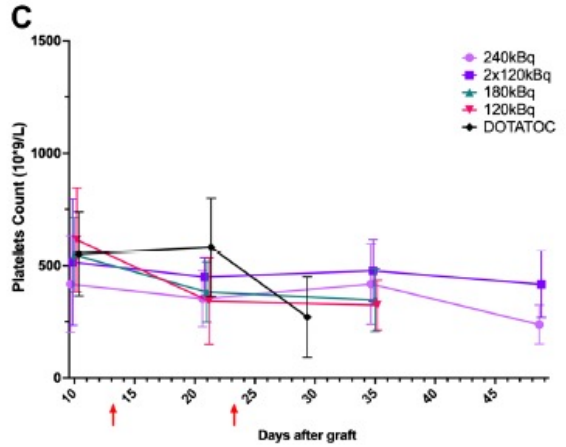
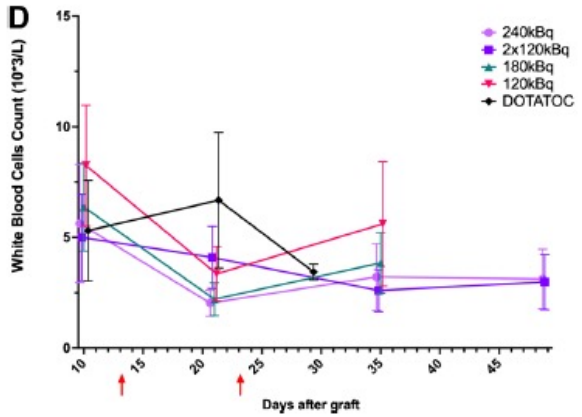
α-particle therapy with ^{225}Ac-DOTATOC

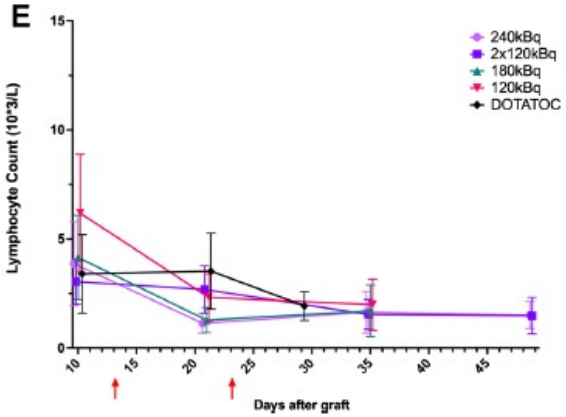
Hematotoxicity











Efficacy without toxicity up to 240 kBq

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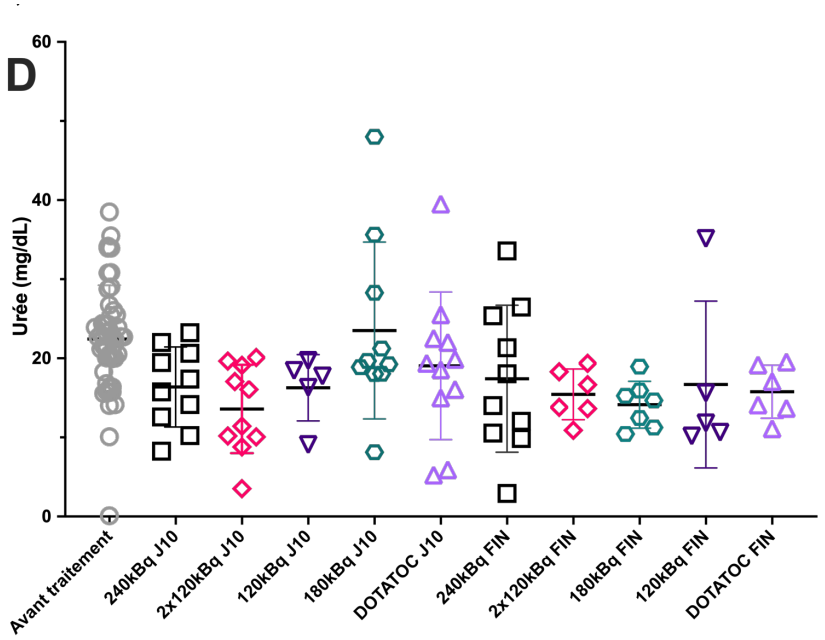
α-particle therapy with ^{225}Ac-DOTATOC

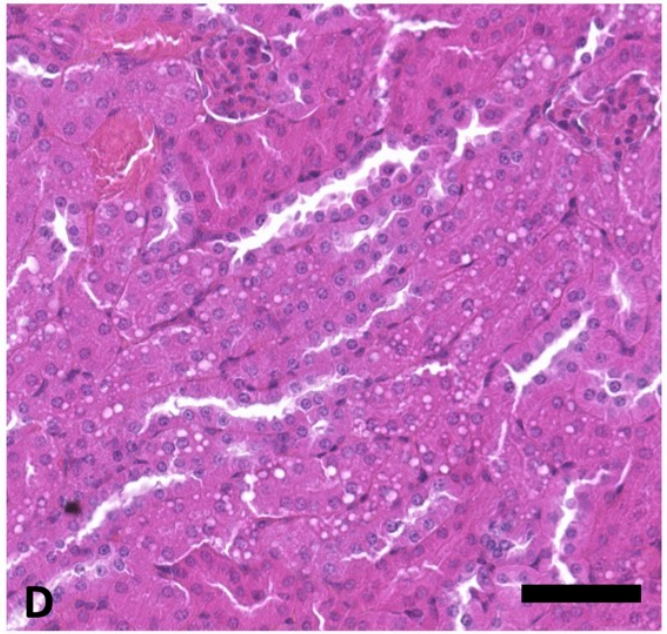
Kidney toxicity

Efficacy without toxicity up to 240 kBq

Biology



Pathology



Dosimetry

Organes/Tissu	Dose moyenne absorbée (Gy/MBq) ± ET	Dose moyenne absorbée (Gy) ± ET pour une activité de 240kBq
Sang	2,4 ± 0,3	0,58 ± 0,07
Tumeur	61,9 ± 4,8	14,86 ± 1,15
Foie	51 ± 10,1	12,24 ± 2,42
Reins	47,1 ± 4,4	11,3 ± 1,06
Intestin	4,1 ± 0,5	0,98 ± 0,12
Poumons	15,2 ± 21,8	3,65 ± 5,23
Muscle	1,7 ± 0,2	0,41 ± 0,05
Rate	13,5 ± 9,0	3,24 ± 0,22
Peau	3,8 ± 0,3	0,91 ± 0,07
Cerveau	1,2 ± 0,2	0,29 ± 0,05
Cœur	4,1 ± 0,4	0,98 ± 0,1
Os plat	33,9 ± 9,9	8,14 ± 2,38
Estomac	10,9 ± 1,4	2,62 ± 0,37
Pancréas	6,2 ± 0,4	1,49 ± 0,01
Glandes salivaires	3 ± 0,3	0,72 ± 0,07

ET : écart-type

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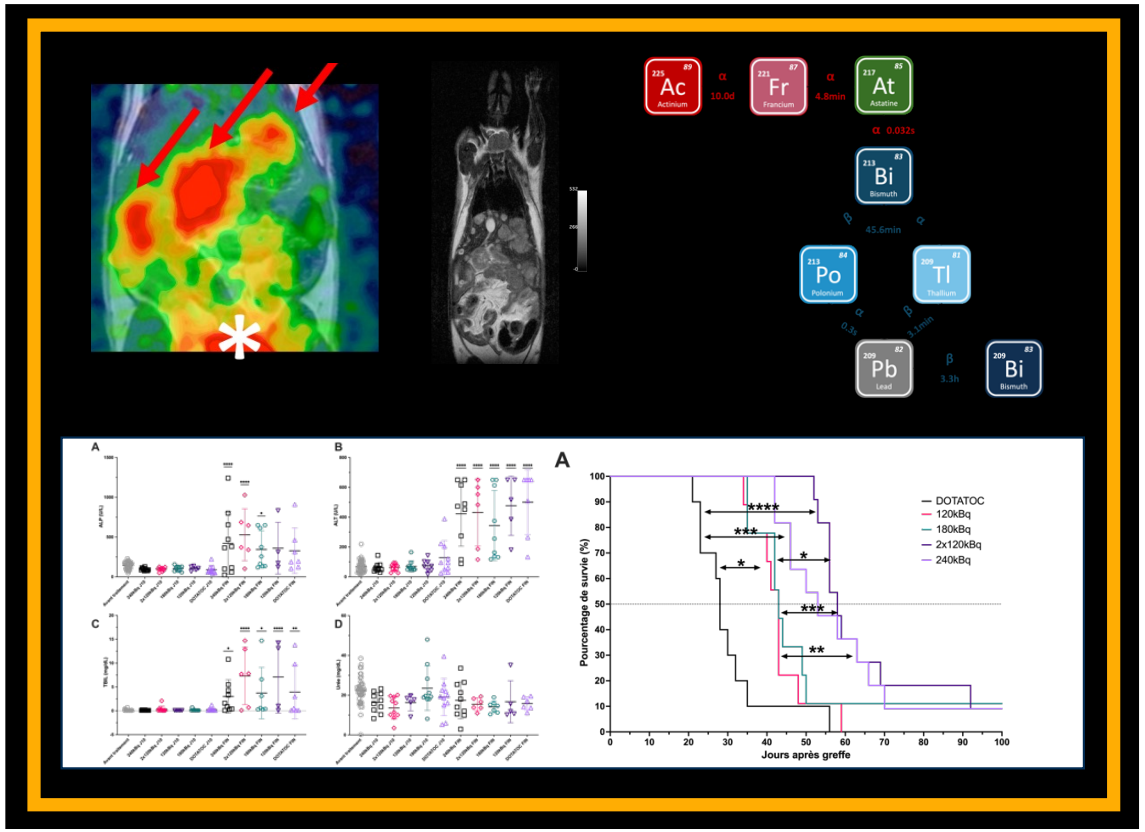
General discussion

Conclusion

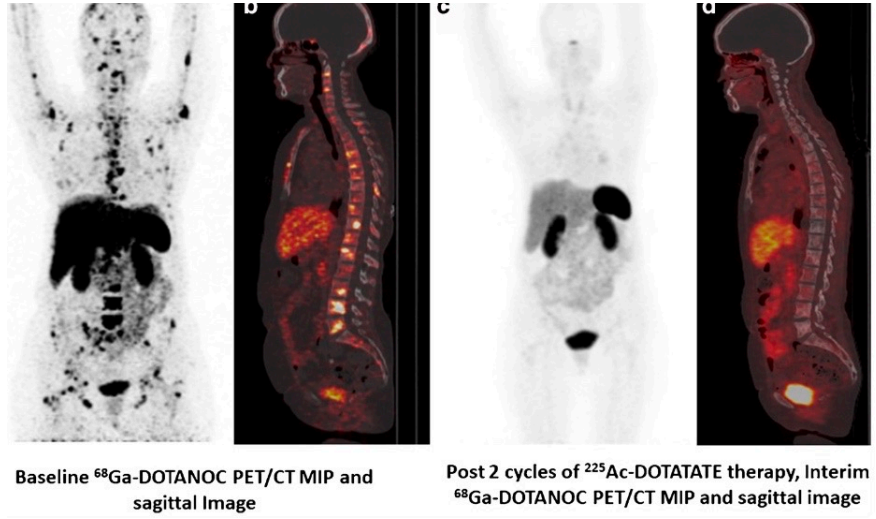
- First mouse model of well-differentiated pNET liver metastases
- High ^{68}Ga-DOTATOC uptake and no ^{18}F-FDG uptake
- Limited reproduction of natural course and tumoral heterogeneity
- Efficacy of ^{225}Ac-DOTATOC therapy with only transient blood toxicity and no liver or kidney toxicity

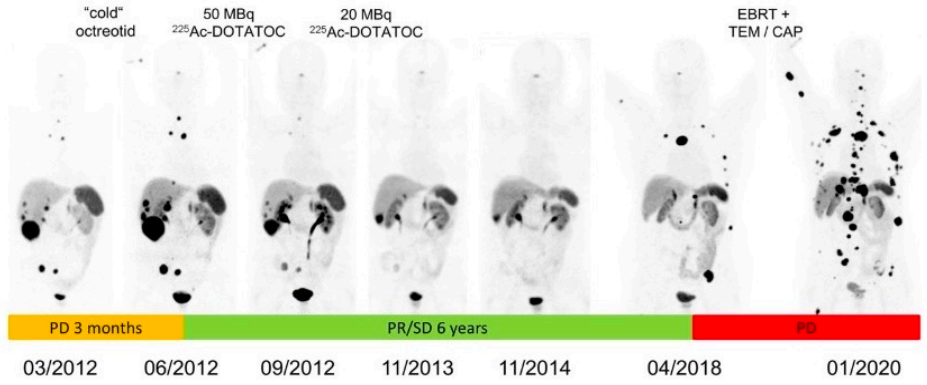


Discussion générale

Perspective

- Phase I/II with ^{225}Ac-SSA are already ongoing
- But … ^{225}Ac shortage
- Developpement of ^{211}At therapy
- Association PRRT and chemo/targeted therapies
- To study high grade neuroendocrine tumors with liver metastasis





Ballal S, et al. Eur J Nucl Med Mol Imaging. 2019.
Kratochwil C, et al. Eur J Nucl Med Mol Imaging. 2021

CRCI²NA

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