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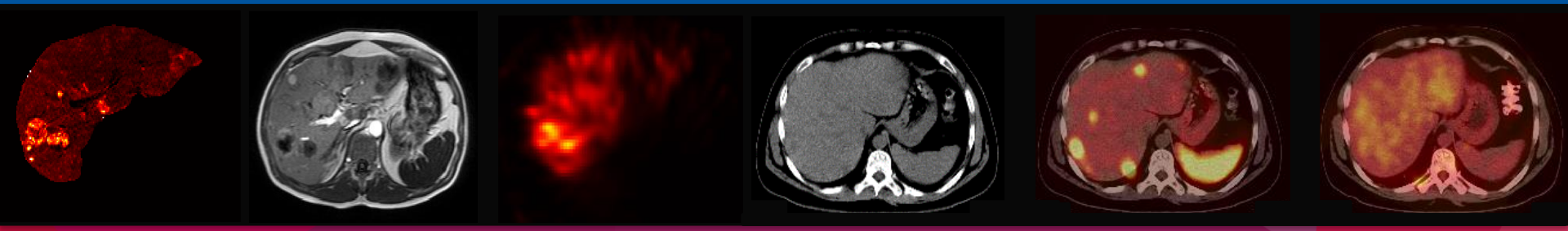
Current and Future Perspectives of Radiometabolic Treatments in Neuroendocrine Tumours

Arthur J.A.T. Braat, MD

ENETS Center of Excellence, UMC Utrecht and NKI-AVL



Department of Radiology and Nuclear Medicine,
University Medical Center Utrecht, The Netherlands

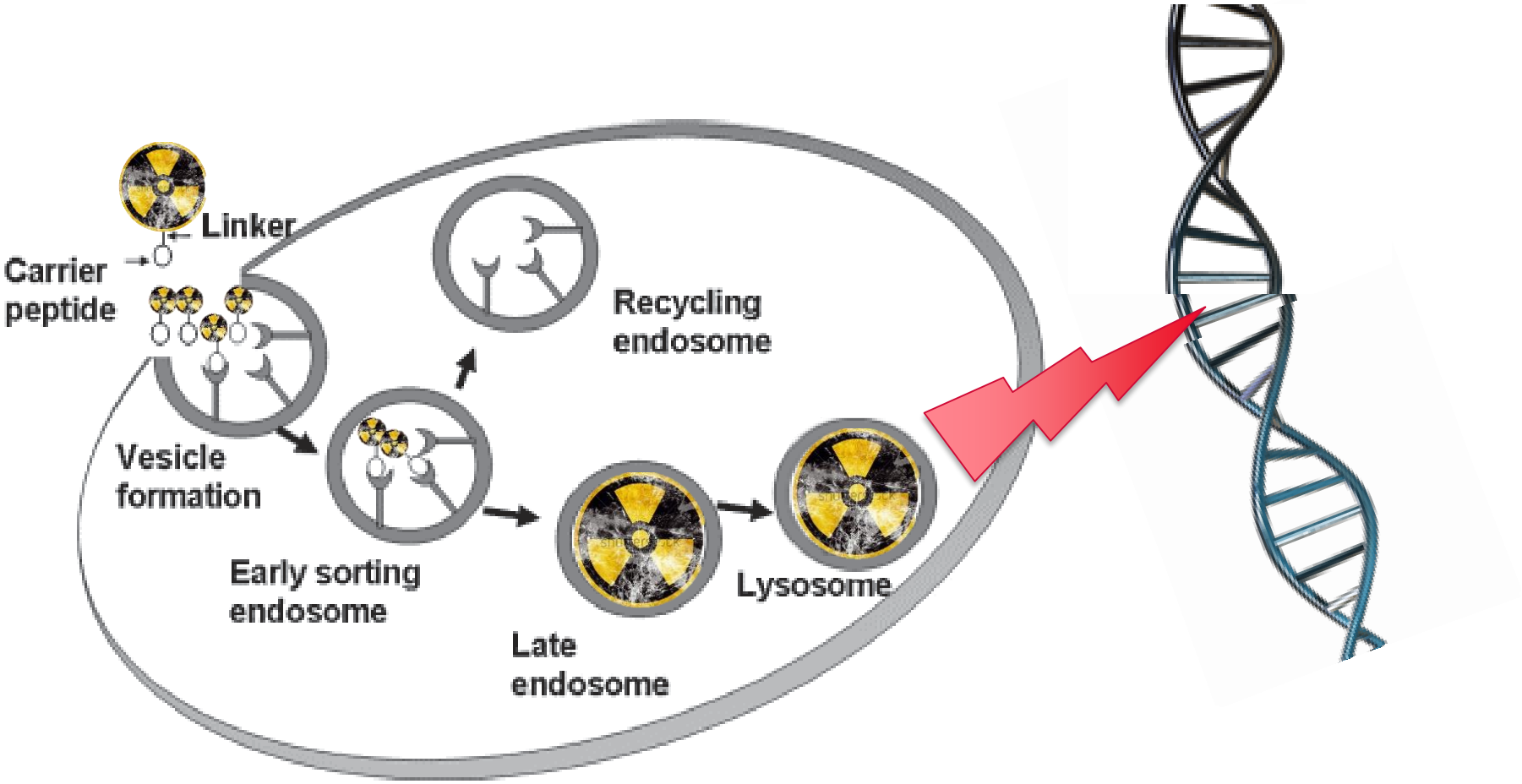
Disclosures

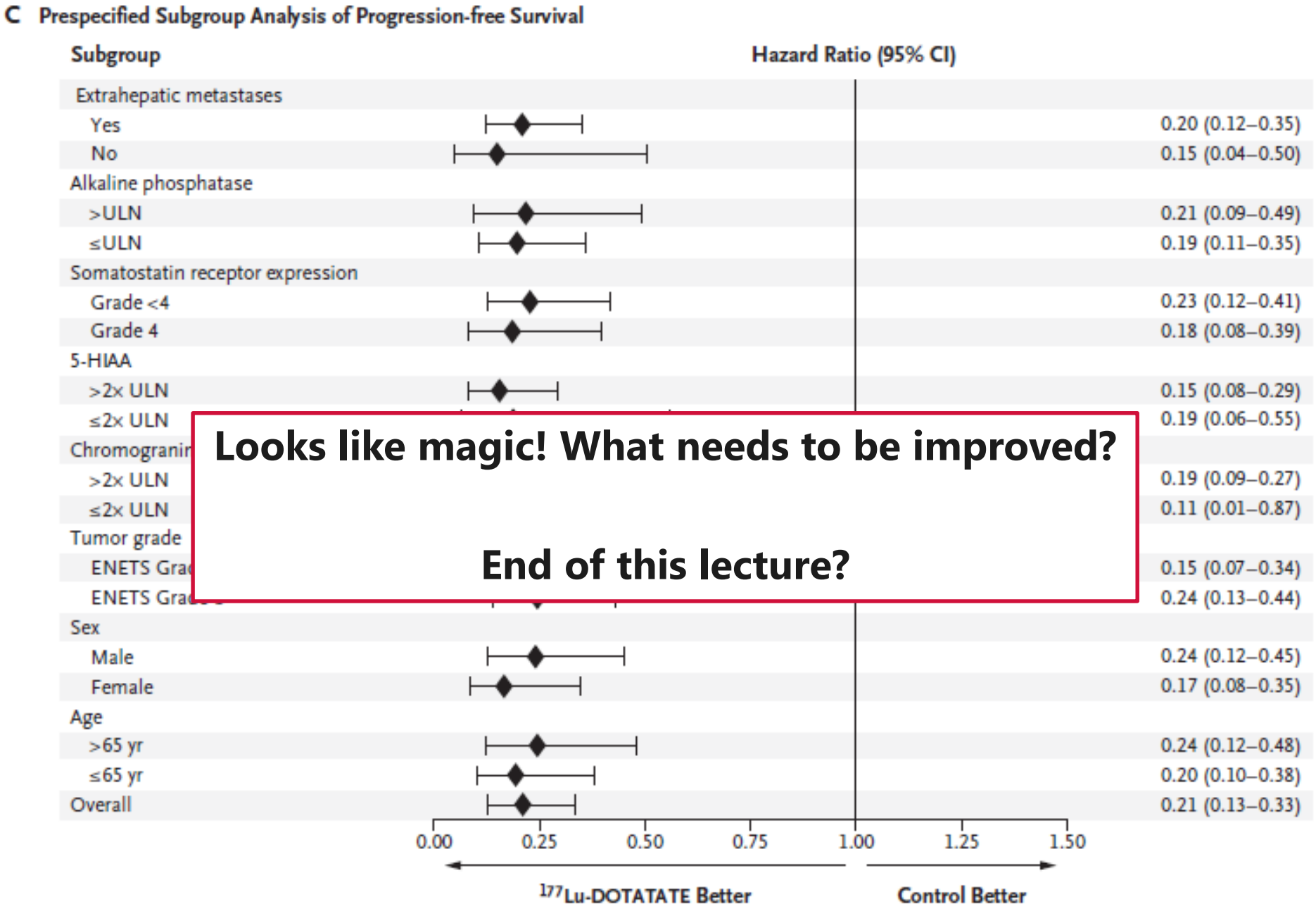
Speaker for Sirtex Medical, BTG, Terumo, Quirem Medical

Radionuclide therapies

Image guided: *see what your treating*

Trapping: Complex transport




C Prespecified Subgroup Analysis of Progression-free Survival
Subgroup
Hazard Ratio (95% CI)
Extrahepatic metastases
Yes
0.20 (0.12–0.35)
No
0.15 (0.04–0.50)
Alkaline phosphatase
>ULN
0.21 (0.09–0.49)
≤ULN
0.19 (0.11–0.35)
Somatostatin receptor expression
Grade <4
0.23 (0.12–0.41)
Grade 4
0.18 (0.08–0.39)
5-HIAA
>2× ULN
0.15 (0.08–0.29)
≤2× ULN
0.19 (0.06–0.55)
Chromogranin
>2× ULN
0.19 (0.09–0.27)
≤2× ULN
0.11 (0.01–0.87)
Tumor grade
ENETS Grad
0.15 (0.07–0.34)
ENETS Grad
0.24 (0.13–0.44)
Sex
Male
0.24 (0.12–0.45)
Female
0.17 (0.08–0.35)
Age
>65 yr
0.24 (0.12–0.48)
≤65 yr
0.20 (0.10–0.38)
Overall
0.21 (0.13–0.33)
0.00
0.25
0.50
0.75
1.00
1.25
1.50
177Lu-DOTATATE Better
Control Better
Looks like magic! What needs to be improved?
End of this lecture?

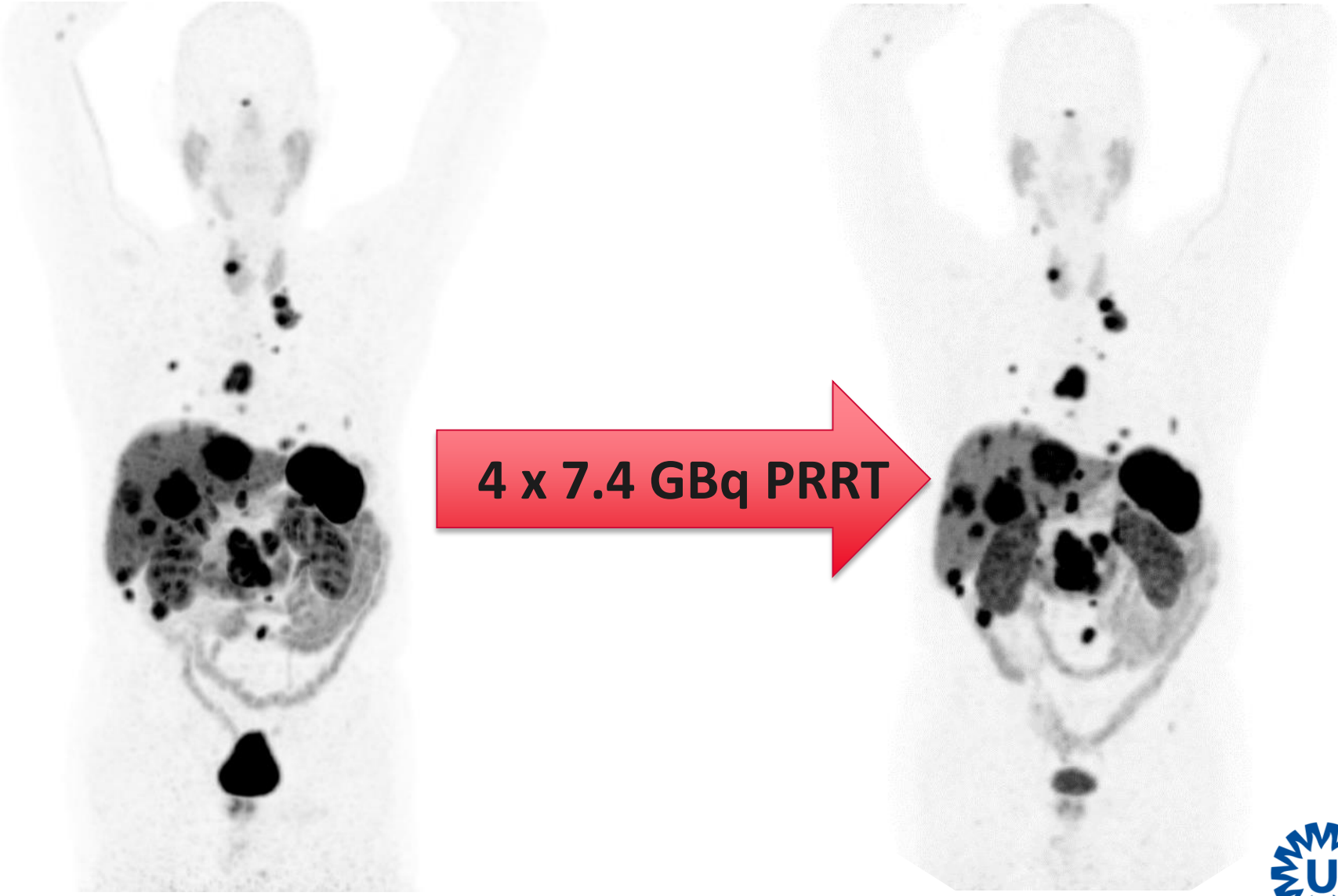
In a nutshell some details[2]

^{177}Lu-DOTATATE arm	SSA arm
• Most patients have liver disease	
– 84%	– 83%
• RECIST 1.1 objective response rate is poor	
– 18%	– 3%
• Adverse events limited compared to control	
– CTCAE grade 1-2 nausea and vomiting*	
– Lymphocytopenia and trombocytopenia	

*No prophylactic (pre-)treatment anti-emetic

[2]*Strosberg et al. NEJM 2017*

It’s awesome, but not good enough!



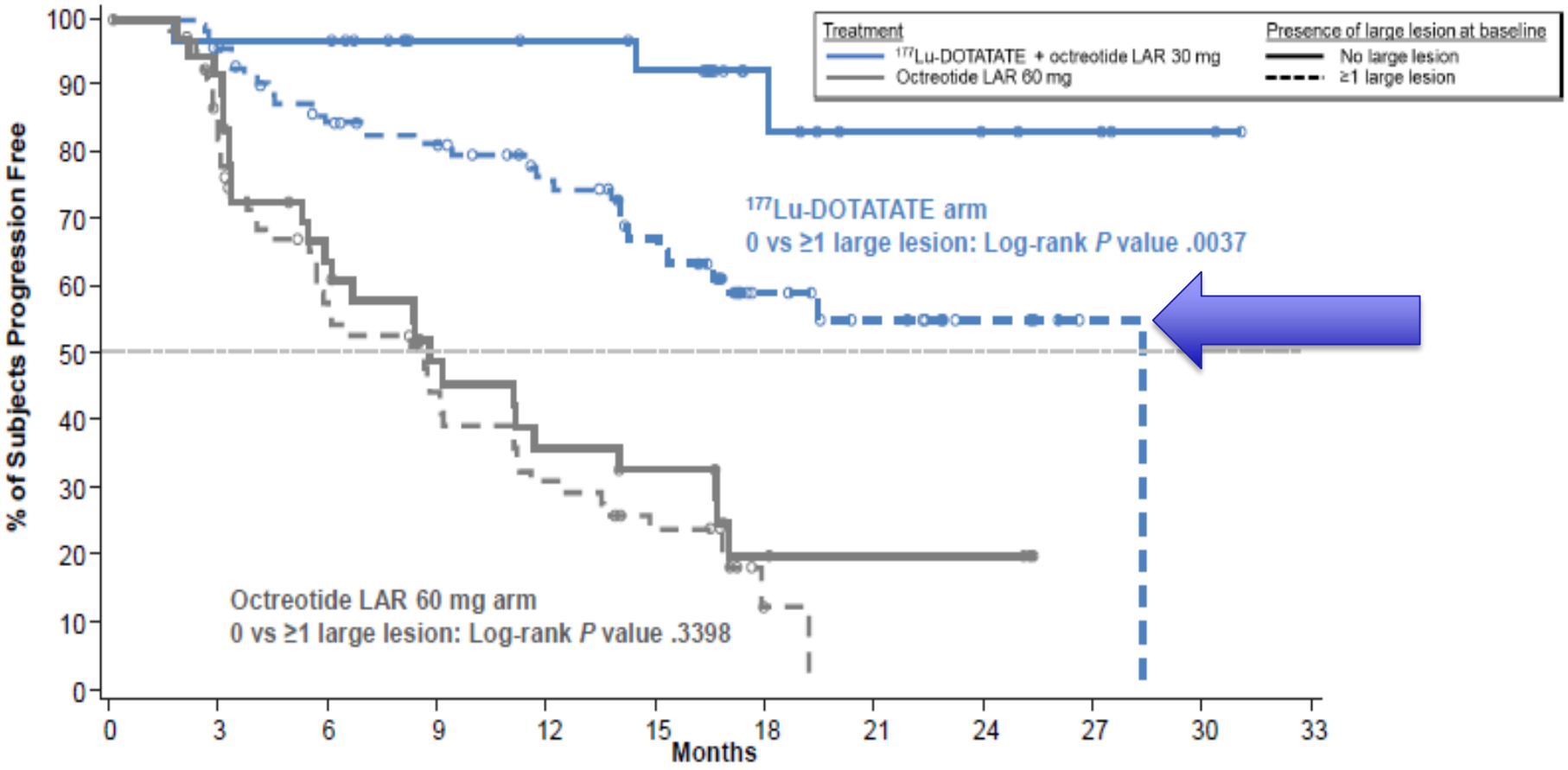
Liver disease remains the major issue[1]

Author	Treatment	N	Liver involvement	Median survival (months)	5-year survival
Chamberlain (2000)	Surgical resection	85	0%-25%	-	90%
			25%-50%	-	83%
			50%-75%	47	80%
			>75%	24	-
Gupta (2005)	TAE or TACE	123	0%-25%	86	-
			25%-50%	30	-
			50%-75%	39	-
			>75%	20	-
Kwekkeboom (2008)	PRRT	310	None	>48	-
			Moderate	>48	-
			Extensive	25	-

Increased liver tumor load = decreased survival

[1]*Braat et al. BMC Gastroenterology 2018*

Bulky liver disease remains a problem even after PRRT



Strosberg et al. *abstract ESMO 2018 and EANM 2018*

Radiation boost in dominant lesions is needed

1. Addition of a locoregional therapies

2. Easiest way in the nearby future for systemic treatments: Go intra-arterial?!?

- Main reason: Enhancing first-pass effect
- Might be logistically challenging
- Added usual related risks of angiography intervention
  - <2% in experienced centers

What do we know on IA diagnostic?

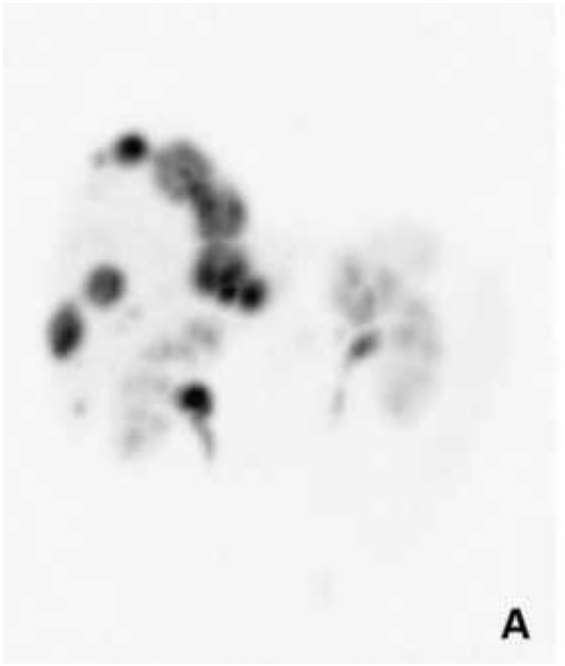
Study	Radiopeptide	IV Liver dose	IV Tumor dose	IA Liver dose	IA Tumor dose	IV T/N ratio	IA T/N ratio	Δ T/N ratio IA vs IV
Kontogeorgakos 2006	^{111}In-DTPA-octreotide	NR	NR	0.14 mGy/MBq	10.8 mGy/MBq	28.1 (n=1)	110.9 (n=1)	3.9*
Limouris 2008	^{111}In-DTPA-octreotide	NR	NR	0.14 mGy/MBq	10.8 mGy/MBq	NR	77.14	NR
Kratochwil 2010	^{68}Ga-DOTATOC	4.7 SUV_{mean}	14.1 SUV_{mean}	6.2 SUV_{mean}	51,8 SUV_{mean}	3*	8.4*	2.8*
Kratochwil 2011	^{111}In-DOTATOC	NR	NR	NR	NR	NR	NR	two-fold
Pool 2014	^{111}In-DTPA-octreotide	NR	NR	NR	NR	NR	NR	1.06 - 2.4
Limouris 2016	^{111}In-DTPA-octreotide	0.39 mGy/MBq	10.8 mGy/MBq	0.14 mGy/MBq	11.2 mGy/MBq	27.07	80.00	3*
Limouris 2016	^{177}Lu-DOTATATE	0.39 mGy/MBq	10.8 mGy/MBq	0.14 mGy/MBq	35.0 mGy/MBq	27.07	250	9.2*

Table 3: Reported liver- and tumor absorbed doses of different radiopeptides used in intra-arterial injection.
NR = not reported. * calculated from reported values
IV: intravenous; IA: intra-arterial; T/N: tumor-to-non-tumor ratio; SUV: standardized uptake value

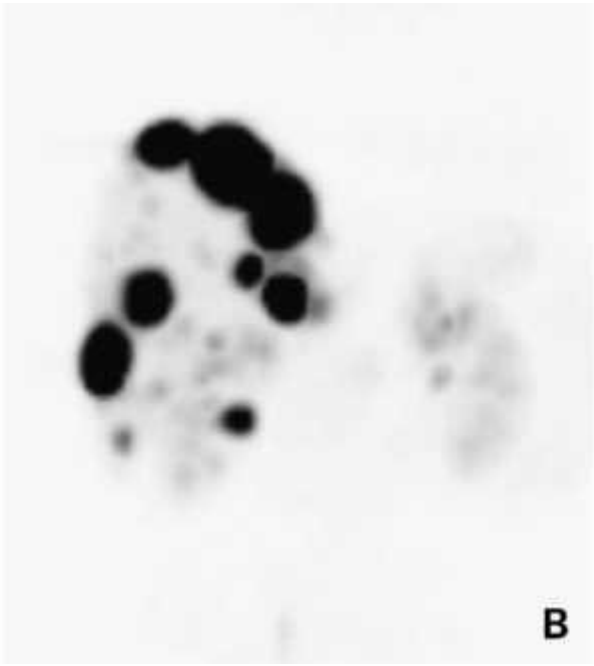
1.06 – 9.2 fold increase in tumor uptake/dose

Ebbers et al.

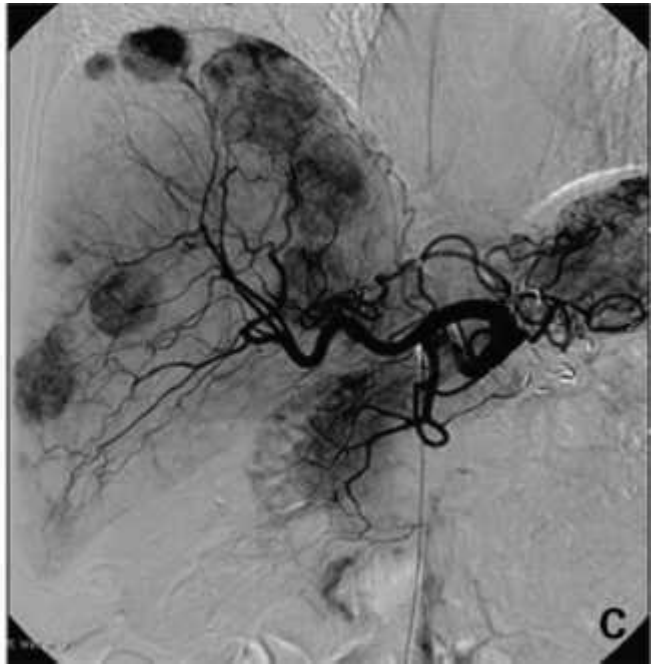
Example IV versus IA ^{68}Ga-DOTATOC



Intravenous



Intra-arterial



DSA

[1]*Kratochwil et al. Clin Cancer Res 2010*

Will it give us the results we seek?

Study	Radiopeptide	Response criteria	CR	PR	SD	PD	OS	PFS
McStay 2005	^{90}Y-DOTA -lanreotide	WHO	0% (0/23)	13% (3/23)	52% (12/23)	17% (4/23)	15 mo	9 mo
Limouris 2008	^{111}In-DTPA -octreotide	RECIST	6% (1/17)	47% (8/17)	18% (3/17)	29% (5/17)	32 mo	NR
Kratochwil 2011	^{90}Y-DOTATOC + ^{177}Lu-DOTATOC	RECIST 1.0	7% (1/15)	53% (8/15)	40% (6/15)	0% (0/15)	NR	NR
Limouris 2016	^{111}In-DTPA -octreotide	RECIST 1.1	6% (1/17)	47% (8/17)	18% (3/17)	29% (5/17)	NR	NR
Limouris 2016	^{177}Lu-DOTATATE	RECIST 1.1	0% (0/13)	69% (9/13)	23% (3/13)	8% (1/13)	NR	NR

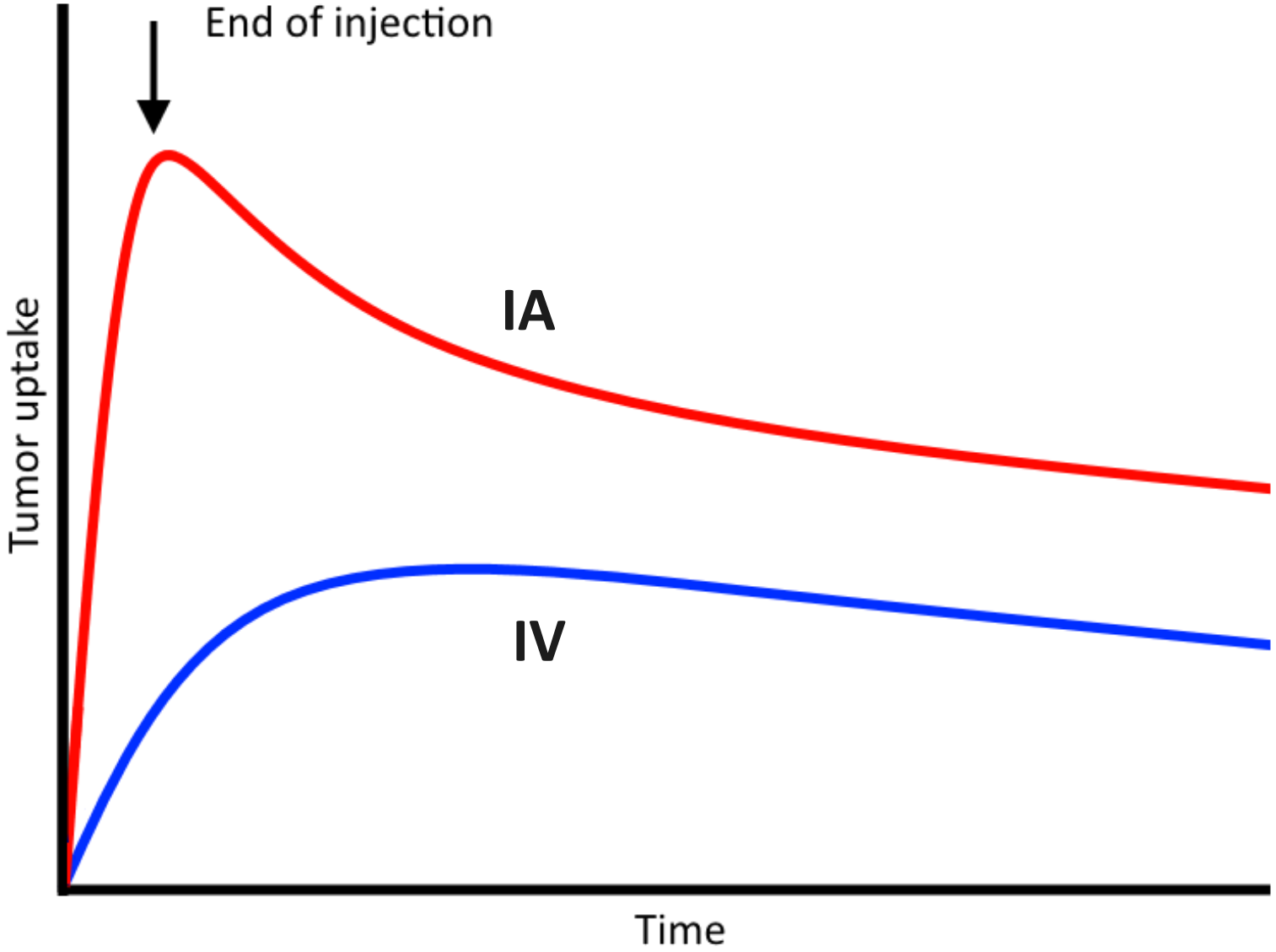
Table 5: Reported response rates and outcomes of intra-arterial PRRT with different radiopeptides.

RECIST objective response rates** 53%-**69%

NETTER-1 18%

Ebbers et al.

Wash-out in time?



Ebbers et al.

Small retrospective cohort studies

Patient selection bias?

Really less non-target radiation absorbed dose? Less kidney damage?[1]

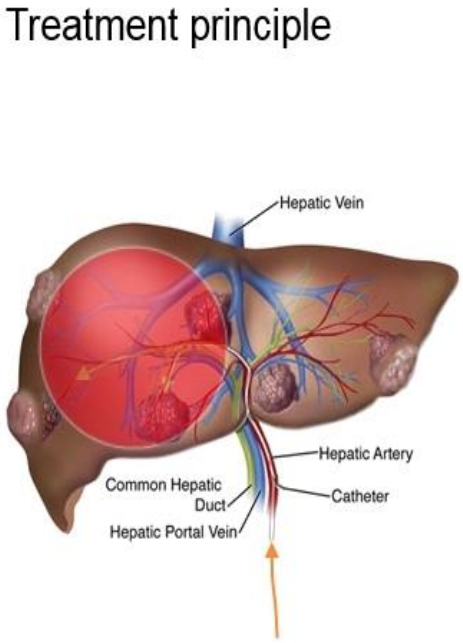
Inter-patient / tumor bias? No NEN is the same

Coverage of extrahepatic disease?

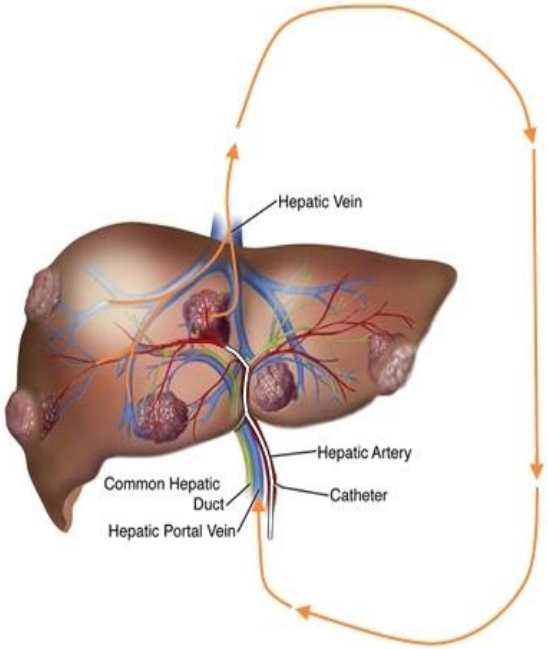
[1]*Pool et al. Cancer Biother Radiopharm 2014*

Prospective data? LuTIA-trial

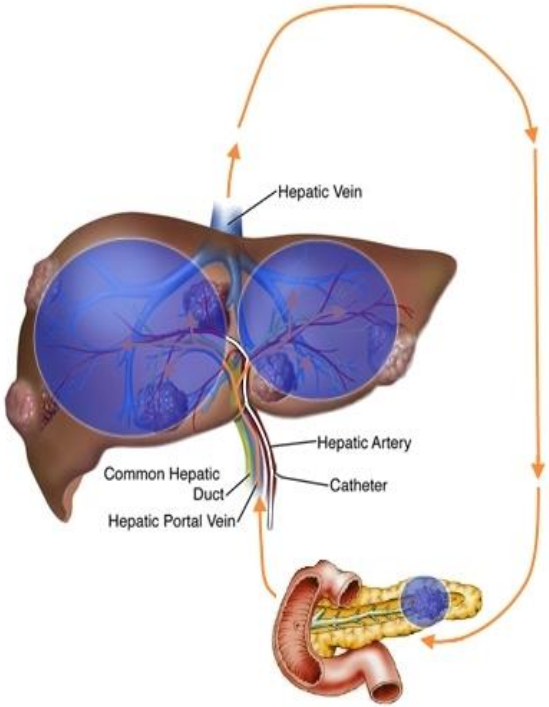
Treatment principle



1. IA administration of 177Lu-dotatate, selectively in the right or left hepatic artery.



2. Systemic circulation of 177Lu-dotatate, after IA administration



3. Treatment of whole liver (second pass) and other organs

In-patient randomization!

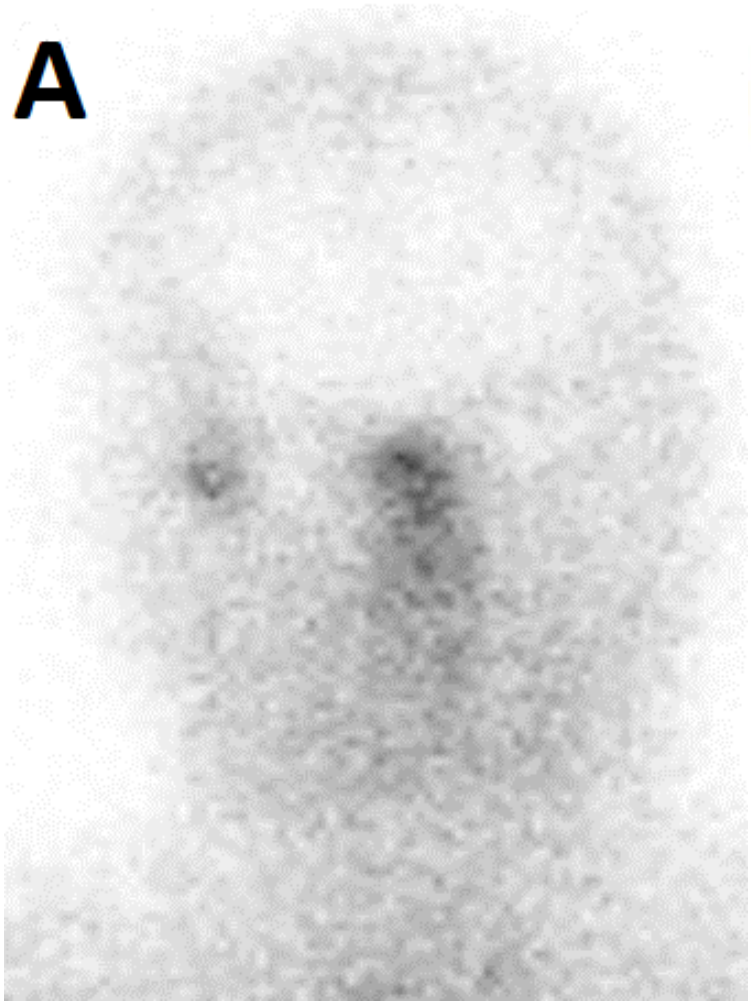
Teaser 1st LuTIA: IA left hepatic artery

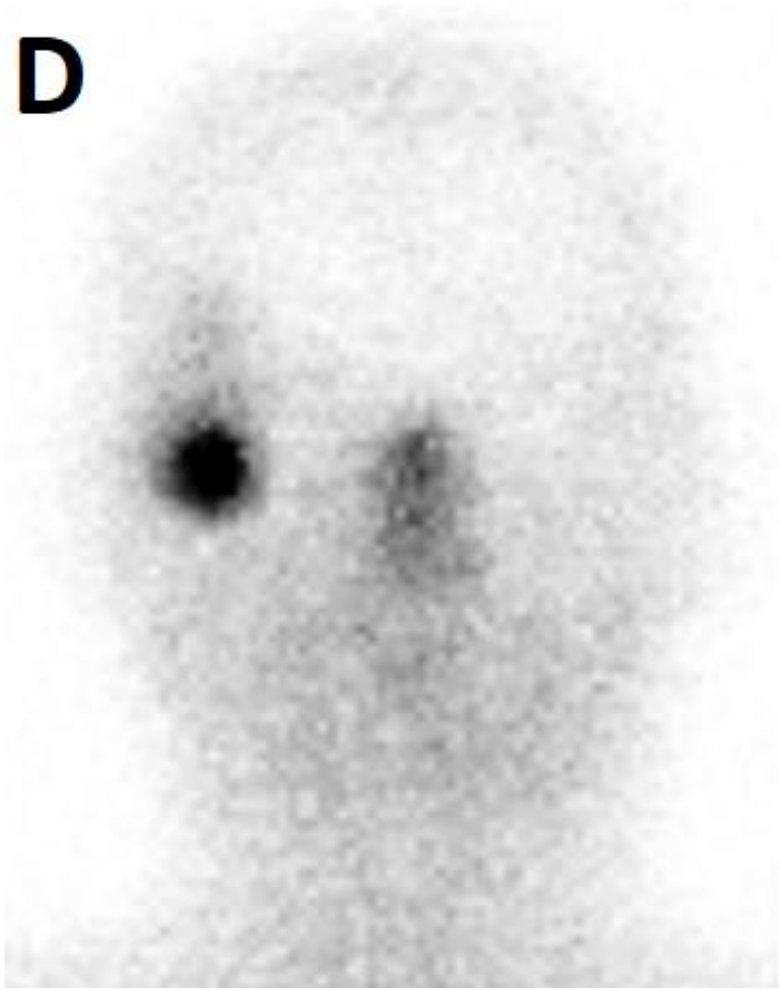
Baseline ^{68}Ga-DOTATOC PET/CT

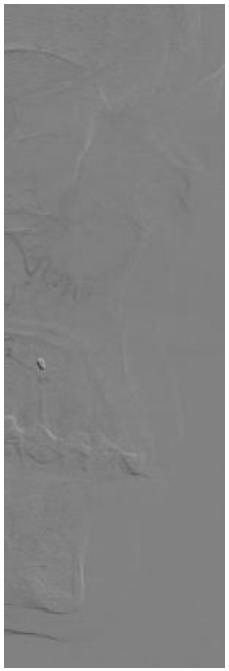
Post-treatment ^{177}Lu SPECT/CT

5-fold uptake increase!

Limited to the liver? No!





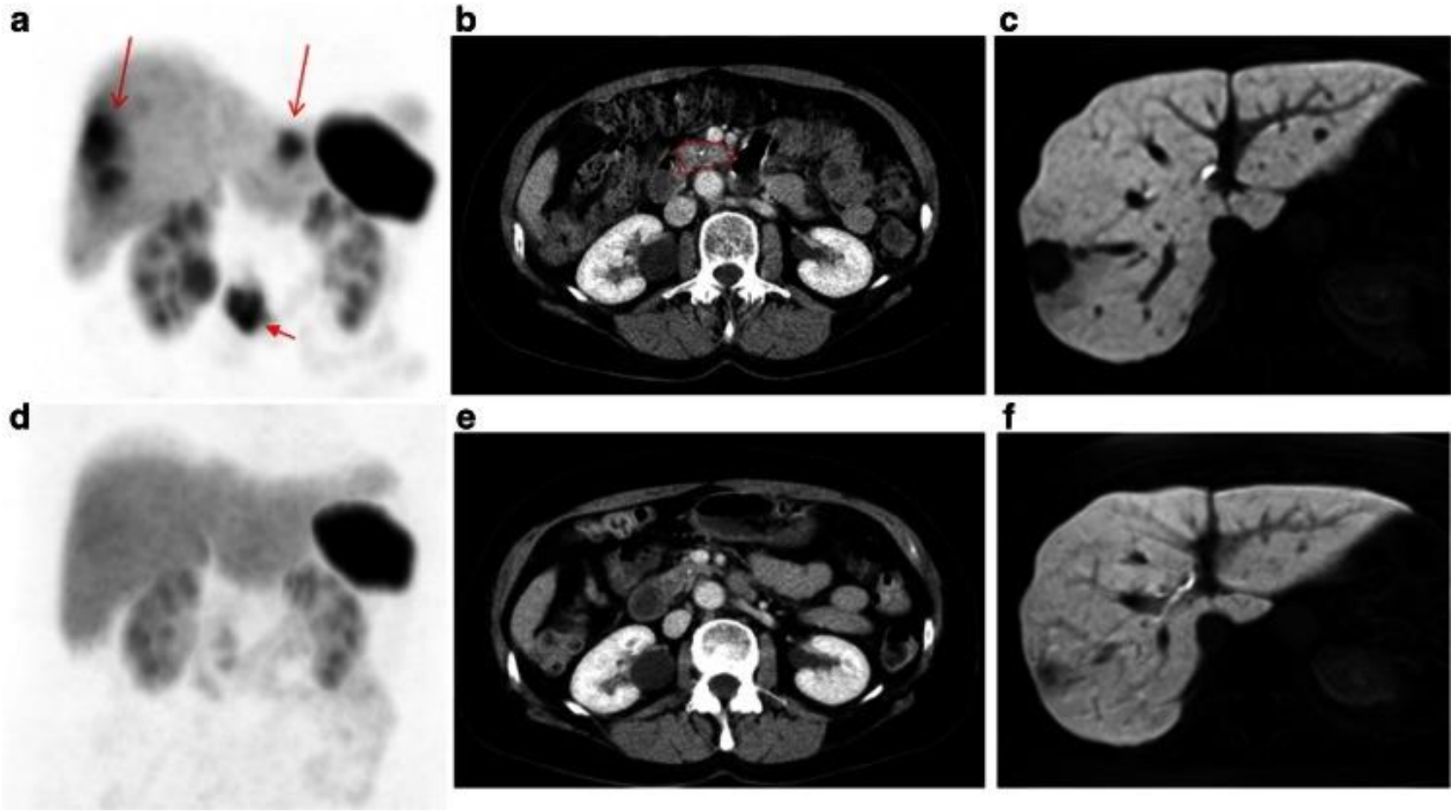


tery

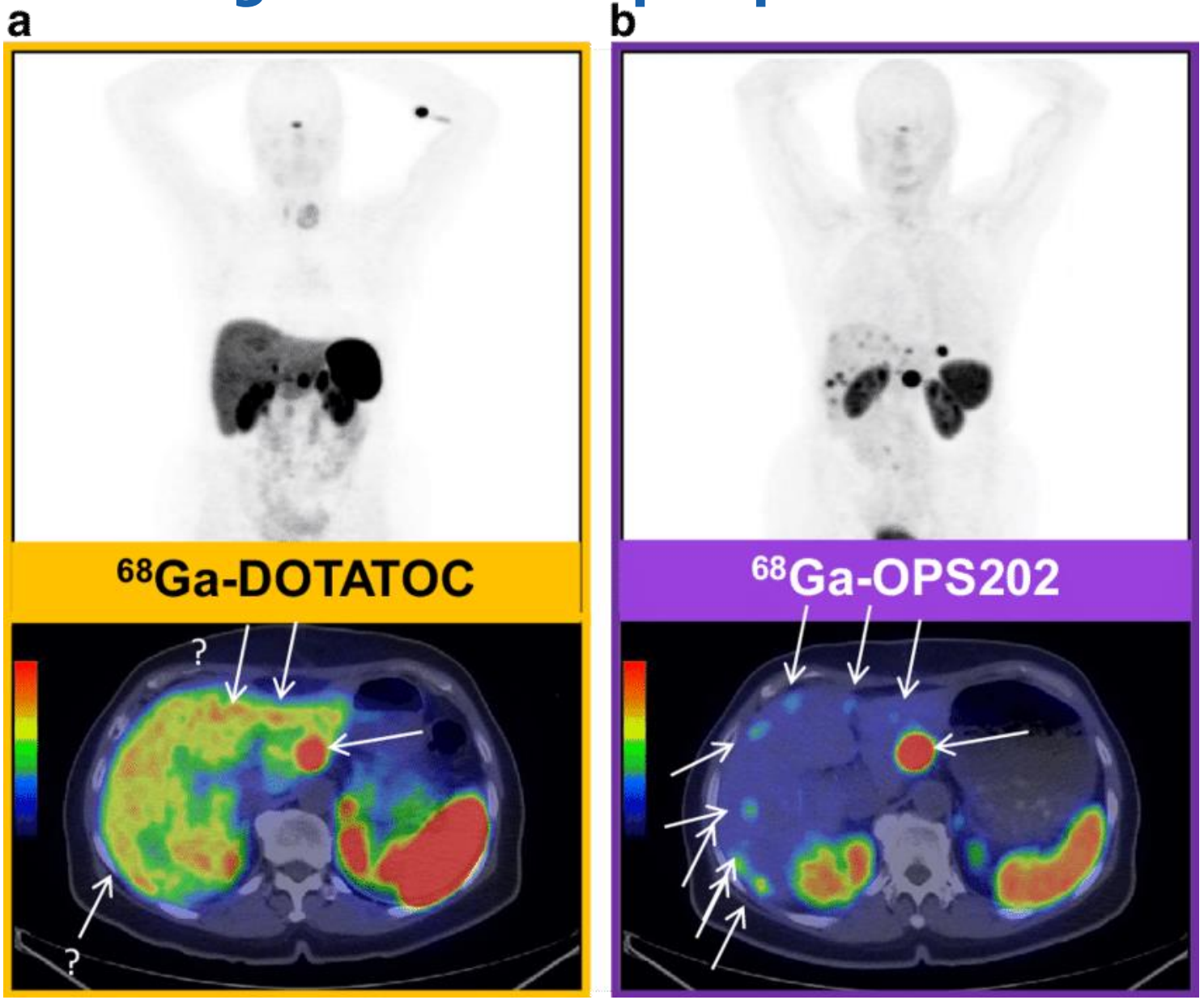
11-fold increase!

[1]*Braat et al. Cardiovasc Interv Radiol 2019*

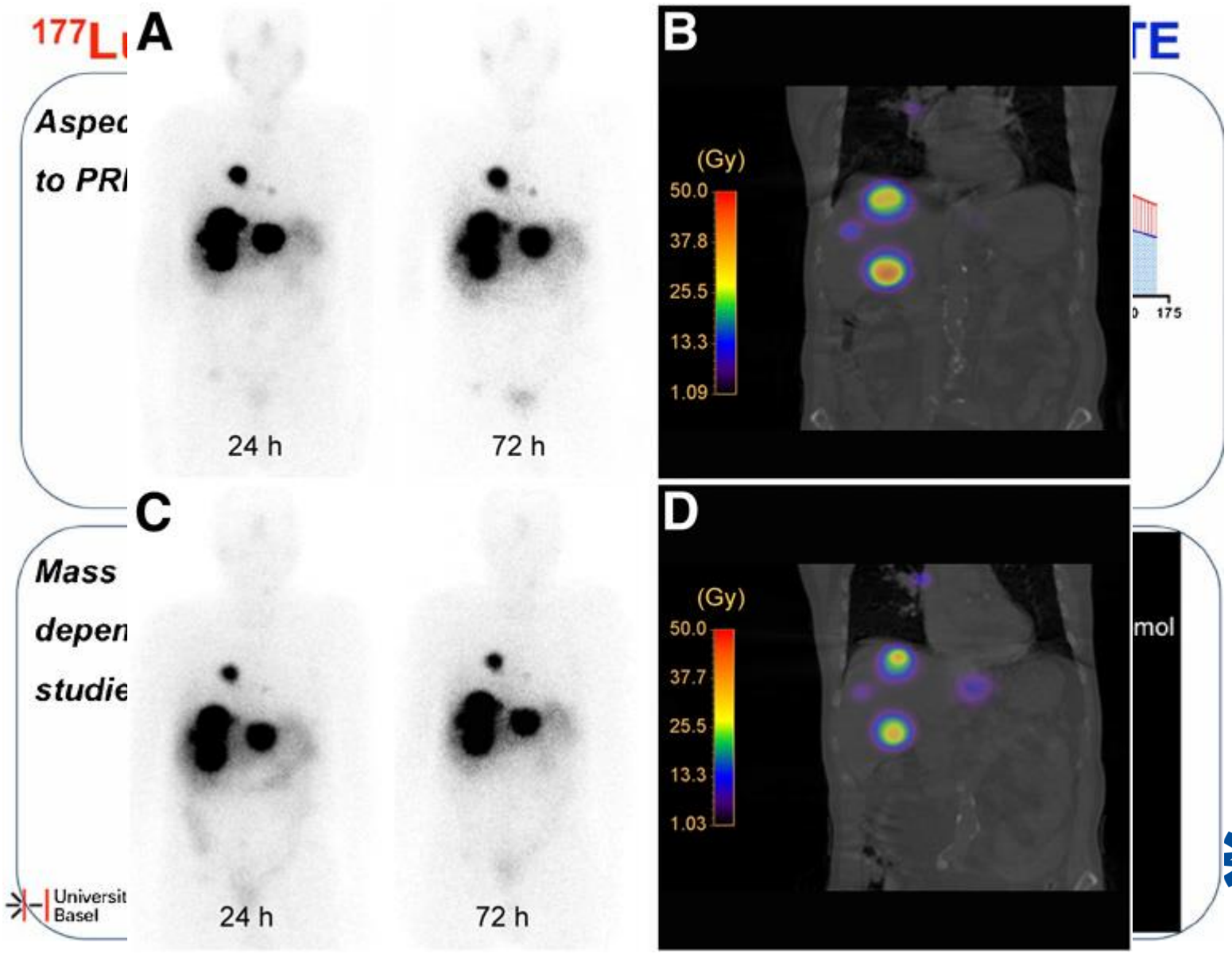
Alpha emmitters? ^{213}Bi-DOTATATE



Other long term future perspectives

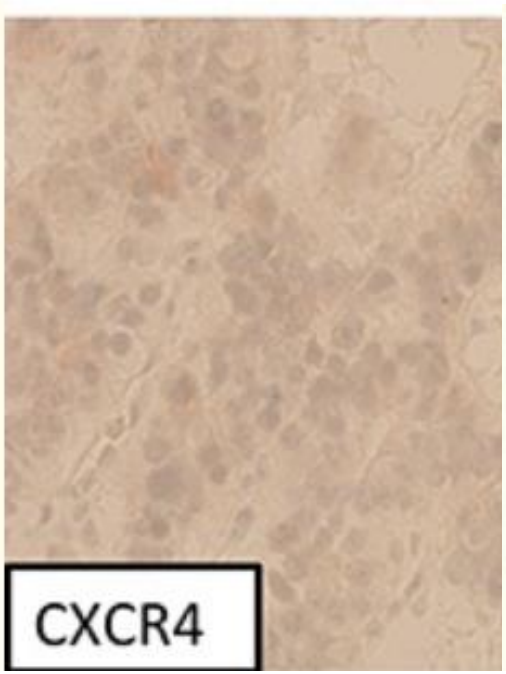


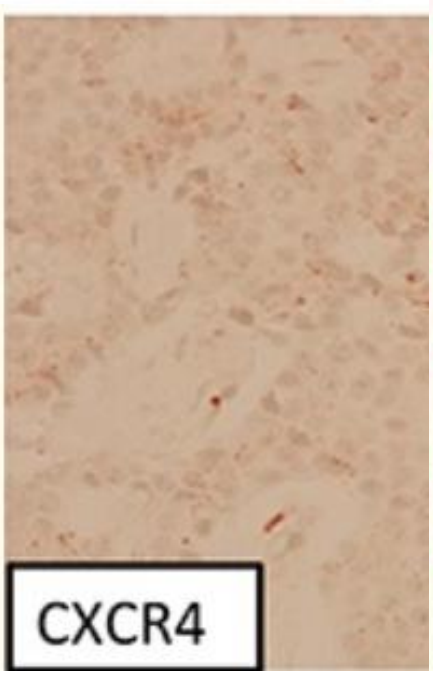
Therapeutic antagonist



Outside the scope of somatostatin

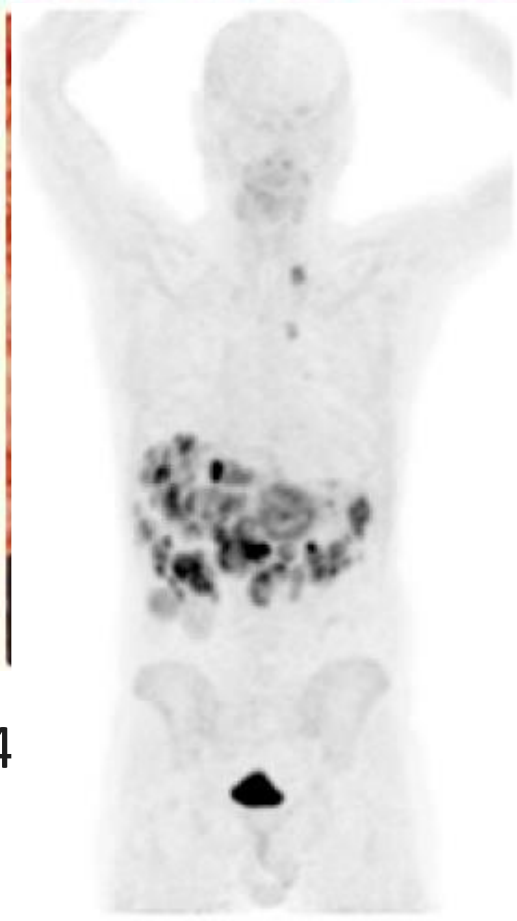
CXCR4 (chemokine 4)

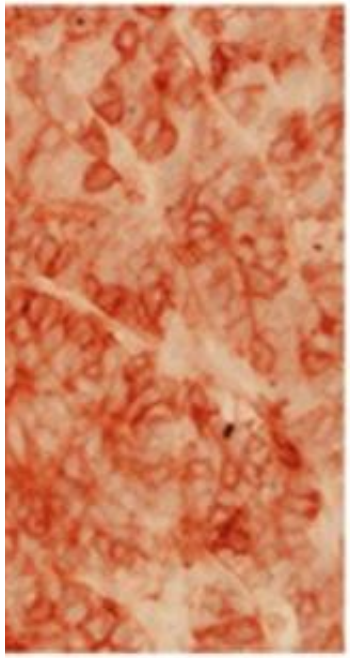




G1NET (Ki67 <2%) G2NET (Ki67 4

^{68}Ga-FAPI (Brand new!)





30%)

Kaemmerer D et al. Oncotarget 2015; Kratochwil C et al. JNM 2019

Summary

- IV PRRT is good, but not good enough
- Intra-arterial administration: an easy way to improve?
- Many new interesting ligands available for different NEN

UMC Utrecht

Thank you for your attention

Arthur J.A.T. Braat, MD
a.j.a.t.braat@umcutrecht.nl

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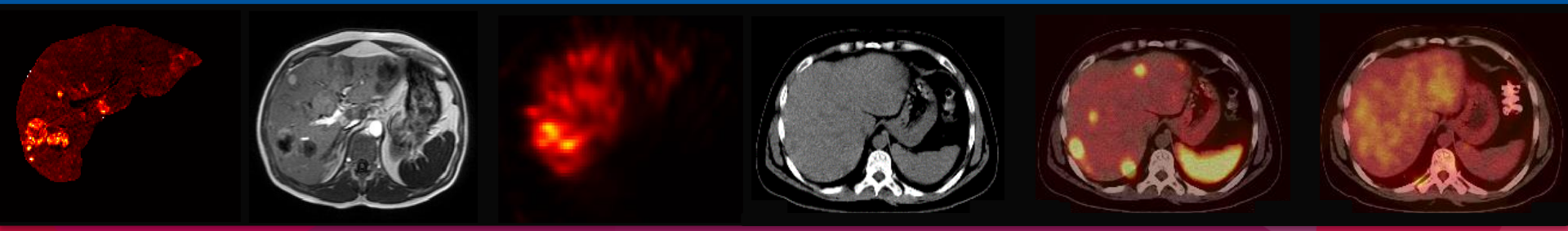

Department of Radiology and Nuclear Medicine
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