PRRT- Who should we treat?

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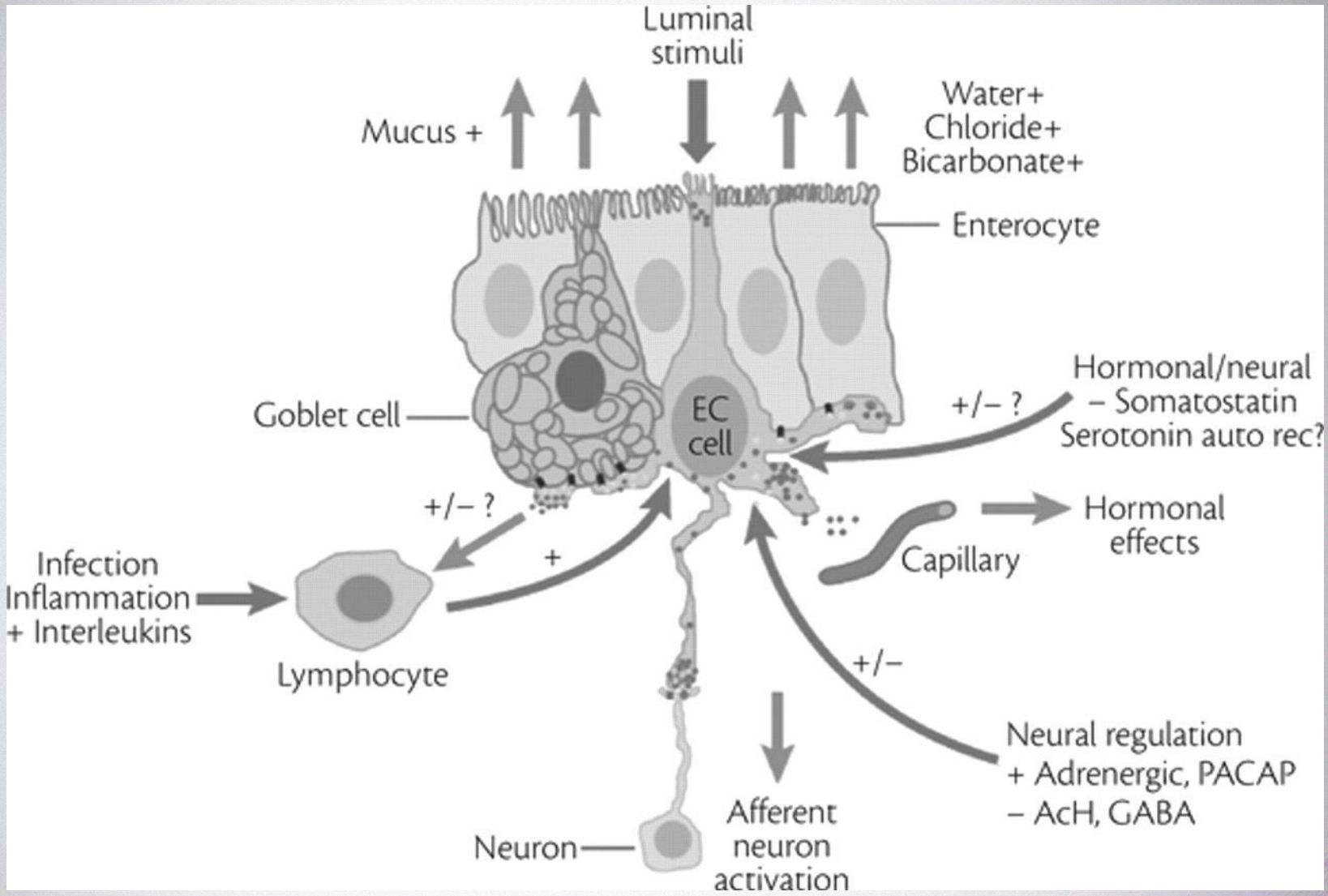
World NEN Lives 2020 Congress

September 23—24, 2020

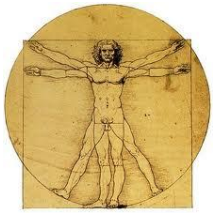
Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

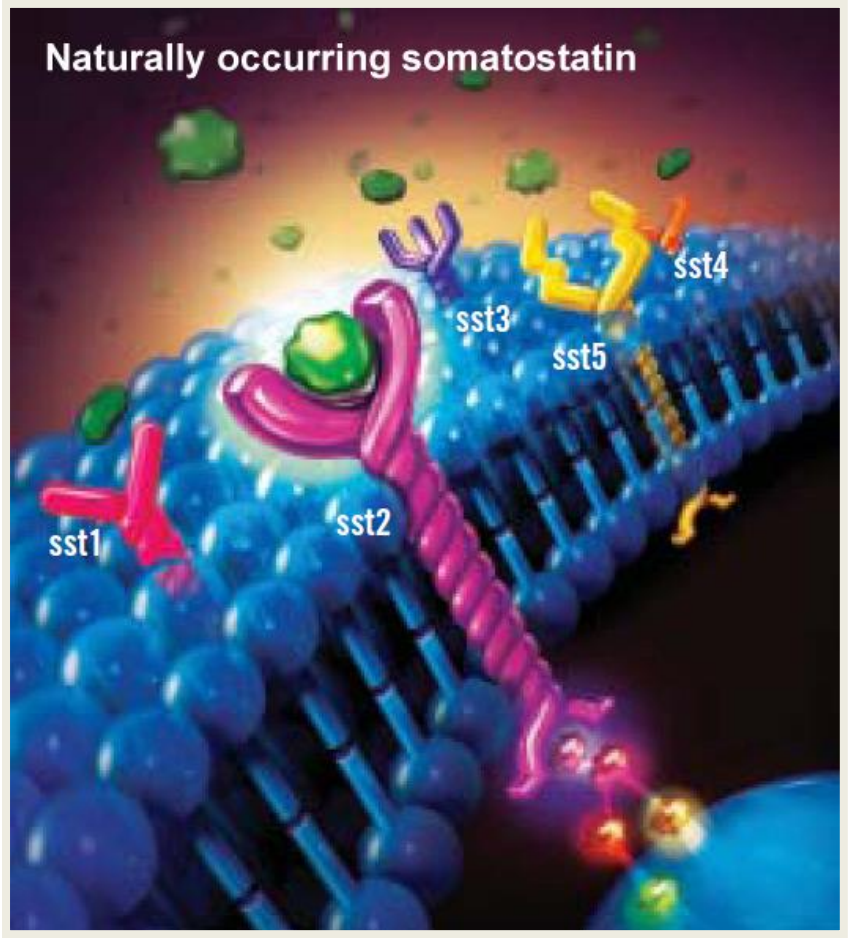
Neuroendocrine cells are like women!

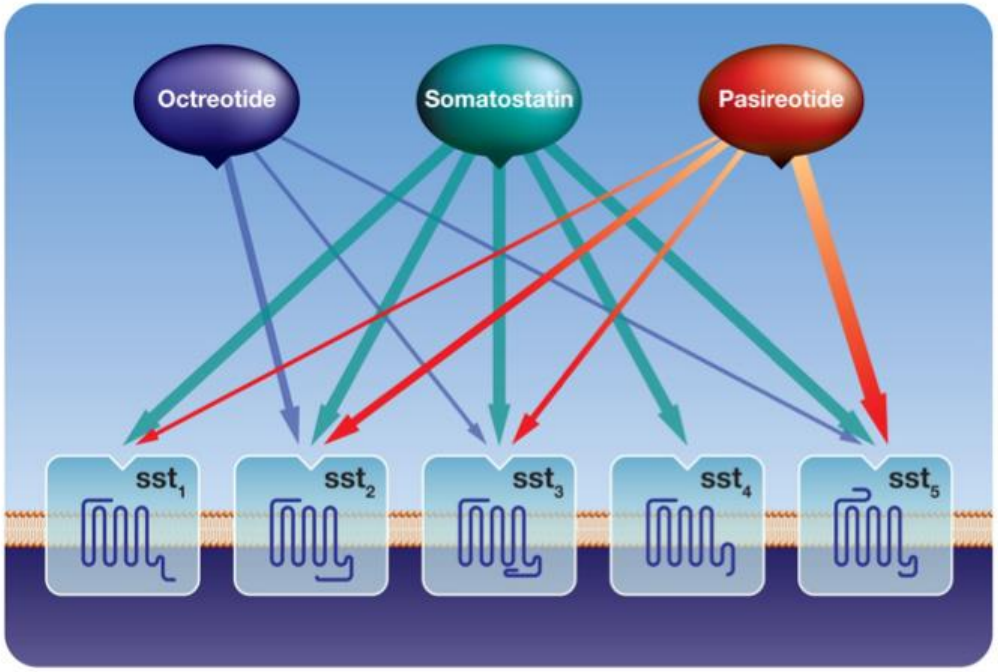


Great talkers but also very good listeners!

Most but not all turn off the same way…

Somatostatin =  + 





Copies of somatostatin are “conversation killers”

Targeting a common vulnerability of NET

If the somatostatin receptor is like a revolving door into the neuroendocrine cell, then ...

Dangly Bits

Radioactive chemical

Keys

Peptides

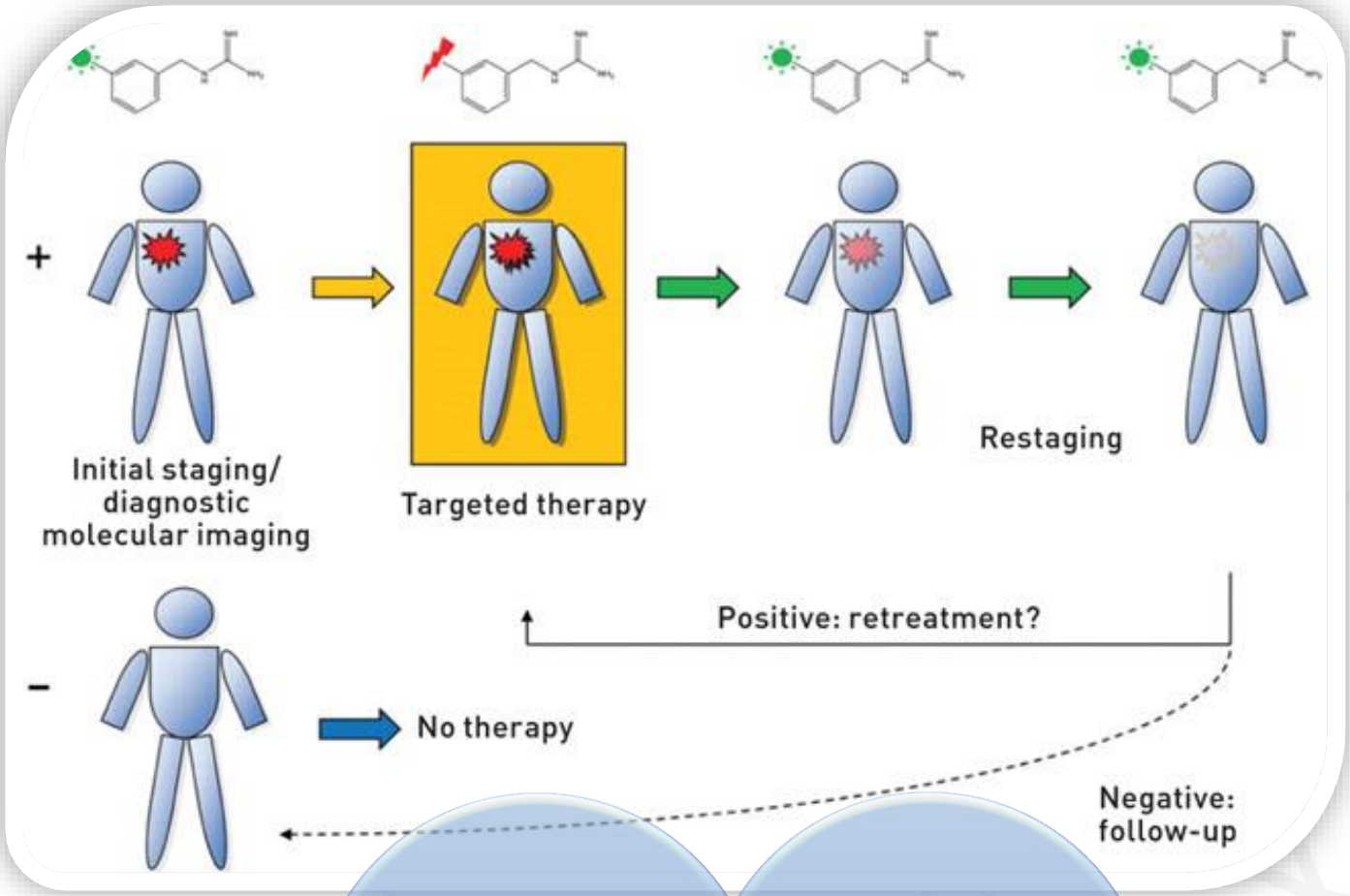
Key Rings

Chelating Agents

Gallium-68 or Lutetium-177 DOTA or NOTA octreotate or octreotide

GaTate (NETSpot) / LuTate (LutaThera)

Theranostics – Changing the Dangly Bits



The right therapy for the right patient at the right time

Rays outside the body

Dx

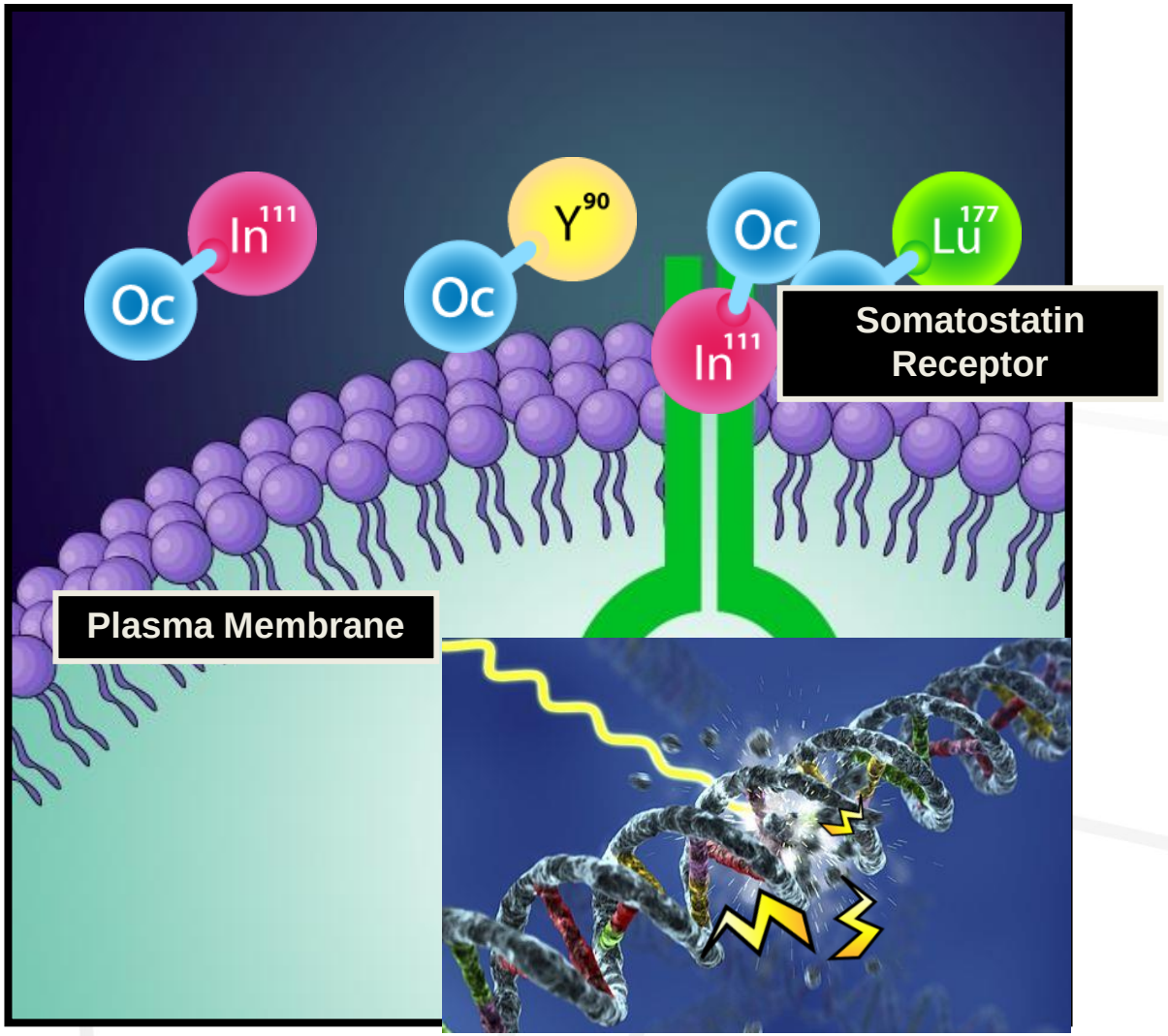
Molecular imaging

Rx

Targeted therapeutic

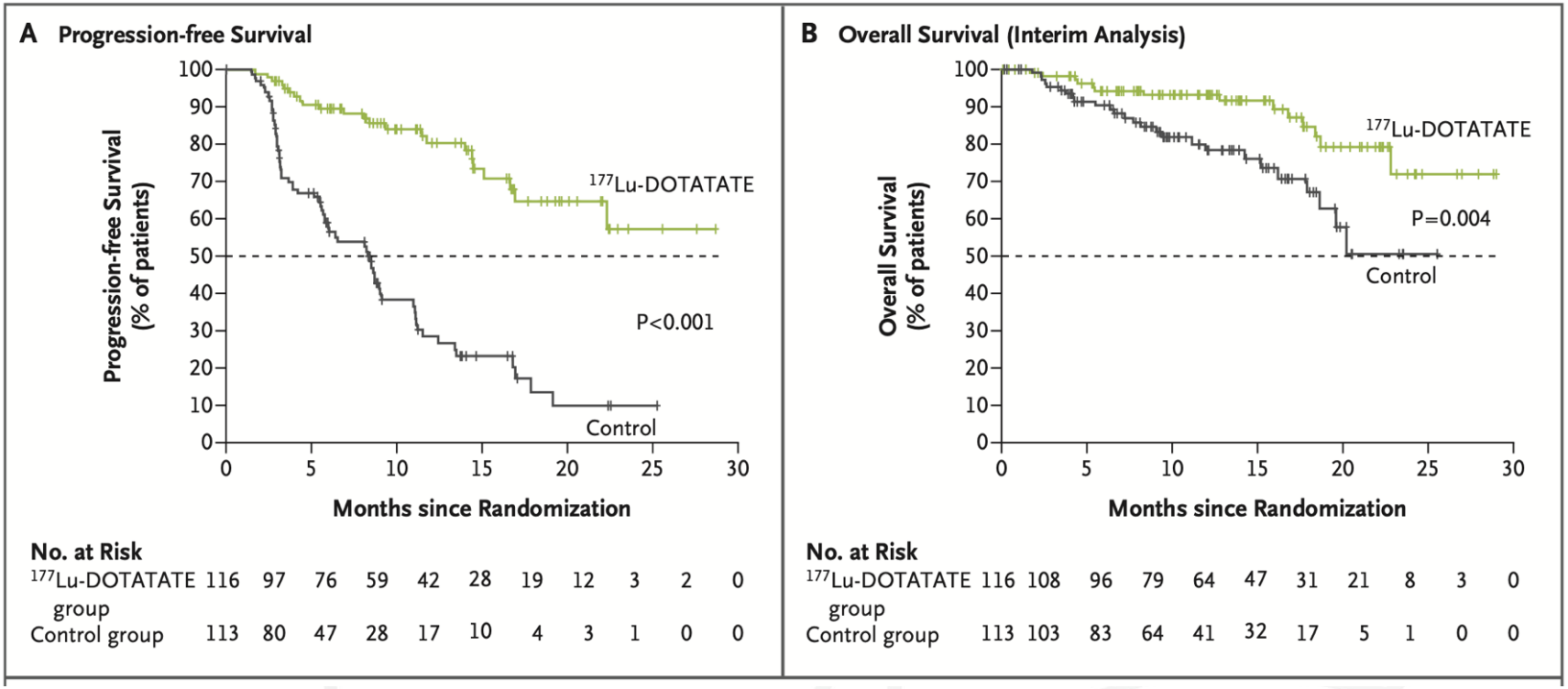
Particles inside the tumour

Peptide Receptor Radionuclide Therapy (PRRT)



Particles break DNA!

NETTER-1 Trial Drives Approval in 2018



Fixed regimen of 4 x 7.4 GBq (200mCi) cycles every 8 weeks
Selected based on Octreoscan positivity

PRRT comes of age!

Strosberg et al. NEJM 2017;376:125-35

Why did it take so long?

Table 2. Survival data in patients with gastroenteropancreatic neuroendocrine tumours, treated with different radiolabeled somatostatin analogues

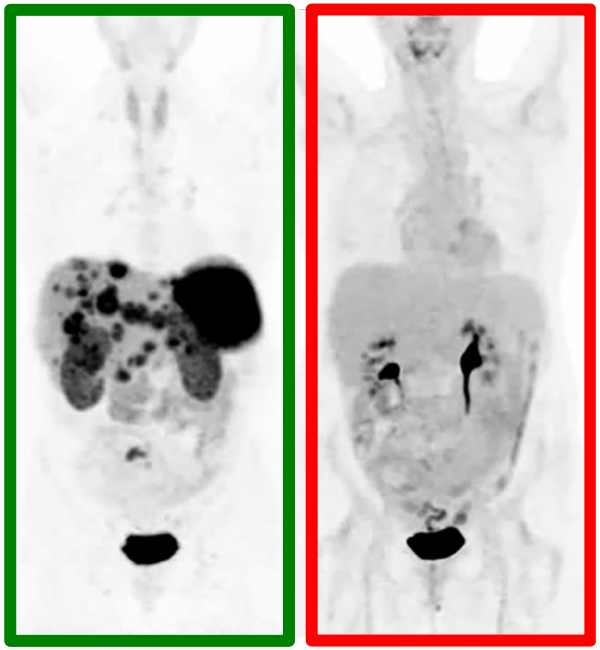
Center	Reference	Ligand	Patient, *n*	PFS	OS
Multicenter	Valkema et al., 2006 [87]	[^{90}Y-DOTA^0,Tyr^3] octreotide	58	29	37
Multicenter	Bushnell et al., 2010 [19]	[^{90}Y-DOTA^0,Tyr^3] octreotide	90	16	27
Copenhagen	Pfeifer et al., 2011 [88]	[^{90}Y-DOTA^0,Tyr^3] octreotide	53	29	
Warsaw	Cwikla et al., 2010 [89]	[^{90}Y-DOTA^0,Tyr^3] octreotate	58	17	22
Basel	Villard et al., 2012 [42]	[^{90}Y-DOTA^0,Tyr^3] octreotide	237	NA	47.5
Warsaw	Kunikowska et al., 2011 [84]	[^{90}Y-DOTA^0,Tyr^3] octreotate	25	NA	26.2
Rotterdam	Kwekkeboom et al., 2008 [25]	[^{177}Lu-DOTA^0,Tyr^3] octreotate	310	33	46
Milan	Bodei et al., 2011 [92]	[^{177}Lu-DOTA^0,Tyr^3] octreotate	42	NA	>36
Meldola	Sansovini et al., 2013 [37]	[^{177}Lu-DOTA^0,Tyr^3] octreotate[c]	26	>30	>30
Meldola	Paganelli et al., 2014 [93]	[^{177}Lu-DOTA^0,Tyr^3] octreotate[d]	25	36	>60
Bonn	Ezziddin et al., 2014 [35]	[^{177}Lu-DOTA^0,Tyr^3] octreotate[c]	68	34	53
Bonn	Sabet et al., 2015 [36]	[^{177}Lu-DOTA^0,Tyr^3] octreotate[d]	61	33	61
Melbourne	Kong et al., 2014 [50]	[^{177}Lu-DOTA^0,Tyr^3] octreotate	68	NA	>60
Melbourne	Kashyap et al., 2014 [51]	[^{177}Lu-DOTA^0,Tyr^3] octreotate[a]	40	48	55[a]
Bad Berka	Baum et al., 2016 [21]	[^{177}Lu-DOTA^0,Tyr^3] octreotide	43	30.3	34.7
Multicentre	Strosberg et al., 2017 [40]	[^{177}Lu-DOTA^0,Tyr^3] octreotide	101	>20	NA
Warsaw	Kunikowska et al., 2011 [84]	[^{90}Y+^{177}Lu-DOTA^0,Tyr^3] octreotate	25	NA	>34.6
Basel	Villard et al., 2012 [42]	[^{90}Y+^{177}Lu-DOTA^0,Tyr^3] octreotide	249	NA	66.1
Melbourne	Kong et al., 2016 [94]	[^{90}Y+^{177}Lu-DOTA^0,Tyr^3] octreotate[b]	26	33	>35

PFS, progression-free survival; OS, overall survival. [a] Overall survival updated in [60]. [b] Sequential use in patients with at least 1 lesion >4 cm. [c] Study limited to pancreatic NET. [d] Study limited to gastrointestinal NET.

Many reports from many countries using different protocols but response rates and survival consistently much better than other therapies used before

Hicks et al. *Neuroendocrinology* 2017;105:295-309

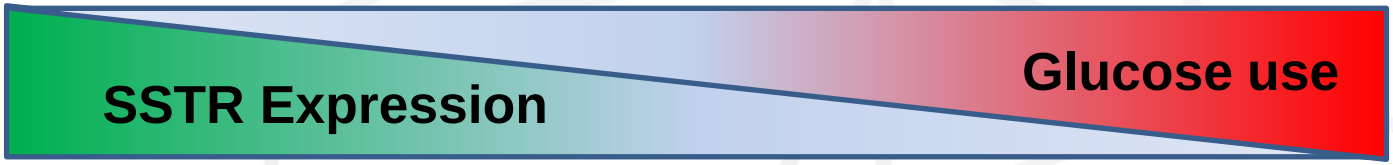
Neuroendocrine cancers vary in aggressiveness



GaTate FDG

G1 NET (Ki-67 <1%)

If we can't see it, we can't treat it!



Grade	G1	G2	G3
Ki-67	≤2	3-20	>20
	NET		NEC

PRRT @ Peter Mac- Initial Cohort

	Reason for treatment					
	Disease progression (*N* =58)		Uncontrolled symptoms (*N* = 10)		All patients (*N* = 68)	
	N	%	*N*	%	*N*	%
Median	18.1		12.6		16.0	
Range	5.8 – 40.9		5.6 – 39.2		5.6 – 40.9	
Grade of tumour differentiation						
Grade 1 (Ki67 index < 3%)	7	12%	2	20%	9	13%
Grade 2 (Ki67 index 3% – 20%)	26	45%	4	40%	30	44%
Grade 3 (Ki67 index > 20%)	0	0%	0	0%	0	0%
Unknown	25	43%	4	40%	29	43%
FDG avidity prior to treatment						
Grade 0 (no uptake)	2	3%	0	0%	2	3%
Grade 1 (< liver)	0	0%	0	0%	0	0%
Grade 2 (= liver)	1	2%	0	0%	1	1%
Grade 3 (mildly > liver)	11	19%	2	20%	13	19%
Grade 4 (markedly > liver)	10	17%	1	10%	11	16%
Unknown	34	59%	7	70%	41	60%
Cumulative LuTate activity (Gbq)						
Median	30.9		32.7		31.0	
Range	21.0 – 45.3		23.0 – 39.5		21.0 – 45.3	

58/68 treated for progression within 12 months

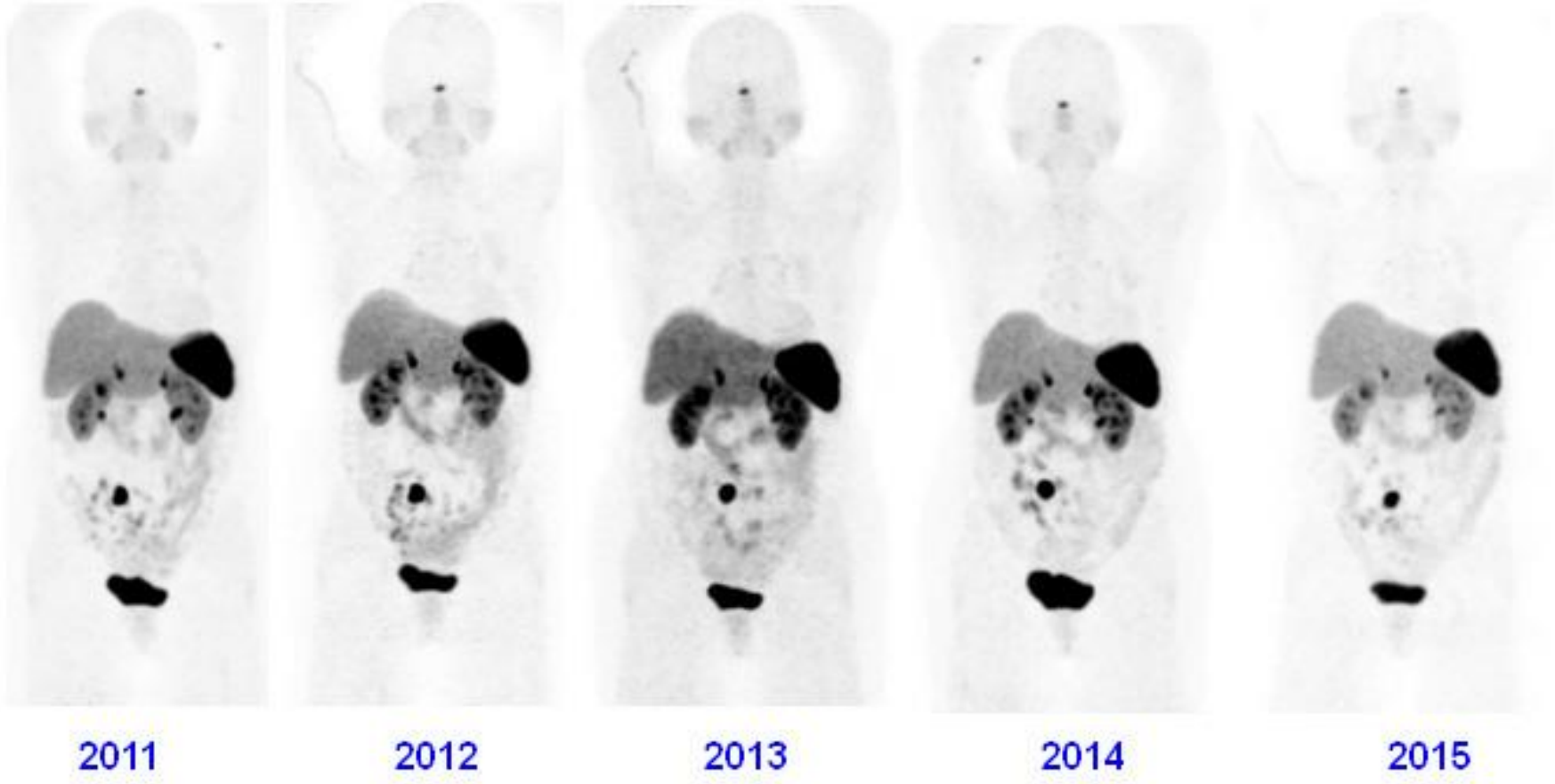
44% G2

36% FDG +ve

Compassionate-use meant treating the worst not the best candidates

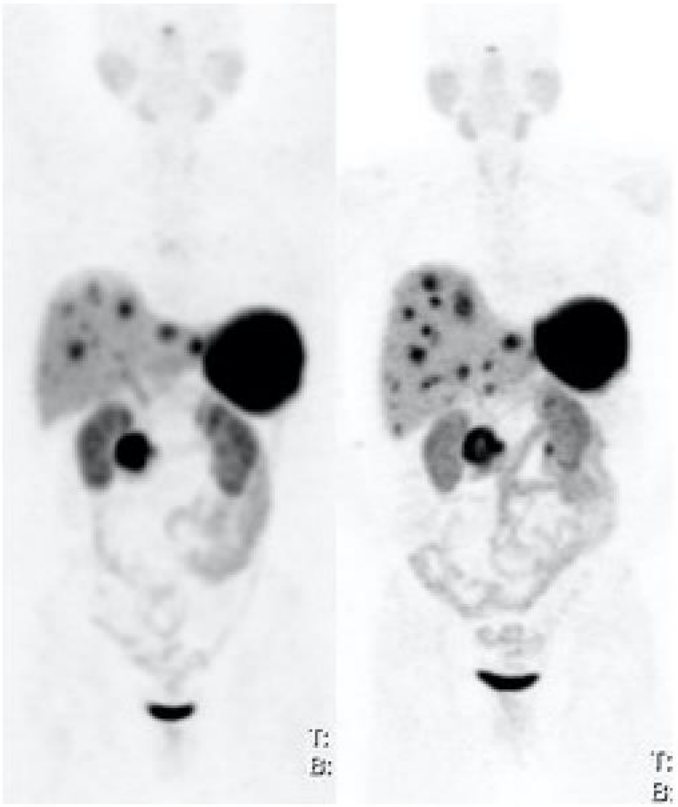
Kong G et al. *EJNMMI* 2014;41:1831-44

We should treat patients not scans…



Asymptomatic patient with stable NET on long-term SSA

…but scans help!

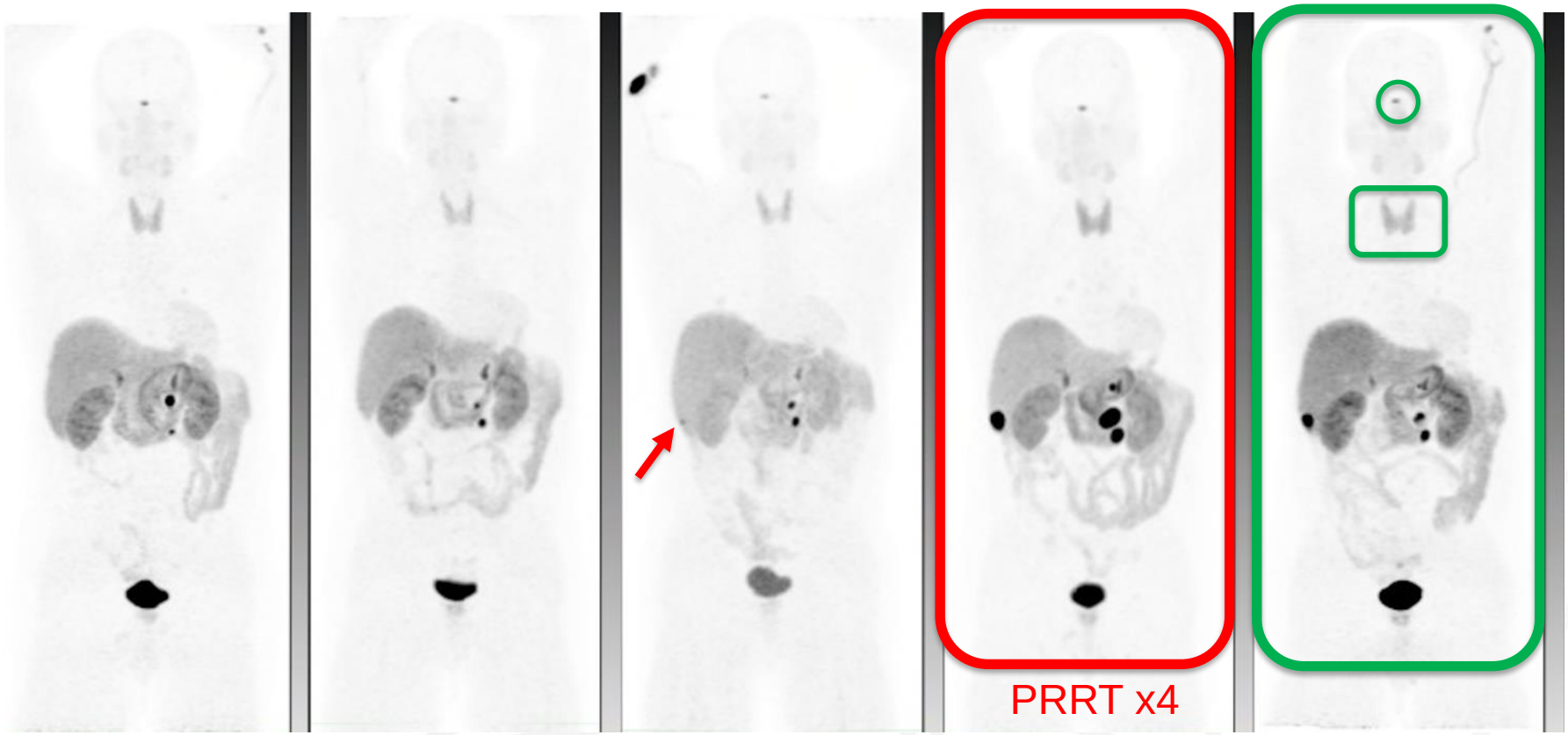


Late 2012 **Early 2013**

Patient suitable for PRRT

Asymptomatic patient but progressive disease on SSA

Delaying Treatment Until Progression Helps not Hurts

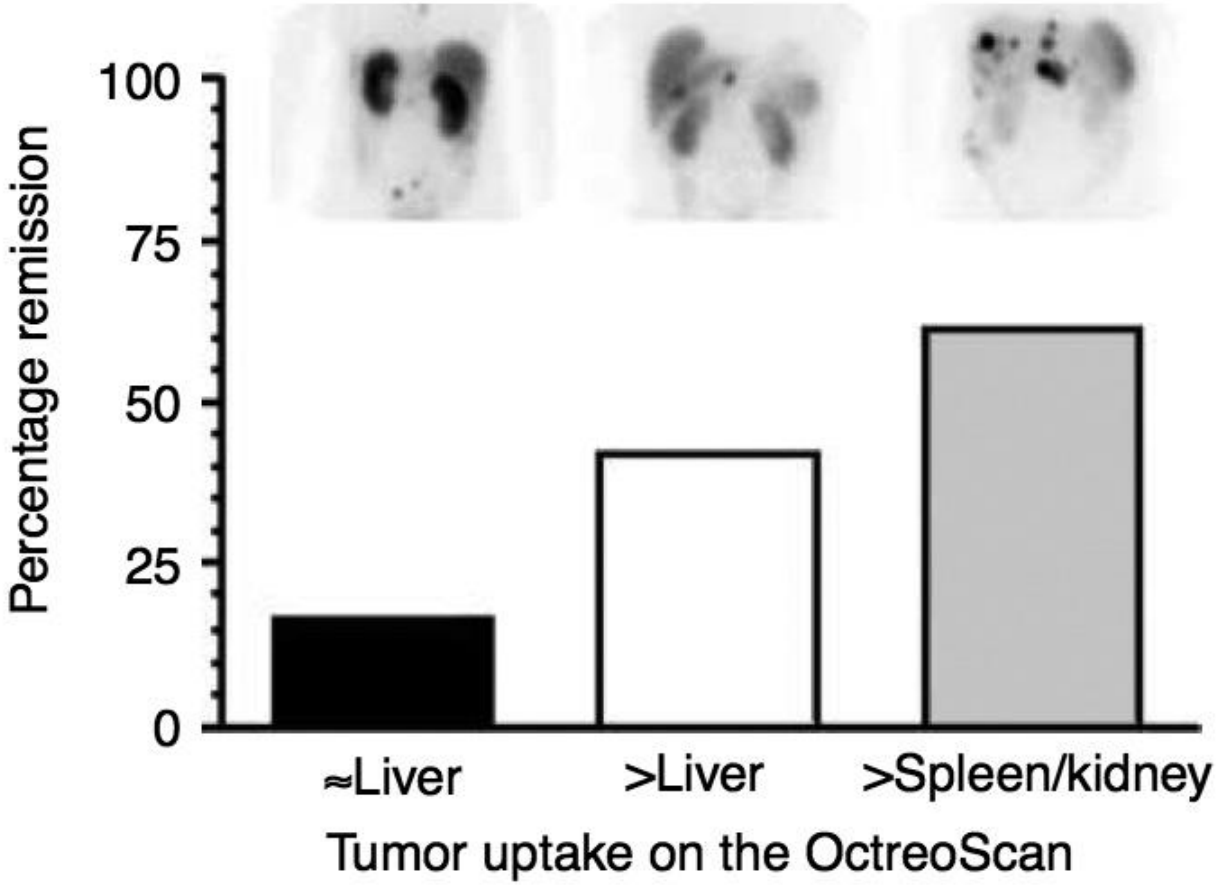


Actively growing cells are more sensitive to radiation than resting cells

Who should we treat with PRRT?

- Target expression is needed
  - Intensity matters
- Need to determine the goal of treatment
  - Symptom control versus survival
- Hormonal control can occur rapidly and therefore progression is not needed to justify treatment
  - Hormone-secreting NET often have slow or no regression
  - Failure or intolerable side-effects of medical therapy and prolonged loss of quality-of-life provide rationale for treatment
- Cancer control
  - Demonstrated progression on imaging
  - High likelihood of progression based on higher grade
  - FDG-avid disease

Importance of the Radiopeptide Uptake

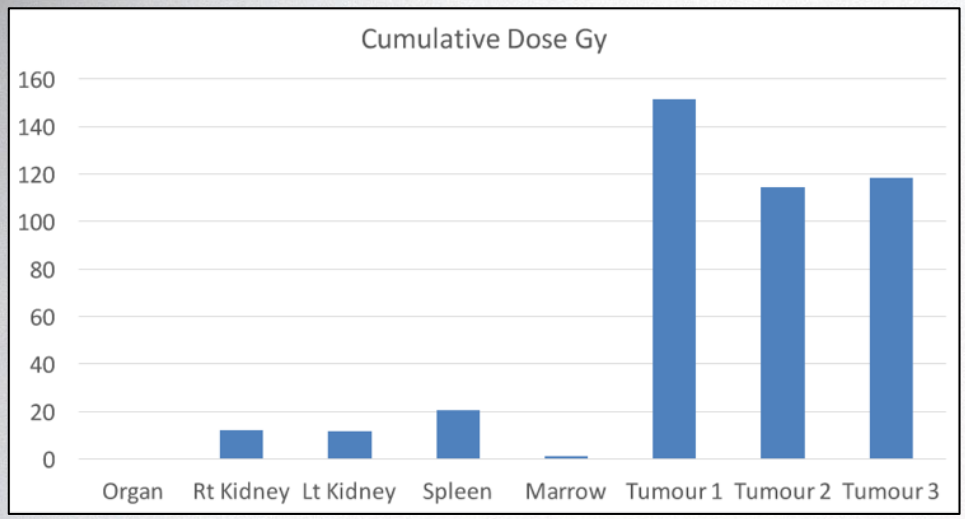


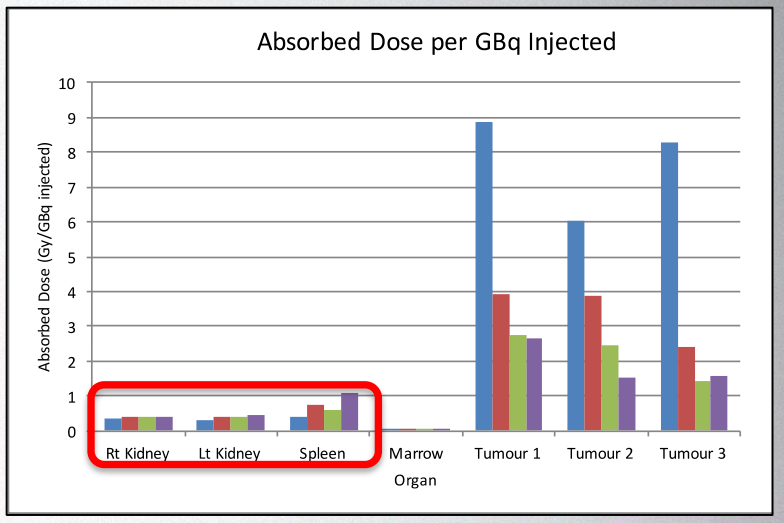
What we see translates to the radiation dose that tumour gets from PRRT!

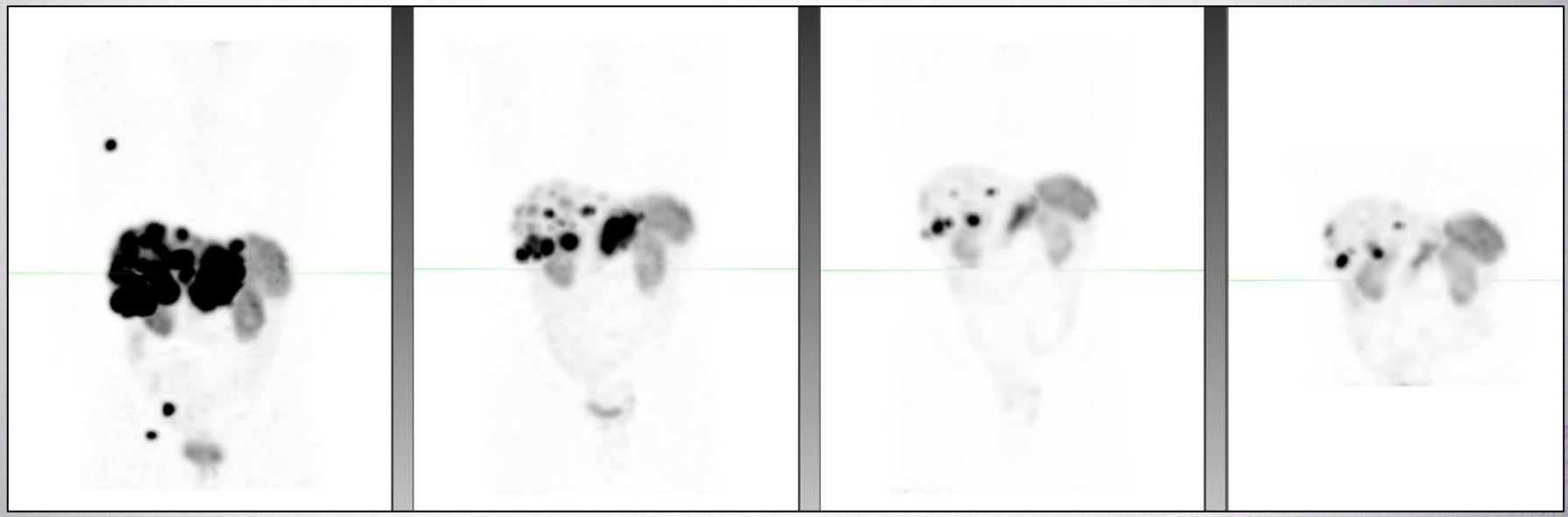
Response rate to PRRT determined by SSTR expression

Kwekkeboom D et al. *J Clin Oncol* (2008) 26:2124-2130.

Diminishing benefit as radiation dose falls



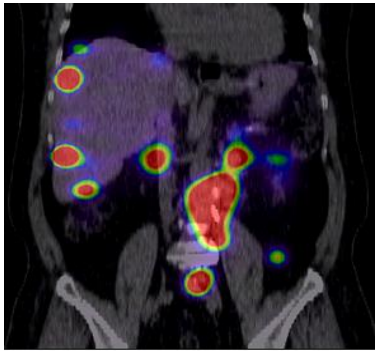


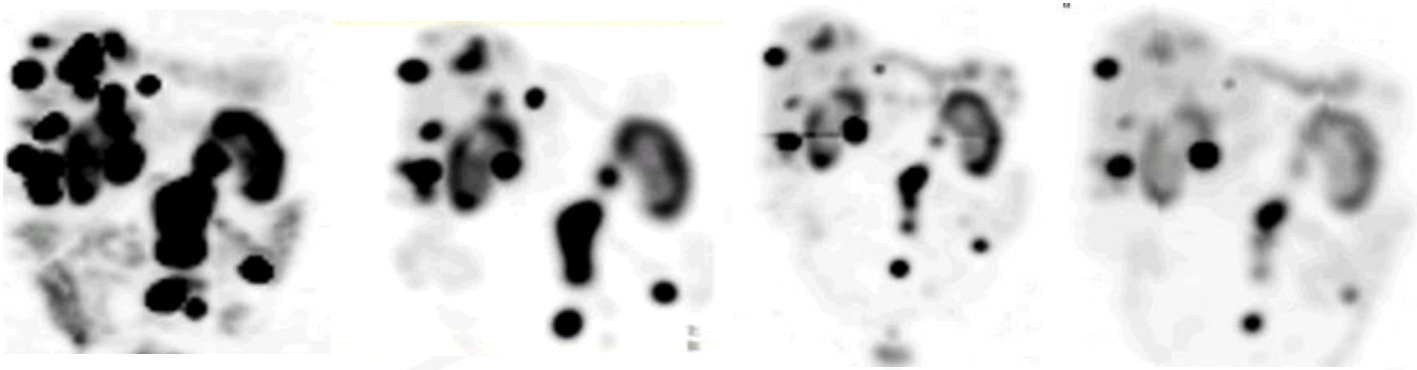


Cycle #1 Cycle # 2 Cycle #3 Cycle #4

PRRT Provides Benefits Beyond Shrinkage

77 y.o., metastatic insulinoma (Ki-67 2%)





Baseline

3 months post- 4 x LuTate

18 months

2 years

- **Intensive care and heavy medication to raise blood glucose**

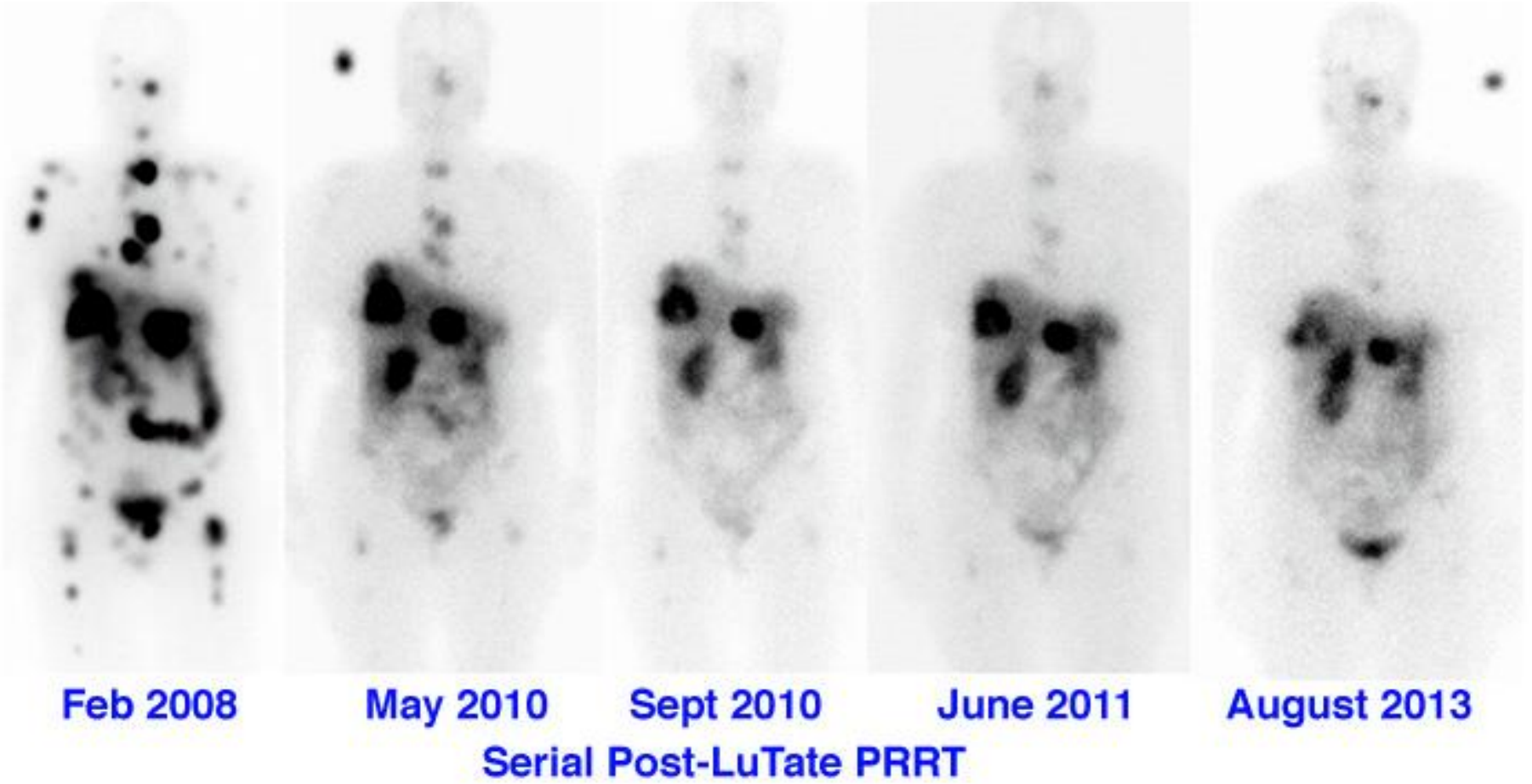
At home, low medications

Off all medications

Partial scan response
COMPLETE symptom response

Seen this month aged 85, normal blood sugars

Relief can be fast even if response is slow

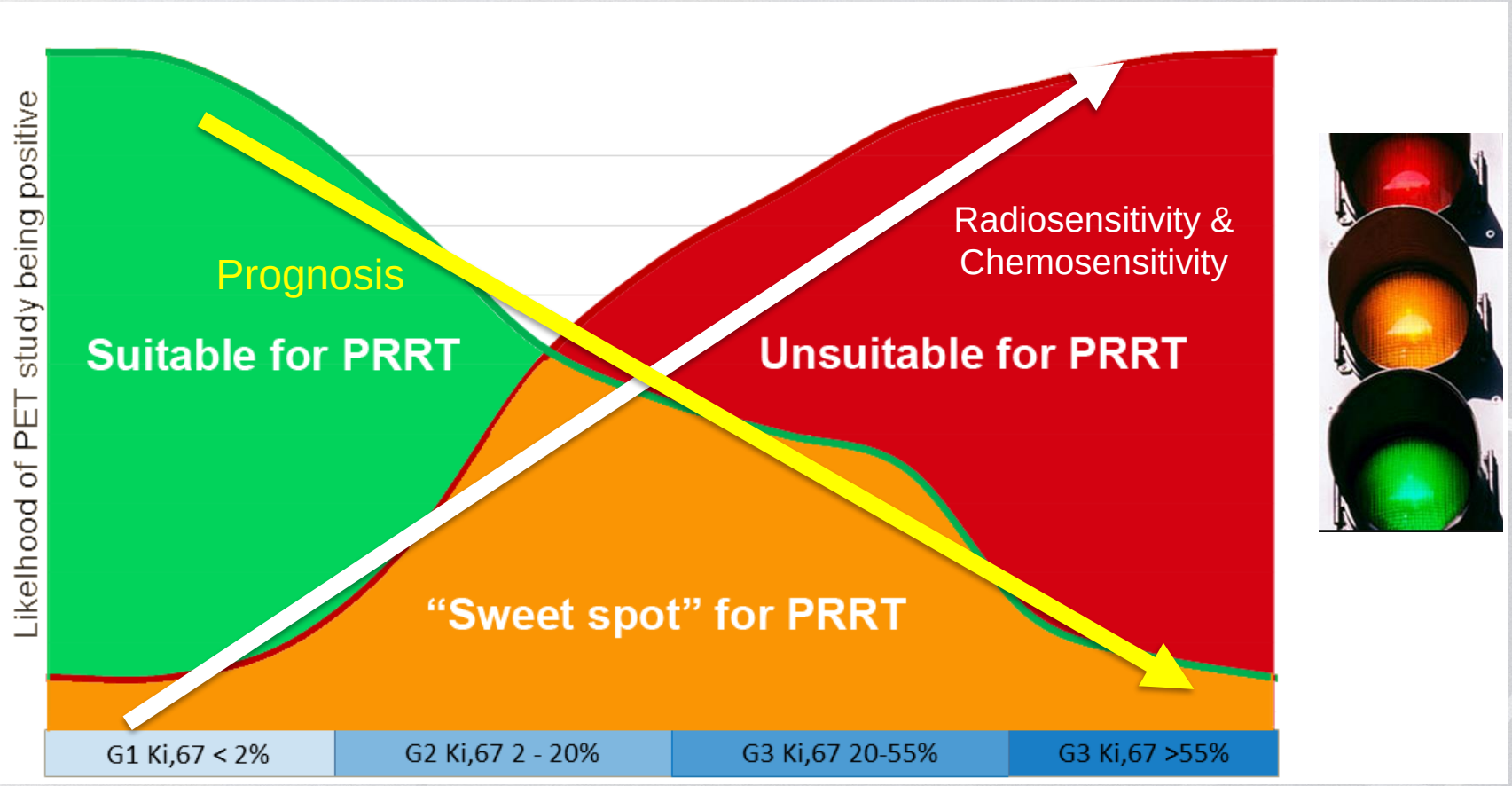


Metastatic Small Bowel NET (G1)

Pain gone by 2 weeks after cycle #1 and out of wheel-chair by cycle #2

Working by 1 year!

Using Imaging to Select for PRRT

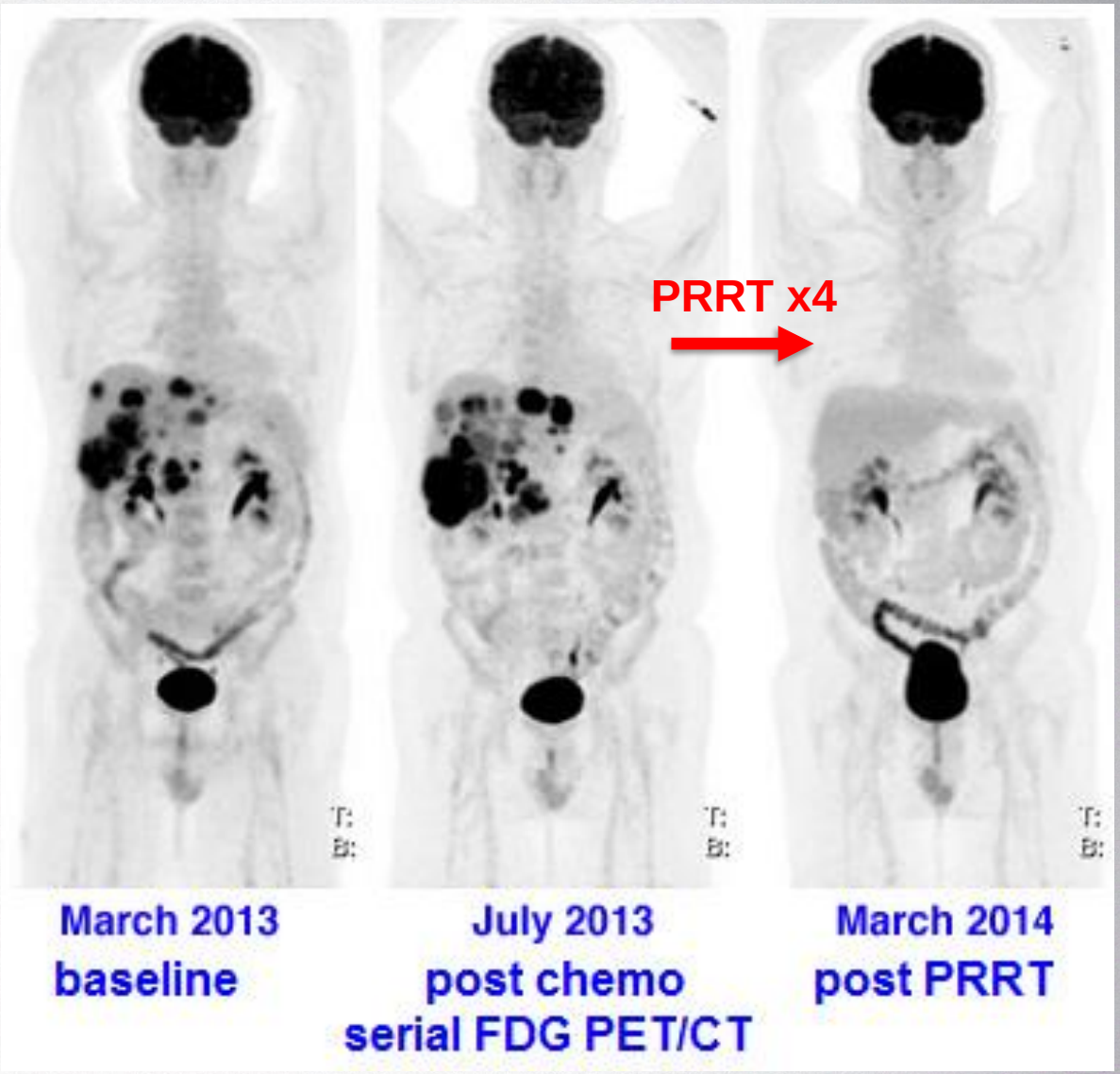


Caution required in selecting FDG-avid disease for treatment

Adapted from; Hofman MS, Hicks RJ. *Discovery Medicine* 2012;14(74):71-81

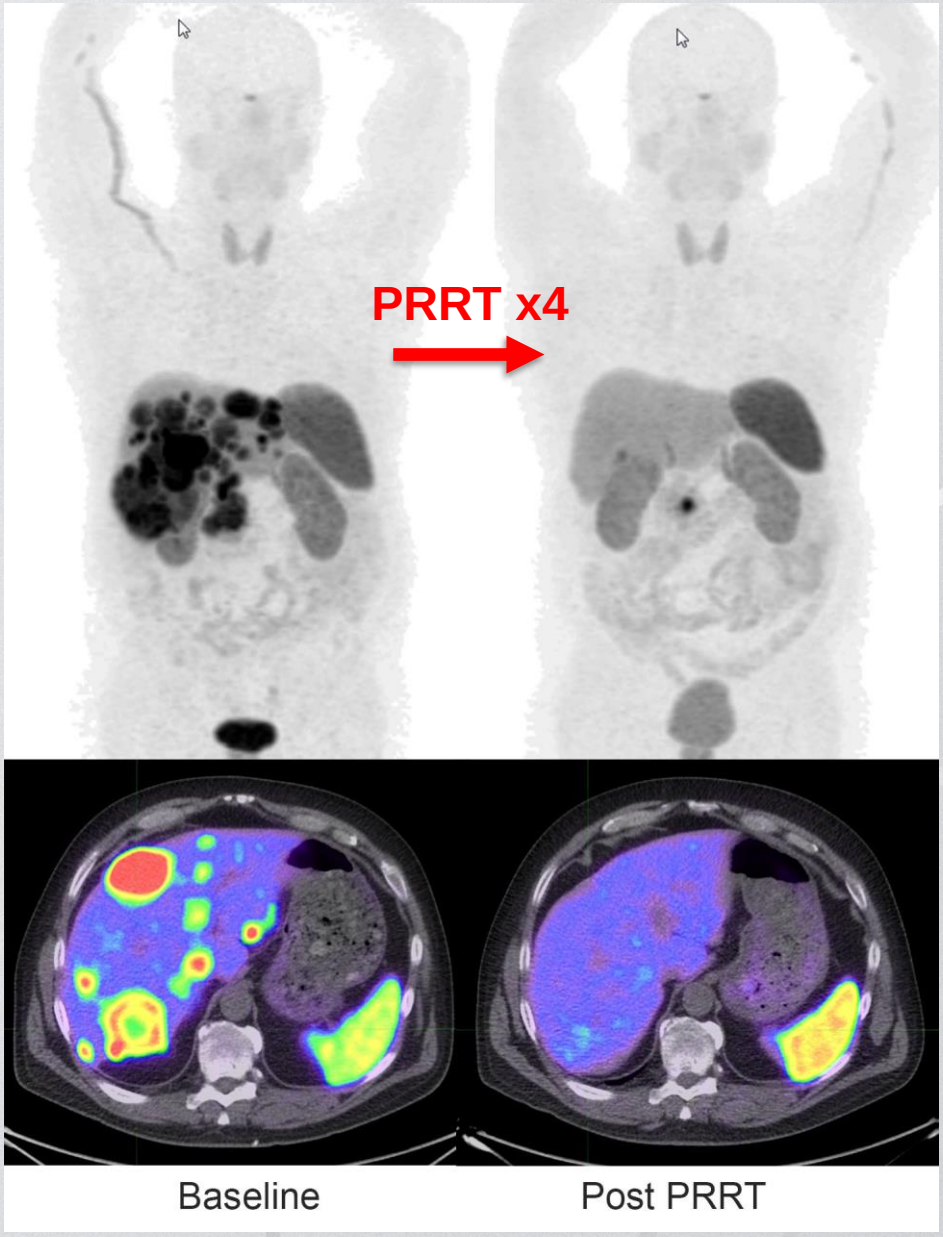
FDG Response to PRRT

G3 (Ki-67 50%)
Pancreatic NET



DA

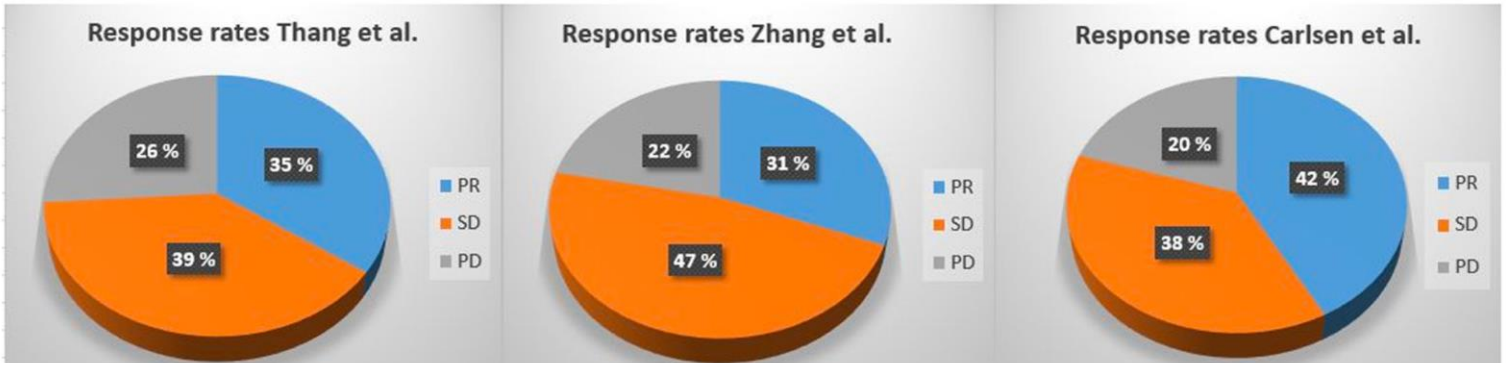
GaTate Response to PRRT

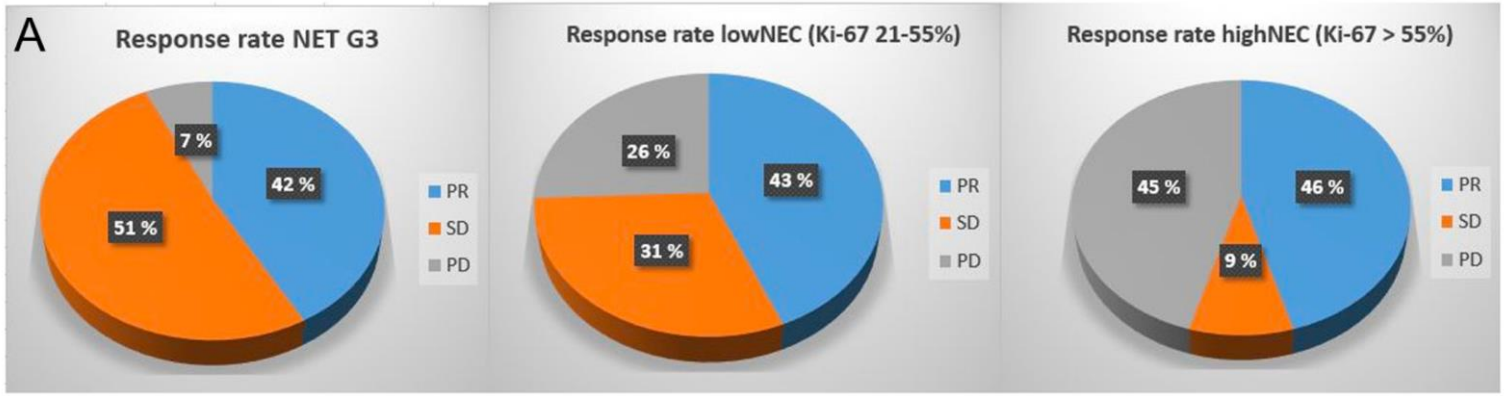


G3 (Ki-67 50%)
Pancreatic NET
ECOG 3 to 0 using
PRRT without
concommitant
chemotherapy

DA

Reproducibly High Response Rates in G3



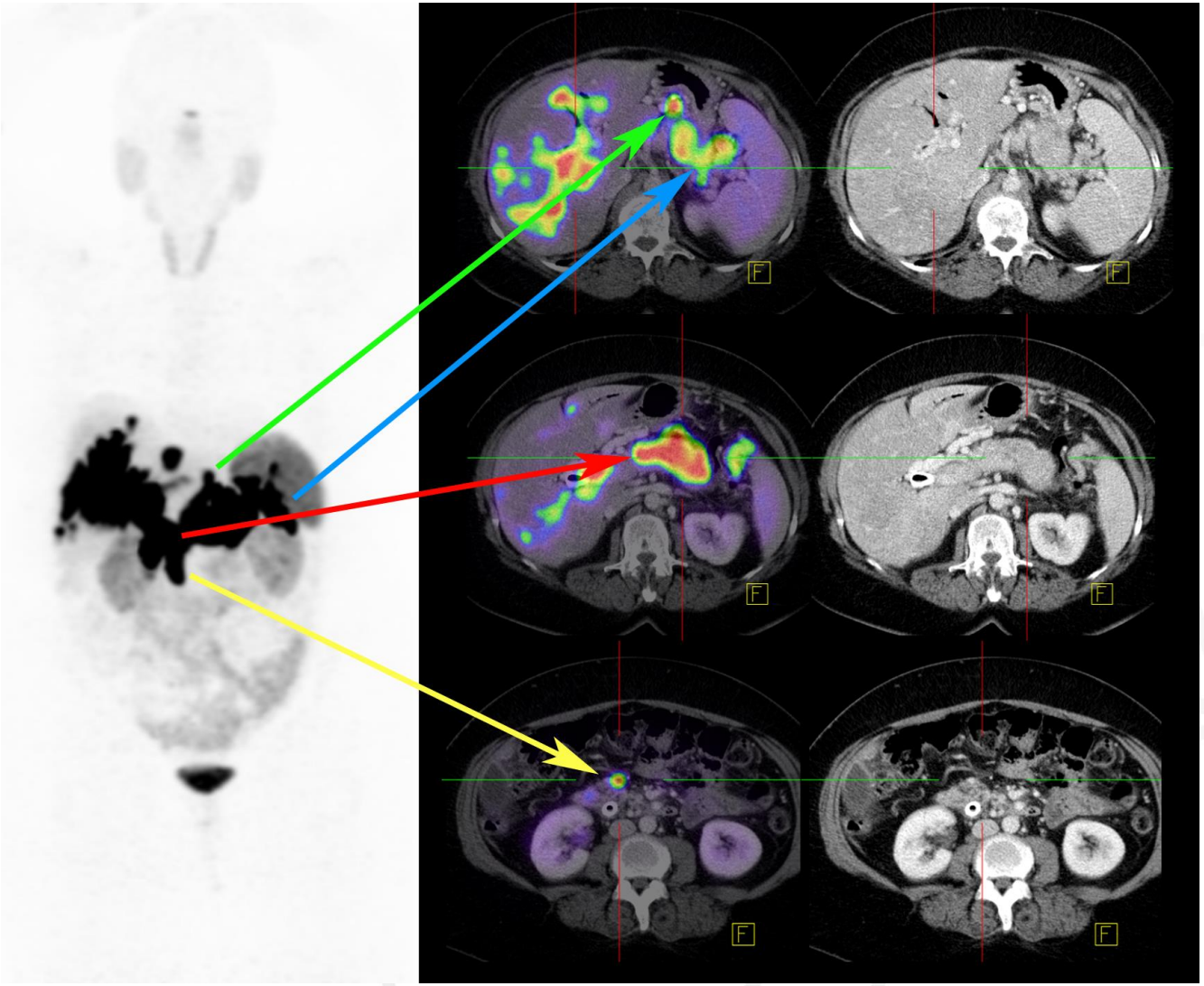


Similar results from 3 separate series

Very encouraging disease control rates

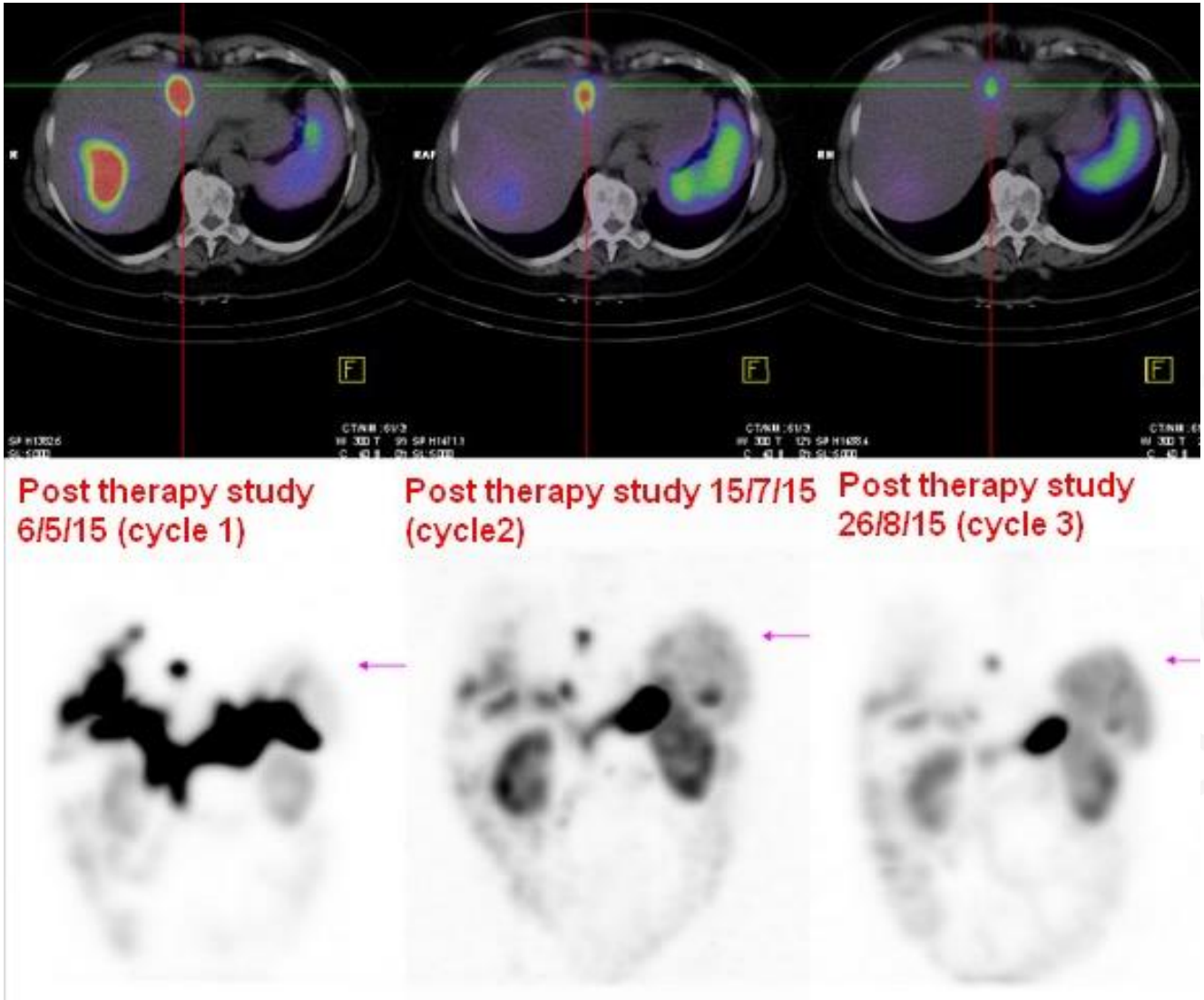
Sorbye et al. *Endocrine-Related Cancer* 2020;27:R67-R77

Is first-line PRCRT appropriate in G3 NET?



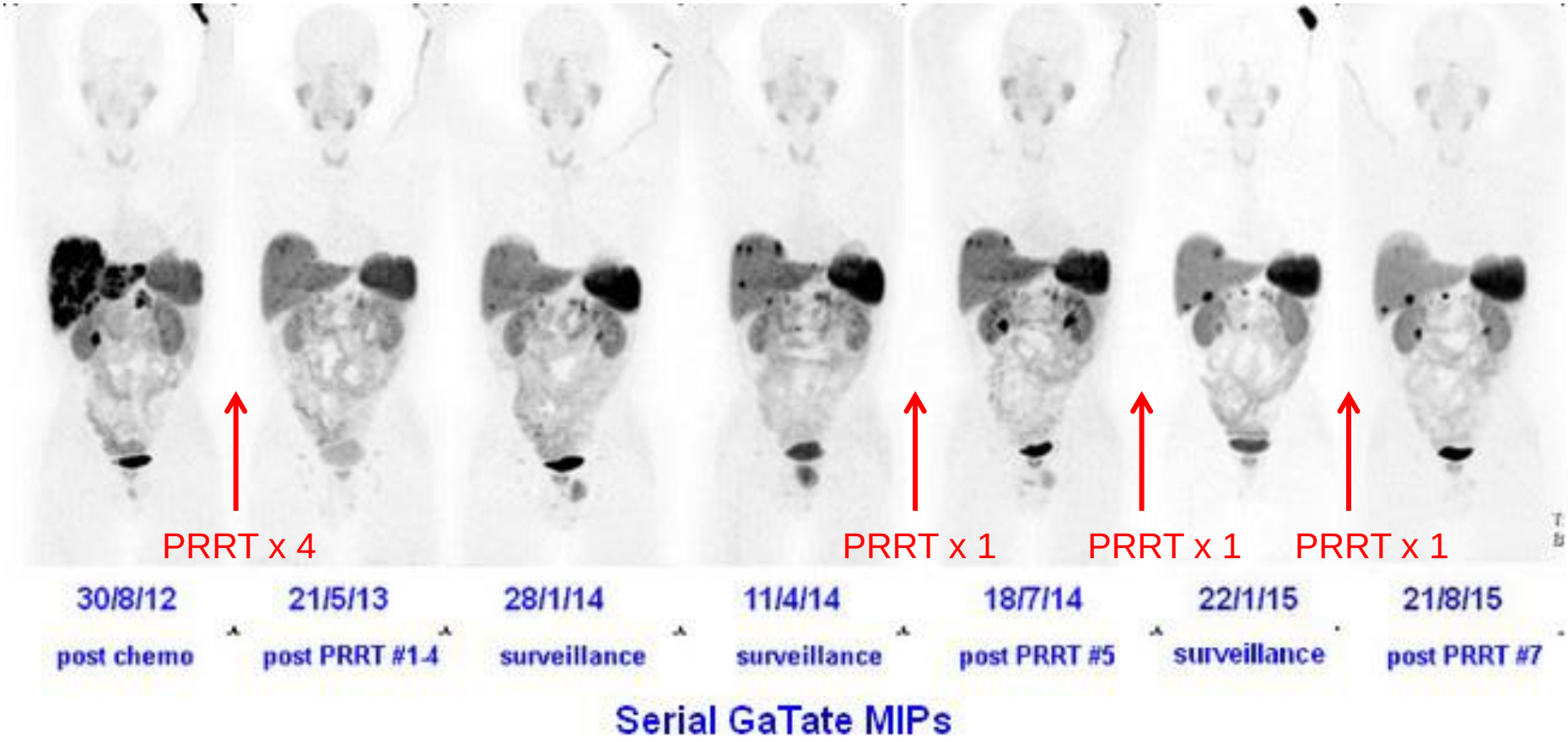
Ki-67 50%
Severe epigastric pain and increasing weight loss

The Results Speak for Themselves!



Went holidaying in France after cycle 3!

Durable Control with Maintenance PRRT



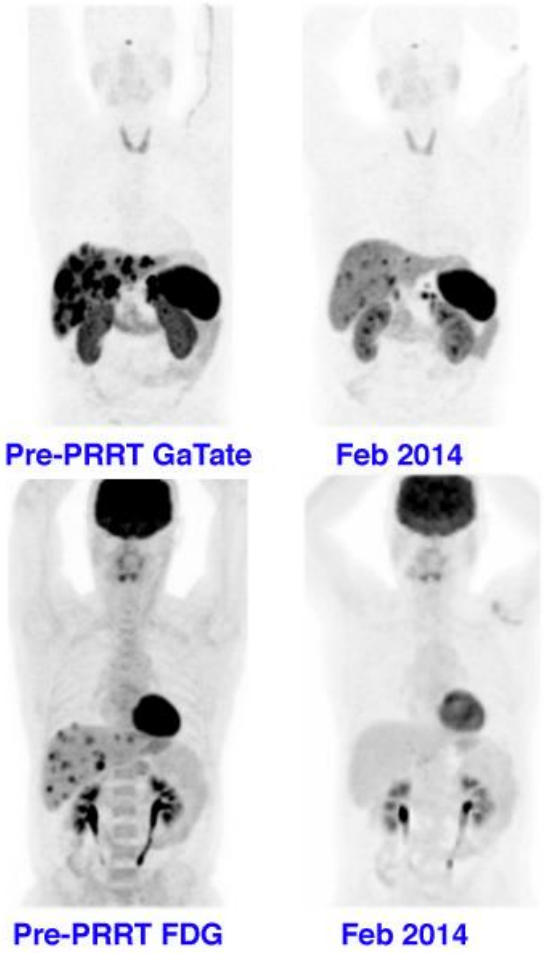
G3 (Ki-67 30%) pancreatic G3 NET with poor performance status post chemotherapy in 2012

Life is more than scans or treatment!

Travel photos following PRRT for advanced G3 NET in 2012

Off the edge or by the donkey trial – the destination may be the same, but the journey is very different

Remember what is important!



Tour de France 2015

My team thanks you all

… and our funding bodies

Australian Government
National Health and Medical Research Council

PheoPara ALLIANCE
Pheochromocytoma & Paraganglioma

AUSTRALIAN CANCER RESEARCH FOUNDATION

Unicorn Foundation
Seeking the cure for Neuroendocrine Cancers

Linking research and patient care
Victorian Cancer Agency

the PARADIFFERENCE foundation

NET NEUROENDOCRINE TUMOR RESEARCH FOUNDATION
DEDICATED TO CURING NEUROENDOCRINE CANCER