

# PRRT in Canada: The CHU de Québec – Université Laval Experience

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CANM Annual Meeting  
Toronto, April 21<sup>st</sup>, 2017

# Disclosure

- None

# Objectives

- Compare PRRT experiences across Canadian centers.
- Explain how personalization of PRRT can improve its efficacy

# PRRT at CHU de Québec – Université Laval

- PRRT program started in 2012
  - 3<sup>rd</sup> Canadian PRRT center after Edmonton and London
  - Supported by Gastrointestinal Oncology MDT
    - NET cases presented almost weekly
- Prior staff experiences:
  - Dr. Jean-Mathieu Beauregard
    - 3 y. at Peter MacCallum Cancer Centre, Melbourne, Australia
  - Dr. François-Alexandre Buteau
    - 2 y. at the Cross Cancer Institute, Edmonton
  - Dr. Alexis Bealieu
    - 1 y. at Peter MacCallum Cancer Centre (ongoing)
- Still recruiting Nuclear Oncologists!

# PRRT at CHU de Québec – Université Laval

- 36 patients treated under Special Access Program
  - Empiric (fixed-IA) PRRT
  - 124 cycles
- 37 patients treated under P-PRRT clinical trial
  - 26 PRRT-naïve patients
  - 11 previously exposed patients
  - 93 cycles to date
- Varied NETs:
  - Gastrointestinal and lung carcinoids
  - Functional and non-functional pNETs
  - Pheochromocytomas and paragangliomas
  - Esthesioneuroblastoma

# Retrospective analysis

Eur J Nucl Med Mol Imaging  
DOI 10.1007/s00259-017-3688-2



ORIGINAL ARTICLE

## Personalized $^{177}\text{Lu}$ -octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: a simulation study

Michela Del Prete<sup>1,2</sup> & François-Alexandre Buteau<sup>1,2</sup> & Jean-Mathieu Beaugard<sup>1,2</sup> 

Received: 21 October 2016 / Accepted: 20 March 2017  
# Springer-Verlag Berlin Heidelberg 2017

### Abstract

**Purpose** Peptide receptor radionuclide therapy (PRRT) with  $^{177}\text{Lu}$ -octreotate is commonly administered at empiric, fixed amounts of injected radioactivity (IA). This results in highly variable absorbed doses to critical organs and suboptimal treatment of most patients. The primary aims of this study were to design a personalized PRRT (P-PRRT) protocol based on dosimetry, and to perform a simulation of this protocol in a retrospective cohort of patients with neuroendocrine tumours, in order to assess the impact of personalized IA on absorbed doses

adjusted at each cycle in order to reach the prescribed renal absorbed dose of 23 Gy over four cycles (with a 25-50% reduction when renal or bone marrow function was impaired). Simulated IA and absorbed doses were based on actual patient characteristics, laboratory values and absorbed doses per IA delivered at each cycle.

**Results** In the P-PRRT regime, cumulative IA could have been increased to  $43.7 \pm 16.5$  GBq over four induction cycles ( $10.9 \pm 5.0$  GBq per cycle), yielding cumulative kidney, bone

# Retrospective analysis

- 36 NET patients,
  - Total of 122 fixed-IA  $^{177}\text{Lu}$ -octreotate cycles
    - 114 induction, 8 maintenance cycles
  - 22 patients completed a 4-cycle induction
  - Quantitative SPECT (QSPECT)-based dosimetry
- 1<sup>ary</sup> aim: design and simulation of a personalized PRRT (P-PRRT) regime
- 2<sup>ary</sup> aim: report on efficacy and toxicity

# Patients characteristics

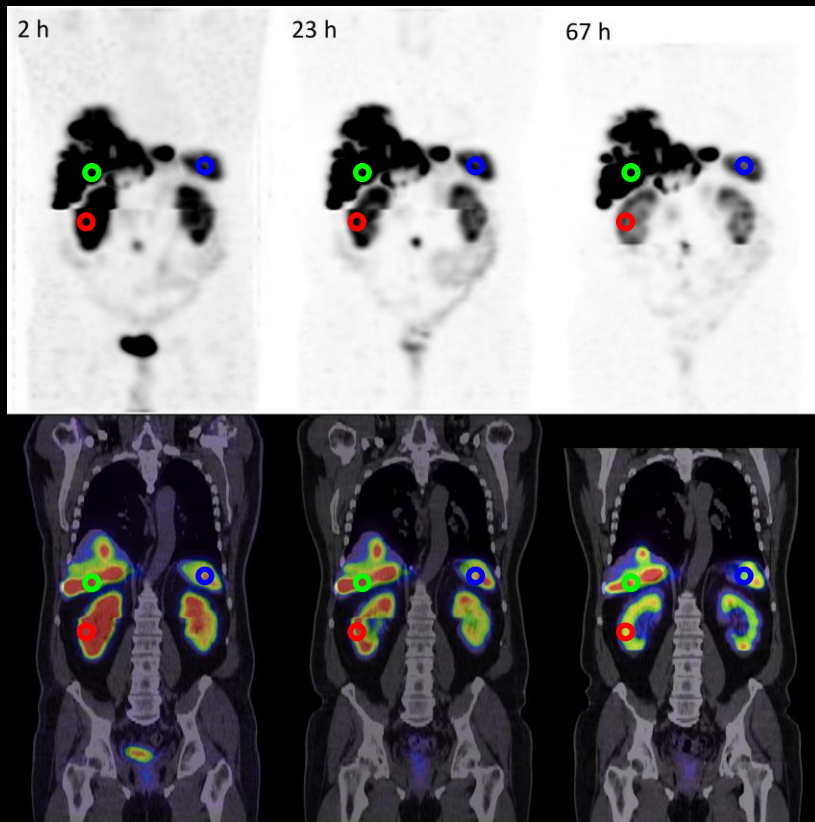
**Table 1** Patient Characteristics

	All patients (n = 36)	Patients assessed for efficacy (n = 27)		All patients (n = 36)	Patients assessed for efficacy (n = 27)
Gender, n (%)					
Female	12 (33.3)	10 (37.0)			
Male	24 (66.7)	17 (63.0)			
Age, median [range]			Tumour burden at baseline, n (%)		
At diagnosis	55.5 [24.7-78.5]	55.4 [24.7-78.5]	Extensive	4 (11.1)	3 (11.1)
At first cycle	63.5 [37.6-81.6]	63.1 [34.6-81.6]	Moderate	24 (66.7)	19 (70.4)
Baseline weight loss, n (%)	7 (19.4)	4 (14.8)	Limited	8 (22.2)	5 (18.5)
Site of primary tumour, n (%)			Tumour uptake at baseline, n (%)		
Small intestine	17 (47.2)	13 (48.2)	4	17 (47.2)	11 (40.8)
Pancreas	10 (27.8)	8 (29.6)	3	18 (50.0)	15 (55.5)
Lung	3 (8.3)	2 (7.4)	2	1 (2.8)	1 (3.7)
Adrenal gland <sup>a</sup>	2 (5.6)	2 (7.4)	Hormonal symptoms, n (%)	25 (69.4)	17 (63.0)
Colon	1 (2.8)	1 (3.7)	Previous treatments, n (%)		
Unknown	3 (8.3)	1 (3.7)	Somatostatin analogues	33 (91.7)	23 (85.2)
Grade, n (%)			Surgery	27 (75.0)	22 (81.5)
G1	6 (16.7)	3 (11.1)	Everolimus and/or sunitinib	20 (55.5)	12 (44.4)
G2	15 (41.6)	11 (40.8)	Loco-regional therapy	16 (44.4)	8 (29.6)
G3	2 (5.6)	2 (7.4)	Chemotherapy	14 (38.8)	11 (40.8)
Unknown	13 (36.1)	11 (40.8)	Concomitant treatments, n (%)		
Metastases, n (%)			Somatostatin analogues	27 (75.0)	21 (77.8)
Liver	29 (80.6)	19 (70.4)	Capecitabine	2 (5.6)	1 (3.7)
Lymph nodes	14 (38.9)	11 (40.8)	Everolimus	1 (2.8)	1 (3.7)
Bone	8 (22.2)	5 (18.5)	Baseline laboratory abnormalities, n (%)		
Lung	5 (13.8)	3 (11.1)	Haemoglobin < 10.0 g/dL	3 (8.3)	2 (7.4)
Other <sup>b</sup>	9 (25.0)	8 (29.6)	eGFR < 60 ml/min/1.73 m <sup>2</sup>	4 (11.1)	3 (11.1)



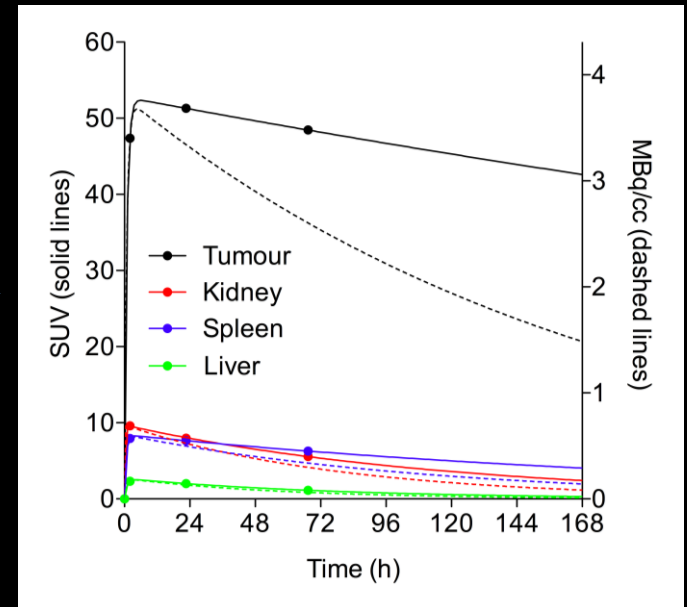
# $^{177}\text{Lu}$ QSPECT Dosimetry

## Serial post-therapy QSPECT/CT



2-cm VOI activity sampling

## Time-activity curves integration



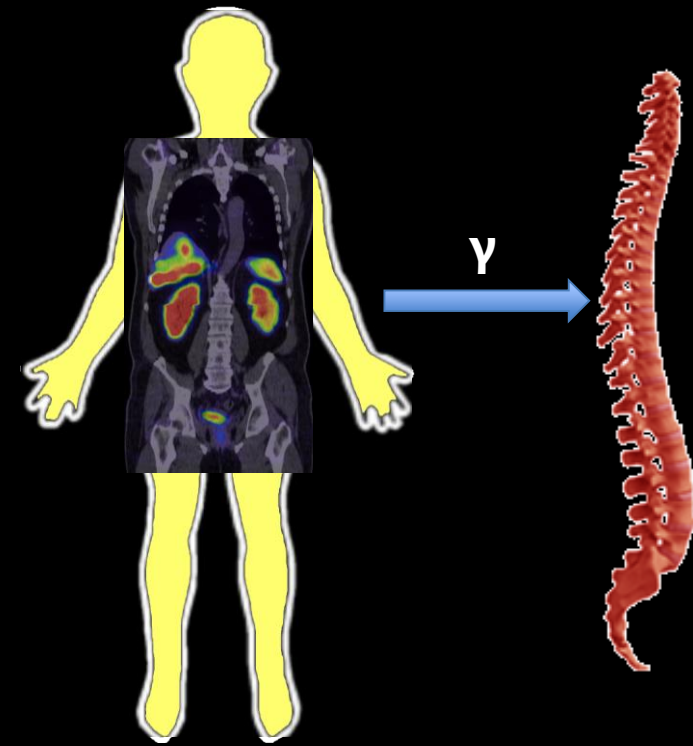
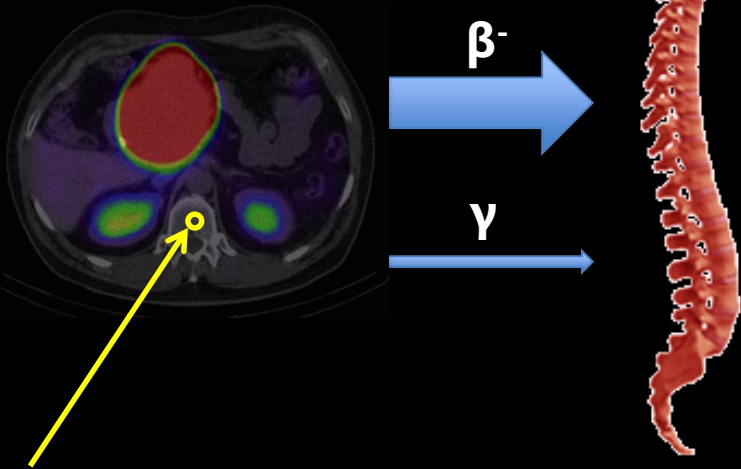
## DOSIMETRY

	Radiation dose (Gy)
Liver	0.97
Kidney	4.8
Spleen	6.0
Tumor	56.8

# QSPECT bone marrow dosimetry

Self-dose

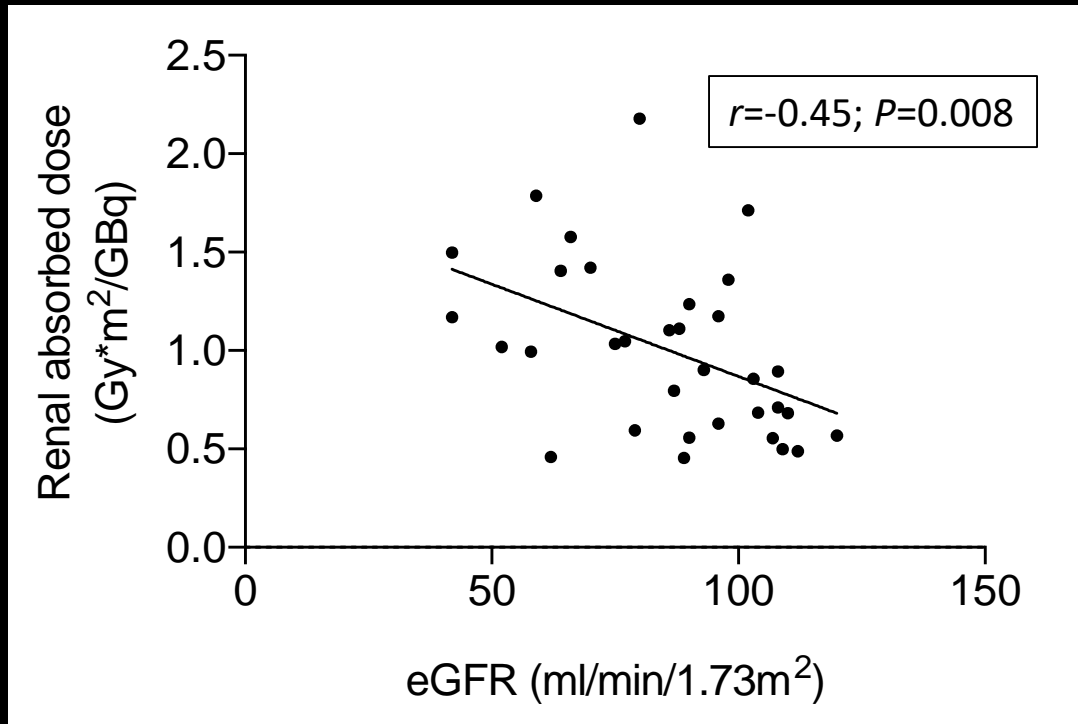
Cross-dose



Direct sampling (e.g. L4 body)

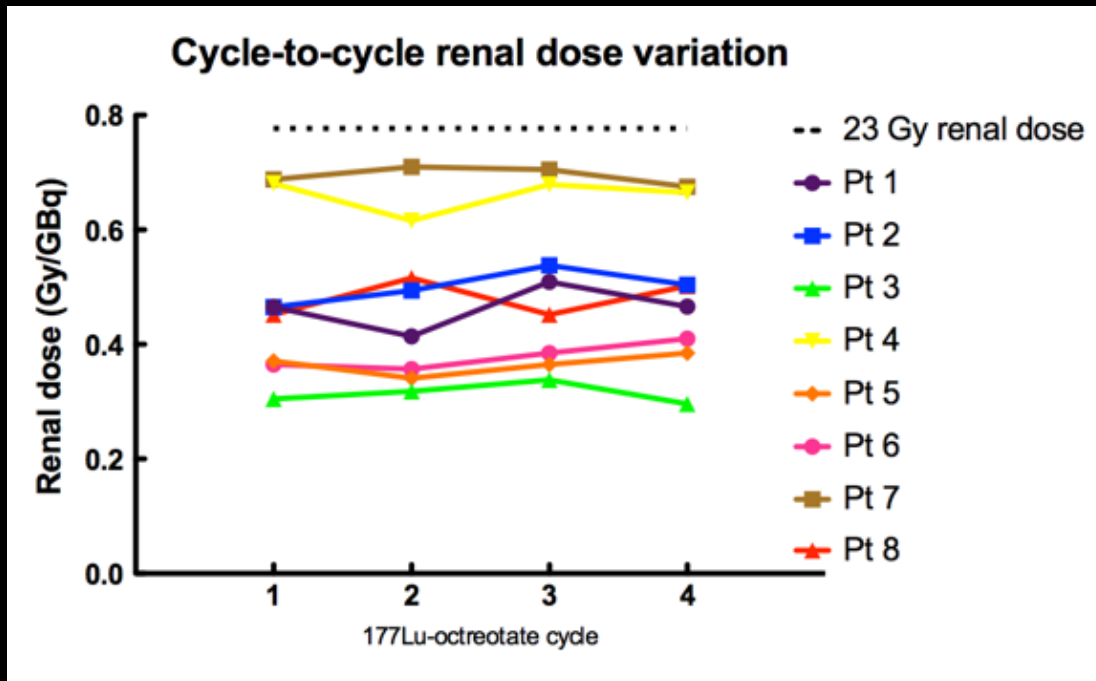
Whole-body %ID retention: total QSPECT activity  
+ extrapolation to remainder of body

# Personalized IA: Cycle 1



$$\text{Personalized IA (GBq)} = \frac{\text{Prescribed renal absorbed dose (Gy)} * \text{BSA (m}^2\text{)}}{-0.0094 * \text{eGFR (mL/min/1.73m}^2\text{)} + 1.81}$$

# Personalized IA: Cycles 2-3-4



Mean cycle-to-cycle renal dose difference =  $-0.7 \pm 9.9\%$   
(range: -18.5 to 14.3 %)

Montegiani JF, et al.  
*J Nucl Med* 2014; 55(S1):198

Personalized IA = Prescribed renal dose \* Prior cycle(s) renal absorbed dose/IA  
(GBq) (Gy) (Gy/GBq)

# Personalized PRRT Simulation

- Prescribed renal dose:
  - 23 Gy over 4 induction cycles
    - 5 Gy at 1<sup>st</sup> cycle
    - Remaining dose divided between following cycles
  - 6 Gy at each consolidation/maintenance cycle
- Dose reduction if impaired renal or BM function
  - 25% if grade 2 impairment
  - 50% if grade 3+ impairment
- IA increase limited to 50% above highest IA received
  - 25% if grade 2 subacute toxicity
  - 0% if grade 3+ subacute toxicity

# P-PRRT Simulation Results

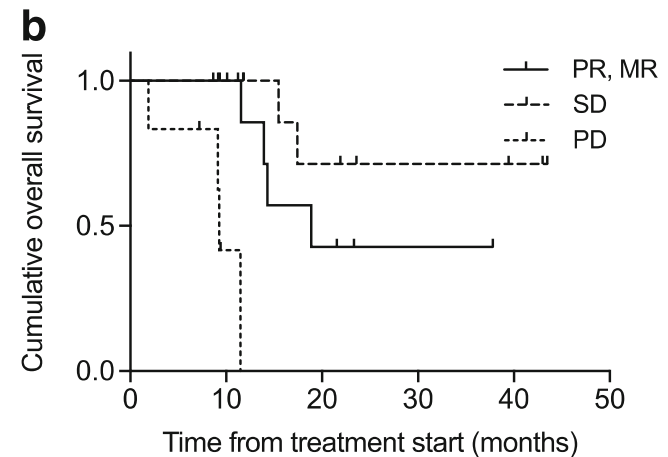
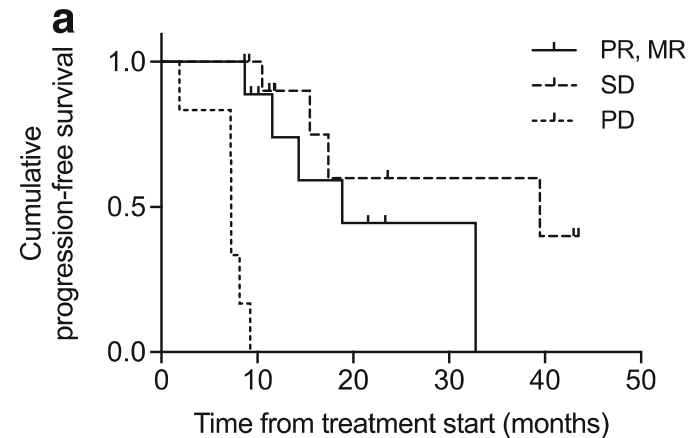
**Table 2** Comparison of administered activity and absorbed doses between the empiric and personalized PRRT regimes

	Per cycle ( <i>n</i> = 122)			Per four-cycle induction course ( <i>n</i> = 22)		
	Empiric	Personalized	Ratio	Empiric	Personalized	Ratio
Injected activity (GBq)	7.4 ± 0.8	10.9 ± 5.0	1.47 ± 0.66	29.6 ± 2.4	43.7 ± 16.5	1.47 ± 0.53
Doses (Gy)						
Kidney	4.0 ± 1.4	5.4 ± 1.9	1.47 ± 0.66	16.0 ± 5.1	21.5 ± 2.5	1.49 ± 0.54
Bone marrow <sup>a</sup>	0.33 ± 0.23	0.43 ± 0.27	1.46 ± 0.67	1.30 ± 0.73	1.63 ± 0.61	1.45 ± 0.52
Tumour (maximum)	30.0 ± 18.8	43.0 ± 29.7	1.47 ± 0.66	115.6 ± 58.3	163.4 ± 85.9	1.48 ± 0.51
Dose per injected activity (Gy/GBq)						
Kidney	0.55 ± 0.20			0.55 ± 0.19		
Bone marrow <sup>a</sup>	0.046 ± 0.033			0.045 ± 0.025		
Tumour (maximum)	4.2 ± 2.9			4.0 ± 2.2		

- Induction P-PRRT vs. empiric PRRT:
  - Average **1.48-fold** increase in cumulative tumor dose
    - range, 0.68–**2.64-fold**; P = 0.0013
  - No patient significantly exceeding 23 Gy to the kidney

# Efficacy ( $n=27$ )

- Response rates at 3 mo. post-induction
  - PR/MR: 33%
  - SD: 44%
  - PD: 22%
- Survival
  - PFS: 17.4 mo.
  - OS: 18.9 mo.
- PFS and OS significantly shorter in patients with PD



# Safety

	Per cycle	Per patient
<b>Commonest acute side effect</b>		
Nausea	7.4 %	25 %
<b>Grade 3-4 subacute toxicity</b>		
Lymphocytopaenia	18 %	36 %
Worsening of liver function tests	9 %	19 %
Leukopeania	0.8 %	2.8 %
<b>Grade 3-4 chronic toxicity (&gt;3 mo. post-induction)</b>		
Lymphocytopaenia	—	16 %
Acute myeloid leukaemia	—	5.3 % (n=1)

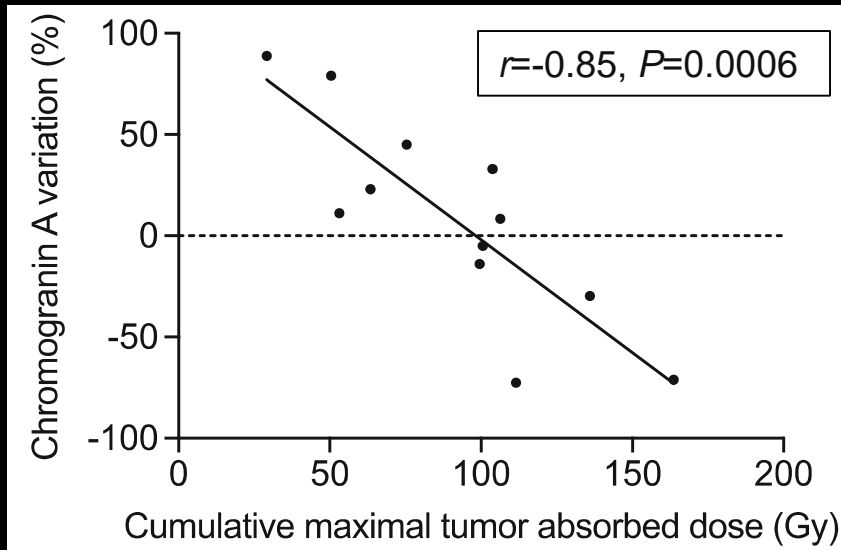


# Dose-effect relationships

Cg-A variation

vs.

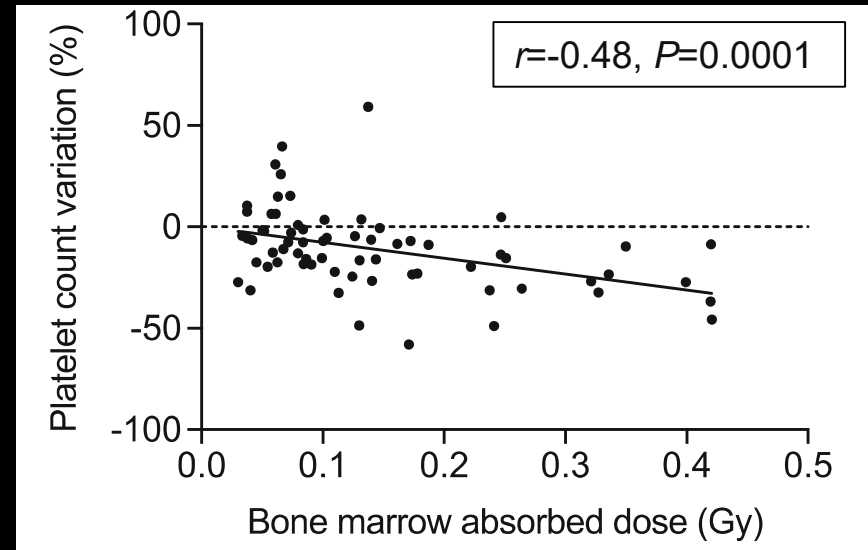
Cumulative max tumor dose



Platelet count variation

vs.

Per-cycle bone marrow dose

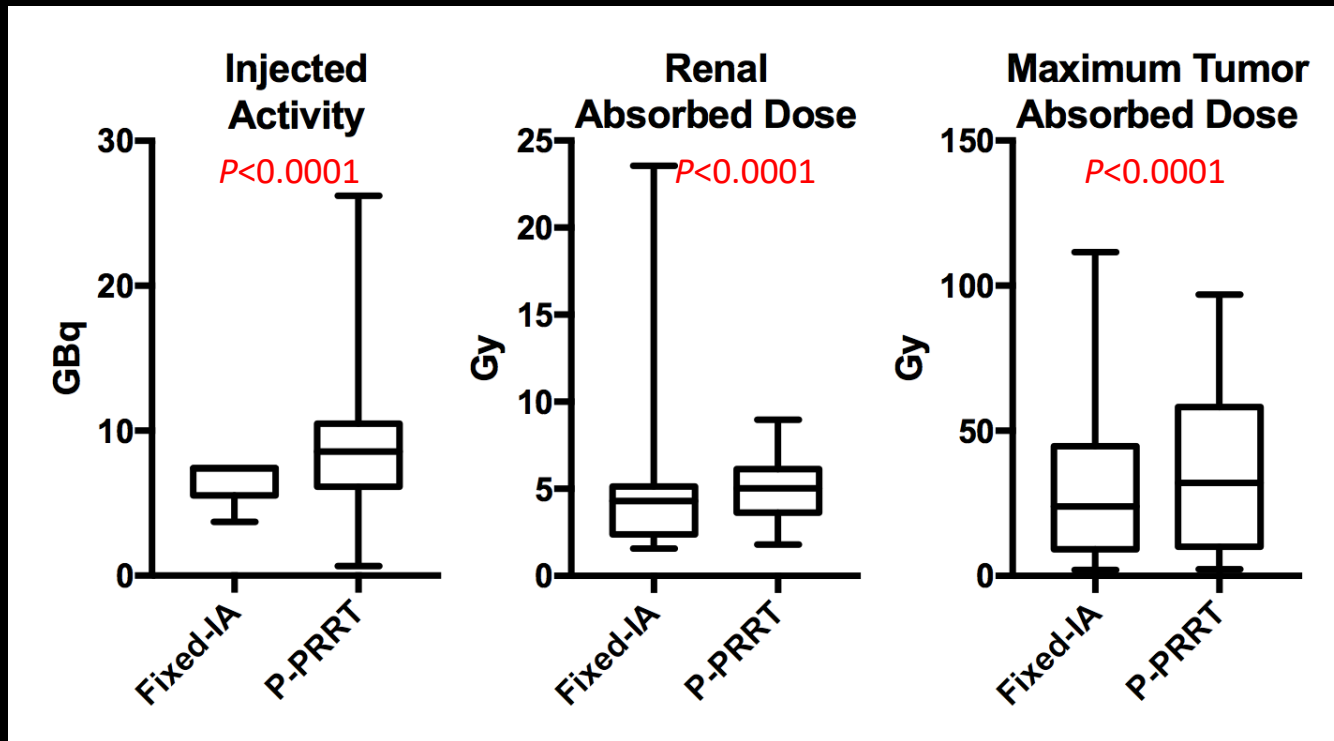


# Personalized PRRT of Neuroendocrine Tumors: The P-PRRT Trial

*ClinicalTrials.gov: NCT02754297*

- Prospective, open-label, single-arm, phase 2 trial
- Progressive or symptomatic NET of any origin
  - Octreoscan or  $^{68}\text{Ga}$  SSTR-PET positive
- 4 induction cycles of  $^{177}\text{Lu}$ -octreotate
  - Prescribed renal dose: 23 Gy
- Additional maintenance cycles offered to responders
- Endpoints
  - Primary: response rates 3 mo. post-induction
  - Secondary: PFS, OS, safety

# Administered activity and dosimetry (preliminary results from 55 cycles in 27 patients)



Median **1.26-fold** increase in IA and doses (vs. simulated fixed-IA PRRT)  
*Up to 3.54-fold increase in patients with low renal dose/IA*

# Short-term safety

## Commonest acute side effects

	<b>Per cycle (n=55)</b>	<b>Per patient (n=27)</b>
Nausea	18.2 %	22.2 %
Vomiting	5.5 %	7.4 %
Abdominal pain/discomfort	5.5 %	7.4 %

## Grade 3 or 4 subacute toxicity

	<b>Per cycle (n=45)</b>	<b>Per patient (n=26)</b>
Lymphocytopenia	24.4 %	30.8 %
Altered liver function tests	4.4 %	7.7 %
Anemia	2.2 %	3.8 %
Thrombocytopenia	2.2 %	3.8 %

# P-PRRT at CHU de Québec – Université Laval

- Standard renal dose over 4 induction cycles
  - Personalized injected activity
- Maximized tumor absorbed dose
  - And thus potential benefits
- Safe on the short term
  - No excess severe chronic toxicity anticipated
- Feasible
  - Low excess resources over  $^{177}\text{Lu}$ -octreotate cost

# Referral for PRRT

- We accept all Canadian patients
- Referral package (everything including CDs in a single mailing):
  - Case summary
  - Pathology and surgery reports
  - Reports and images on CDs of:
    - 2 latest Octreoscans or Ga-68 PET (latest <3 months)
    - 2 latest CT or MRI (latest <3 months)
    - FDG-PET and/or MIBG scan if any performed
  - Recent labs (CBC, renal/hepatic biochemistry, tumor markers)
- Telephone consult for out-of-province patients

# Acknowledgements

- Nuc. oncologist colleagues
  - Dr. François-Alexandre Buteau
  - Dr. Alexis Beaulieu
- CHU de Québec  
Gastrointestinal Oncology  
Multidisciplinary Team
  - Dr. Jean-François Ouellet
  - Dr. Félix Couture
- NM technologists and PRRT  
nursing staff
- Radiopharmacists:
  - Gilbert Matte
  - Doug Abrams
- Clinical Research Platform:
  - Geneviève Filion
- Physicists:
  - Anna Celler
  - Curtis Caldwell
  - Philippe Després
- Research Funding (related  
to clinical PRRT program):
  - Fonds de recherche du  
Québec – Santé
  - Canadian Institutes of Health  
Research

*Thank you !*