

Peptide Receptor Radiation Therapy (PRRT) in Patients with Neuroendocrine Tumors: The Edmonton Experience

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Granting Agencies

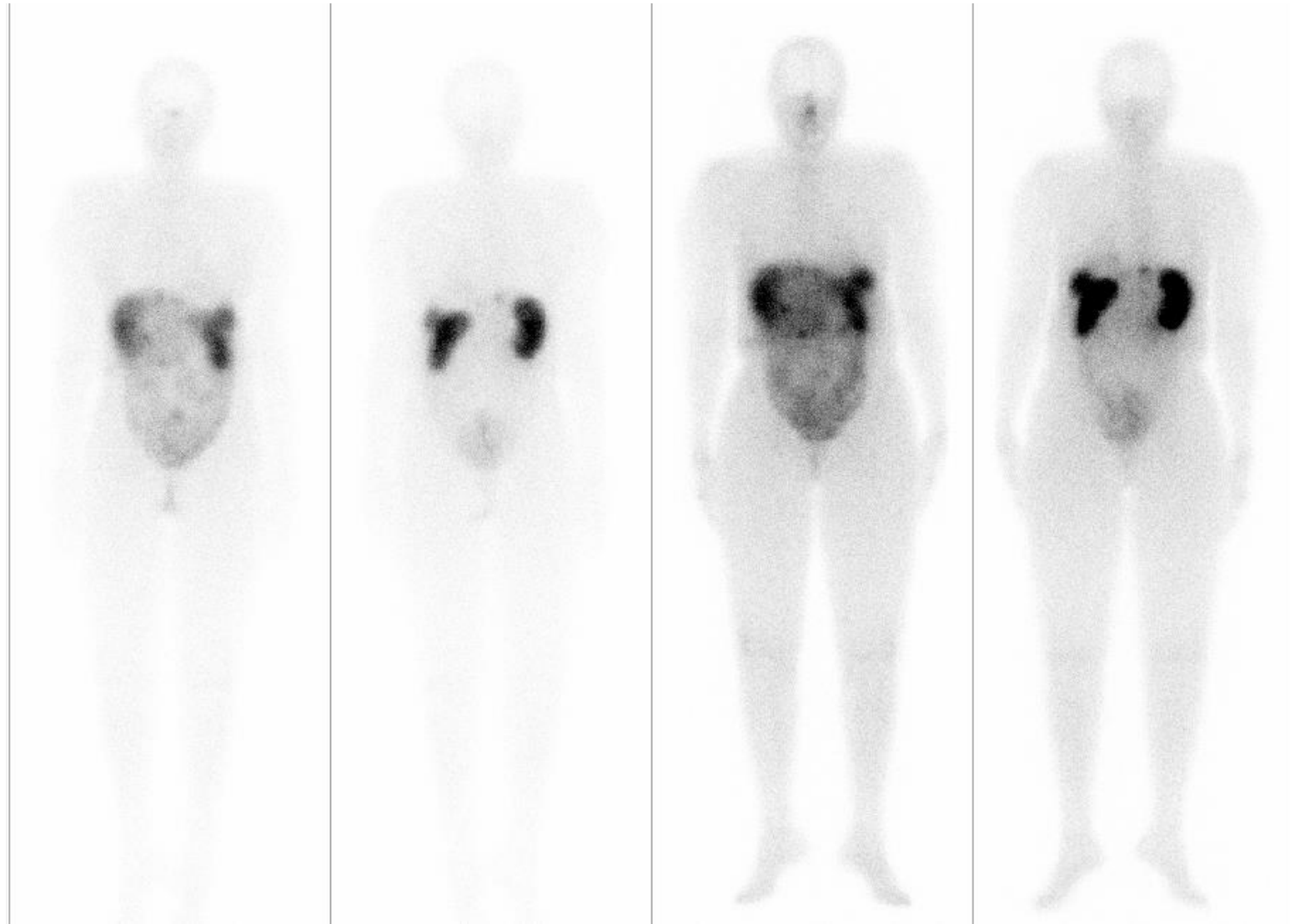
- AHFMR
- CIHR
- ACF
- CFI

Peptide Receptor Radiation Therapy (PRRT) Systemic Radiation Therapy

The systemic administration of a targeted radionuclide utilizing short range beta (alpha) particles or electron emissions to achieve a clinically important outcome for a patient with primary or metastatic cancer:

- Symptom control/increased QOL
- Disease stabilization
- (Good) Partial remission
- Complete remission

My Personal Experience

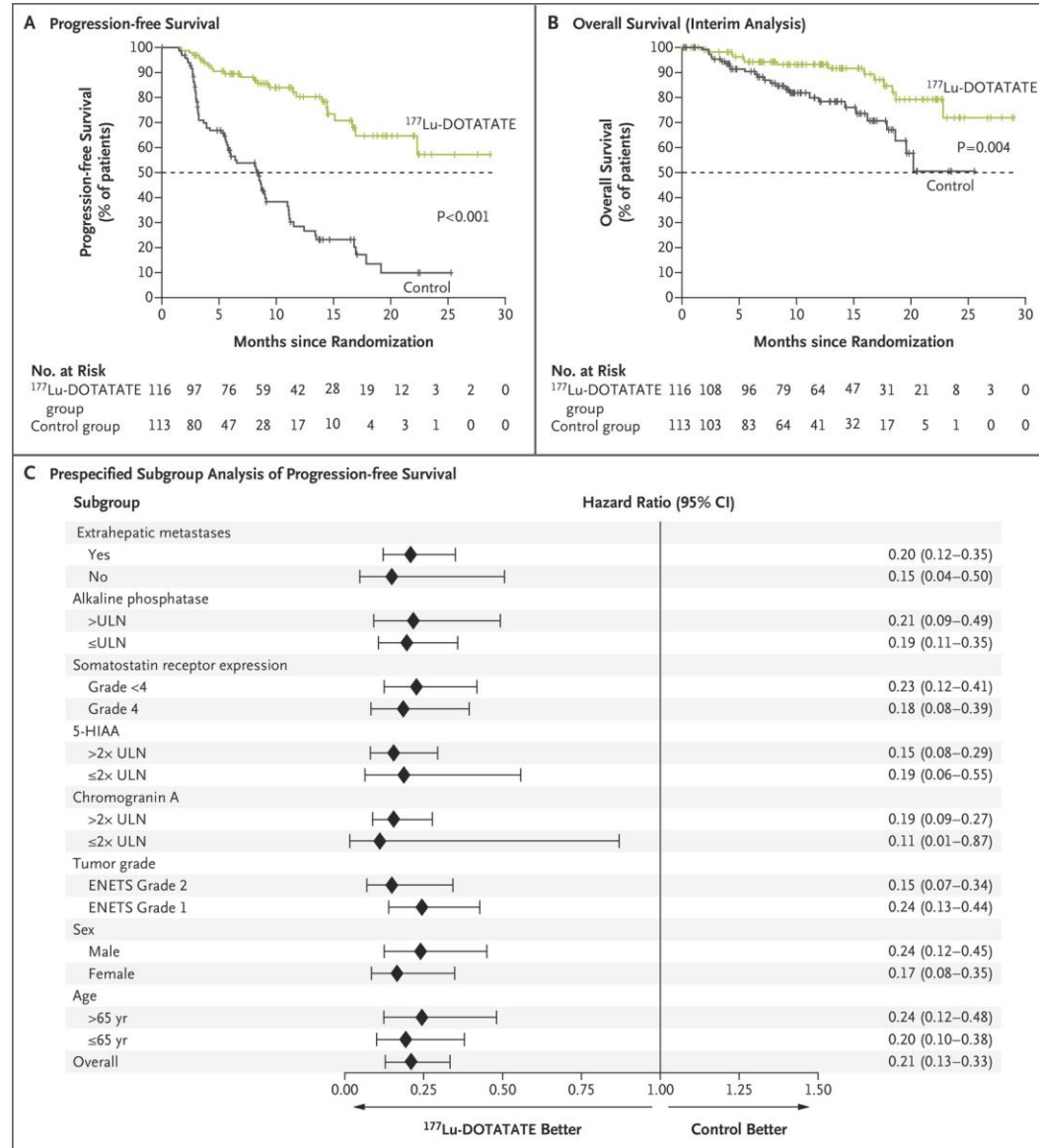


Strosberg J. et al.

N Engl J Med 2017;376:125-35

- Locally advanced or metastatic midgut neuroendocrine tumour
- 229 Patients
 - 116: Active arm
 - 30 mg. Sandostatin LAR q. 28 days
 - 7400 MBq. ¹⁷⁷Lu DOTATATE q. 8 weeks X 4
 - Amino Acid Solution in 2 litres with ¹⁷⁷Lu DOTATATE infusion
 - 113 Control Arm
 - 60 mg. Sandostatin LAR q. 28 days

Progression-free Survival and Overall Survival.



The Edmonton Lu-177 Protocol

Hypothesis: Induction & long-term maintenance therapy with Lu-177 improves outcomes in patients with NETs, and is effective and safe for these patients.

The Edmonton Lu-177 Protocol

- Clinical Protocol: up to 12 cycles in total
 - *Induction*: 4 cycles of up to 5.55 GBq/cycle every 2.5 – 3.5 months
 - *Maintenance*: up to 8 cycles of up to 3.7 GBq/cycle every 6 – 10 months

Edmonton Lu-177 Protocol

Therapy Number	Year	Frequency	Evaluations
Induction 1 - 4	1	Every 10 - 12 weeks	CT/MRI scans and blood work/urine 4 months after therapy 4.
Maintenance 5 - 6	2	Every 6 months (range 5 – 8 months)	CT/MRI scans and blood work/urine 4 months after therapy 5 & 6.
7 - 8	3	Every 6 months (range 5 – 9 months)	CT/MRI scans and blood work/urine 4 months after therapy 7 & 8.
9 +	4	Every 6 - 9 months (range 6 – 12 months)	CT/MRI scans and blood work/urine 4 months after each subsequent therapy.

Edmonton Lu-177 Protocol Interim Analysis

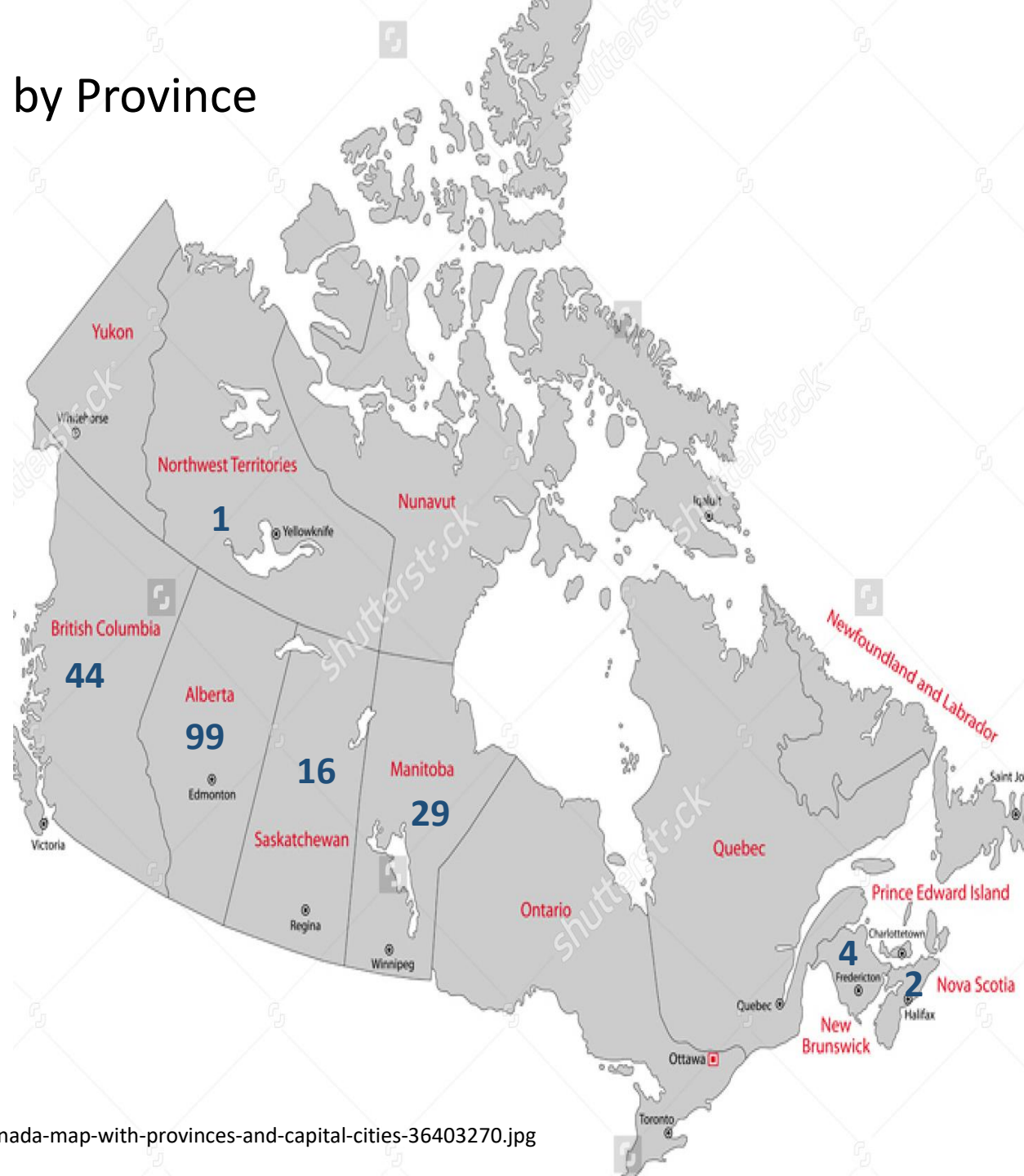
- First Treatment: October 2010
- Total Patients treated: 248
 - SAP: 53
 - CTA 195
PNET=50, GNET=102, pGNET=18 , Pheo=6, Pulmonary=8 , Other=11
- Total # individual treatments: 1342
- Average # treatments per patient: 5.2
- Total GEPNETs: 170
- GEPNETs in interim analysis: 138

Total # Patients Treated in Edmonton with ¹⁷⁷Lu DOTATATE (to December 2016)

Lu treatments to 31 Dec 16 (6 years)	On Trial	On SAP*	Total
1	13	8	21
2	18	9	27
3	11	6	17
4	38	18	56
5	21	4	25
6	25	8	33
7	20	-	20
8	12	-	12
9	16	-	16
10	9	-	9
11	5	-	5
12	7	-	7
TOTAL	195	53	248

* Special Access Program (Health Canada)

Total Trial Referrals by Province



Distribution of PRRT Patients (PNETs and GNETs only) at CCI – Edmonton Lu-177 Protocol:
Interim Analysis March 31, 2016

Patients enrolled with at least 1 Rx	138
Mean age at start of Rx	61.3 years (26.5-84.4)
Male/Female	74/64
Total PNETS	44
Total GNETS	84
Total Presumptive GNETS	10

Cumulative Administered Doses - GEPNETs

Patients (n= 138)	Cycles of Lu-177	Cumulative Dose (GBq)	Patients Discontinued after cycles (n = 13)	Mean time from 1 st Rx (months)
30	1 – 2	5.76 ± 2.39	2	3.1
26	3 – 4	17.90 ± 3.35	3	9.2
33	5 – 6	23.67 ± 3.87	1	17.7
28	7 – 8	32.98 ± 4.34	4	34.2
13	9 – 10	40.25 ± 2.88	2	46.9
8	11 – 12	44.88 ± 6.02	1	58.1

Current Active Patients: March 31, 2016

Patients	Number
Active Therapy	109
No Longer on therapy	29
Deceased	13
Progressive Disease	9
On Hold - Toxicity	5
Complete Remission	2

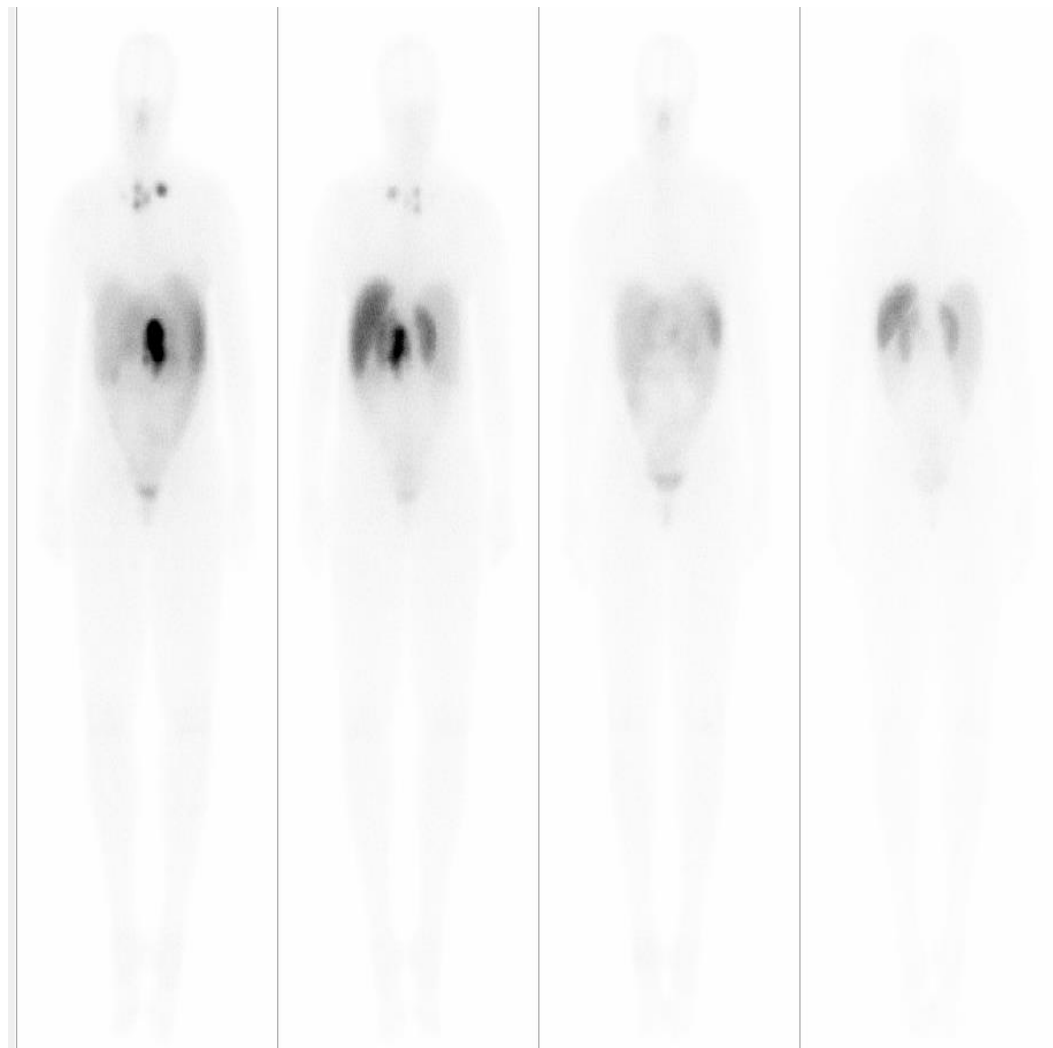
Treatment Failures by Primary Site

Site	No Longer on Rx	Deceased	PD	CR	On Hold
PNET	11	5	4	0	2
GNET	15	6	4	2	3
pGNET	3	2	1	0	0

Toxicities

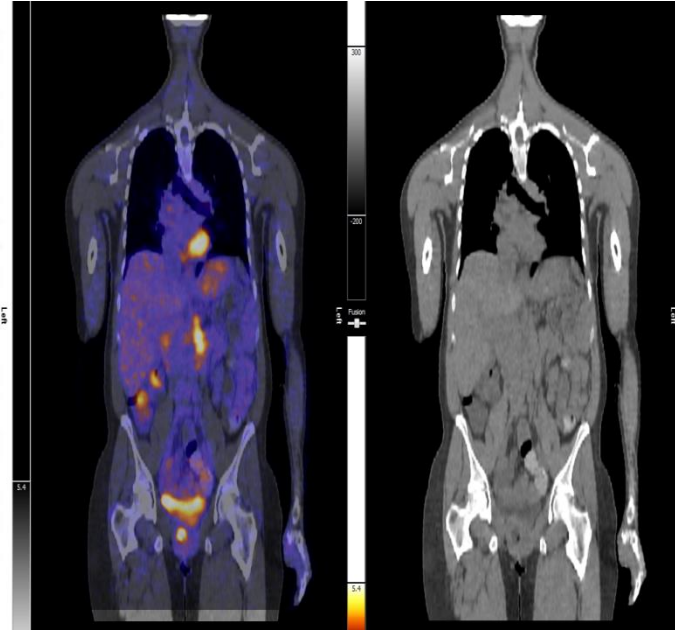
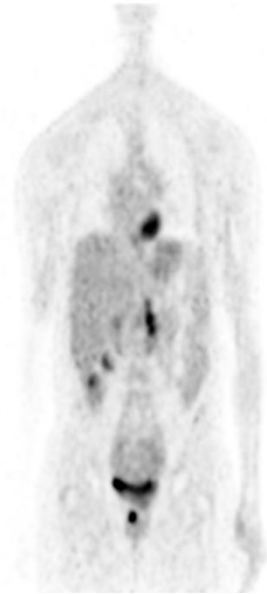
- Transient and reversible grade 3 renal was seen in up to 20% of patients
 - 2 patients long term reduction in GFR
- Transient grade 3 haematological toxicity was seen in 20% of patients
 - Predominant long term observation is lymphopenia
- No grade 4 toxicity was observed.
- No myelodysplasia seen
- Fatigue seen in most patients over 5 – 10 days post administration
- Nausea seen in approximately 20% of patients
 - Severe in 5
- 3 patients had acute febrile episodes during the infusion

NM “CR” After 6 Cycles

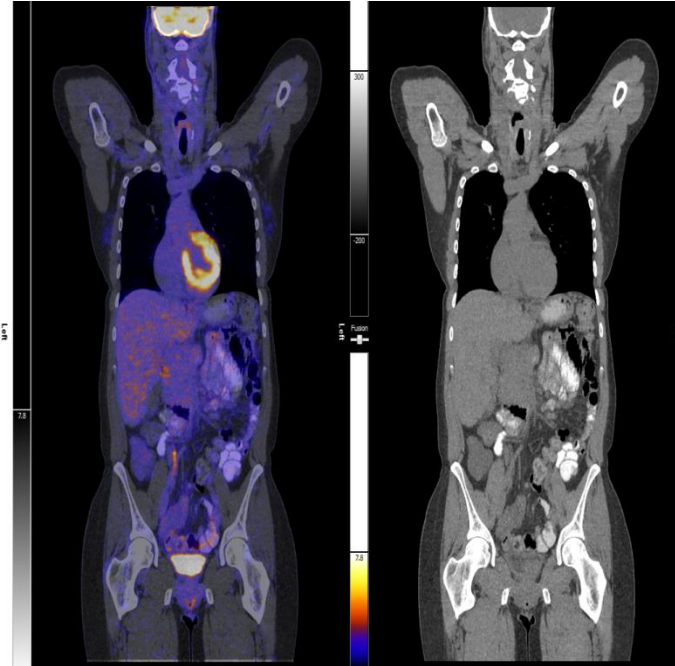


PET "CR" After 6 Cycles

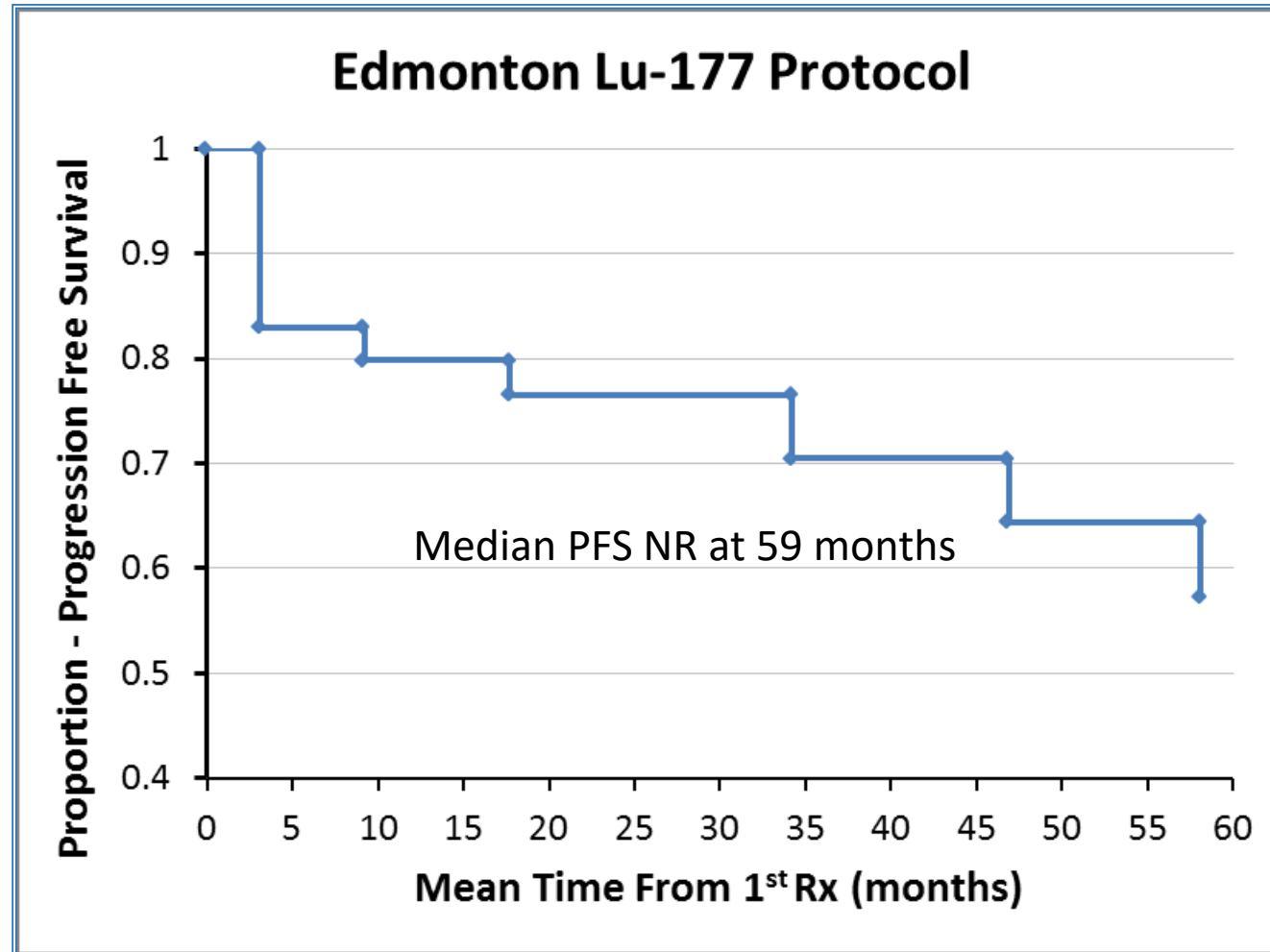
Jan 2013



Jan 2015



Edmonton Lu-177 Protocol Interim Analysis Kaplan Meier Plot



Manuscripts Assessed in Kim Meta-analysis

Author	Year	Tumour	# Patients	Cycles	Average Cum. Dose	CR/PR/SD (%)	PFS (months)	OS (months)
Bodei	2011	All	51	4 - 6	26	82	36	NA
Van Vliet	2013	GEPNET	281	+/- 4	32	76	27	55
Delpassand	2014	GEPNET	32	4	30	72	19	NA
Romer	2014	All	141	2	13.5	NA	NA	45.5
Paganelli	2014	GNET	43	5	22	84	36	> 60
Ezziddin	2014	PNET	68	4	32	85	36	53

Adapted from Baum R. et al,
Theranostics 2016. 6(4) 501-510 DOI: 10.7150/thno.13702

Edmonton Lu-177 Protocol Summary

- Data support hypothesis that induction and maintenance therapy with Lu-177 improves PFS in patients with PNETs/GNETs.
- This regimen is more effective than literature reported treatment regimens.
- In this cohort, median PFS has not been reached at 59.3 months.
- Toxicity is comparable to that reported in the literature.

Characteristics of Radioisotope Therapy

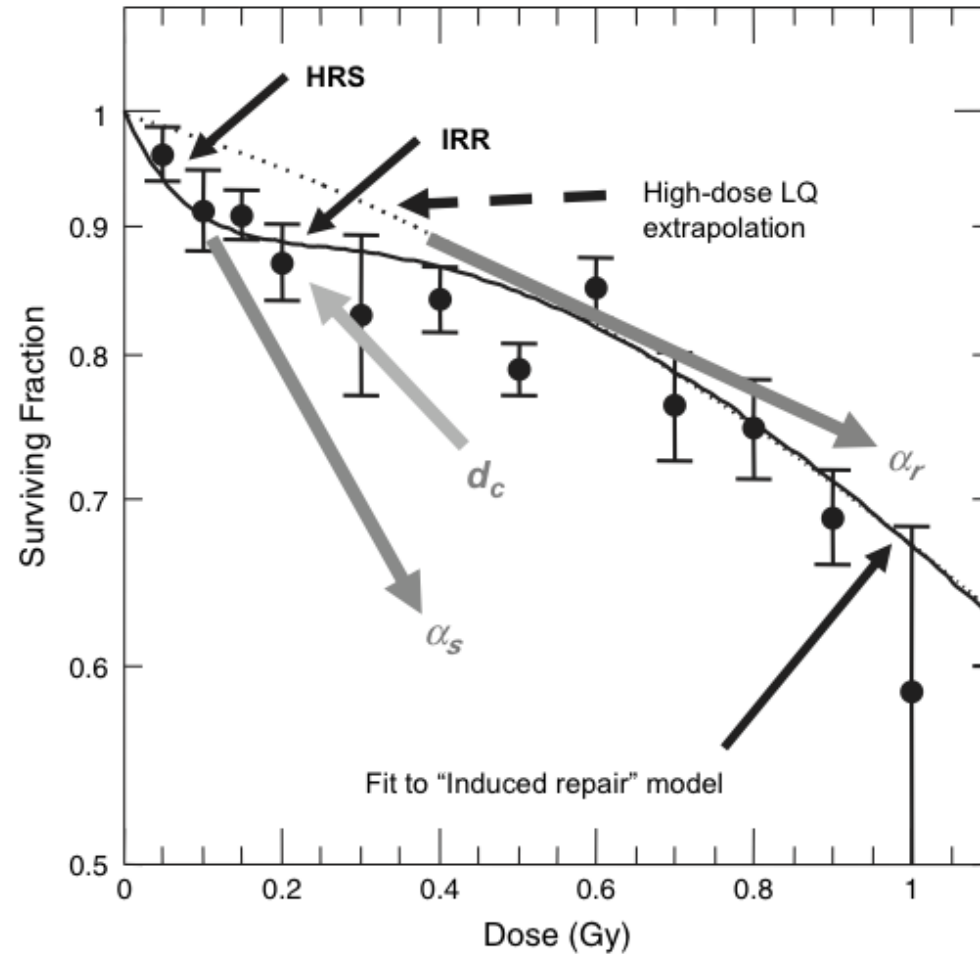
Clinical Characteristics

- **Systemic administration**
- Specific targeting
- Low toxicity
- **Retreatment**
- Adjuvant treatment
- Low complexity
- Ability to image

Scientific Characteristics

- **VLDR/LDR**
- Microdosimetry
- T_p correlates with T_b
- Chemistry
- Availability/half life
- Cost effective supply

Survival Curves - LDHRS



LDR Evades DNA Repair Sensors

- Reduced activation of ATM following LDR
- Reduced activation of downstream target γ H2A
- Increased cell killing after LDR

“Failure to activate ATM-associated repair pathways contributes to the increased lethality of continuous LDR radiation exposures”

Management of Patients with Neuroendocrine Tumors at the Cross Cancer Institute

- Provincial and Local Endocrine Tumor Groups
 - Thyroid sub group
 - Neuroendocrine tumor sub group
 - Specialist surgery in Edmonton and Calgary
 - Interventional radiology in Edmonton & Calgary
 - RIT only at CCI
- CCI multidisciplinary thyroid clinic
- CCI multidisciplinary NET clinic

MDT Neuroendocrine Clinic

- Nuclear medicine physician
 - This means a commitment to practice as an oncologist
 - “Nuclear Oncologist”
- Endocrine surgeon
- Medical oncologist
- Endocrinologist
- Radiation oncologist
- (Radiologist)
- Radioisotope therapy nurses
- Trained technologists
- Medical physicist
- {Radiobiologist}

Radioisotope therapy should be considered in the same class of treatments as other systemic anti-cancer therapies; it requires the treating physician to commit to long term management of the patient receiving treatment.

This has significant implications for training nuclear medicine physicians

Surgical CR After 6 Cycles

Aug 2014

Nov 2014

Feb 2015

Apr 2015

Apr 2016

