Hong Kong International Oncology Forum 2017

Concurrent Session 4: Neuroendocrine Tumour

Use of Peptide Receptor Radionuclide Therapy (PRRT) for Treatment of Neuroendocrine Tumour

Dr. Thomas K.C. Cheng

Honorary Consultant in Nuclear Medicine
Department of Nuclear Medicine & Positron Emission Tomography

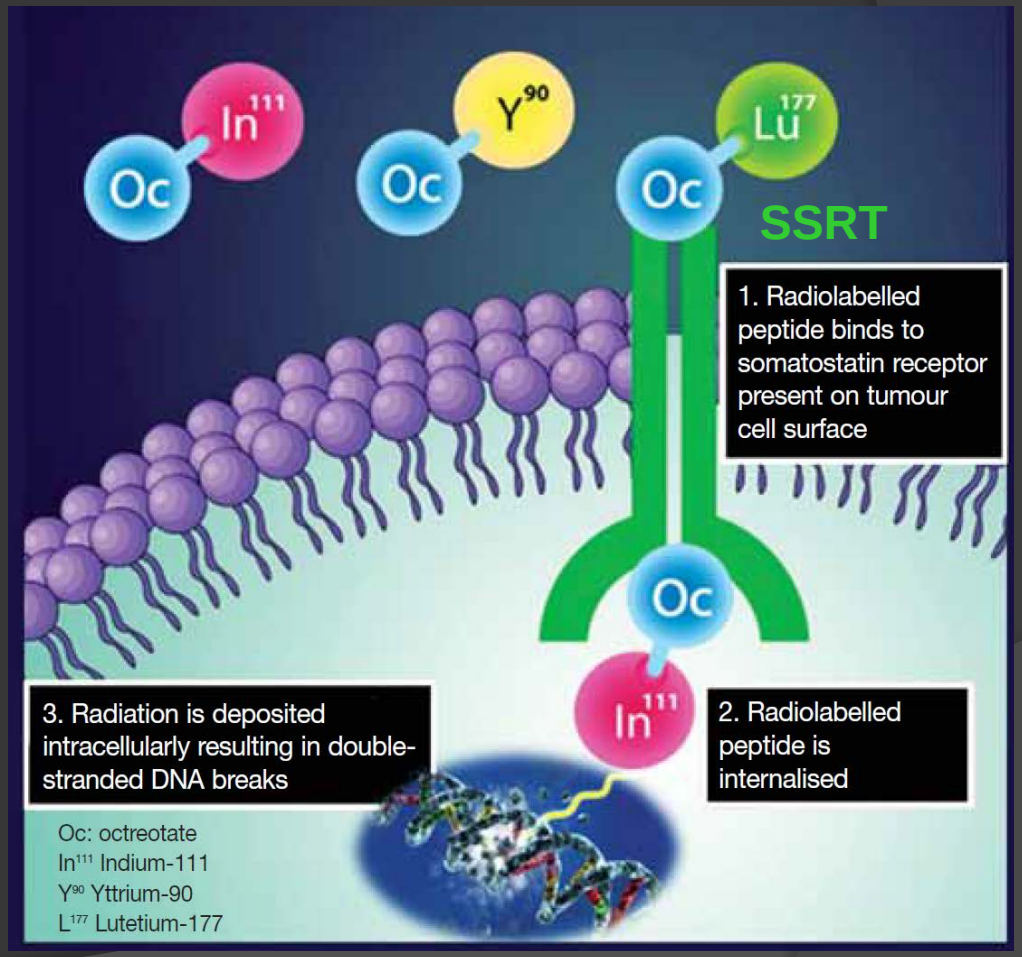
Hong Kong Sanatorium and Hospital

Peptide Receptor Radionuclide Therapy

- Radionuclide-molecular therapy

Radionuclide (^{90}Y/^{177}Lu)
+
Peptide (Octreotate)

- 1st performed in HKSH in 08/2011



PRRT

- Neuroendocrine tumor
  - Overexpressed somatostatin receptor 2 (sstr2)
  - Well and moderately differentiated tumor (WHO classification grade 1 or 2)
  - Metastatic or inoperable
  - Neoadjuvant therapy for pre-operative downstaging in advanced pancreatic NET
  - Others: pheochromocytoma, paraganglioma, neuroblastoma or medullary thyroid carcinoma

PRRT

- Most studies report objective response rates in 15–35% of patients.
- progression free survival (PFS) and overall survival compares very favorably with that for somatostatin analogs, chemotherapy, or targeted therapies.
- compare favorably to PFS data for liver directed therapies such as ^{90}Y-labelled microspheres.

Advantages of Radionuclide Therapies

- use of radiolabeled tumor-seeking molecules to deliver a cytotoxic dose of radiation to specific tumor cells.
- difference between radionuclide therapy and external beam irradiation is the finite range of ionizing particles emitted.
- avoid or minimize toxic effects to normal organ.
- Radiation can be delivered to subclinical tumors and metastases that are too small to be imaged and treated by surgical excision and external beam therapy.

Eligibility of PRRT

	Well-differentiated		Poorly differentiated
Grade (ENETS)	Low (G1)	Intermediate (G2)	High (G3)
Ki-67 index (%)	≤2	3-20	>20
Anatomic imaging	more rapid growth on serial imaging		
Functional imaging	Octreoscan SPECT or SSTR PET +ve		FDG PET +ve
Prognosis	Indolent (slowly growing)		Aggressive

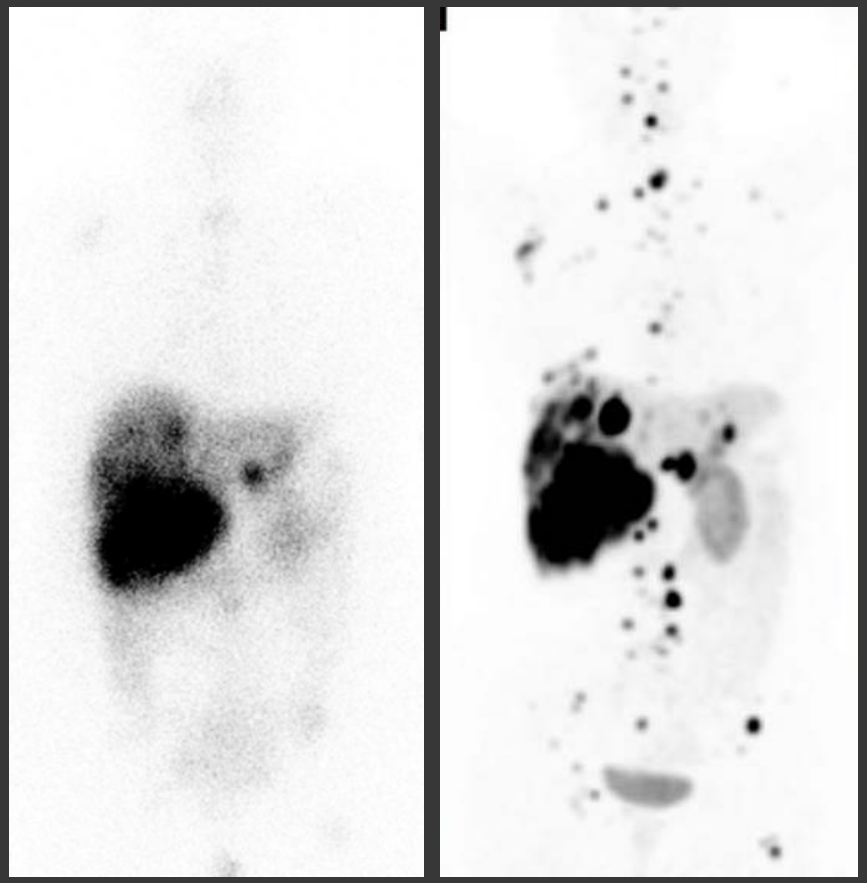
^{111}In-octreotide SPECT/CT
^{68}Ga DOTATOC PET/CT (available at HKSH since 09/2015)

Theranostics

- “ Therapeutics + Diagnostics ”
- Use of radionuclide-labeled agents that specifically diagnose disease and then use identical or closely related agents for therapy

Therapeutics	Diagnostics
^{90}Y DOTATOC	^{68}Ga DOTATOC
^{177}Lu DOTATATE	^{111}In pentetreotide

Somatostatin receptor Imaging



^{111}In-pentetreotide

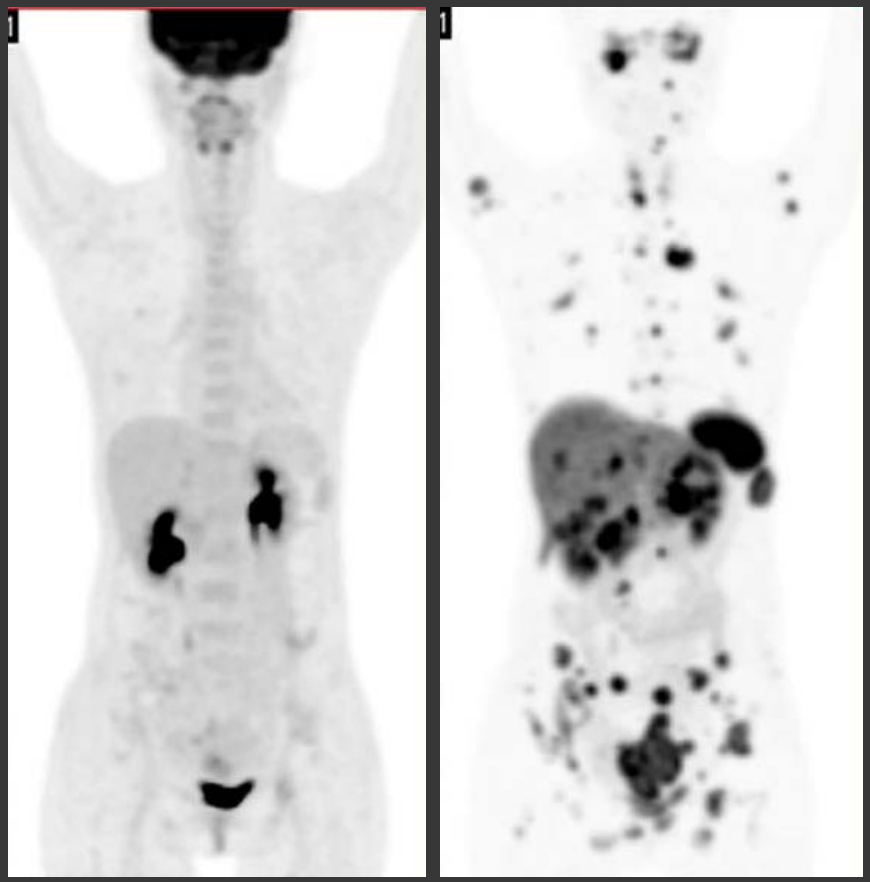
^{68}Ga-DOTATOC

^{68}Ga DOTATOC vs ^{111}In-pentetreotide

1. ssrt PET is superior to SPECT (2x higher sensitivity) in detecting NET metastases
2. PET is the scintigraphic method for accurate depiction of NET tumor burden
3. Quantification feasible in ^{68}Ga DOTATOC PET (SUVmax) but not in^{111} In pentetreotide scintigraphy

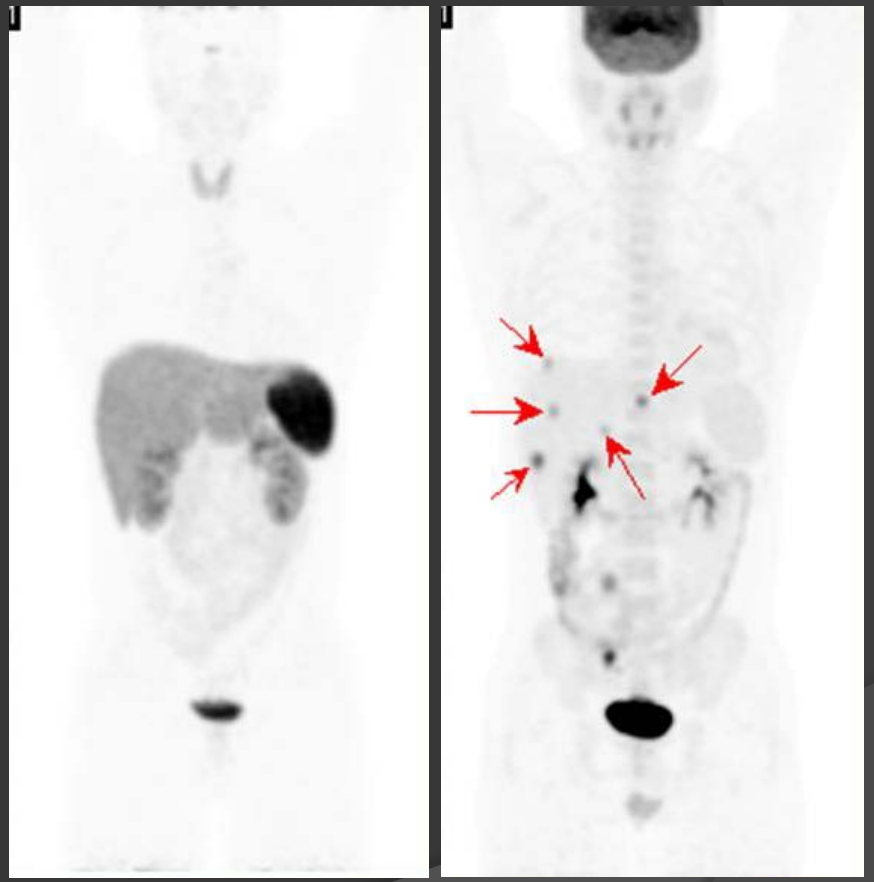
Somatostatin receptor + Metabolic Imaging

Rectal Biopsy: G2 NET



Candidate for PRRT

Small bowel resection: G2 NET



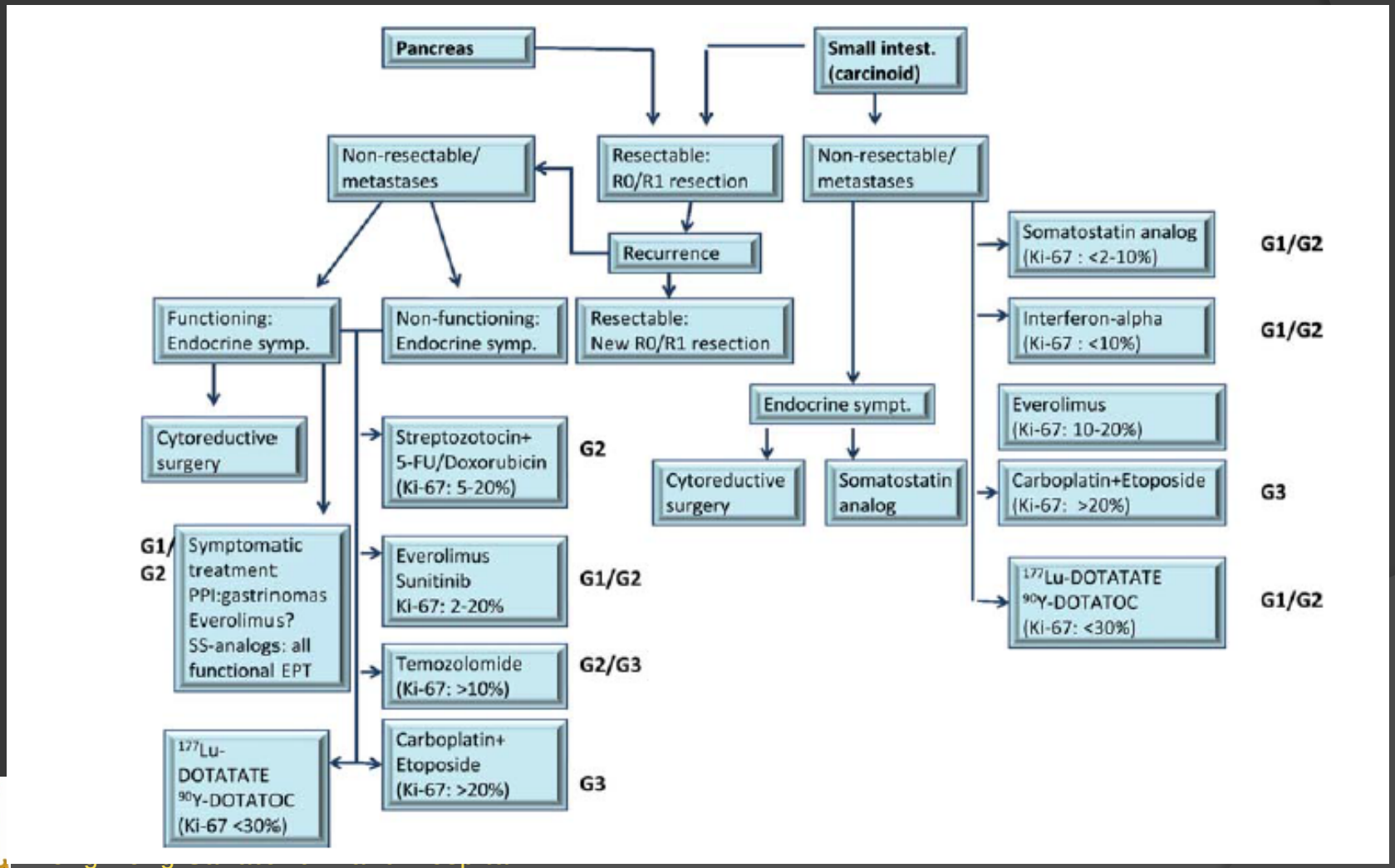
NOT candidate for PRRT

ESMO guideline for Neuroendocrine gastro-entero-pancreatic tumors in 2012

- PRRT can be considered in both functioning and nonfunctioning NETs with positive somatostatin receptor scintigraphy irrespective of the primary tumor site.
- more than 1000 patients in total have been treated in Europe with objective response rates ranging between 20% and 40%
- Response rates are higher in pancreatic compared with small intestinal NETs

ESMO guideline for Neuroendocrine gastro-entero-pancreatic tumors in 2012:

Treatment algorithm



Contraindications

- Absolute:
  - Pregnancy
  - Severe acute concomitant illnesses
  - Severe unmanageable psychiatric disorder

- Relative:
  - Breast feeding (if not discontinued)
  - Severe compromised renal function
    - ^{90}Y-labeled peptide:
      - normal age-adjusted renal function
    - ^{177}Lu-labeled peptide:
      - mild to moderate grade of renal impairment can be tolerated (Creatinine ≤ 1.7mg/dl or GFR & TEF ≥ 60% of mean age-adjusted normal values)
  - Severe compromised bone marrow
    - WBC <3000/ul with absolute neutrophil count <1000/ul
    - ^{177}Lu-labeled peptide: Plt <75000/ul
    - ^{90}Y-labeled peptide: Plt <90000/ul

^{90}Y DOTATOC vs ^{177}Lu DOTATATE

	^{90}Y DOTATOC	^{177}Lu DOTATATE
Physical T1/2	2.7 days	6.7 days
Radiation	β	β & γ
Max. tissue penetration	12 mm	2 mm
Useful on	Large tumor	Small tumor
Toxicity	More renal toxicity	Less renal toxicity
Radiation isolation	No	1st few hours
Post-treatment Imaging & Dosimetry	Not applicable	Applicable

Treatment regime of PRRT

	^{90}Y DOTATOC	^{177}Lu DOTATATE	^{90}Y DOTATOC/ ^{177}Lu DOTATATE
Administered Activity	72-120 mCi	150-200 mCi	^{90}Y: 68-135 mCi ^{177}Lu: 150-200 mCi *adjusted on individual basis
No. of cycles	2-4	3-5	2-6
Time intervals	6-12 weeks	6-12 weeks	6-16 weeks

Concurrent therapies, administering a cocktail of ^{177}Lu and ^{90}Y peptides are also emerging

Renal Protection

- Kidney is the critical organ in PRRT especially using ^{90}Y DOTATOC
- Renal irradiation:
  - Proximal tubular reabsorption and interstitium retention
- Amino acid (AA) protection:
  - Counteract and reduce the high kidney retention of radiopeptides by positively charged AA (L-lysine and/or L-arginine)

Somatostatin analogue withdrawal

- Long-acting somatostatin (Sandostatin LAR)
  - 4-6 weeks
  - Substitute by short-acting somatostatin 1 month prior PRRT
- Short-acting somatostatin
  - at least 24 hours

Adverse effect

- Acute
  - Nausea, headache & vomiting due to metabolic acidosis induced by amino acid coadministration is well managed by hydration with normal saline and possibly by repeating corticosteroid or antiemetic administrations
  - Exacerbate syndromes related to the respective functional tumors

Adverse effect

Delayed

- Hepatic toxicity in massive liver metastases
- Renal toxicity:
  - ^{90}Y: incidence of Grade 4 & 5 renal toxicity is 9.2%
  - Average annual decreased in creatinine clearance:
    - ^{90}Y DOTATOC: 7%; ^{177}Lu DOTATATE: 3%
- Marrow toxicity:
  - Grade 3 or 4 acute marrow toxicity – mostly reversible
    - ^{90}Y DOTATOC: 10-13% of treatment cycles
    - ^{177}Lu DOTATATE: 2-3% of treatment cycles
  - Sporadic cases of MDS or overt AML

PRRT: efficacy

Table 1 Tumor responses in patients with gastroenteropancreatic neuroendocrine tumors, treated with different radiolabeled somatostatin analogs.

Center (reference)	Ligand	*n*	Tumor response					
			CR	PR	MR	SD	PD	CR+PR (%)
Rotterdam (6)	[^{111}In-DTPA^{0}]octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0
New Orleans (7)	[^{111}In-DTPA^{0}]octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8
Milan (13)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29
Basel (14, 15, 41)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24
Basel (15, 41)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33
Multicenter (1)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9
Multicenter (2)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	0	4 (4%)	NA	63 (70%)	11 (12%)	4
Copenhagen (3)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	2 (4%)	10 (19%)	NA	34 (64%)	7 (13%)	23
Warsaw (4)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotate	58	0	13 (23%)	NA	44 (73%)	3 (5%)	23
Rotterdam (5)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29
Gothenburg (42)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	26	0	6 (38%)	NA	8 (50%)	2 (13%)	38
Lund (43)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	12	0	2 (17%)	3 (25%)	5 (40%)	2 (17%)	17
Milan (10)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	42	1 (2%)	12 (29%)	9 (21%)	11 (26%)	9 (21%)	31

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease.

Kwekkeboom DJ et al. Journal of Clinical Oncology 2008: 26, 2124–2130

^{90}Y-octreotide vs ^{177}Lu-octreotate

Complete and partial responses obtained after treatment with 90Y-DOTATOC are in the same range as after treatment with 177Lu-octreotate.

Ligand	n	SD	PD	CR + PR (%)
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	21	11 (52%)	4 (19%)	29
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	74	48 (65%)	8 (11%)	24
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	33	19 (57%)	3 (9%)	33
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	33 (61%)	10 (19%)	9
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	63 (70%)	11 (12%)	4
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	34 (64%)	7 (13%)	23
[^{90}Y-DOTA^{0},Tyr^{3}]octreotate	58	44 (73%)	3 (5%)	23
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	07 (35%)	61 (20%)	29
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	26	8 (50%)	2 (13%)	38
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	12	5 (40%)	2 (17%)	17
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	42	11 (26%)	9 (21%)	31

Kwekkeboom DJ et al. Journal of Clinical Oncology 2008: 26, 2124–2130

^{177}Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumours: Results of the Phase III NETTER-1 Trial

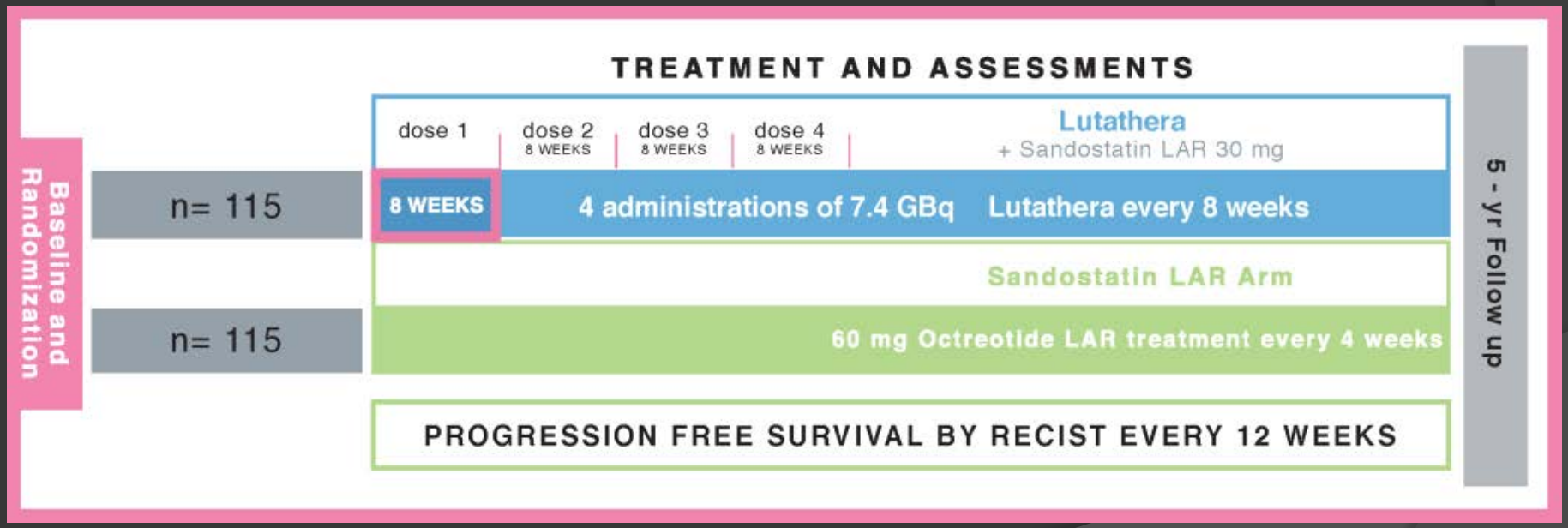
Jonathan Strosberg[1], Edward Wolin[2], Beth Chasen[3], Matthew Kulke[4], David Bushnell[5], Martyn Caplin[6], Richard P. Baum[7], Erik Mittra[8], Timothy Hobday[9], Andrew Hendifar[10], Kjell Oberg[11], Maribel Lopera Sierra[12], Philippe Ruszniewski[13], Dik Kwekkeboom[14]
on behalf of the NETTER-1 study group

[1] Moffitt Cancer Center, Tampa, FL 33612, USA;[2] Markey Cancer Center, University of Kentucky, Lexington, KY 40536-0093, USA;[3] University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA;[4] Dana-Farber Cancer Institute, Boston, MA 02215, USA;[5] University of Iowa, Iowa City, IA 52242, USA;[6] Royal Free Hospital, London, United Kingdom;[7] Zentralklinik, Bad Berka, Germany;[8] Stanford University Medical Center, Stanford, CA 94305, USA;[9] Mayo Clinic College of Medicine, Rochester, MN 55905, USA;[10] Cedars Sinai Medical Center, Los Angeles, CA 90048, USA;[11] University Hospital, Uppsala University, Uppsala, Sweden;[12] Advanced Accelerator Applications, New York, NY 10118, USA;[13] Hopital Beaujon, Clichy, France;[14] Erasmus Medical Center, Rotterdam, Netherlands

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

NETTER-1 Trial

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate plus Octreotide30 mg compared to Novartis Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group Phase III study conducted in 51 centers with 230 patients randomized



NETTER-1 Trial

Advanced Accelerator Applications

N = 229 (ITT)

Number of events: 91

^{177}Lu-Dotatate: 23

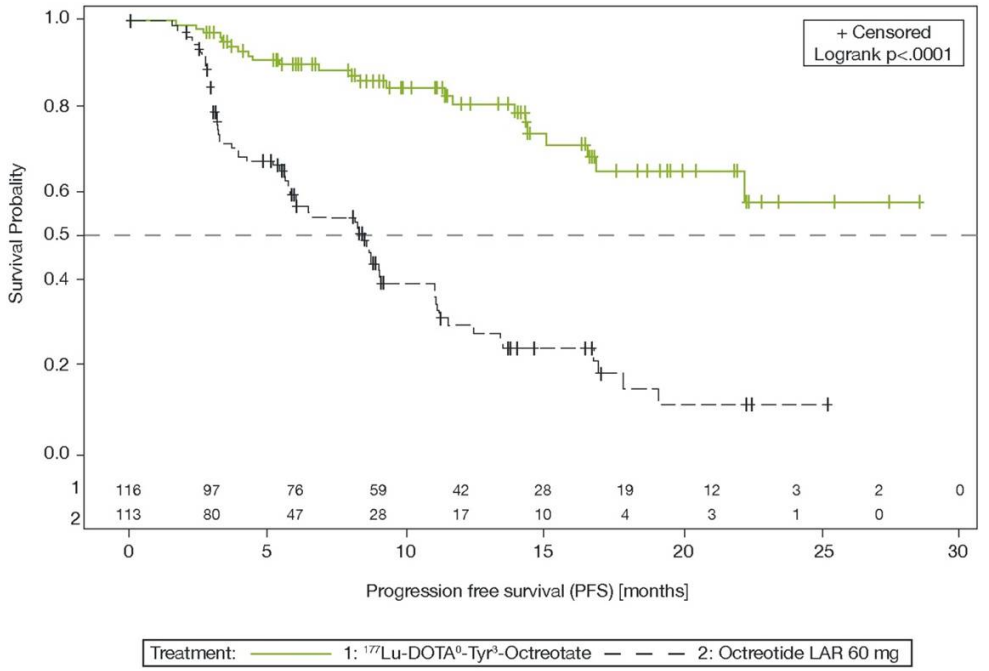
Oct 60 mg LAR: 68

Hazard ratio: **0.21**
[0.13 – 0.33]
p < 0.0001

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 months

Progression-Free Survival



Median PFS in Octreotide LAR 60mg was 8.4 months

All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Presented By Jonathan Strosberg at 2016 ASCO Annual Meeting

NETTER-1 Trial

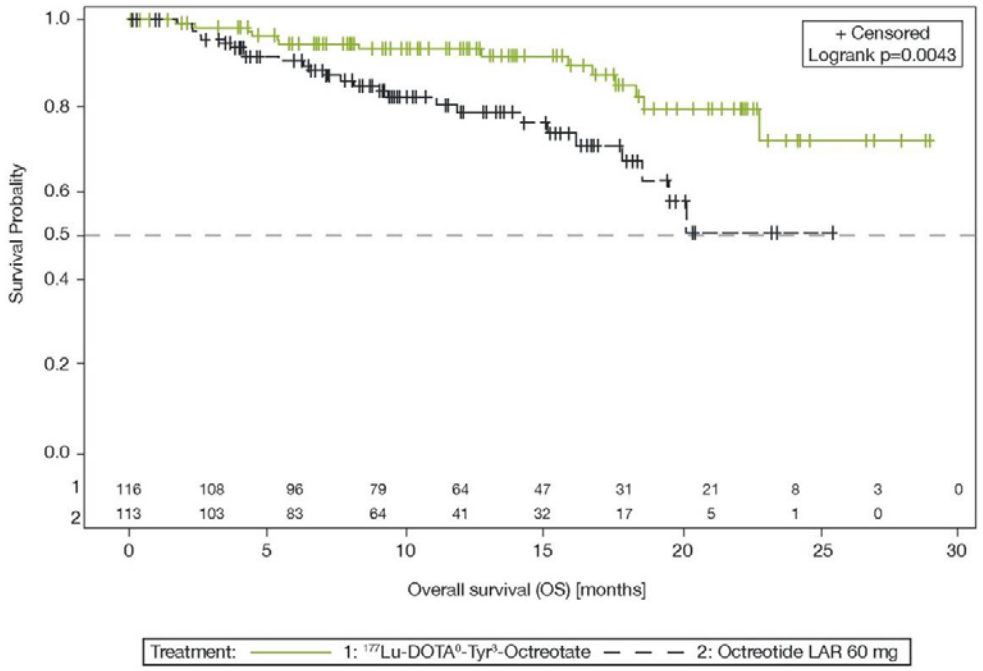
Advanced Accelerator Applications

Overall Survival (interim analysis)

N = 229 (ITT)
Number of deaths: 40

^{177}Lu-Dotatate: 14
Oct 60 mg LAR: 26

Hazard ratio: **0.398**
[0.21 – 0.77]
P = 0.0043



All cases independently reviewed for eligibility (SAP)

Prespecified interim analysis significance level p<0.000085

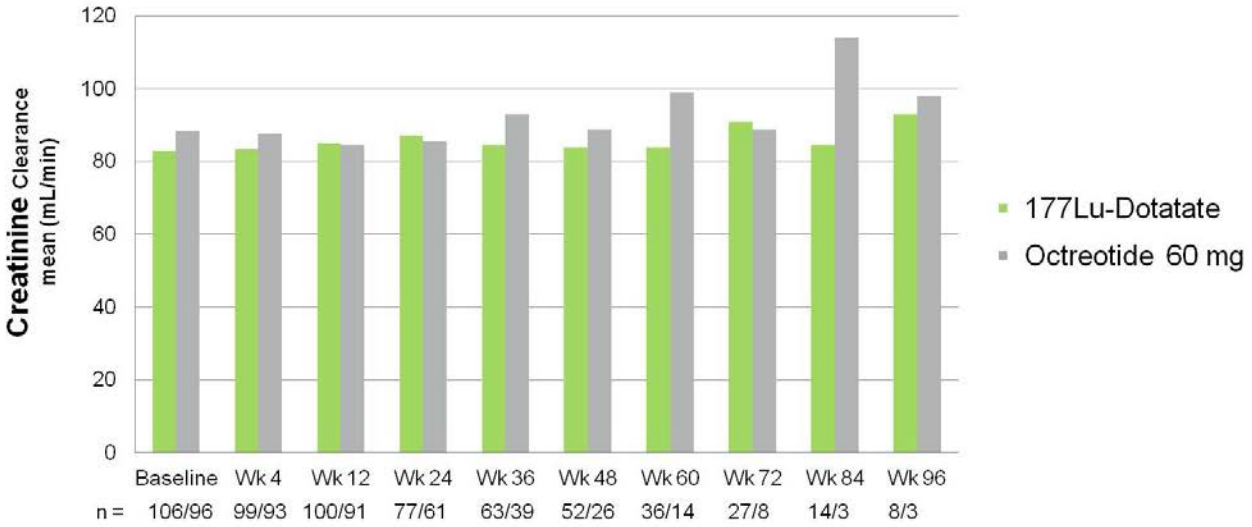
Presented By Jonathan Strosberg at 2016 ASCO Annual Meeting

NETTER-1 Trial

Advanced Accelerator Applications

Creatinine Clearance
Renal function remains stable over the 2-year observation period

	^{177}Lu-Dotatate (N = 111)	Octreotide LAR (N = 110)
	Grade 3/4	Grade 3/4
Creatinine increased	0%	0%



Presented By Jonathan Strosberg at 2016 ASCO Annual Meeting

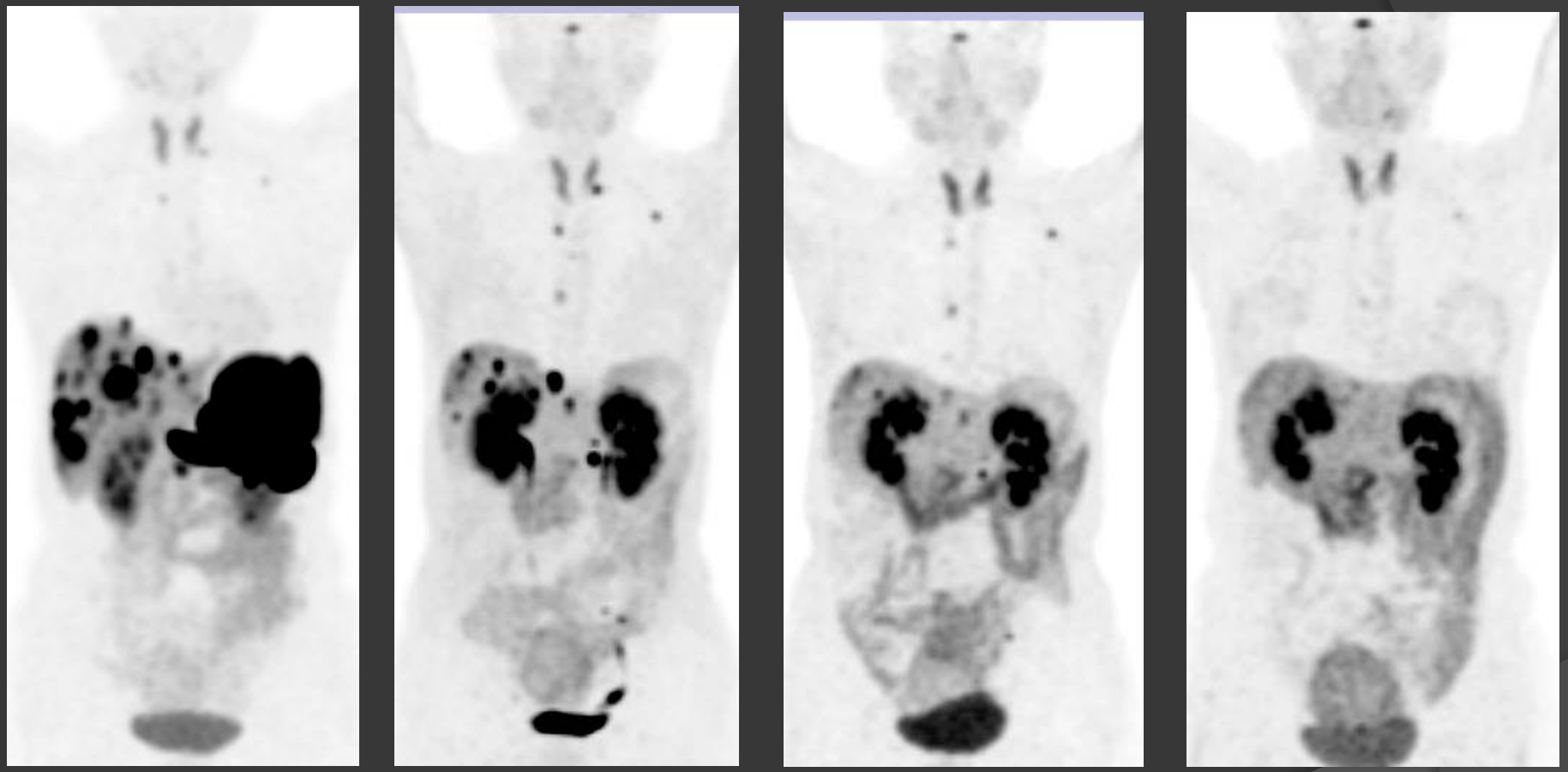
NETTER-1 Trial

Summary and Conclusions

- Final analysis : In this first prospective randomized study in patients with progressive metastatic midgut NETs, ^{177}Lu-Dotatate was superior to Octreotide 60 mg in terms of:
  - PFS (Not Reached vs 8.4 months, p<0.0001)
  - ORR (18% vs 3%, p=0.0008)
- Interim analysis suggests increased OS (14 vs 26 deaths), to be confirmed by final analysis
- ^{177}Lu-Dotatate demonstrates a favorable safety profile, with no clinically relevant findings especially regarding hematological, renal and hepatic parameters
- Consistent benefits seen across prognostic subgroups
- While few treatment options are available for patients progressing under SSAs, ^{177}Lu-Dotatate has a major therapeutic benefit for this patient population

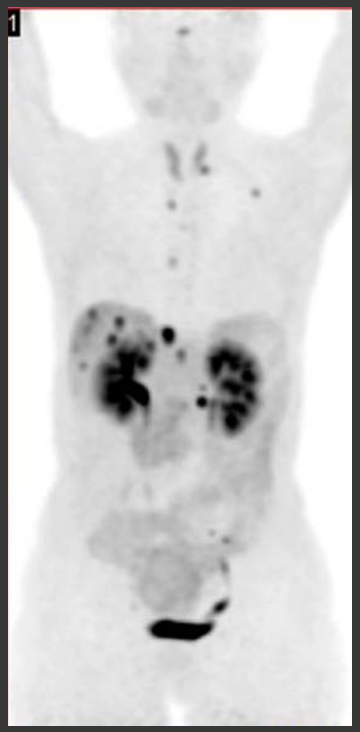
Presented By Jonathan Strosberg at 2016 ASCO Annual Meeting

F/44 Grade 2 pancreatic NET with multiple liver and mesenteric metastases (^{68}Ga-DOTATOC PET/CT scan)

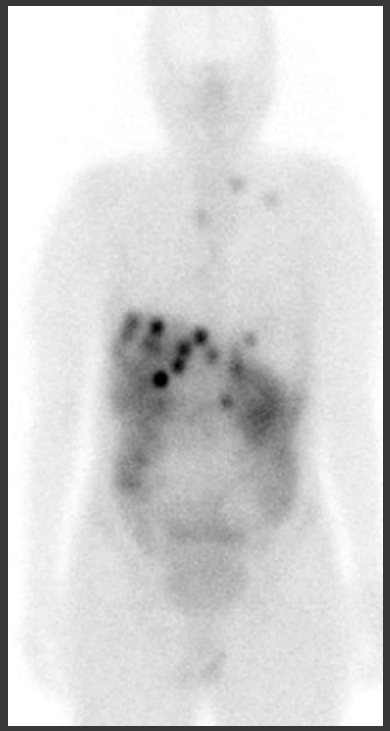


05/2016	07/2016	09/2016	01/2017
Baseline	Post-op	after 1st PRRT	after 2nd PRRT

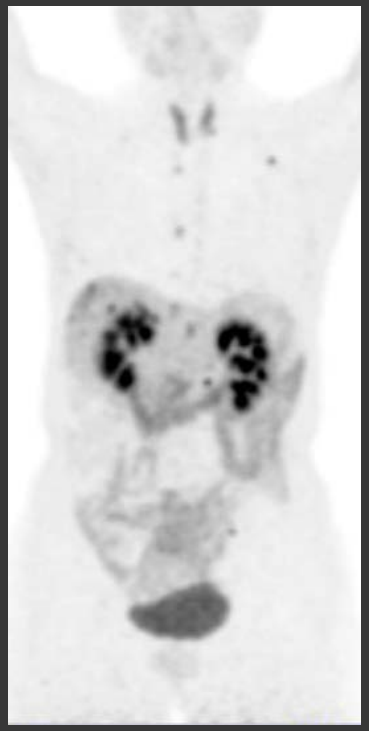
F/44 pNET (glucagonoma) with nodal, liver & bone metastases
– 200mCi ^{177}Lu DOTATATE in 07/2016



^{68}Ga DOTATOC PET
Post-operation



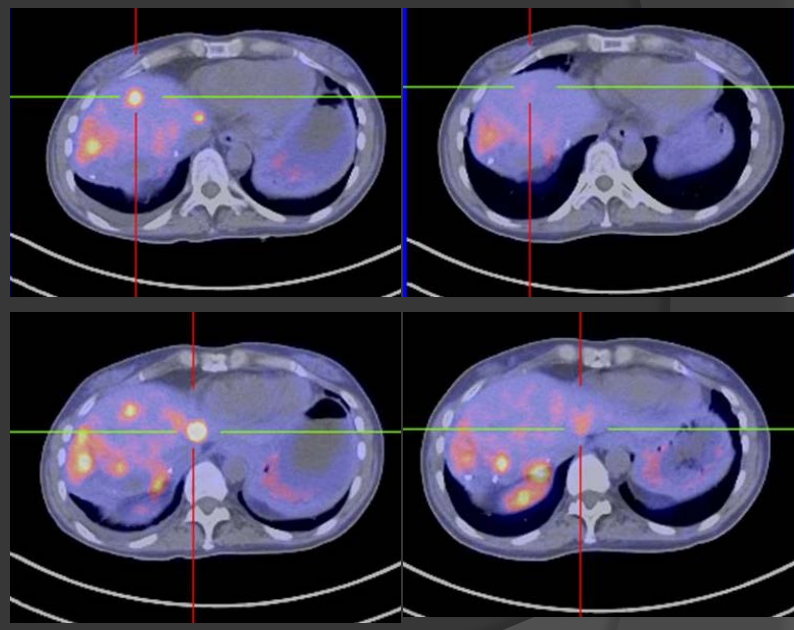
^{177}Lu DOTATATE Rx
24 hr.



^{68}Ga DOTATOC PET
8 wk post-^{177}Lu DOTATATE Rx

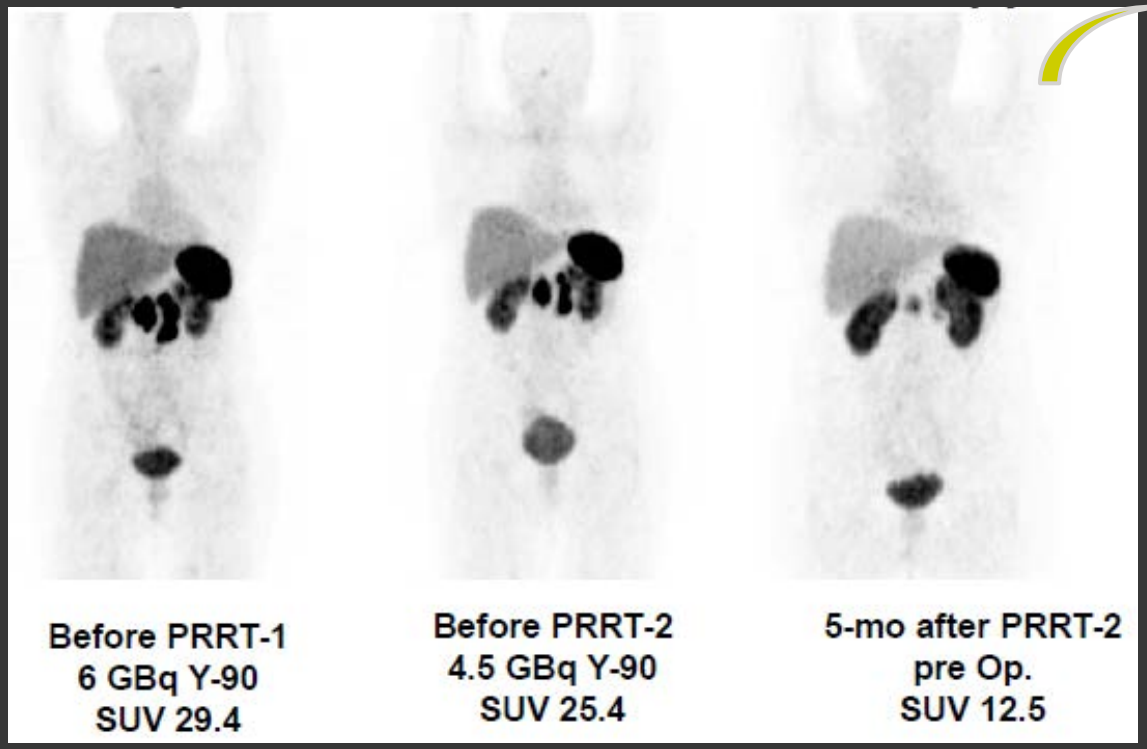
^{68}Ga DOTATOC PET
Post-operation

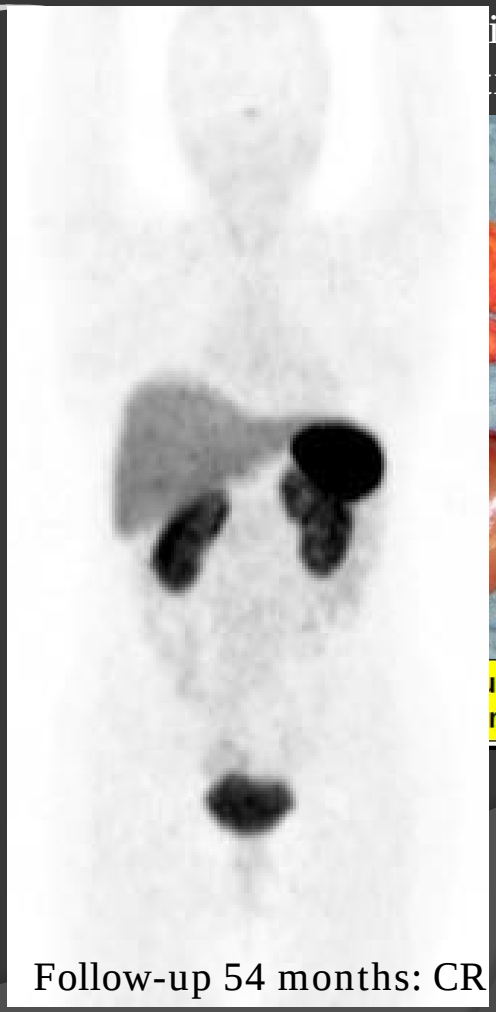
^{68}Ga DOTATOC PET
8 wk post-^{177}Lu DOTATATE Rx



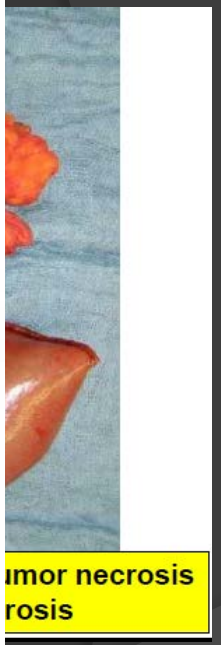
	05/2015	06/2016	09/2016
Chromogranin A	317	400+	155

F/32 pNET G2 (inoperable, progressive) – 160 + 120mCi ^{90}Y DOTATOC

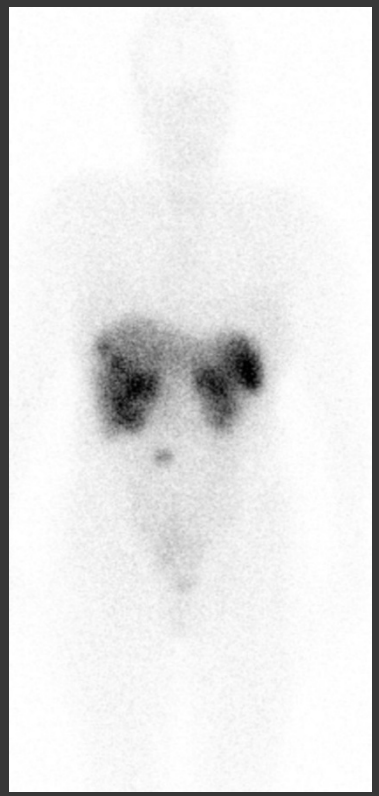




ion –
tion



F/47 eNET G2 with mesenteric & liver metastases – 200mCi ^{177}Lu DOTATATE (12/2012; 03&10/2013 & 05/2014)

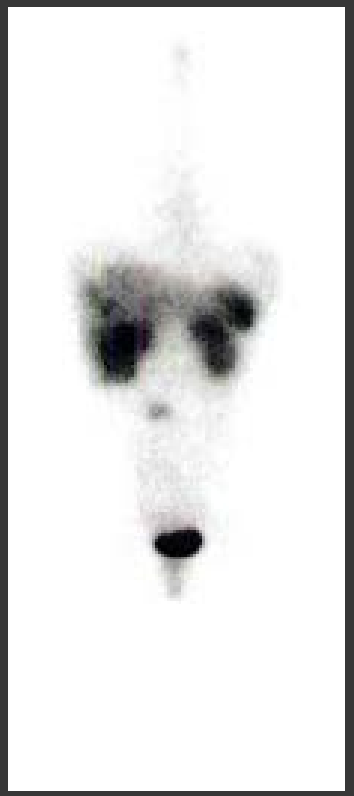


^{111}In-pentetreotide

(12/2012 Baseline)

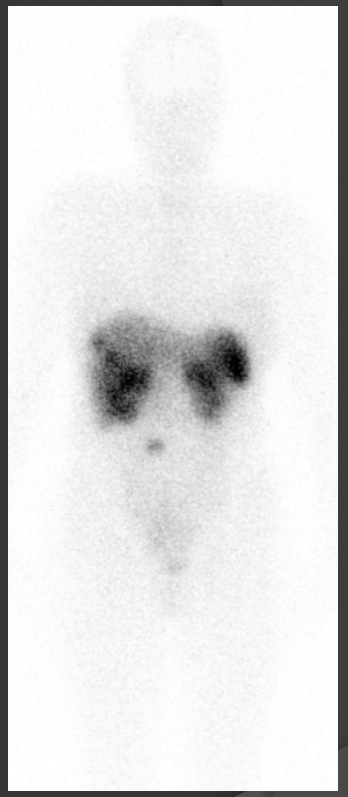
^{111}In-pentetreotide

(09/2013 After 2 Tx)



^{111}In-pentetreotide

(10/2014 After 4 Tx)



^{111}In-pentetreotide

(05/2016 2 yr. after 4th Tx)

Stable disease with no significant progression

Conclusion

- PRRT is a new and valuable treatment modality for patients with inoperable or metastasized NETs.
- PRRT is well tolerated and acute side-effects are usually mild and self-limiting.
- PRRT compares favorably to other treatment modalities in terms of PFS and OS.

Acknowledgement

- **Referring physicians & patients**
- **Research partners**
- **NM & PET colleagues of HKSH**

Thank You