Network of Centres of Excellence in Radioisotope Therapy: Neuroendocrine tumours

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Granting Agencies

- AHFMR
- CIHR
- ACF
- CFI

A Brief History…

- Radioiodine:
  - (^{128}I) was first used in 1938 to assess metabolism in rabbits
  - (^{132}I) was first used in 1946 for the treatment of toxic goitre
- Therapeutic use of ^{131}I-mIBG first reported in 1984 by James Sisson at the University of Michigan
  - Diagnostic use by same group in 1982
- The use of somatostatin labelled radiopharmaceuticals started in the early 1990's with ^{111}In, ^{90}Y, ^{177}Lu
- Future possibilities

  RIT + biologics

  RIT + chemotherapy

Theranostics and Personalized Medicine

- Theranostics:
  - … a proposed process of diagnostic therapy for individual patients - to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results. ...
  - http://en.wikipedia.org/wiki/Theranostics
- Personalized medicine:
  - the right treatment for the right patient at the right time with the right dose

What is Measurable with Molecular Imaging

Workman P, et al. JNCI, 2006; 98(9):580-598

Objectives	Measurable Endpoints
Patient selection	Expression of molecular target (**SSRT2**), (**NAT Transporter**) (**GLUT Transporter**)
↓	↓
Concentrations needed for activity at the site of action	Pharmacokinetic properties in plasma and/or tissue
↓	↓
Specific action on the molecular target or pathway	Target inhibition in tumors and/or surrogate normal tissue **(? Functional Response)**
↓	↓
Induction of the desired biologic effect	Inhibition of proliferation, invasion, angiogenesis, induction of cell death
↓	↓
Resulting clinical response	Tumor regression, cytostasis
↓	↓
Patient outcome	Disease-free survival, performance status, quality of life, overall survival

Radioisotope Therapy

The systemic administration of a targeted radionuclide utilizing short range beta (alpha) particle 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

RIT at CCI

	mIBG (>2003)	Total mIBG (1987)	Lutetium 3 years	Total all Rx
G/PNET	172	325	102	439
Pheo/PGL	15	54	3	57
Neuroblastoma	10	44		44
MTC	0	14		14
Others			10	10
Total	197	437	115	749

177Lu-Dotatate Therapies at CCI

- 115 patients
  - 70 GENETS
  - 35 PNETS
  - 10 Others
- Indications
  - Progressive symptoms
  - Progressive disease
  - Uncontrolled symptoms
  - Pre surgery debulking
- Maximum follow-up: 42 months

Distribution of Lu-177 Treatments

- Rx 1 - 2: 22
- Rx 3 - 4: 46
- Rx 5 - 6: 37
- Rx 7 - 8: 19
- Rx 9 - 10: 1

- Total # treatments: 554

Why Have We Stopped PRRT Therapies

- PRRT performed under SAP
- SAP issued cease and desist order
  - Insisted on a CTA
  - Insisted on a path to product registration
- ^{177}Lu-DOTATATE and a-a solution supplied from the Netherlands
- Amino-acid manufacturing stopped because of facility upgrade
- Administrative and leadership changes in ERC (AHS) have refused to support the CTA as it is “research” and outside their mandate

Questions About Radioisotope Therapy for a Network of Centres of Excellence

- Does it work
  - What are the outcomes
  - How does it compare with other therapies
  - For how long does it work
- How does it work
- How is most effectively used
  - How is the patient population defined
  - What is the optimum administration schedule
  - When should it be used
  - Is there advantage in combination therapy
- What is the required infrastructure
  - Physical
  - Intellectual

Does it Work

Treatment of Patients with Metastatic NETs

Cytoreductive Therapies

- Surgery
- Radiofrequency ablation
- Bland embolization
- TACE
- Cryosurgery
- Alcohol injection
- Radioactive microsphere embolization

Systemic Therapies

- Somatostatin analogues
- Interferon
- Chemotherapy
- **Radioisotope therapies**
- **Kinase inhibitors**
- **mTOR inhibitors**

Radionuclide Therapy in Neuroendocrine Tumours: A Systematic Review

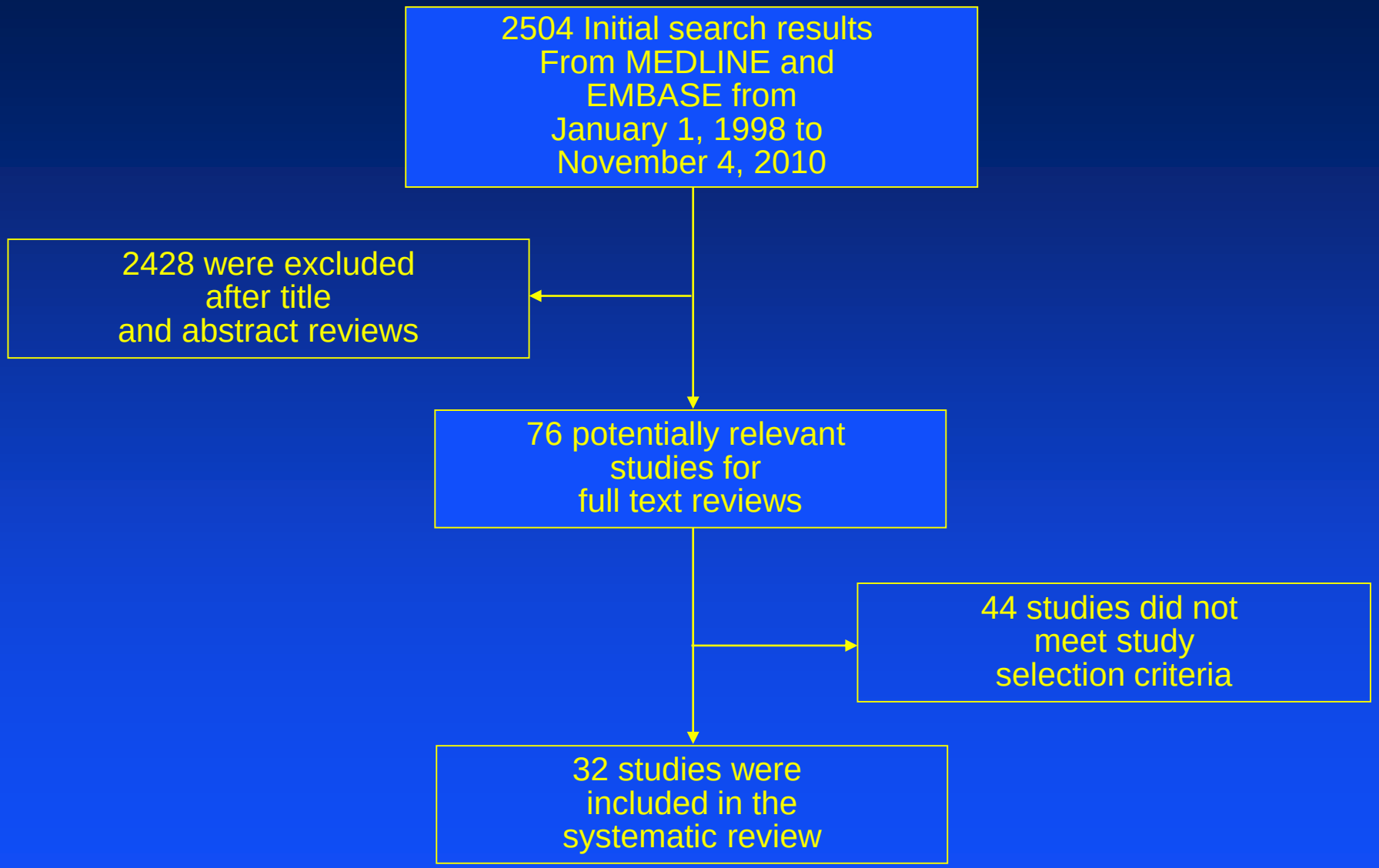
K.Y. Gulenchyn, X. Yao, S.L. Asa, S. Singh, C. Law

doi:10.1016/j.clon.2011.12.003

Radiopharmaceuticals Considered

^{111}In-DTPAOC	[^{111}indium-DTPA^{0}]octreotide, ^{111}indium-DTPA-D-Phe-octreotide, ^{111}indium-pentetreotide
^{111}In-DOTATATE	^{111}indium-DOTA-TYR^{3}-octreotate, ^{111}indium-octreotate
^{90}Y-DOTATOC	^{90}yttrium-DOTA-TYR^{3}-octreotide, ^{90}yttrium-SMT487, ^{90}yttrium-edotreotide
^{90}Y-DOTALAN	^{90}yttrium-DOTA-lanreotide
^{90}Y-DOTATATE	^{90}yttrium-DOTA-TYR^{3}-octreotate, ^{90}yttrium-octreotate
^{177}Lu-DOTATOC	^{177}lutetium-DOTA-TYR^{3}-octreotide, ^{177}lutetium-octreotide
^{177}Lu-DOTATATE	^{177}lutetium-DOTA-TYR^{3}-octreotate, ^{177}lutetium-octreotate
^{131}I-MIBG	^{131}iodine-metaiodobenzylguanidine, ^{131}iodine-iobenguane

doi:10.1016/j.clon.2011.12.003



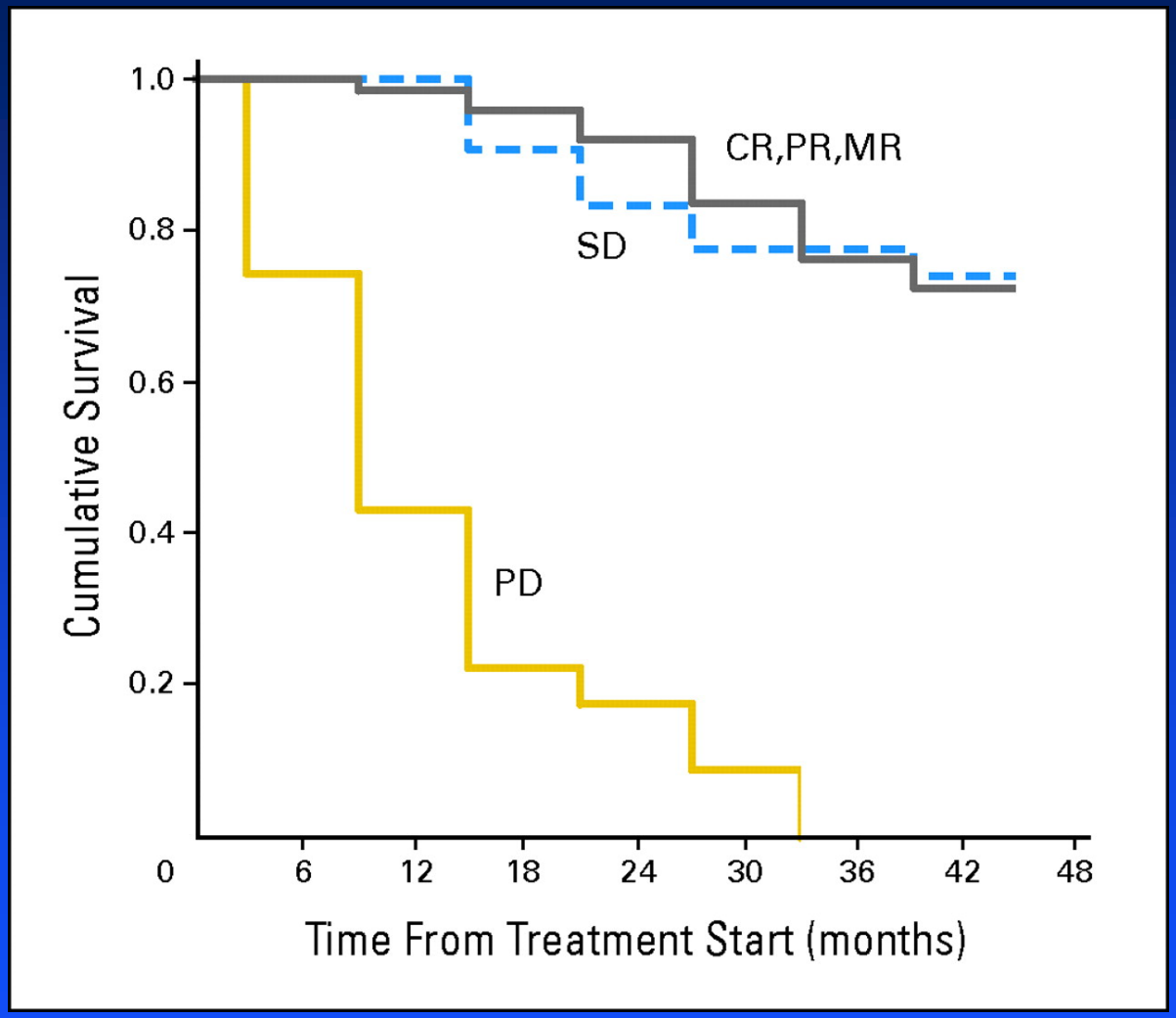
doi:10.1016/j.clon.2011.12.003

Conclusions

- PRRT seems to be an acceptable option and is relatively safe with renal protection of lysine and arginine amino acid solution in adult patients with advanced NETs
- ^{131}I-MIBG may be effective for malignant neuroblastoma in pediatric patients, paraganglioma or pheochromocytoma
- Hematological toxicity, severe infections and secondary malignancies need to be considered
- Insufficient evidence exists to suggest ^{131}I-MIBG's efficacy for adult neuroendocrine carcinoma patients
- No strong evidence exists to support that one therapeutic radiopharmaceutical is more effective than others
- Need for RCTs –well designed with controlled entry criteria

doi:10.1016/j.clon.2011.12.003

Lutetium Octreotate Rx Survival in GEPNETS



Kwekkeboom, D. J. et al. J Clin Oncol; 26:2124-2130 2008

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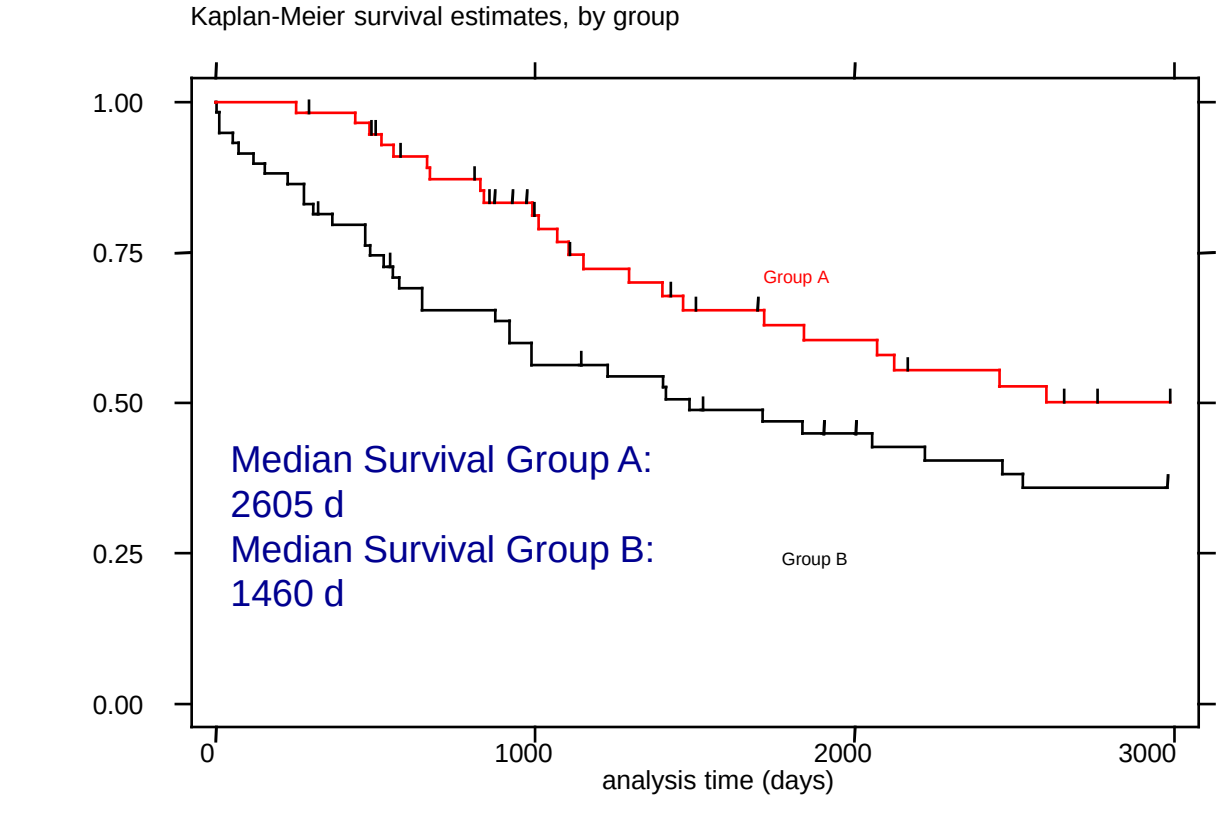
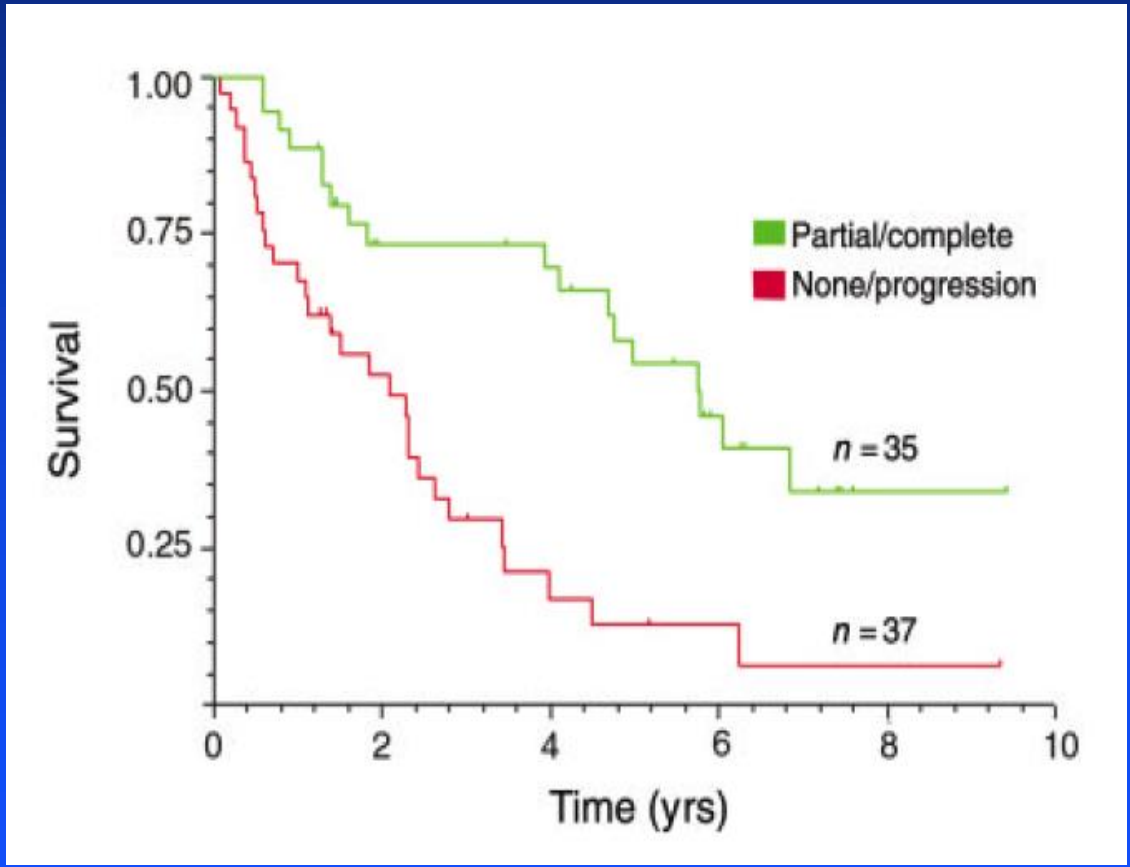
Kaplan-Meier Overall Survival Estimates



P=0.06

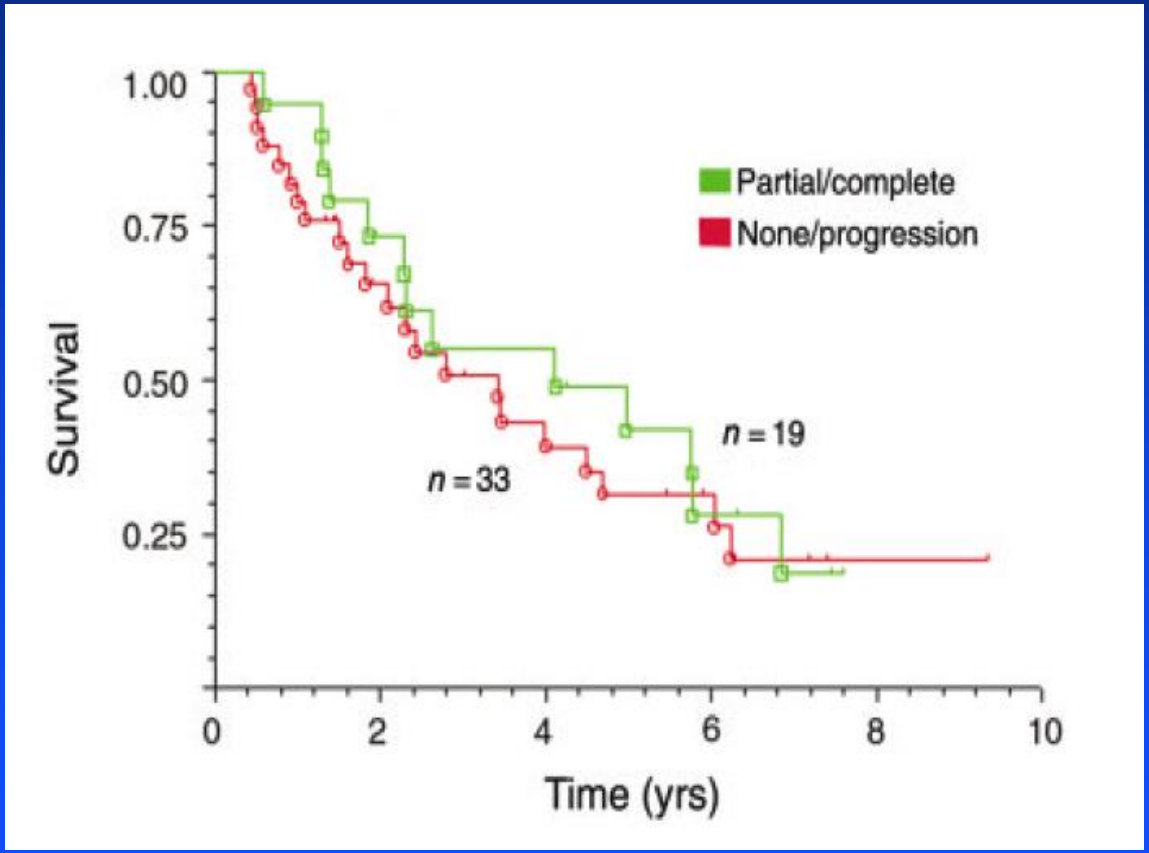
World J. Surg. 28, 1157–1162, 2004

Kaplan-Meier curve comparing symptomatic responders with nonresponders. Median survival for symptomatic responders 5.76 yrs, compared with 2.09 yrs for nonresponders ($P < 0.001$; hazard ratio 1.57-5.17).



Safford SD, et al. Cancer 2004; 101:1987-1993.

Kaplan-Meier curve comparing hormone responders with nonresponders. Median survival for hormone responders was 4.11 yrs, compared with 3.42 yrs for nonresponders ($P = 0.2$)



Safford SD, et al. Cancer 2004; 101:1987-1993.

Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumors in Germany: First Results of a Multi-institutional Cancer Registry.

Hörsch D, et al. Recent Results Cancer Res. 2012;194:457-65.

- 297 patients from 5 centres registered
  - PNET: 117
  - GNET: 80
  - Unknown Primary: 56
- Ki67: 0.9 – 70% (median 5%)
- 1 – 8 cycles of PRRT (Lu-177 and Y 90)
- Mean survival: 203 months initial diagnosis
  87 months (f/u 1-92 months)
  - Median OS not reached
  - Best responses with Ki67 < 205

Bodel L et al. Eur J Nucl Med 28:2125 – 2135, 2011

- Assess safety and efficacy of multiple cycles
- 51 consecutive patients
  - Group 1 – 3.7 – 5.18 GBq/cycle
  - Group 2 – 5.18 – 7.4 GBq/cycle
- Cumulative activities
  - Group 1 – 3.7 to 29.2 GBq (median 26.4 GBq in median 6 cycles): 21 patients
  - Group 2 – 5.5 to 28.9 GBq (median 25.2 GBq in median 4 cycles): 30 patients

Bodel L et al. Eur J Nucl Med 28:2125 – 2135, 2011

- No differences in toxicities between the 2 groups
- No differences in outcomes between the 2 groups
- CR, PR, SD in 42/51 patients (82%)
  - CR: 1
  - PR: 14
  - SD: 27
  - PD: 9
- Median time to progression: 36 months

Lutetium Octreotate Rx & Chemo in GEPNETS

Kwekkeboom, D. J. et al. J Clin Oncol; 26:2124-2130 2008

Table 4. Results of Recent Chemotherapy Reports Compared With Treatment With ^{177}Lu-Octreotate

Regimen	Tumor Type	No. of Patients	PR/CR (%)	Median PFS (months)	Median OS (months)	Study (year)
STZ + doxorubicin	PNET	16	6	NA	NA	Cheng (1999)[21]
Dacarbazine	Carc	56	16	NA	20	Bukowski (1994)[22]
Dacarbazine	Carc	7	14	NA	NA	Ritzel (1995)[23]
FU + IFN-α	Carc/PNET	24	21	8	23	Andreyev (1995)[24]
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt (1995)[25]
Paclixatel	Carc/PNET	24	4	3	18	Ansell (2001)[26]
STZ + FU + doxorubicin	PNET	84	39	18	37	Kouvaraki (2004)[27]
Doxorubicin + FU	Carc	85	13	5	16	Sun (2005)[28]
STZ + FU	Carc	78	15	5	24	Sun (2005)[28]
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux (2006)[29]
Oxaliplatin + capecitabine	Well-differentiated NET	27	30	NA	40	Bajetta et al (2007)[30]
^{177}Lu-octreotate	Carc/PNET	310	30	32	46	Present results

Summary of OS and PFS for Rx in NETs

Therapy	Author	Median OS (months)	Median PFS
Everolimus	Yao	> 28	17
Bevacizumab	Yao		16
Sunitinib	Kulke	G 25 (P > 30)	
mIBG	Safford	72 (Sx) 26 (NSx)	
mIBG	Sywak	84	
Lu - PRRT	Kwekkeboom	46	32
Lu/Y - PRRT	Villard	66	
Best Chemo	Bajetta (ref Kwekkeboom)	40	
Y - PRRT	Valkema		30
Y - PRRT	Waldherr		26

Table 2. Summary of the Ongoing Pivotal Clinical Trials for Molecular Therapy in Neuroendocrine Tumors

Agent	Molecular Target (s)	Patient (Phase)	Tumor Type	Tumor Response Rate (%)	Median TTP or PFS (weeks)	Reference
Octreotide acetate (depot)	Somatostatin receptors	90(III)	Midgut Carcinoid	NA	57.2 (TTP)	Rinke *et al* 2009 [19]
Pazopanib	VEGFR-1,2,3; PDGFR-α,β; KIT	51(II)	Carcinoid/ Pancreatic endocrine	0 (C) 17%(P)	51 (C-TTP) 47 (P-TTP)	Phan *et al* 2010 [40]
Sunitinib	VEGFR-1,2,3; PDGFR-α,β; KIT;CSF-1R;FLT3	41	Carcinoid	2	44 (TTP)	Kulke *et al*. 2008 [31]
		66(II)	Pancreatic endocrine	17	33 (TTP)	Kulke *et al*. 2008 [31]
		171(III)	Pancreatic endocrine	9.3	46(TTP)	Raymond *et al* 2011[42]
Sorafenib	VEGFR-1,2,3; PDGFR-α; KIT; FLT3,RET	93(II)	Pancreatic endocrine and Carcinoid	19	NR	Hobday at al. 2007 [33]
Everolimus	mTOR	18(I/II)	Carcinoid	11	NR	Yao *et al*. 2010 [28]
	mTOR +/- Sandostatin LAR	115(mTOR) 45(Combo)	Pancreatic endocrine	10%(mTOR) 4.4%(Combo)	40(TTP) 67(TTP)	Yao *et al* 2010 [28]
		410(III)	Pancreatic endocrine	5	46(TTP)	Yao *et al*. 2011[29]
	mTOR vs mTOR+Sandostatin LAR	429(III)	Neuroendocrine (non-pancreas)	NA	45 vs 66 (TTP)	Yao *et al* 2011[43]
Temsirolimus	mTOR	21	Carcinoid	5		Duran *et al*. 2006 [30]
		15	Pancreatic endocrine	7		Duran *et al*. 2006 [30]
Bevacizumab	VEGF	22 (II)	Carcinoid	18	63 (PFS)	Yao *et al*. 2008 [36]

CSF-1R, colony-stimulating factor receptor; EGFR epidermal growth factor receptor; FLT3, FMS like tyrosine kinase-3;KIT, stem cell factor receptor; NR, not reported; PFS, progression free survival; RET, Rearranged during transfection or glial cell line derived neutrophic factor; TTP, time to progression.

Anti-Cancer Agents in the Medicinal Chemistry, 2013,13,382-88

^{131}ImIBG - Adverse Events

Nausea	-	mild and common in adults w liver metastases; rare in pediatric patients		
	-	severe in advanced disease or with extensive liver metastases		
Thrombocytopenia	-	grade IV	-	rare
		grade III	-	not uncommon at LDR
		grade II	-	frequent
Neutropenia	-	grade I/II	-	not infrequent with increasing dose
	-	nadir occurs at 4 - 6 weeks recovery occurs at 6 - 10 weeks		
Post therapy fatigue	-	seen in most adult patients		
Myelodysplasia	-	5/235 patients (all adults)		
Thyroid failure	-	6/235 patients (4 children)		

^{177}Lu Octreotate - Adverse Events

Nausea	-	Common following a-a infusion
		Occasionally severe (10%)
Carcinoid crisis	-	rare (6/310)
Hematological	-	Occasional (10%)
	-	nadir occurs at 4 - 6 weeks
		recovery occurs at 6 - 10 weeks
Post therapy fatigue	-	seen in most patients
Myelodysplasia	-	4/310
Renal/Liver toxicity	-	5/310

Clinical Outcomes after Steady State RIT

- Stable disease is common
- Response is inversely related to tumor burden.
- Palliative responses are normal
  - There appears to be a cumulative dose response
  - Tolerance probably has not been reached.
  - Treatments may continue as maintenance (mIBG)
  - Response may be sustained for several years
- Toxicity is acceptable at the doses administered and should not reduce therapy goals
- Probable overall survival benefit
- Probable progression free interval

How Does it Work

Characteristics of Radioisotope Therapy

Clinical Characteristics

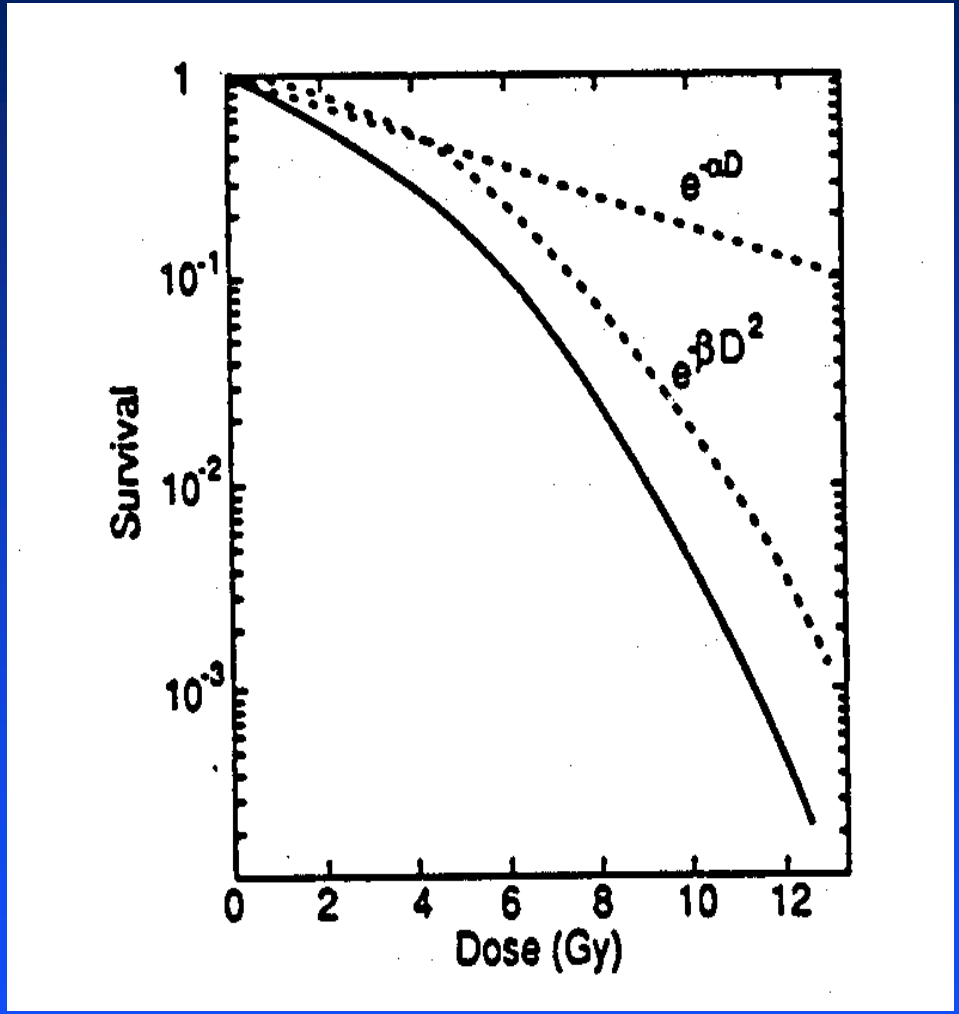
- **Systemic administration**
- Specific targeting
- Low toxicity
- **Retreatment**
- Adjuvant treatment
- Low complexity
- Ability to image

Scientific Characteristics

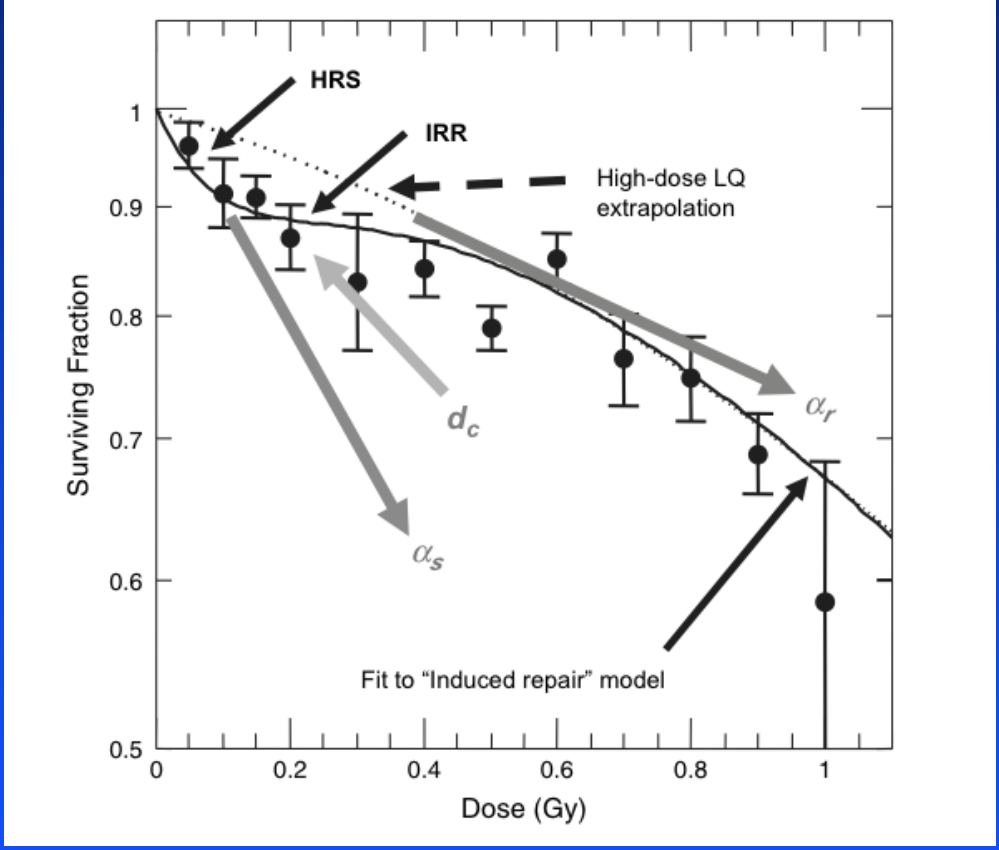
- **VLDR/LDR**
- Microdosimetry
- T_p correlates with T_b
- Chemistry
- Availability/half life
- Cost effective supply

“Classical” Cell Survival Curves

- Cell killing is well described by shouldered models such as multi-target [MT] or linear-quadratic [LQ].
- Cells must be “hit” to be killed, and DNA is the principal “target”.



Survival Curves - LDHRS



Int. J. Radiation Oncology Biol. Phys., 70: 1310 - 1318, 2008

Clinical relevance for LDH in RIT

- If localized dose/dose rate is below the threshold for triggering IRR, cell killing should follow the initial slope of the survival (α_s) rather than α_r estimated from high-dose LQ model
- If so RIT should exert much greater cytotoxicity than would be predicted by conventional LQ models.
- Is RIT effectively" ultra fractionation" which fails to activate IRR

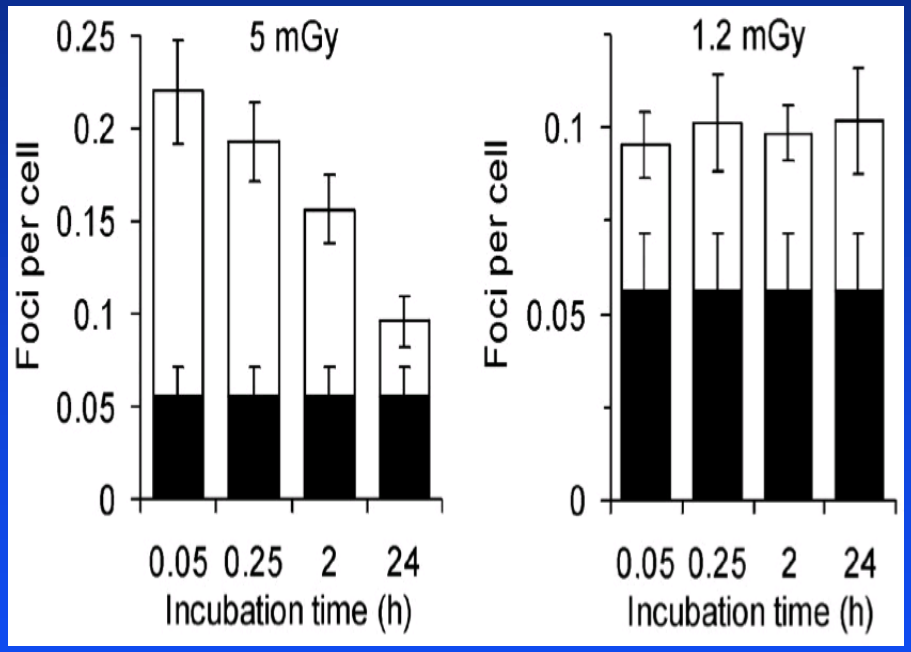
DNA Repair

- Early models focused mostly on the mechanical problems that DNA lesions such as DSBs present to a cell when it tries to replicate its DNA (S-phase) or divide (mitosis).

- It is now recognized that cellular responses to DNA damage are genetically regulated and involve specialized damage-recognition factors and signaling pathways

Lack of DSB Repair After Very Low Doses

- Rothkamm and Löbrich (2003) observed a decreasing capacity for DSB repair with decreasing dose
- Between 2 Gy and 5 mGy, H2AX foci were extensively repaired.
- Below 1.2 mGy, repair of foci did not occur up to 24 h.



LDR Evades DNA Repair Sensors

- Reduced activation of ATM following LDR
- Reduced activation of downstream target γH2AX
- Increased cell killing after LDR

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

Collis SJ, et al. *J Biol Chem* 2004, Sept 17

Radioisotope therapy should be considered in the same class of treatments as systemic therapies; it has little in common with external beam radiation therapy

Effective Use

Significant Factors Predicting Disease-Specific Survival in Patients (n = 310)

Factor		# Patients	Survival (mo)	*P*
Treatment outcome	- PD	61	11	
	- SD	107	> 48	<.001
	- Remission	142	> 48	
Liver involvement	- Extensive	85	25	
	- Moderate	191	> 48	<.001
	- None	34	> 48	
KPS ≤ 70	- Yes	39	16	
	- No	271	> 48	.001
Baseline weight loss	- Yes	75	30	
	- No	235	> 48	.001
Bone Metastases	- Yes	68	37	
	- No	242	> 48	.004
Gastrinoma/ insulinoma/VIPoma	- Yes	19	33	
	- No	291	> 48	.04

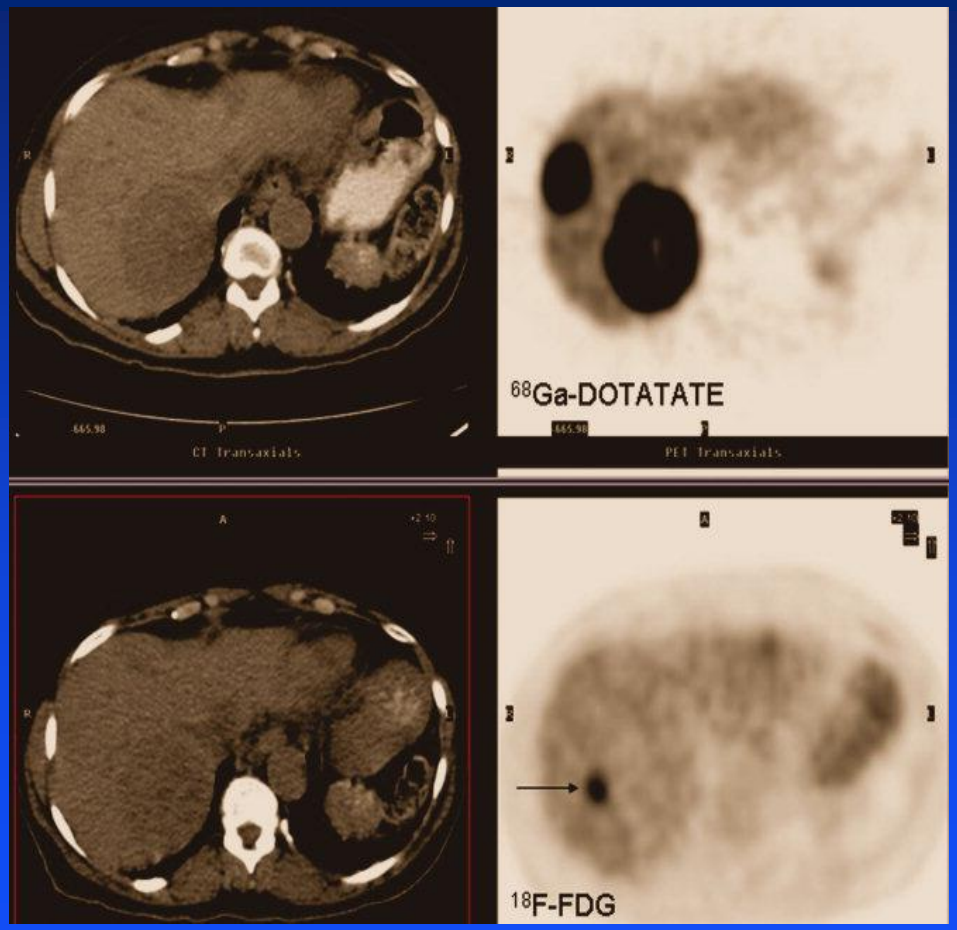
Kwekkeboom DJ et al. *J Clin Oncol* 2008; 26:2124-2130

Functional Imaging of Neuroendocrine Tumors with combined PET/CT using ^{68}Ga-DOTA-TATE and ^{18}F-FDG

- 38 patients with prior diagnosis of NETs
  - 34 GEP
  - 4 Unknown primary
- Gold standard: Histology, markers, progressive imaging
- Ga-68 sensitivity: 82%
- FDG sensitivity: 66%

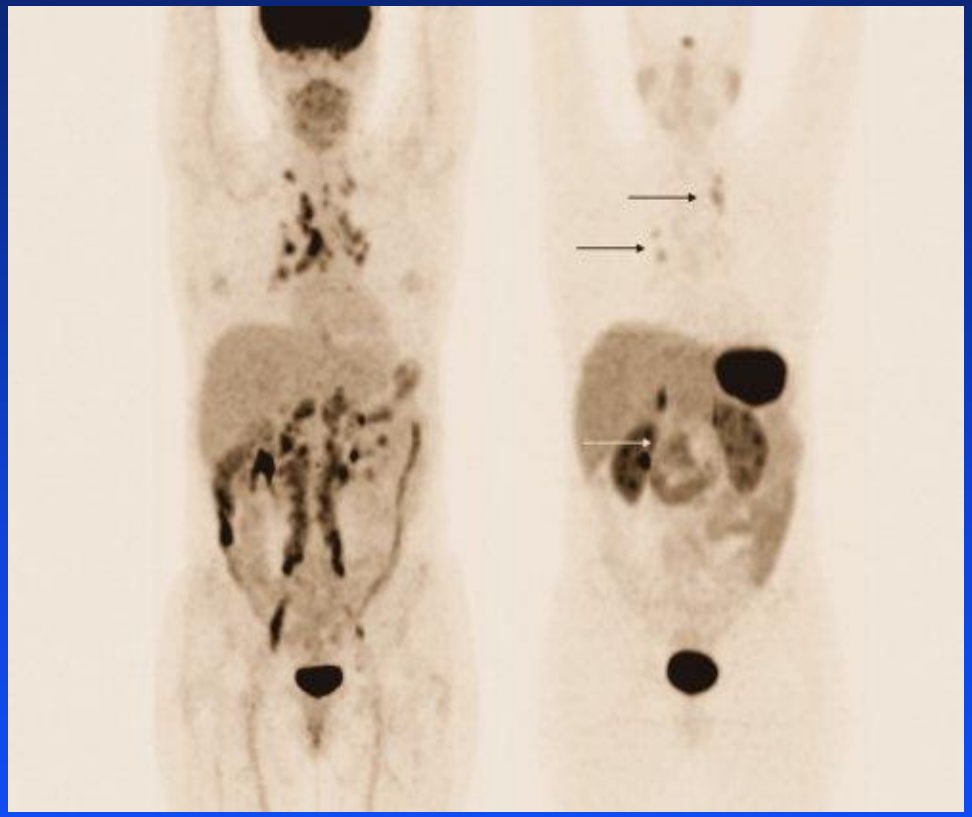
Kayani et al. *Cancer* 2008;112:2447-2455

54-year-old Female Patient with Metastatic Carcinoid Tumor (Primary Cecal Carcinoma)



Kayani I, et al. *Cancer* 2008;112:2447-2455

55-year-old Female Patient with Metastatic Neuroendocrine Carcinoma with Unknown Primary



FDG Ga-68

Kayani I, et al. *Cancer* 2008;112:2447-2455

Numbers of Lesions Demonstrating ^{68}Ga-DOTA-TATE and/or ^{18}F-FDG Uptake in High-, Intermediate-, and Low-Grade NET Tumors

	High Grade NET	Intermediate Grade NET	Low Grade NET	Total
Ga-68 +ve & FDG +ve	5	45	21	71
Ga-68 +ve & FDG -ve	0	18	97	115
Ga-68 –ve & FDG +ve	72	33	0	105
Ga-68 -ve & FDG -ve	2	5	3	10
Total	79	101	121	303

Kayani I, et al. *Cancer* 2008;112:2447-2455

SUVmax of Ga-68 DOTA-TATE and F-18 FDG According to Tumor Grade

	Ga-68 DOTA-TATE	**F-18 FDG**	***P***
All NET	16.9 (1.6 – 50)	4.2 (1.4 – 16.4)	0.005
Ki-67 Index ≤ 2%	29 (3.3 – 45)	2.9 (1.5 – 1.2)	<0.001
Ki-67 Index 3 – 20%	15.5 (1.8 – 50)	10.5 (2.0 – 13.9)	NS
Ki-67 Index > 20%	4.4 (1.6 – 8.9)	11.7 (4.1 – 16.4)	0.03

Kayani I, et al. *Cancer* 2008;112:2447-2455

Infrastructure/ Next Steps

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

NET Care in Edmonton

- All new NET patients in Northern Alberta are referred to the tumor group
- All reviewed in tumor board
  - Initially monthly, bi-weekly from June
- All patients seen in multi-disciplinary clinic
- CPGs define workup and treatment options
- All referrals for RIT from Western Canada reviewed by tumor board – in particular surgical review
  - Standard imaging workup
- Active Phase 1 unit for referral if progression

Cross Cancer Institute Neuroendocrine Clinic

- Endocrine Surgeon
- Endocrinologist
- Nuclear Medicine Physician
- Medical Oncologist
- Radiation Oncologist
- Radioisotope Therapy Nurse

Clinical Infrastructure Required for Radioisotope Therapy

- Joint clinic
- RIT nurse
- Trained technologist complement
- CNSC Licensing
  - Outpatient therapy approval
- Consent forms
- Information Sheets
- Shielded rooms
- Trained nursing staff
- Outreach

Radioisotope Therapy

- ^{131}mIBG and ^{177}Lu-Octreotate both offered routinely
  - Choice defined by relative uptake on pre-therapy scanning
- Decision made at tumor board
- Time intensive consultations
- Significant infrastructure requirements
- Rapidly increasing referral numbers

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RIT Inclusion Criteria

- Progressive disease
  - Symptoms
  - CT/MRI/RNI
- Diagnostic image positive
  - Quality of scan
  - mIBG - tumour : liver
  - Lutetium - tumour : liver; ? renal uptake
- Haematology
  - Platelets ≥ 150
- GFR ≥ 50
- KPI ≥ 60

RIT Exclusion Criteria

- Biochemistry
  - LFT > 3 x Normal
  - GFR < 50
- Haematology
  - Recent rapid fall in counts
- Significant recent weight loss
- Age > 80 (relative exclusion)
- Extensive hepatic metastases
- Severe nausea and vomiting
- Ki67 >20 (?>15)

Current Registry Study

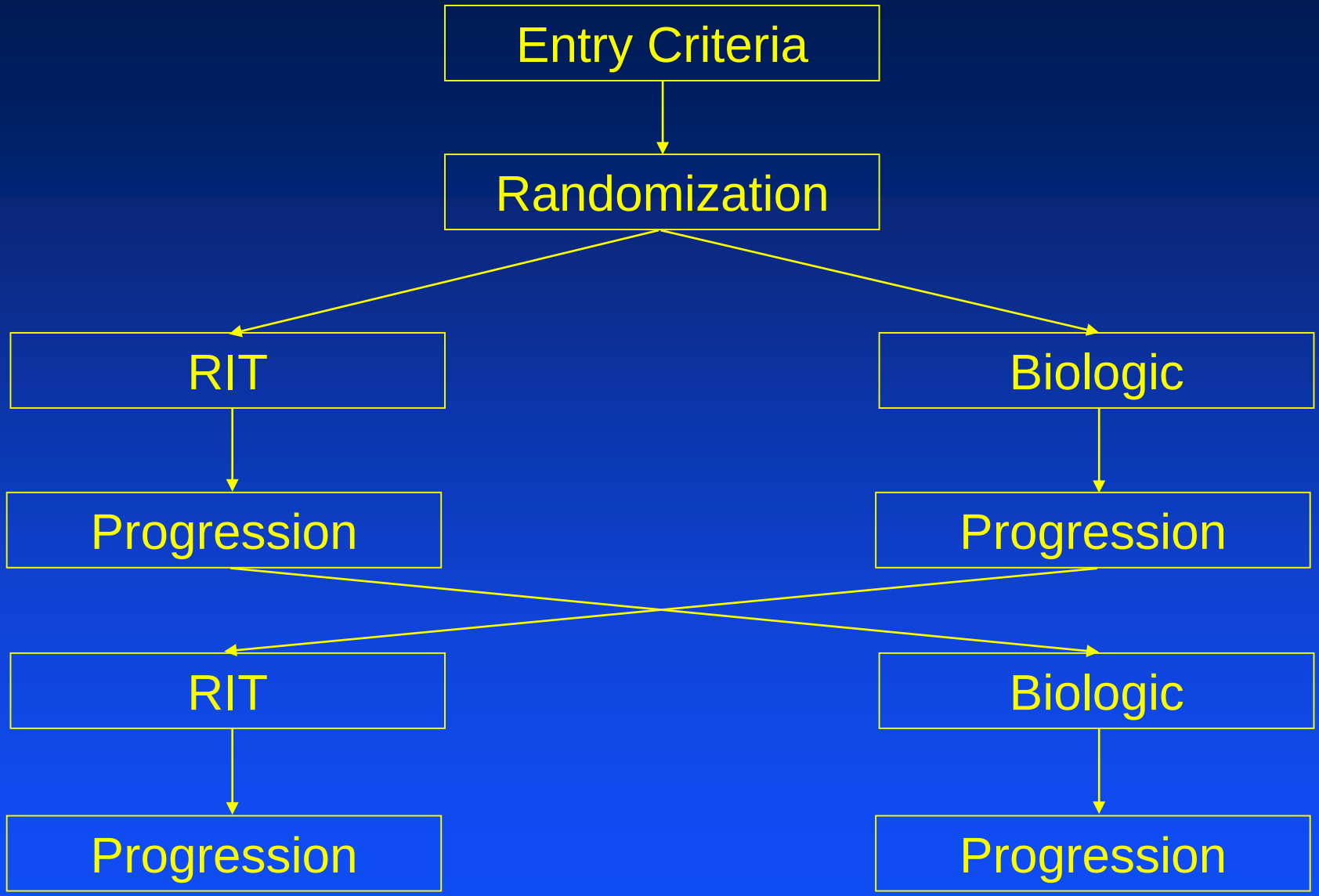
Trial Design – PRRT Restart

- Registry study
  - Database open to all referring physicians
- 400 patients with Octreotide (In-111 or Ga-68) avid NETs
- 2 entry pathways:
  - New patients who have never had Lutetium
  - Patients who have previouslyreceived Lutetium therapy
- We plan to open a second trials for patients with non-NET octreotide avid tumours

Treatment Plan

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

Clinical Trial Concept


Entry Criteria
Randomization
RIT
Biologic
Progression
Progression
RIT
Biologic
Progression
Progression

Entry Criteria

- Neuroendocrine tumour
  - ? GNET
  - ? PNET
  - ? Both
- Progressive disease
  - ? Imaging
  - ? Symptoms
  - ? Biochemical
- Sandostatin status
  - ? Stable for 3 months
  - ? Can start for progressive symptoms
- ? Debulking opportunity

Response Assessments

- At cross over:
  - Progression free survival
  - Toxicity
  - QOL
- After cross over treatment:
  - Progression free survival (from crossover)
  - Toxicity (cross over/cumulative/additive)
  - Overall survival
  - QOL (from cross over and overall)

Wish List

- National Network of Centres of Excellence
  - Common protocols
  - Common assessment pathway
  - Educational mandate
  - National registry
- Cross over trial
- Phase 1 trial
- National meetings
- CPGs that overtly include RIT

To Cure Sometimes
To Help Often
To Care Always