Dose escalation clinical trials (update paradigm shifts in NET therapy)

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CANCER RESEARCH UK | EPSRC Engineering and Physical Sciences Research Council

CANCER IMAGING CENTRE

European ENETS Neuroendocrine Tumor Society

MAHSC Manchester Academic Health Science Centre (MAHSC)

2014 Overall Assessment (excerpt):
"…the NET Service at The Christie is exemplary well organized and equipped. The Christie fulfils all major criteria of excellence and represents one of the leading NET institutions in Europe"

CANCER RESEARCH UK | MANCHESTER INSTITUTE

Over 500 active clinical trials currently open with 8 in NET alone

The Christie

MRT in NET

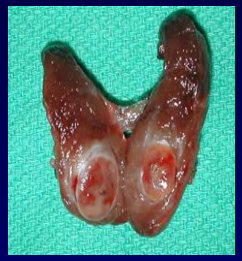
PRESS THE RESET BUTTON

Objectives/Concepts

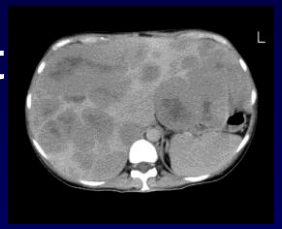
- NET brief disease description – setting the scene
- Pancreatic NET- a model for consideration
- Therapeutics- core principles and ideas
- Future

Spectrum of Disease(s)

Neuroendocrine tumours

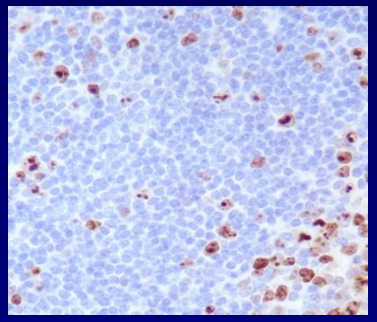


Benign — **G1** — **G2** — **G3** → **Malignant**



Increasing grade

<2%----------20%----------70%+



Mitotic activity (Ki-67 or MIB-1)

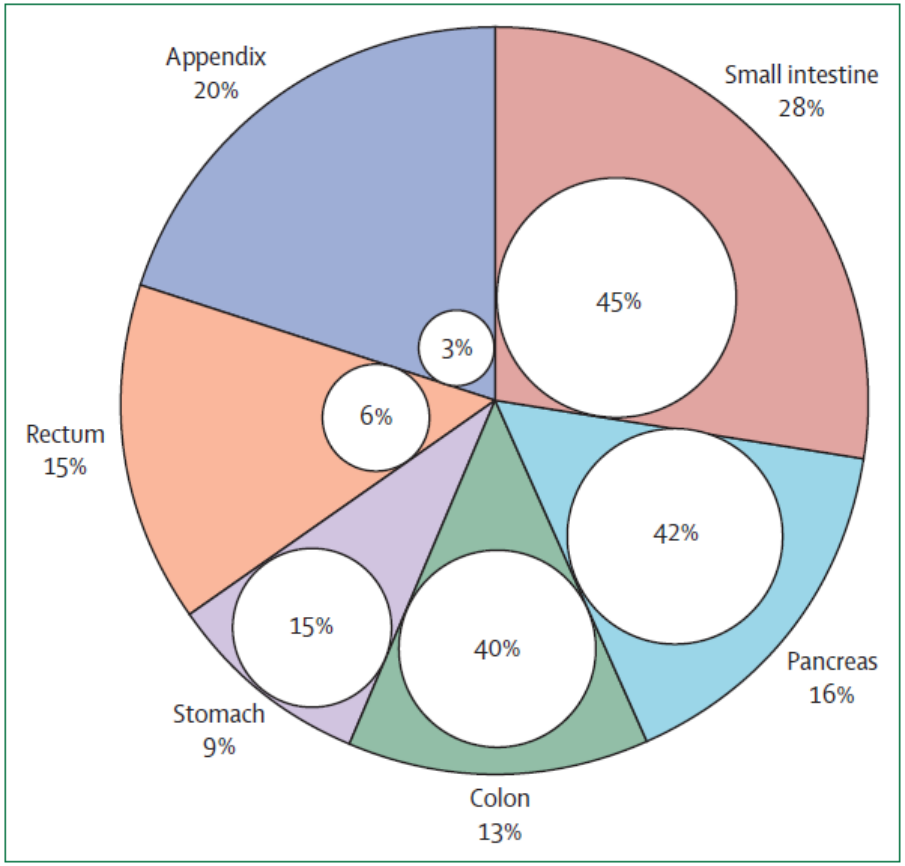
Functional vs. non-functional

Anatomical site of origin

Progressive vs. stable

Neuroendocrine Tumours

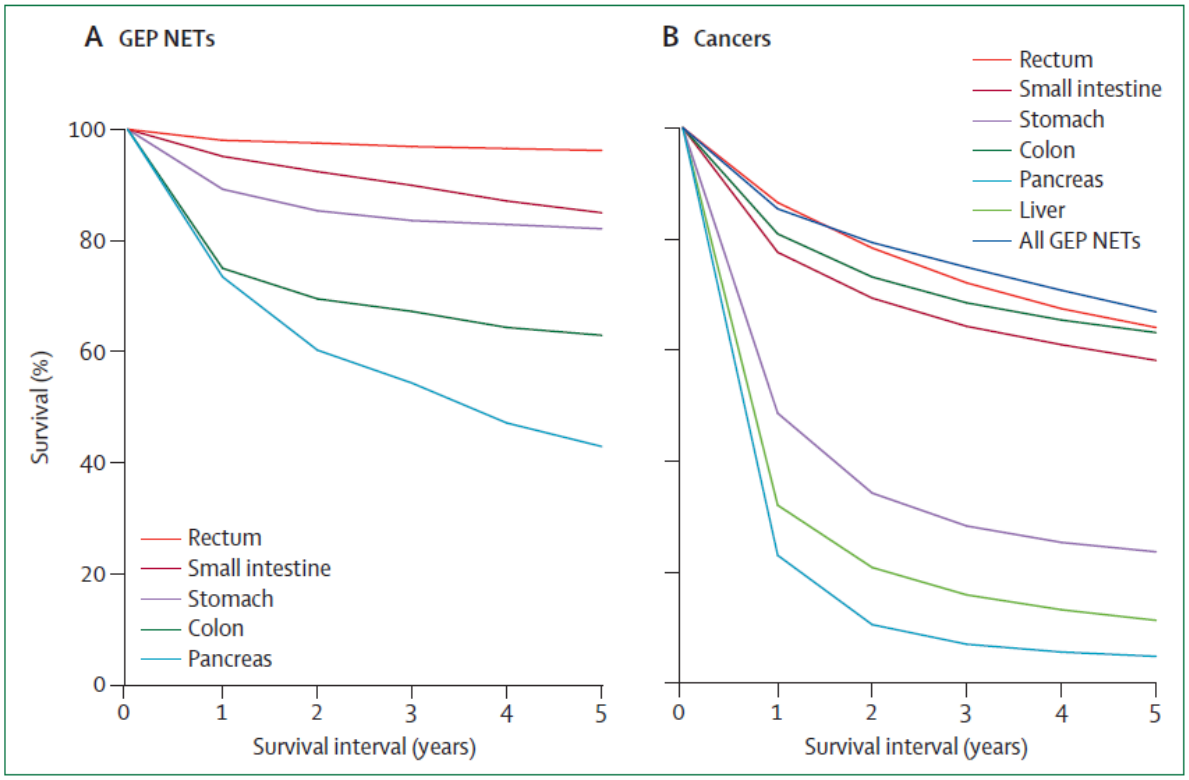
- Rare tumours and heterogenous group of patients, so small numbers in literature
- Rare, but in fact are increasing in incidence (3·65 per 100 000 individuals per year)
- Frequently as testicular tumours, Hodgkin's disease, gliomas, and multiple myeloma



Recommendations for management of patients with neuroendocrine liver metastases

Andrea Frilling, Irvin M Modlin, Mark Kidd, Christopher Russell, Stefan Breitenstein, Riad Salem, Dik Kwekkeboom, Wan-yee Lau, Catherine Klersy, Valerie Vilgrain, Brian Davidson, Mark Siegler, Martyn Caplin, Enrico Solcia, Richard Schilsky, for the Working Group on Neuroendocrine Liver Metastases

Lancet Oncol 2014; 15: e8–21



The 5 year survival of neuroendocrine liver metastases is less than 50%

NET 46%–93% liver involved at the time of diagnosis

*JG Touzios et al. The survival for the Resection/Ablation and the TACE groups was significantly better **(P 0.05)** when compared with the Nonaggressive group. Patients with more than **50%** liver involvement had a poor outcome **(P 0.001).** Ann Surg 2005;241: 776–785*

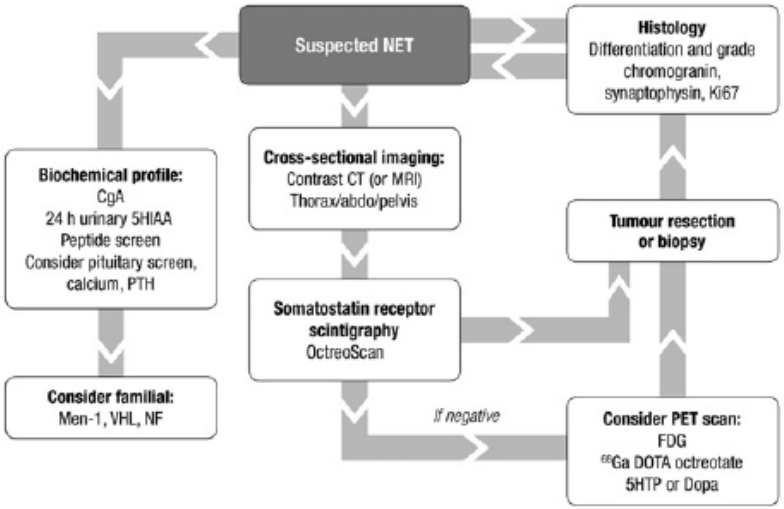
NET survival

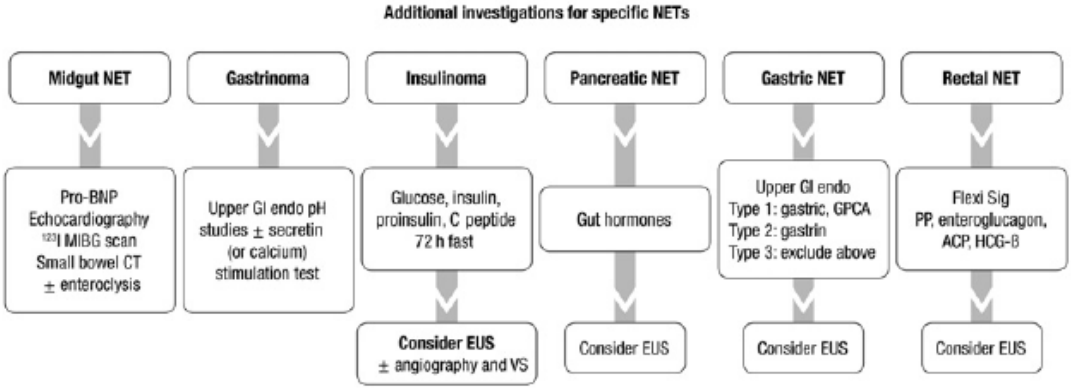
- Overall 5 year survival of 47.5% (58.1% for differentiated and 8.1% for small cell tumours)
- 55.9% for age ≤65 years and 37.5% for age >65 years
- 5 year survival was worse with distant metastases (about 30–60%)

Neuroendocrine Tumours

- Rare tumours and heterogeneous group of patients, so small numbers in literature.
- **But high prevalence- majority are in the palliative setting at clinical presentation**
- In fact not **so rare** as high prevalence and increasing incidence

Investigating NET





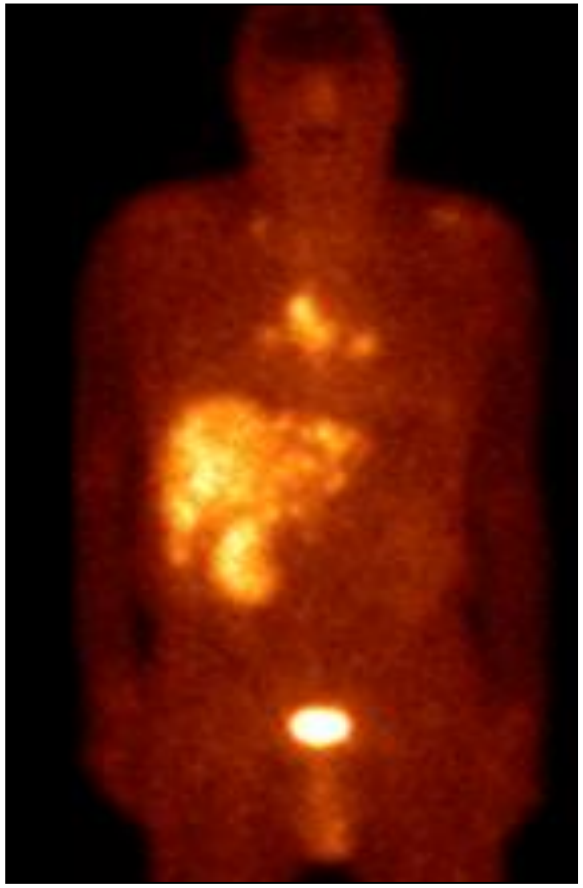
Gut 2012;**61**:6–32. doi:10.1136/gutjnl-2011-300831

"Molecular Imaging is aimed at the exploitation of specific molecules as the source of image contrast"Weissleder R 1999

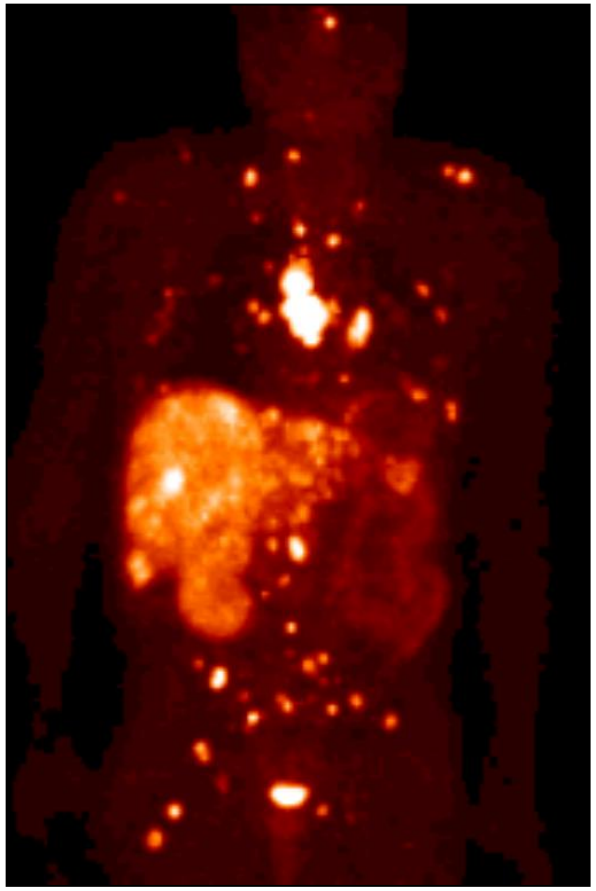
Aims:

- Earlier detection and characterisation of disease ("molecular signature" prior to irreversible damage)
- Understanding of underlying biology
- Selection of specific treatment option for targeted therapy
- Concept of '**THERANOSTICS**'

Molecular imaging allows better staging



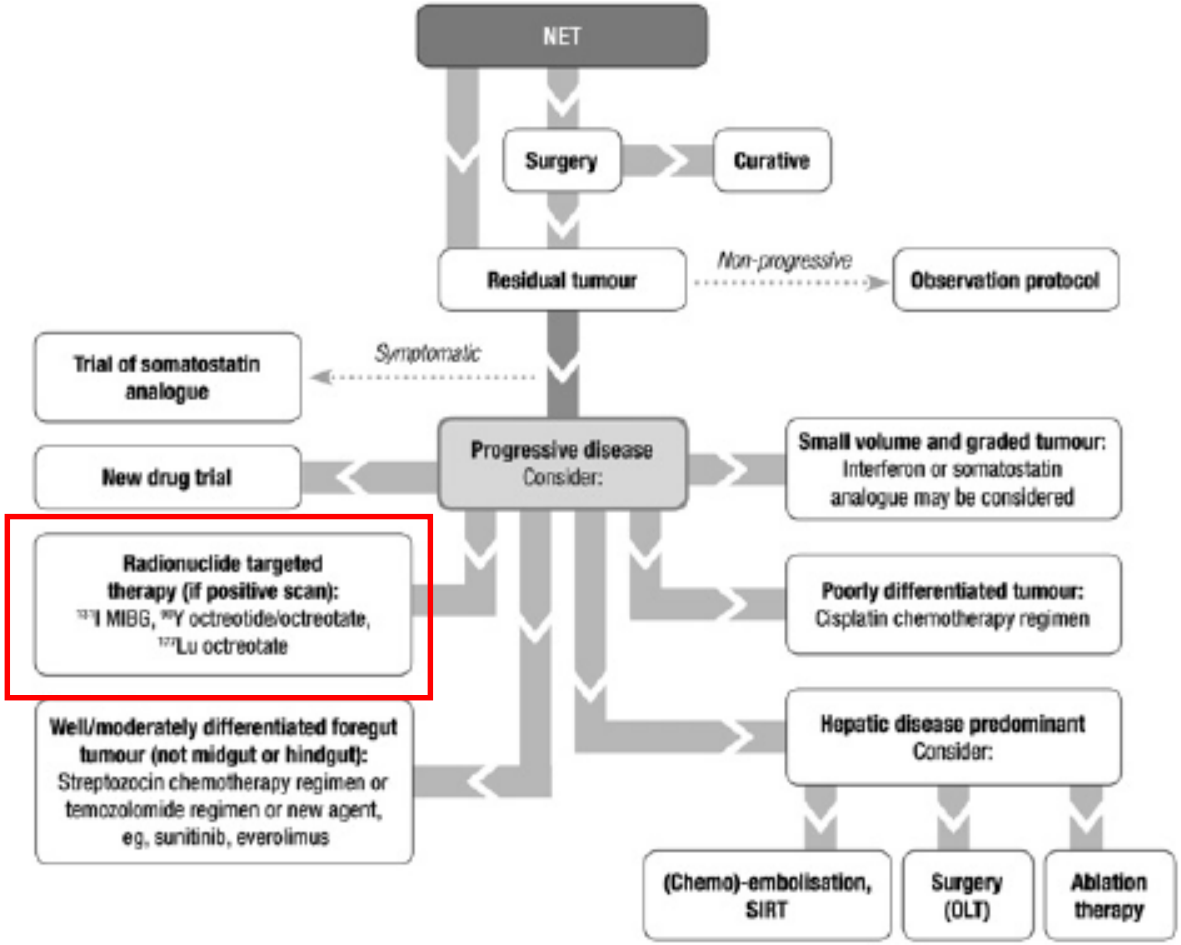
[^{111}In]Octreotide



[^{18}F]FP-Gluc-TOCA PET

Courtesy of Dr Morand Piert, UMICH, Ann Arbor, USA

NET therapy algorithm: Eminence vs Evidence



Gut 2012;**61**:6–32. doi:10.1136/gutjnl-2011-300831

Table 1. Tumour responses in patients with GEP tumours treated with different radiolabelled somatostatin analogues.

Centre	Ligand	Patient number	Tumour response					
			CR	PR	MR	SD	PD	CR+PR
Rotterdam[23]	[^{111}In-DTPA^0] octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0%
New Orleans[24]	[^{111}In-DTPA^0] octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8%
Milan[28]	(^{90}Y-DOTA^0,Tyr^3) octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29%
Basel[26,27]	(^{90}Y-DOTA^0,Tyr^3) octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24%
Basel[28]	(^{90}Y-DOTA^0,Tyr^3) octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33%
Rotterdam[31]	(^{90}Y-DOTA^0,Tyr^3) octreotide	54	0	4 (7%)	7 (13%)	33 (61%)	10 (19%)	7%
Rotterdam[35]	(^{177}Lu-DOTA^0,Tyr^3) octreotate	76	1 (1%)	22 (29%)	9 (12%)	30 (39%)	14 (18%)	30%

GEP, gastroenteropancreatic; CR, complete remission; PR, partial remission; MR, minor remission; SD, stable disease; PD, progressive disease.

EU survey	^{131}ImIBG	537						30%

So PRRT has a biological effect….so does bleach!

Theranostics at The Christie

- Used in the context of inoperable/ metastatic disease to reduce disease volume and relieve symptoms at present.
- Goal is improving outcomes through individualised treatment
- Feasibility studies have shown promise for combined 90Y and 177Lu therapy- **The Christie palliative care protocol**
- **CURRENTLY NO RCT DATA AVAILABLE**

Objectives/Concepts

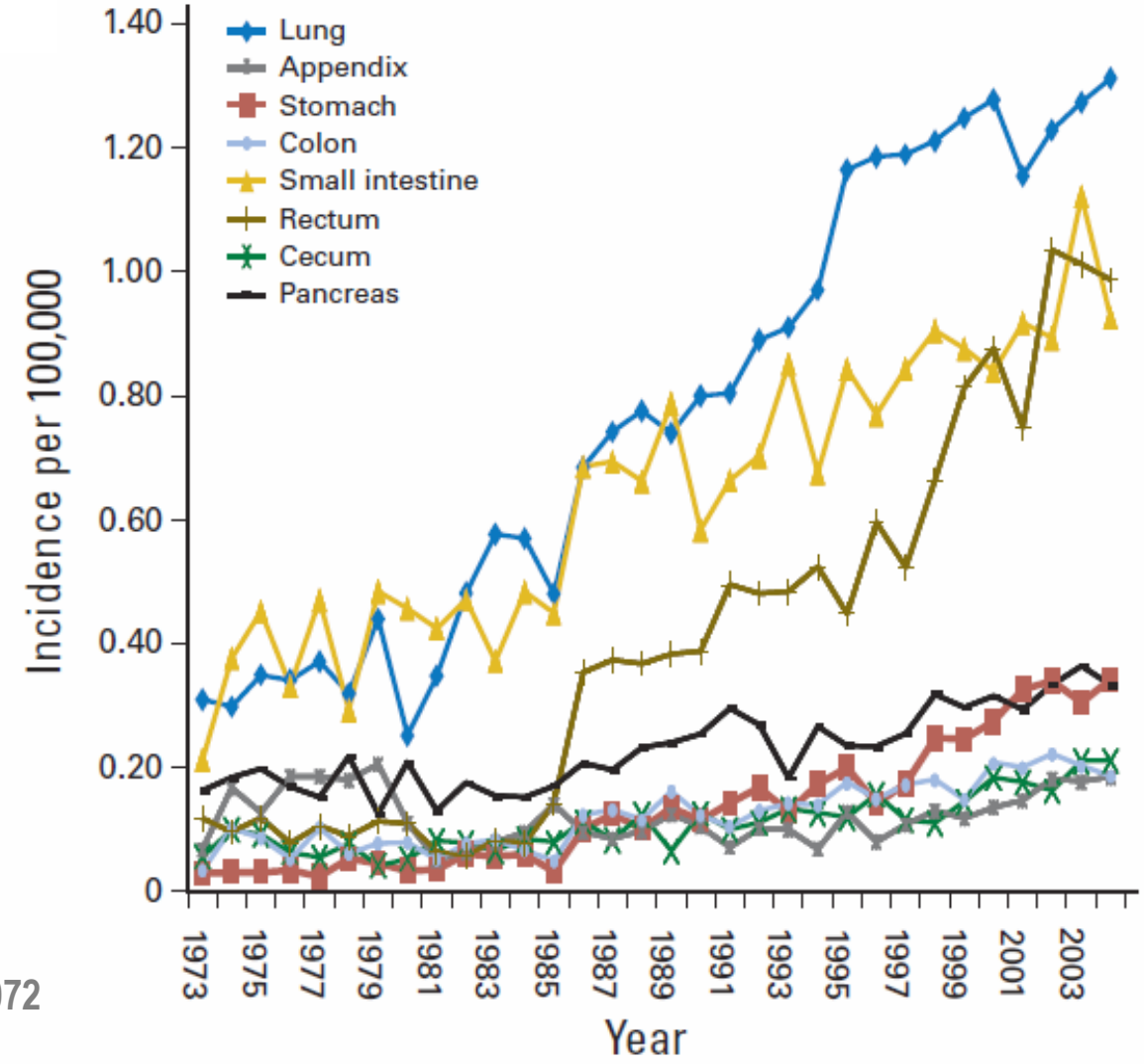
- NET brief disease description – setting the scene
- Pancreatic NET- a model for consideration
- Therapeutics- core principles and ideas
- Future

Pancreatic NET- paradigm shift in GEP treatment strategy

- Tools of the trade
  - Surgery
  - **Somatostatin analogues**
  - **Chemotherapy**
  - **Targeted therapies**
  - Other options
    - liver-directed therapy
    - PRRT (peptide receptor radionuclide therapy)
- Principles to aid decision-making

Pancreatic NET - epidemiology

- 2% of pancreatic cancers
- 6% of NETs
- Peak incidence: age 60–80 years
- Significant % diagnosed at age <50 years
- Increasing incidence / high(er) prevalence



Yao et al, JCO 2008;26:3063-3072

Histologic Classification of NETs[1]

Differentiation and grade	Mitotic count*	Ki-67 index† (%)	Traditional classification	ENETS/WHO classification[2]	Moran et al[3]
Well differentiated					
Low grade (grade 1)	<2	≤2	Carcinoid, islet cell, pancreatic (neuro) endocrine tumor	NET, grade 1	NEC, grade 1
Intermediate grade (grade 2)	2–20	3–20	Carcinoid, atypical carcinoid,‡ islet cell, pancreatic (neuro) endocrine tumor	NET, grade 2	NEC, grade 2
Poorly differentiated					
High grade (grade 3)	>20	>20	Small-cell carcinoma	NEC, grade 3, small cell	NEC, grade 3, small cell
			Large-cell NEC	NEC, grade 3, large cell	NEC, grade 3, large cell

NET = Neuroendocrine tumours

NEC = neuroendocrine carcinoma

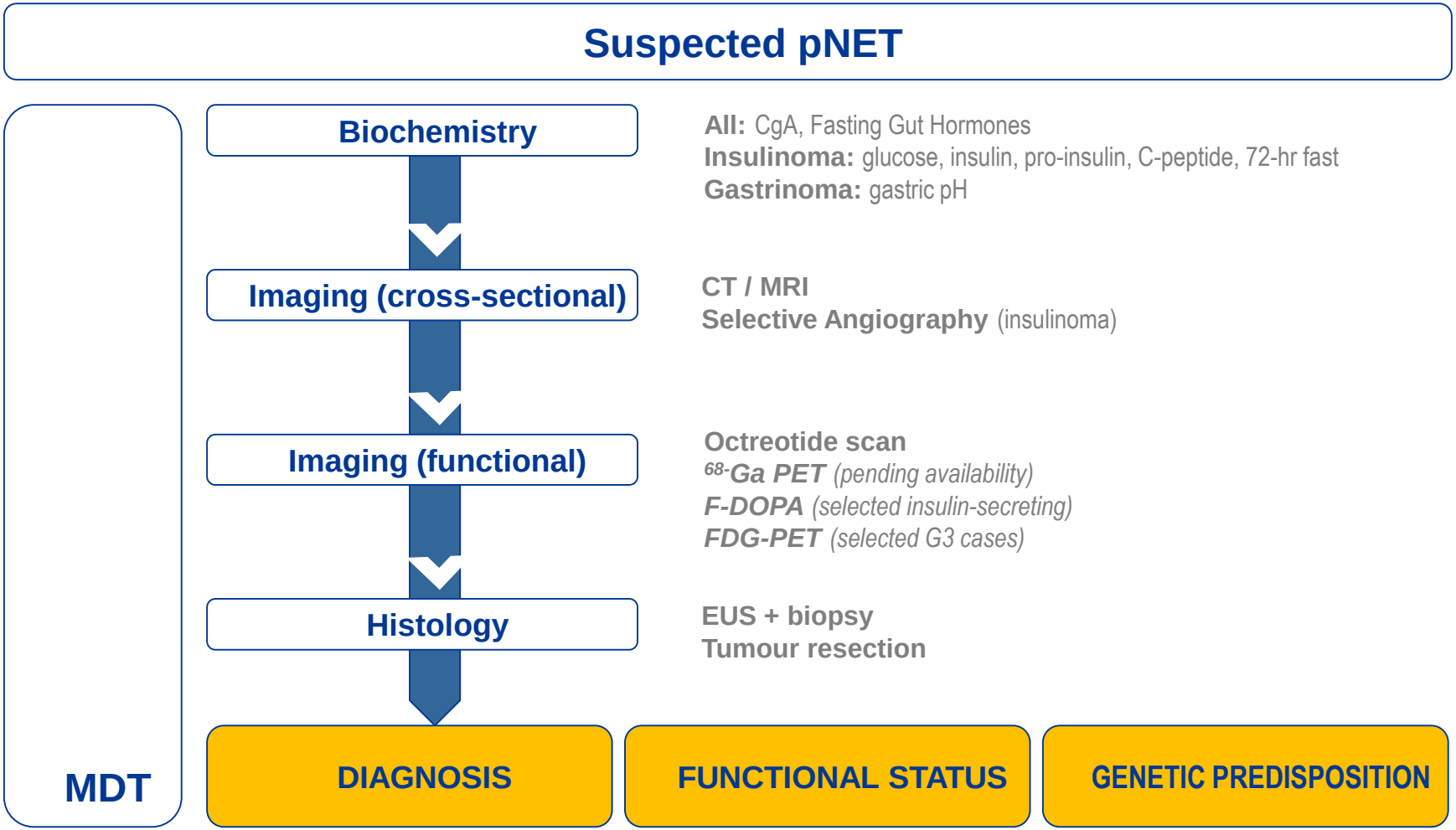
*Per 10 high-power fields

†Cellular proliferation marker

‡Applies only to intermediate-grade NET of the lung

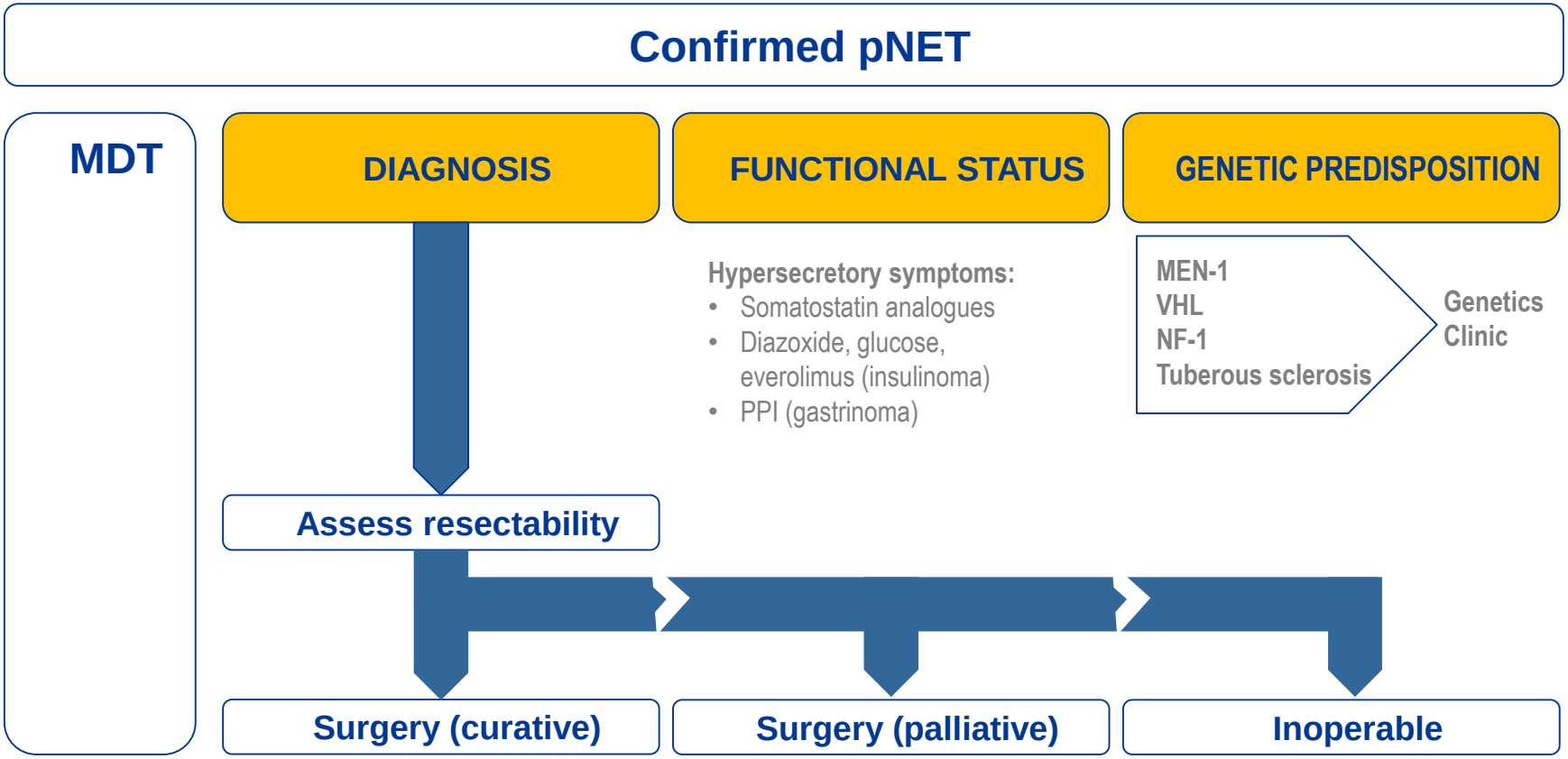
1. Kulke MH, et al. *J Clin Oncol* 2011;29:934–943
2. WHO Classification of Tumours of the Digestive System, 4th ed., 2010
3. Moran CA, et al. *Am J Clin Pathol* 2009;131:206–221

Diagnosis

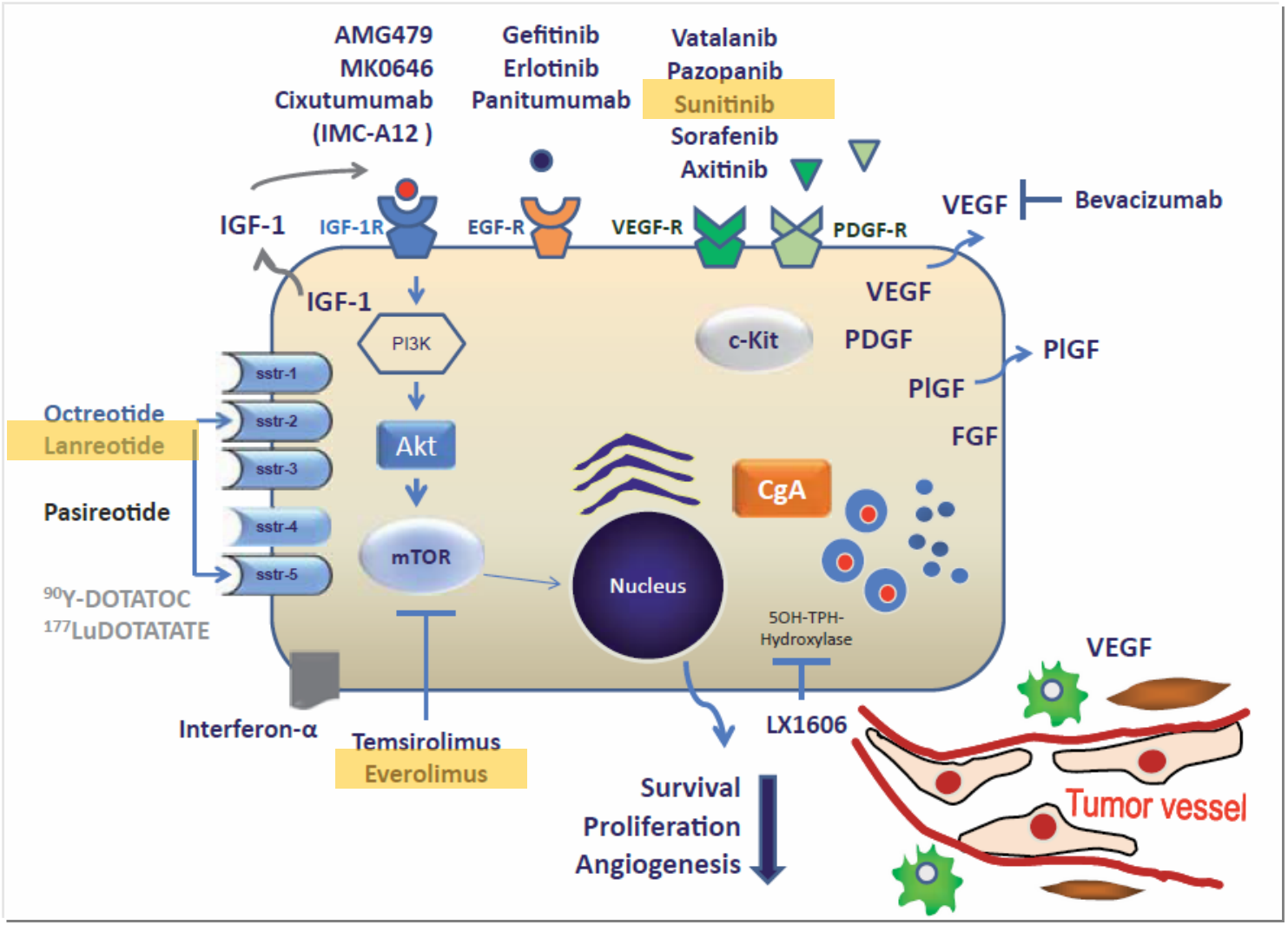


The Christie

Treatment (i)


Confirmed pNET
MDT
DIAGNOSIS
FUNCTIONAL STATUS
GENETIC PREDISPOSITION
Hypersecretory symptoms:
• Somatostatin analogues
• Diazoxide, glucose, everolimus (insulinoma)
• PPI (gastrinoma)
MEN-1
VHL
NF-1
Tuberous sclerosis
Genetics Clinic
Assess resectability
Surgery (curative)
Surgery (palliative)
Inoperable

Understanding the biology

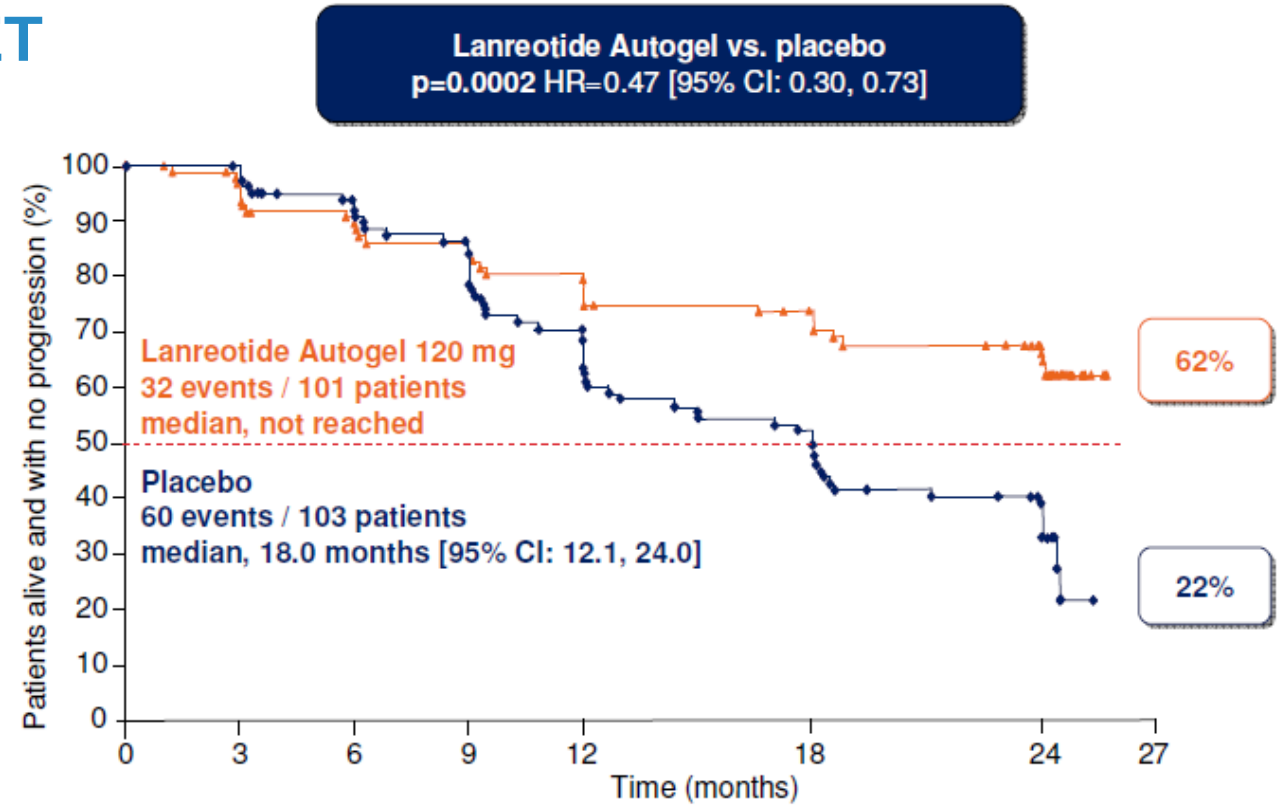


Pavel Neuroendocrinology 2013;97:99–112

Somatostatin analogues – anti-proliferative effect

Primary endpoint: PFS (ITT population, N=204)

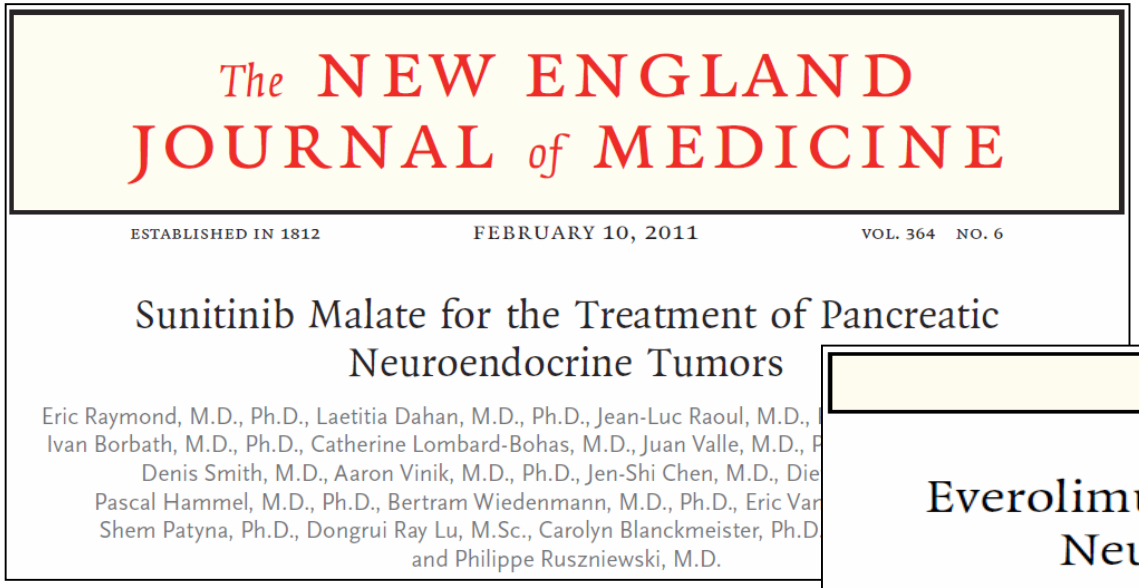
CLARINET study



P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.
HR, hazard ratio; ITT, intention-to-treat.

Presentation Presidential Session of the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress, 28 September 2013, abstract E17-7103 , Amsterdam- EJC, vol 49 (3), 2013

Targeted therapies

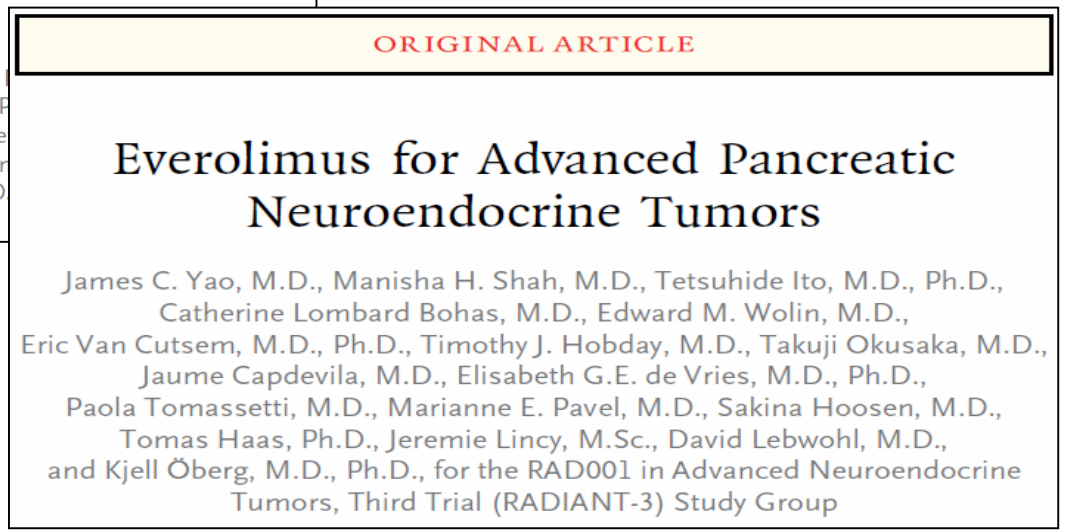


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2011 VOL. 364 NO. 6

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D. and Philippe Ruszniewski, M.D.



ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

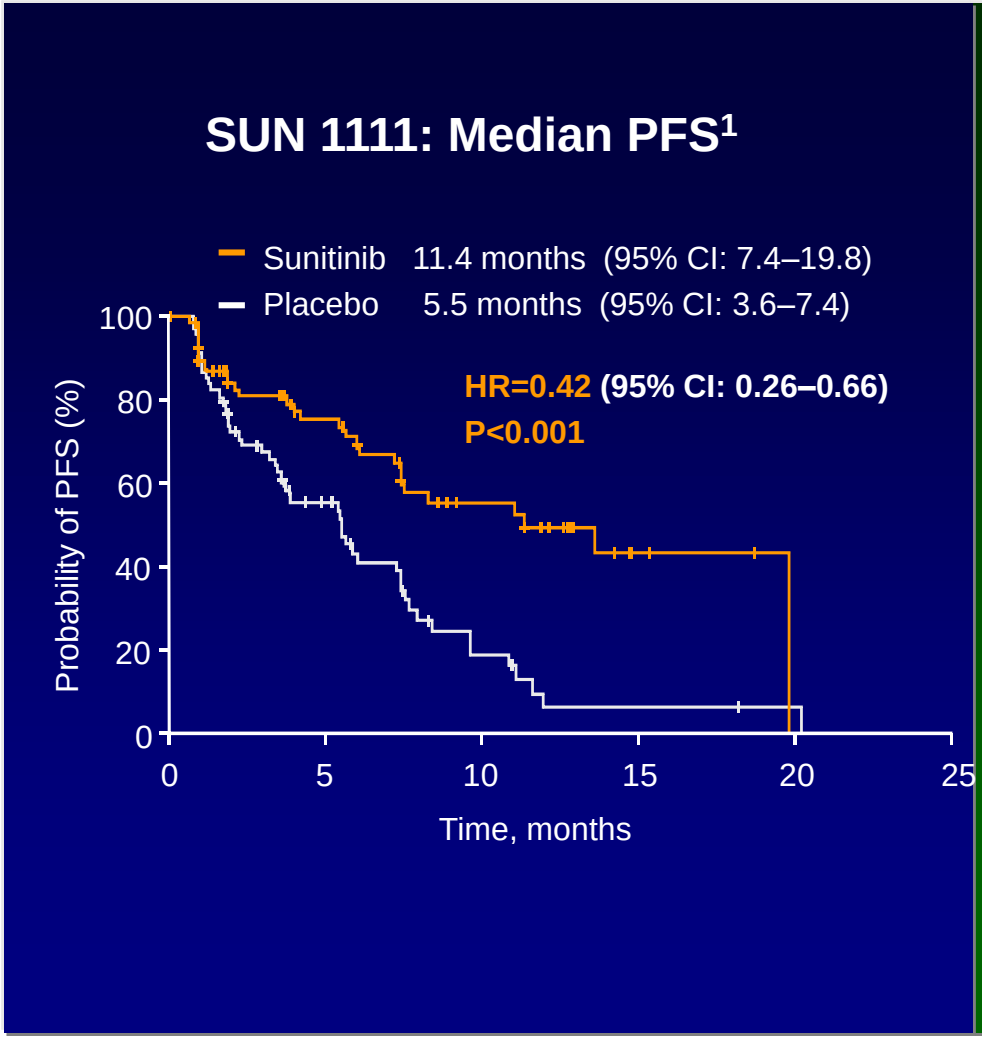
James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

'These studies provide optimism regarding the treatment of malignant pancreatic neuroendocrine tumors…'

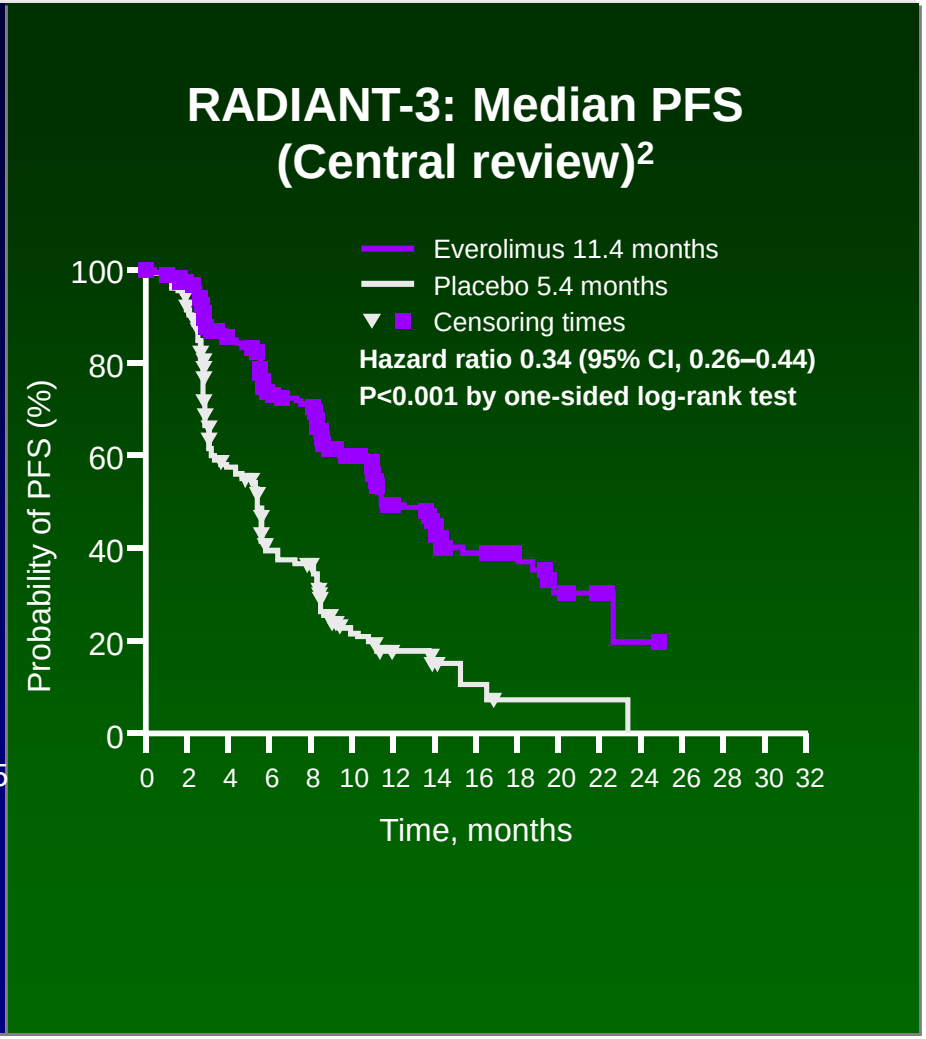
***NEJM* Editorial, February 2011**

Targeted therapies

Sunitinib (VEGF)



Everolimus (mTOR)



1. Raymond E et al. *NEJM* 2011;364:501–13 2. Yao JC et al. *NEJM* 2011;364:514–23

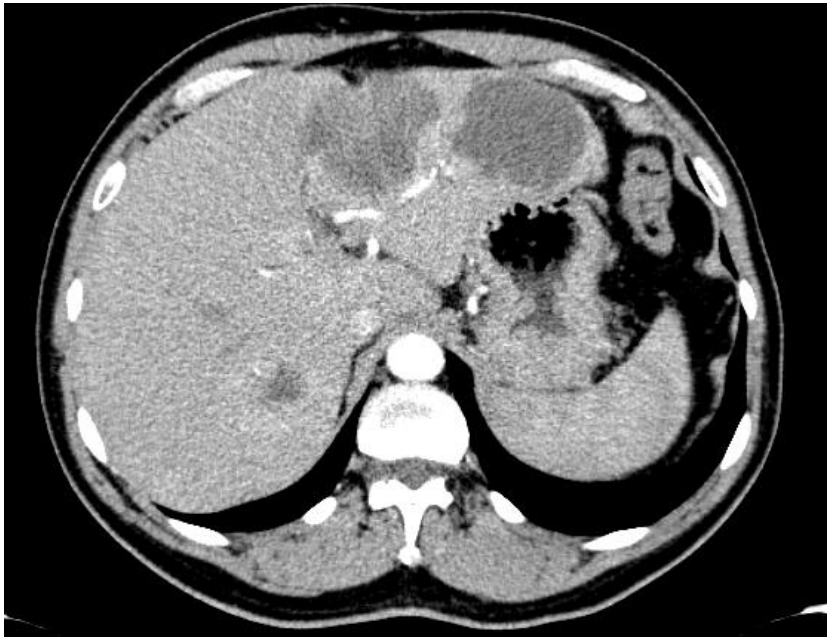
Chemotherapy for pancreatic NET: streptozocin-based

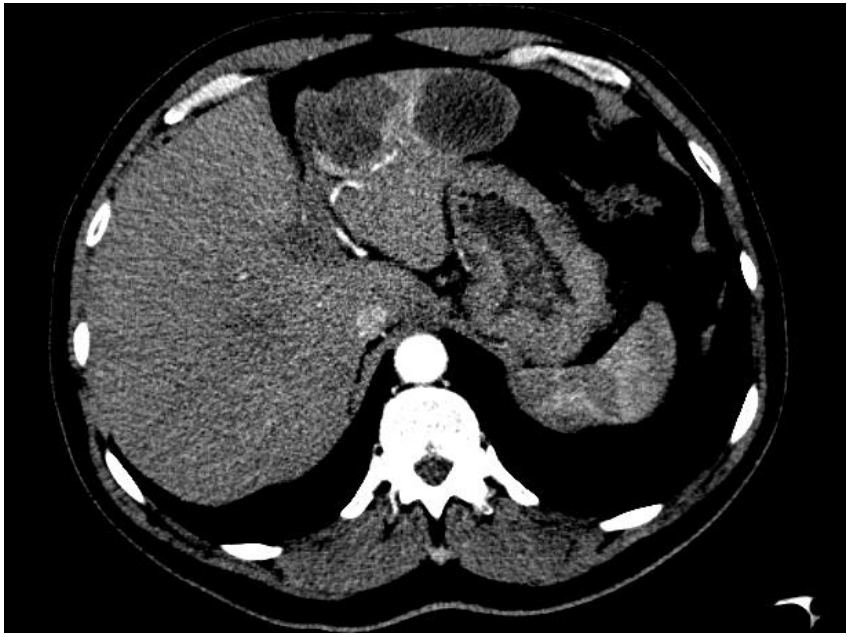
Regimen	Reported outcomes
Streptozocin/Doxorubicin[1] Streptozocin/Fluorouracil[1]	RR 69%, OS 26 mo RR 45%, OS 18 mo
Streptozocin/Doxorubicin[2], Streptozocin/Fluorouracil/Doxorubicin[3] Streptozocin/Fluorouracil/Cisplatin[4]	RECIST: RR ~40%, median OS 24–32 months
NET-01 study (NCRN): Streptozocin/Capecitabine +/- Cisplatin[5]	48/86 patients had pNETs RECIST RR +/-Cisplatin 14%/8%; Median OS (all) 34.7 months

RR: response rate
OS: overall survival
CR: complete response
PR: partial response

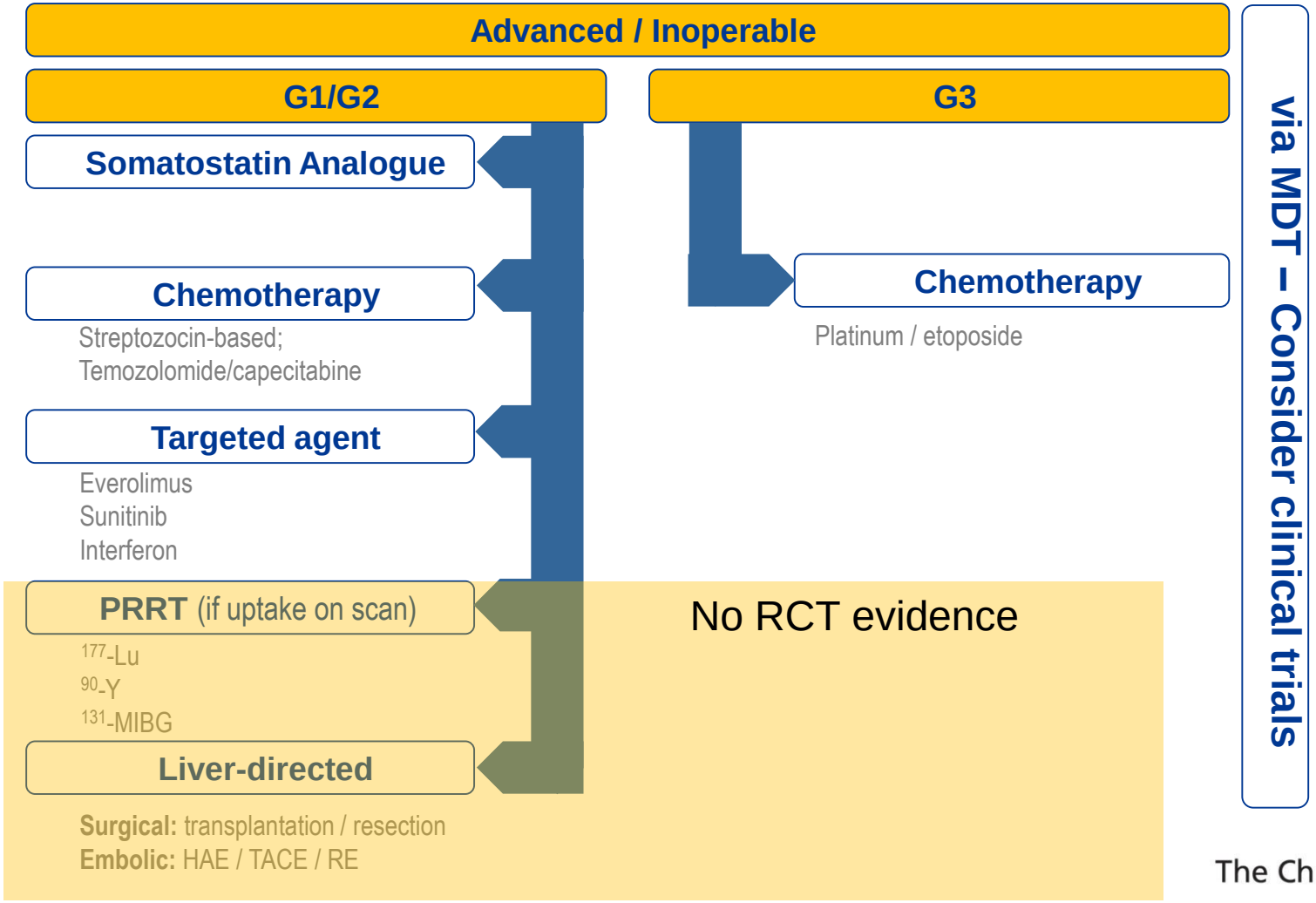
[1]Moertel CG, *NEJM* 1992;326(8): 519–523
[2]Delaunoit T, et al. *Eur J Canc* 2004;40:515–20;
[3]Kouvaraki M, et al. *J Clin Oncol* 2004;22:4762–71
[4]Turner N, et al. *Br J Cancer* 2010;102:1106–12;
[5]Corrie P, et al. *J Clin Oncol* 2012;30(suppl; abstr 4121)

Chemotherapy for pancreatic NET: streptozocin-based

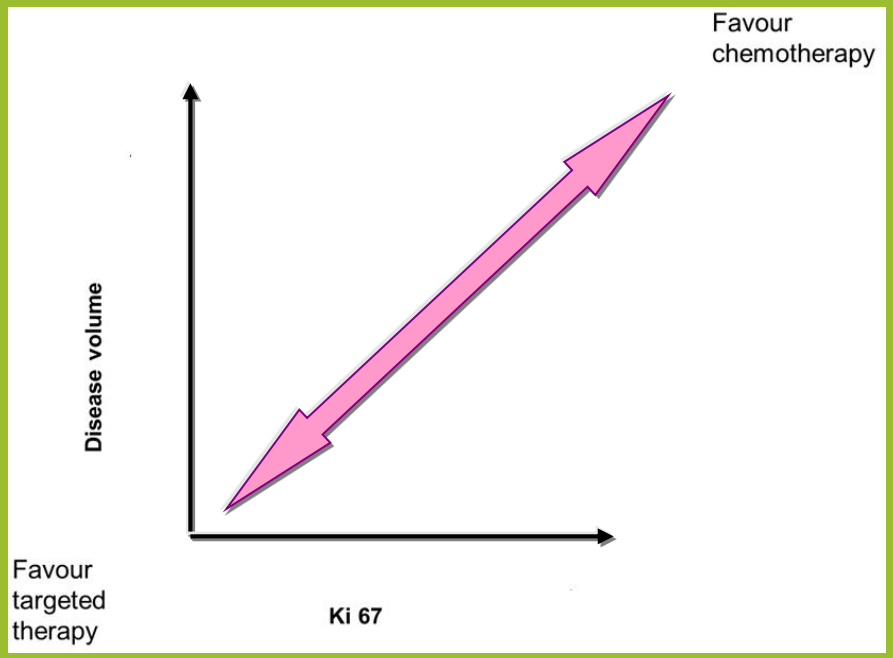


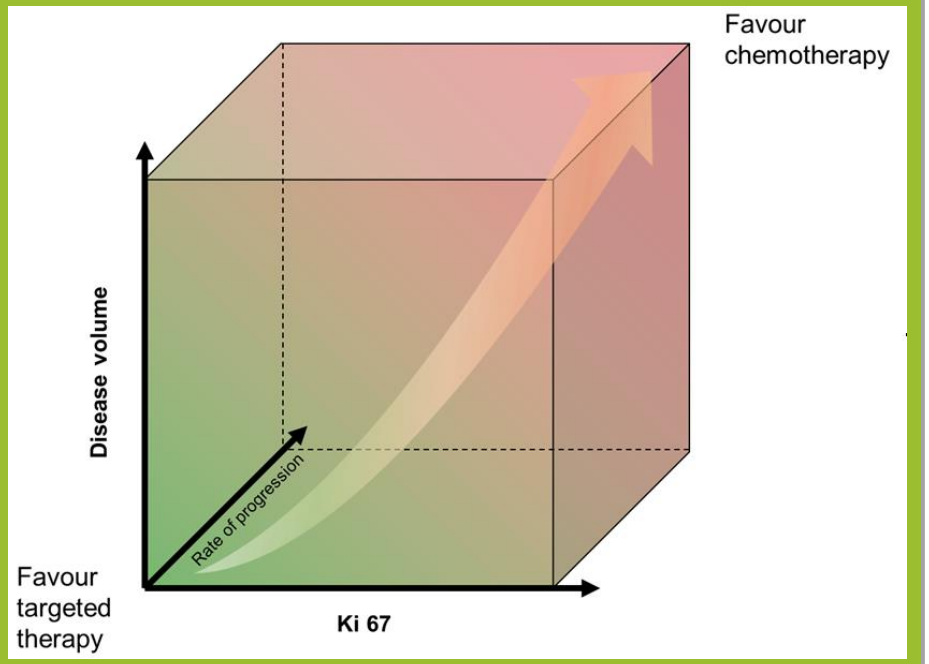


Treatment (ii)



Concept of “mitotically-active” disease- where does PRRT fit?





Principles to aid decision-making

- Targeted therapies are effective in treatment-naïve as well as chemotherapy pre-treated patients
- Chemotherapy is associated with a higher response rate
- Treatment decision is based on the aims of therapy (disease response vs. TTP)
- Decision may depend on expected toxicities
- Concept of “mitotically-active” disease
- Patients usually live long enough to **receive multiple therapies**
- Need to identify sub-groups of patients (through research) who benefit most from each therapy
- **One-size does not fit all**

Objectives/Concepts

- NET brief disease description – setting the scene
- Pancreatic NET- a model for consideration
- Therapeutics- core principles and ideas
- Future

MRT in NET

- MRT established in NET or is it a veneer?
- Is ‘standard’ truly ‘standard’ ?
- What do the other NET MDT partners actually think of MRT? (not very complimentary in a Cancer Centre!!)

Principles of therapeutics- Clinician's view

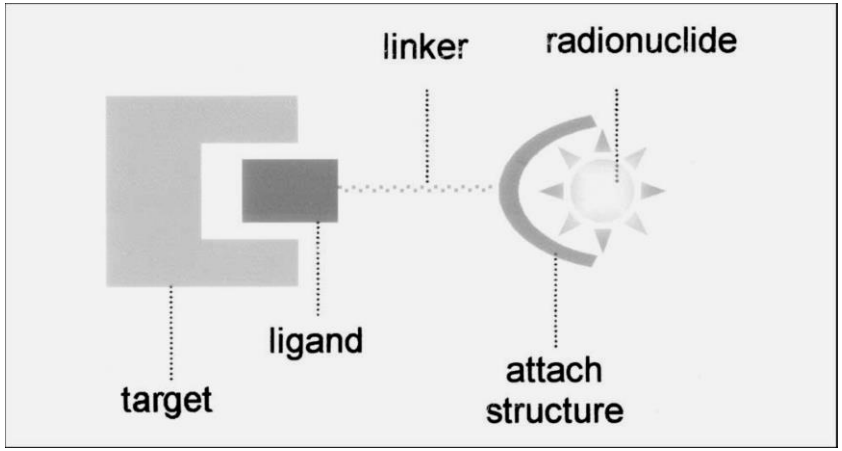
Therapeutics: treatment and care of a patient for the purpose of both preventing and combating disease or alleviating pain or injury. The term comes from the Greek therapeutikos, which means "inclined to serve." Encyclopedia Britannica

Underlying ethos:

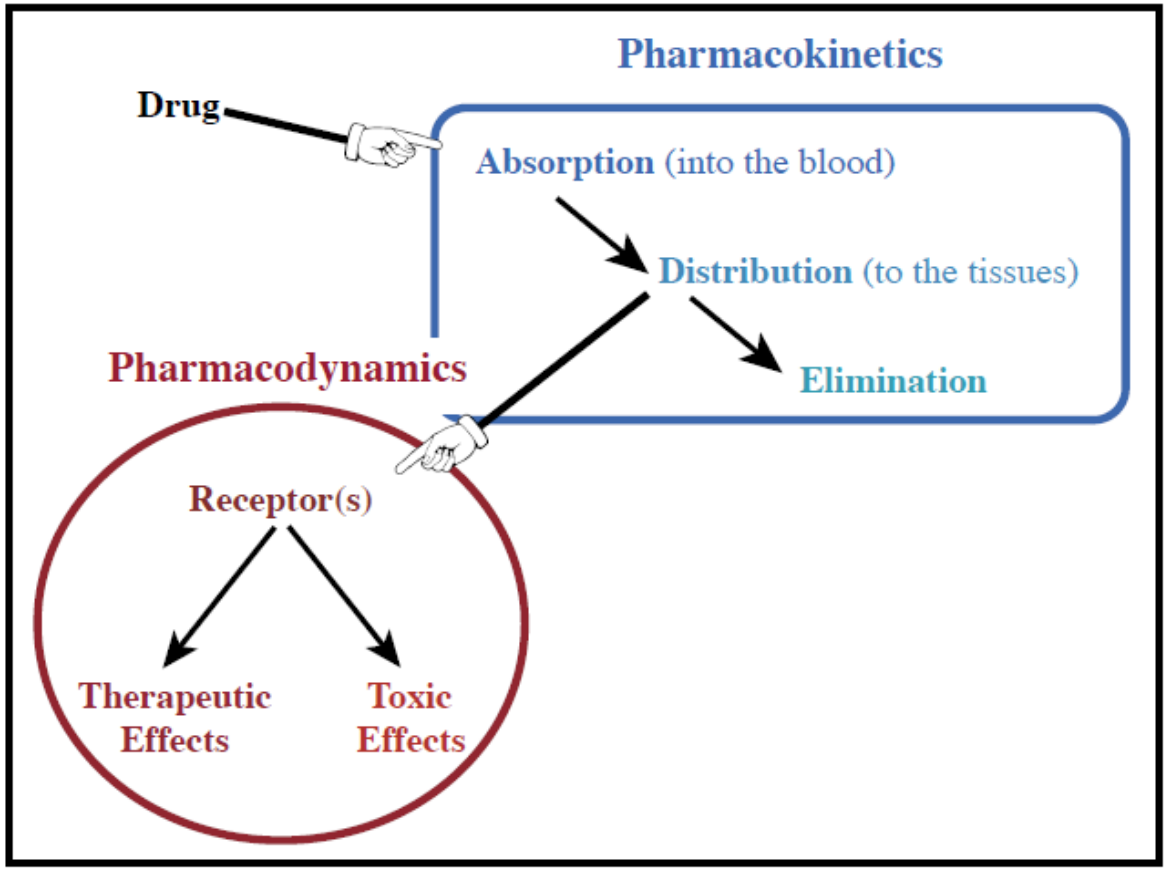
- No harm (toxicity), **lowest dose with highest efficacy**
- Benefit more than risk
- Driving principle

Therapeutics: Radiopharmaceutical

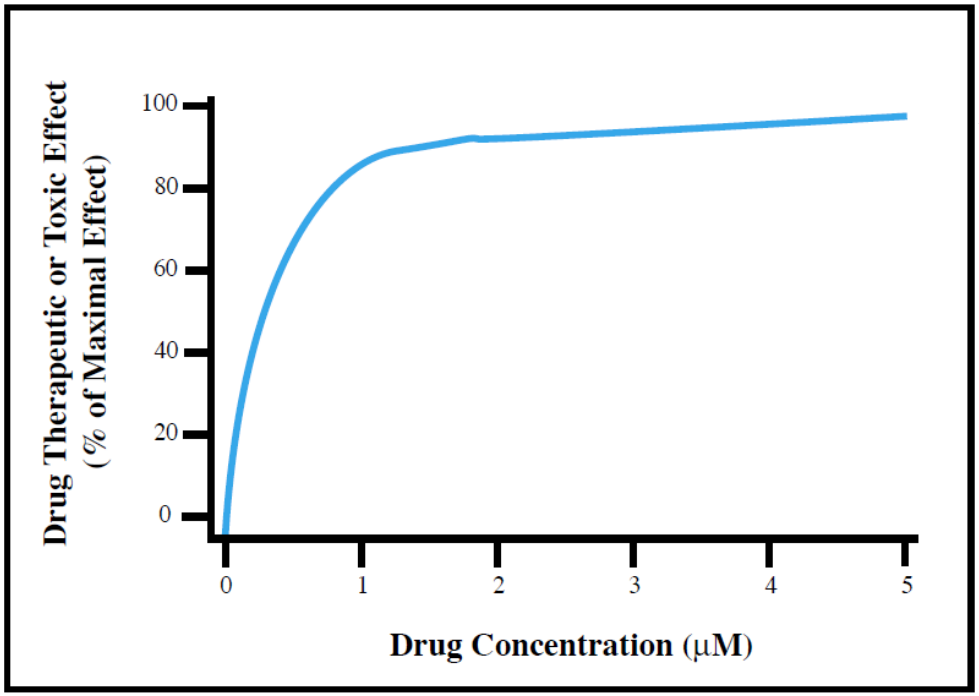
- Unique set of challenges
- Receptor density
- Phamacokinetic effects
- Radiobiology effects
- Stability of final compound- metal, linker matters
- Not the easiest therapeutic tool!



Pharmacokinetics



So what is the plateau for radionuclide therapies (177 Lu) in relation to therapeutic effects and toxicity ?



177Lu 'high' versus 'low'

? 3, 5, 6, 11 GBq

Concept of maximum tolerable dose might have to be revised

Dose escalation in PRRT

Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Lisa Bodei et al. Eur J Nucl Med Mol Imaging (2011) 38:2125–2135

51 patients divided into two groups

Group 1 received escalating activities (3.7–5.18 GBq/cycle)

Group 2 received (5.18–7.4 GBq/cycle)

Phase 1 non randomised prospective data

Sub-analysis

- The median cumulative administrated activity in group 1 was 26.4 GBq (3.7–29.2 GBq). Overall objective responses (partial+complete) were registered in **eight patients (38%)**.

- The median cumulative administrated activity in this group was 25.2 GBq (5.55–28.9 GBq).Overall objective responses (partial) were registered in **seven patients (23%)**.

- Thirty patients showed an objective response or stabilization during PRRT (median administered activity at response was **11.1 GBq, range 4.44–29.2)** that was maintained after the end of therapy in 28 cases (93%). Tumour dosimetry showed absorbed doses of 0.56– 56.4 Gy/GBq.

- Conclusion:
- 177Lu-DOTATATE was well tolerated up to 29 GBq cumulative activity (up to 7.4 GBq/cycle).

- The maximum tolerated dose/cycle was not reached.

- However, considering the individual bone marrow function and the presence of risk factors for kidney toxicity, it seems safer to divide cumulative activities into lower activity cycles.

Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Lisa Bodei et al. Eur J Nucl Med Mol Imaging (2011) 38:2125–2135

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- NOT HIGHLIGHTED- ? HOOKED TO HIGHER DOSES

Does dose matter in PRRT treatment?

- The results imply a significant correlation between absorbed dose and tumor reduction. However, further studies are necessary to address **the large variations in response for similar absorbed doses**

Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using 177Lu-DOTATATE. Ilan E et al. J Nucl Med. 2015 Feb;56(2):177-82.

Long term effects of PRRT

Haematological (retrospective 632 patients)

- The only preexisting factor that contributed to hematotoxicity was initial cytopenia (P , 0.001).
- A high level of cumulative administered activity (.29.6 GBq) was associated with relevant leukopenia (P , 0.001).

Long-Term Hematotoxicity After Peptide Receptor Radionuclide Therapy with 177Lu-Octreotate. Amir Sabet et al. J Nucl Med 2013; 54:1857–1861

Long term effects of PRRT

Renal (prospective dose escalation/safety study)

- A median decrease of creatinine clearance of 21.7% 6 months after PRRT
- 23.9% after 1 year and 27.6% after 2 years was observed.
- Higher losses (>20%) occurred in patients with risk factors for renal toxicity, particularly hypertension and diabetes.

Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Lisa Bodei et al. Eur J Nucl Med Mol Imaging (2011) 38:2125–2135

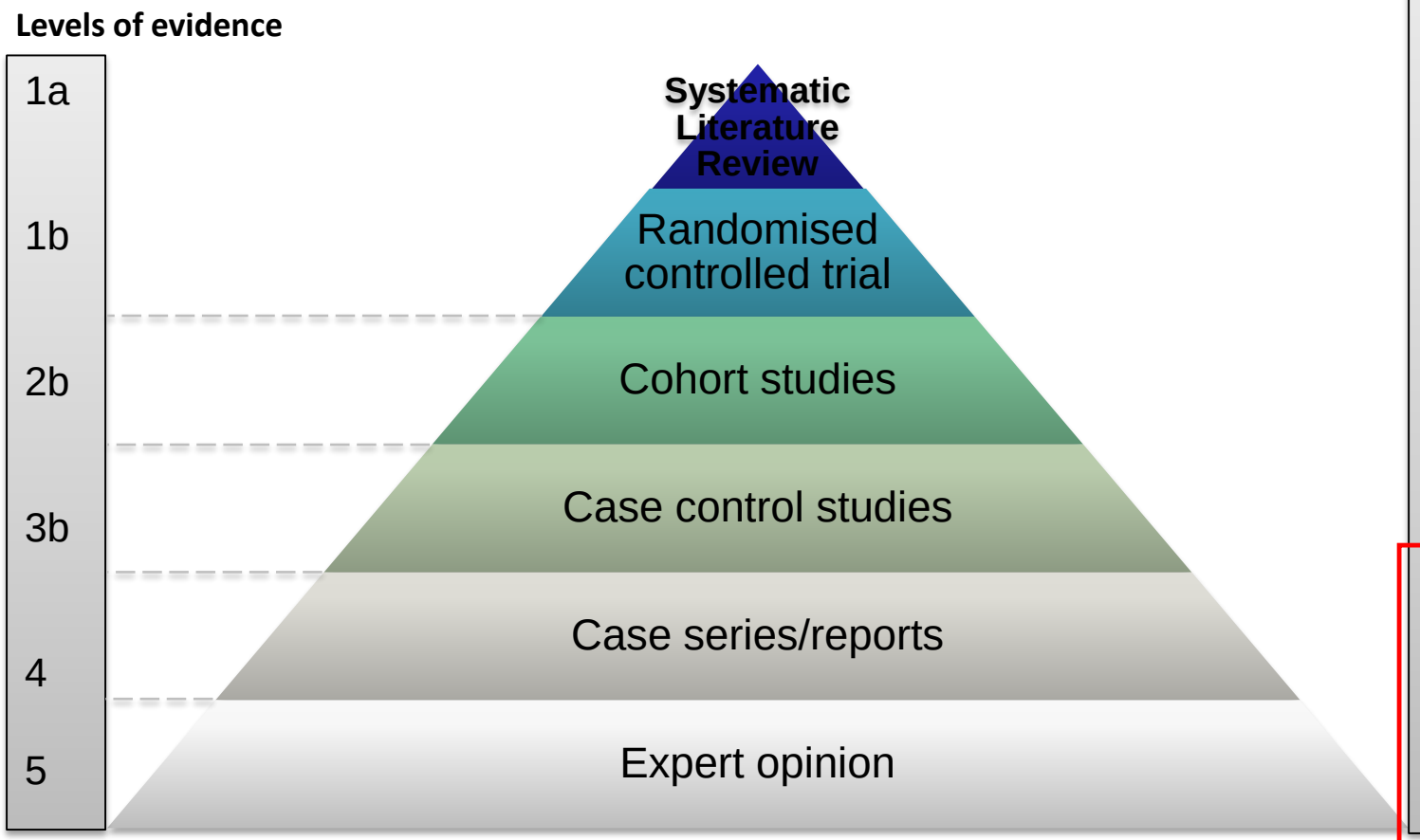
Underlying ethos:

- No harm (toxicity), **lowest dose with highest efficacy- no PRRT RCT yet**
- Benefit more than risk
- Driving principle
- By opting for unproven therapies might negatively impact patient care by denying access to future therapies

Objectives/Concepts

- NET brief disease description – setting the scene
- Pancreatic NET- a model for consideration
- Therapeutics- core principles and ideas
- Future

Oxford Levels of Type of Evidence & Grades of recommendation



Grades of recommendation:

A: Consistent level 1 studies

B: Consistent level 2 or 3 studies or extrapolations from level 1 studies

C: level 4 studies/extrapolations from level 2/3 studies

D: Level 5/inconsistent studies of any level

MRT in NET: Many unanswered questions

- NET patients have a long survival
- Which patients, dose?
- Which dosimetry method/software package?
- Predictive and prognostic indicators (some signals in relation to these)

MRT in NET- proposals for the future

- RCT with differing doses- NETTER-2 (5 GBq versus 7 GBq) with genetic, blood and patient sub analysis
- RCT- PRRT + Molecular targets- chose well
- Standardised dosimetry package and its correlation with patient outcomes
- Prospective registry- all NET networks need to implement this with agreed standardisation/dosimetry package

Summary – pNETs (future GEP NETS?)

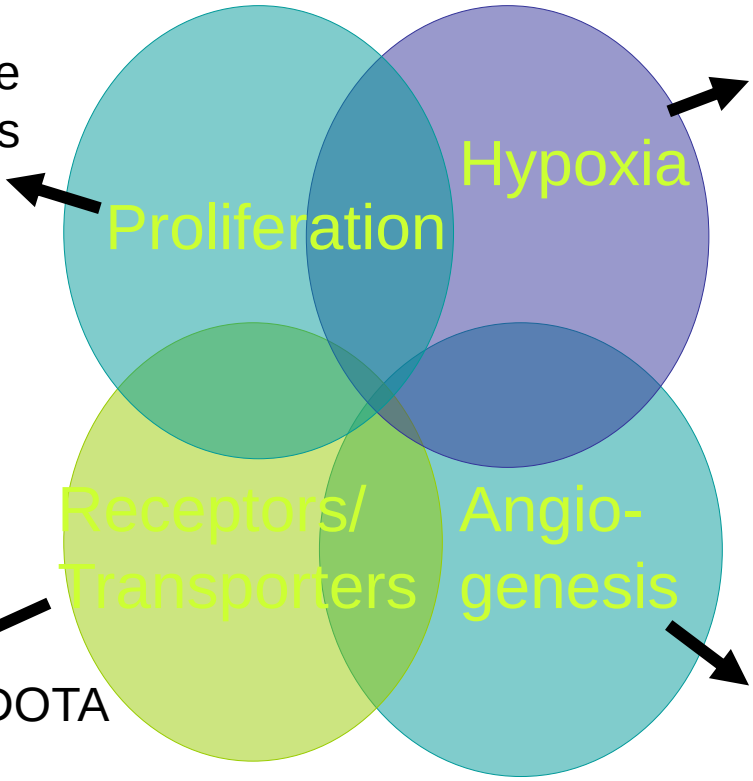
- NETs are not so rare…surgery remains the only chance of long-term cure in malignant tumours
- Treatment principles may held in decision-making in the changing therapy paradigm:
  - VEGF-inhibition: sunitinib
  - mTOR inhibition: everolimus
  - Somatostatin analogues: lanreotide
- Molecular insights may allow “enrichment” of patient populations
- Clinicians and patients should be encouraged to participate in clinical trials

Summary 2

- NO EVIDENCE TO SUPPORT DOSE ESCALATION- ON THE CONTRARY
- Paradigm shift will happen to all GEP NET we need to prepare and work out future RCTs
- Novel tracers/Theranostics/targeted therapies showing promise for future- NET complex
- More standardised prospective registry based protocols prior to acceptance as ‘standard of care’
- Imperative to develop this service to deliver individualised therapy and provide best standard of care to our patients.
- Sequencing!!

Individualisation of Tumour Therapy

•Conventional anti-proliferative chemotherapies



•Hypoxia-directed therapies (EPO, carbogen, HBO, chemotherapy with NLCQ1,TPZ)
•Targeting hypoxic fraction (IMRT)

•Somatostatin DOTA
•SIRT

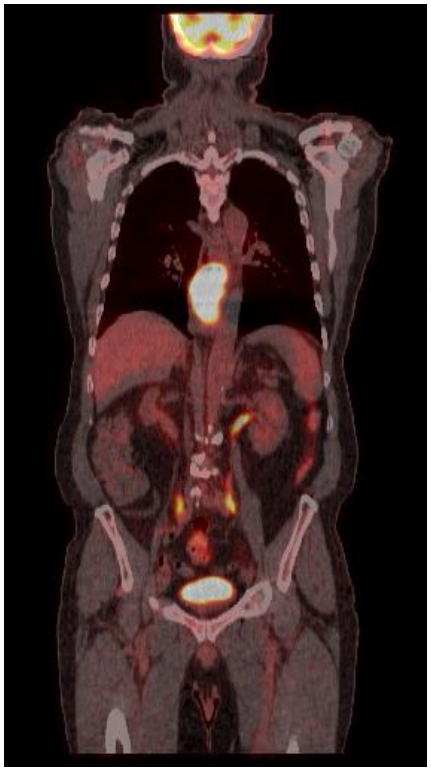
•Anti-angiogenic therapy (i.e. Avastin, Cu-chelators)
Molecular targeted therapies

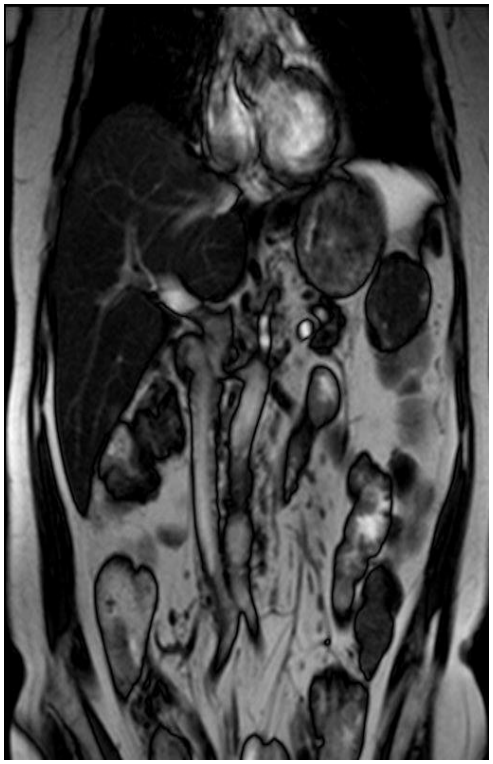
Acknowledgements

- The Christie Nuclear Medicine/ CMPE department
- Department of Radiology
- ENETs NET team- especially Professor Valle for a number of slides

Thank you

Era of molecular imaging/ therapy





MRT dose escalation in NET a Clinicians view

- ? RCT
- ? RCT
- ? RCT
- Ongoing trials
  - NETTER-1
  - VIBRaNT