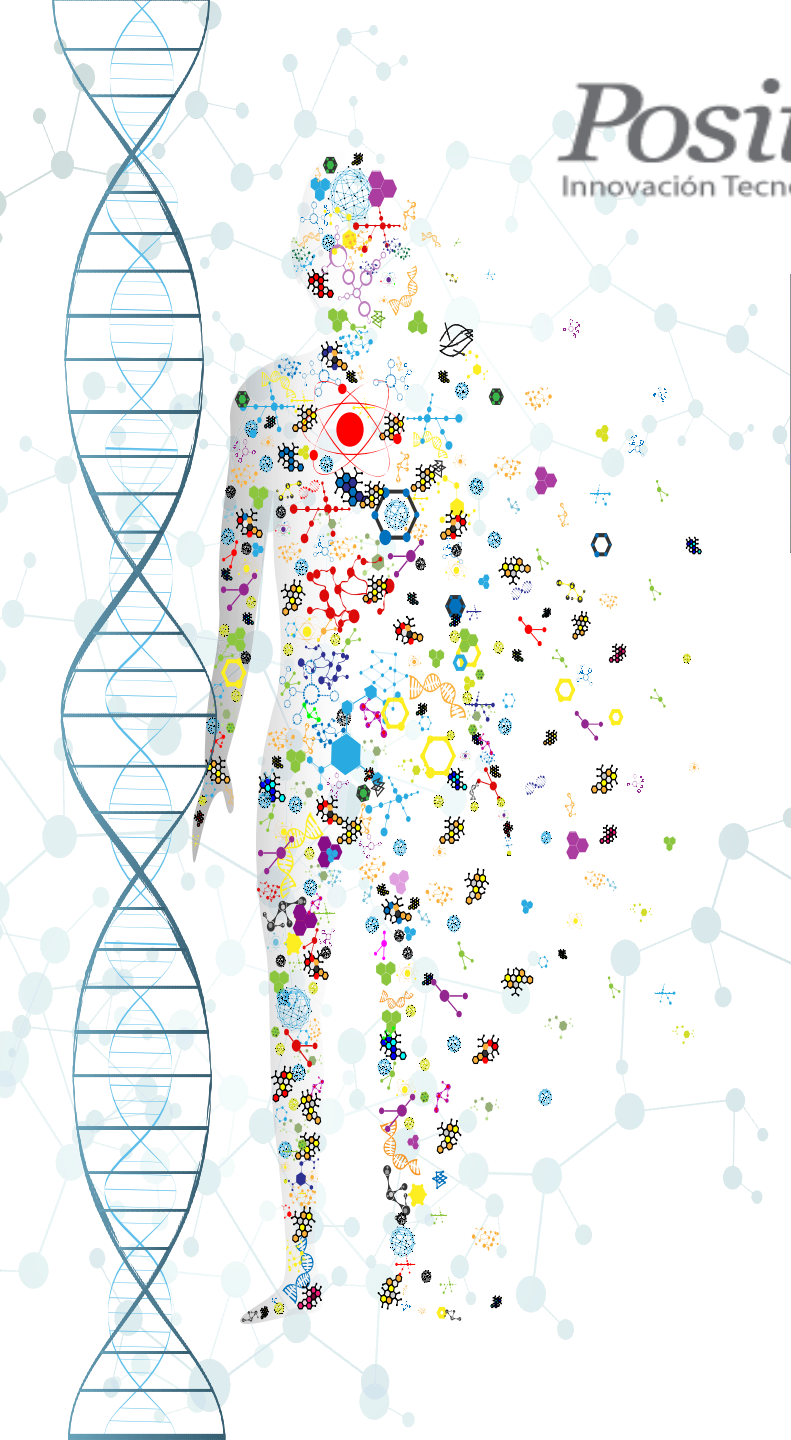


Positronmed
Innovación Tecnológica en Imágenes Moleculares

falp
Juntos contra el cáncer

"PRRT en Tumores Neuroendocrinos"

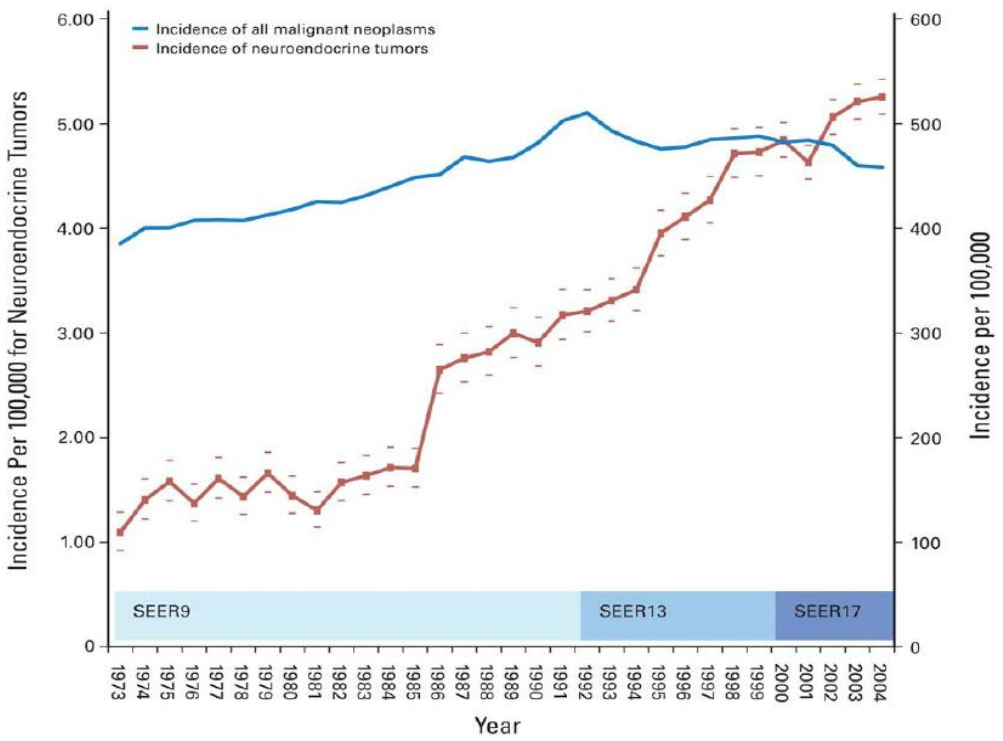
Dr. Horacio Amaral
Director Centro de Medicina Nuclear y PET/CT.

PositronMed
INSTITUTO ONCOLÓGICO | Fundación Arturo López Pérez
Santiago, CHILE

NET Epidemiology
A growing population of patients

- From 1973 to 2004, incidence of NETs has grown by **almost 500%** (from 1,09/100,000 to 5,25/100,000 respectively)[1]

Incidence of NETs vs all malignant neoplasms from 1973 to 2004[2].



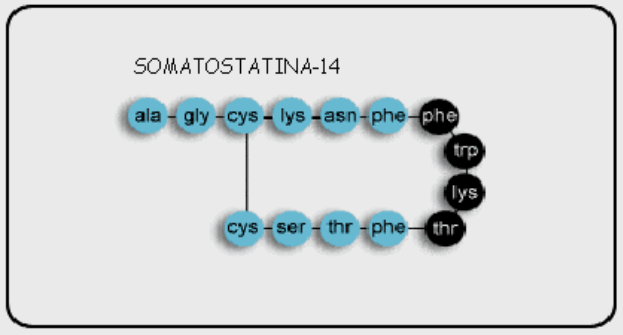
Year	Incidence (95% CI)
1973	1.09 (0.92 to 1.28)
1974	1.40 (1.22 to 1.61)
1975	1.58 (1.39 to 1.78)
1976	1.37 (1.20 to 1.56)
1977	1.61 (1.42 to 1.81)
1978	1.43 (1.27 to 1.62)
1979	1.66 (1.48 to 1.86)
1980	1.44 (1.28 to 1.63)
1981	1.30 (1.14 to 1.48)
1982	1.57 (1.40 to 1.76)
1983	1.63 (1.46 to 1.83)
1984	1.71 (1.53 to 1.91)
1985	1.70 (1.53 to 1.90)
1986	2.65 (2.42 to 2.88)
1987	2.76 (2.53 to 3.00)
1988	2.82 (2.59 to 3.06)
1989	3.00 (2.76 to 3.24)
1990	2.91 (2.68 to 3.15)
1991	3.17 (2.94 to 3.41)
1992	3.21 (3.01 to 3.41)
1993	3.31 (3.11 to 3.51)
1994	3.41 (3.21 to 3.62)
1995	3.95 (3.74 to 4.17)
1996	4.11 (3.89 to 4.33)
1997	4.27 (4.05 to 4.49)
1998	4.71 (4.49 to 4.95)
1999	4.73 (4.50 to 4.96)
2000	4.84 (4.68 to 5.01)
2001	4.63 (4.47 to 4.79)
2002	5.06 (4.90 to 5.23)
2003	5.21 (5.04 to 5.38)
2004	5.25 (5.09 to 5.42)

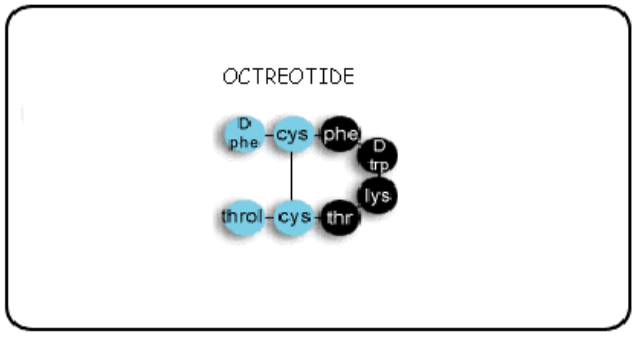
1.Yao et al: One hundred years after « carcinoid »: epidemiology of and prognostic factors for NET in 35,825 cases in the US. J. Clinical Oncology 26:3063-3072; 2. SEER: National Cancer Institute's Surveillance, Epidemiology, and End Results

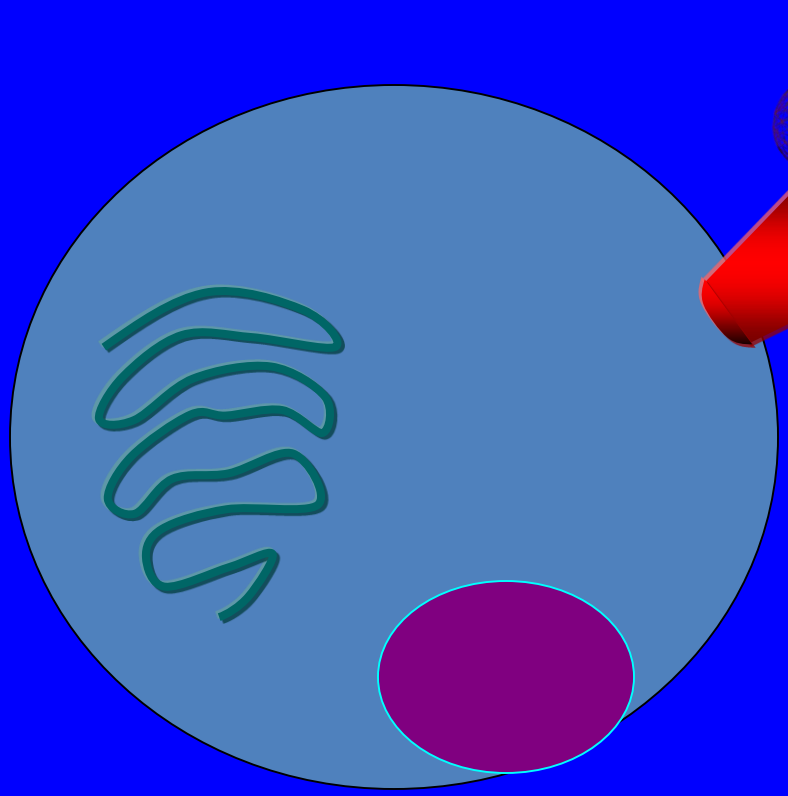
Bases para el Diagnóstico y Tratamiento de los Tumores Neuroendocrinos con Péptidos Marcados

- Sobre-expresión de receptores de somatostatina (SSR), principalmente de los sub-tipos 2 y 5 en la membrana celular de tumores ***neuroendocrinos.***

- Péptidos radiomarcados análogos de la SST permiten de manera no tóxica su fijación a la membrana de las células tumorales y su posterio internación.
    - Radiación entregada específicamente a las células con SSR.
    - Tejido normal protegido







^{111}In

^{68}Ga (β^{+})

^{90}Y

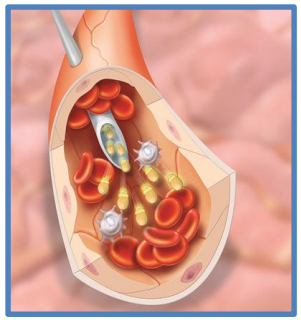
^{177}Lu

[DOTA^{0}-Tyr^{3}]-octreotide

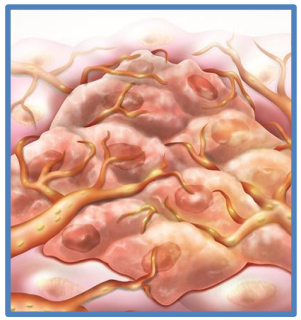
Receptor sst2

radionucleido — unión — péptido — blanco

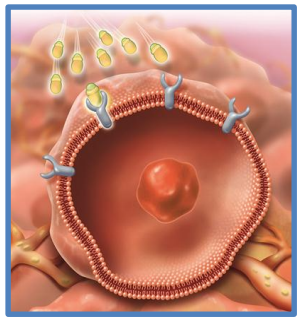
^{177}Lu-DOTATATE mode of action



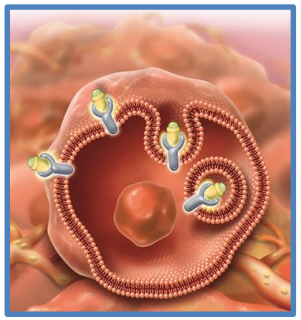
1.Injection



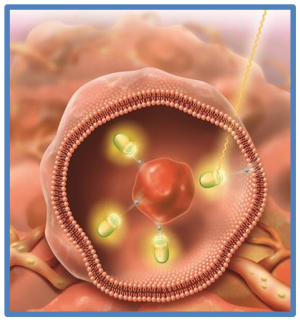
2.Concentration into neuroendocrine tumor (NETs) sites



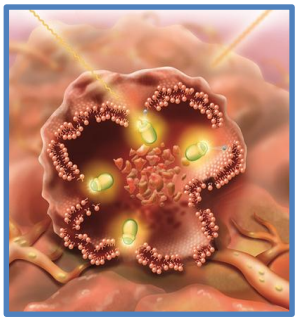
3.The radiopeptide binds to somatostatin receptors type 2 (sstr2) overexpressed by NETs



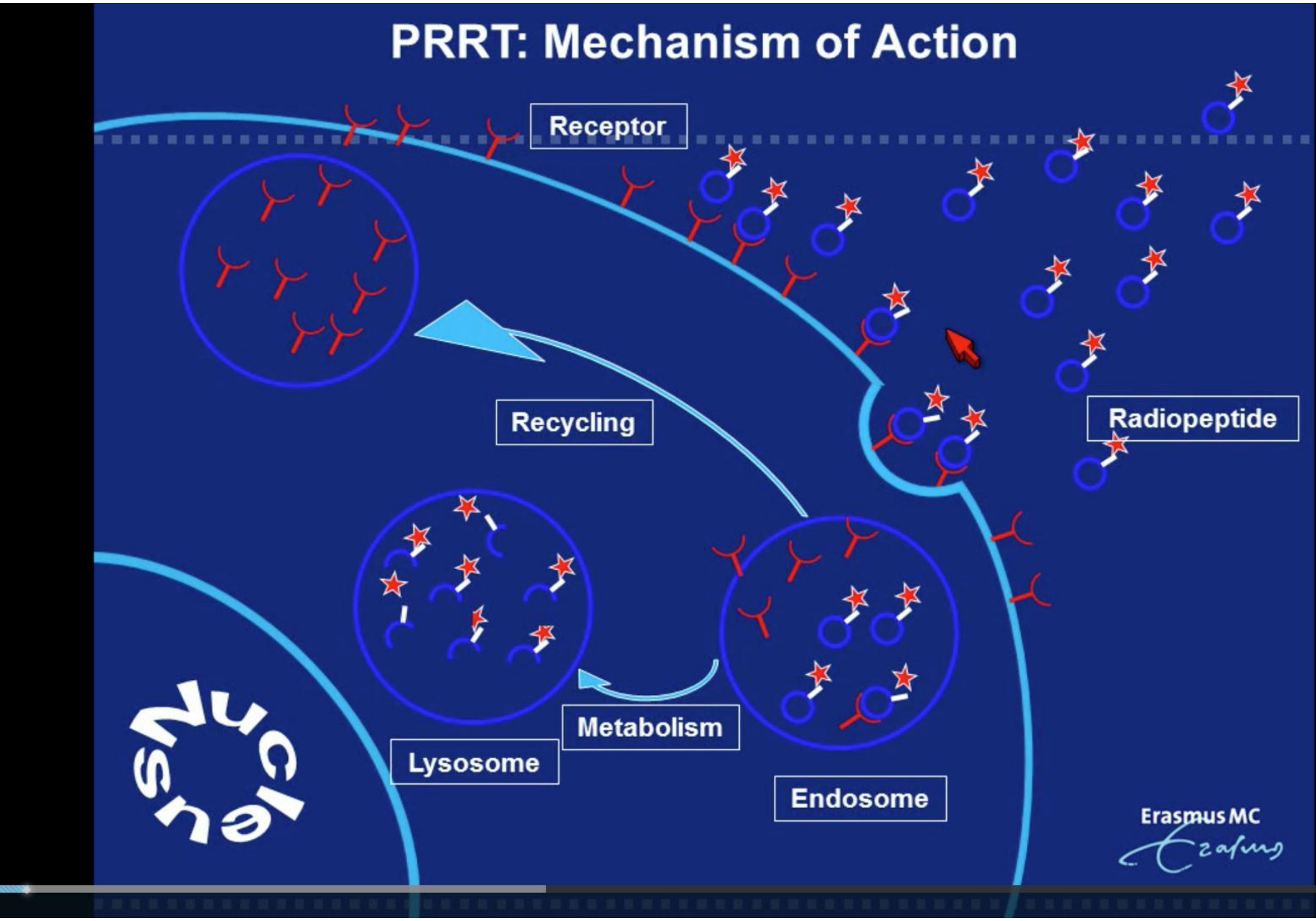
4.The radiopeptide is internalized in the NET cell



5.The radiopeptide delivers radiation within the cancer cell



6.Radiation induces DNA strands break causing tumor cell death


PRRT: Mechanism of Action
Receptor
Recycling
Radiopeptide
Metabolism
Lysosome
Endosome
Nucleus
Erasmus MC

Radiofármacos para diagnóstico y terapia de carcinomas neuroendocrinos

- Diagnóstico:
  - PET/CT con ^{68}Ga-DOTATATE
- Tratamiento:
  - ^{177}Lu-DOTATATE
  - ^{90}Y-DOTATATE

THERANOSTICS

MOLECULE

for diagnosis
for therapy

WANTED

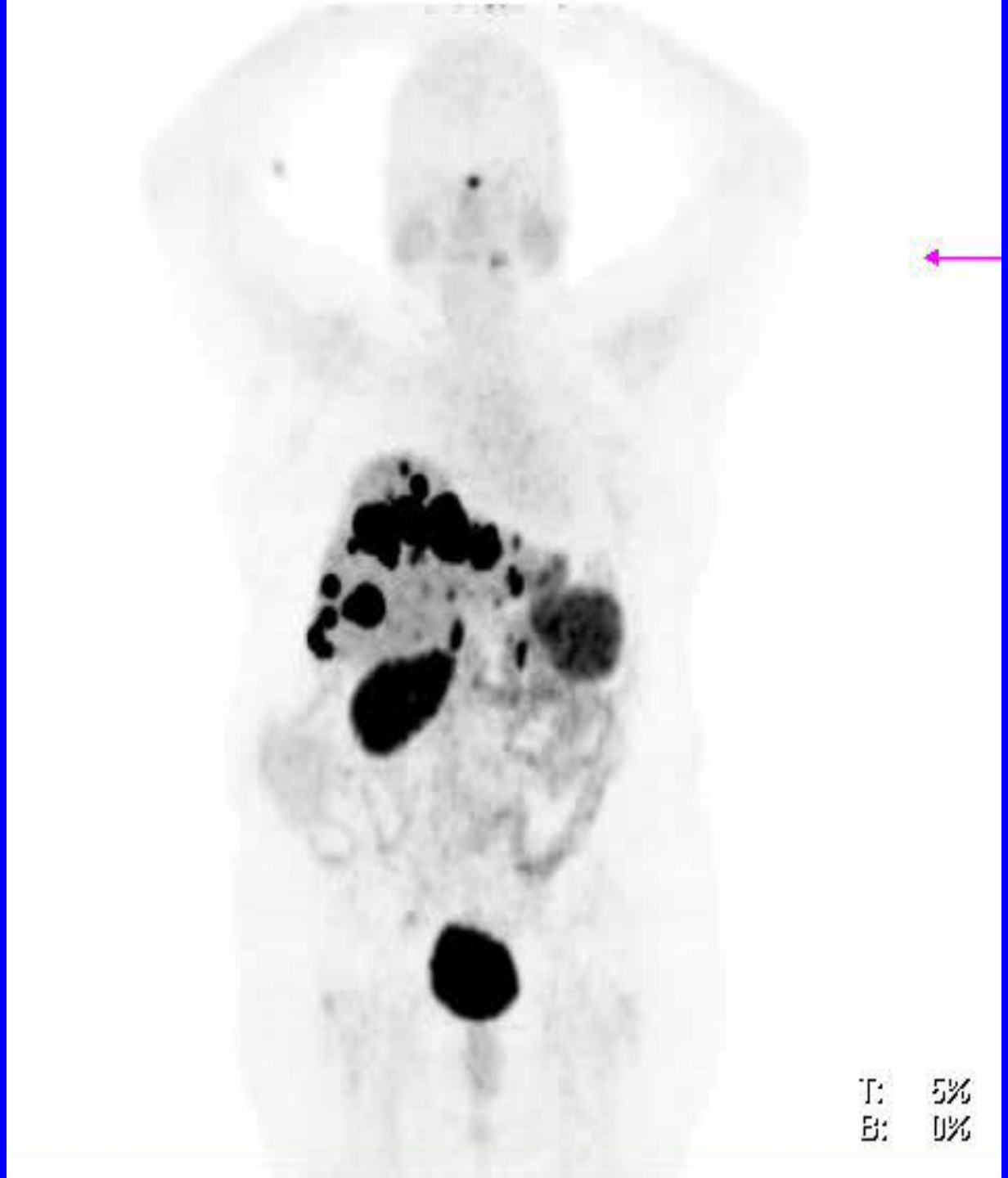
(available)
matched pairs
of therapeutic & PET nuclide

Tratamiento con análogos de SST marcados con radionúclidos

- Pre-requisitos:
  - Enfermedad metastásica
  - Alta captación tumoral confirmada con OctreoScan (^{111}In) ó idealmente con PET/CT ^{68}Ga-DOTATATE
  - Condición hematológica y bioquímica estable
  - Función renal adecuada clearance >60 mL/min.

Tratamiento con análogos de SST marcados

- Características:
  - Tratamiento sistémico
  - Alta dosis de radiación selectiva
  - Tratamiento bien tolerado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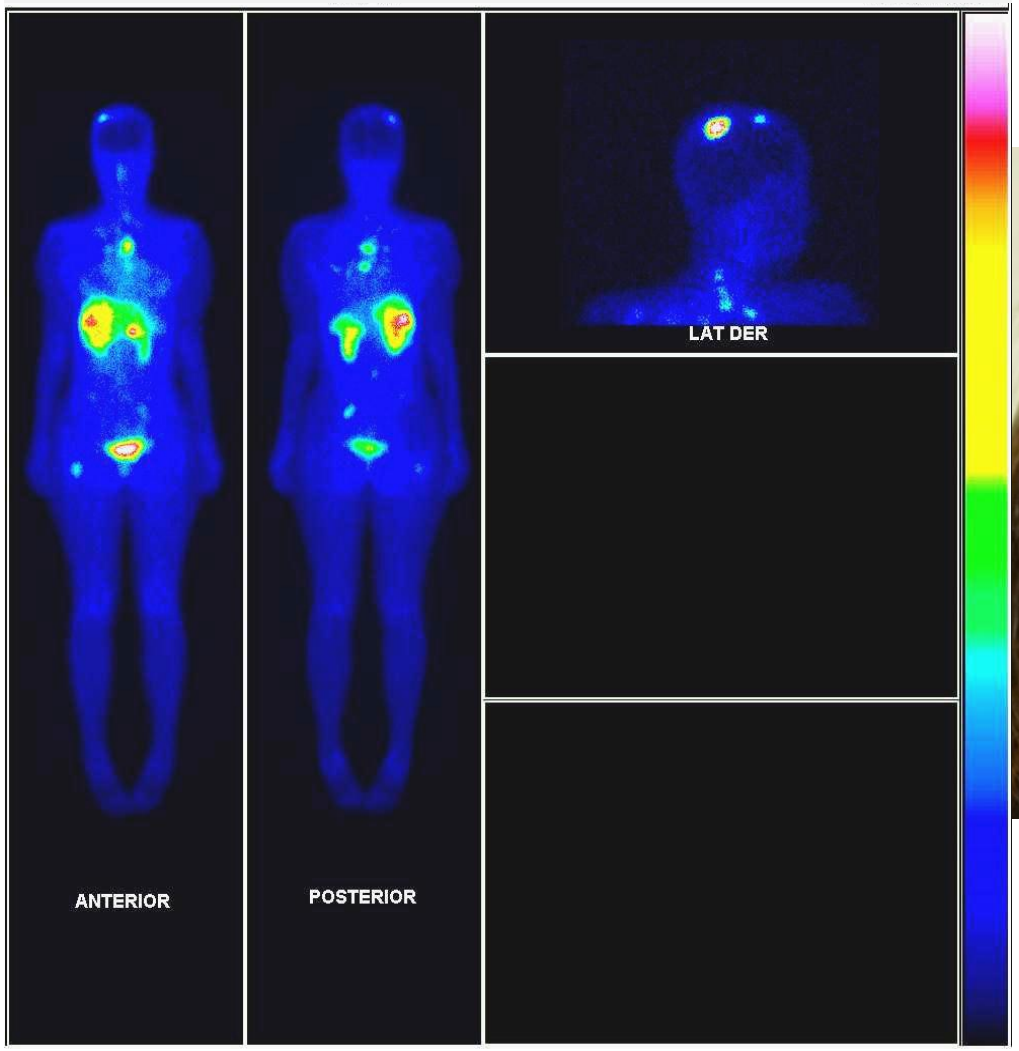
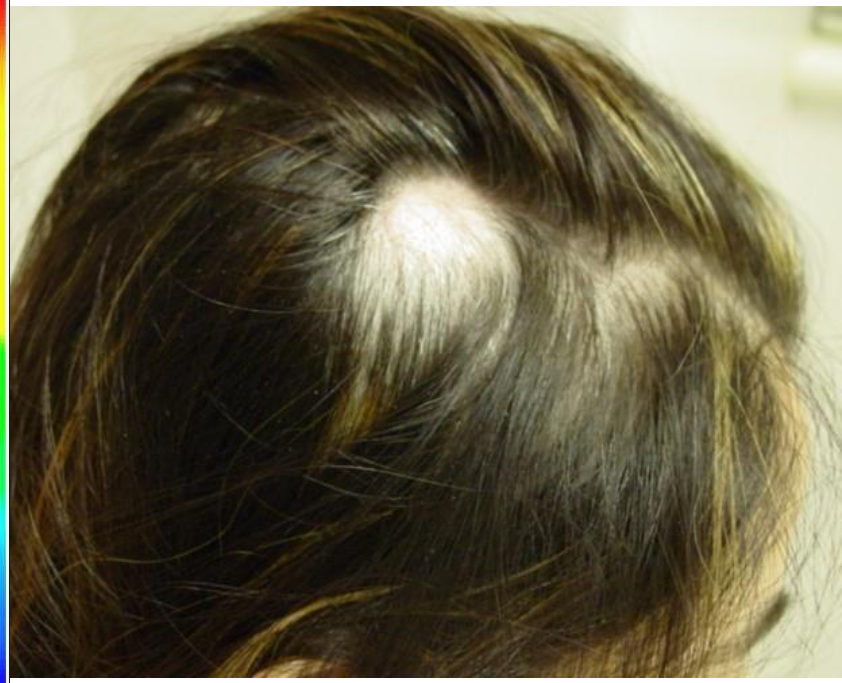
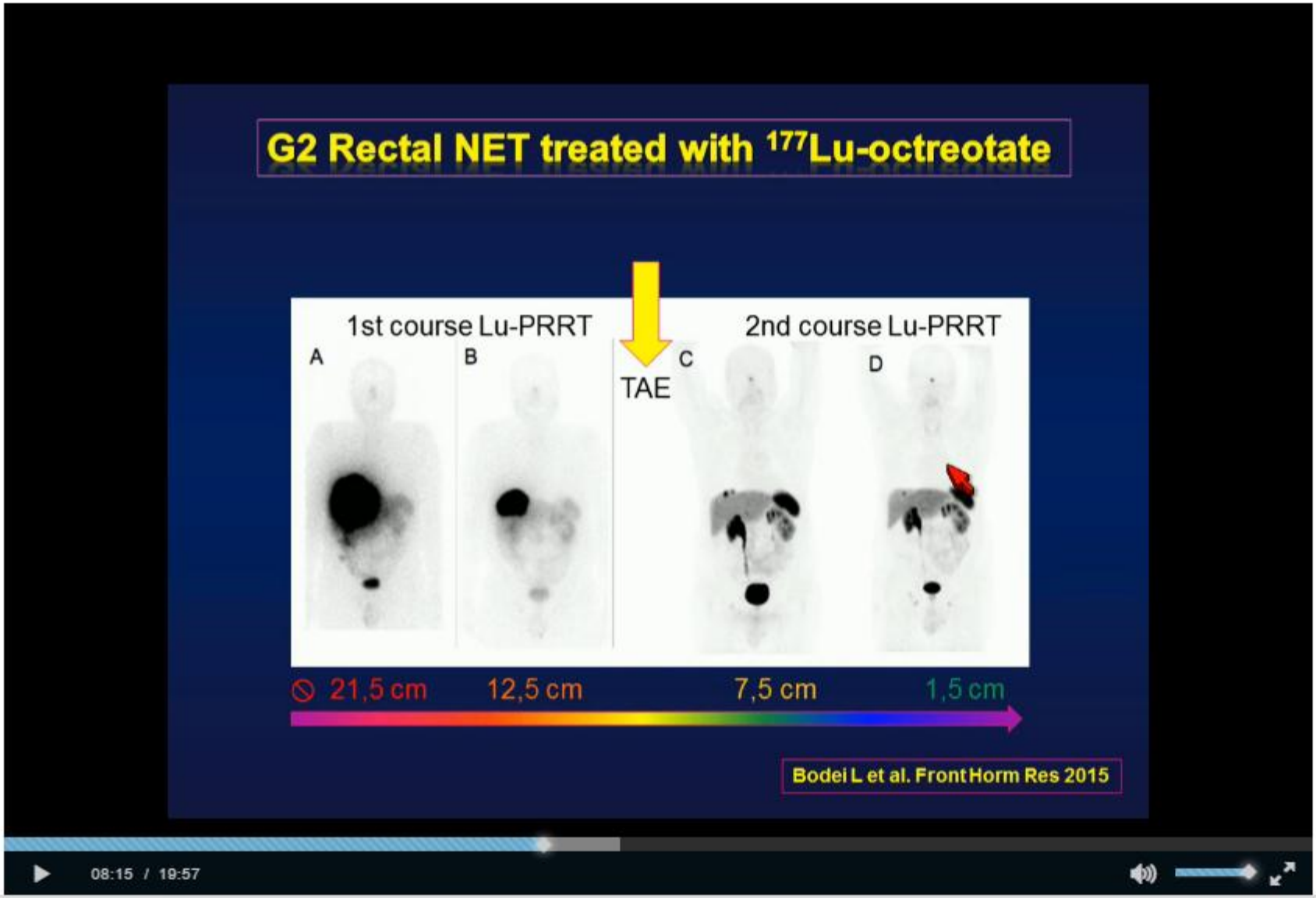
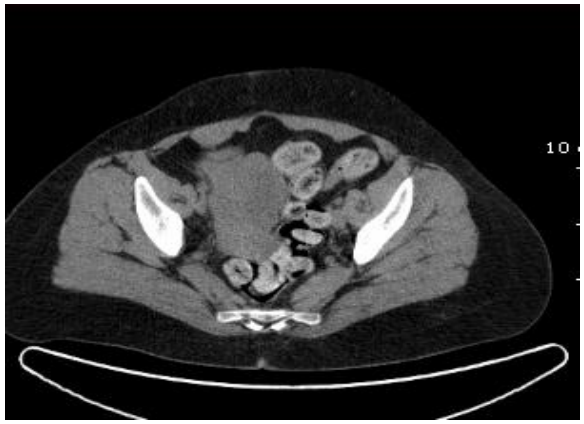
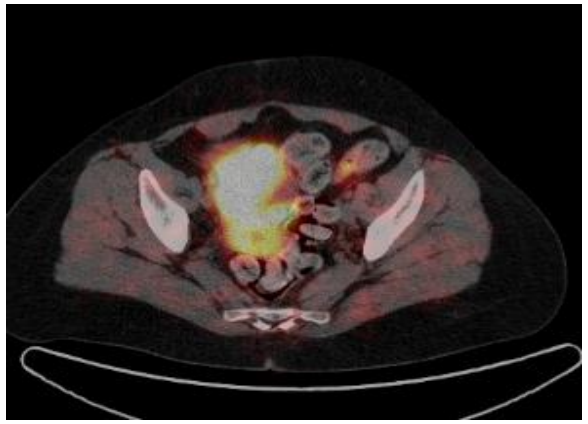

LAT DER
ANTERIOR
POSTERIOR

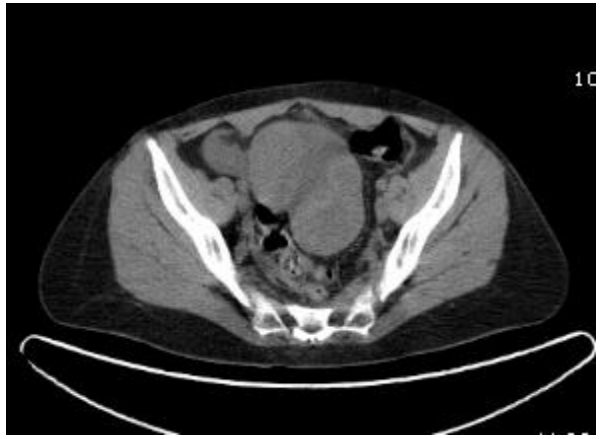


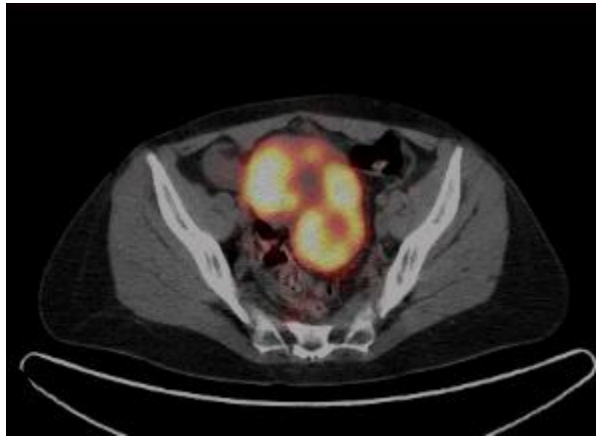
Breakout Session: Recent Advances in the Treatment of Neuroendocrine Tumors
Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract Track

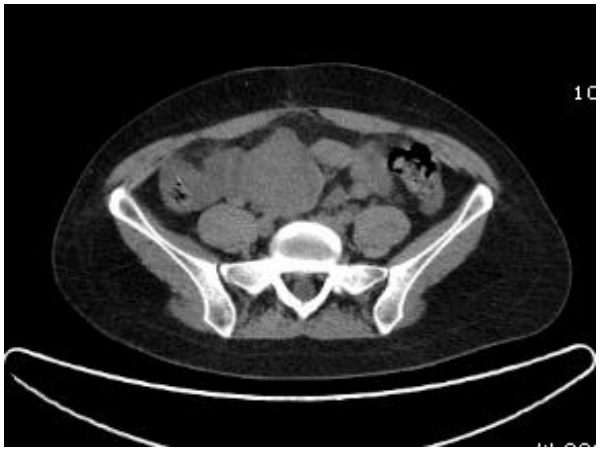


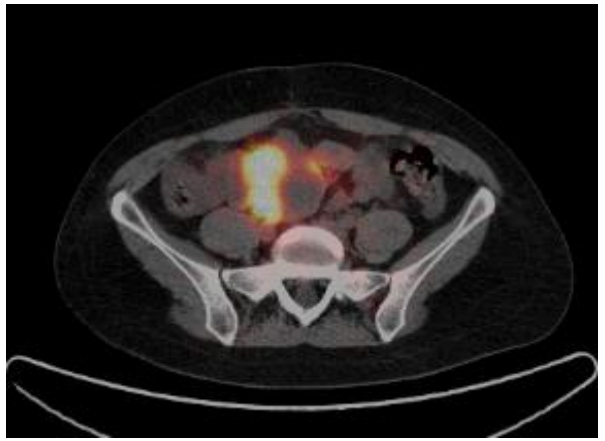


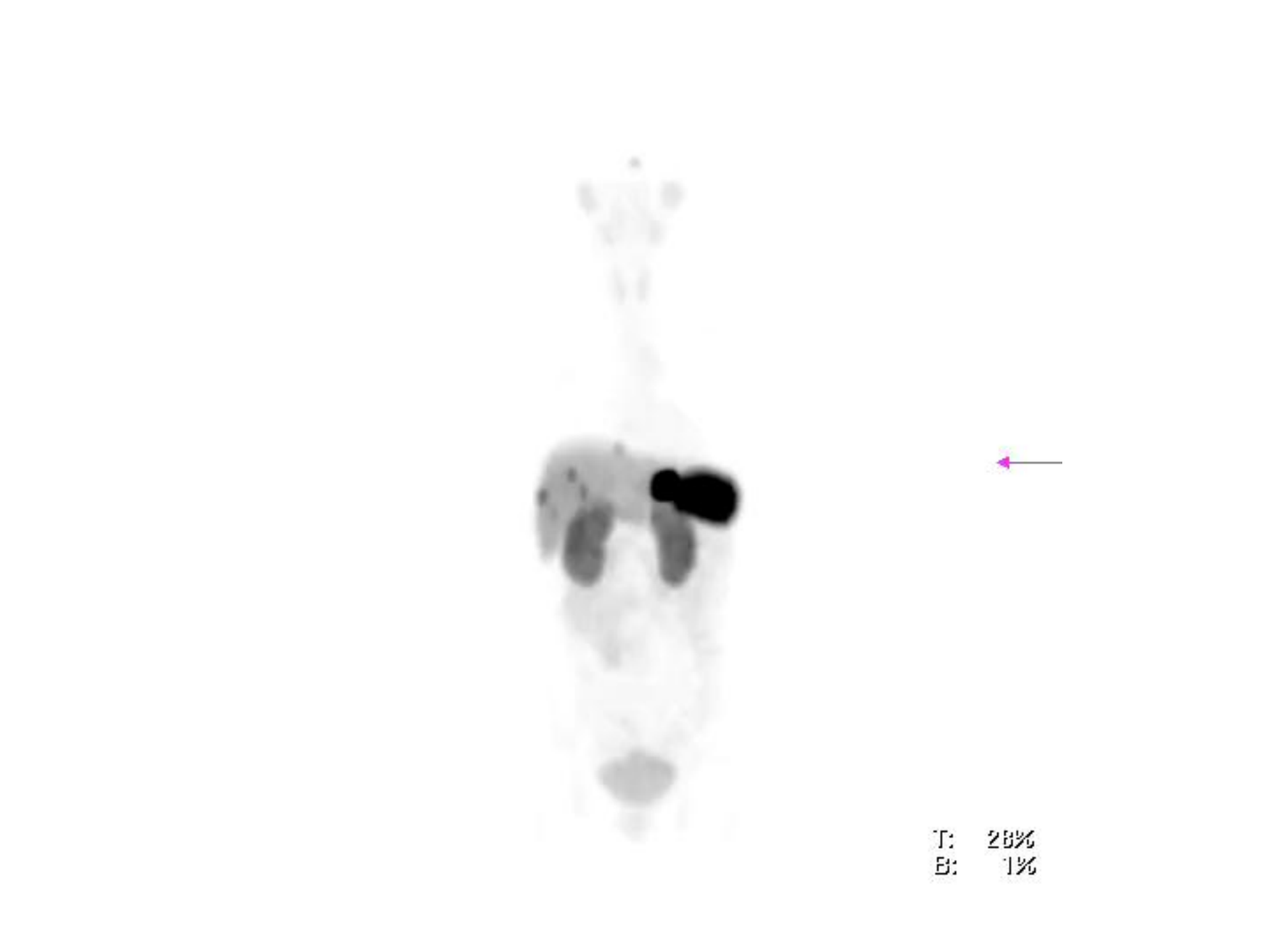








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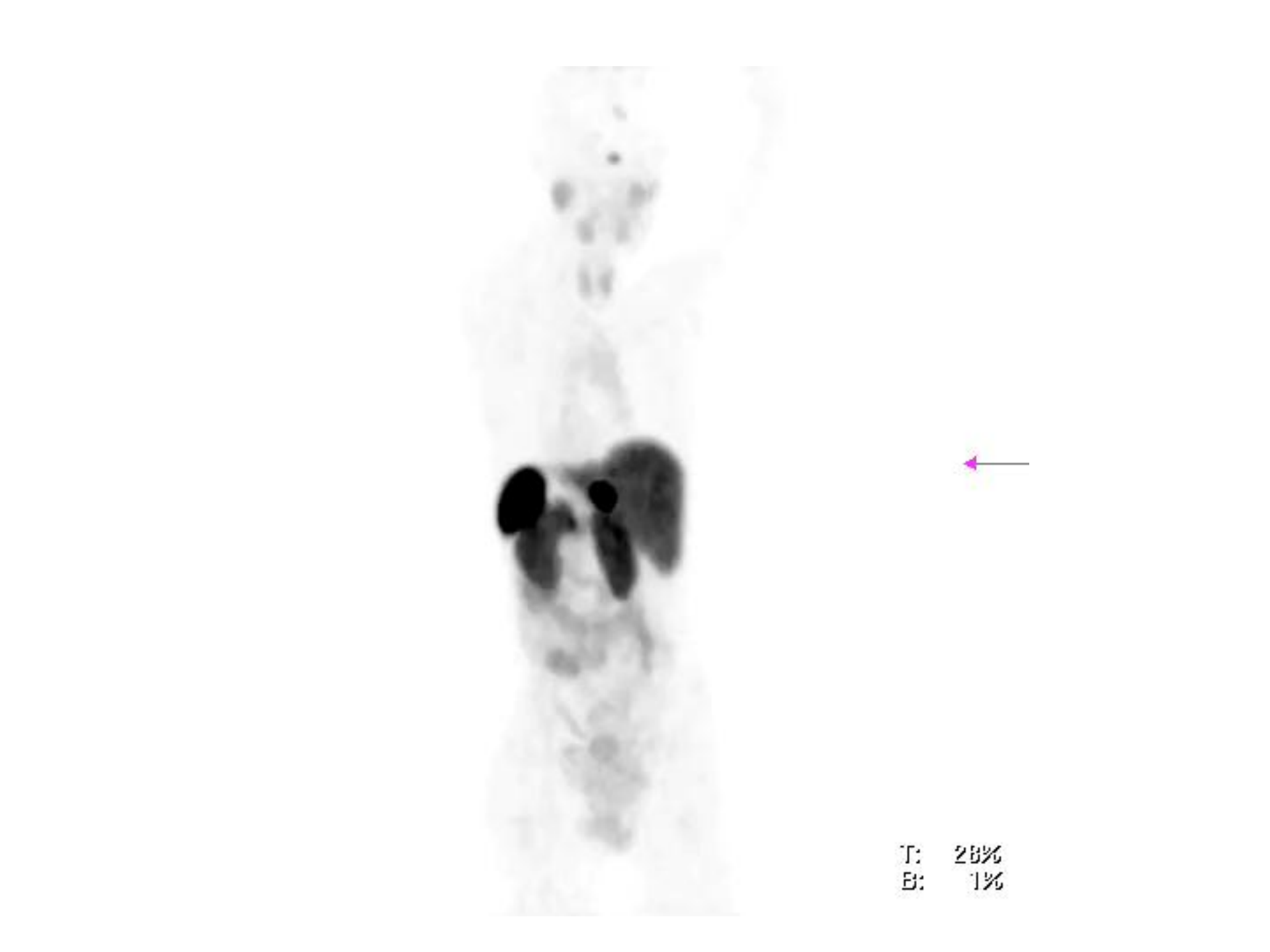
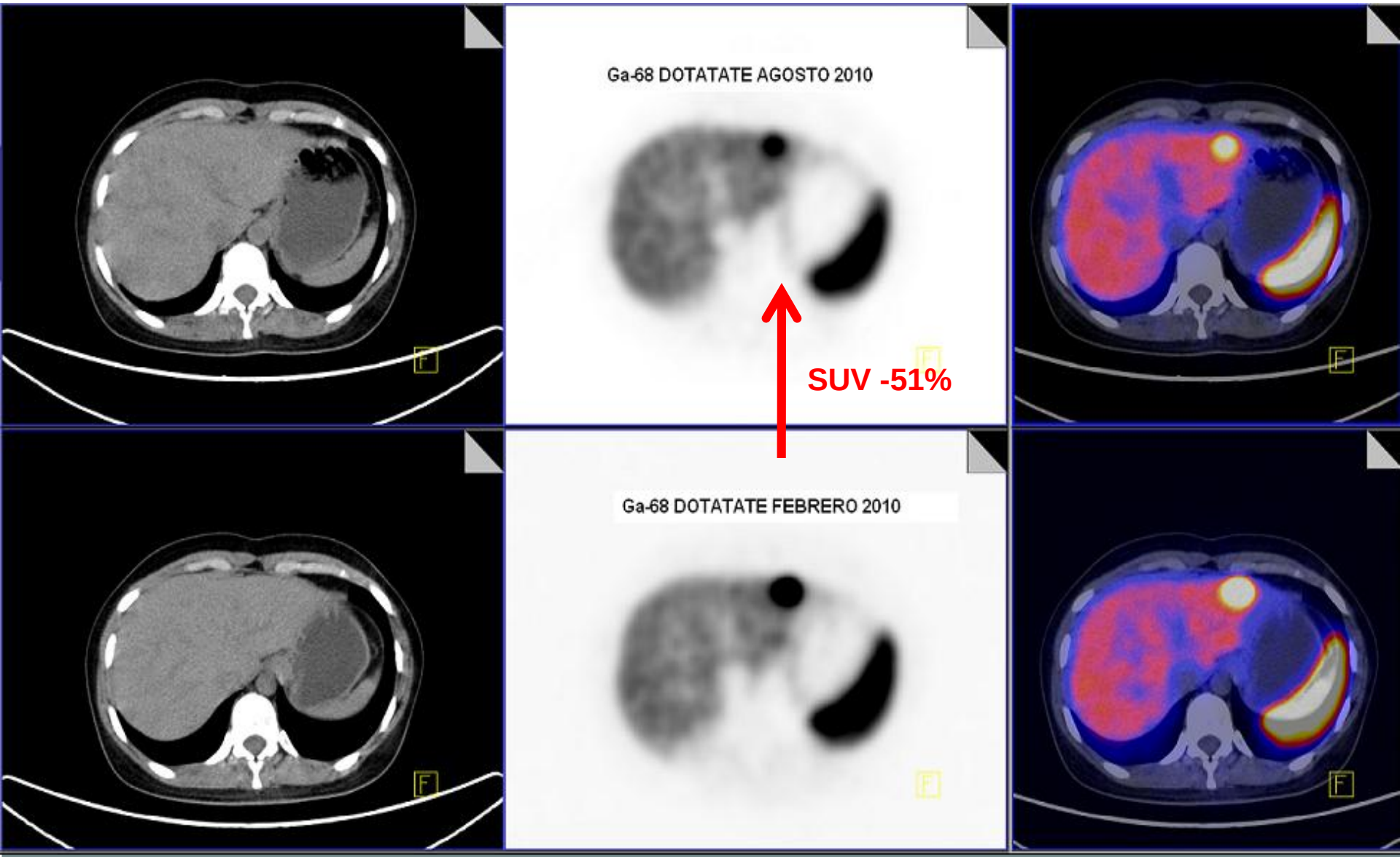
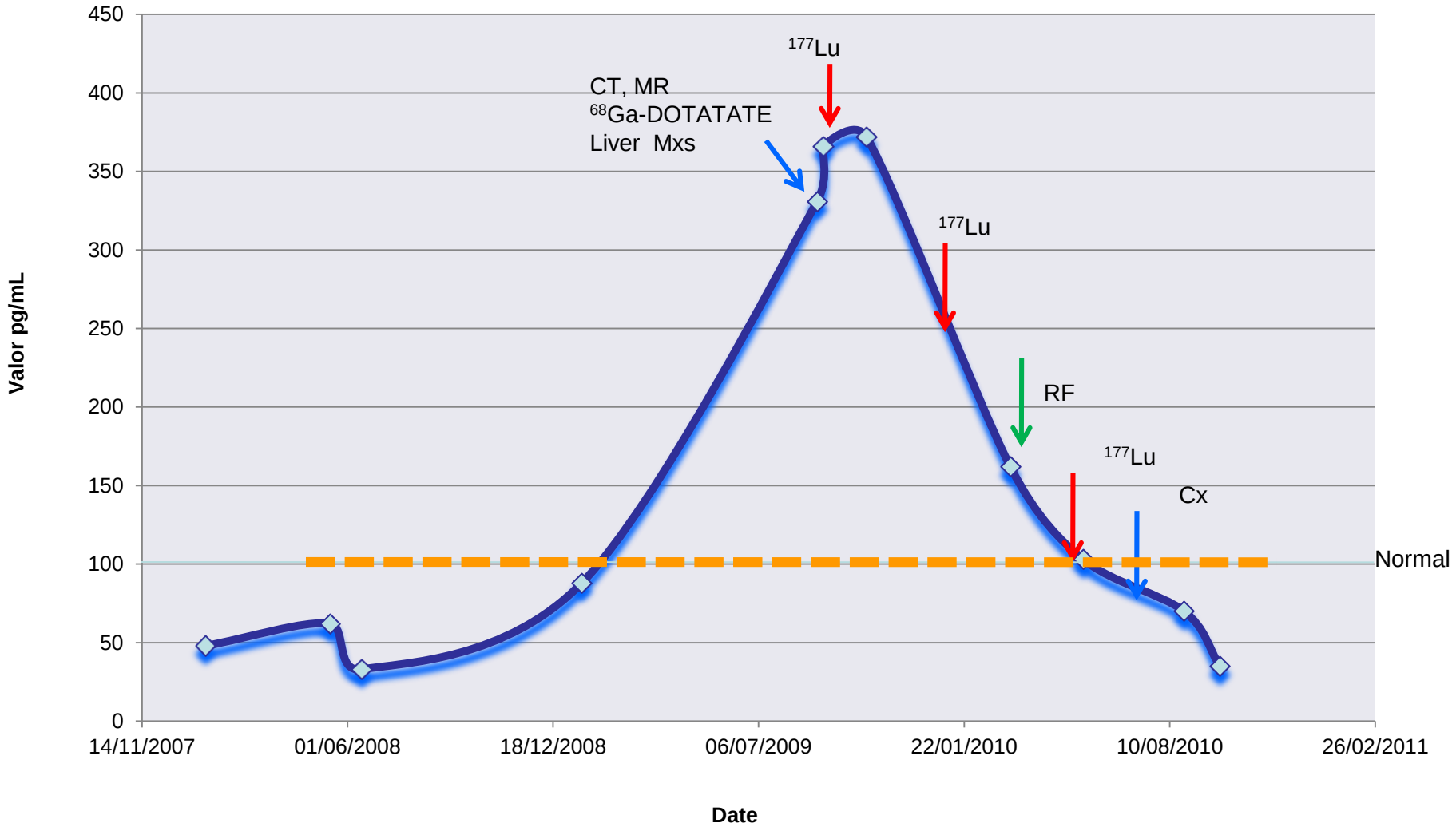
B: 1%

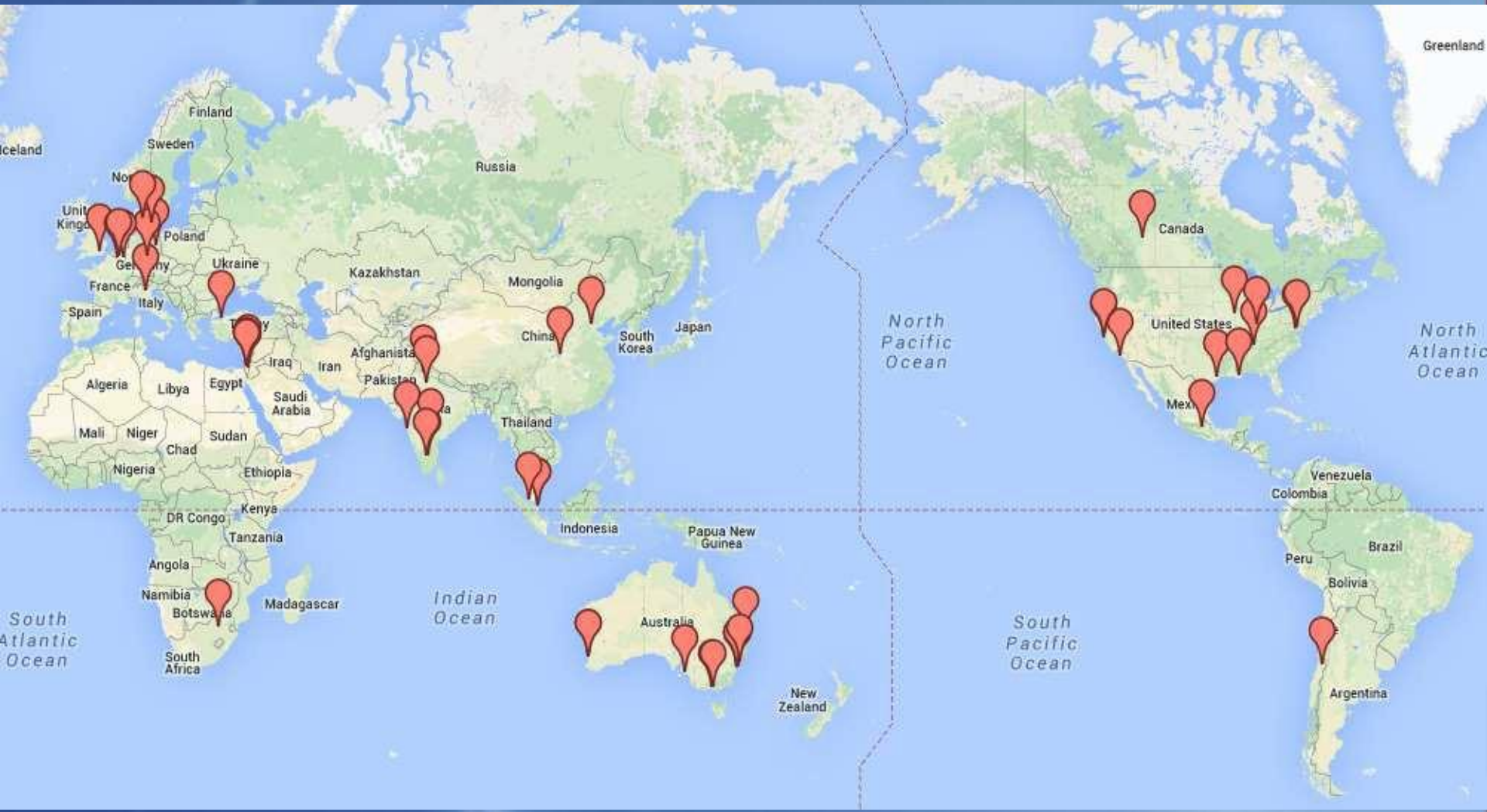

T: 28%
B: 1%


Ga-68 DOTATATE AGOSTO 2010
SUV -51%
Ga-68 DOTATATE FEBRERO 2010

Gastrin Values years 2008- 2014



PRRT: expansion of a concept



IEO
Istituto Europeo di Oncologia

Courtesy Lisa Bodei

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: 504 patients treated according to protocol; Acute Toxicity

Side-effect	Present	Absent	Total
Nausea	450 25%	1322 75%	1772
Vomiting	170 10%	1602 90%	1772
Pain	173 10%	1599 90%	1772

Temporary Hairloss (no baldness; WHO grade 1): 62% of patients

Nausea/Vomiting WHO grade 1-2, duration <24h

Erasmus MC

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: 504 patients treated according to protocol; Subacute Toxicity

WHO Toxicity	Grade 3	Grade 4	Total
Hgb	0.4%	0.1%	0.4%
WBC	1.4%	0.1%	1.5%
PLT	1.9%	0.8%	2.6%

Percentages are treatment based

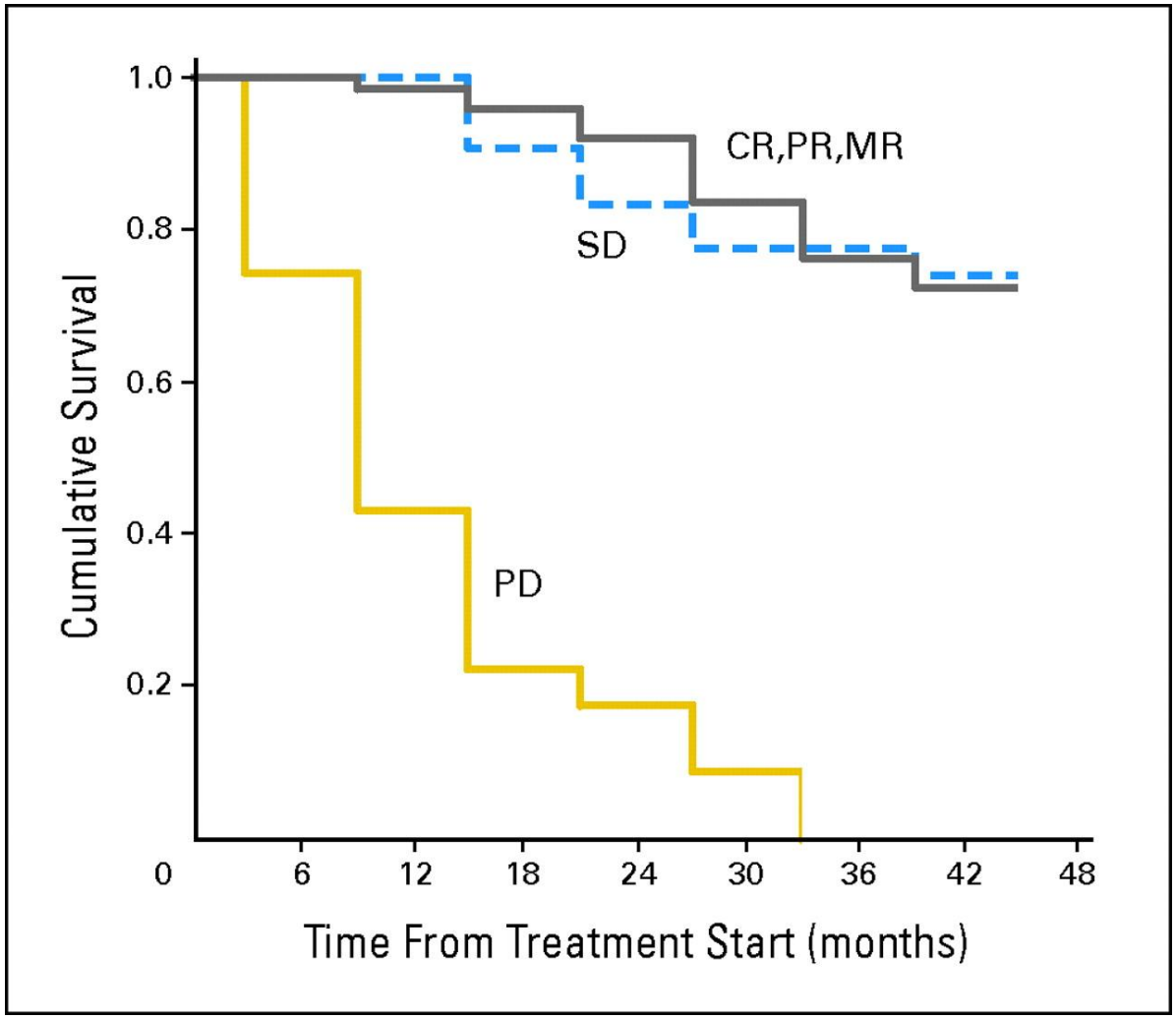
Any grade 3/4 toxicity: 3.6%

Any grade 3/4 toxicity patient based: 9.5%

Temporary Hairloss (no baldness; WHO grade 1): 62% of patients

Hormonal crises, need for special care ± 1 %

Erasmus MC



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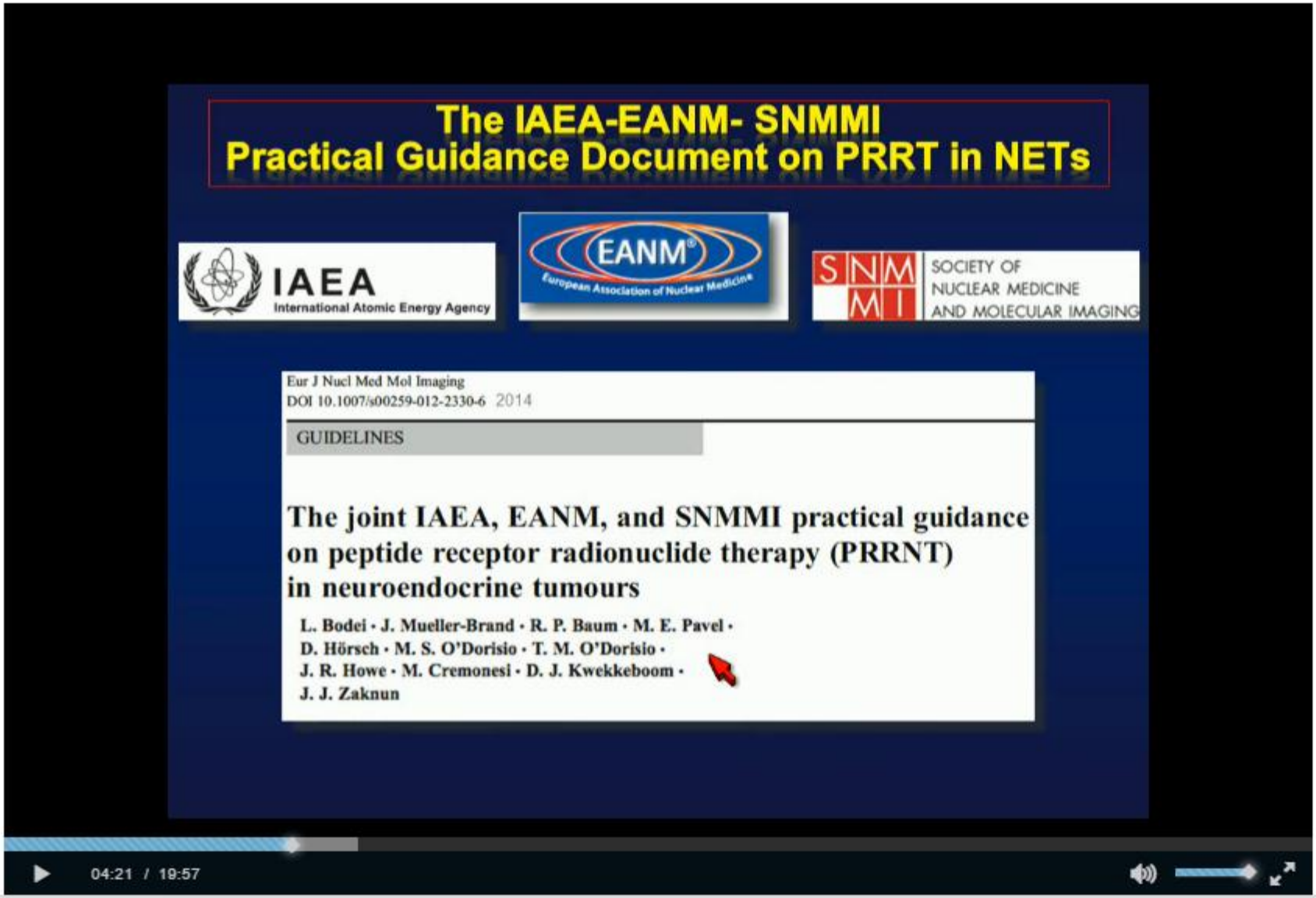
Comparative Median Time to Progression and relative cost of treatment

Medicamento	mTTP (meses)	USD $	Duración
Sunitinib 37, mg	[1] 11.4	8.300 / mes	Indefinido
Afinitor 10 mg	[2] 10.0	6.350 / mes	Indefinido
Sandostatin LAR 20	[3] 14.3	2.000 / mes	Indefinido
^{177}Lu-DOTATATE	[4] 40.0	6.700 /3 meses	4 a 6 dosis

[1] Raymon E, NEJM 2011
[2] Yao JC, NEJM 2011
[3] Rinke A, JCO 2009
[4] Kwekkeboom DJ, JCO 2008

Breakout Session: Recent Advances in the Treatment of Neuroendocrine Tumors
Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract Track



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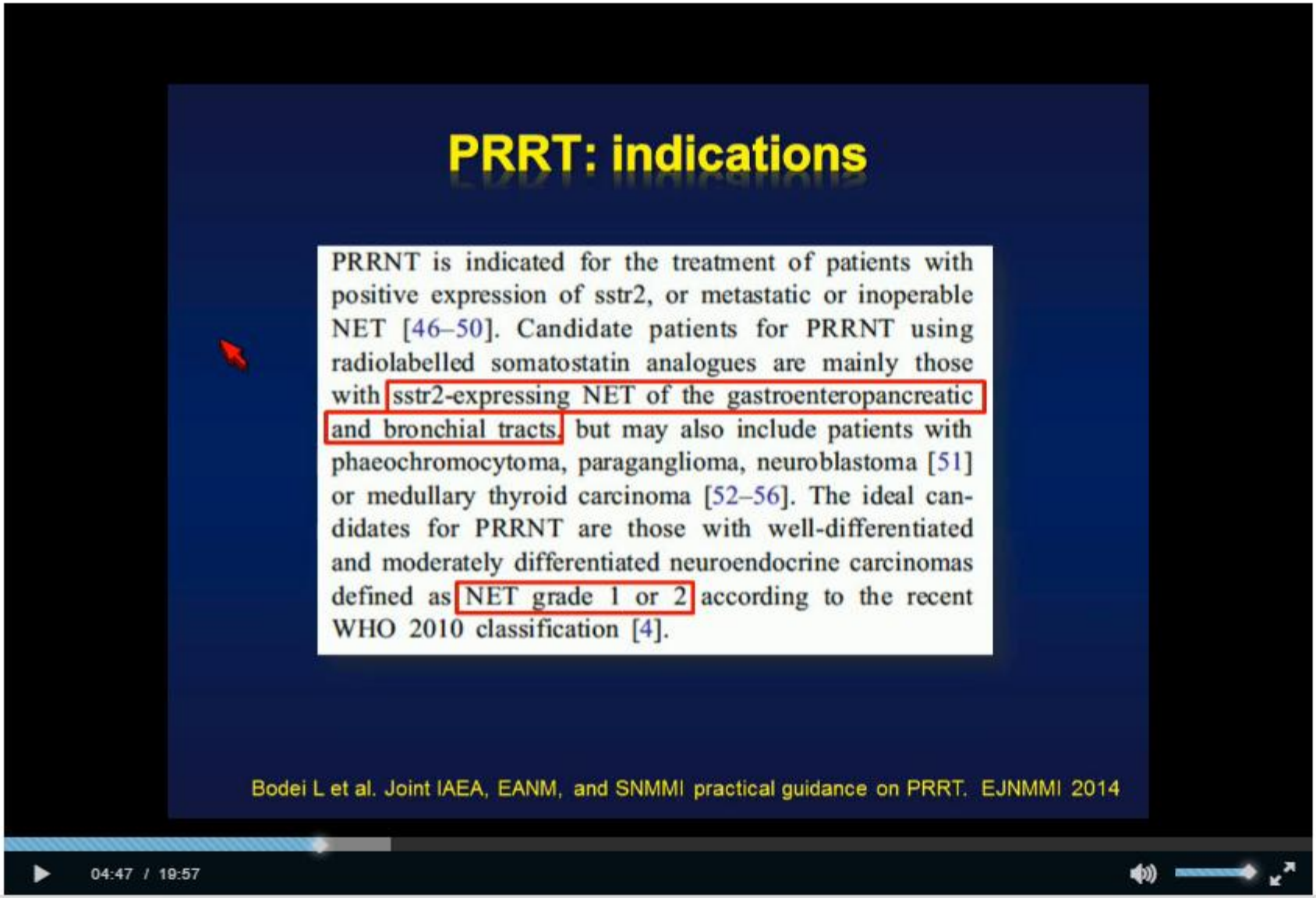
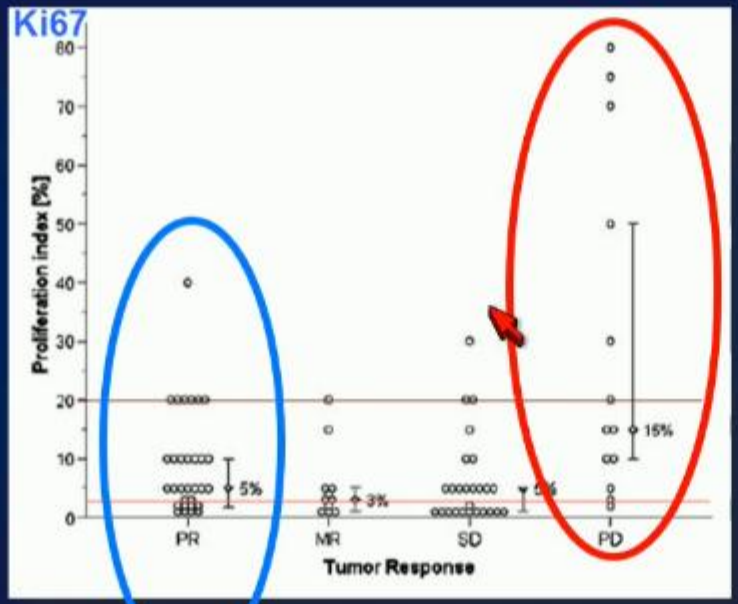


Breakout Session: Recent Advances in the Treatment of Neuroendocrine Tumors
Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract Track

Impact of Proliferation Rate (^{177}Lu-octreotate)



Ezzidin S et al EJNMMI 2011

09:06 / 19:57

Breakout Session: Recent Advances in the Treatment of Neuroendocrine Tumors
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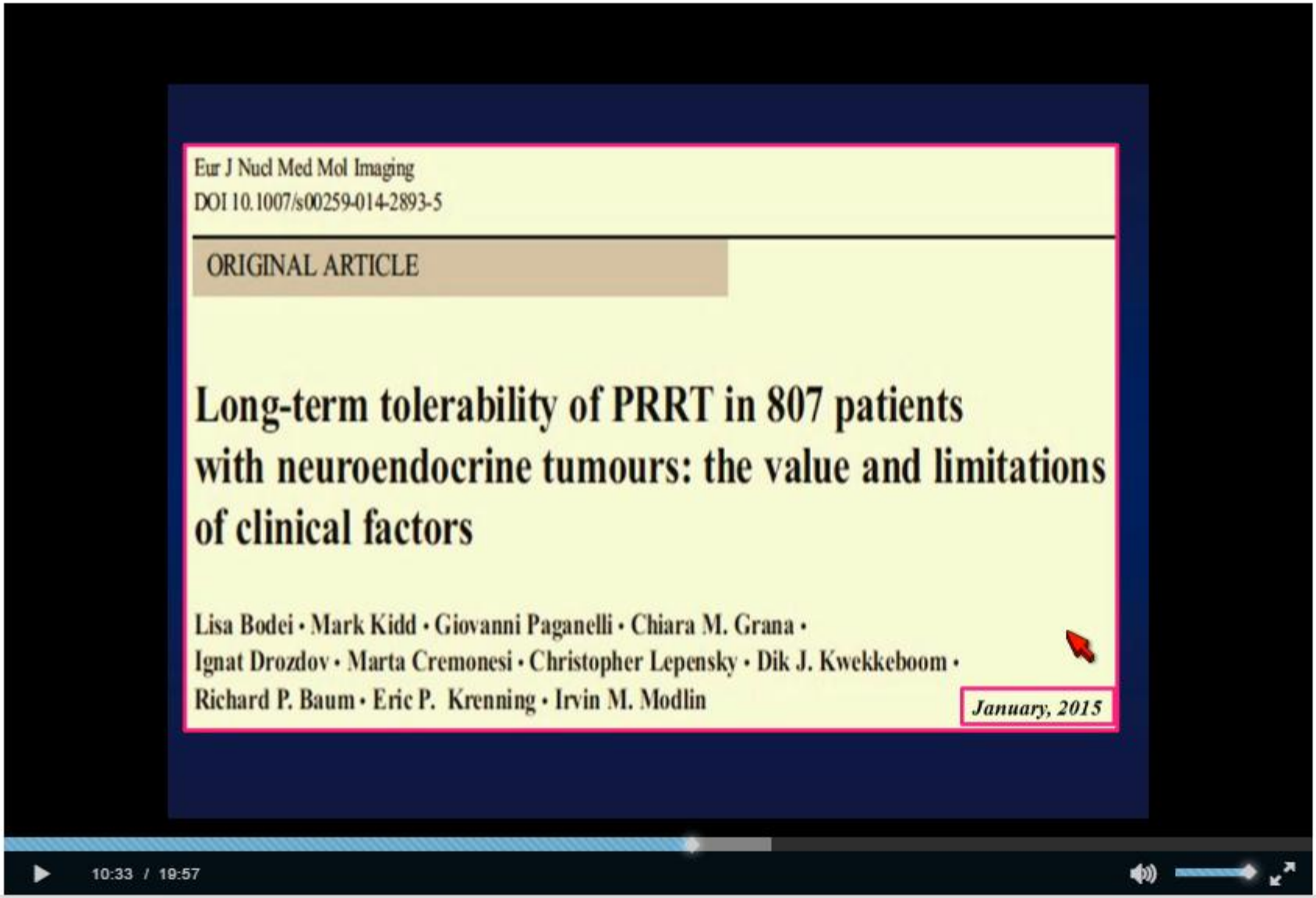

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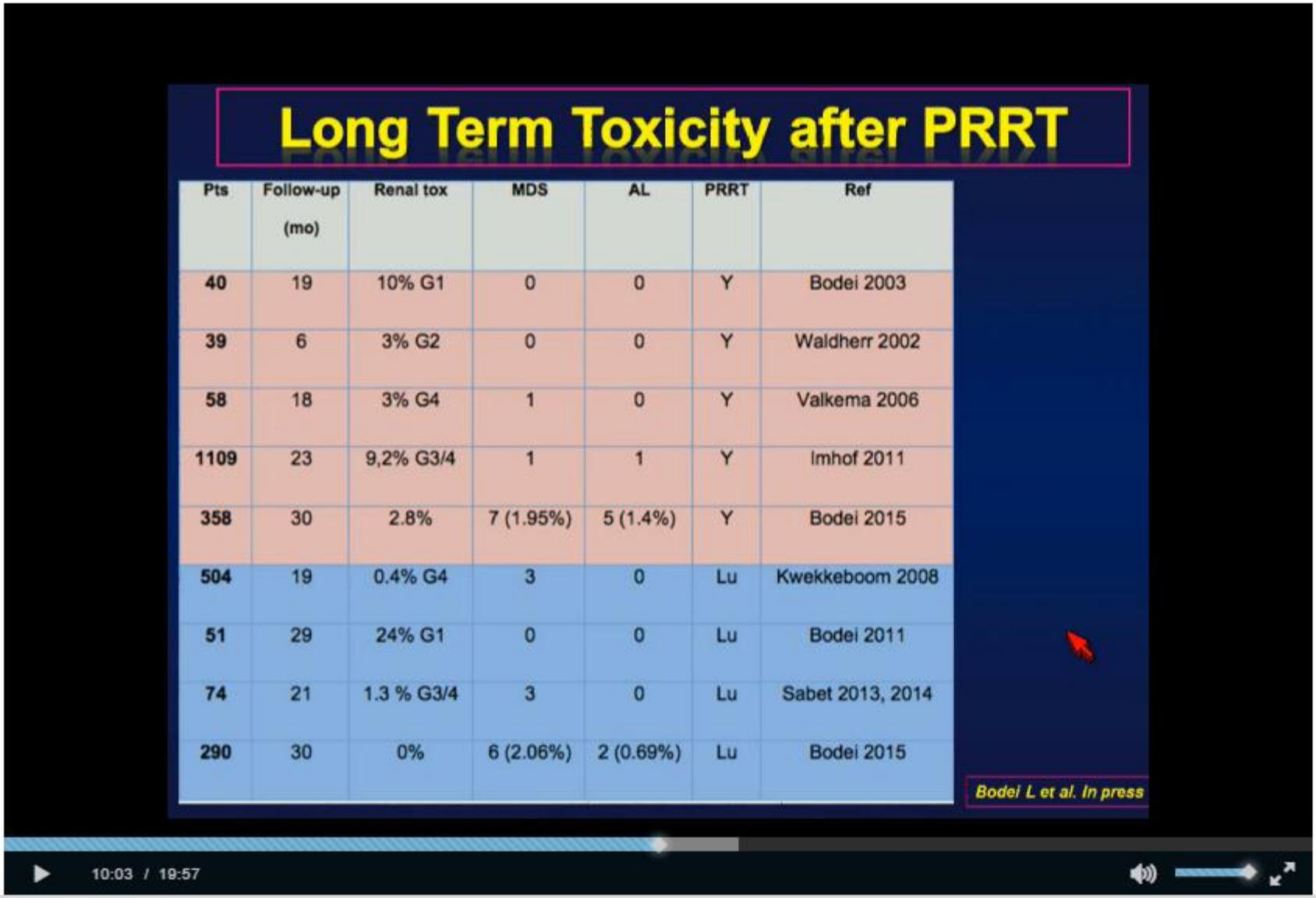

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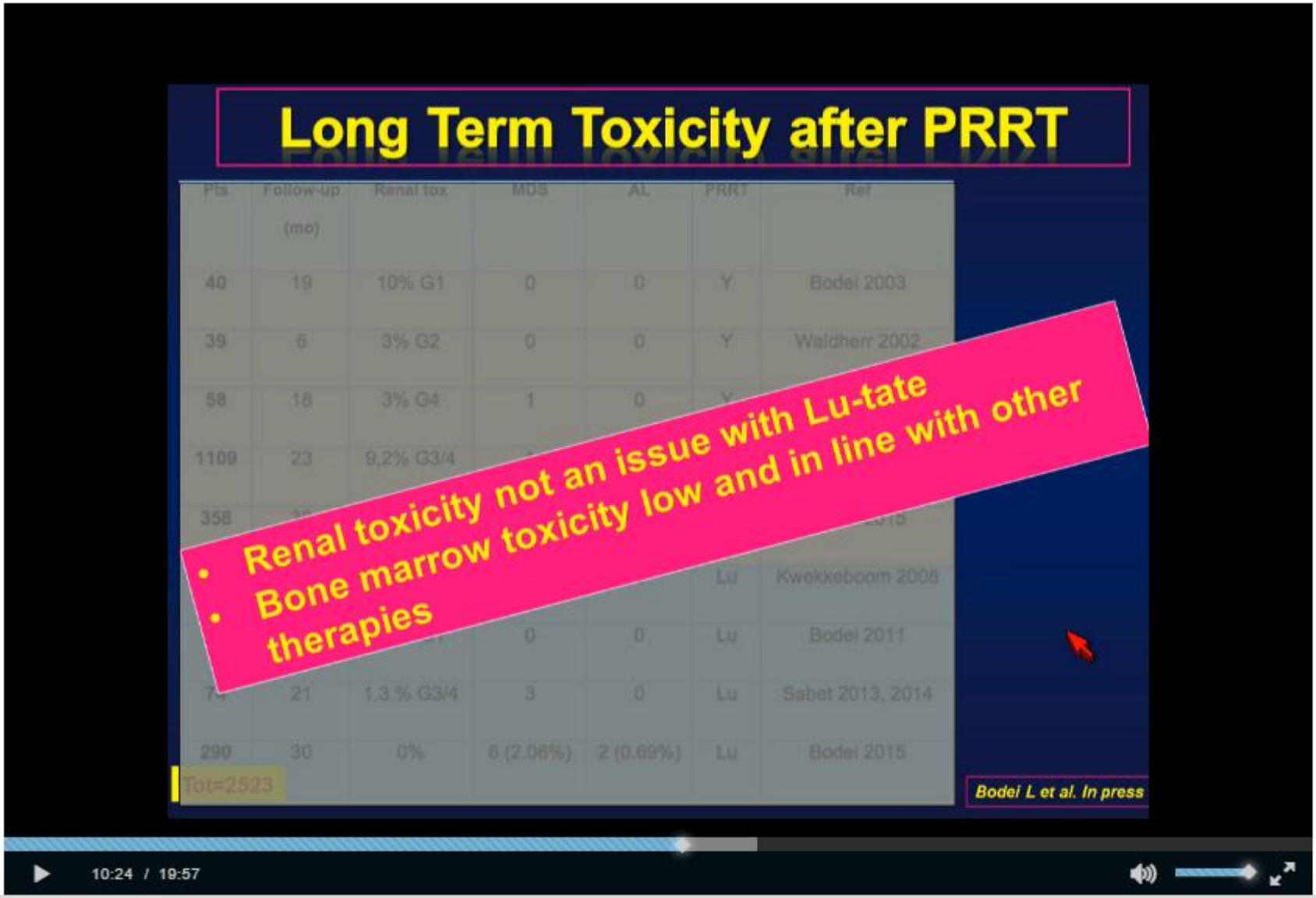

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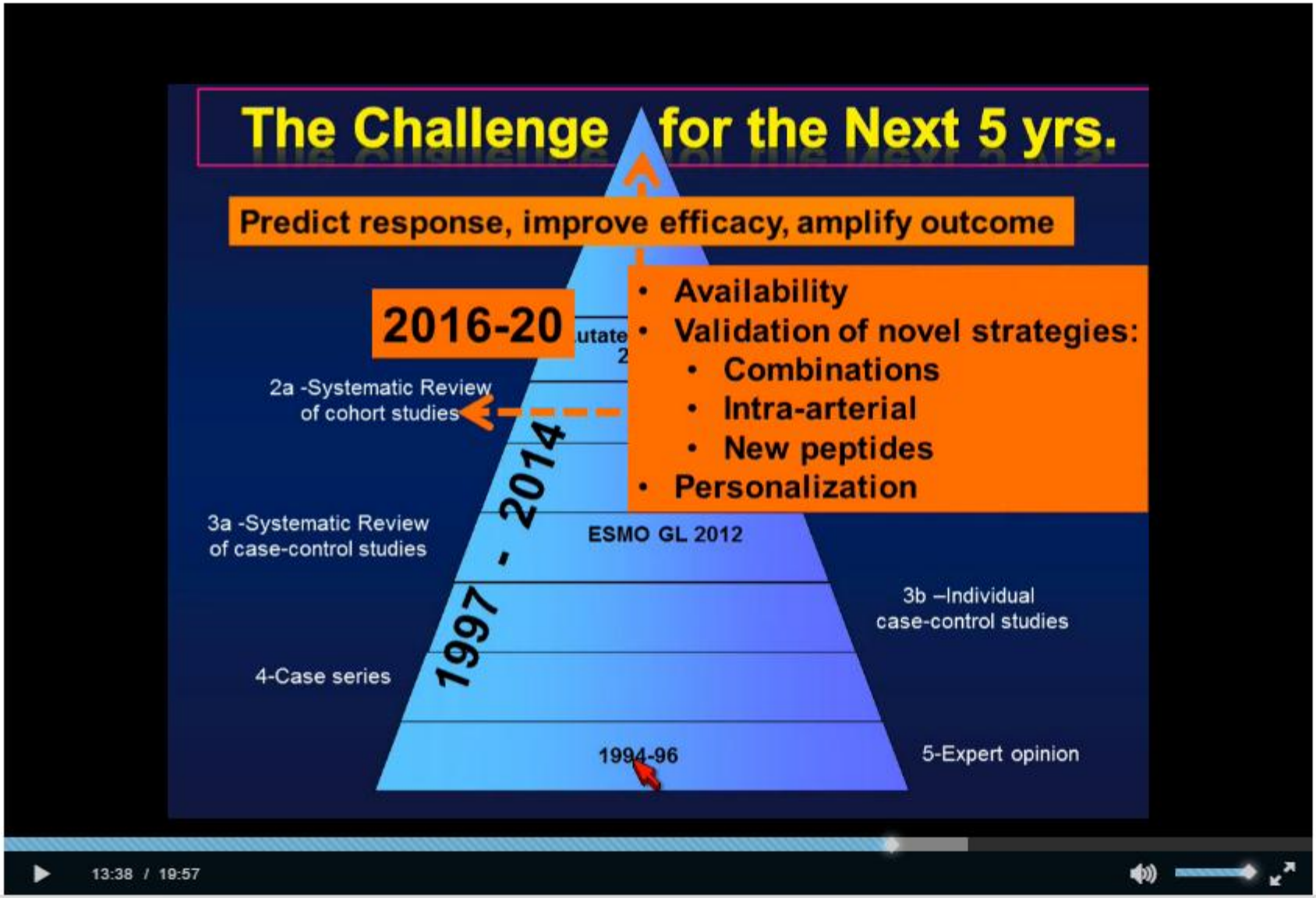


Supervivencia en pacientes con tumores neuroendocrinos

Horacio Amaral

Resultados (1) :

Toxicidad:

- Depresión medular severa reversible en un paciente por alteración de la biodistribución del péptido por causa en estudio. Se considera no tratado.
- Depresión medular crónica moderada en un paciente con metástasis ósea múltiples. ¿Invasión tumoral?

Respuesta al Tratamiento (n = 40 pacientes):

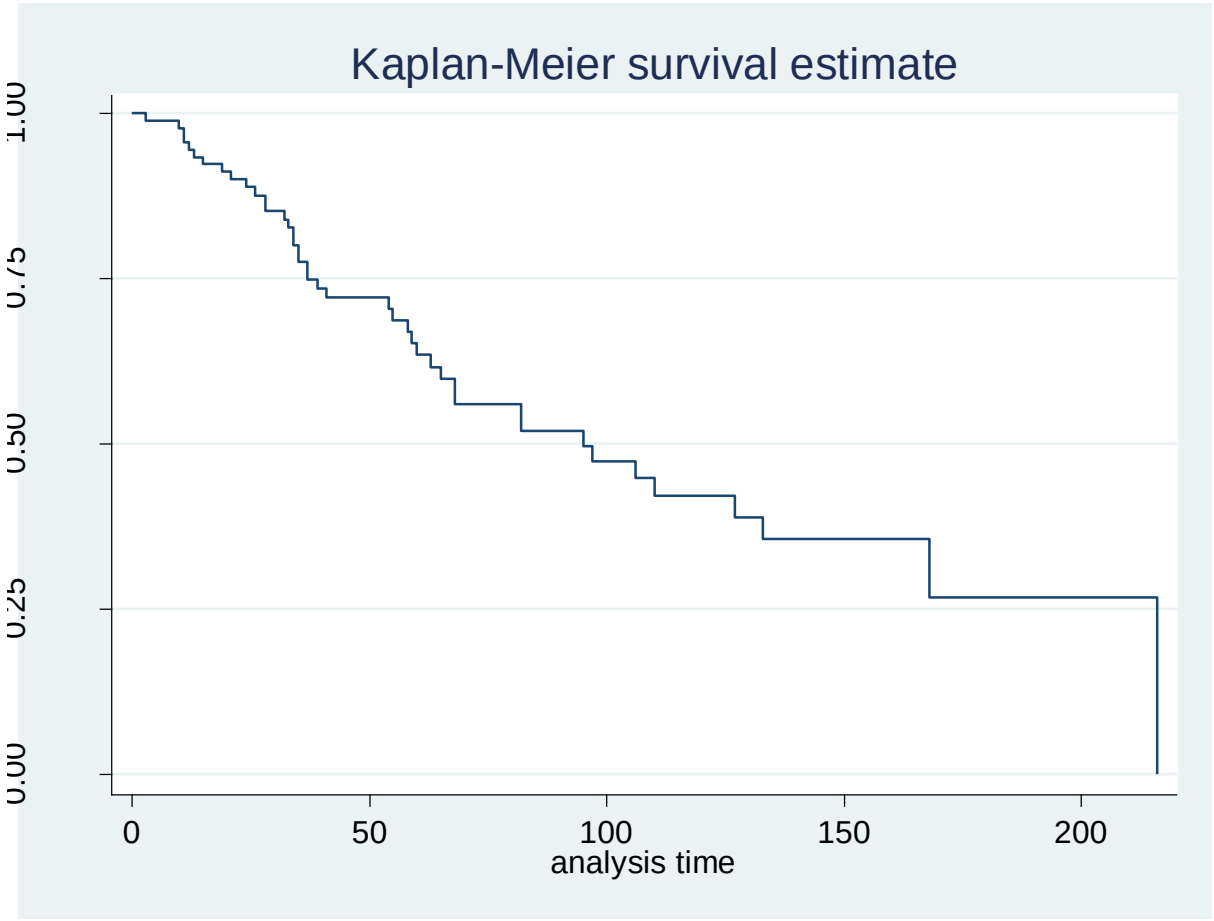
Progresión	10	25%
Remisión parcial:	25	62%
Enfermedad estable	3	8%
Remisión completa:	2	5%

75%

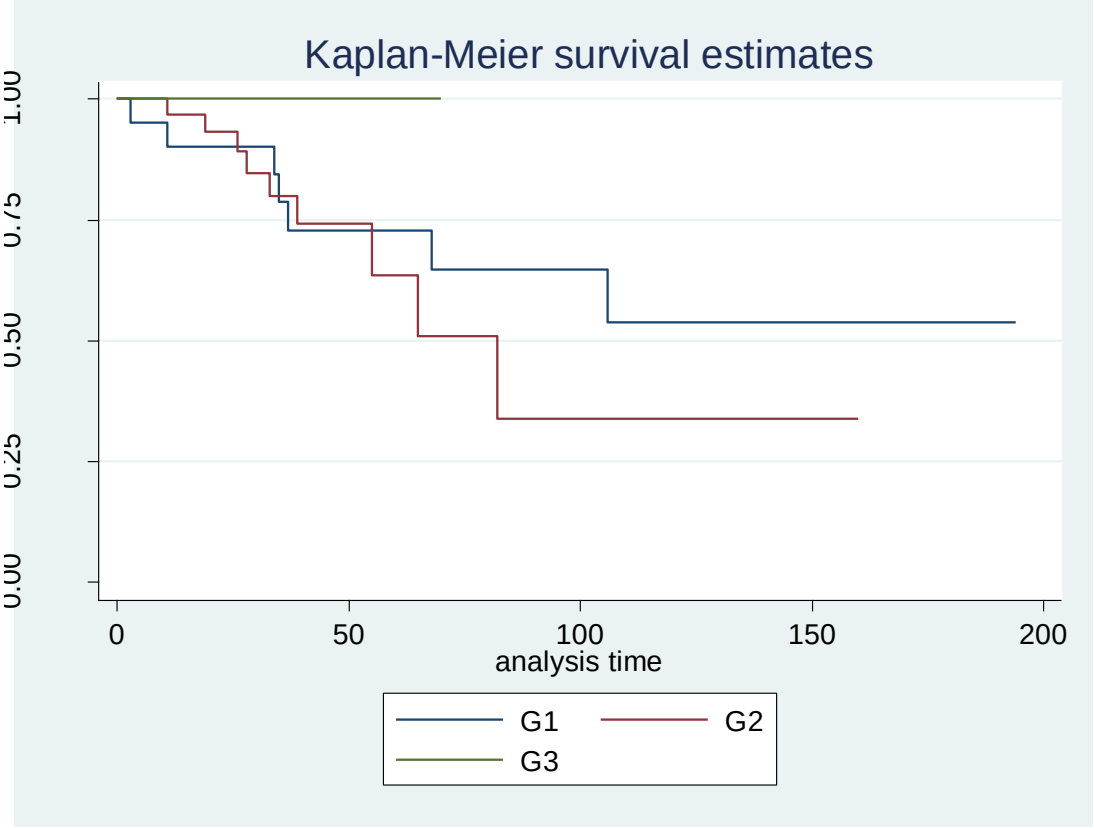
Amaral H. et al. Alasbimn Journal 12 (47): January 2010. Article N° AJ47-1
http://www.alasbimnjournal.cl/

Antecedentes clínicos

Variable	Categoría	n	%
Sexo (n=95)	Femenino	43	45.3
	Masculino	52	54.7
Origen tumor (n=95)	Páncreas	30	21.05
	Entérico	45	47.37
	Otro	20	31.58
Grado de diferenciación (n=53)	G1	20	37.74
	G2	31	58.49
	G3	2	3.77
Status actual de supervivencia	Vivo	51	53.7
	Fallecido	44	46.3
Numero de terapias (n=87), media (DE)	4, (2.17)		
Sero. Intrap. (n=41), media (DE)	2780 (2304)		
Seguimiento meses, mediana (min-máx.)	48 (3-216)		

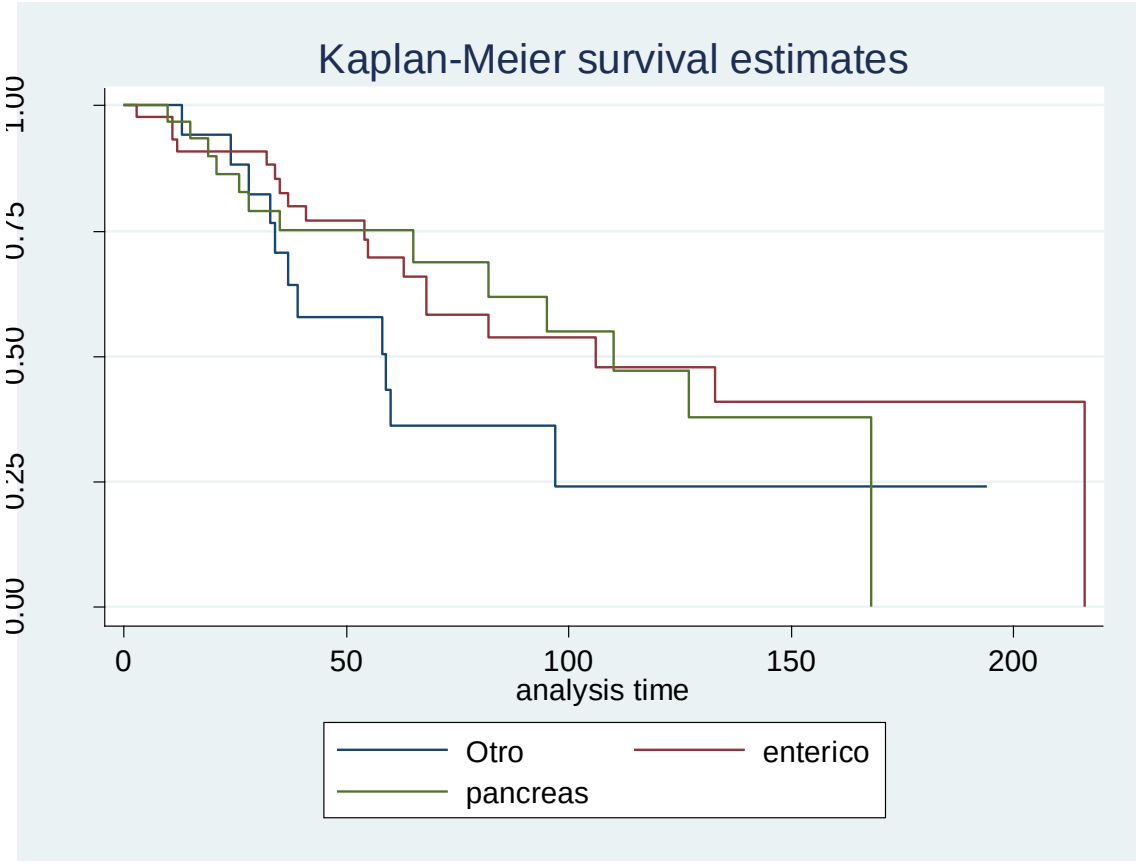

Kaplan-Meier survival estimate
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
analysis time

Supervivencia según grado de diferenciación



Log Rank test, P value=0.60 (no es significativa la diferencia de sobrevida según grado de diferenciación)

Grado de diferenciación	mediana seguimiento (meses)	fallecidos: n(%)
G1	74	7 (35%)
G2	42.9	9 (23%)
G3	70	1 (50%)



Supervivencia según Origen

Origen	Mediana de seguimiento (meses)	fallecidos: n(%)
Otro	39	12 (60%)
enterico	49.5	19(42%)
Páncreas	46.5	13 (43%)

Log Rank test, p value=0.26 (no hay diferencia)

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

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on behalf of the NETTER-1 study group

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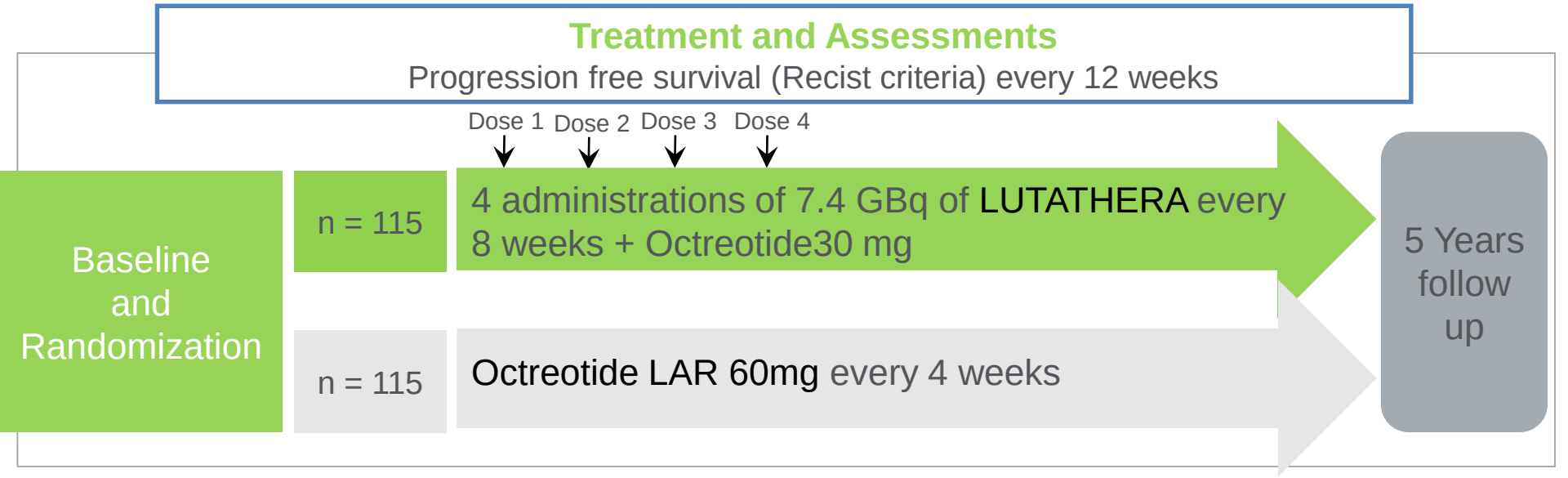
Main Inclusion Criteria

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, midgut NET
- Ki67 index ≤ 20% (Grade 1-2)
- Progressive disease (RECIST Criteria 1.1 centrally confirmed) on uninterrupted fixed dose of octreotide LAR (20-30 mg every 3-4 weeks)
- Somatostatin receptor positive disease
- Karnofsky Performance Score ≥ 60
- Including functioning and non-functioning

NETTER -1 Study Objectives and Design

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



1. FDA and EMA recommendation

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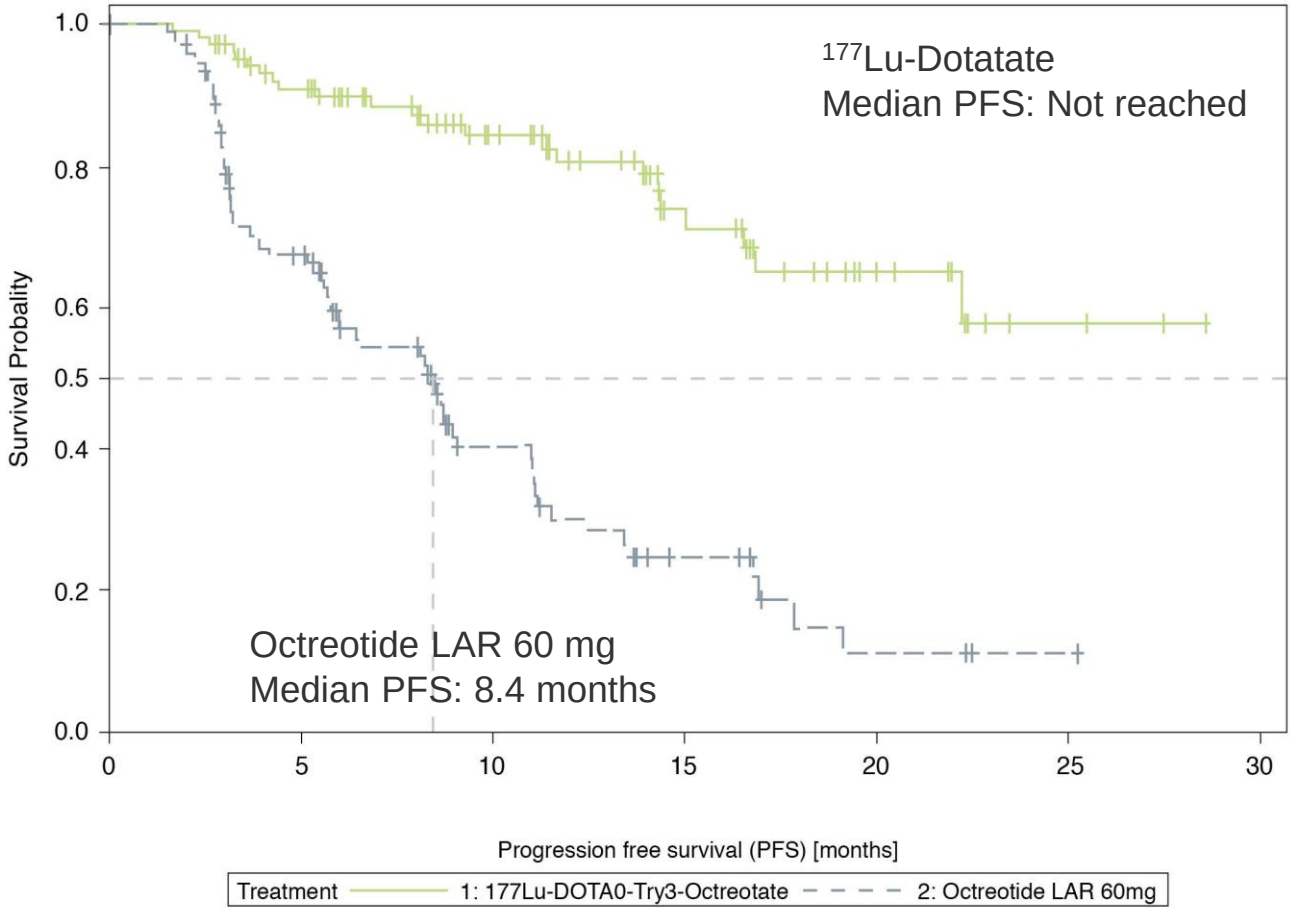
Progression-Free Survival

N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
Risk reduction: 79.1
p < 0.0001



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

Tumour Response Rate (currently evaluable patients)

	^{177}Lu-Dotatate (n=101)	Octreotide LAR 60mg (n=100)
Complete Response (n)	1	0
Partial Response (n)	18	3
Objective Response Rate (CI 95%)	19 (11-26) %	3 (0-6) % *
Progressive Disease (n, %)	5 (4%)	27 (24%)
Stable Disease (n, %)	77 (66%)	70 (62%)

***P<0.0004**

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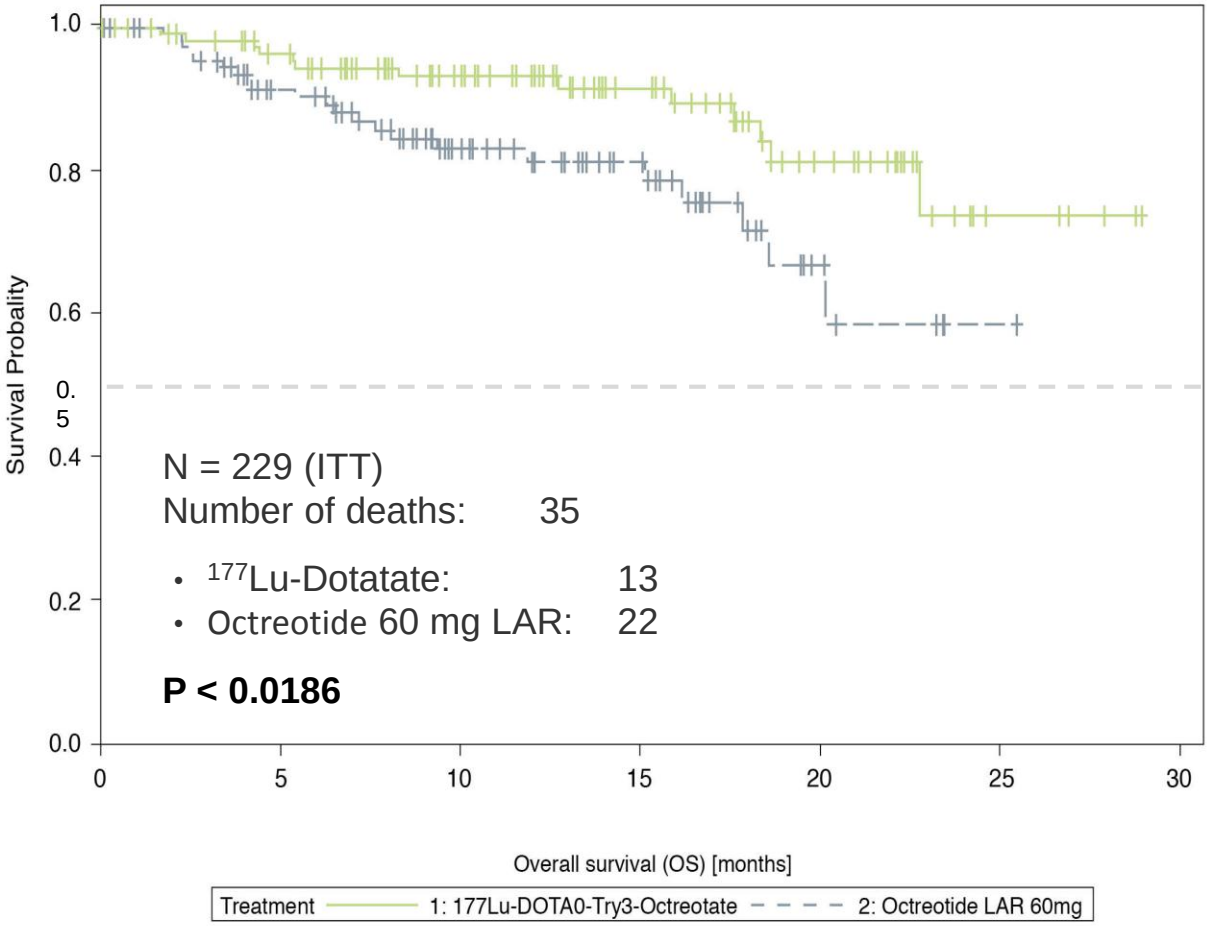
Overall Survival (interim analysis)



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^{177}Lu-Dotatate Safety - SAE

	SAE (n)
Blood & lymphatic system	**7**
Lymphocytopenia	3
Thrombocytopenia	1
Neutropenia	1
Pancytopenia	1
Bicytopenia	1
Renal & urinary disorders	**3**
Acute kidney injury	2
Renal failure	1
Vascular disorders	**1**
Portal hypertension	1

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^{177}Lu-Dotatate Exposure

Patients who completed trt phase, N=102*	Nb of Patients
Drug exposure, n (%)	
800 mCi	81 (79%)
400 – 800 mCi	5 (5%)
200 – 400 mCi	9 (9%)
200 mCi	3 (3%)
No administration	4 (4%)
Number of administrations, n (%)	
4	78 (76%)
3	5 (5%)
2	11 (11%)
1	4 (4%)
0	4 (4%)
Dose modifying toxicity, n (%) **All treated patients – N=111**	
No DMT	105 (95%)
DMT	6 (5%)

*14 pts still under treatment

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Safety and Tolerability
(Nb of patients (%), Safety Set; n=221)

	177-Lu-Dotatate (n=111)	Octreotide LAR 60mg (n=110)
Any adverse event	106 (96%)	95 (86%)
Related to treatment	95 (86%)	34 (31%)
Serious adverse events	29 (26%)	26 (24%)
Related to treatment	10 (9%)	1 (1%)
Withdrawals due to adverse events	7 (6%)	10 (9%)
Related to treatment	5 (5%)	0 (0%)

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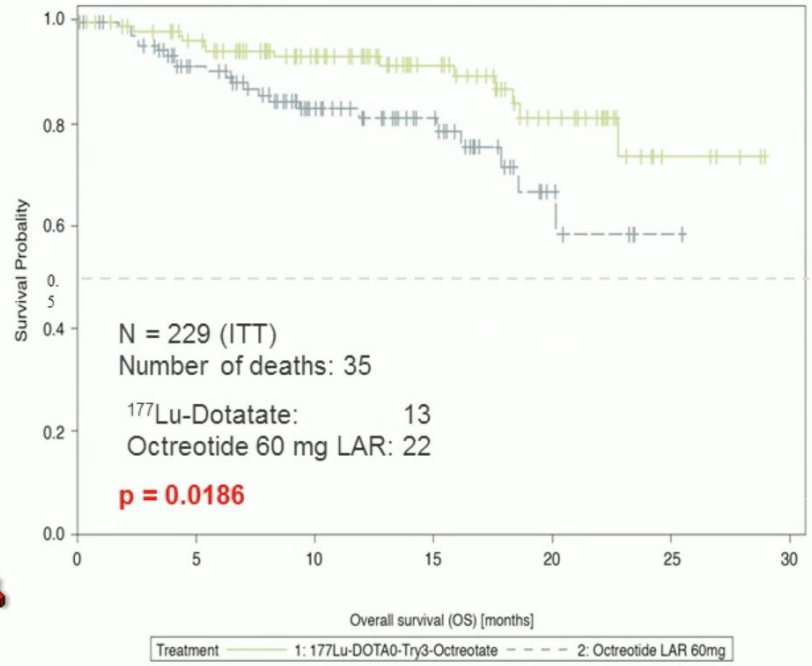
Summary and Conclusions

- 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 (NR vs 8.4 months, p<0.0001) and ORR (19% vs 3%, p<0.0004)
- Interim analysis suggests increased overall survival (13 vs 22 deaths), to be confirmed by final analysis
- Currently available safety data confirm the results of Phase I-II study, with favorable safety profile
- While few treatment options were up to now available, ^{177}Lu-Dotatate appears as a major advance in this patient population

Overall Survival (interim analysis)



Summary and Conclusions

- Final analysis : ^{177}Lu-Dotatate superior to Octreotide 60 mg:
  - PFS (Not Reached vs 8.4 months, p<0.0001)
  - ORR (19% vs 3%, p=0.00043)
- Interim analysis suggests increased OS (13 vs 22 deaths), to be confirmed by final analysis.
- Currently available safety data confirm the results of Phase I-II study, with favorable safety profile.
- While few treatment options are available for patients progressing under SSAs, ^{177}Lu-Dotatate has a major therapeutic benefit for this patient population.

¿Cuál es la mejor terapia para pacientes con metátasis hepáticas de TNE?.

Visión de Futuro:

- PRRT aparece como la más terapia más promisoria
- Re-tratamiento frente a recidiva o progresión con ^{177}Lu-DOTATATE
- Administración PRRT intra-arterial selectiva en metástasis hepáticas
- Terapias combinadas:
  - Radiosensibilizadores (Capecitabina – 5FU)
  - mTOR (Everolimus – Afinitor)
  - Inhbidores de tyrosin kinase (Sunitinib – Sutent)
  - Octreotido LAR
- PRRT como neoadyuvancia
- Trasplante en lesiones hepáticas exclusivas (PET/CT con ^{68}Ga-DOTATATE)

GRACIAS!