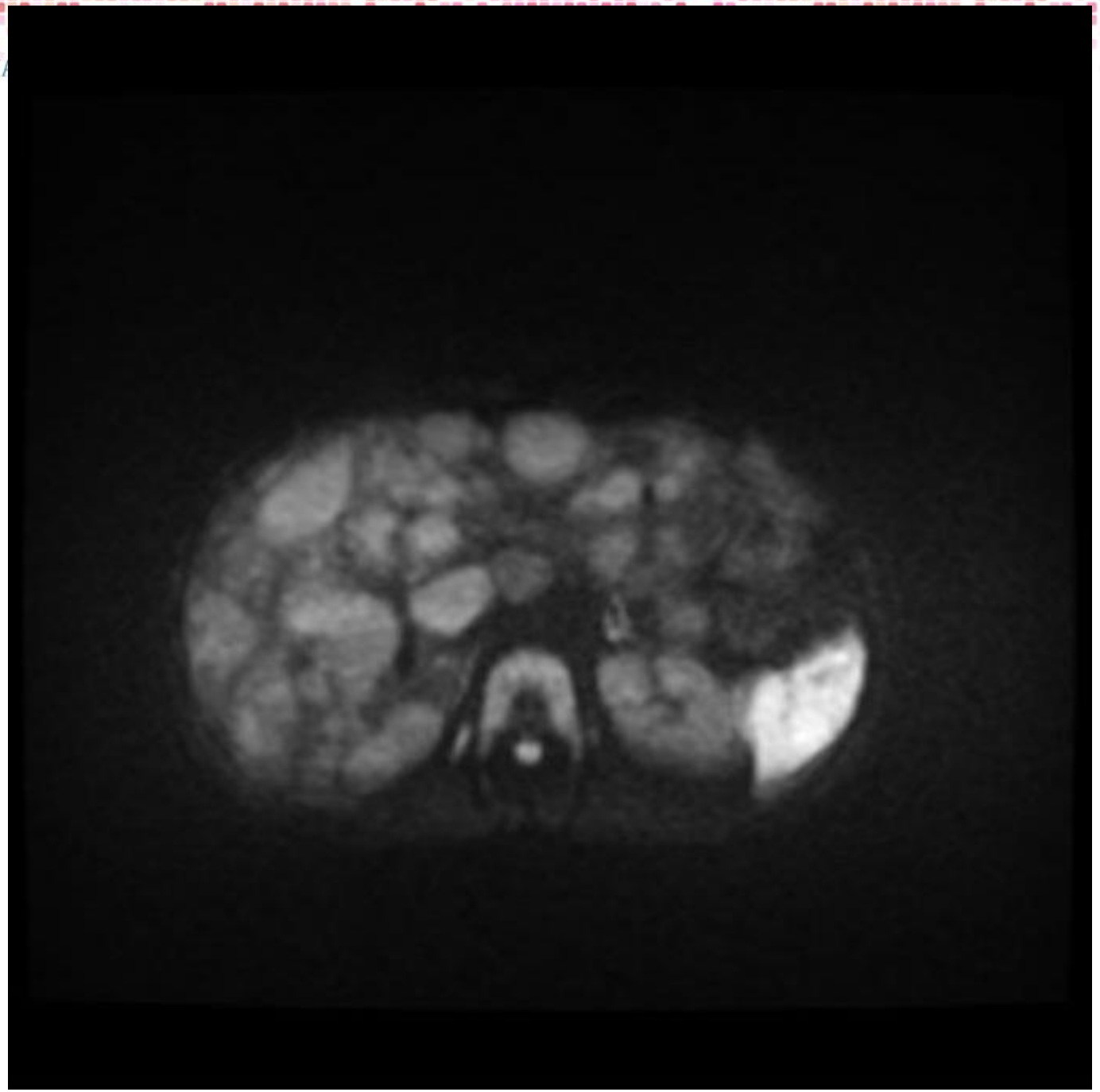
21 jun 2019

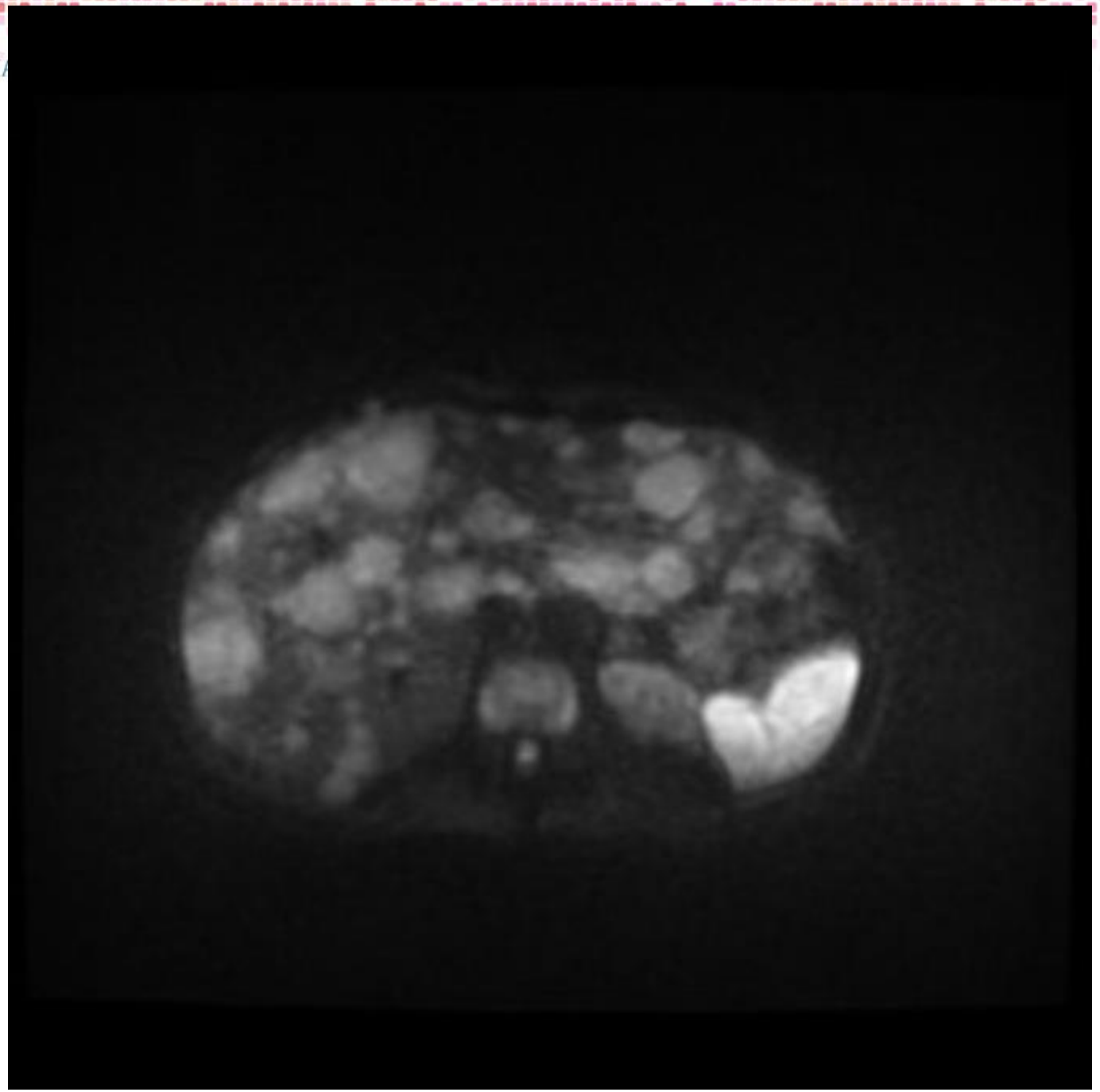
6ºCURSO
MANEJO DE NEOPLASIAS NEUROENDOCRINAS Y ENDOCRINAS

HOTEL RAFAEL ATOCHA, MADRID

Caso clínico
TNE GEP

- Mujer de 14 años
- Sin antecedentes personales ni familiares de interés
- Ingresa en M Interna por leve pérdida de peso y diarrea
- No fiebre
- EF conjuntivitis y telangiectasias malares
- Hem normal
- BQ GOT 50 resto normal
- Ecografía abdominal: metástasis hepáticas
- TAC Múltiples lesiones hepáticas metastásicas resto normal





Qué hacemos?

1)Biopsia
2)M nuclear
3)Otros: cardio, nutrición
4) analítica/ marcadores tumorales

AP

- **HIGADO (biopsia-cilindro) : TUMOR NEUROENDOCRINO ALTAMENTE SUGESTIVO DE CARCINOIDE.**

DIAGNÓSTICO:

NOTA : Las características histológicas de la neoplasia junto a los datos clínicos facilitados (presencia de LOES hepáticas) nos hacen pensar como 1º posibilidad diagnóstica que se trate de metástasis de un tumor carcinoide,(probablemente gastrointestinal u ovárico) , o de un tumor endocrino pancreático; aunque no podemos descartar un tumor carcinoide primario hepático, si bien estos últimos son extremadamente raros. Las técnicas inmunohistoquímicas realizadas han mostrado positividad para CROMOGRAMINA, ENOLASA, CAM 5.2 y SINAPTOFISINA, y negatividad para AE1/AE3, S100 Y AFP. Por otro lado, las células tumorales muestran argirofilia (GRIMELIUS +) y débil argentafinidad (FONTANA-MASON+/-

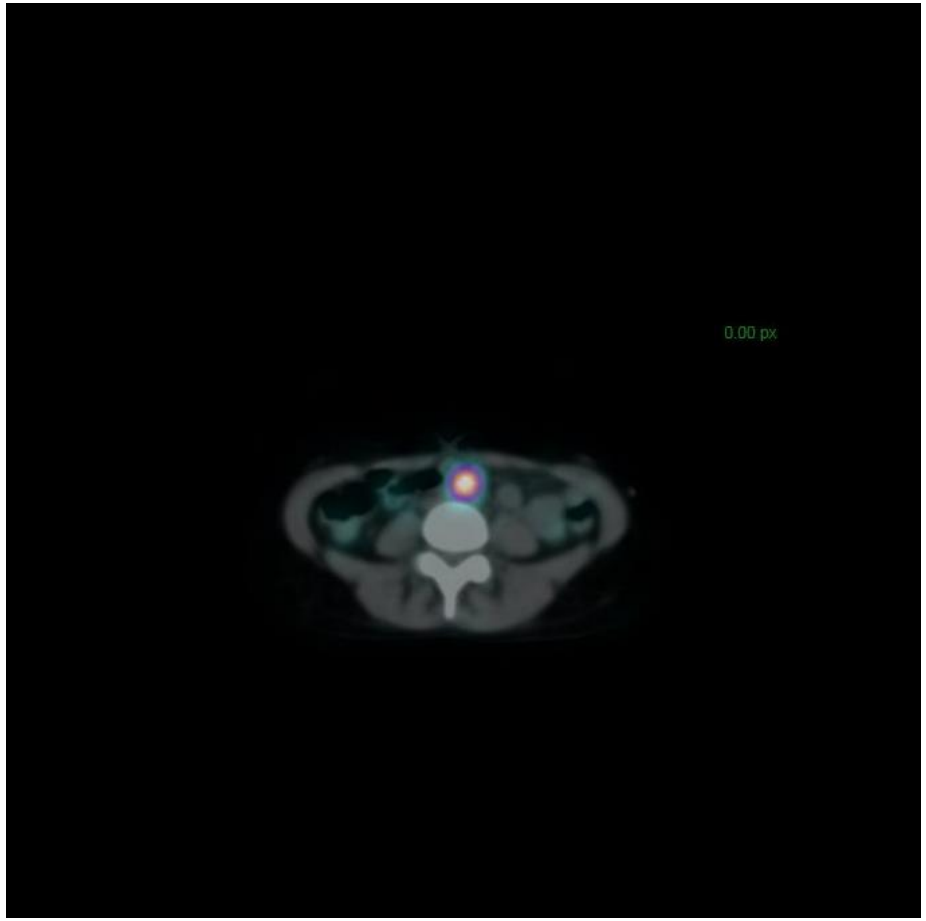
Qué datos faltan?

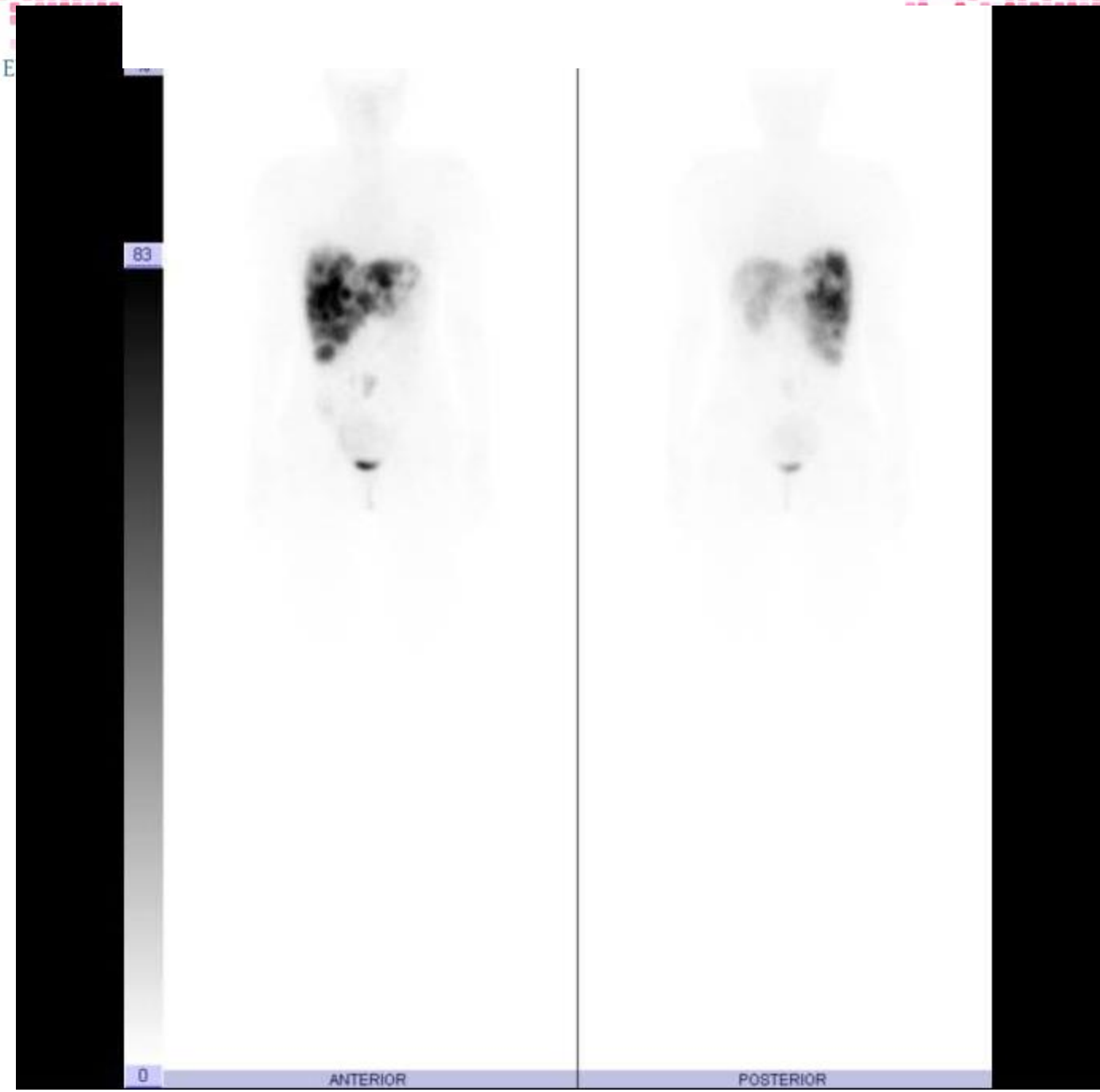
- 1.Ki 67
- 2.Mitosis
- 3. Morfología
- 4 CDX2

Qué datos faltan?

- 1.Ki 67 1%
- 2.Mitosis 1/10CGA
- 3. Morfología bien diferenciado
- 4 CDX2 +

Octreoscan





Localización del tumor primario

- Colonoscopia normal
- EDA normal
- Enteroclisis normal

Diagnóstico

- NNE G1 de origen desconocido probable I delgado con MTS hepáticas irresecales y síndrome carcinoide
- Insistimos en búsqueda de primario? Por qué?

Is Resection of Primary Midgut Neuroendocrine Tumors in Patients with Unresectable Metastatic Liver Disease Justified? A Systematic Review and Meta-Analysis

Diamantis I. Tsilimigras [1] · Ioannis Ntanasis-Stathopoulos [2] · Ioannis D. Kostakis [3] · Demetrios Moris [4] · Dimitrios Schizas [2] · Jordan M. Cloyd [1] · Timothy M. Pawlik [1,5]

Journal of Gastrointestinal Surgery (2019) 23:1044–1054
https://doi.org/10.1007/s11605-018-04094-9

Conclusion PTR was safe with a low peri-operative risk of mortality and was associated with an improved OS for patients with MNET and unresectable NELM. Given the poor quality of evidence, however, strong evidenced-based recommendations cannot be made based on these retrospective single center–derived data. Future well-design randomized controlled trials will be critical in elucidating the optimal treatment strategies for patients with MNET and advanced metastatic disease.

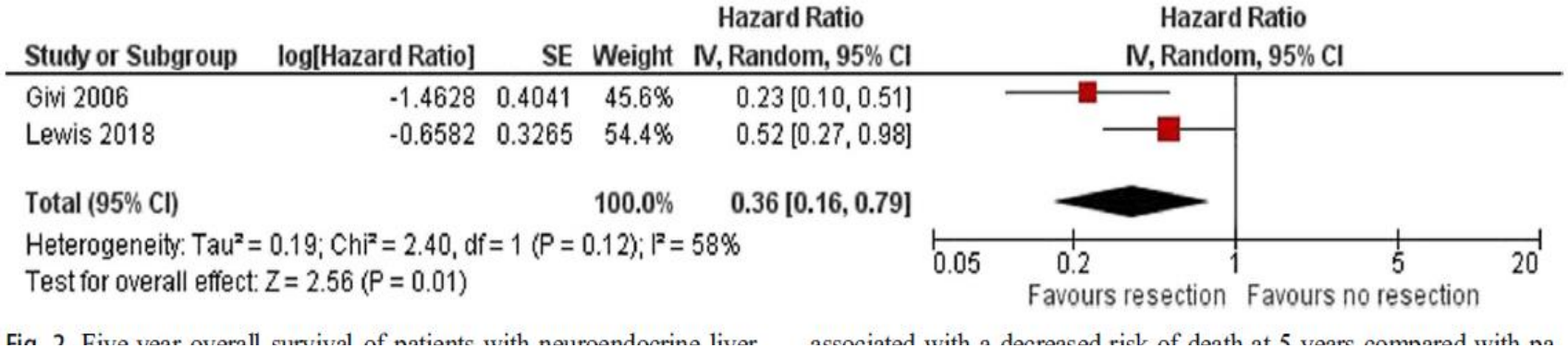


Fig. 2 Five-year overall survival of patients with neuroendocrine liver ... associated with a decreased risk of death at 5 years compared with na...

Mortalidad por cx 1.4%
Estudio prospectivo en marcha

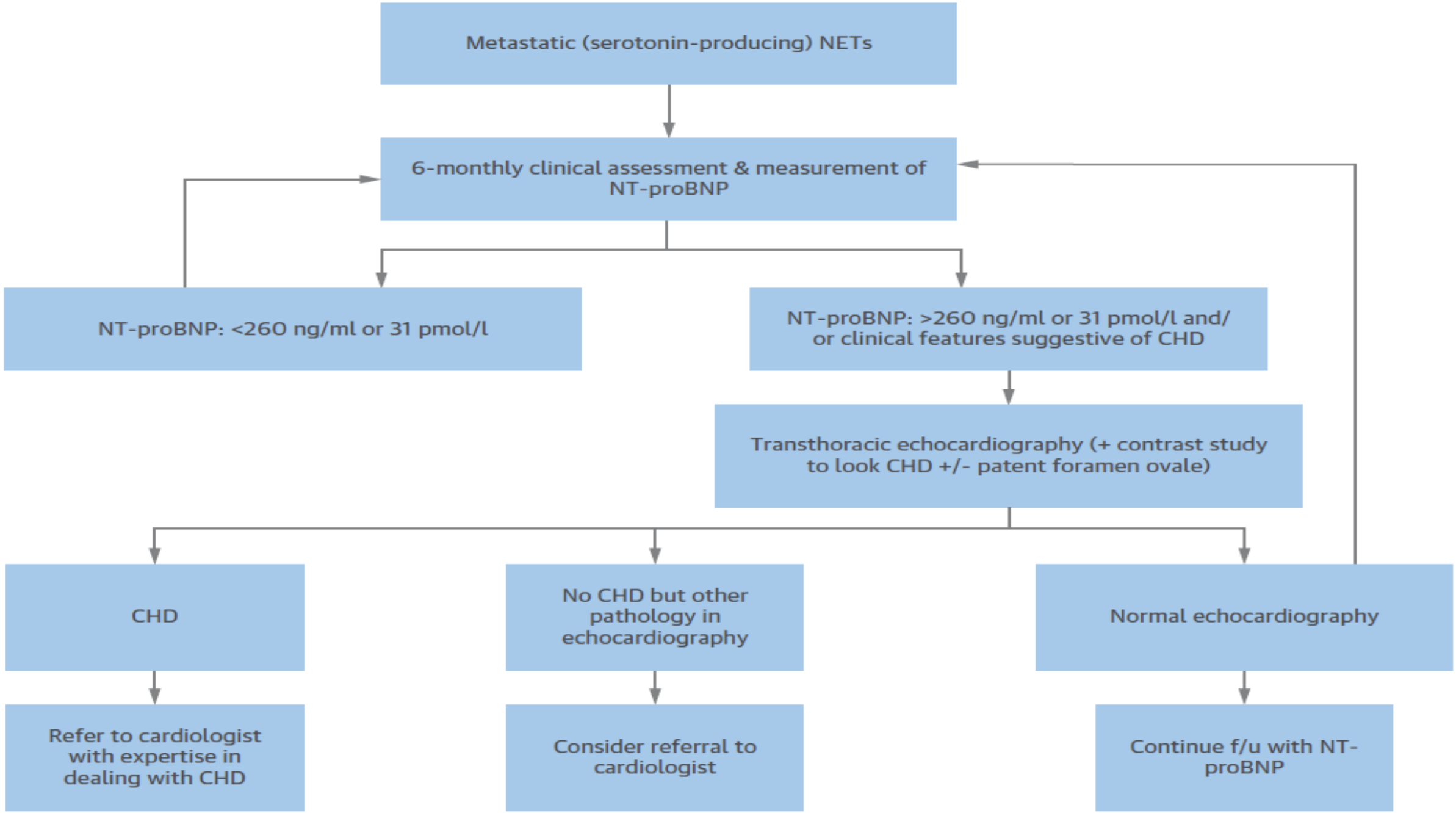
Estudio cardiaco

Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors

An Expert Statement

Joseph Davar, MD, PhD,[a] Heidi M. Connolly, MD,[b] Martyn E. Caplin, BSc Hons, DM,[c] Marianne Pavel, MD,[d] Jerome Zacks, MD,[e] Sanjeev Bhattacharyya, MBChB, MD,[f] Daniel J. Cuthbertson, BSc Hons, PhD,[g] Rebecca Dobson, MBChB Hons,[h] Simona Grozinsky-Glasberg, MD,[i] Richard P. Steeds, MA, MD,[j] Giles Dreyfus, MD,[k] Patricia A. Pellikka, MD,[b] Christos Toumpanakis, MD, PhD[c]

JACC VOL. 69, NO. 10, 2017
MARCH 14, 2017:1288–304


Metastatic (serotonin-producing) NETs
6-monthly clinical assessment & measurement of NT-proBNP
NT-proBNP: <260 ng/ml or 31 pmol/l
NT-proBNP: >260 ng/ml or 31 pmol/l and/ or clinical features suggestive of CHD
Transthoracic echocardiography (+ contrast study to look CHD +/- patent foramen ovale)
CHD
No CHD but other pathology in echocardiography
Normal echocardiography
Refer to cardiologist with expertise in dealing with CHD
Consider referral to cardiologist
Continue f/u with NT-proBNP

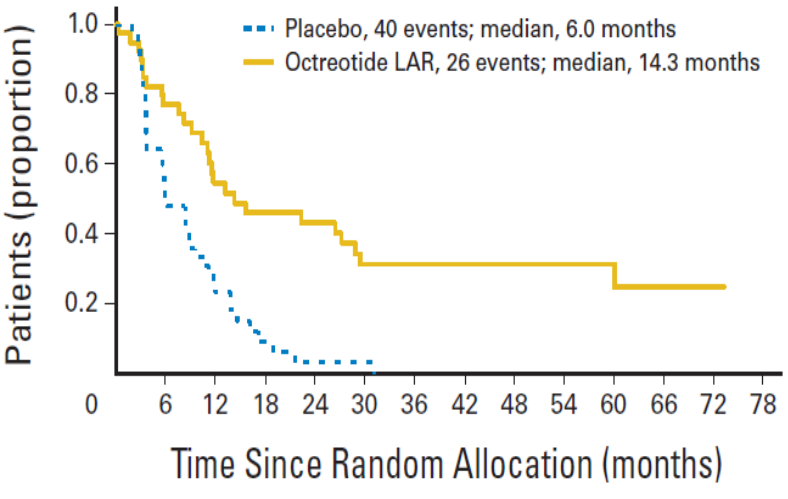
- NNE G1 OD MTS hepáticas irresecables.
- S carcinoide
- 5HIAA 53
- IT leve
- No MEN
- Octreoscan positivo
- Complemento nutricional

Tratamiento: opciones

1. Análogos de somatostatina
2. Everolimus
3. Análogos de somatostatina+ everolimus
3. Embolización hepática
4. Lutecio
5. Transplante hepático

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold



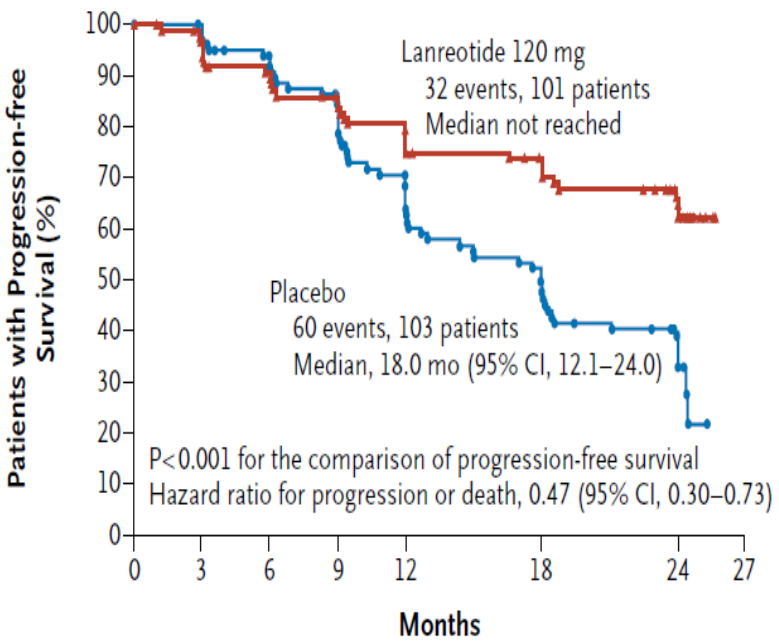
		Per-Protocol Analysis			
		Median Time to Progression or Tumor-Related Death (months)			
Factor	No. of Patients	Octreotide LAR	Placebo	HR	95% CI
Carcinoid syndrome	33	14.3	5.5	0.23	0.09 to 0.57
Inactive tumor	52	28.8	5.9	0.25	0.10 to 0.59
Liver involvement					
0%	12	13.1	8.2	0.55	0.10 to 3.09
0%-10%	52	29.4	6.1	0.17	0.08 to 0.40
10%-50%	14	11.2	5.5	0.40	0.10 to 1.67
> 50%	7	4.6	2.8	0.71	0.11 to 4.45

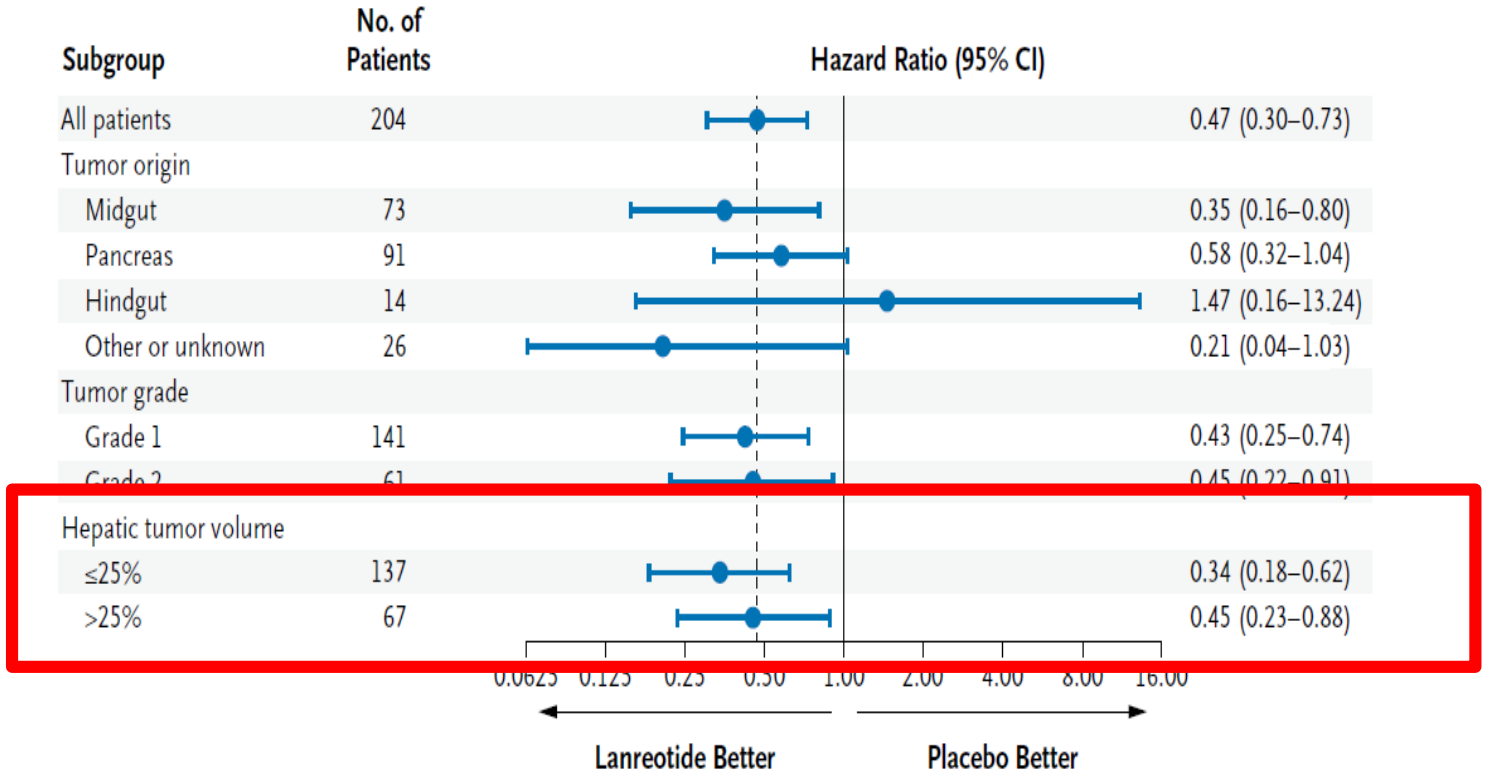
SLP

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

N ENGL J MED 371;3 NEJM.ORG JULY 17, 2014





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SUBMIT

CALCULATOR

Ki67%	1
Neutrophil-to-lymphocyte ratio (NLR)	1
Primary tumor location	Unknown
Hepatic burden disease	>50%
Peritoneal metastases	Yes / **No**
Bone metastases	Yes / **No**
Alkaline phosphatase	Normal

Documented progression status prior to SSA

Stable disease not documented, or <3 months

Symptoms from the tumor

Tumor or endocrine-related symptoms

CLEAR | CALCULATE

Median progression-free survival: **36.9 months**

12-month progression-free survival rate: **86.0%**

24-month progression-free survival rate: **66.0%**

Predictions are only orientative, and often approximate, so decisions should be taken at the discretion of the attending physician

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21/06/2019

1997

- Sandostatín sbc
- 1998 aumento de 5HIAA
- 1999 progresión hepática, empeoramiento del s carcinoide (ocasionalmente atípico con edema facial) con ocasionales síncopes y elevación confirmada de 5HIAA

1999

1. Análogos de somatostatina: aumento de dosis
2. Everolimus con análogos de somatostatina
3. Embolización hepática
4. Lutecio
5. Trasplante hepático
6. Quimioterapia

Interferón

Table 2. NETs IFN-α treatment

Response	Regular dose 3–6 MU × 3–7/w	High dose 24 MU/m^2 × 3/w
Subjective	53	32
Biochemical	49	39
Tumor	12	20

Interferón

- Respuesta clínica
- Respuesta bioquímica 40%
- Respuesta radiológica10%-EE 40-60%
- Duración de la respuesta 36 m
- Dosis 3-5MU x 3-5 días en semana
- Más toxicidad que análogos

Combinación

Author	No. pts	Arms	Results
			5-year-survey (%)
Kölby 2003	68	IFNα	36.6
	1991–98	OCT+IFNα	56.8
			HR 0.62 (CI 95% = 0.3–1.1)
			$P = 0.132$
			1-year PFS (%)
Faiss 2003	80	IFNα	44.4
	1995–98	LAN	44
		IFNα+LAN	50 $p = 0.69$
			Median survival (months)
Arnold 2005	109	OCT	35
	1995–98	OCT+IFNα	51
			HR 1.19 (CI 95% = 0.67–2.13)
			$P = 0.55$

Se añade IFN

- Intrón A 3MU L X V
- 1999 se cambia a Sandostatín lar 20 mg/28 días
- Enfermedad estable
- 2002 progresión hepática

2002

- Análogos de somatostatina: aumento de dosis
- Everolimus con análogos de somatostatina
- Embolización hepática
- Lutecio
- Trasplante hepático
- Quimioterapia

2002

- Se sube Sandostatín a 30mg cada 28 días e IFN a 4,5 MU LXV

Efectos secundarios de IFN

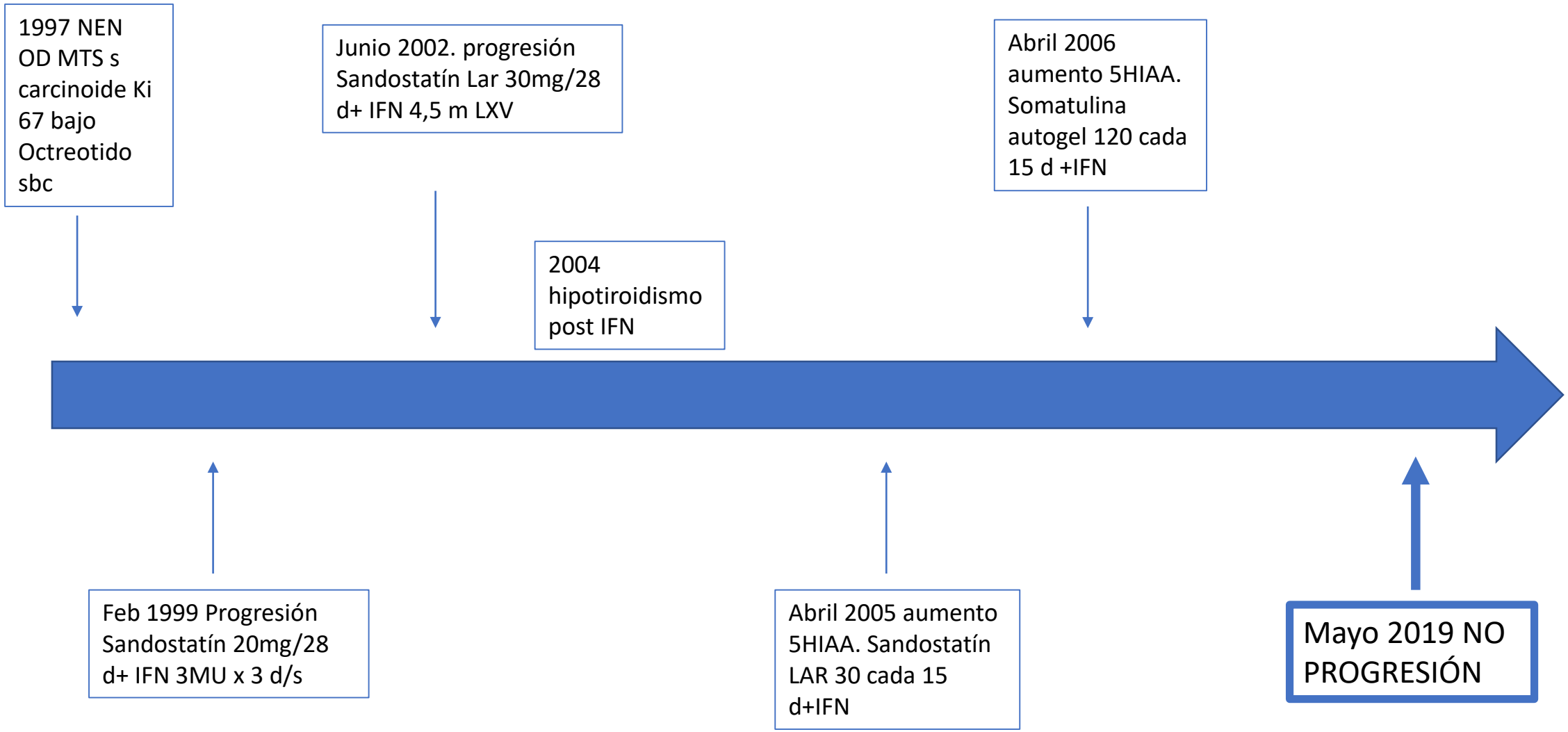
- Astenia
- Toxicidad hepática
- Depresión
- Fiebre…

Hipotiroidismo post IFN

- Acs antitiroideos

Table 3. Potential Mechanisms for the Development of IIT

Immune Mediated Effects of IFN-α
Enhanced expression of Class I MHC antigens on thyrocytes
Activation of cytotoxic T cells
Enhanced expression of cellular adhesion molecules (ICAM, B7.1)
Increased activity of lymphocytes, macrophages, NK cells, neutrophils, monocytes
Increased activity of IL-6
Modulation of immunoglobulin production
Inhibition of T regulatory cells
Th1 polarization
Direct Effects of IFN-α on the Thyroid
Inhibition of TSH-induced gene expression of Tg, TPO, and NIS
Decreased iodine organification
Decreased thyroxine (T4) release


1997 NEN OD MTS s carcinoide Ki 67 bajo Octreotido sbc
Junio 2002. progresión Sandostatín Lar 30mg/28 d+ IFN 4,5 m LXV
2004 hipotiroidismo post IFN
Abril 2006 aumento 5HIAA. Somatulina autogel 120 cada 15 d +IFN
Feb 1999 Progresión Sandostatín 20mg/28 d+ IFN 3MU x 3 d/s
Abril 2005 aumento 5HIAA. Sandostatín LAR 30 cada 15 d+IFN
Mayo 2019 NO PROGRESIÓN

Si progresión

1. Everolimus
2. Lutecio
3. Embolización

Conclusiones

- El volumen tumoral no limita el uso de análogos exclusivos pero hay que estar muy pendiente de la progresión
- Algunas NNE de evolución muy lenta
- En este tiempo (22 años) no deterioro cardiaco, no clínica abdominal. S carcinoide controlado
- Cuál es el mejor seguimiento???

Otro caso

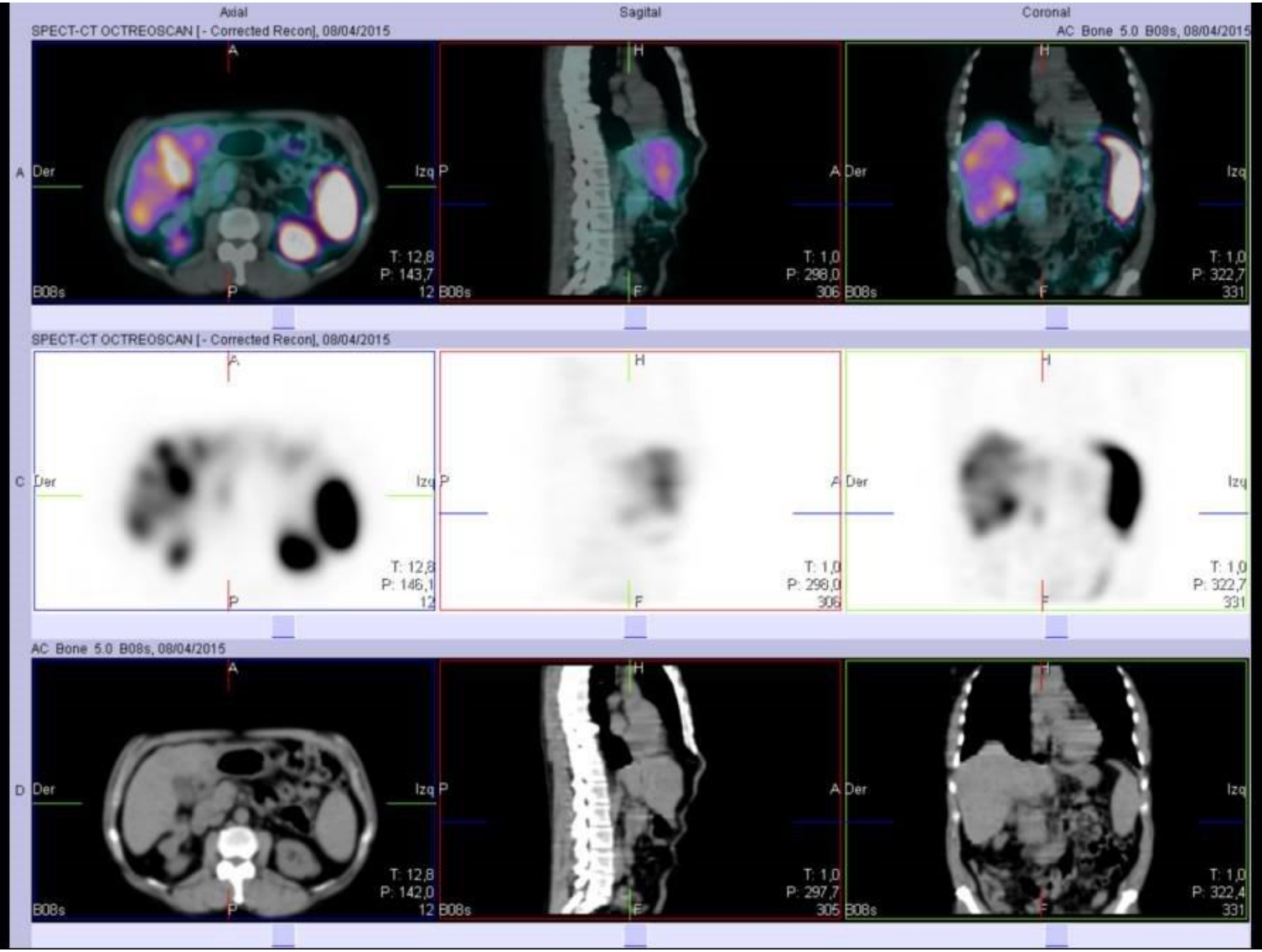
- Varón de 67 años
- Hipertrofia benigna de próstata
- EPOC
- HTA
- hiperuricemia

Historia oncológica

- Finales 2014 astenia, anorexia,pérdida de 15 Kgs
- Sofocos, diarrea 7-8 deposiciones/d
- M de familia: no importante
- Control HBP eco abdominal múltiples MTS hepáticas

RNM Marzo 2015

Octreoscan


Axial
Sagital
Coronal
SPECT-CT OCTREOSCAN [- Corrected Recon], 08/04/2015
AC Bone 5.0 B08s, 08/04/2015
Der
Izq
B08s
SPECT-CT OCTREOSCAN [- Corrected Recon], 08/04/2015
AC Bone 5.0 B08s, 08/04/2015

AP

- NNE G2
- Ki 67 15%
- 2M/10CGA
- Cromogranina y Sinaptofisina +
- CDX 2 +

- 5HIAA 46
- Plaquetas 86000
- Palc normal
- CGA 848
- Sandostatín lar 30 cada 28 días en Abril 2015
- Cardiología
- Nutrición
- Mejoría del s carcinoide

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SUBMIT

CALCULATOR

Ki67%	15
Neutrophil-to-lymphocyte ratio (NLR)	4
Primary tumor location	Small intestine
Hepatic burden disease	>50%
Peritoneal metastases	Yes / **No**
Bone metastases	**Yes** / No
Alkaline phosphatase	Normal

Documented progression status prior to SSA

Stable disease not documented, or <3 months

Symptoms from the tumor

Tumor or endocrine-related symptoms

CLEAR | CALCULATE

Median progression-free survival: **11.4 months**

12-month progression-free survival rate: **47.9%**

24-month progression-free survival rate: **23.6%**

Predictions are only orientative, and often approximate, so decisions should be taken at the discretion of the attending physician

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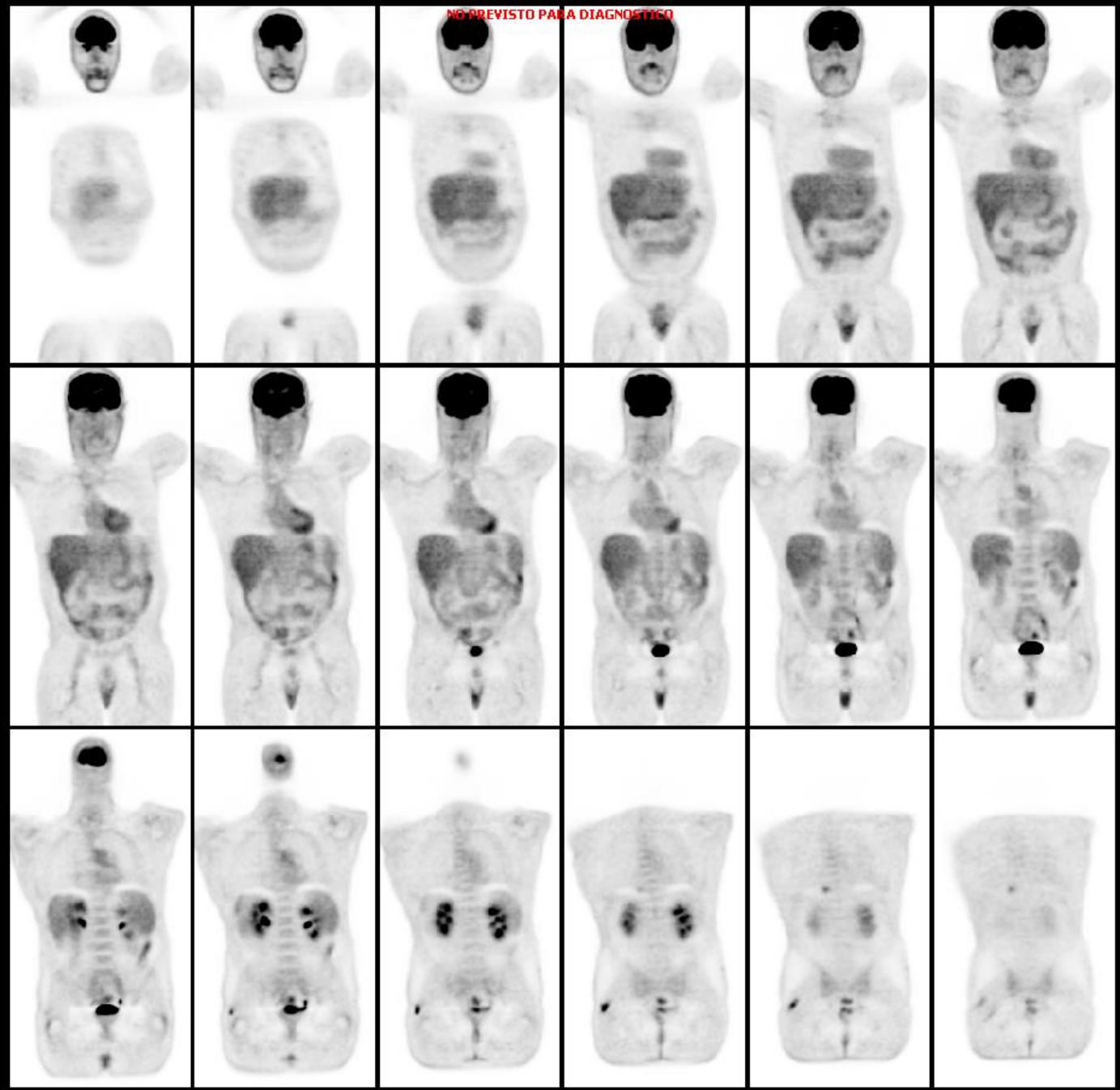
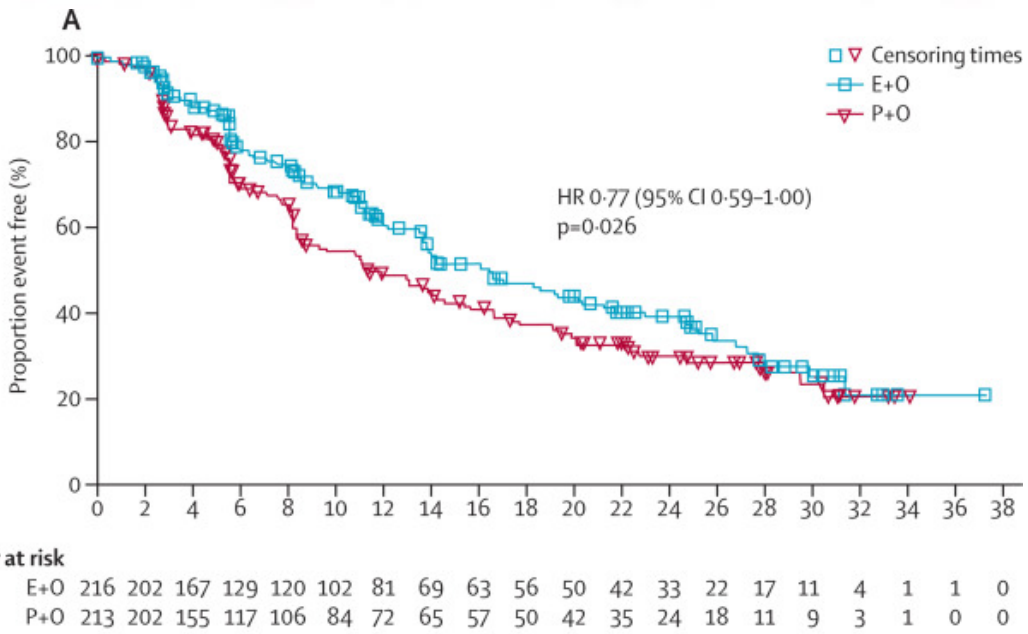
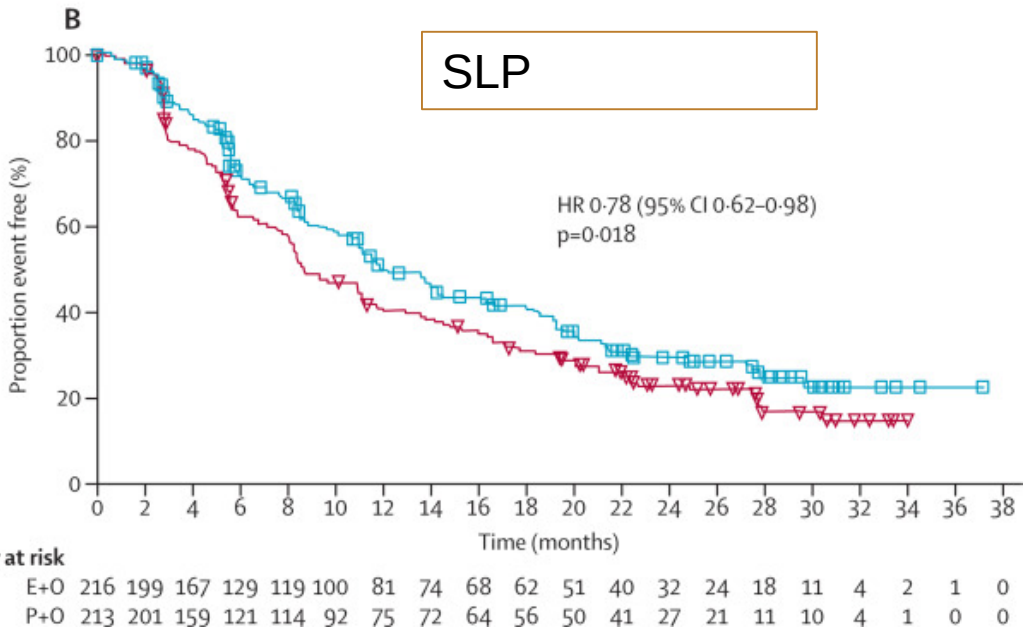
21/06/2019

- Agosto 2015 progresión. 5HIAA 128
- CGA 2470: everolimus
- PET FDG negativo
- En pacientes con Ki67 G2 y st si evolución rápida.

NO PREVISTO PARA DIAGNOSTICO



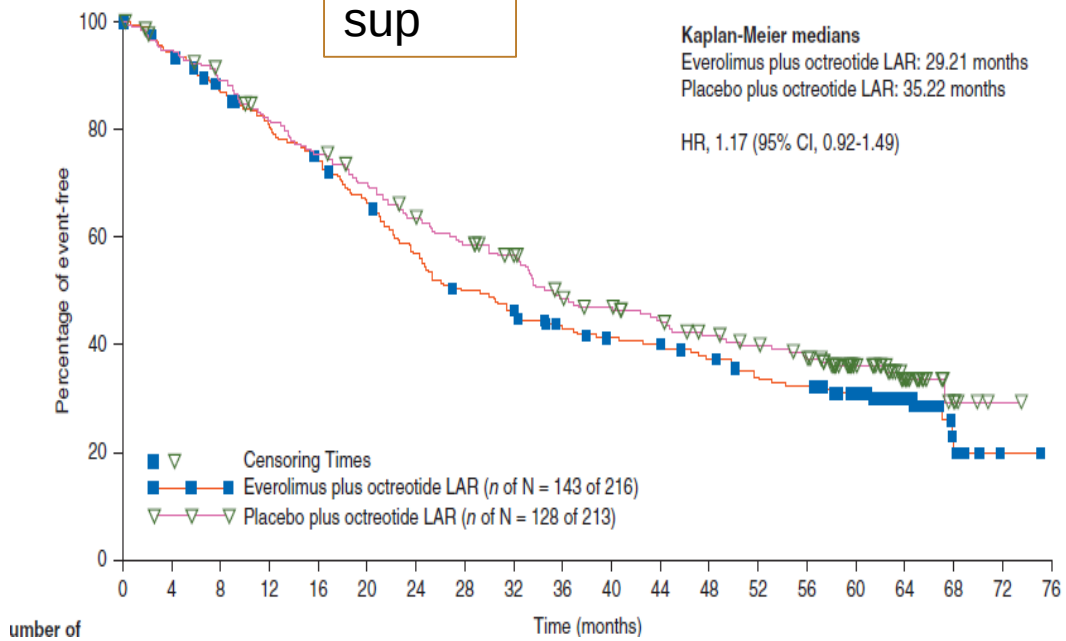




SLP

Radiant 2
2011
2017

sup



Toxicidad

- Trombopenia G2
- Diarrea g1
- Mucositis G2
- Neumonitis G1

Feb 2016

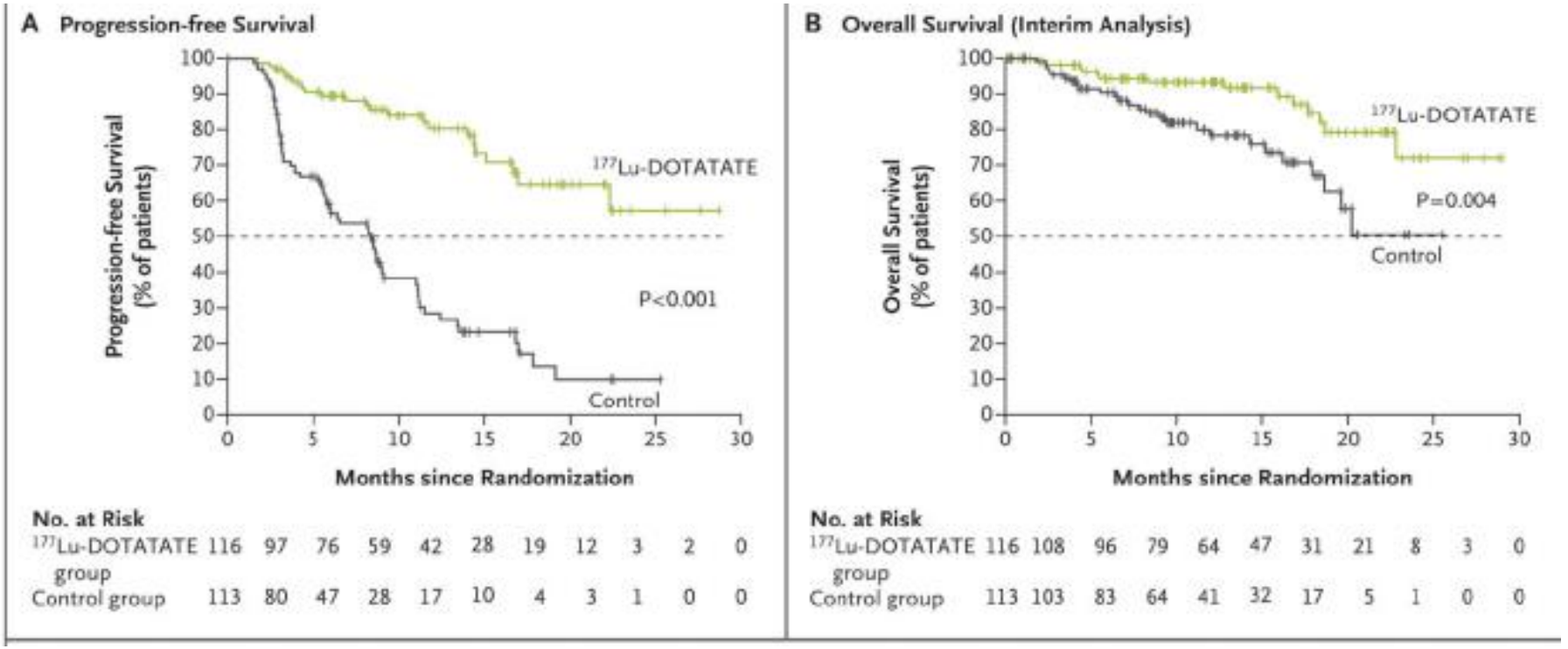
- Progresión hepática y ósea con dolor
- CGA 3410
- 5HIAA 167

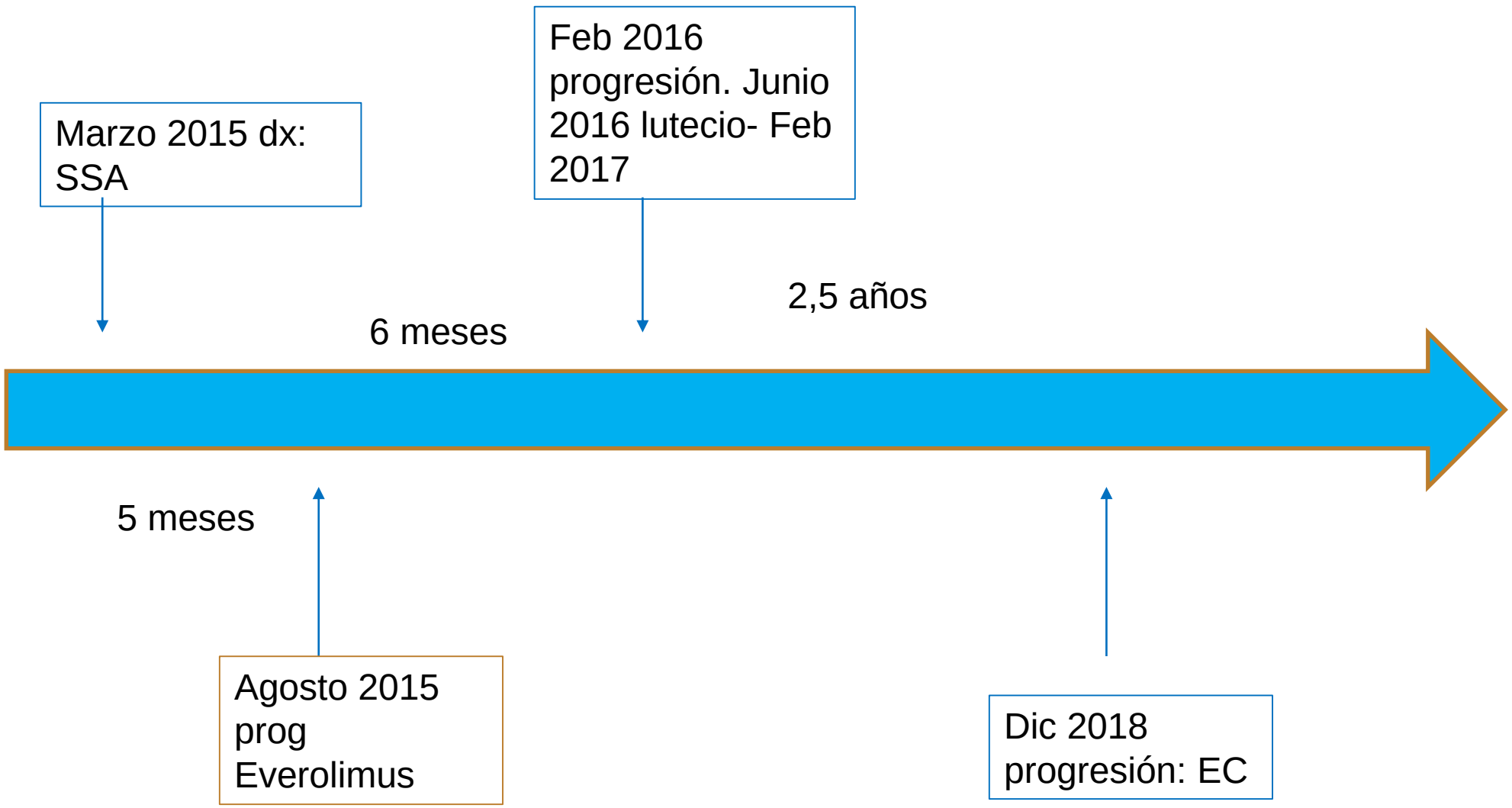
- Junio 2016 a feb 2017 tratamiento con Lutecio
- Mejoría clínica y an. Sin toxicidad
- Enero 2019 progresión: ensayo clínico DUNE

N Engl J Med. 2017 January 12; 376(2): 125–135. doi:10.1056/NEJMoa1607427.

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, E. Krenning, and **for the NETTER-1 Trial Investigators***




Marzo 2015 dx: SSA
Feb 2016 progresión. Junio 2016 lutecio- Feb 2017
6 meses
2,5 años
5 meses
Agosto 2015 prog Everolimus
Dic 2018 progresión: EC