GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

Castilla-La Mancha

"JORNADA SEGURIDAD DEL PACIENTE EN EL USO DE LAS RADIACIONES IONIZANTES"

FECHA: 19 de abril de 2018.

17.00 h. **MESA DE DEBATE IV. DOSIMETRÍA INDIVIDUALIZADA EN PROCEDIMIENTOS TERAPÉUTICOS DE MEDICINA NUCLEAR**

Modera: Juan Antonio Vallejo Casas. Director UGC / Jefe de Servicio de Medicina Nuclear. Hospital Universitario Reina Sofía. Córdoba. Medicina Nuclear Hospital Reina Sofía.

Merche Mitjavila
H.U. Puerta de Hierro Majadahonda

DIRECTIVA 2013/59/EURATOM DEL CONSEJO

de 5 de diciembre de 2013

por la que se establecen normas de seguridad básicas para la protección contra los peligros derivados de la exposición a radiaciones ionizantes, y se derogan las Directivas 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom y 2003/122/Euratom

Artículo 1

Objeto

La presente Directiva establece normas básicas de seguridad uniformes aplicables a la protección de la salud de las personas sometidas a exposición ocupacional, médica y poblacional frente a los riesgos derivados de las radiaciones ionizantes.

Cuantas causas de muerte y/o efectos secundarios severos descritos por ttº radiometabólico???

CAPÍTULO II

DEFINICIONES

Artículo 4

Definiciones

81) «Radioterapéutico»: relativo a la radioterapia, incluida la medicina nuclear con fines terapéuticos.

En todo el texto se considera lo mismo la radioterapia externa y la terapia metabólica, teniendo ambas bases y aplicaciones diferentes:

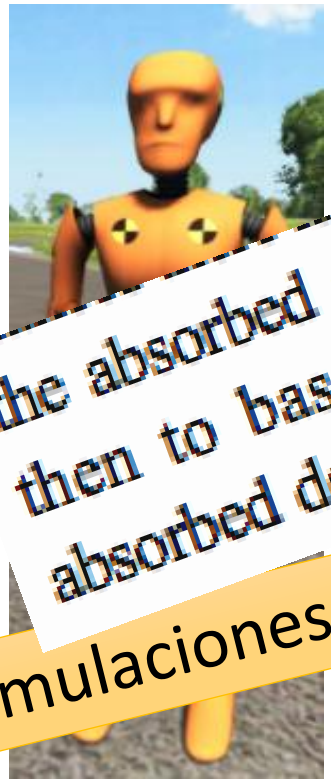
- La radioterapia se usa para campo localizado, “fácil” cálculo volumen, la terapia metabólica en enfermedad “sistémica” con volumen “blanco” incalculable.
- Sabemos actividad, pero no la biodistribución ni dosis exacta que llega.
- Efecto terapéutico: SLP, SG…

CAPÍTULO VII

EXPOSICIONES MÉDICAS

Artículo 55

Justificación



simulaciones

Artículo 56

Optimización

1. Los Estados miembros velarán por que [illegible] debidas a exposiciones médicas con fin[illegible] lógico, radiología intervencion[illegible] ción se mantengan [illegible] ble, para [illegible] [illegible]

[illegible]dicas de pacientes con fines ra- [illegible]posiciones del volumen blanco se planifi- [illegible]adamente y se verificará convenientemente su re- [illegible]ación, teniendo en cuenta que las dosis de los volúmenes y tejidos fuera del blanco deberán ser lo más bajas que sea razonablemente posible y estarán de acuerdo con el fin radioterapéutico deseado de la exposición.

the absorbed dose to target tissues. The next best alternative is then to base therapy planning on the maximum tolerable absorbed dose (MTAD) to nontarget organs or tissues.

Radioterapia

Radioterapia externa:

Radioterapia interna:

la radiación procede de implantes o líquidos colocados dentro del cuerpo.

Hospital Universitario
Puerta de Hierro Majadahonda

SALÓN DE ACTOS

RADIOFÍSICA DE LA DOSIMETRÍA INTERNA EN LOS PROCEDIMIENTOS TERAPÉUTICOS CON RADIOFÁRMACOS

(Bq ≠ Gy)

COORDINACIÓN DE LA JORNADA

- Dr. Luis Núñez, Servicio de Radofísica y Protección Radiológica. Hospital Universitario Puerta de Hierro Majadahonda.
- Dra. Raquel Barquero, Servicio de Radiofísica y Protección Radiológica del Hospital Clínico de Valladolid.

Objetivo de la Jornada:

Preparación para el *cumplimiento en 2018*
de la Directiva Europea EURATOM 2013/59

Rev Esp Med Nucl Imagen Mol. 2017;**36(3)**:137–138

F.J. de Haro del Moral[a,*] y R. Barquero[b]
[a] *Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, España*
[b] *Hospital Clínico Universitario de Valladolid, Valladolid, España*

Editorial

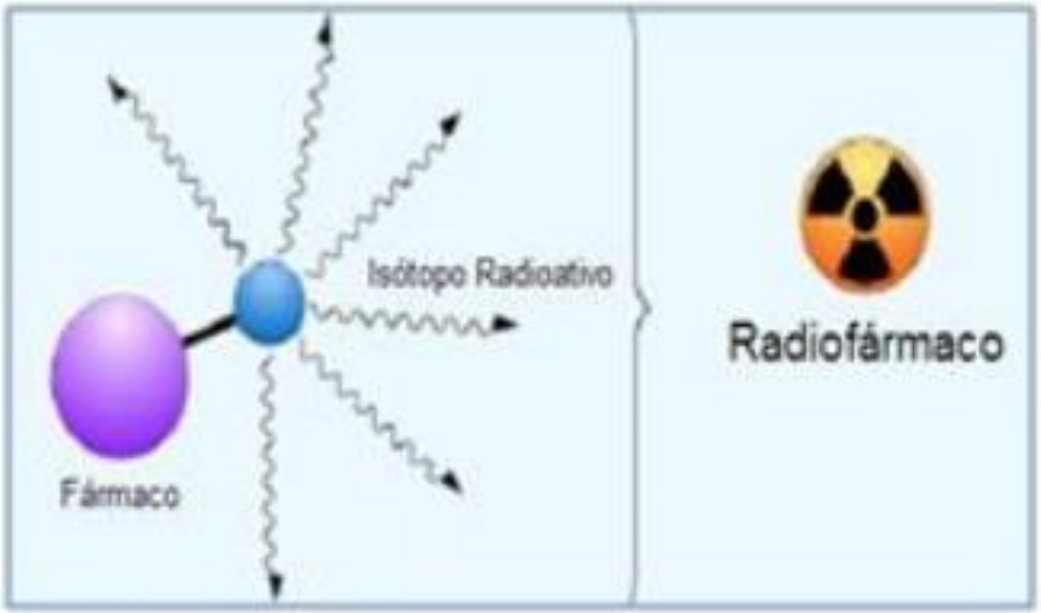
La directiva ya está aquí. ¿Estamos preparados?

Sí, la directiva europea 2013/59/EURATOM[1] ya está aquí. El próximo 6 de febrero del 2018 debe estar transpuesta a la legislación española. Pero ¿la conocemos?

DIRECTIVA 2013/59/EURATOM DEL CONSEJO

de 5 de diciembre de 2013

por la que se establecen normas de seguridad básicas para la protección contra los peligros derivados de la exposición a radiaciones ionizantes, y se derogan las Directivas 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom y 2003/122/Euratom



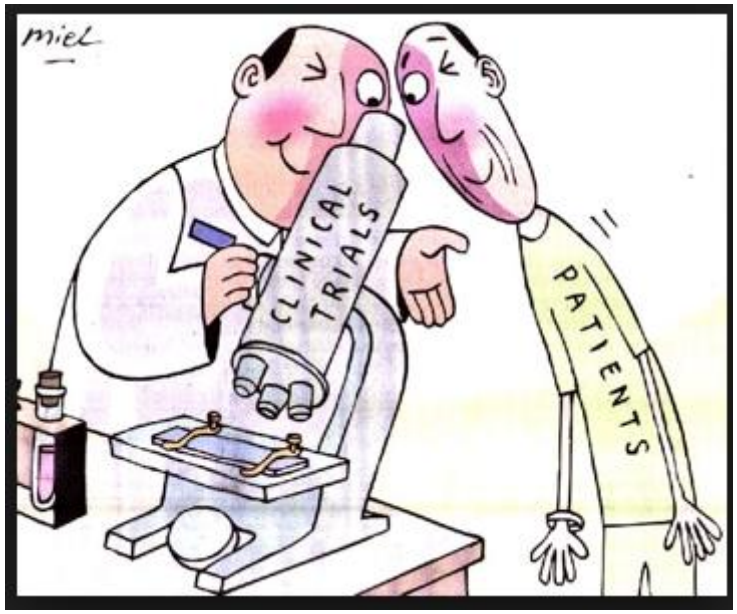
REAL DECRETO 479/1993, DE 2 ABRIL. REGULA LOS MEDICAMENTOS RADIOFÁRMACOS DE USO HUMANO
(BOE núm. 109, de 7 mayo)

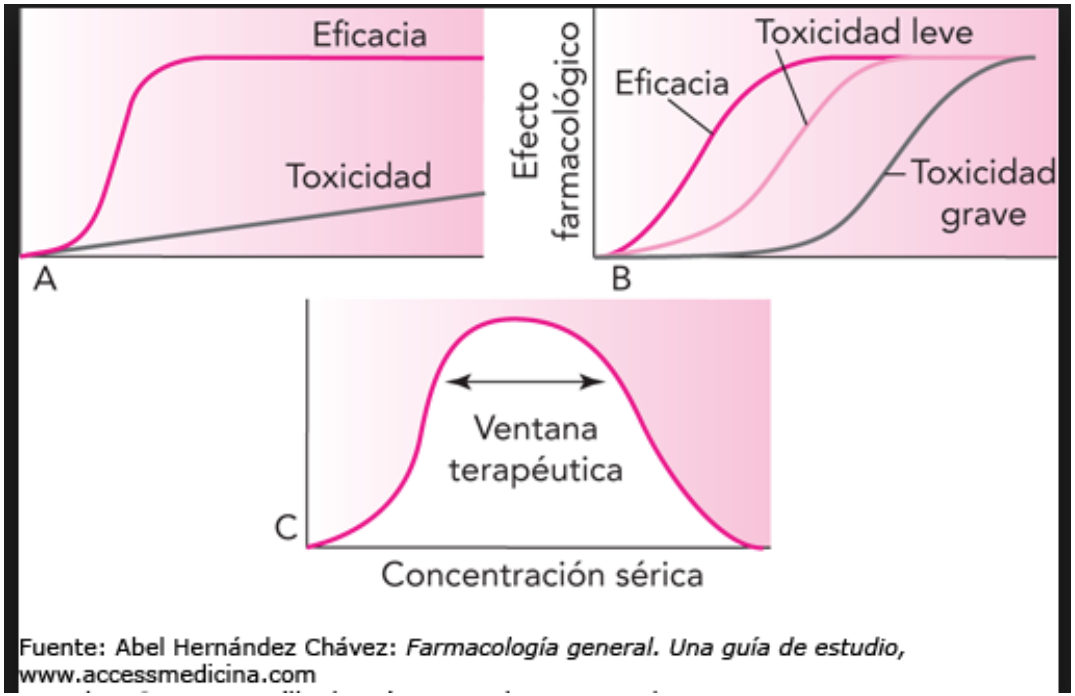
Los radiofármacos son medicamentos que han adquirido gran importancia en la práctica clínica por su aplicación con finalidades tanto terapéuticas como diagnósticas.

¿Qué aseguran las Agencias Reguladoras?

- CALIDAD
- EFICACIA
- SEGURIDAD

biodistribución / farmacocinética





Fuente: Abel Hernández Chávez: *Farmacología general. Una guía de estudio*, www.accessmedicina.com

Radionuclide Therapy

EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds (2011)

EANM procedure guidelines for therapy of benign thyroid disease (2010)

EANM procedure guidelines for ^{131}I-meta-iodobenzylguanidine (^{131}I-mIBG) therapy (2008)

EANM procedure guideline for treatment of refractory metastatic bone pain (2008)

Guidelines for radioiodine therapy of differentiated thyroid cancer (2008)

EANM procedure guideline for ^{32}P phosphate treatment of myeloproliferative diseases (2007)

EANM procedure guideline for radio-immunotherapy for B-cell lymphoma with 90Y-radiolabelled ibritumomab tiuxetan (Zevalin) (2006)

EANM Procedure Guidelines for Radiosynovectomy (2002)

Guidelines for ^{131}I – ethiodised oil [Lipiodol] Therapy (2002)

Dosimetry for Therapy procedures
^{131}I NaI for the treatment of benign thyroid disease
^{131}I NaI for the treatment of differentiated thyroid cancer (DTC) with ablative intent and in the case of recurrent disease
^{131}I mIBG for the treatment of neuroblastoma in children and young people adults
^{131}I mIBG for the treatment of neuroendocrine tumours in adults
^{177}Lu-DOTATATE for the treatment of neuroendocrine tumours
^{90}Y somatostatin analogues for the treatment of neuroendocrine tumours
Beta emitters for bone pain palliation
^{223}Ra dichloride for the treatment of bone metastases from castration resistant prostate cancer
^{177}Lu-PSMA ligands for the treatment of metastatic castration-resistant prostate cancer
^{90}Y microspheres for the treatment of primary and metastatic liver cancer
^{90}Y-ibritumomab tiuxetan for radioimmunotherapy of non-Hodgkin lymphoma
Radiosynovectomy

Internal Dosimetry Task Force Report on:

Treatment Planning For Molecular Radiotherapy: Potential And Prospects

European Association of Nuclear Medicine

SURVEY ON THE IMPLEMENTATION OF THERAPY AND DOSIMETRY PROCEDURES IN EUROPE

To date there has been little investigation of the extent and implementation of MRT and dosimetry throughout Europe for either clinical routine or research. A survey was therefore conducted between June 2016 and September 2016 to obtain an initial overview of current practices. The primary route of dissemination was via European Association of Nuclear Medicine (EANM) national delegates although it was also distributed via national networks for medical physicists and nuclear medicine.

Realizados 2015
26 países, 208
Pacientes 34.838
Procedimientos 42.853

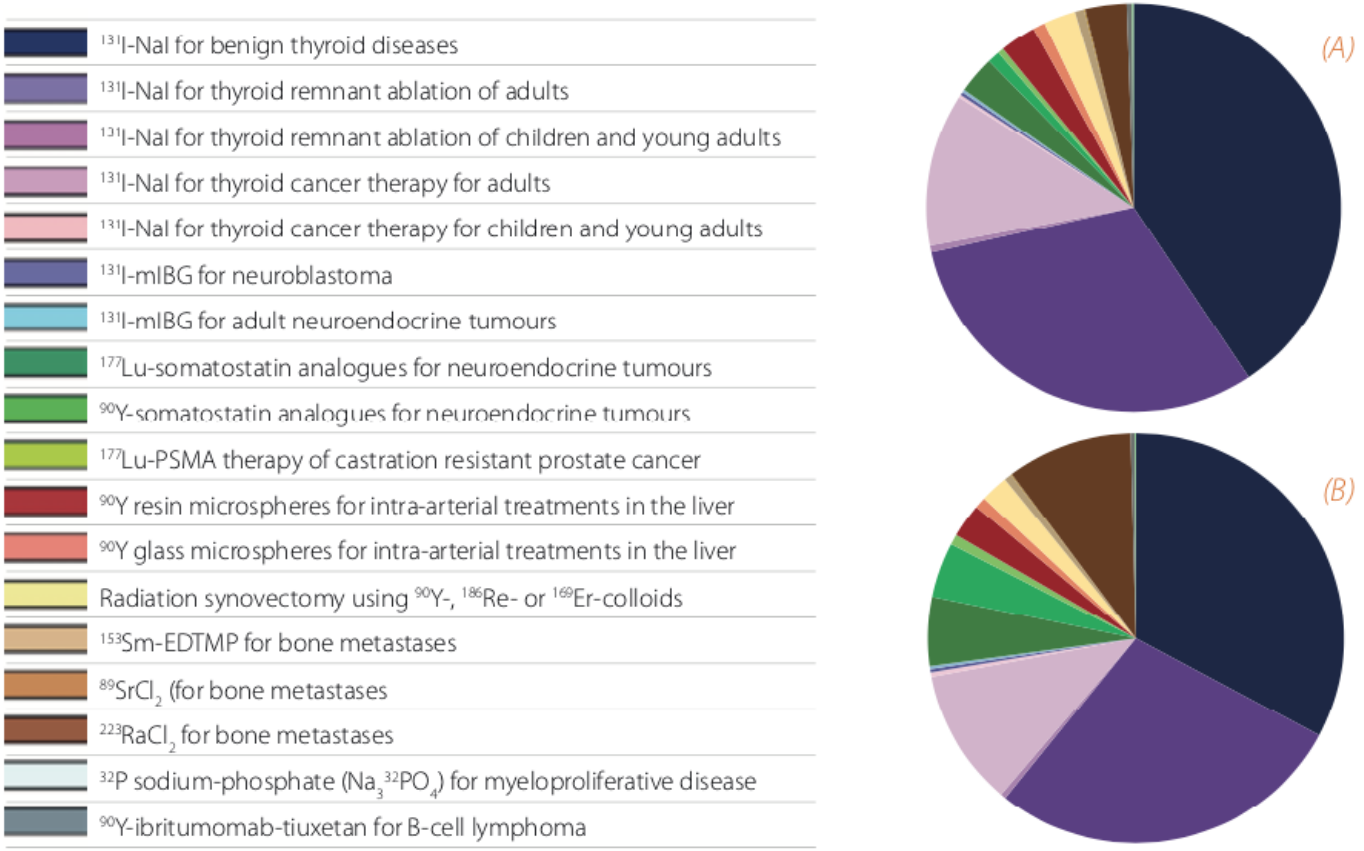


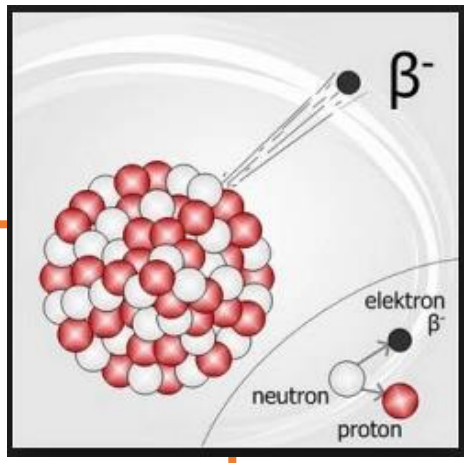
Figure 1. *The proportion of (A) the total number of treated patients, (B) the total number of administered therapies that comprised the different kinds of therapies*

ABSORBED-DOSE PLANNING

The absorbed dose was reported to be individually planned for each patient either always or in the majority of treatments in only 36% of cases. In 63% of cases, absorbed dose planning was never carried out, or carried out in a minority of treatments. The highest number of responses were obtained for ^{90}Y-labeled microspheres, 82% (resin) and 84% (glass), and for ^{131}I-NaI for benign thyroid diseases (54%).

POST-THERAPY DOSIMETRY

Post-therapy dosimetry was performed always or in the majority of treatments in only 26% of the cases. More than 50% of the centres indicated that post-therapy dosimetry was performed always or in the majority of cases for ^{177}Lu PSMA (100%) and ^{131}I mIBG for neuroblastoma (59%). For PRRT with ^{90}Y or ^{177}Lu and ^{131}I mIBG for adult neuroendocrine tumours this percentage was approximately 40%.



Terapia metabólica:

-benigna: hipertiroidismo: 131I
sinoviortesis: 90Y, 186Re

-maligna:

- CDT: 131I
- 131-I-MIBG
- PRRT: 177Lu, 90Y
- SIRT: 90Y
- Metástasis óseas: β (153Sm, 89Sr)
- 90Y-ibritumomab-tiuxetam

Dosimetry in clinical radionuclide therapy: the devil is in the detail

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3820-3

Francesco Giammarile[1,2] · Kristoff Muylle[1,3] · Roberto Delgado Bolton[1,4] · Jolanta Kunikowska[1,5] · Uwe Haberkorn[6,7,8] · Wim Oyen[1,9]

Radionuclide therapy (RNT), also known as "targeted", "metabolic" or "molecular" radiotherapy, uses open (i.e. "unsealed") radioactive isotopes, and is generally administered orally or intravenously, enabling delivery of a high radiation dose to the target, while minimizing toxicity to normal tissues. This systemic form of radiation therapy has distinct similarities to, but also profound differences from, the more commonly used external beam radiotherapy (EBRT). From another perspective, RNT can be better characterized as a tumour-selective treatment modality with more similarities to systemic chemotherapy [1].

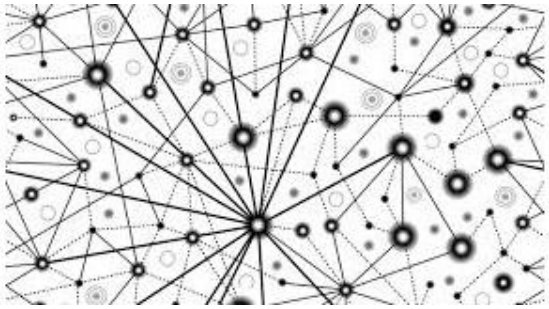
While CT can be used for relatively straightforward calculation of the absorbed dose in EBRT, in RNT the spatial and temporal distribution of radiation during the decay time of the isotope is extremely complex, depending on a highly dynamic interplay of pharmacokinetics aspects (such as perfusion, metabolism, target expression heterogeneity, transmembrane cellular uptake, intracellular degradation, radionuclide release, and excretion), repair mechanisms, and radiobiological phenomena (low and continuously decreasing dose rate).

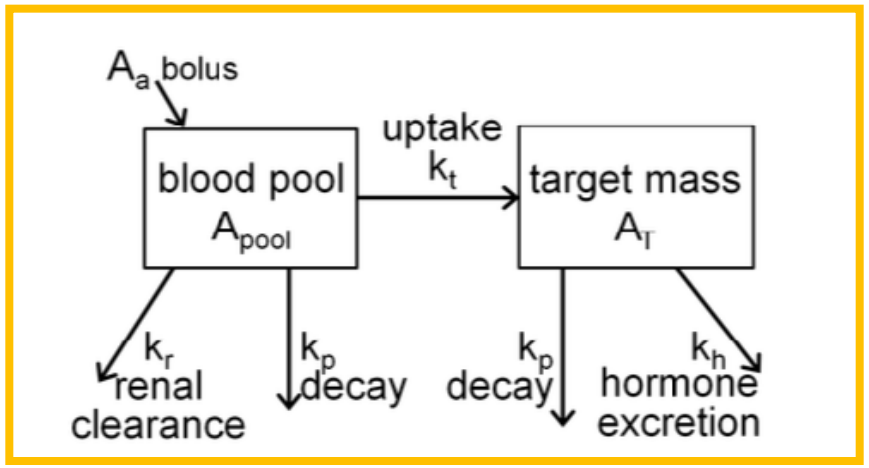
For these reasons, rather than seeking [illegible]
it is more appropriate to devel[illegible]
chemotherapeutics[illegible]
weight or [illegible]dependent
[illegible]aximum tolerated
[illegible]olished during clinical stud-
[illegible]ical practice, the level of chemothera-
[illegible]lood is not checked to investigate the
[illegible]distribution and delivery to the tumours.

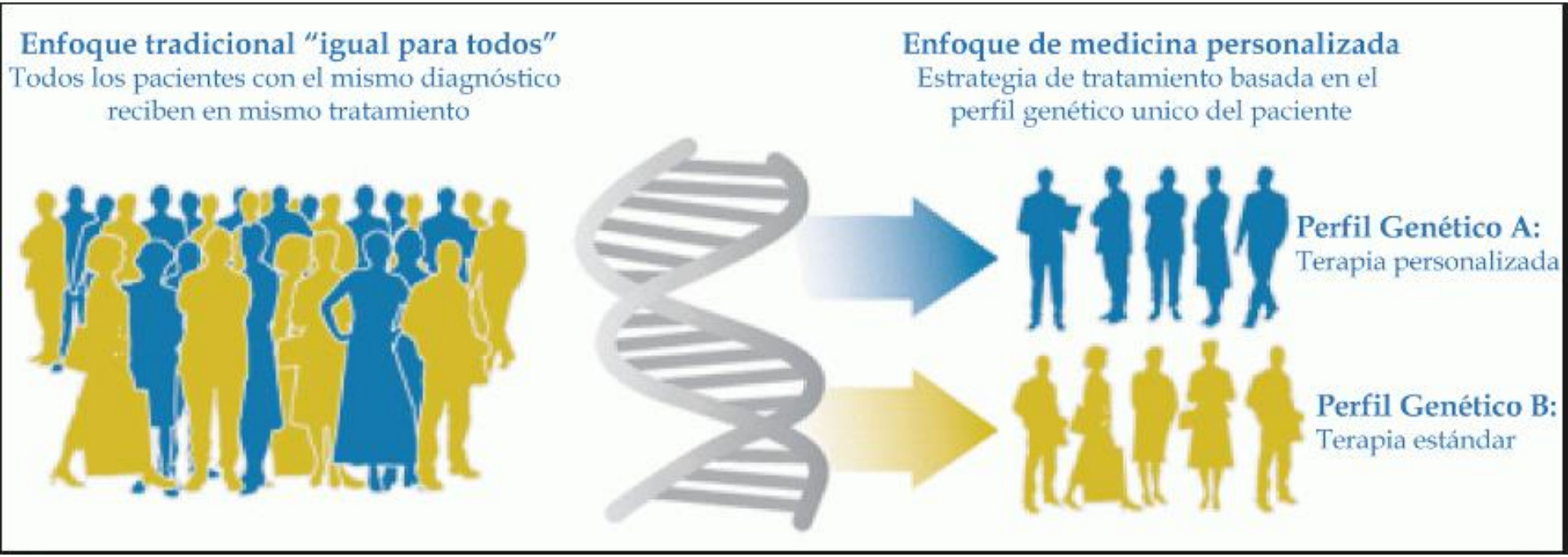
the absorbed dose to target tissues. The next best alternative is then to base therapy planning on the maximum tolerable absorbed dose (MTAD) to nontarget organs or tissues.

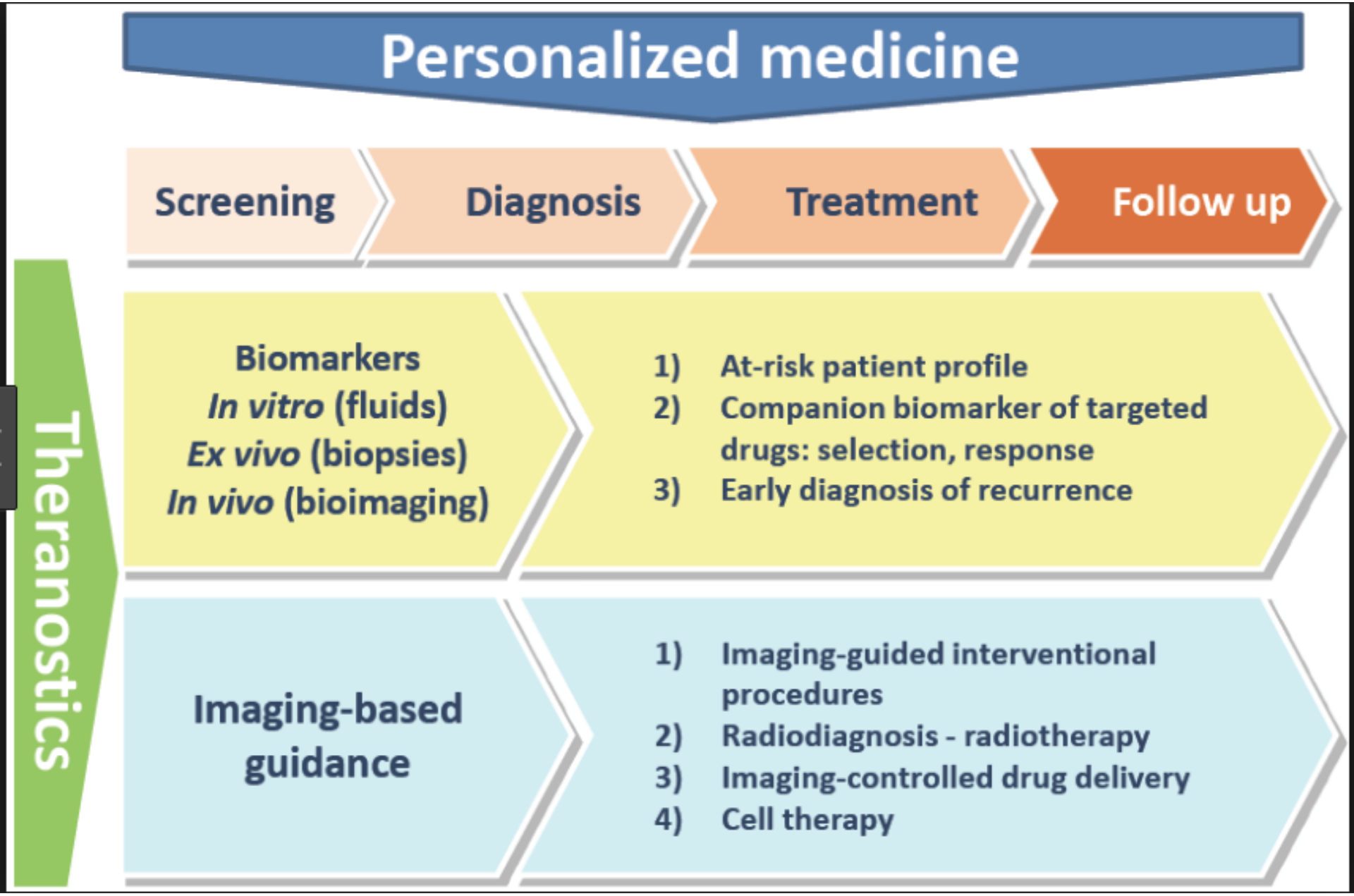
Factores que influyen en la terapia metabólica

- Actividad administrada
- Expresión del “target” en el tumor/ volúmen
- Heterogeneidad tumoral
- Farmacocinética
- Mecanismos de reparación
- …….





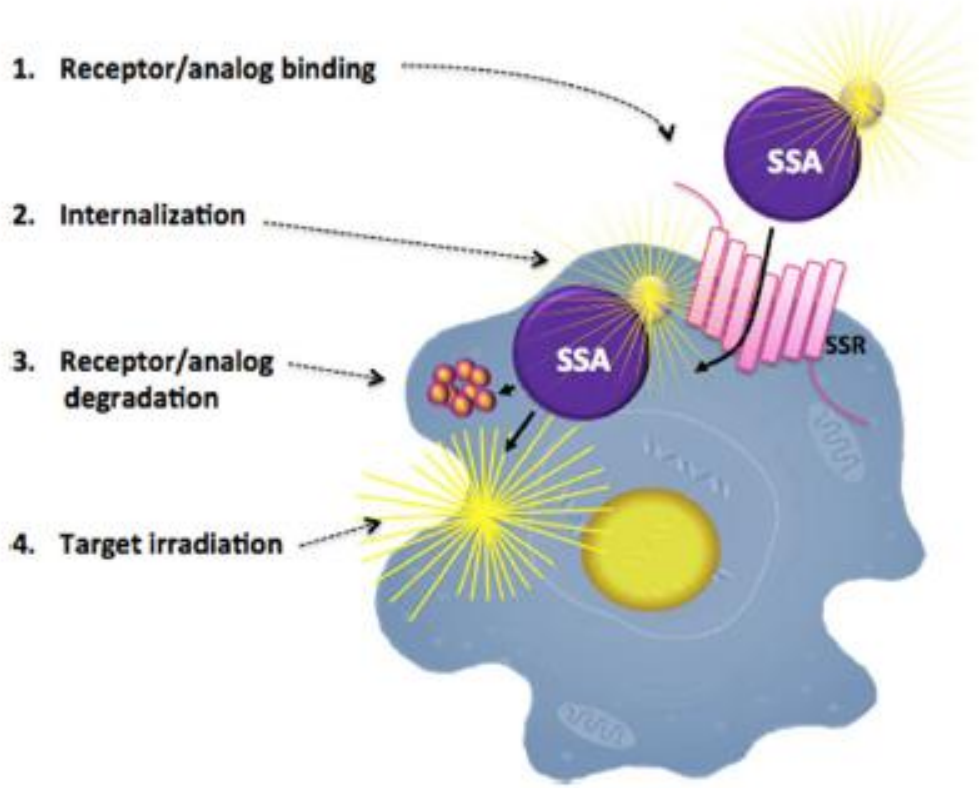

Enfoque tradicional "igual para todos"
Todos los pacientes con el mismo diagnóstico reciben en mismo tratamiento
Enfoque de medicina personalizada
Estrategia de tratamiento basada en el perfil genético unico del paciente
Perfil Genético A:
Terapia personalizada
Perfil Genético B:
Terapia estándar


Personalized medicine
Screening
Diagnosis
Treatment
Follow up
Theranostics
Biomarkers
In vitro (fluids)
Ex vivo (biopsies)
In vivo (bioimaging)
1) At-risk patient profile
2) Companion biomarker of targeted drugs: selection, response
3) Early diagnosis of recurrence
Imaging-based guidance
1) Imaging-guided interventional procedures
2) Radiodiagnosis - radiotherapy
3) Imaging-controlled drug delivery
4) Cell therapy

Diagnosis +Therapy = Theragnosis

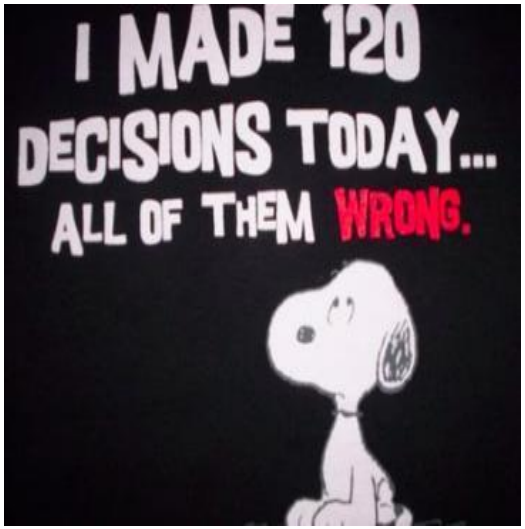
111-In
99mTc
68Ga

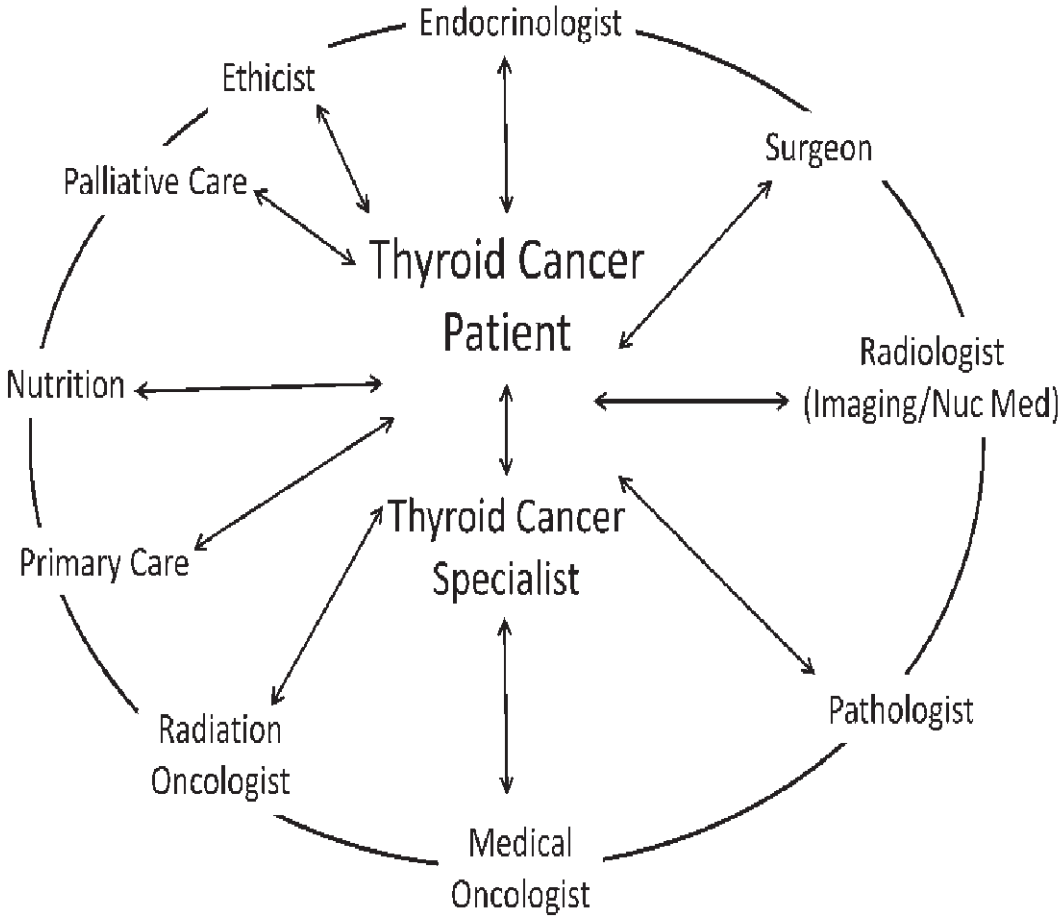
90Y
177Lu



Lisa Bodei

Semin Nucl Med 46:225-238





Uso de 131-I desde 1940

Radioiodine Therapy for Thyroid Cancer in the Era of Risk Stratification and Alternative Targeted Therapies

Daniel A. Pryma and Susan J. Mandel

J Nucl Med. 2014;55:1485-1491.

Objetivo	Beneficio	Dosis
Destrucción tejido tiroideo **normal** residual (**ablación**)	Aumentar la especificid… Tg sérica (facilit… seguimi…	…efectiva
Destruir focos **CDT ocul…** (**adyuvante**)		¿? Minimizar toxicd.
Destruir … **(Ttº)**	…ar SLP, SLE y SG	Máxima tolerada
Permitir la … de un RCT post 131-I con elevada sensibilidad	Detectar enfermedad locorregional (valoración cirugía) y a distancia	

Objetivo del tratamiento depende del riesgo del paciente

Curr Opin Endocrinol Diabetes Obes 2014, 21: 363

UpToDate®

- When the primary goal is to **ablate residual normal** thyroid tissue (remnant ablation), administered activities of **30 mCi** (1.1 GBq) are typically used. Higher doses may be necessary for patients who have had less than a total thyroidectomy where a larger remnant is suspected .

- When the primary goal is to provide **adjuvant therapy of subclinical micrometastatic** disease, administered activities of **75 to 150 mCi** are used, based on assessment of the individual's risk of having clinically significant microscopic residual disease.

- When the primary goal is to provide **treatment of clinically apparent** residual or metastatic thyroid cancer, administered activities of **100 to 200 mCi** are typically used.

Clin Thyroidol 2016;28:366–368.

Clinical THYROIDOLOGY®

RAI Dosimetry Does Not Improve Survival As Compared with Empiric Doses of ^{131}I for RAI-avid Metastatic Thyroid Cancer

Conclusions

For treatment of radioiodine-avid metastases, the use of whole-body/body-clearance radioiodine dosimetry did not provide any advantage in overall survival as compared with empiric fixed dosing of ^{131}I.

Clinical Oncology 29 (2017) 310–315

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Ten Year Experience of Radioiodine Dosimetry: is it Useful in the Management of Metastatic Differentiated Thyroid Cancer?

Aims: When a fixed activity of radioiodine is given for differentiated thyroid cancer (DTC), absorbed doses of radioiodine can vary widely and are not usually measured. Leeds Cancer Centre has routinely used a form of lesion-specific dosimetry for radioiodine patients. This study investigated if the results of dosimetry influenced treatment decisions for patients with advanced DTC.

Materials and methods: Since 2005, patients with regionally advanced/metastatic DTC, who underwent radioiodine treatment together with dosimetry were included in this study. Patients were excluded if their radioiodine post-treatment scan showed no abnormal uptake. Dosimetry was calculated using images taken 2, 3 and 7 days post-radioiodine. Regions of interest were drawn around lesions that required dosimetry and a time–dose activity curve was created. The total cumulative activity was equal to the area under the curve. Each patient's results were prospectively assessed by their oncologist regarding the usefulness of dosimetry in making management decisions.

Results: Thirty patients were studied and underwent 102 admissions of radioiodine between them. Dosimetry was carried out during 83 of 102 admissions. An absorbed dose of >20 Gy was taken as significant from dosimetry calculations, following which further radioiodine was considered. In 80% of patients, dosimetry was found to be useful when making treatment decisions. Only on 1/19 admissions did dosimetry calculate a minimum dose above 20 Gy in patients who had a total of four or more admissions for radioiodine. Ten per cent (3/30) had a complete response to radioiodine, both biochemically and radiologically, with a median follow-up of 6.7 months. Thirty-three per cent had a partial response/stable disease to radioiodine. The remainder had progressive disease. The decision to discontinue radioiodine therapy was often based on dosimetry and thyroglobulin results. Dosimetry was very useful for patients with thyroglobulin antibodies.

Conclusion: Only 10% had a complete response. Therefore, a significant number of patients became refractory to radioiodine during a course of repeat admissions for treatment. Dosimetry (often together with thyroglobulin and anatomical scans) helped to identify these patients to avoid further futile radioiodine therapy.

Dosimetría en 131I CDT hoy en España

- Al menos, por ahora,
  - Seguir con el esquema de actividades fijas
  - Colaboración con física médica y PR
- Oportunidad de mejora: hacer mejor lo que hacemos bien
- Búsqueda método sencillo que responda a la medicina nuclear, NO somos radioterapia externa
- Que el esfuerzo tenga “repercusión clínica”

Dosimetría de pacientes con cáncer diferenciado de tiroides en tratamiento de terapia metabólica con ^{131}I a partir de medidas de tasa de dosis externa

Dosimetry by means of external dose rate measurements in patients undergoing ^{131}I thyroid cancer theraphy

MA Ruiz[1*], N Ferrer[2], D Córdoba[2], L Alonso[2], JM Sastre[2] y L Arranz[2]

[1] Servicio de Radiofísica y Protección Radiológica. Hospital Universitario Doce de Octubre. Madrid.
[2] Servicio de Radiofísica y Protección Radiológica. Hospital Universitario Ramón y Cajal. Madrid.

Fecha de Recepción: 29/10/2009 - Fecha de Aceptación: 11/01/2010

Tabla 1. Protocolo de medidas de niveles de radiación seguido.

Tiempo	Tarea	Detalles
0	Administración de la actividad de ^{131}I	Evitar defecación o micción
1 h	Medida de la tasa de dosis equivalente en contacto, a 1 m y a 2 m	Antes de que el paciente excrete actividad, evitar defecación o micción
24 h (1 d)	Medida de la tasa de dosis equivalente en contacto, a 1 m y a 2 m	Preferiblemente que el paciente miccione antes de la medida
48 h (2 d)	Medida de la tasa de dosis equivalente en contacto, a 1 m y a 2 m	Preferiblemente que el paciente miccione antes de la medida
72 h (3 d)	Medida de la tasa de dosis equivalente en contacto, a 1 m y a 2 m	Preferiblemente que el paciente miccione antes de la medida
168 h (7 d)	Medida de la tasa de dosis equivalente en contacto, a 1 m y a 2 m	Si a 1 m está prácticamente en el fondo del equipo, se utilizan las medidas en contacto

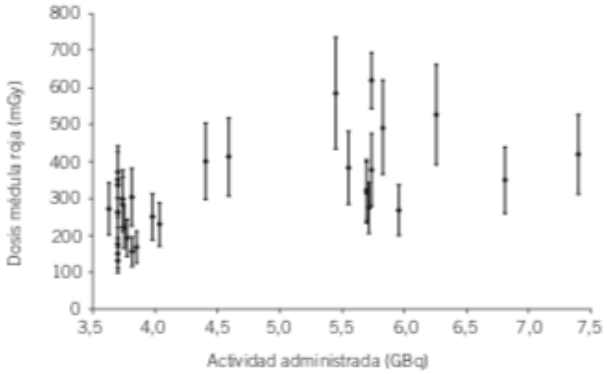


Fig. 2. Dosis en Médula Roja frente a la actividad administrada.

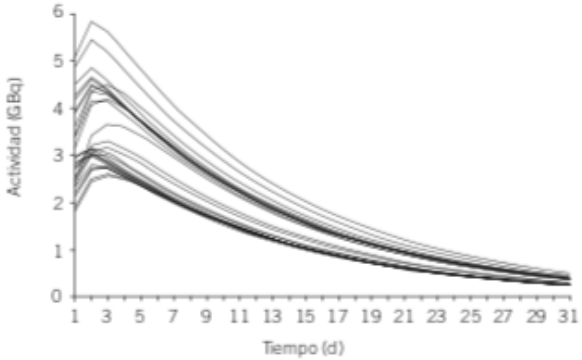


Fig. 3. Evolución temporal de la actividad de ^{131}I en la orina, para cada uno de los pacientes.

Individualized Dosimetry for Theranostics: Necessary, Nice to Have, or Counterproductive?

J Nucl Med 2017; 58:97S–103S
DOI: 10.2967/jnumed.116.186841

importantly, the demonstration of a tumor dose–response relationship (*42*) and the observation of minimal differences between cycles (*12,41*) indicate that posttherapeutic dosimetry after a first treatment cycle predicts the absorbed doses in further cycles.

The conflict between treatment optimization and registration of radiopharmaceuticals with fixed activity posology in oncological nuclear medicine therapy

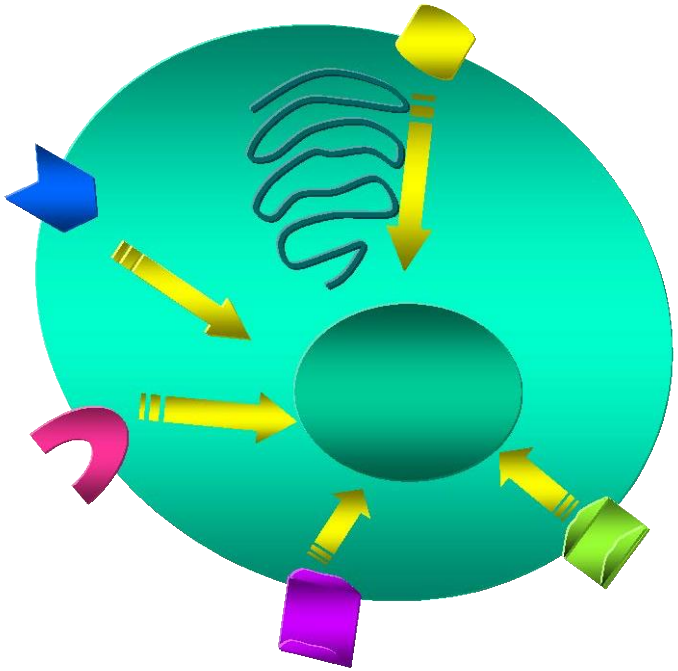
Eur J Nucl Med Mol Imaging (2017) 44:1783–1786
DOI 10.1007/s00259-017-3707-3

C. Chiesa[1] · K. Sjogreen Gleisner[2] · G. Flux[3] · J. Gear[3] · S. Walrand[4] · K. Bacher[5] · U. Eberlein[6] · E. P. Visser[7] · N. Chouin[8] · M. Ljungberg[2] · M. Bardiès[9] · M. Lassmann[6] · L. Strigari[10] · M. W. Konijnenberg[11]

with the introduction of the acronym AHASA (as high as safely attainable) instead of ALARA. This type of approach thus aims to pursue *the intended radiotherapeutic purpose of the exposure*.

Somatostatin Receptors

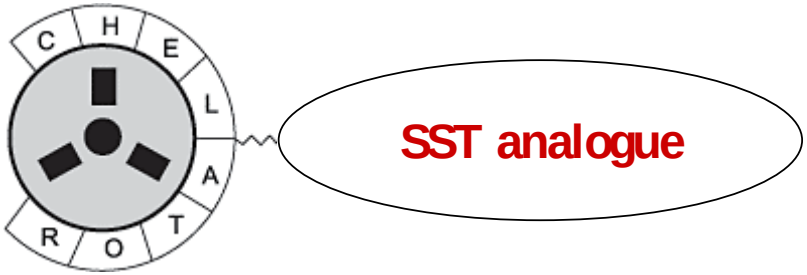
Ala-Gly-Cys-Lys-Asp-Phe-**Phe -Trp-Lys-Thr**-Phe-Thr-Ser-Cys **SST-14 (1973)**

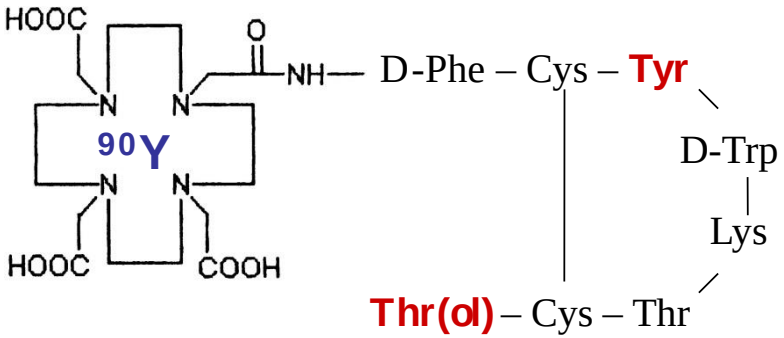


- **5 subtype receptors (SSTR1-5)**
- **predominant expression of SSTR2 in most NET tumours**
- **SSTR1 (4): Prostate, Sarcoma some: Pheochromocytma, GEP**
- **SSTR3: Inactive Pituitary Adenoma**
- **SSTR5: Gastric Carcinomas, GH Pituitary A.**

Reubi EJNM 2001

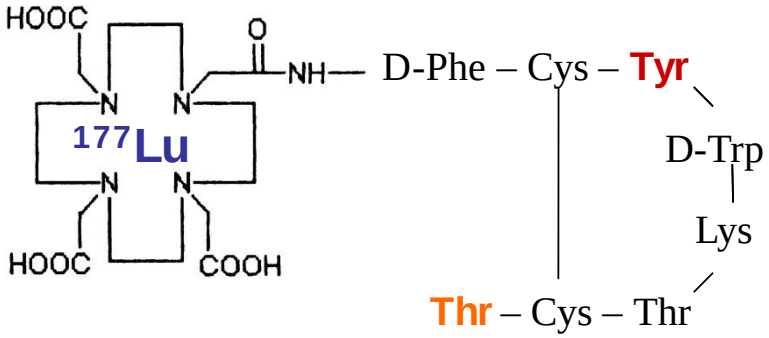
Radioparmaceuticals





Chelator = DOTA

^{90}Y-DOTA-TOC



^{177}Lu-DOTA-TATE

Radiolabeled Somatostatin Analogue Therapy Of Gastroenteropancreatic Cancer

Lisa Bodei, MD, PhD,[*,†] Dik J. Kwekkeboom, MD, PhD,[†,‡] Mark Kidd, PhD, DABCC, Irvin M. Modlin, MD, PhD, DSc, MA, FRCS,[†,‖] and Eric P. Krenning, MD, PhD[†,§]

Semin Nucl Med 46:225-238 C 2016

Table 1 PRRT Clinical Results in GEP-NEN Based Upon the Different Treatment Schedules Utilized

	Schedule	Patients	CR	PR	DCR	Progression at Baseline	Response Criteria	Outcome (Median PFS or TTP)
^{90}Y-Octreotide	7.4 GBq/m^2 in four cycles[49]	36 GEP	4%	20%	92%	100%	WHO	Not assessed
	2.96-5.55 GBq/cycle × 2[78]	21 GEP	0%	28%	71%	n.a.	WHO	TTP 10 months
	0.93-2.78 GB/m^2/cycle[50]	58 GEP	0%	9%	71%	81%	SWOG	TTP 29 months
	4.4 GBq/cycle × 3[23]	90 SI	0%	4%	74.4%	100%	SWOG	PFS 16 months
	1-10 cycles (median = 2), various activity[22]	821 GEP	0.2%	38%	n.a.	n.a.	RECIST	n.a.
^{177}Lu-octreotate	27.8-29.6 GBq in three to four cycles[26]	310 GEP	2%	28%	81%	43%	SWOG	PFS 33 months
	3.7-29.2 GBq in four to six cycles of 3.7-7.4 GBq[21]	39 GEP	3%	31%	88%	76%	RECIST	TTP 36 months
	Mean 25.5 GBq in five cycles, normal subjects; mean 17.8 GBq in risk patients[56]	52 P	8%	21%	81%	88%	SWOG	PFS 20 months in reduced dosage, not reached in full dosage
	32 GBq in four cycles[48]	68 P	0%	60.3%	85.3%	67.6%	SWOG	PFS 34 months
	Median 25.7 vs 18.4 GBq (normal vs risk patients)[58]	43 SI	7%	0%	84%	100%	SWOG	PFS 36 months
	32 GBq in four cycles[59]	61 SI	0%	13.1%	91.8%	75.4%	SWOG	PFS 33 months
	27.8-29.6 GBq in three to four cycles vs octreotide LAR 60 mg/mo[60]	201 SI	19% (Lu) vs 3% (LAR) CR + PR		58% (Lu) vs 20% (LAR)	100%	RECIST	PFS not reached (Lu) vs 8.4 months (LAR)
Combinations with ^{177}Lu	31 GB1 in four cycles + capecitabine, 1650 mg/m^2 (14 d per cycle)[64]	33 GEP	0%	24%	94%	100%	RECIST	Median PFS not reached in a 16-month follow-up
	31 GBq in >three cycles + 5-FU[65]	68 GEP	0%	29%	68%	85.2%	RECIST	n.a.
	31 GB1 in four cycles + capecitabine 1500 mg/m^2 (14 days d per cycle) + temozolomide (100-200 mg/m^2)[66]	33 GEP	16%	41%	94%	100%	RECIST	PFS 31 months
	31 GB1 in four cycles + everolimus (from 5-10 mg daily for 24 weeks)[67]	16 GEP	0%	44%	94%	100%	RECIST	n.a.

CR, complete response; DCR, disease-control rate (CR + PR + stability); n.a., not available or assessed; P, pancreatic; PR, partial response; SI, small intestine.

The efficacy of ^{177}Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis

Seong-Jang Kim[1] · **Kyoungjune Pak**[1] · **Phillip J. Koo**[2] · **Jennifer J. Kwak**[2] · **Samuel Chang**[2]

Eur J Nucl Med Mol Imaging (2015) 42:1964–1970

Table 2 Studies included in the current meta-analysis

First author	Year	Country	Compound	Dose (GBq)	^{177} Lu cycles	Cumulative Activity (GBq)	No. of patients	% of pancreatic NETs	Study design	Follow-up (months): median (range)	Response criteria
Septiembre 2014											
Bodei [13]	2011	Italy	DOTATATE	3.7~7.4	4~6	3.7~29.2	51	14	*P* (phase I–II)	60 (5~86)	RECIST
Romer [6]	2013	Switzerland	DOTATOC	–	1~5	13.5	16	–	–	9 (1~80.1)	RECIST
van Vliet [17]	2013	Netherlands	DOTATATE	3.7/7.4	4	22.2~29.6	257	27	*R*	–	RECIST/ SWOG
Delpassand [14]	2014	USA	DOTATATE	7.4	1~4	29.6	32	–	*P* (phase II)	0.3~26.8	RECIST
Paganelli [15]	2014	Italy	DOTATATE	3.7/5.5	5	14.4~27.8	43	0	*P* (phase II)	38 (11~59)	SWOG
Ezziddin [16]	2014	Germany	DOTATATE	7.9	4	-	74	45	*R*	47	SWOG

P prospective, *R* retrospective

473

	Respuesta	Control
RECIST	29%	81%
SWOG	23%	82%

Conclusion

In conclusion, although the treatment protocols are not standardized and the treatment effects should be further verified through prospective randomized controlled trials, ^{177}Lu-labelled PRRT is an effective treatment option for patients with inoperable or metastatic NETs, based on this meta-analysis of the published data.

Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors

Eur J Nucl Med Mol Imaging (2015) 42:5–19

Lisa Bodei · Mark Kidd · Giovanni Paganelli · Chiara M. Grana · Ignat Drozdov · Marta Cremonesi · Christopher Lepensky · Dik J. Kwekkeboom · Richard P. Baum · Eric P. Krenning · Irvin M. Modlin

feb 1996- abr 2013
Media sgto 20 m

Table 1 PRRT treatment protocols in 807 patients

Protocol				No. of cycles
				Median Range
PRRT protocol (*n*=				1–10
				1–19
				1–11
PRRT protocol+Othe				3–9
Adjunctive salvage PRI			3.5	1–12.9
		55	13	1.9–21.3
	Lu-octreotate	11	2.8+5.6	1.9–7.8, 2.2–19
	^{177}Lu-octreotate+metronomic capecitabine	1	18	

sion is that individual susceptibility to adverse sequelae of PRRT requires rigorous delineation of mechanistic biological events, which are likely to have a specific, individual genetic basis. Until these are identified, the guiding principle in PRRT should be the minimal effective rather than the maximum tolerated activity.

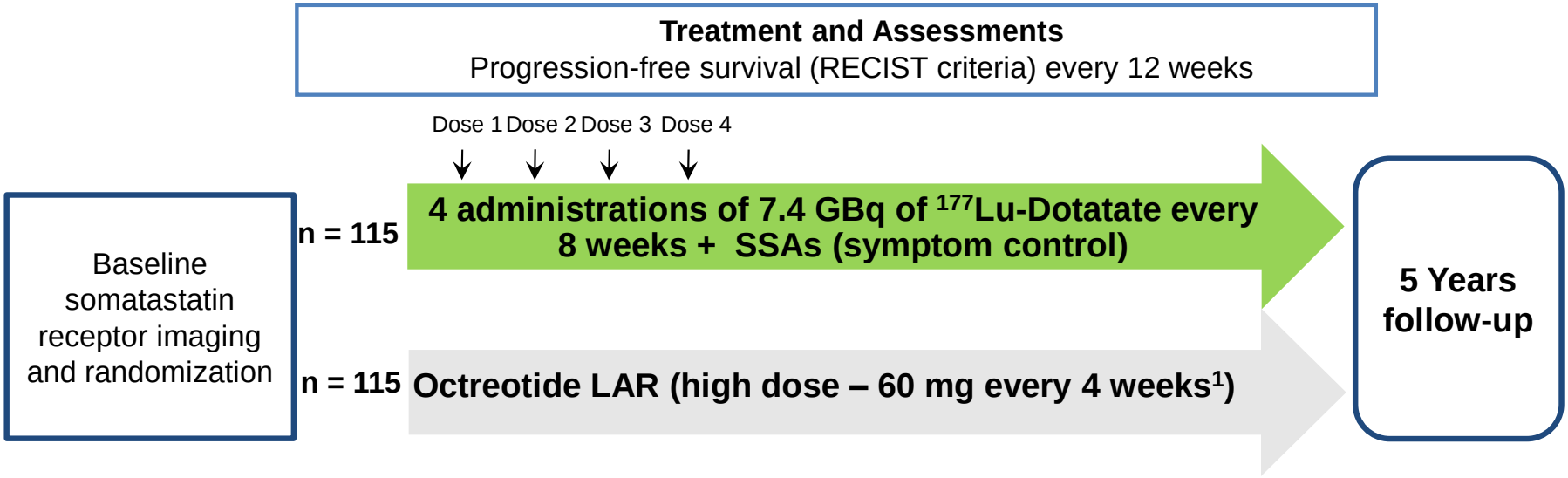
Nefrotoxicidad 34.6%, severa (3+4) 1.4%
SMD 2.35%
LA 1.1%

Factores de riesgo < 30% estimación

NETTER-1 Trial: Objectives and Design

Aim: **Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptom control) compared to octreotide LAR 60 mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive midgut NET that is progressive under octreotide LAR 30 mg (label use)**

Design: International, multicenter, randomized, comparator-controlled, parallel-group



1. FDA and EMA recommendation

RECIST, Response Evaluation Criteria in Solid Tumors

Strosberg JR, et al. *J Clin Oncol.* 2016;34(suppl 4S): Abstract 194.

Strosberg J et al. NEJM 2017;376:125-35

N = 229 (ITT)
Number of events: 91

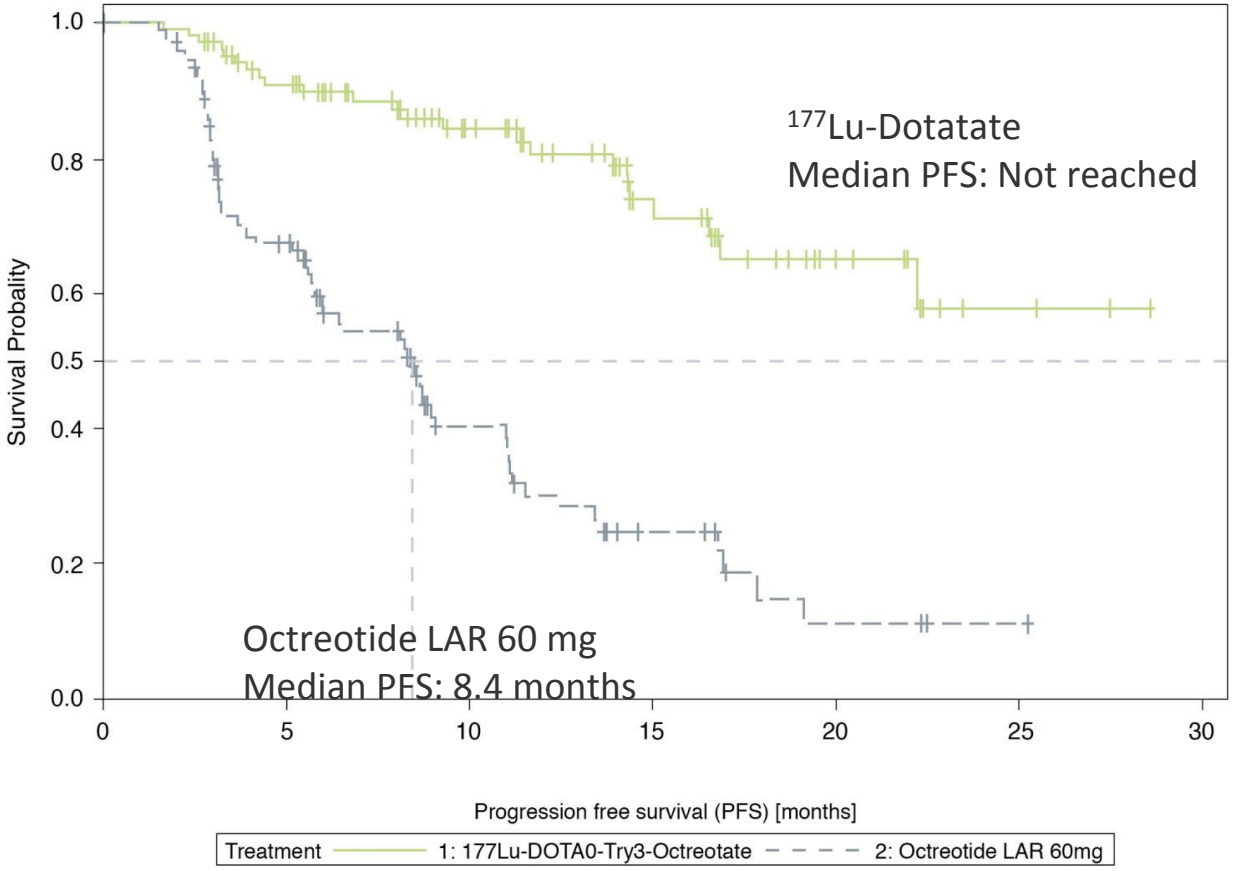
- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 68

^{177}Lu-DOTATATE. NETTER-1 P.F.S.

Hazard ratio (cociente de riesgo) : **0.21** [0.129 – 0.338]
p < 0.0001

reducción del 79% en el riego de progresión/muerte

Mediana estimada en PFS para el brazo de Lu-DOTATATE
≈ 40 meses



PFS a los 20 meses: 177Lu 65.2% vs 10.8% control
Indice respuesta: 177Lu 18% vs 3% control

Strosberg J et al. NEJM 2017;376:125-35

Eventos adversos Netter

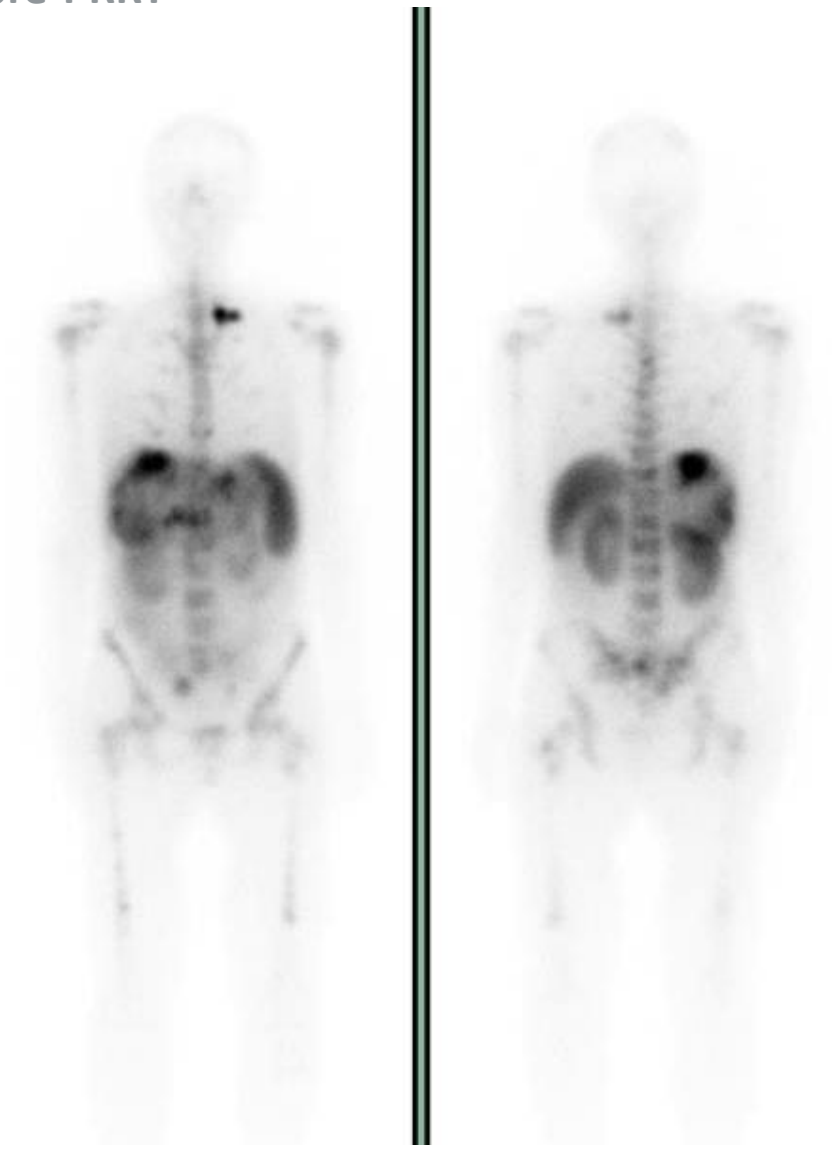
eventos	177Lu		control		p
%		º3-4		º3-4	
nauseas	**59**	**4**	**12**	**2**	**<0.001**
vómitos	**47**	**7**	**10**	**1**	**<0.001**
diarrea	29	3	19	2	0.11
fatiga	40	2	25	2	0.03
plaqts	**25**	**2**	**1**	**0**	**<0.001**
anemia	14	0	5	0	0.04
linfo	**18**	**9**	**2**	**0**	**<0.001**
leucos	**10**	**1**	**1**	**0**	**0.005**
neutrofs	5	1	1	0	0.12
apetito	18	0	8	3	0.04
flushing	13	1	9	0	0.22

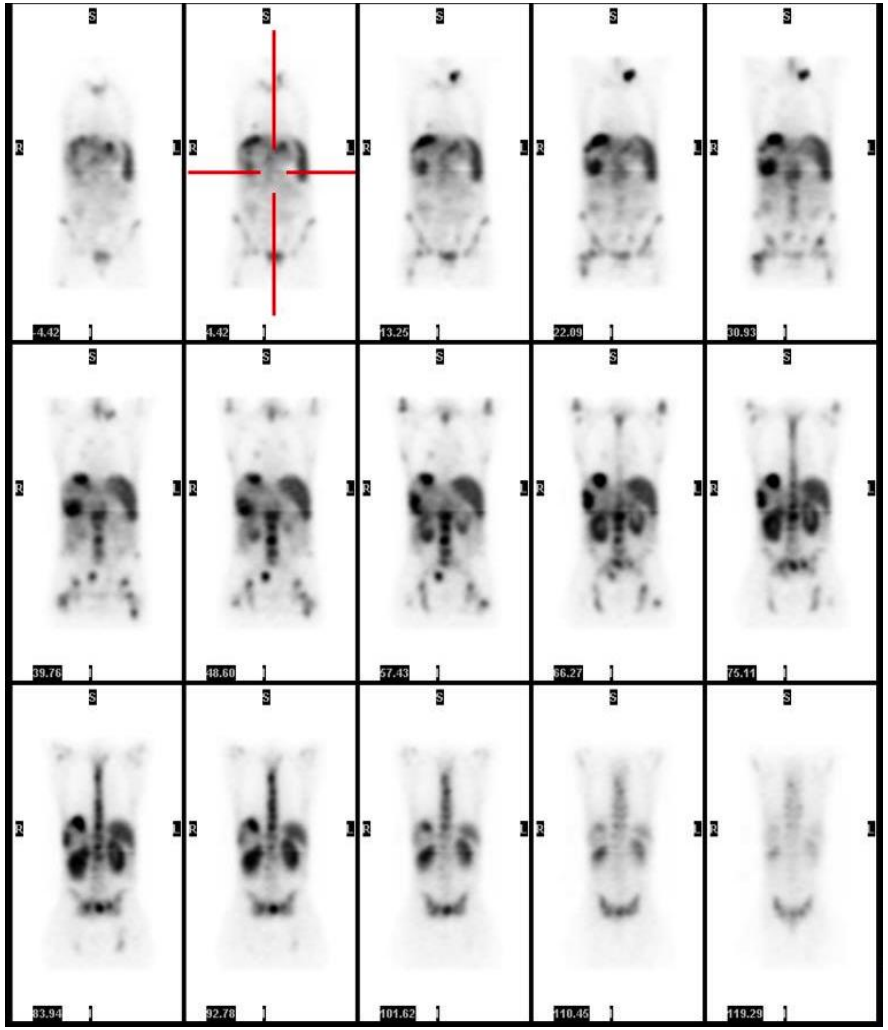
In the ongoing ILUMINET clinical study based on ^{177}Lu-DOTATATE, the number of cycles is tailored to the absorbed dose to the kidneys in the individual patient, and in an interim analysis the number of delivered cycles was found to vary between three and eight [15]. In the group of patients in whom treatment was terminated because they had reached the protocol-specified dose limit, 73% received more and 9% received fewer than four cycles. In other words, it is

Eur J Nucl Med Mol Imaging (2017) 44:1783–1786
DOI 10.1007/s00259-017-3707-3

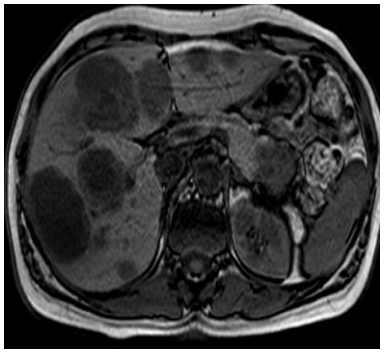
NET pancreatico no funcionante, Ki-67 index 11%

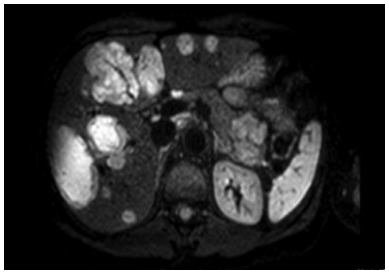
SRS pre-PRRT



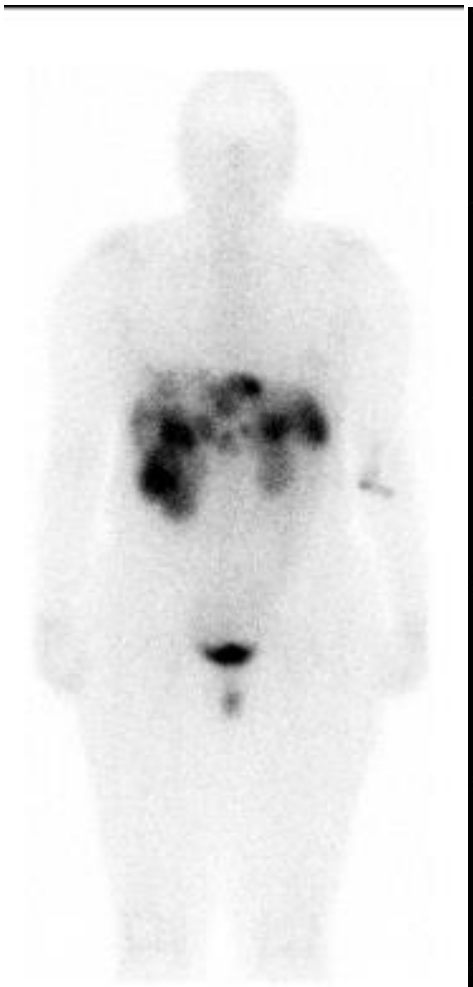


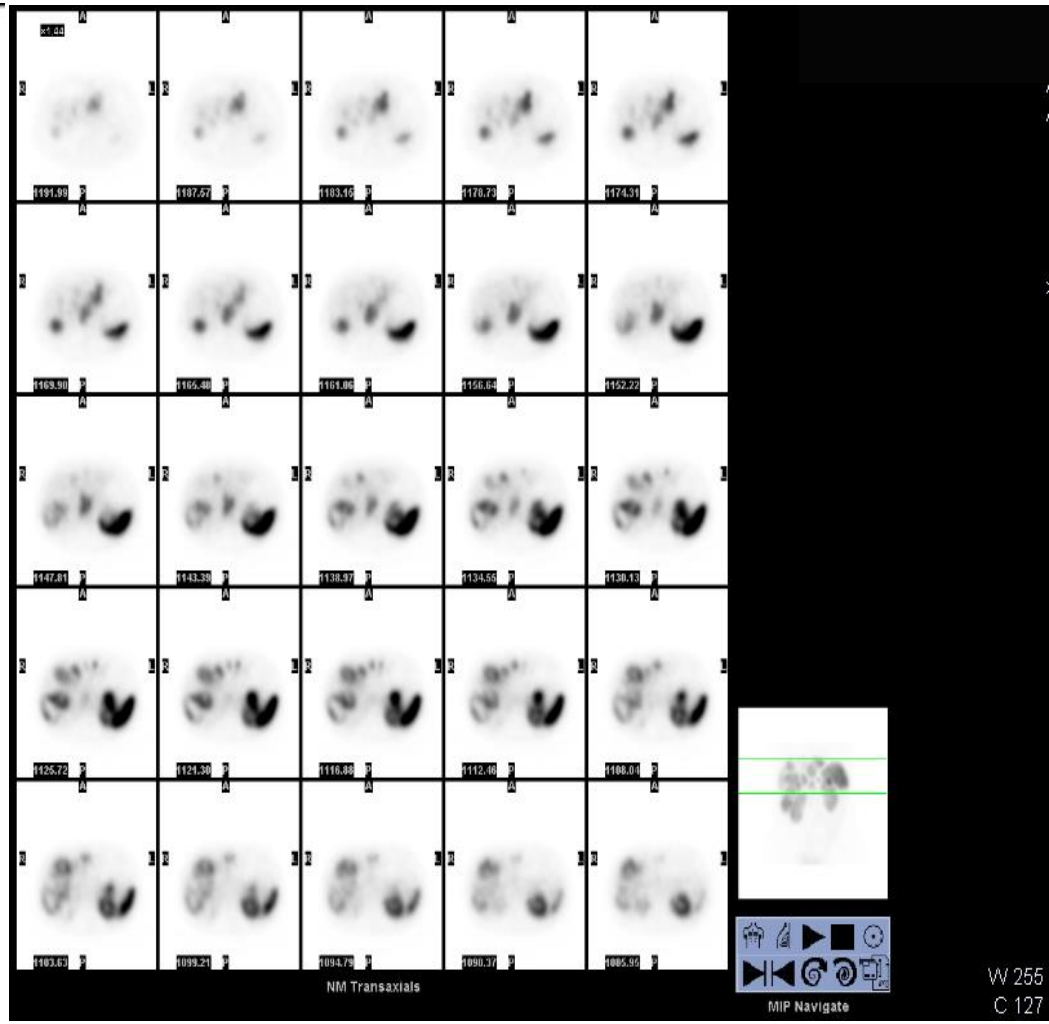
Insulinoma metastásico. Ki-67 5%, CgA 5867 ng/ml





MR

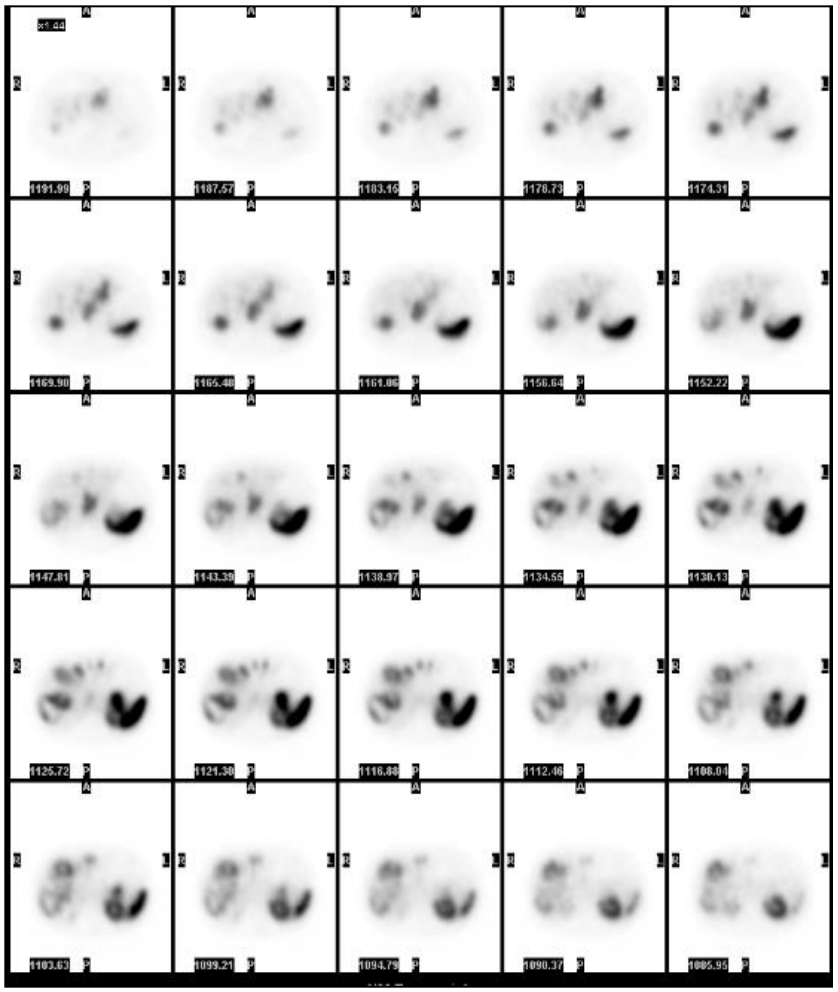




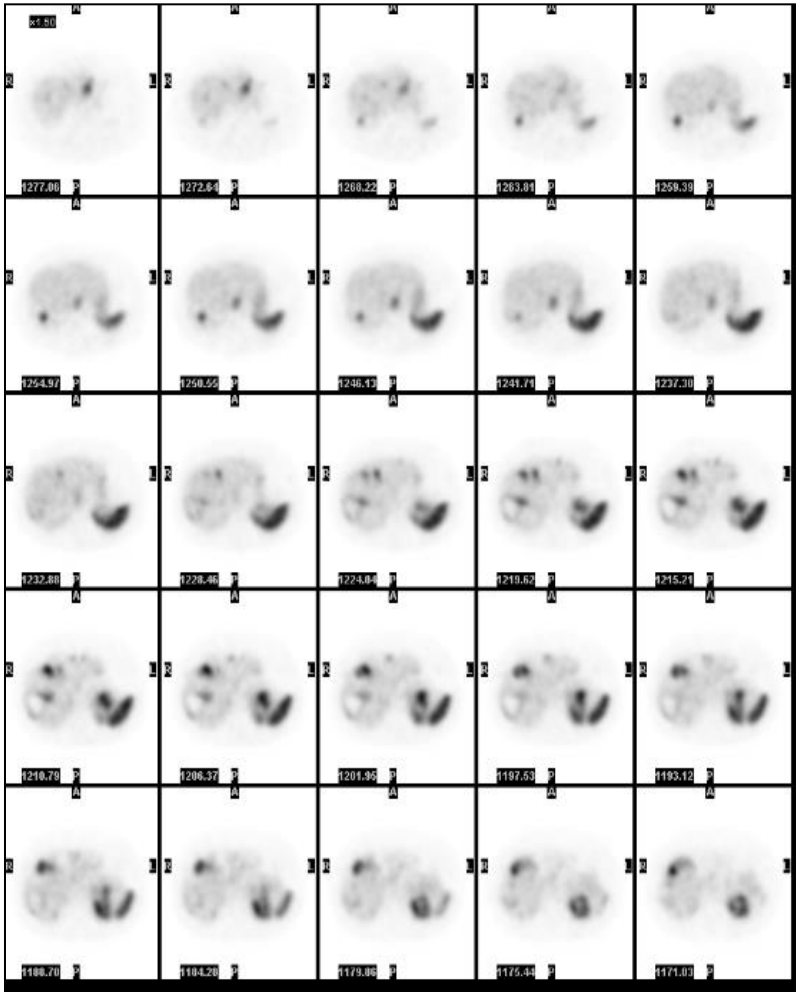
2/2015 111-In-SRS

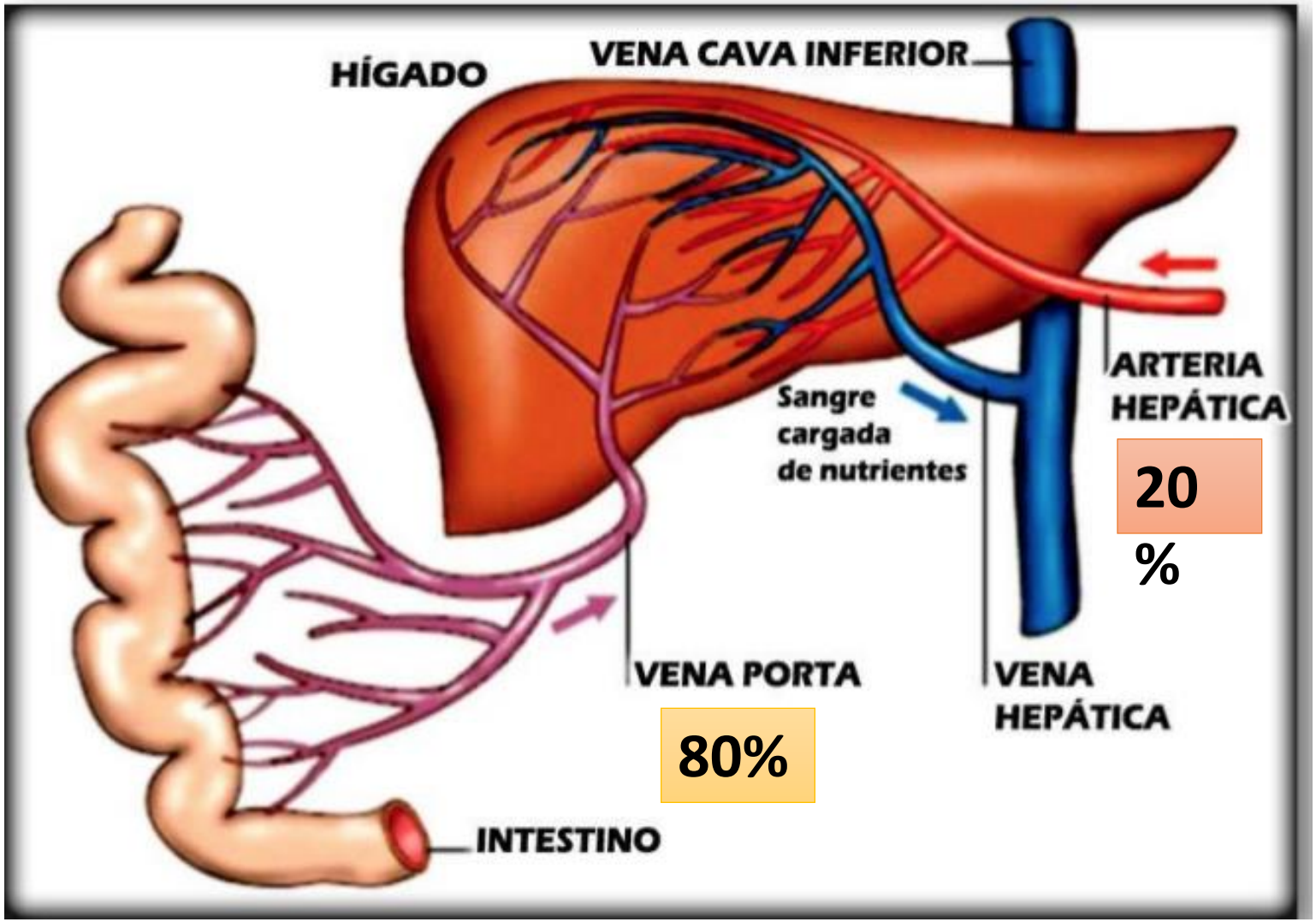
SRS

2/2015 diagnóstico

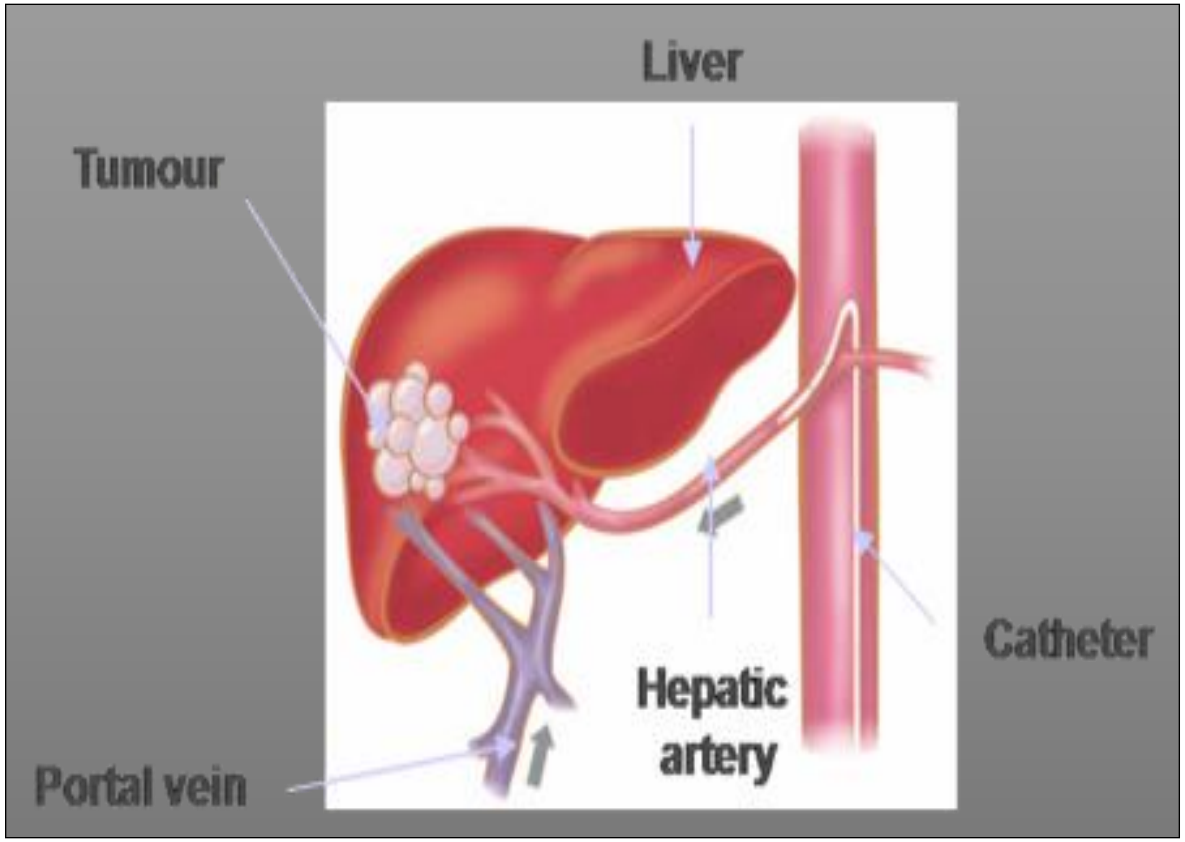


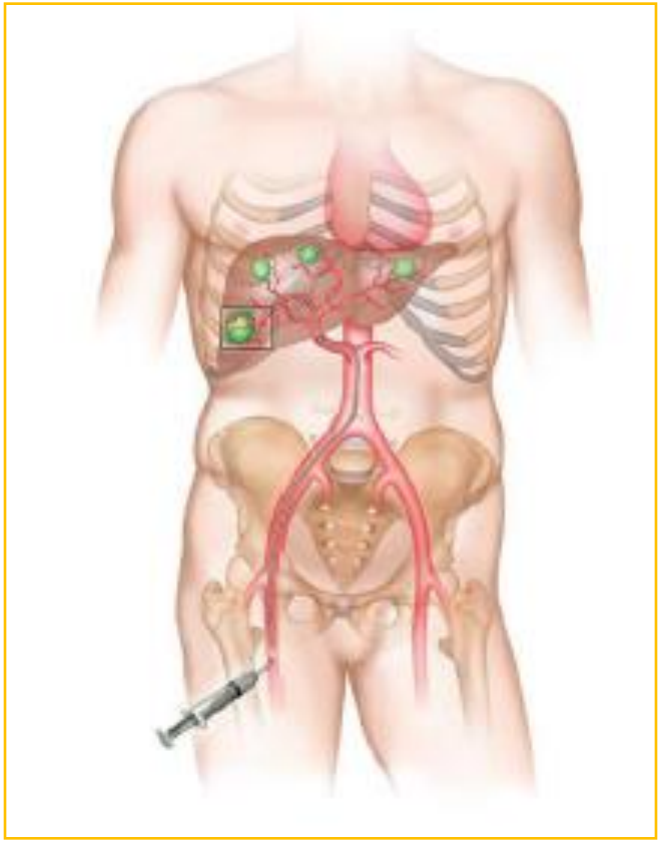
9/2017 seguimiento



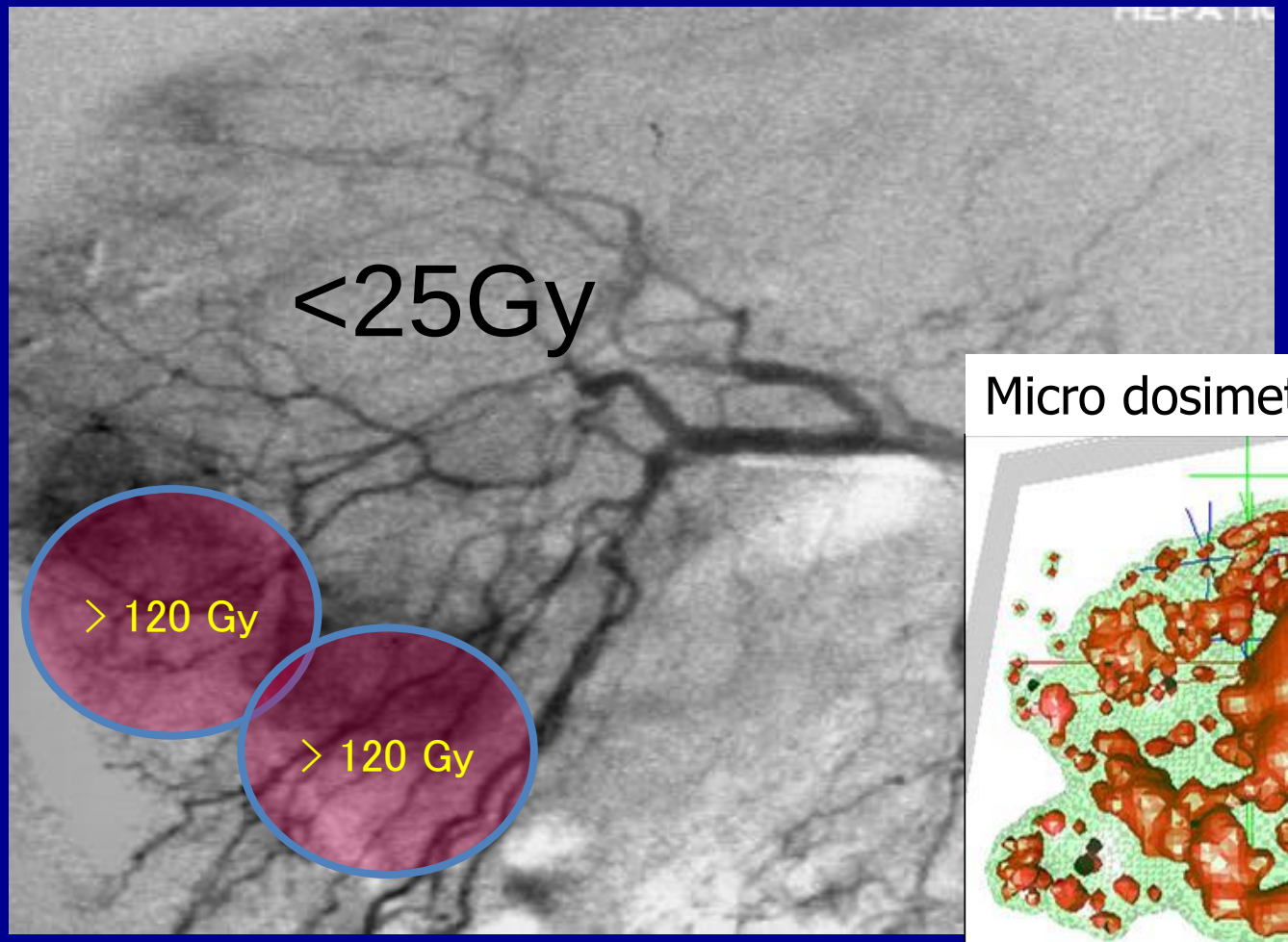

HÍGADO
VENA CAVA INFERIOR
ARTERIA HEPÁTICA
Sangre cargada de nutrientes
20 %
VENA PORTA
80%
VENA HEPÁTICA
INTESTINO

TERAPIAS INTRARTERIALES

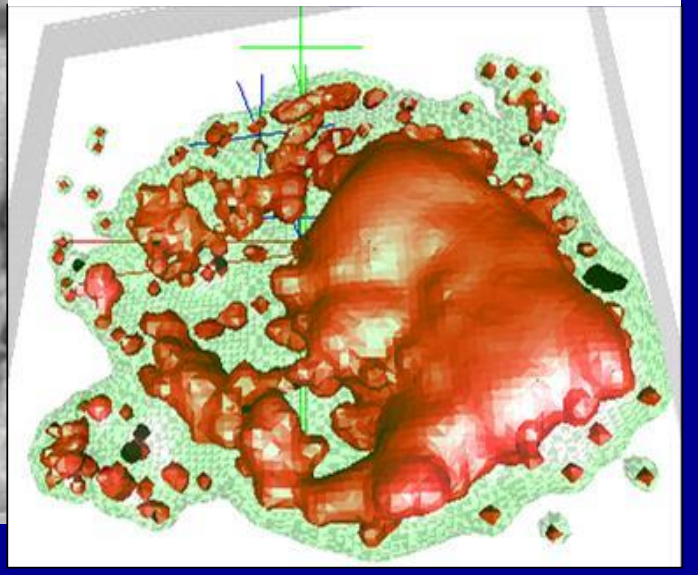




SIRT – Radiation Dosimetry



Micro dosimetrie Explantat



1000 Gy Dose Volume

Comité multidisciplinar
Criterios clínicos para SIRT

Valoración anatomía vascular
Simulación distribución 90Y

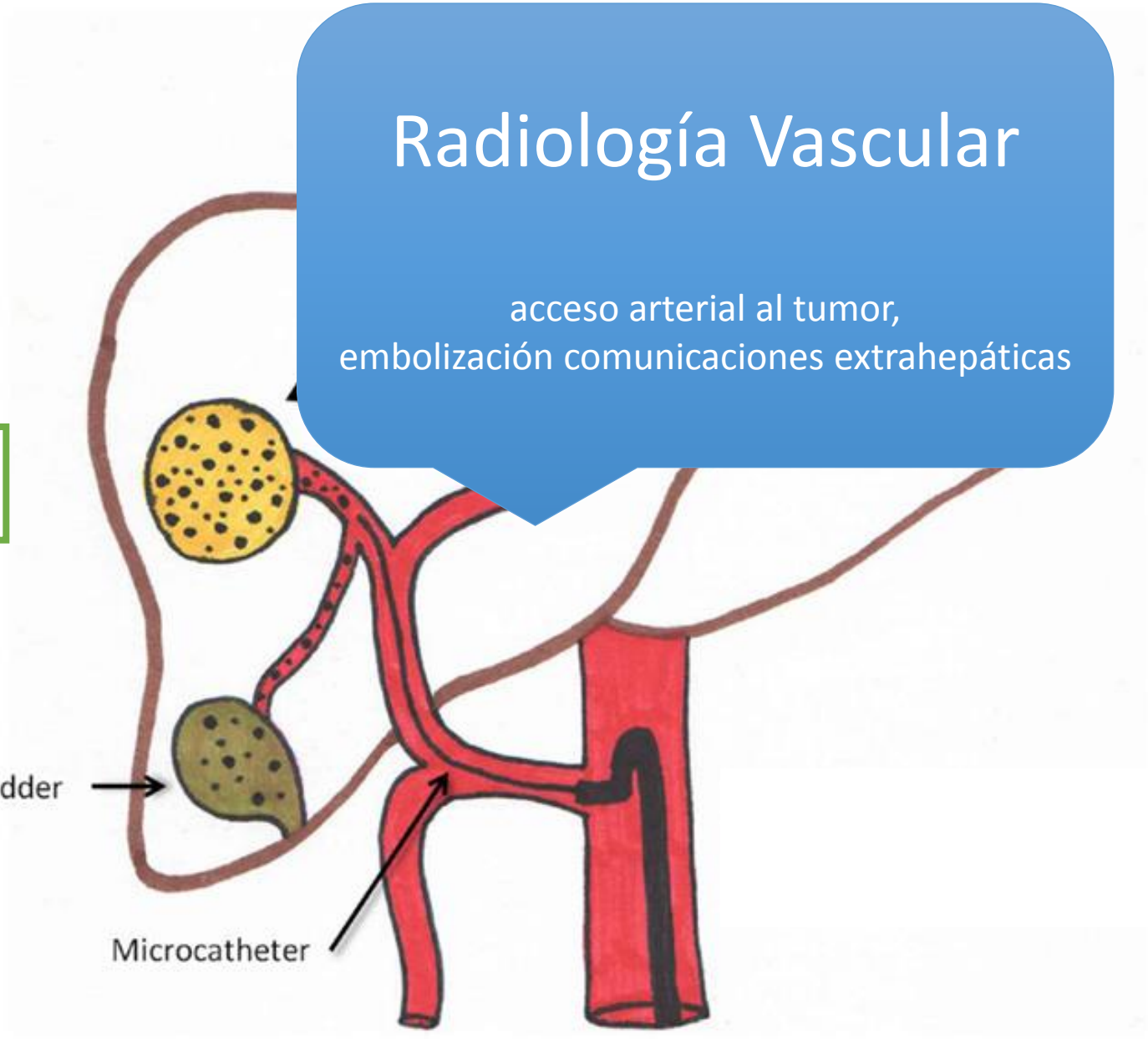
Volumen hepático y Tumoral
TC / RM

Garin et al. [23] make the following interesting comment about dosimetry in this field: "*this type of powerful, pretherapeutic predictor of response and survival represents a clear advantage of radioembolization. This advantage is unfortunately not available with other therapeutic approaches used for liver cancer, such as chemotherapy, biotherapy, or chemoembolization*". This "*clear advantage*", available in

Radiología Vascular

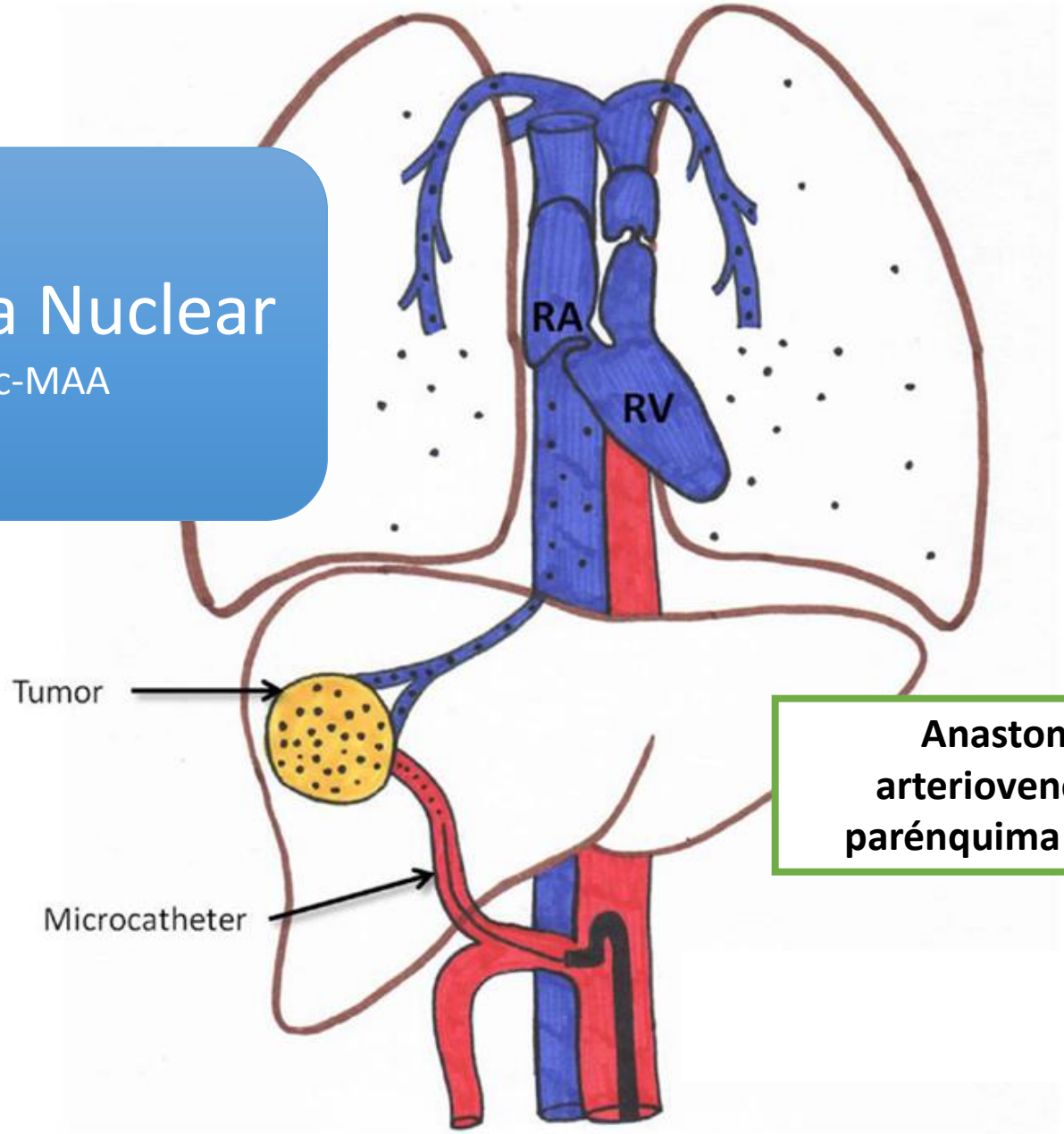
acceso arterial al tumor,
embolización comunicaciones extrahepáticas

Visualización árbol arterial



Medicina Nuclear

99mTc-MAA

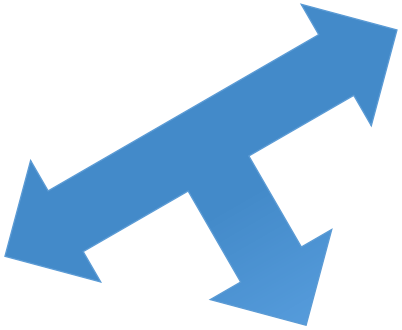


Anastomosis arteriovenosas en parénquima hepático

99mTc-MAA: shunt hepatopulmonar

captación extrahepática

relación captación tumor/hígado“sano” (selectividad del ttº)



Reserva hepática
TVP
Vía biliar

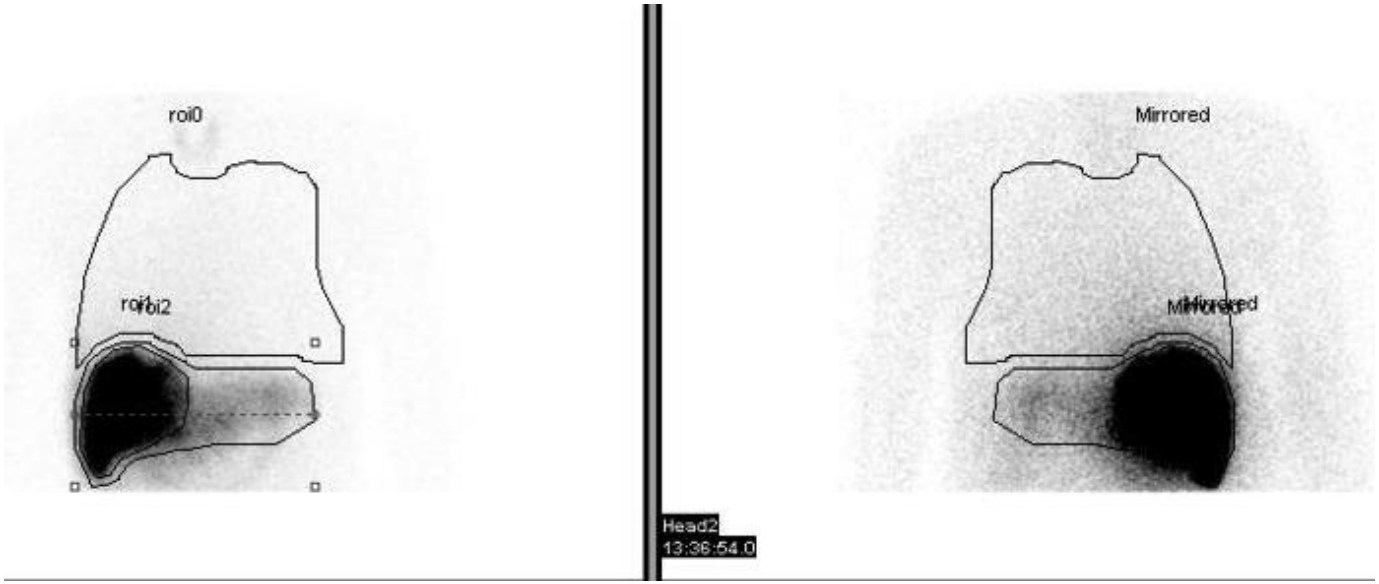
Planificación tratamiento
Cálculo actividad

La dosis recomendada para el hígado está entre 80 Gy y 150 Gy (8.000 rad a 15.000 rad). La cantidad de radioactividad requerida para proporcionar la dosis deseada al hígado podrá ser calculada mediante la siguiente fórmula:

$$Cantidad\ \mathrm{Re}querida\ (GBq) = \frac{[Dosis\ deseada\ (Gy)]\ [Masa\ \ hepática\ \ (kg)]}{50}$$

$$Dosis\ (Gy) = \frac{50\ [Cantidad\ \ inyectada\ \ (GBq)\ ]\ [1-F]}{Masa\ \ hepática\ \ (kg)},$$

Dosis Pulmón (Gy)= 50 x (actividad inyectada GBq) x F



$$\%\ \text{SHUNT} = \frac{\text{cuentas pulmón}}{\text{cuentas pulmón} + \text{cuentas hígado}}$$

HIGADO
874086,00
564706,00

PULMON DCHO	PULMON IZQ
22788,00	16558,00
24984,00	16990,00

>20 %
30 Gy dosis o 50 Gy acumulados

The importance of scatter correction for the assessment of lung shunting prior to yttrium-90 radioembolization therapy

Jim O'Doherty, James Scuffham and Paul Hinton Nuclear Medicine Communications 2011, 32:628–634

Table 1 Acquisition parameters for scanning of the torso phantom

Parameter	Value
Head	Anterior and posterior
Photopeak	140 keV ± 10%
W_{s1}	127–130 keV
W_{s2}	151–154 keV
Collimator	LEGP
Matrix	128
Frames	2
Time/counts	1000 kcnt
Zoom	0

LEGP, low-energy general purpose; W_s, width of the scatter window.

Table 2 Results of scatter correction on the phantom and three patient studies

	Planar	
	LS (%; uncorrected)	LS (%; corrected)
Phantom	3.20 ± 0.02	0.30 ± 0.01
Patient 1	10.30 ± 0.03	4.80 ± 0.03
Patient 2	7.40 ± 0.03	5.40 ± 0.04
Patient 3	5.70 ± 0.03	0.80 ± 0.02

The effect of correction results on a significant reduction in the lung shunting (LS).

Cuando se aplica corrección del scatter se obtiene una reducción significativa de la actividad detectada en pulmones que proviene de los fotones hepáticos

Hepatopulmonary Shunting: A Prognostic Indicator of Survival in Patients with Metastatic Colorectal Adenocarcinoma Treated with ^{90}Y Radioembolization[1]

10.1148/radiol.2016152100

Estudio retrospectivo
606 pacientes CCRm

Kaplan-Meier Statistics Indicating Significant Differences in Survival bet… of Patients with Varying LSF

LSF	No. of Patient…
<5%	
5%–10%	
>10%–15%	
>15%–20%	
>20%	
All levels	

…raction (LSF) …tive of poor sur- …ndergoing …for metastatic …cinoma $P < .001$).

Tumores más agresivos??
Relación con la angiogénesis??
Hay que reducir actividad?? :
Respuesta subóptima
Valorar Gy en pulmón

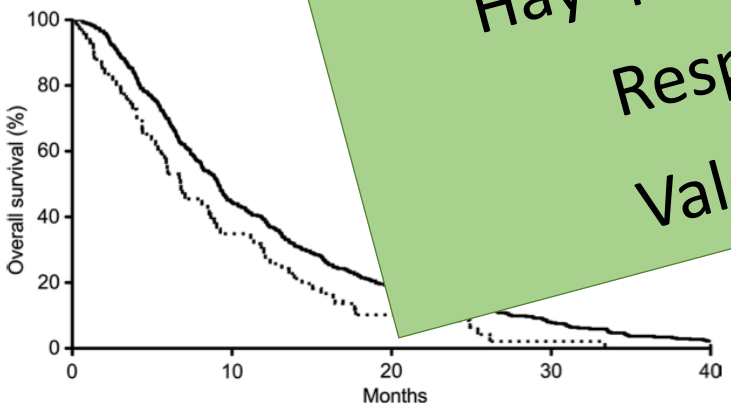
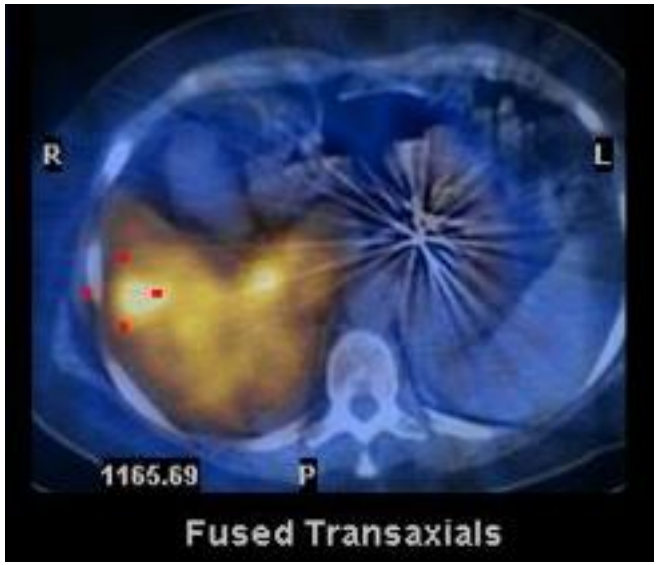
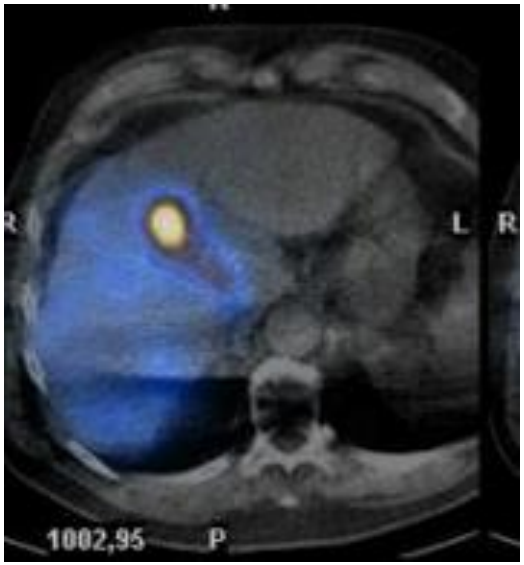
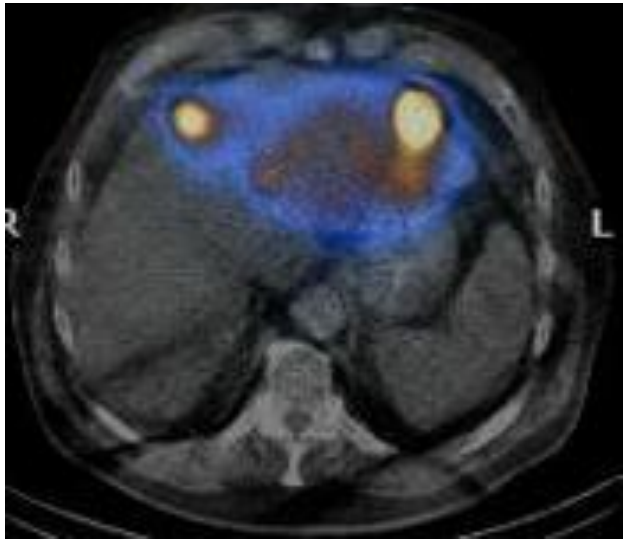


Figure 2: Kaplan-Meier survival curve generated after the first ^{90}Y radioembolization procedure. Patients with increased LSF of more than 10% demonstrate significantly poorer survival when compared with patients with low LSF.

Patients with high LSF have a poorer prognosis with limited overall survival, irrespective of other prognostic indicators.


R
L
1165.69
P
Fused Transaxials


L
R
1002,95
P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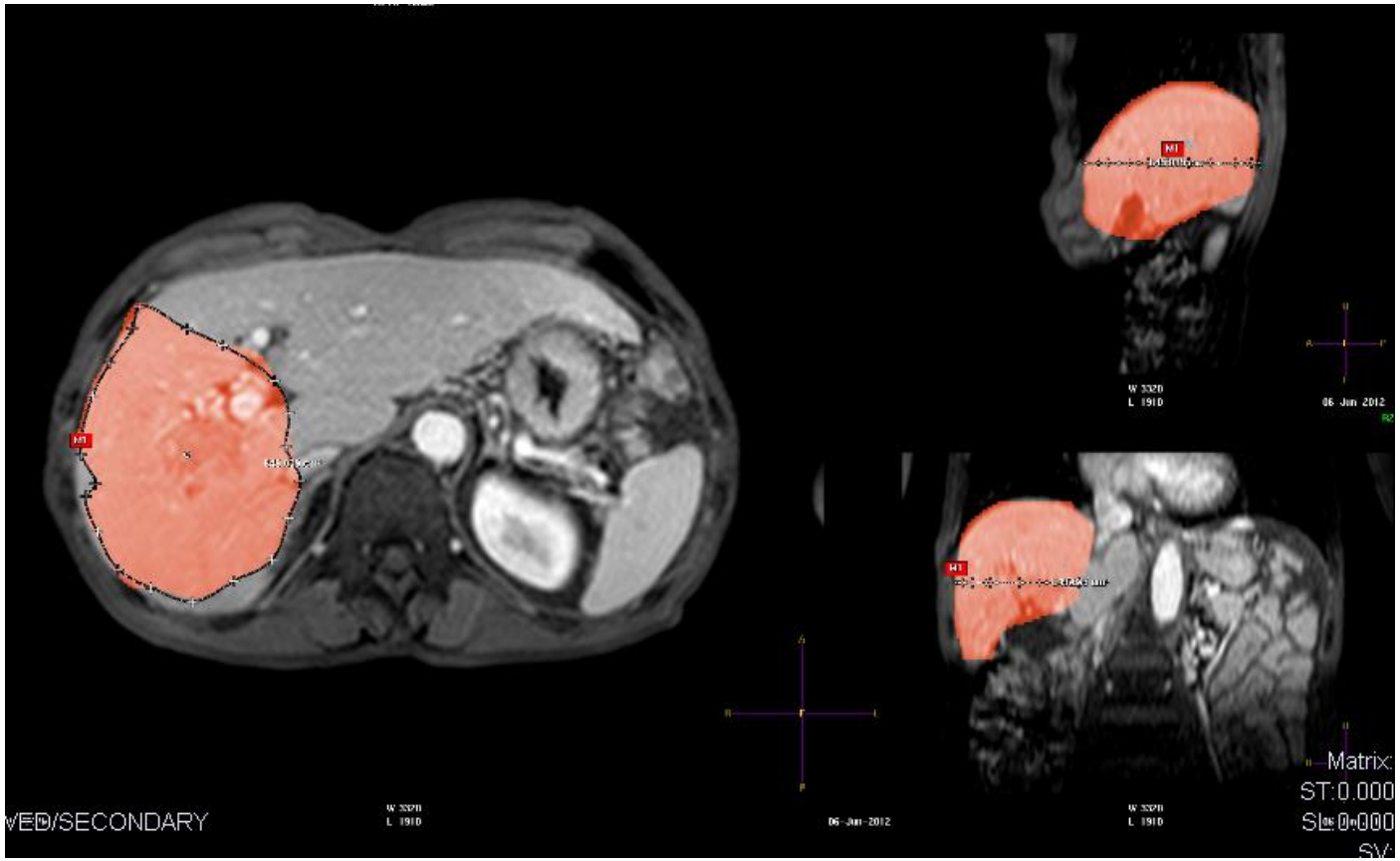
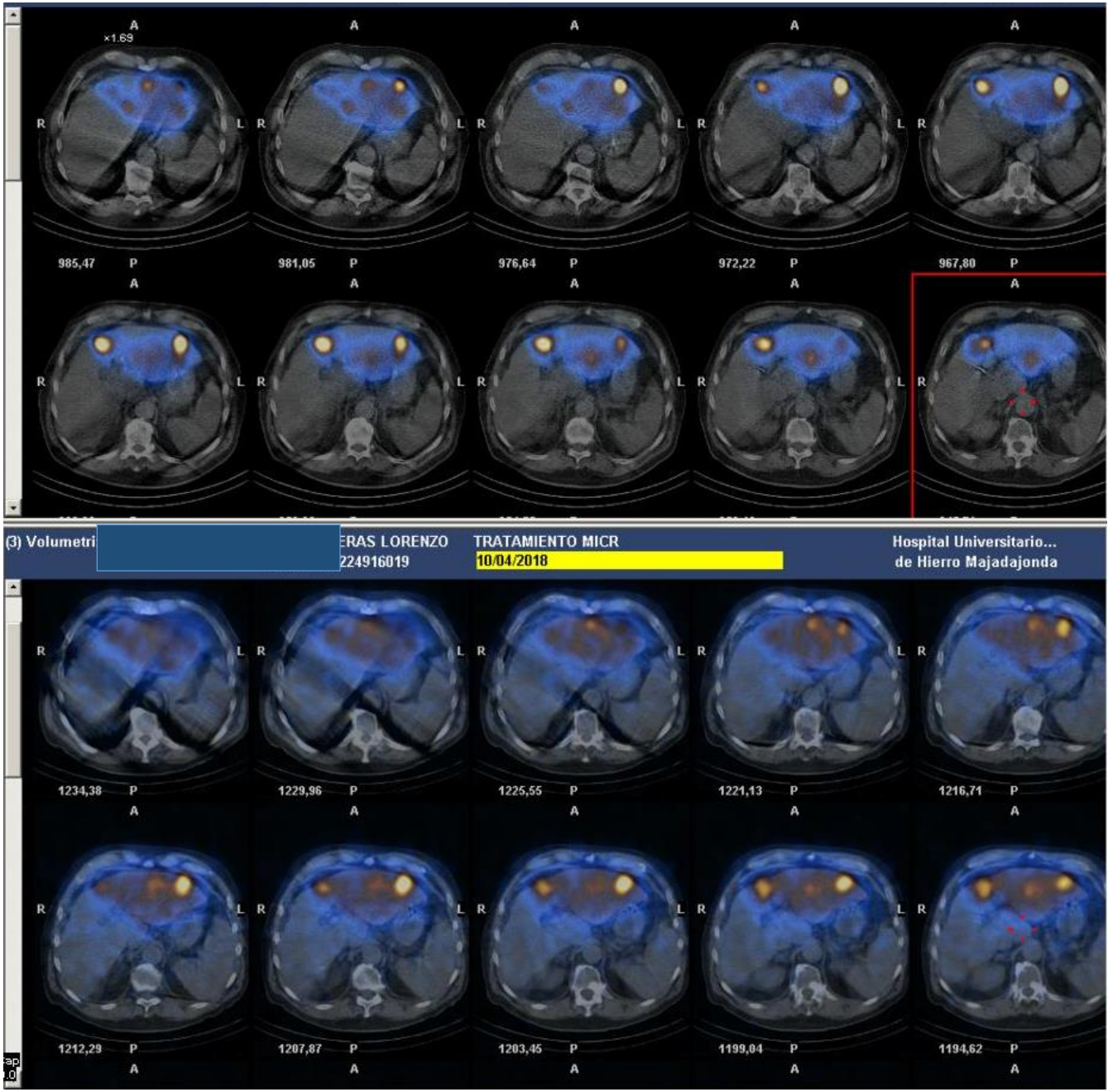


Volumen: 649 cc

Paso a kg x factor 1.03 g/cm^3

99mTc-MAA

90Y microesferas



Personalized Dosimetry with Intensification Using ^{90}Y-Loaded Glass Microsphere Radioembolization Induces Prolonged Overall Survival in Hepatocellular Carcinoma Patients with Portal Vein Thrombosis

J Nucl Med 2015; 56:339–346

Estudio retrospectivo de 41 pacientes. 66% SIRT primera línea

MIRD: Tumor ≥ 205Gy, hígado sano < 120 Gy, pulmón < 30 o 50 Gy acumulados

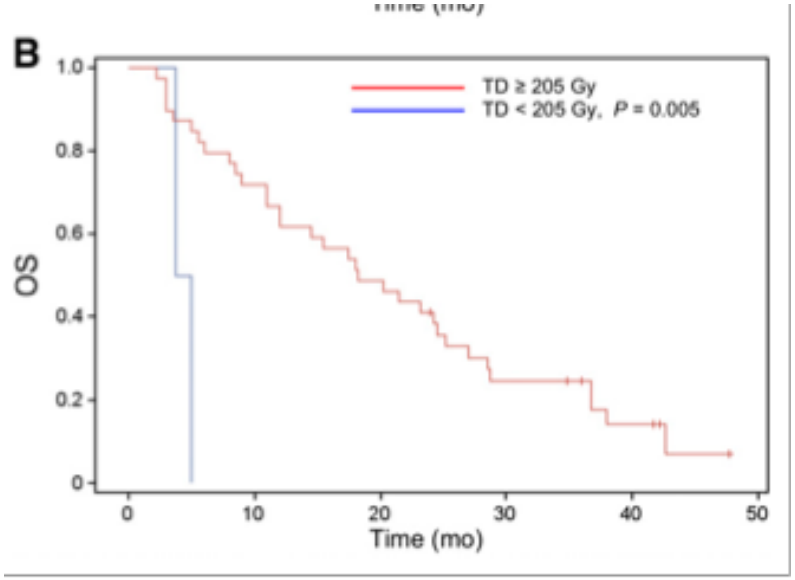
99mTc-MAA SPET-TC dosimetría

Dosis tumor y captación en PVT factores pronósticos

Treatment-Intensification Patients (n = 15), Baseline Characteristics, Percentage of Intensification, Dosimetry, and Response

Clinical variable	Value
Tumoral involvement (%)	35.6 ± 15.6
Tumoral size (cm)	8.8 ± 3.5
Child A/B (n)	15/1
Injected activity (GBq)	3.3 ± 1.8
Boost* (%)	56 ± 40
ILD (Gy)	187 ± 48
TD (Gy)	353 ± 103
HILD (Gy)	85 ± 25
Response rate (%)	81

*Percentage increase in injected activity with reference to standard activity that should have been injected to achieve ILD of 120 Gy.



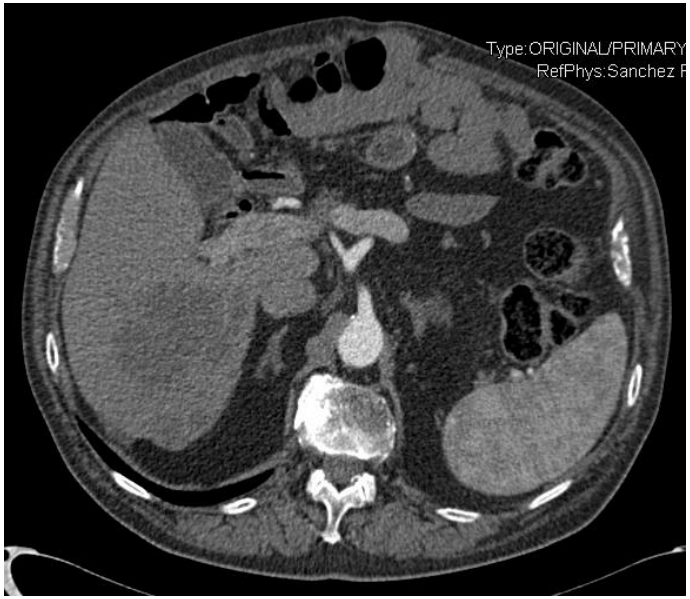
Índice respuesta 85%

Conclusiones

- Terapia metabólica tiene unas características propias
- Como medicamento : toxicidad y eficacia, ficha técnica
- Radiactivo: obtener imagen, dosimetría “un dato más”
    - Método “sencillo”
    - Repercusión clínica

Tenemos mas preguntas que respuestas

Pero estamos en camino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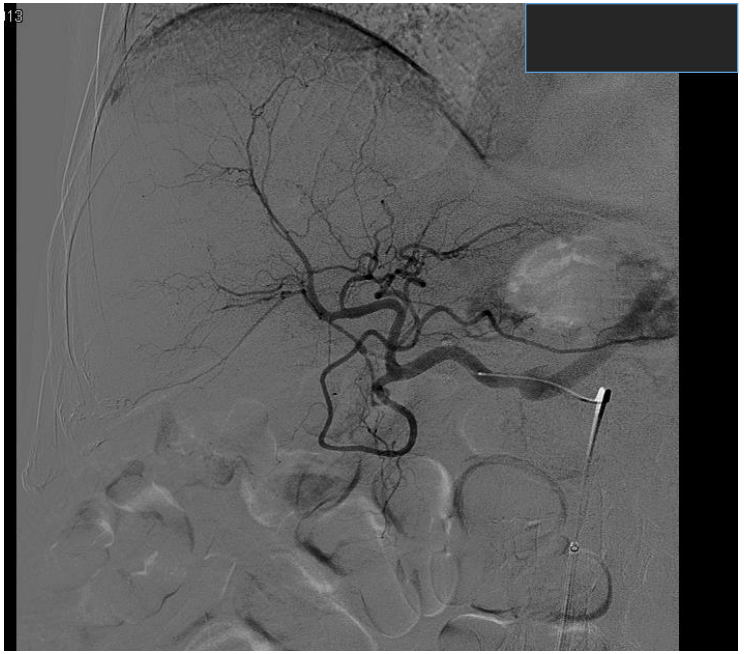
RefPhys:Sanchez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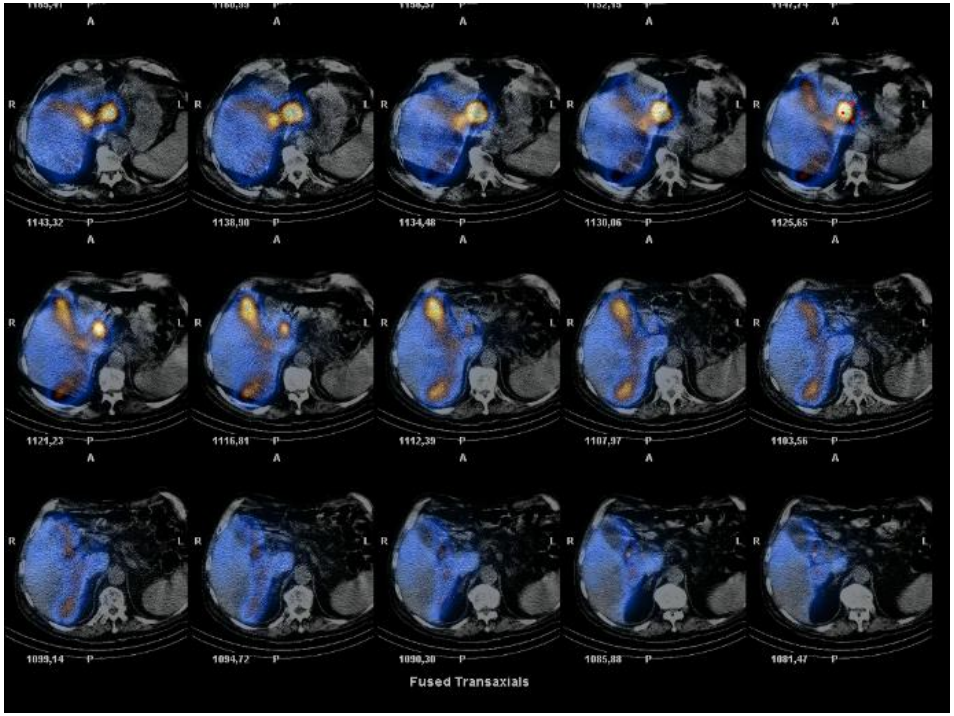
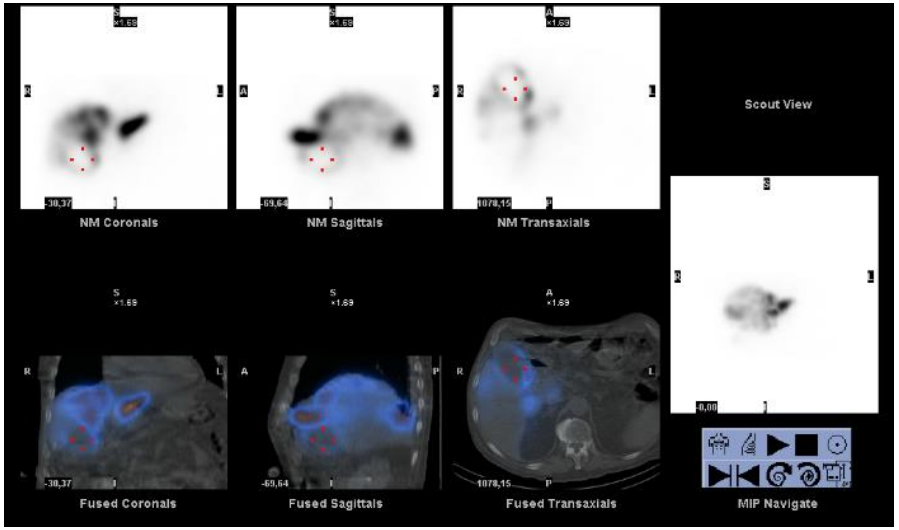

Fused Transaxials


NM Coronals
NM Sagittals
NM Transaxials
Scout View
Fused Coronals
Fused Sagittals
Fused Transaxials
MIP Navigate

Is a Technetium-99m Macroaggregated Albumin Scan Essential in the Workup for Selective Internal Radiation Therapy with Yttrium-90? An Analysis of 532 Patients

J Vasc Interv Radiol 2017; ■:1–7

Criterios que contraindican o modifican SIRT:

-**Shunt hepatopulmonar** > 20% (radiación pulmonar)

- Tumor primario único
  - 18% mts hepáticas shunt >10%
- Invasión vascular

-**Captación gastrointestinal de MAA**

- Localización catéter, administración selectiva

-**Mismatch entre la captación hepática** de MAA y la distribución tumoral:

- Experiencia del grupo
- Tumor solitario
- Ttº previo con antiangiogénicos

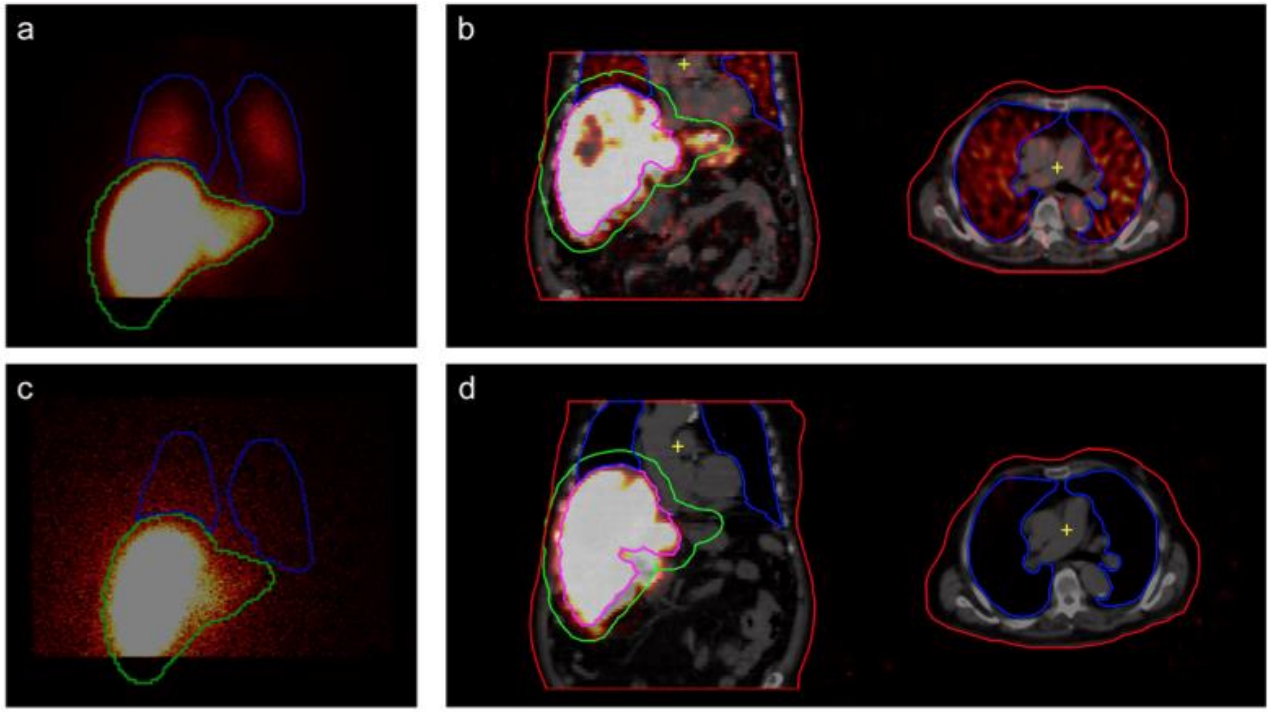
^{99m}Tc-MAA overestimates the absorbed dose to the lungs in radioembolization: a quantitative evaluation in patients treated with ^{166}Ho-microspheres

Eur J Nucl Med Mol Imaging (2014) 41:1965–1975

Cuantificación del shunt pulmonar sobreestimado en las imágenes planares : sin corrección por scatter ni atenuación. Mejora SPET-TC

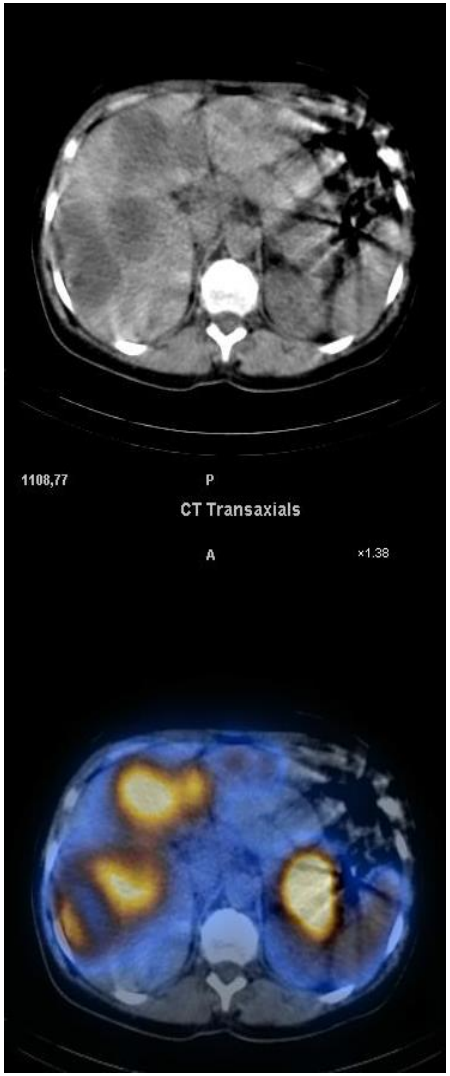
99mTcMAA

166Ho-micro

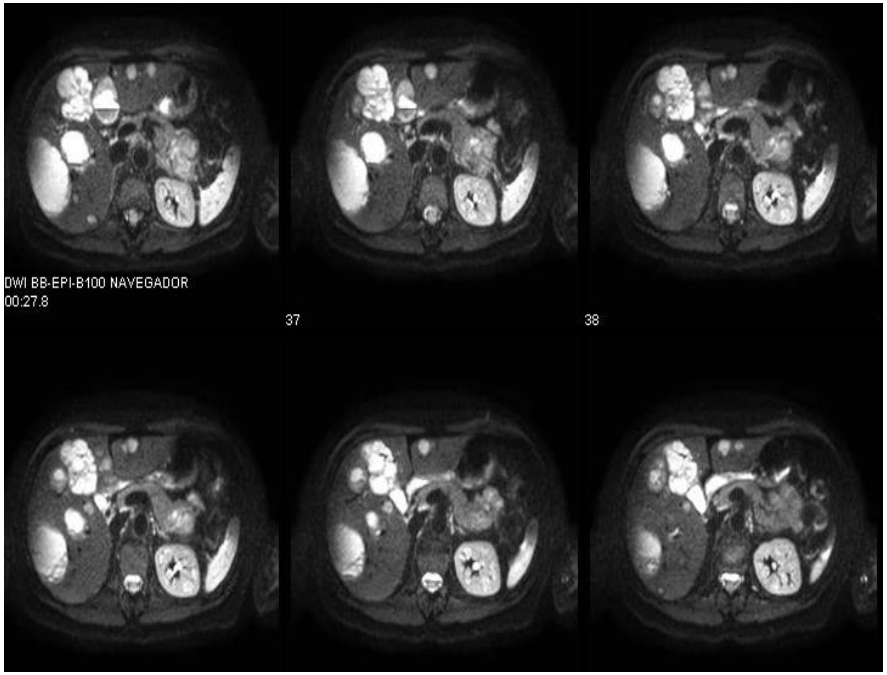


Mejoría de los resultados si se utilizaran las mismas microesferas para diagnóstico y tratamiento

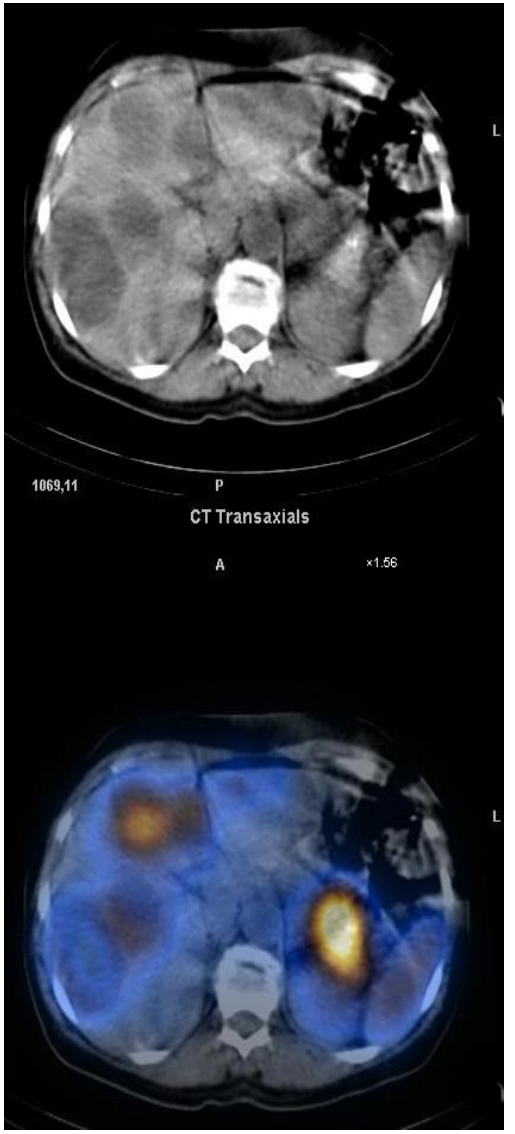
3-2015

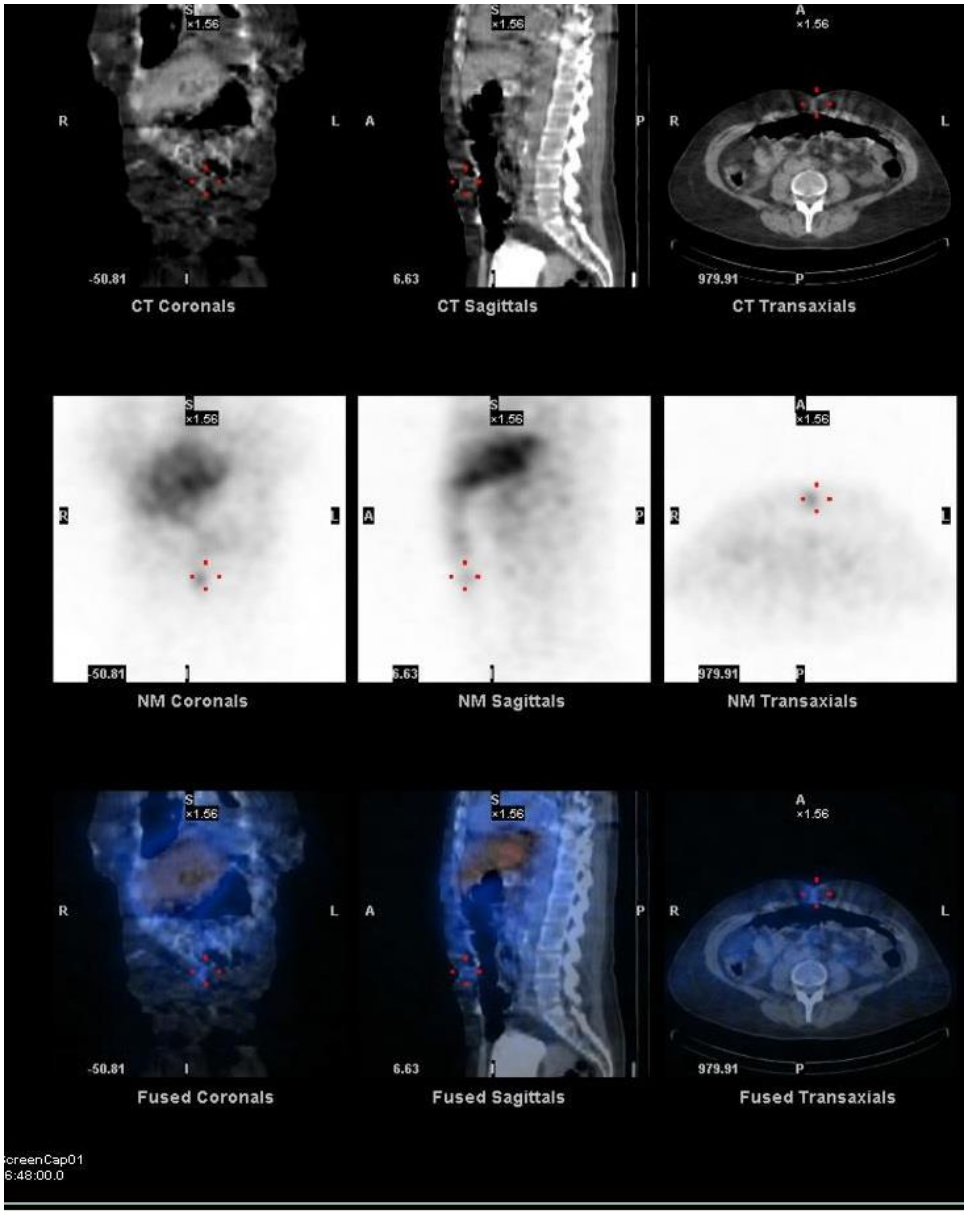


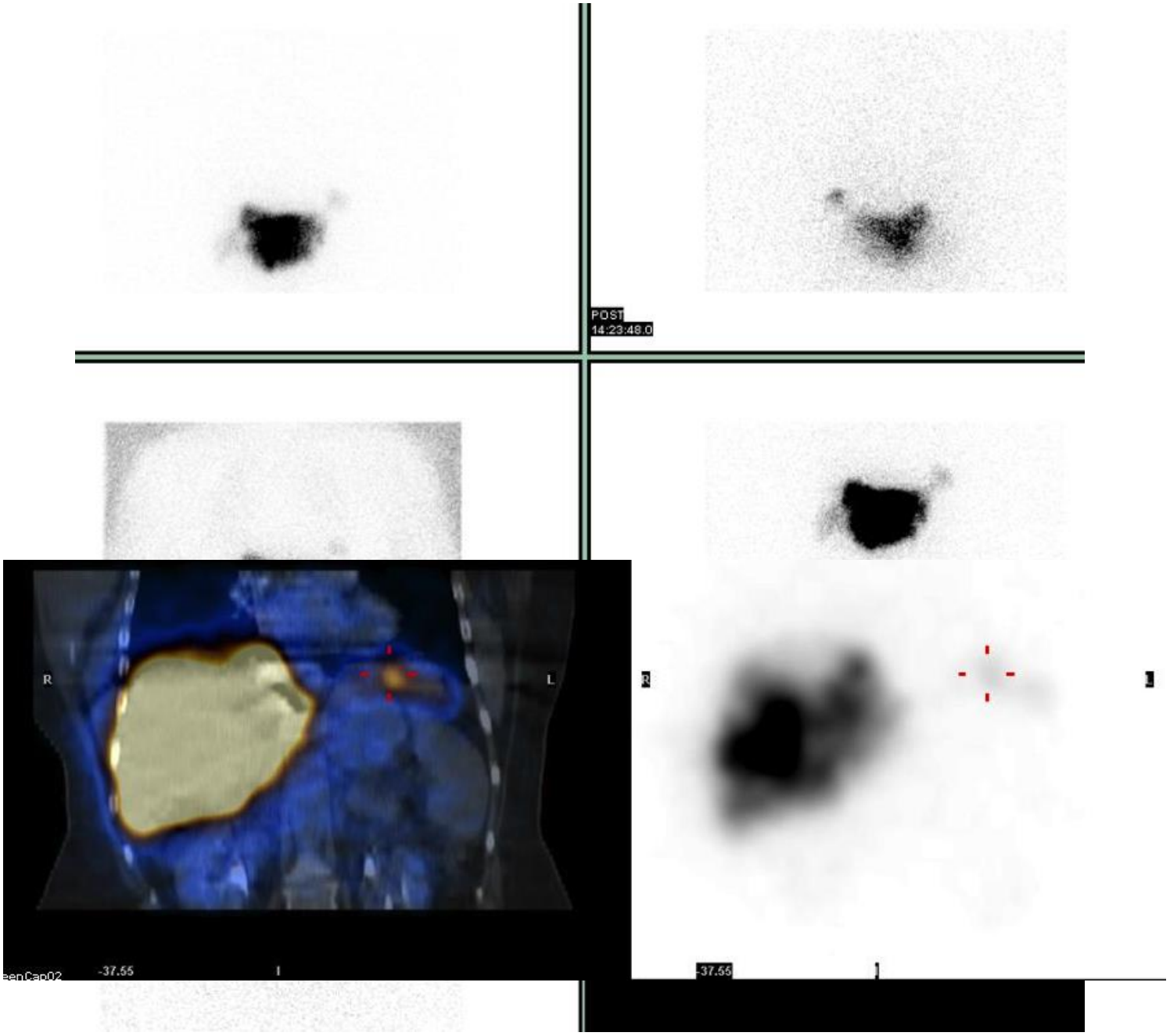
6-2015



7-2015




CT Coronals
CT Sagittals
CT Transaxials
NM Coronals
NM Sagittals
NM Transaxials
Fused Coronals
Fused Sagittals
Fused Transaxials


POST
14:23:48.0
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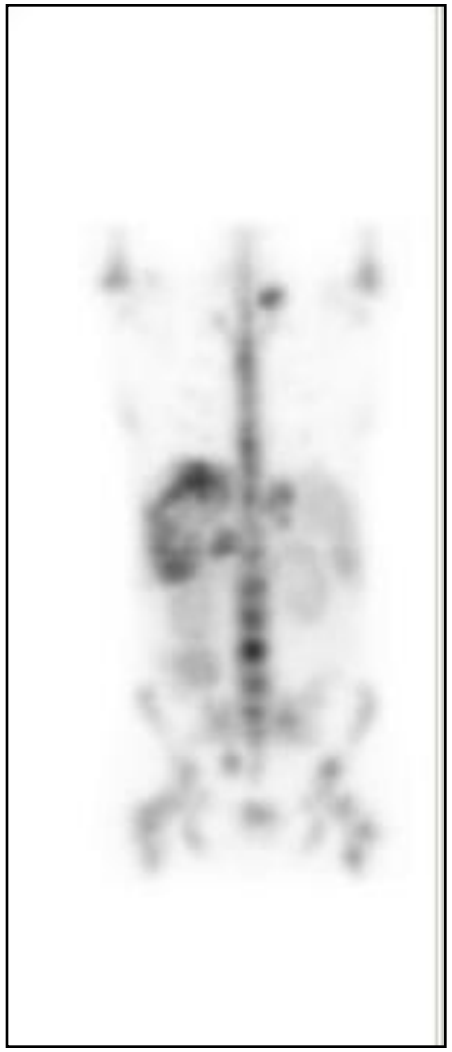
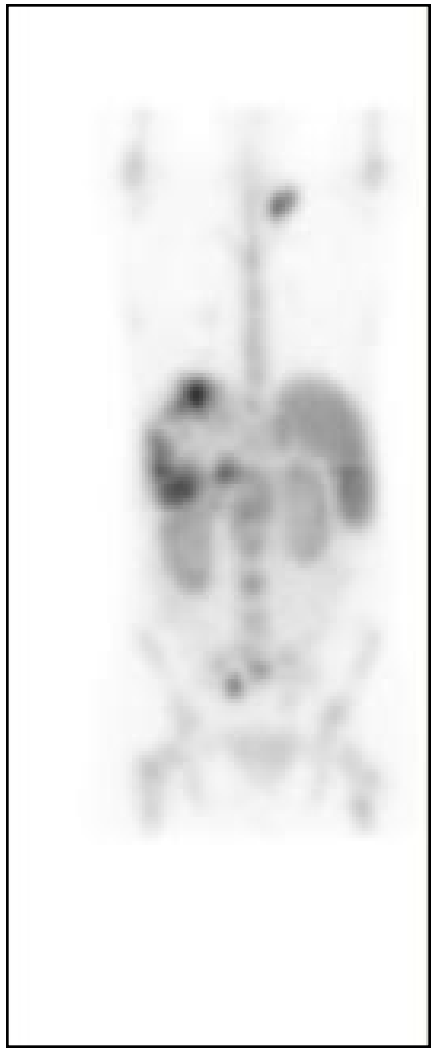
-37.55

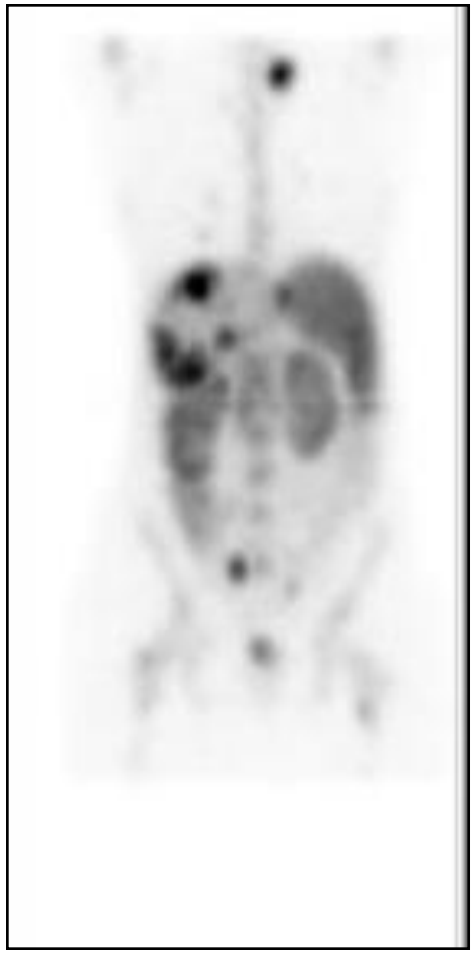
p-NET 177LU-DOTATATE



1st cycle



3rd cycle



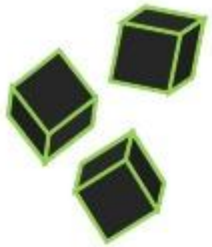
4th cycle

Dosimetría 131I en CDT: retos

- Actividad (MBq) ≠ dosis absorbida (Gy)
- Buscamos una sola administración
- Imposible hasta ahora relacionar actividad – supervivencia

Cambio cultura

Casos especiales:
niños, alto riesgo,
radiorresistencia ….



MAGNITUDES UTILIZADAS PARA CUANTIFICAR EFECTOS ESTOCÁSTICOS

- Dosis absorbida: Energía absorbida por unidad de masa.
  Julio/kilogramo; Gray (Gy).

- Dosis equivalente: Dosis absorbida ponderada por el factor de ponderación de la radiación.
  Julio/kilogramo; Sievert (Sv).

- Dosis efectiva: Dosis equivalente ponderada por el factor de ponderación de tejido.
  Julio/kilogramo; Sievert (Sv).

ATA risk staging (TNM)	Description	Body of evidence suggests RAI improves disease specific survival?	Body of evidence suggests RAI improves disease free survival?	Postsurgical RAI indicated?
▪ ATA low risk ▪ T1a ▪ N0, Nx ▪ M0, Mx	Tumor size ≤1 cm (uni- or multifocal)	No	No	No
▪ ATA low risk ▪ T1b, T2 ▪ N0, Nx ▪ M0, Mx	Tumor size >1 to 4 cm	No	Conflicting observational data	Not routine* — May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk)
▪ ATA low to intermediate risk ▪ T3 ▪ N0, Nx ▪ M0, Mx	Tumor size >4 cm	Conflicting data	Conflicting observ	nsider presence of other ing age may favor RAI use age and tumor size certainty.¶
▪ ATA low to intermediate risk ▪ ▪ ▪ N	Micr		ional data	Consider* — Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
▪ ATA inte risk ▪ T1-3 ▪ N1a ▪ M0, Mx	tral compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider* — Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2 to 3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.¶ However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
▪ ATA low to intermediate risk ▪ T1-3 ▪ N1b ▪ M0, Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider* — Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.¶

individualizar

Radiopharmaceutical	Procedure	Compounds used for pre-treatment imaging
^{131}I NaI	Benign thyroid disease	^{131}I NaI ^{124}I NaI ^{123}I NaI
^{131}I NaI	Differentiated thyroid cancer (DTC) with ablative intent and in the case of recurrent disease	^{131}I NaI ^{124}I NaI ^{123}I NaI
^{131}I mIBG	Neuroblastoma in children and young adults	^{131}I mIBG ^{124}I mIBG ^{123}I mIBG
^{131}I mIBG	Neuroendocrine tumors in adults	^{131}I mIBG ^{124}I mIBG ^{123}I mIBG
^{177}Lu DOTATATE	Neuroendocrine tumors	Radiolabelled somatostatin analogs
^{90}Y somatostatin analogs	Adult neuroendocrine disease	Analogs, as ^{86}Y–DOTATOC ^{111}In-DOTATATE
$^{89}SrCl_2$, ^{153}Sm-EDTMP, ^{186}Re-HEDP, and ^{188}Re-HEDP	Bone pain palliation	^{99m}Tc-MDP for ^{153}Sm-EDTMP
^{223}Ra dichloride	Bone metastases from castration-resistant prostate cancer	^{99m}Tc-MDP
^{177}Lu PSMA ligands	Metastatic castration-resistant pros tate cancer	Analog PET ligands
^{90}Y microspheres	Liver metastases or primary tumors	^{99m}Tc-albumin macro aggregate
^{90}Y-ibritumomab tiuxetan	Non-Hodgkin's lymphoma	^{111}In-ibritumomab tiuxetan
^{90}Y, ^{32}P, and ^{186}Re colloid, ^{169}Er citrate	Radiosynovectomy	^{99m}Tc MDP/HDP/HEDP and/or ^{99m}Tc-HIG