I SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

Vigo, del 28 de febrero al 1 de marzo de 2019

Medicina Nuclear: la imagen molecular

Dra. María José García Velloso
Servicio de Medicina Nuclear
Clínica Universidad de Navarra

I SIMPOSIO NACIONAL de ONCOLOGÍA de PRECISIÓN

Vigo, del 28 de febrero al 1 de marzo de 2019

MEDICINA P4

- **PREVENTIVA**
- **PREDICTIVA**

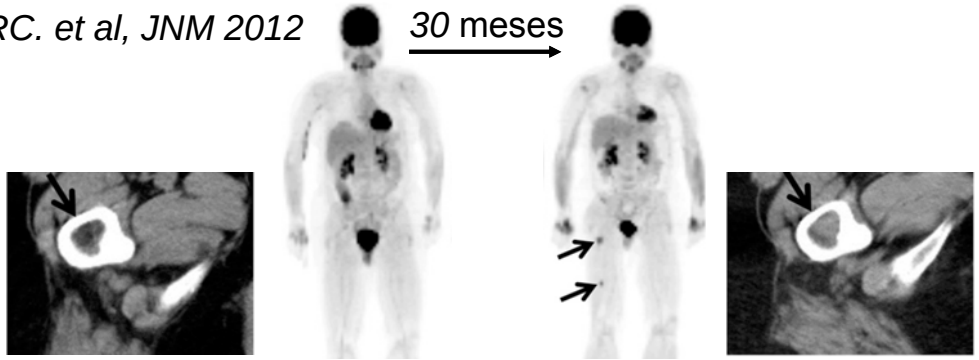
  Test diagnósticos para predecir cuándo se hará sintomática la enfermedad.
- **PERSONALIZADA**

  En cada individuo el tratamiento indicado y en el momento adecuado.
- **PARTICIPATIVA**
  - Investigadores (I. Traslacional)
  - Oncólogos (Asistencia e I. Clínica)
  - Pacientes

O. Schillaci et al. Eur J Nucl Med Mol Imaging. 2017

GMSI **Mieloma quiescente**

Walker RC. et al, JNM 2012 *30* meses



^{18}F-FDG PET/CT lesiones focales, aún sin componenete lítico, predicen la progresión de mieloma quiescente a enfermedad activa.

E. Zamagni et al. Leukemia 2016

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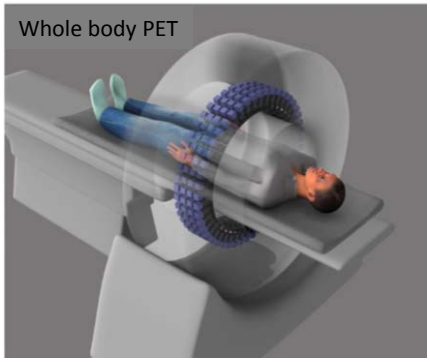
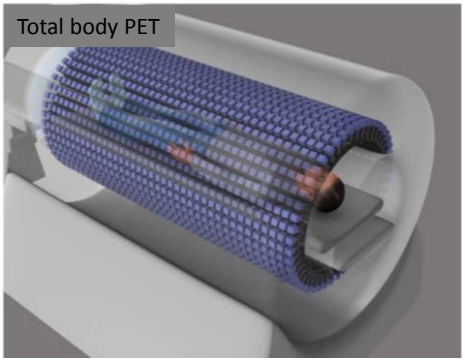
Medicina Nuclear: Imagen Molecular

- Diagnóstico no invasivo de la base molecular de la enfermedad: permite caracterizar procesos biológicos a nivel molecular y celular.
- Detección precoz de cambios o **marcadores** moleculares, celulares y tisulares asociados con la enfermedad.
- Imagen de todo el paciente (identifica heterogeneidad tumoral, permite dirigir biopsias).
- Monitorización no invasiva de la respuesta al tratamiento y de la progresión tumoral.

O. Schillaci et al. Eur J Nucl Med Mol Imaging. 2017





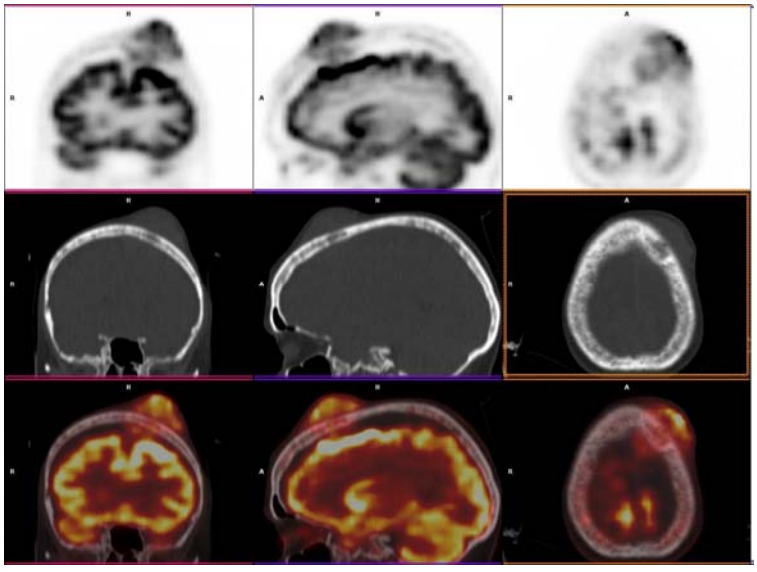
University of California Davis Medical Center

SR Cherry et al. Sci Transl Med. 2017
SR Cherry et al. J Nucl Med 2018

^{18}F-FDG PET/CT

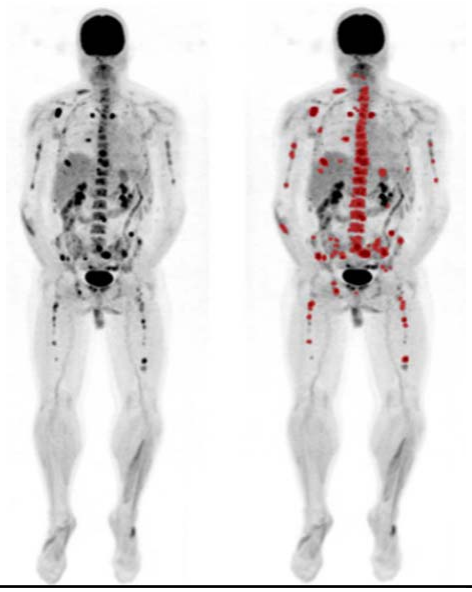
Clínica Universidad de Navarra

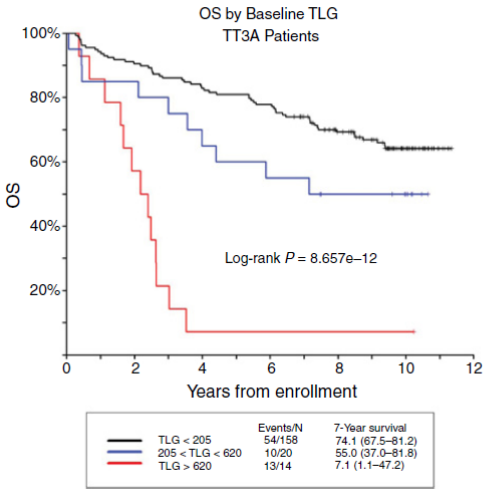
Paciente de 54 años con Mieloma múltiple IgG lambda



Assessment of Total Lesion Glycolysis by FDG PET/CT signigicantly improves prognostic value of GEP and ISS in Myeloma

McDonald et al. Clinical cancer research 2017





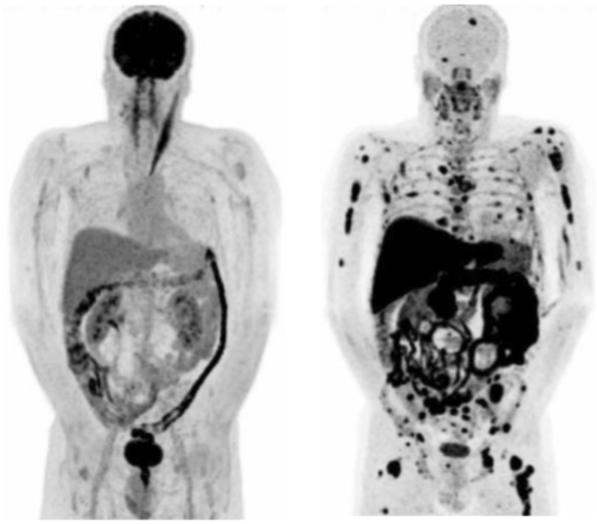
Nuclear medicine imaging of multiple myeloma, particularly in the relapsed setting

Esther G. M. de Waal[1] · Andor W. J. M. Glaudemans[2] · Carolien P. Schröder[3] · Edo Vellenga[1] · Riemer H. J. A. Slart[2,4]

Eur J Nucl Med Mol Imaging 2017

Mechanism of action	Tracer	Target
Cell metabolism		
Glucose	[18 F]-FDG	Glucose uptake
Amino acid	[11C]-MET	Methionine
	[18 F]-FAMT	L-type aminoacid transporter 1
Nucleotide	[18 F]-FLT	Activity of thymidine kinase
	[11C] -4DST	Activity of thymidine kinase
Membrane metabolism	[11C]-ACT	Acetate/fatty acid synthesis
	[11C]-choline	Choline
Receptor targeting		
Somatostatin receptor scintigraphy	[111In]-pentetreotide	Somatostatin receptor
Chemokine receptor 4	[68Ga]-Pentixafor	CXCR-4 receptor
Very-late-antigen-4	[64Cu]-CB-TE1A1P-LLP2	VLA-4
Mitochondrial activity		
	[99mTc]-sestamibi	Mitochondria
	[99mTc]-tetrofosmin	Mitochondria
Angiogenesis and hypoxia		
Hypoxia	[18 F]-FAZA	Hypoxia
Angiogenesis	[89Zr]-bevacizumab	Circulating VEGF

^{11}C-methionine PET/CT in multiple myeloma: comparison with ^{18}FDG PET/CT and diagnostic value through clinical and biological parameters.

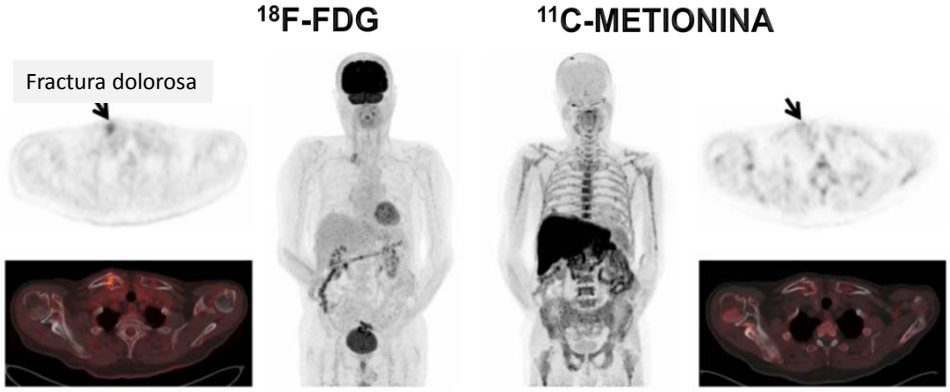


Garcia-Velloso et al. Eur J Nucl Med Mol Imaging. 2016

^{11}C-Methionine-PET in Multiple Myeloma: A Combined Study from Two Different Institutions

Theranostics
2017; 7(11): 2956-2964. doi: 10.7150/thno.20491

Constantin Lapa[1*✉], Maria J. Garcia-Velloso[2*], Katharina Lückerath[1], Samuel Samnick[1], Martin Schreder[3], Paula Rodriguez Otero[2], Jan-Stefan Schmid[1], Ken Herrmann[1,4], Stefan Knop[3], Andreas K. Buck[1], Hermann Einsele[3], Jesus San-Miguel[2#], Klaus Martin Kortüm[3#]



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Vigo, del 28 de febrero al 1 de marzo de 2019

Innovación tecnológica: Impacto del diagnóstico por imagen en la Medicina personalizada

- Biomarcadores de imagen con alta sensibilidad y especificidad.
- Valor pronóstico en el estudio basal.
- Valor predictivo: los nuevos radiofármacos permiten la selección de pacientes para terapias dirigidas y también para terapias dirigidas con radionúclidos.

TERAGNOSIS

Nuclear medicine imaging of multiple myeloma, particularly in the relapsed setting

Esther G. M. de Waal[1] · Andor W. J. M. Glaudemans[2] · Carolien P. Schröder[3] · Edo Vellenga[1] · Riemer H. J. A. Slart[2,4]

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Very-late-antigen-4	[64Cu]-CB-TE1A1P-LLP2	VLA-4
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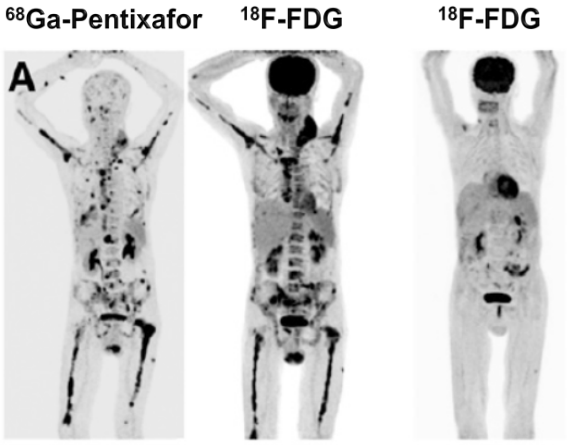
Angiogenesis and hypoxia		
Hypoxia	[18 F]-FAZA	Hypoxia
Angiogenesis	[89Zr]-bevacizumab	Circulating VEGF

First-in-Human Experience of CXCR4-Directed Endoradiotherapy with ^{177}Lu- and ^{90}Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma with Extensive Intra- and Extramedullary Disease

J Nucl Med 2016; 57:248–251



TERAGNOSIS	MIELOMA MÚLTIPLE	CÁNCER DE PRÓSTATA	TUMORES Neuroendocrinos
Diag. no invasivo Nuevos trazadores (Radiofarmacia)	^{68}Ga-pentixafor (CXCR4)	^{68}Ga-PSMA (PSA> 0.2 ng/ml)	^{68}Ga-DOTATATE (FDA 2016) ^{68}Ga-DOTATOC (EMA 2017)
Terapia Nuevos tratamientos (Radiofarmacia)	^{68}Ga-pentixather	^{177}Lu-PSMA	^{177}Lu-DOTATATE
Valoración de respuesta	^{68}Ga-pentixafor FDG	^{68}Ga-PSMA	^{68}Ga-DOTATATE

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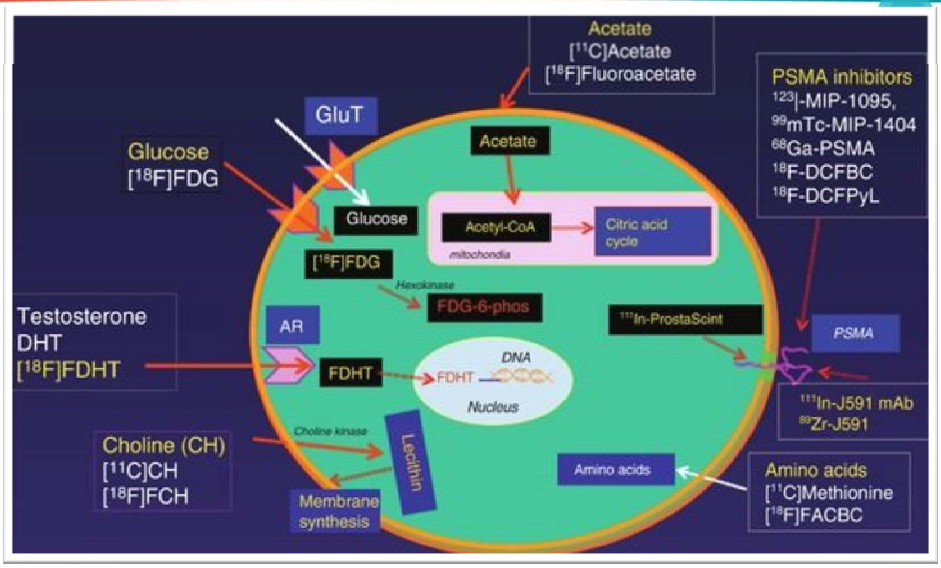
CÁNCER DE PRÓSTATA



Dual Tracer ^{11}C-Choline and FDG-PET in the Diagnosis of Biochemical Prostate Cancer Relapse After Radical Treatment

José A. Richter,[1] Macarena Rodríguez,[1] Jorge Rioja,[2] Iván Peñuelas,[1] Josep Martí-Climent,[1] Puy Garrastachu,[1] Gemma Quincoces,[1] Javier Zudaire,[2] María J. García-Velloso[1]

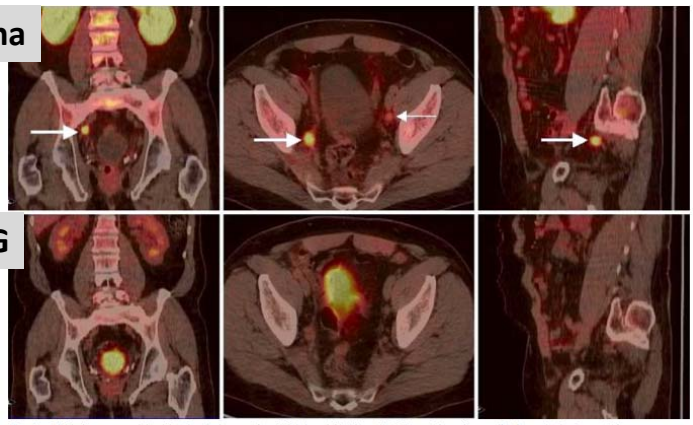
[1]Nuclear Medicine Department, Clínica Universitaria, Universidad de Navarra, Avda. Pío XII 36, 31008, Pamplona, Spain
[2]Urology Department, Clínica Universitaria, Universidad de Navarra, Avda. Pío XII 36, 31008, Pamplona, Spain

Clínica Universidad de Navarra

Mol Imaging Biol. 2010

^{11}C-Colina

^{18}F-FDG



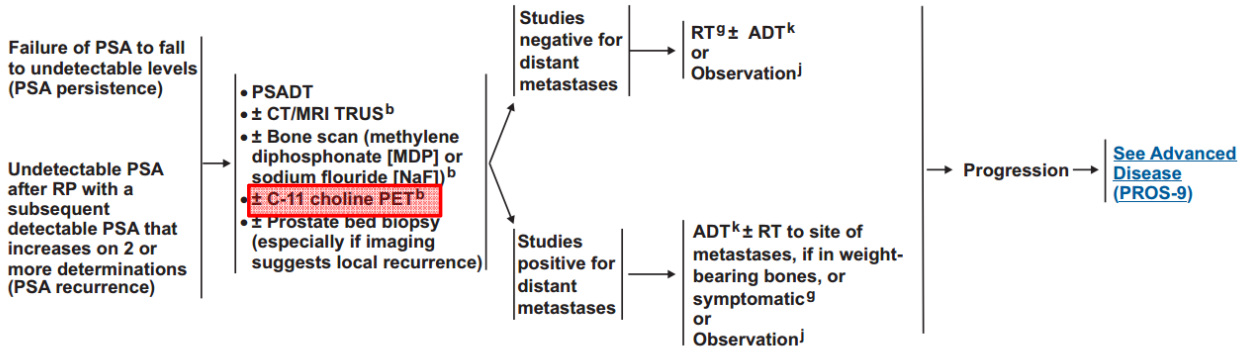
Paciente de 55 años, prostatectomía radical hace 27 meses, PSA 1,4 µg/l

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

RADICAL PROSTATECTOMY BIOCHEMICAL FAILURE

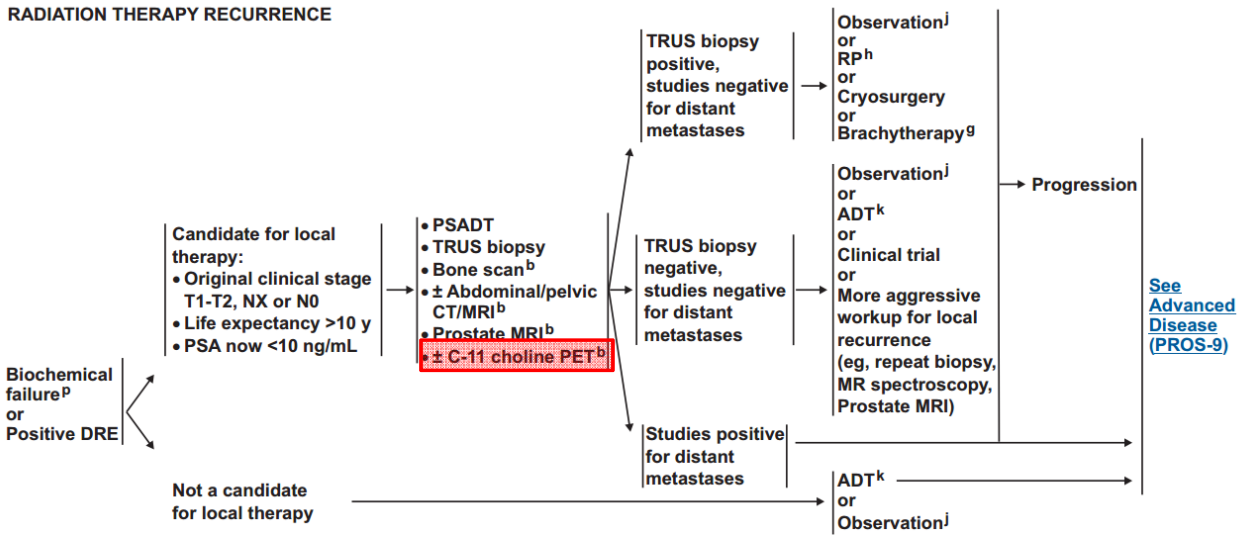


NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

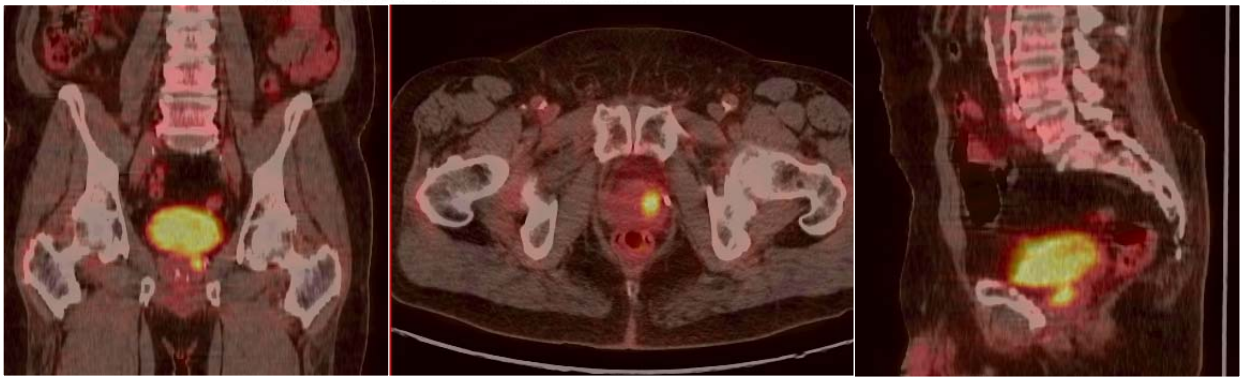
RADIATION THERAPY RECURRENCE



Dual Tracer ^{11}C-Choline and FDG-PET in the Diagnosis of Biochemical Prostate Cancer Relapse After Radical Treatment

José A. Richter,[1] Macarena Rodríguez,[1] Jorge Rioja,[2] Iván Peñuelas,[1] Josep Martí-Climent,[1] Puy Garrastachu,[1] Gemma Quincoces,[1] Javier Zudaire,[2] María J. García-Velloso[1]

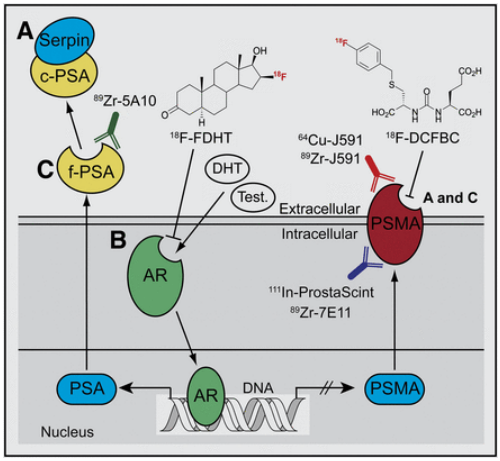
Mol Imaging Biol. 2010



Paciente tratado mediante radioterapia externa 60 meses antes.
BAC por recidiva bioquímica (PSA=2,1 ng/ml). Biopsia prostática negative.

EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer

N. Mottet (Chair), J. Bellmunt, E. Briers (Patient Representative), M. Bolla, L. Bourke, P. Cornford (Vice-chair), M. De Santis, A.M. Henry, S. Joniau, T.B. Lam, M.D. Mason, H.G. van der Poel, T.H. van der Kwast, O. Rouvière, T. Wiegel
Guidelines Associates: N. Arfi, R.C.N. van den Bergh, T. van den Broeck, M. Cumberbatch, N. Fossati, T. Gross, M. Lardas, M. Liew, P. Moldovan, I.G. Schoots, P.M. Willemse

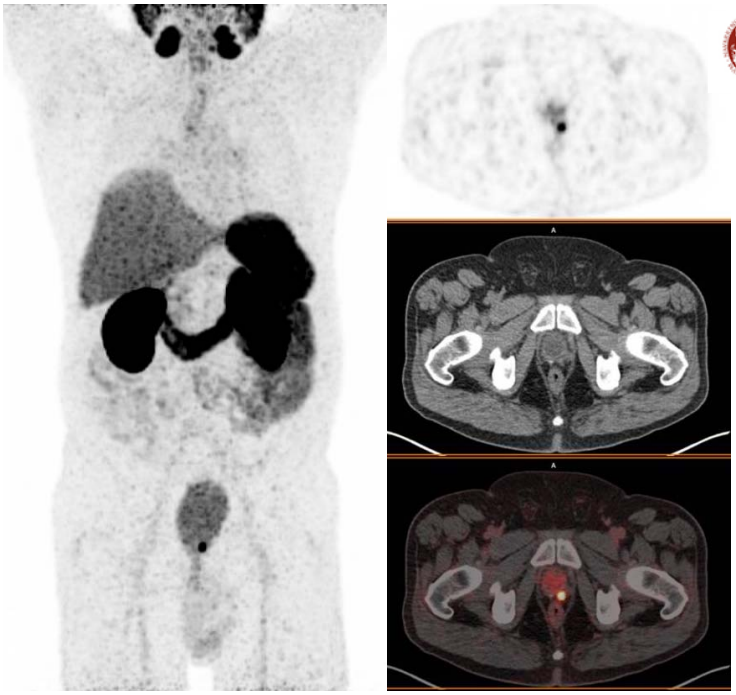


^{68}Ga-PSMA PET/CT has shown promising potential in patients with BCR. Detection rates of 58% and 76% have been reported for PSA ranges of 0.2-1 and 1-2 ng/mL, respectively [256]. This suggests that ^{68}Ga-PSMA is substantially more sensitive at low PSA levels than choline PET/CT. Two head-to-head comparisons confirmed this finding [651, 652]. However, studies incorporated varying proportions of initial therapy (RP or RT) and a majority of studies included patients on current ADT. Further prospective studies on homogeneous populations are needed to better define the role of ^{68}Ga-PSMA PET/CT in patients with BCR. Therefore it cannot yet be considered as a standard evaluation tool. However, in case local salvage treatment is planned and ^{68}Ga-PSMA PET/CT is available, it should be considered as a valuable assessment option.

^{68}Ga-PSMA

CÁNCER DE PRÓSTATA

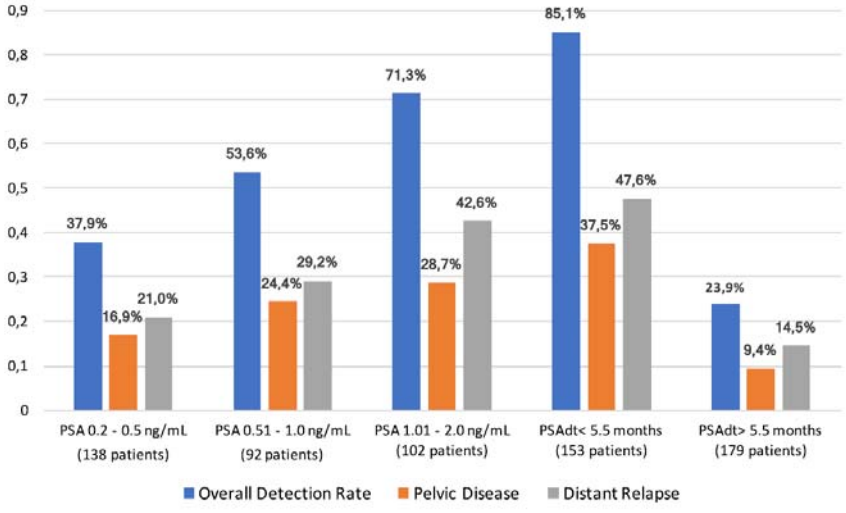
PSA=0,4 ng/ml



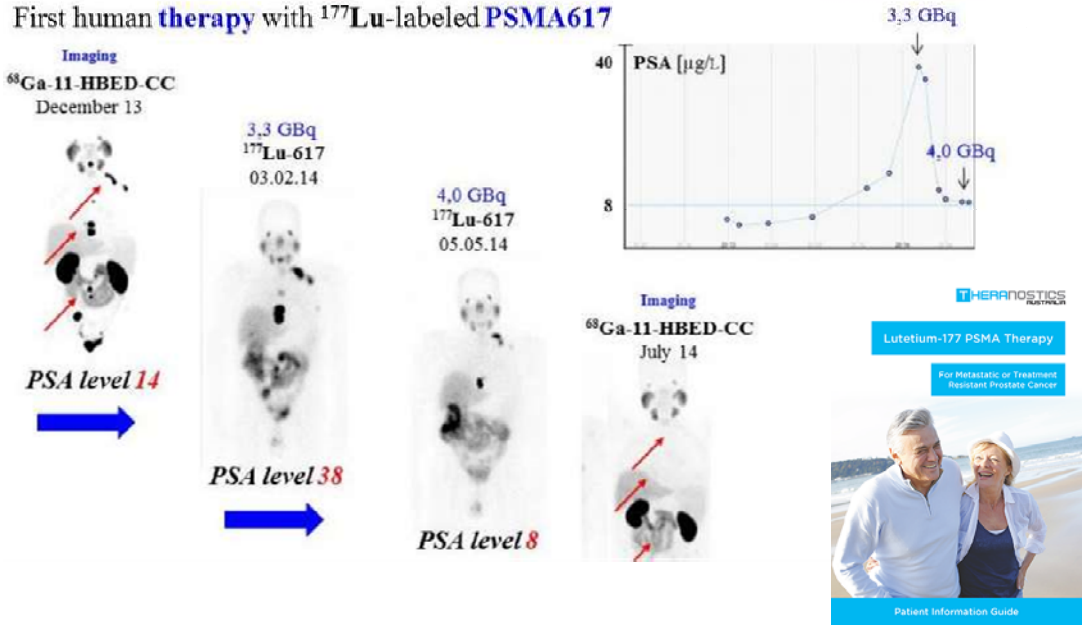
European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:31–39
https://doi.org/10.1007/s00259-018-4189-7

ORIGINAL ARTICLE

^{68}Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy



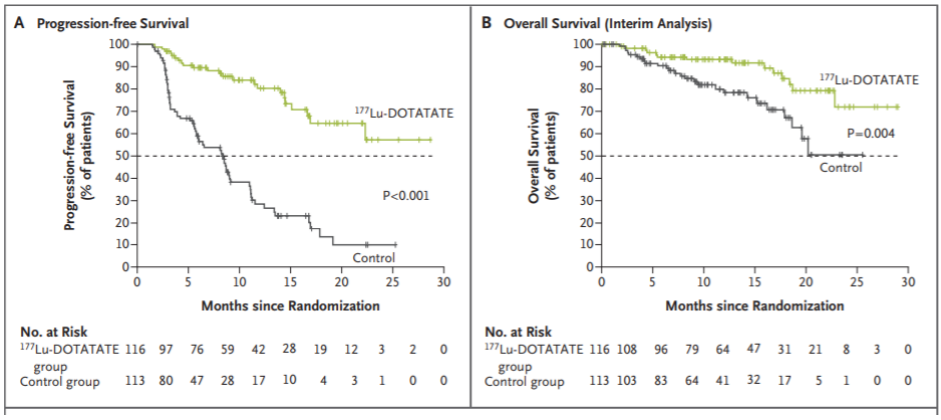
Pacientes con cáncer de próstata metastásico resistente a tratamiento



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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



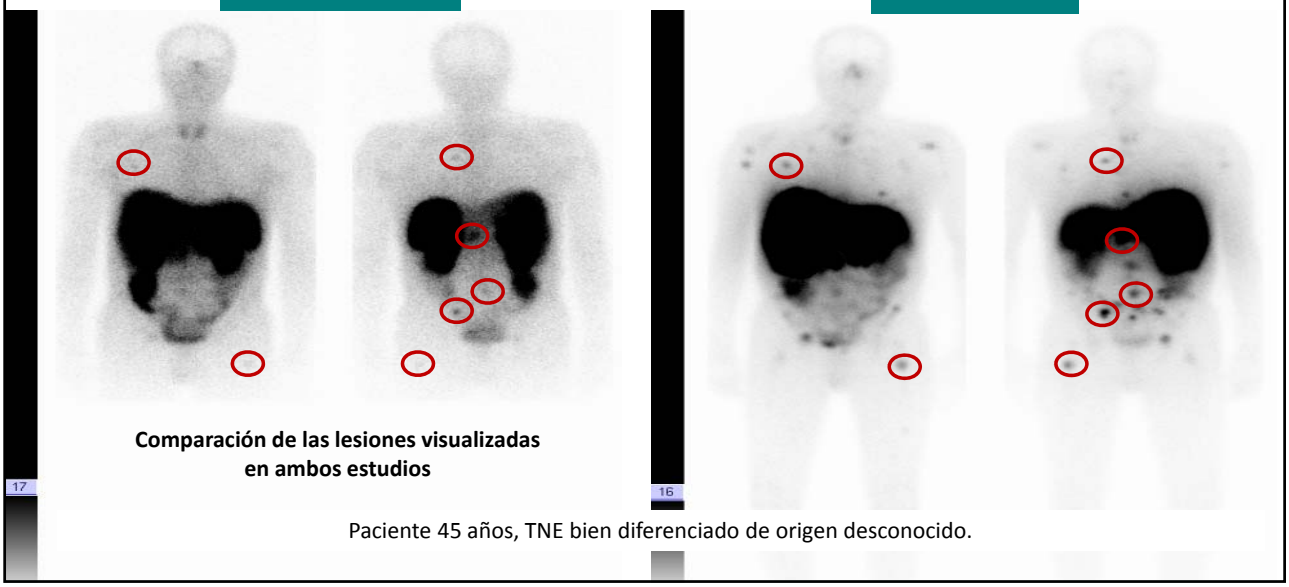
Strosberg J. New England J Med 2017

PRRT y rastreo post-tratamiento

Clínica Universidad de Navarra

^{111} In-Octreotide

^{177} Lu-DOTATATE

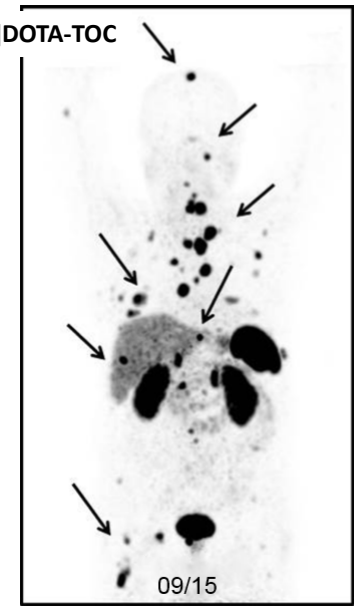


Comparación de las lesiones visualizadas en ambos estudios

Paciente 45 años, TNE bien diferenciado de origen desconocido.

TUMOR NEUROENDOCRINO

[^{68}Ga]DOTA-TOC



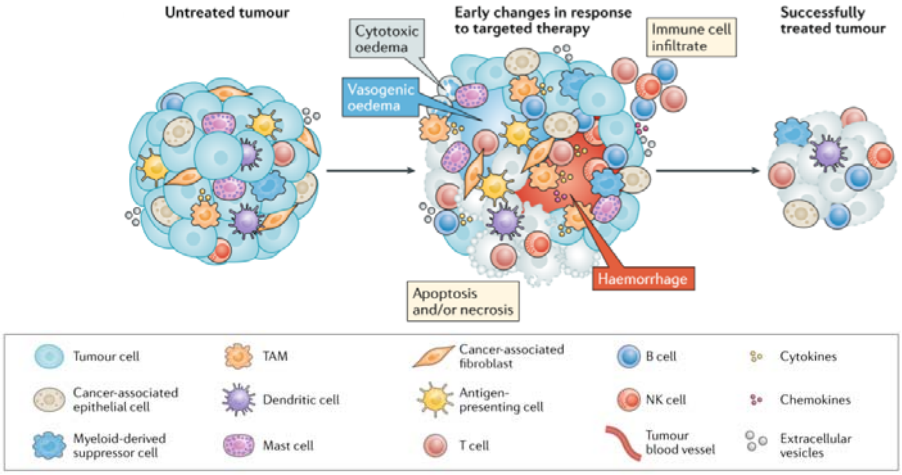
^{177}Lu-DOTA-TATE (3 Dosis)

[^{68}Ga]DOTA-TOC

Yordanova A. Oncotargets and Therapy. 2017

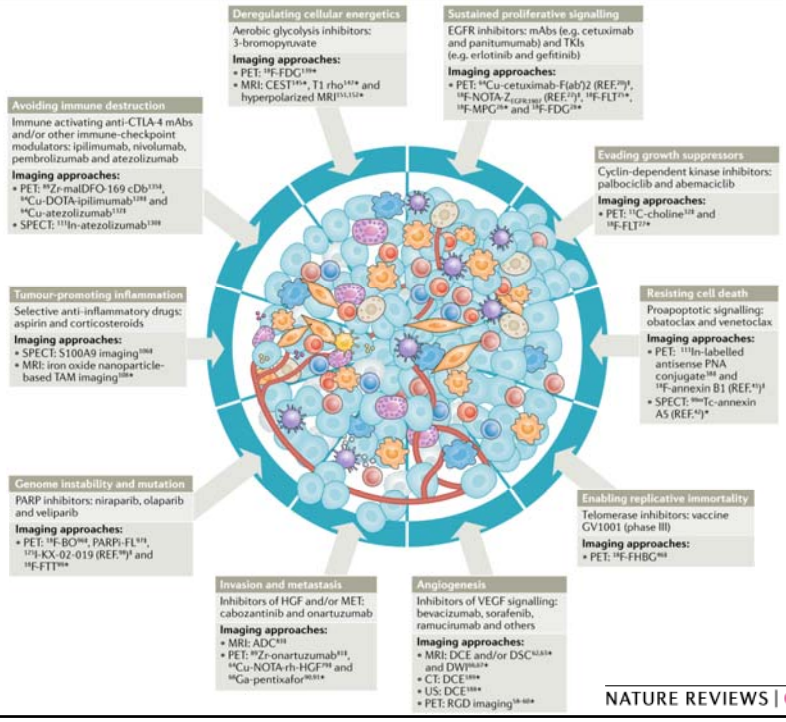
The beginning of the end for conventional RECIST — novel therapies require novel imaging approaches

*Mirjam Gerwing[1], Ken Herrmann[2], Anne Helfen[1], Christoph Schliemann[3], Wolfgang E. Berdel[3,4], Michel Eisenblätter[1,5,6] and Moritz Wildgruber[1,4,6]**



M. Gerwing et al.

NATURE REVIEWS | CLINICAL ONCOLOGY



M. Gerwing et al.

NATURE REVIEWS | CLINICAL ONCOLOGY

Immuno-PET with Zirconium-89-Labeled Monoclonal Antibodies in Oncology: Wath can we learn from initial Clinical Trials?

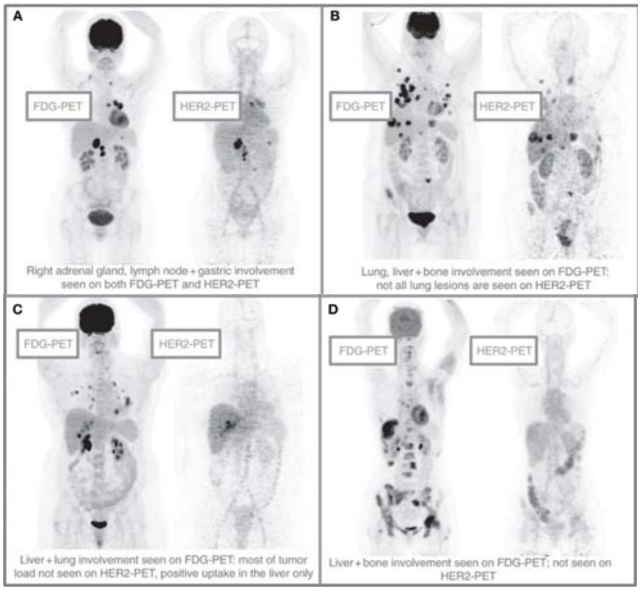
YWS Jauw et al. Front in Pharmacol 2016

Summary of clinical studies on ^{89}Zr-immunoPET in Oncology

Author	Year	Target	mAb	Tumor type
Börjesson	2006	CD44v6	cmAb U36	Head and neck cancer
	2009			
Dijkers	2010	HER2	trastuzumab	Breast cancer
Rizvi	2012	CD20	ibritumomab-tiuxetan	B-cell lymphoma
Gaykema	2013	VEGF-A	bevacizumab	Breast cancer
van Zanten	2013	VEGF-A	bevacizumab	Glioma
van Asselt	2014	VEGF-A	bevacizumab	Neuroendocrine tumors
Bahce	2014	VEGF-A	bevacizumab	Non-small cell lung canc
Pandit-Taskar	2014	PSMA	Hu-J591	Prostate cancer
	2015			
Den Hollander	2015	TGF-β	fresolimumab	Glioma
Gaykema	2015	HER2	trastuzumab	Breast cancer
		VEGF-A	bevacizumab	
Gebhart	2015	HER2	trastuzumab	Breast cancer
Lamberts	2015	MSLN	MMOT0530A	Pancreatic cancer
				Ovarian cancer
Menke-van der Houven van Oordt	2015	EGFR	cetuximab	Colorectal cancer
Muylle	2015	CD20	rituximab	B-cell lymphoma
Oosting	2015	VEGF-A	bevacizumab	Renal cell carcinoma

Molecular imaging as a tool to investigate heterogeneity of advanced HER2-positive breast cancer and to predict patient outcome under trastuzumab emtansine (T-DM1): the ZEPHIR trial.

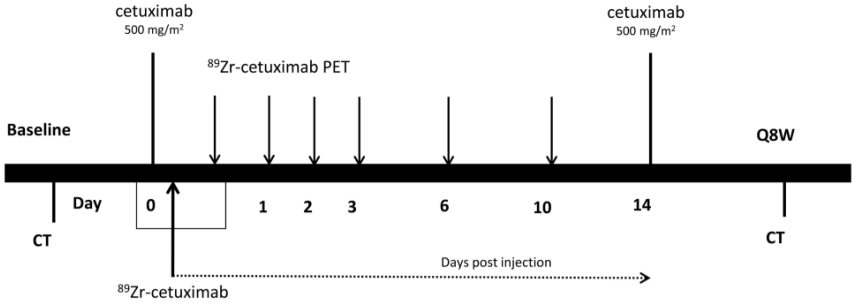
G Gebhart et al. Ann. Oncol. 2016 37, 619–624.



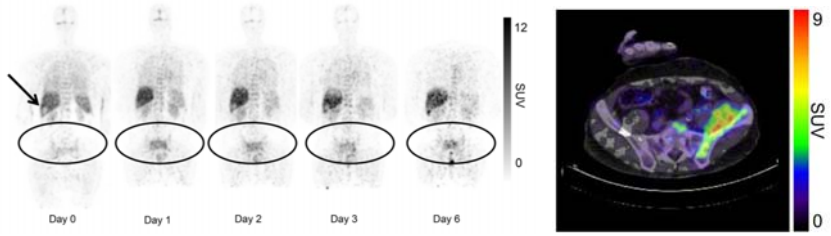
FDG PET y
HER2 InmunoPET
Patrones de captación:
(A)Todo el tumor
(B)Parte del tumor
(C)Mínima captación
(D)Ausencia de captación

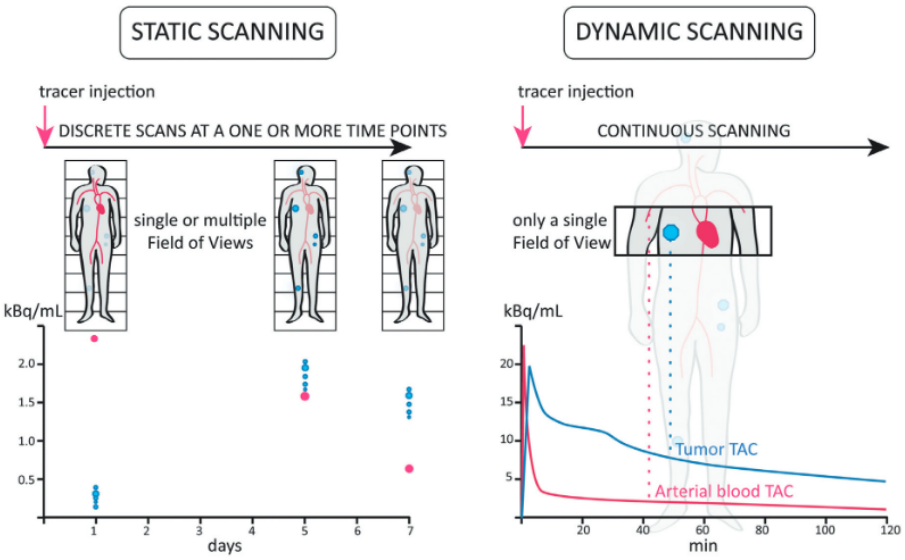
www.impactjournals.com/oncotarget/ 2015 Oncotarget, Vol. 6, No. 30

^{89}Zr-cetuximab PET imaging in patients with advanced colorectal cancer



Progresión en 3/4 sin captación. Respuesta en 4/6 pacientes con captación.





I. Bahce et al. Lung Cancer 2017

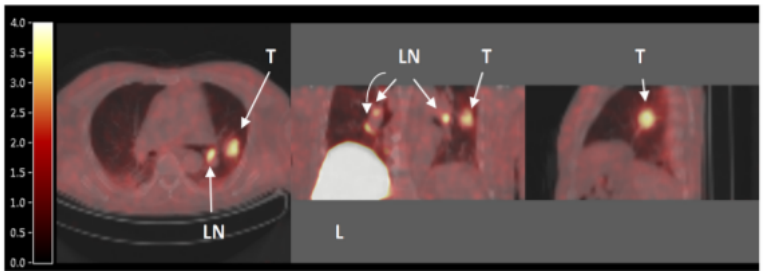
Personalizing NSCLC therapy by characterizing tumors using TKI-PET and immuno-PET.

	Immuno-PET	TKI-PET	
Parent molecule	mAbs	TKIs	
Scanning protocol	Static	Static	Dynamic
Radionuclide (Decay half-life)	• Copper-64 (12,7 h) • Yttrium-86 (14,7 h) • Bromine-76 (16,1 h) • Zirconium-89 (78,4 h) • Iodine-124 (4,2 days)	• Carbon-11 (20,4 min) • Fluorine-18 (109,8 min)	
Scanning parameters • Injection to scanning time interval • Uptake parameters	• up to several days • simplified parameters: SUV (and its variants such as SUVmax and SUVpeak), TBR, TRR, etc.	• up to several hours • simplified parameters: SUV and variants, TBR, TRR, etc.	• up to several hours • dynamic: K1, Ki, VT, etc.
Advantages	• whole body scans • highly specific parent molecules • stable inert labeling • easy to process uptake parameters • shippable for widespread use	• whole body scans • easy to process uptake parameters • shippable for widespread use	• PK modeling • highly accurate uptake parameters
Limitations/caveats	• radiation burden	• accuracy of uptake parameters may be low depending on the PK modeling of the tracer	• no whole body scans possible

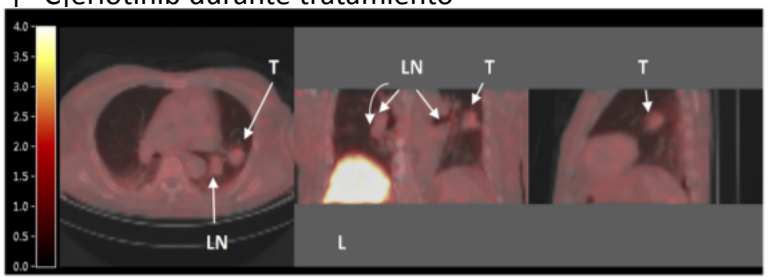
I. Bahce et al. Lung Cancer 2017

Efectos de la terapia con erlotinib en la captación de [^{11}C]erlotinib en pacientes con NSCLC avanzado y EGFR mutado

[^{11}C]erlotinib basal – Estudio dinámico 60 min. TBR 50-60

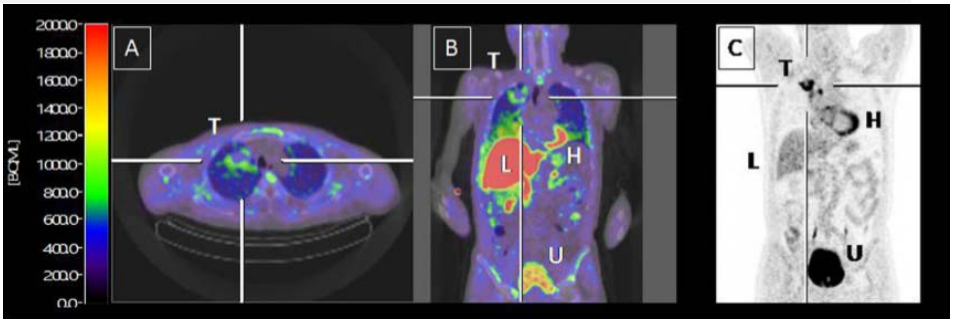


[^{11}C]erlotinib durante tratamiento



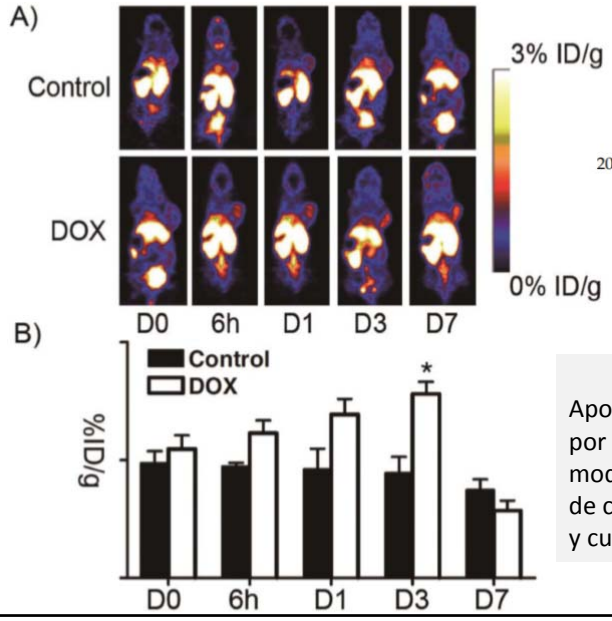
Personalizing NSCLC therapy by characterizing tumors using TKI-PET and immuno-PET. I. Bahce. et al. Lung Cancer 2017

[^{18}F]afatinib 90 min p.i. en paciente con delección de exón 19 **[^{18}F]-FDG**



Molecular Imaging of Apoptosis: From Micro to Macro

Wenbin Zeng[1]✉, Xiaobo Wang[1], Pengfei Xu[1], Gang Liu[2], Henry S. Eden[3], Xiaoyuan Chen[3]✉



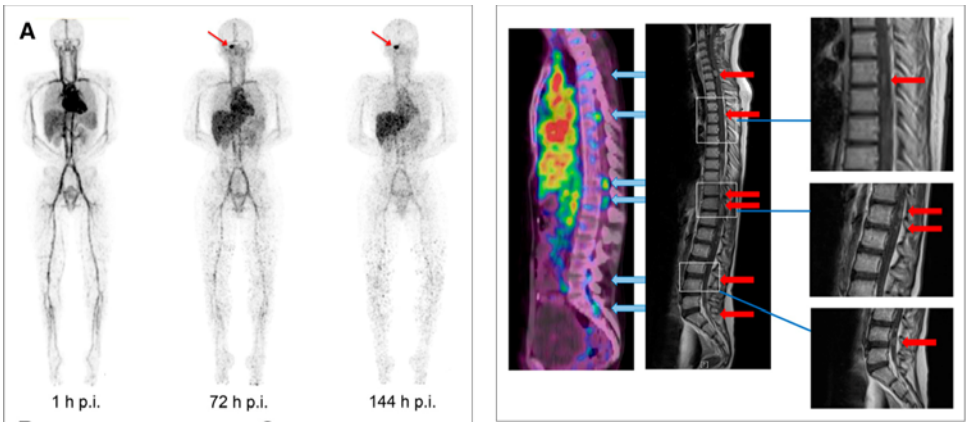
Theranostics
2015; 5(6): 559-582. doi: 10.7150/thno.11548

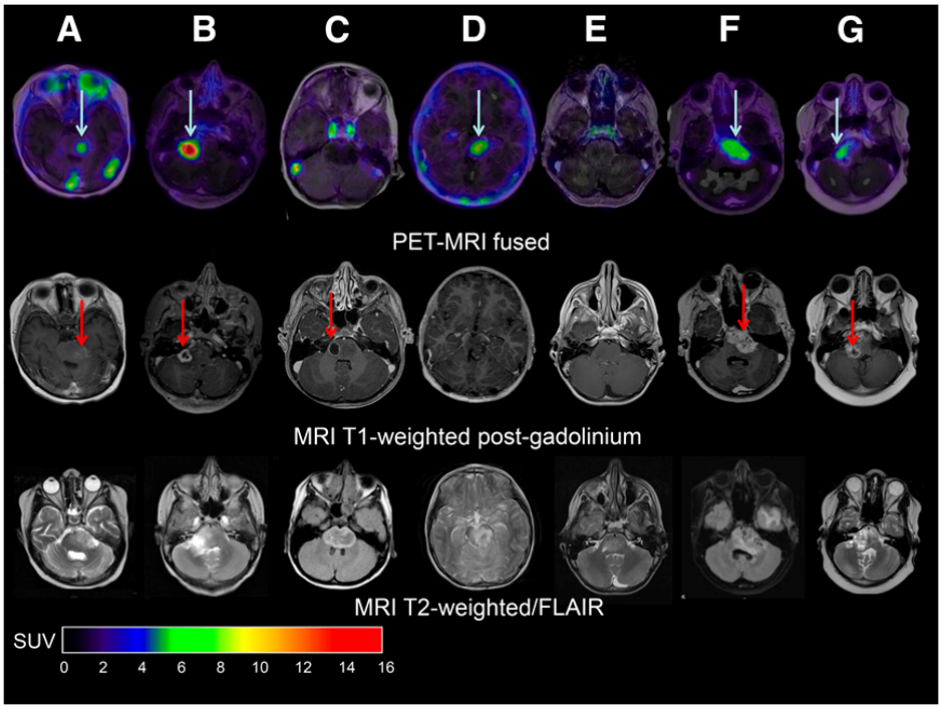
^{18}F-Anexina V PET
Apoptosis inducida por doxorrubicina en un modelo animal con cáncer de células escamosas de cabeza y cuello UM-SCC-22B.

Molecular Drug Imaging: ^{89}Zr-Bevacizumab PET in Children with Diffuse Intrinsic Pontine Glioma.

MH Hansen et al. J Nucl Med 2017

^{89}Zr-bevacizumab PET/MRI fused: diffuse intrinsic pontine glioma and metastases in spinal cord

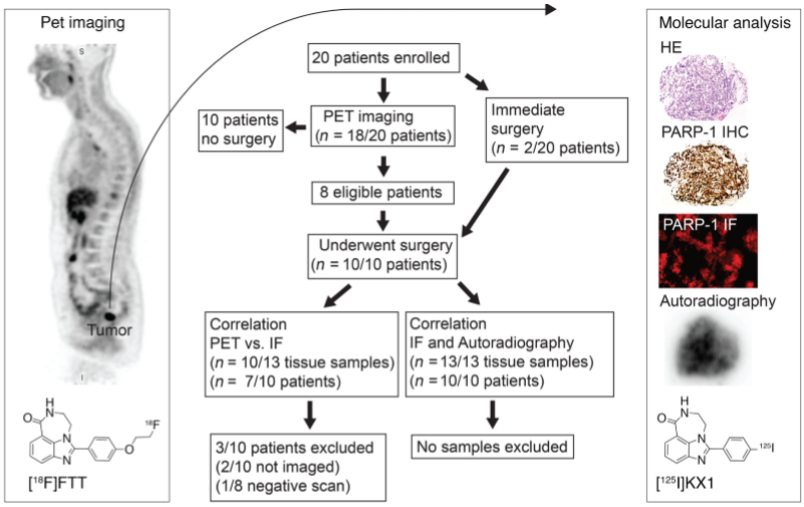




A PET imaging agent for evaluating PARP-1 expression in ovarian cancer

The Journal of Clinical Investigation 2018

Mehran Makvandi,[1] Austin Pantel,[1] Lauren Schwartz,[2] Erin Schubert,[1] Kuiying Xu,[1] Chia-Ju Hsieh,[1] Catherine Hou,[1] Hyoung Kim,[3] Chi-Chang Weng,[1] Harrison Winters,[4] Robert Doot,[1] Michael D. Farwell,[1] Daniel A. Pryma,[1] Roger A. Greenberg,[4] David A. Mankoff,[1] Fiona Simpkins,[3] Robert H. Mach,[1] and Lilie L. Lin[5]



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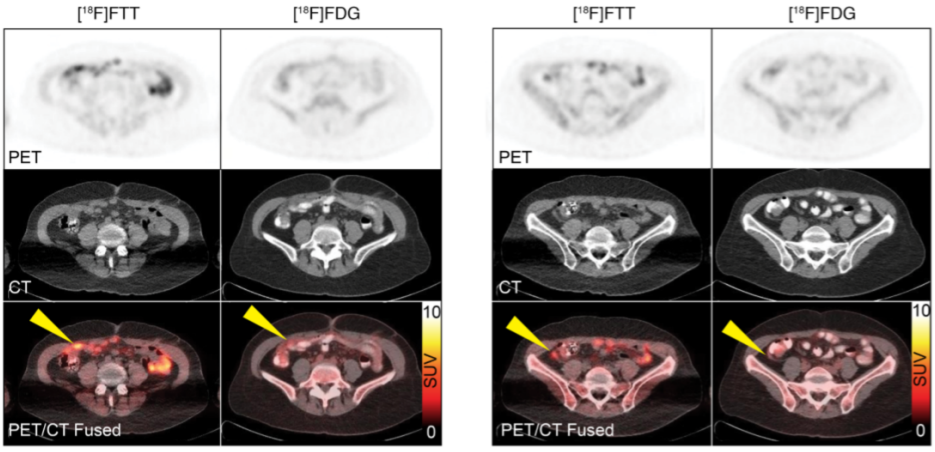
Captación de [18F]FTT (tanatrace) en pacientes con resistencia a platino



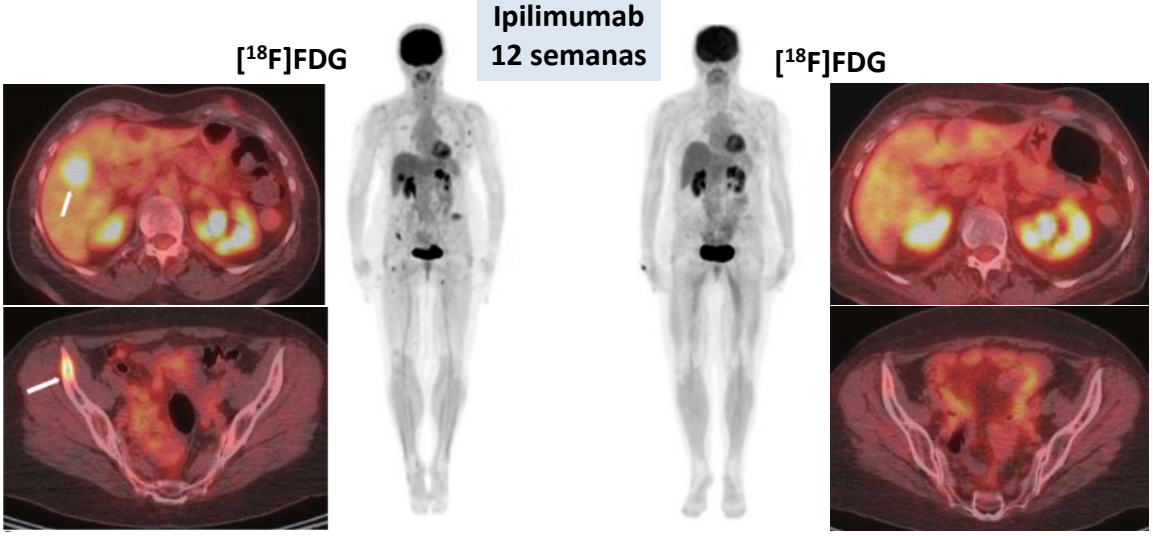
Immune-Checkpoint Inhibitors in the Era of Precision Medicine

M. Braschi-Amirfarzan et al. Korean J Radiol 2017

Paciente con MELANOMA metastásico

Ipilimumab
12 semanas

[^{18}F]FDG **[^{18}F]FDG**



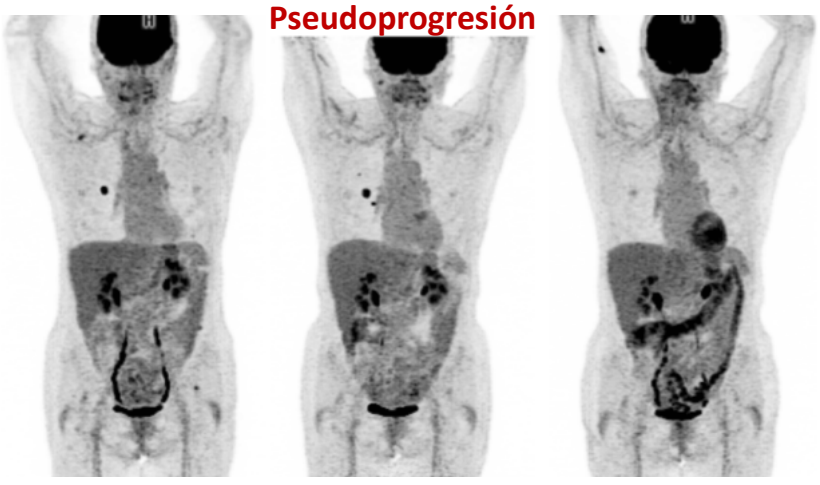
FDG PET/CT for assessing tumour response to immunotherapy

N. Aide et al. Eur J Nucl Med Mol Imaging 2019

Paciente con MELANOMA metastásico tratado con Nivolumab

Basal Post 2 ciclos Post 6 ciclos

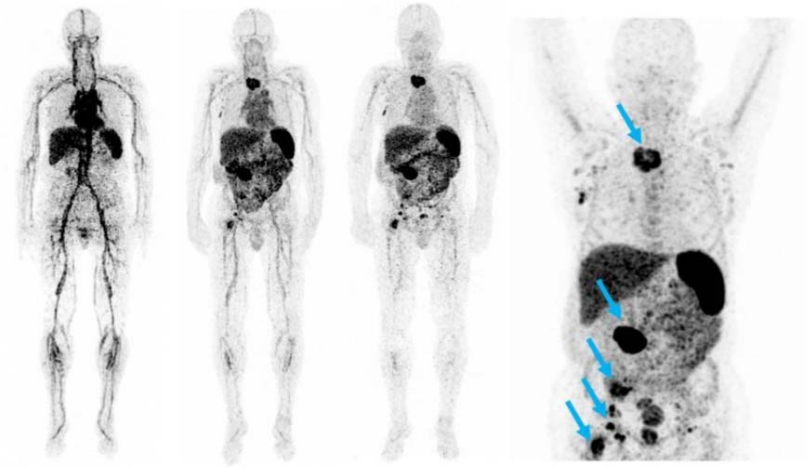
Pseudoprogresión



^{89}Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer

NATURE MEDICINE | VOL 24 | DECEMBER 2018 | 1852-1858

Frederike Bensch[1], Elly L. van der Veen[1], Marjolijn N. Lub-de Hooge[2,3], Annelies Jorritsma-Smit[2],



^{89}Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer

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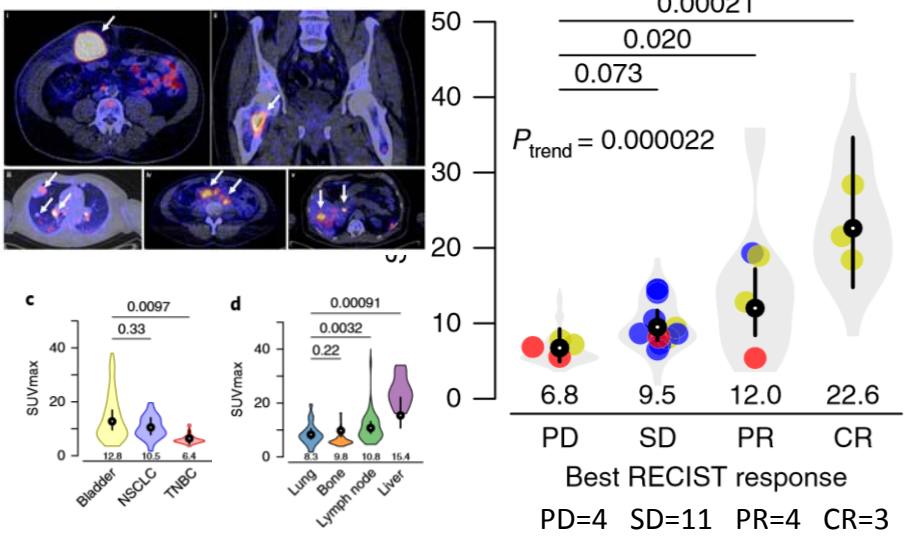


Microenvironment and Immunology

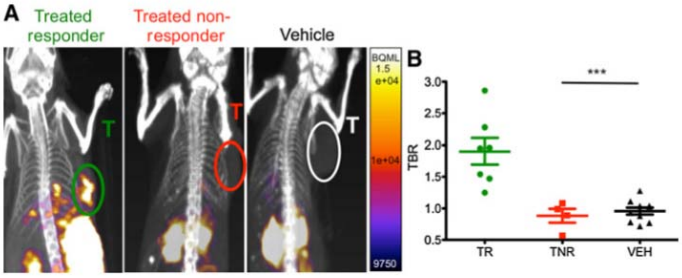
Cancer Research

2017

Granzyme B PET Imaging as a Predictive Biomarker of Immunotherapy Response

Benjamin M. Larimer[1], Eric Wehrenberg-Klee[1], Frank Dubois[1], Anila Mehta[1], Taylor Kalomeris[1], Keith Flaherty[2,3], Genevieve Boland[4], and Umar Mahmood[1]

Granzyme B: enzima liberada por las células T y NK durante la respuesta inmune celular y representa uno de los dos mecanismos dominantes por los cuales las células T median la muerte de las células cancerosas.
^{68}Ga-NOTA-GZP: alta afinidad y especificidad por Granzyme B → Biomarcador predictivo



Cáncer de colon
Modelo murino
Combinación de terapia anti-PD-1 y anti-CTLA-4
(12 días post-tratamiento)

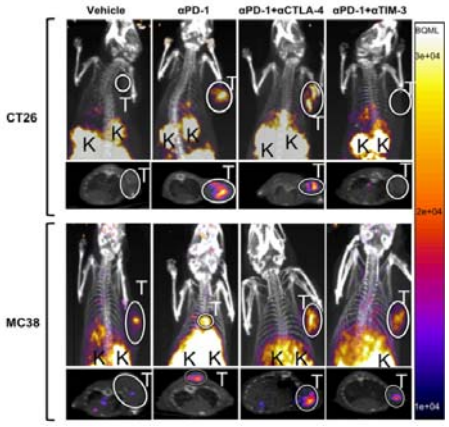
Precision Medicine and Imaging

2019

Clinical Cancer Research

The Effectiveness of Checkpoint Inhibitor Combinations and Administration Timing Can Be Measured by Granzyme B PET Imaging

Benjamin M. Larimer[1], Emily Bloch[1], Sarah Nesti[1], Emily E. Austin[1], Eric Wehrenberg-Klee[1], Genevieve Boland[2], and Umar Mahmood[1]



Cáncer de colon
Modelos murinos:
- Control
- Monoterapia
- Combinación de anti-PD-1 con anti-CTLA-4 simultánea y secuencial
- Combinación de anti-PD-1 con TIM3