

# Optimization of molecular imaging in neuroendocrine tumors

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## Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors **JNM 2018**

Thomas A. Hope<sup>1,2\*</sup>, Emily K. Bergsland<sup>3,4</sup>, Murat Fani Bozkurt<sup>5</sup>, Michael Graham<sup>1</sup>, Anthony P. Heaney<sup>6</sup>, Ken Herrmann<sup>5</sup>, James R. Howe<sup>4,7</sup>, Matthew H. Kulke<sup>3,4,8</sup>, Pamela L. Kunz<sup>3,4,8</sup>, Josh Mailman<sup>9</sup>, Lawrence May<sup>10</sup>, David C. Metz<sup>4,11</sup>, Corina Millo<sup>1</sup>, Sue O'Doriso<sup>1,3,4</sup>, Diane L. Reidy-Lagunes<sup>3,4</sup>, Michael C. Soulen<sup>4,12</sup>, and Jonathan R. Strosberg<sup>3,4</sup>

Representantes de las diferentes Sociedades Europeas y Americanas de Medicina Nuclear, Oncología, Radiología, Digestivo, Endocrinología etc

**Appropriate Use Criteria for Somatostatin Receptor PET  
Imaging in Neuroendocrine Tumors JNM 2018**

Thomas A. Hope<sup>1,2\*</sup>, Emily K. Bergsland<sup>3,4</sup>, Murat Fani Bozkurt<sup>5</sup>, Michael Graham<sup>1</sup>, Anthony P. Heaney<sup>6</sup>, Ken Herrmann<sup>5</sup>, James R. Howe<sup>4,7</sup>, Matthew H. Kulke<sup>3,4,8</sup>, Pamela L. Kunz<sup>3,4,8</sup>, Josh Mailman<sup>9</sup>, Lawrence May<sup>10</sup>, David C. Metz<sup>4,11</sup>, Corina Millo<sup>1</sup>, Sue O'Dorisio<sup>1,3,4</sup>, Diane L. Reidy-Lagunes<sup>3,4</sup>, Michael C. Soulen<sup>4,12</sup>, and Jonathan R. Strosberg<sup>3,4</sup>

**Score 9:**

*Scen 1: **Initial staging** after the histologic diagnosis of NETs (appropriate)*

*Scen 2: **Localization of a primary tumor** in patients **with known metastatic disease**, but an unknown primary (appropriate)*

*Scen 3: **Selection of patients for SSTR-targeted PRRT** (appropriate)*

**Score 8:**

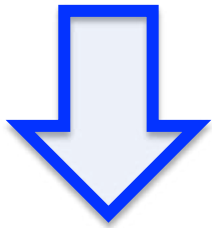
*Scen 4: **Staging NETs** prior to planned surgery (appropriate)*

*Scen 5: **Evaluation of a mass suggestive of a NET** not amenable to endoscopic or percutaneous biopsy  
“ileal lesion, hypervascular mass”  
(appropriate)*

*Scen 6: **Monitoring of NETs seen predominantly on SSTR-PET** (appropriate)*

**PET- DOTA (<sup>68</sup>Ga-Dotatoc)**

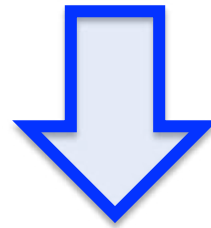
**COMITÉ MULTIDISCIPLINAR**



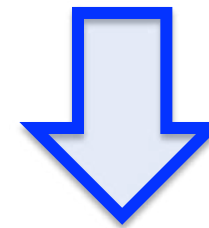
**ESTADIFICACIÓN** ENFERMEDAD

LOCALIZACION **TUMOR PRIMARIO**

CARACTERIZACIÓN LESIONES SOSPECHOSAS



**POSITIVIDAD** PARA RECEPTOR SOMATOSTATINA

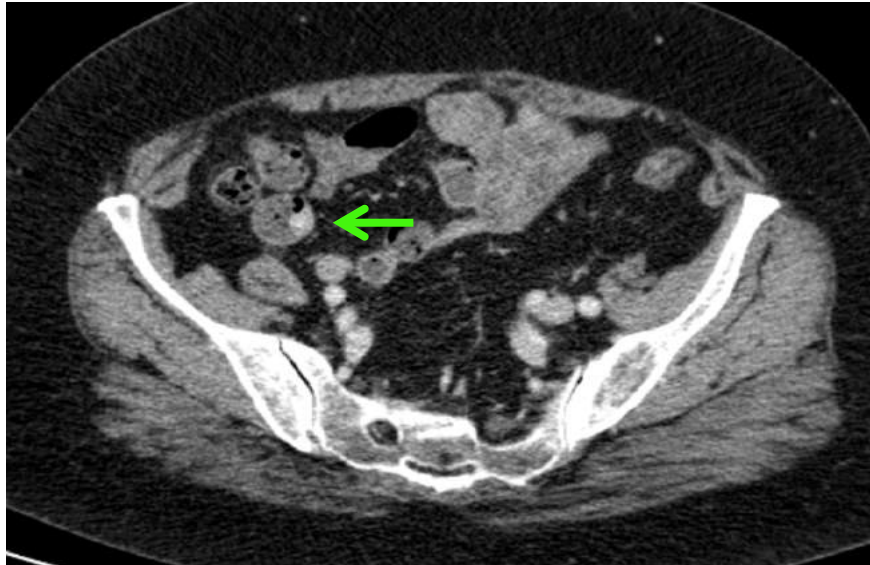


SOSPECHA **PROGRESIÓN**  
(clínica, analítica, radiológica +/-)

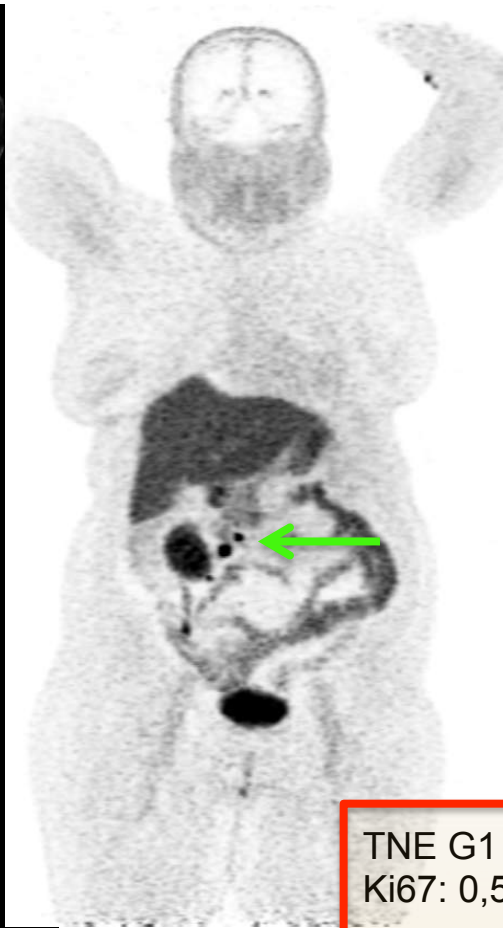
**Caso:**

- \* Paciente varón 65 años
- \* Antecedentes de neoplasia de sigma resecada hace 4 años (T2N0)
- \* Estudio de control por CT muestra: Pequeño engrosamiento mural hipervascular en íleon de carácter indeterminado

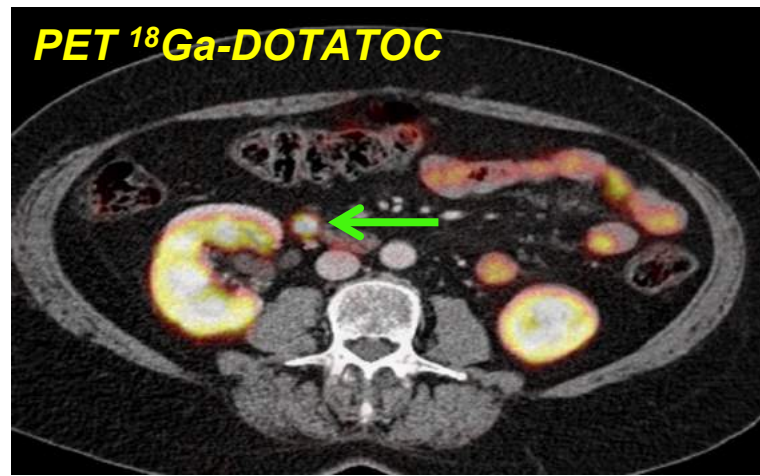
**PET <sup>18</sup>Ga-DOTATOC**



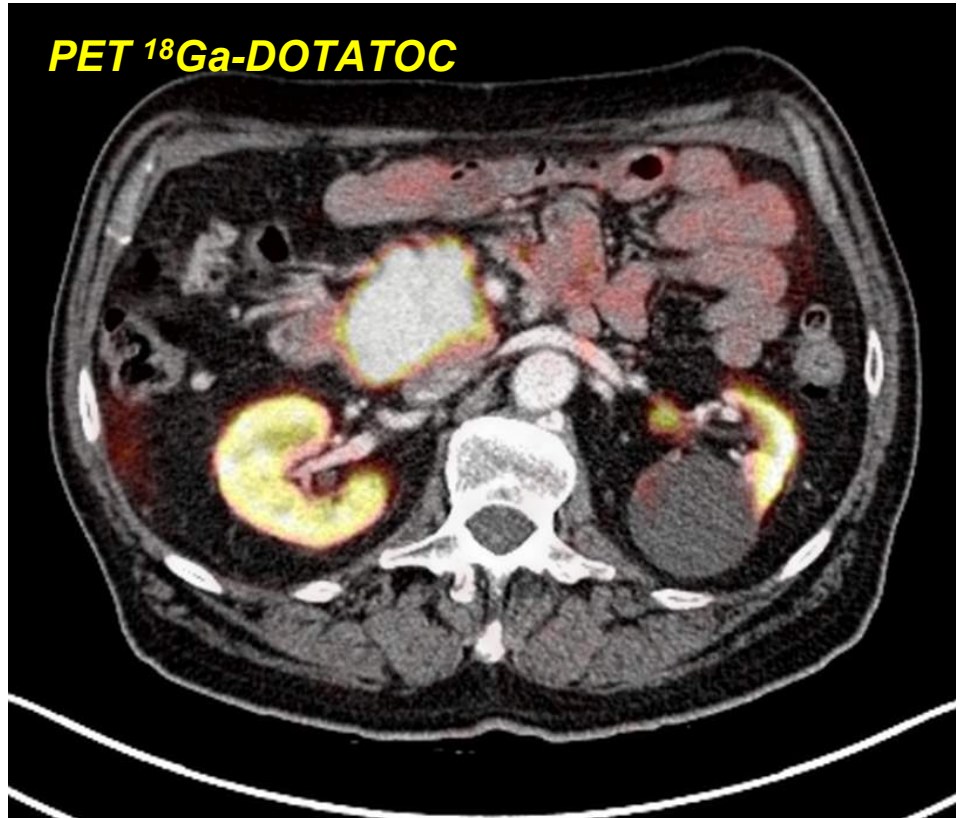
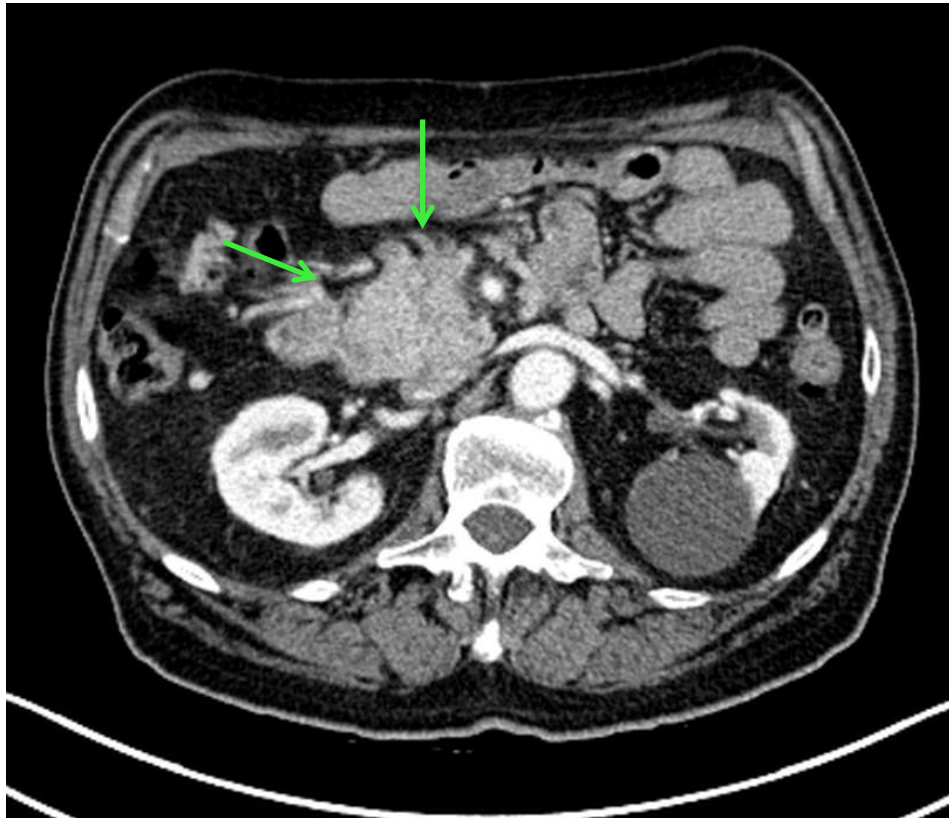
**Positivo**



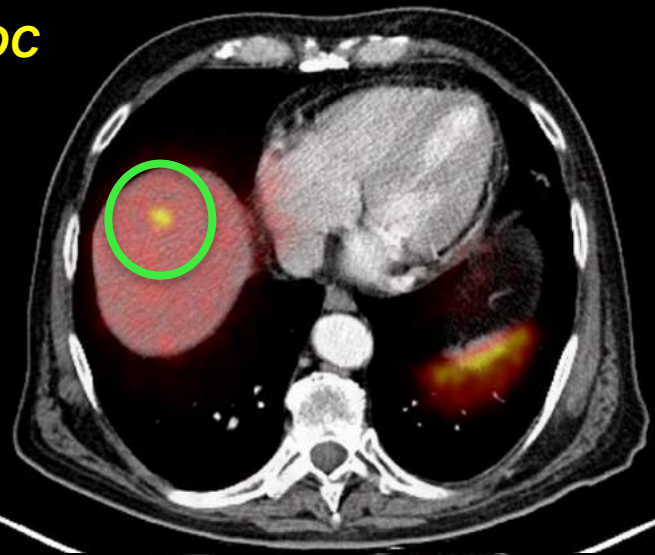
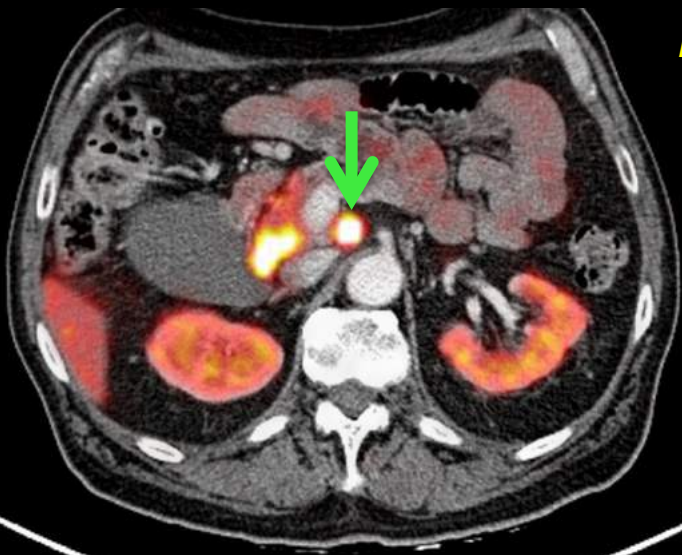
TNE G1 (pT1)  
Ki67: 0,5 %



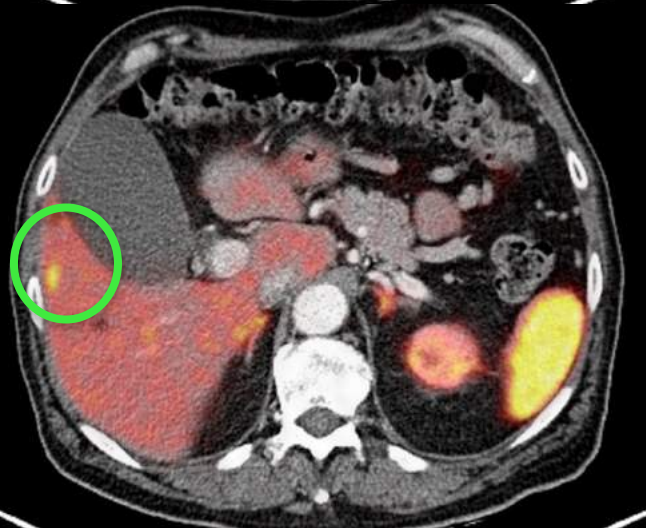
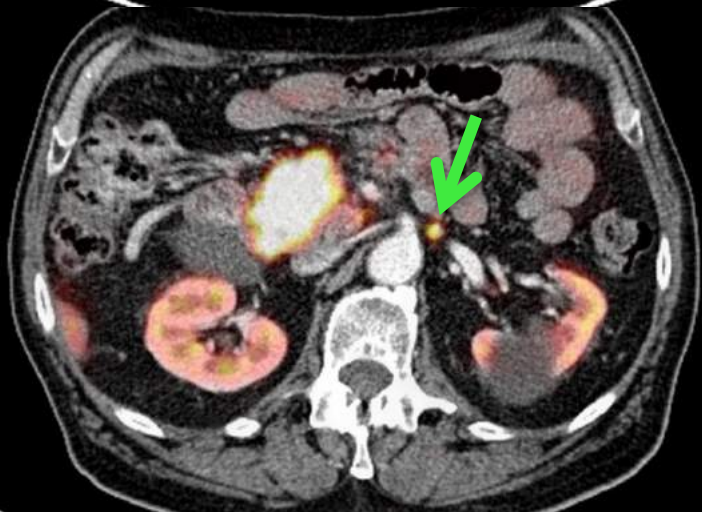
## PANCREATIC TUMOR



**PET  $^{18}\text{Ga}$ -DOTATOC**



UNKNOWN  
NODAL & LIVER  
METASTASES



Prospective Study of  $^{68}\text{Ga}$ -DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites **JCO 2016**

Samira M. Sadowski, Vladimir Neychev, Corina Millo, Joanna Shih, Naris Nilubol, Peter Herscovitch, Karel Pacak, Stephen J. Marx, and Electron Kebebew

**n=131** with biochemical or radiologic suspicion and/or known diagnosis of GEPNET **“Prospective”**

| <b><math>^{68}\text{Ga}</math>-DOTA PET/CT</b> | <b>ANATOMIC IMAGING</b> | <b><math>^{111}\text{In}</math>-pentetrotide SPECT/CT</b> |         |
|--|-------------------------|---|---------|
| <b>95.1%</b>                                   | <b>45.3%</b>            | <b>30.9%</b>  | p< .001 |



- ✓  $^{68}\text{Ga}$ -DOTATE PET/CT detected in **4 of 14 patients (28.6%)** found a **previously UPT**
- ✓ **Serum Ch A & urinary 5-HIAA** levels correlated with number of lesions detected by  $^{68}\text{Ga}$ -DOTATATE
- ✓ n=23 who had no biochemical evidence of GEPNETs but who had possible hormone-related symptoms, such as flushing and diarrhea,  $^{68}\text{Ga}$ -DOTATATE detected more lesions than  $^{111}\text{In}$ -pentetrotide SPECT/CT

<sup>68</sup>Gallium-DOTATATE positron emission tomography-computed tomography (PET CT) changes management in a majority of patients with neuroendocrine tumors ☆ *Surgery 2018*

John F. Tierney, MD<sup>a</sup>, Cory Kosche, BS<sup>a</sup>, Erik Schadde, MD<sup>a,b,c,d</sup>, Amjad Ali, MD<sup>e</sup>, Sumeet Virmani, MD, MS<sup>e</sup>, Sam G. Pappas, MD<sup>a</sup>, Jennifer Poirier, PhD<sup>a</sup>, Xavier M. Keutgen, MD<sup>a,\*</sup>

**STAGING**

Management after <sup>68</sup>Ga-DOTATATE PET CT was performed

| Change in management                             | Number of patients (n = 50) (%) |
|--|---------------------------------|
| <b>Total change in management</b>                | <b>33 (66)</b>                  |
| Intermodality change in management               | 24 (48)                         |
| Surgery  | 3 (6)                           |
| Medical management (eg, somatostatin antagonist) | 7 (14)                          |
| PRRT   | 6 (12)                          |
| Yttrium-90 radioembolization                     | 4 (8)                           |
| Surveillance                                     | 2 (4)                           |
| Percutaneous microwave ablation                  | 2 (4)                           |
| Intramodality change in management               | 9 (18)                          |
| Change in extent of surgery                      | 4 (8)                           |
| Change in type of surveillance                   | 5 (10)                          |

**Tumor debulking**

Change in management: **Surgery to others by extrahepatic disease or more liver metastases**

→ Liver/2° Primary tumor

→ MRI “suspicious bone M1”/ Endoscopy “stomach”

<sup>68</sup>Gallium-DOTATATE positron emission tomography-computed tomography (PET CT) changes management in a majority of patients with neuroendocrine tumors ☆ *Surgery 2018*

John F. Tierney, MD<sup>a</sup>, Cory Kosche, BS<sup>a</sup>, Erik Schadde, MD<sup>a,b,c,d</sup>, Amjad Ali, MD<sup>e</sup>, Sumeet Virmani, MD, MS<sup>e</sup>, Sam G. Pappas, MD<sup>a</sup>, Jennifer Poirier, PhD<sup>a</sup>, Xavier M. Keutgen, MD<sup>a,\*</sup>

**STAGING**

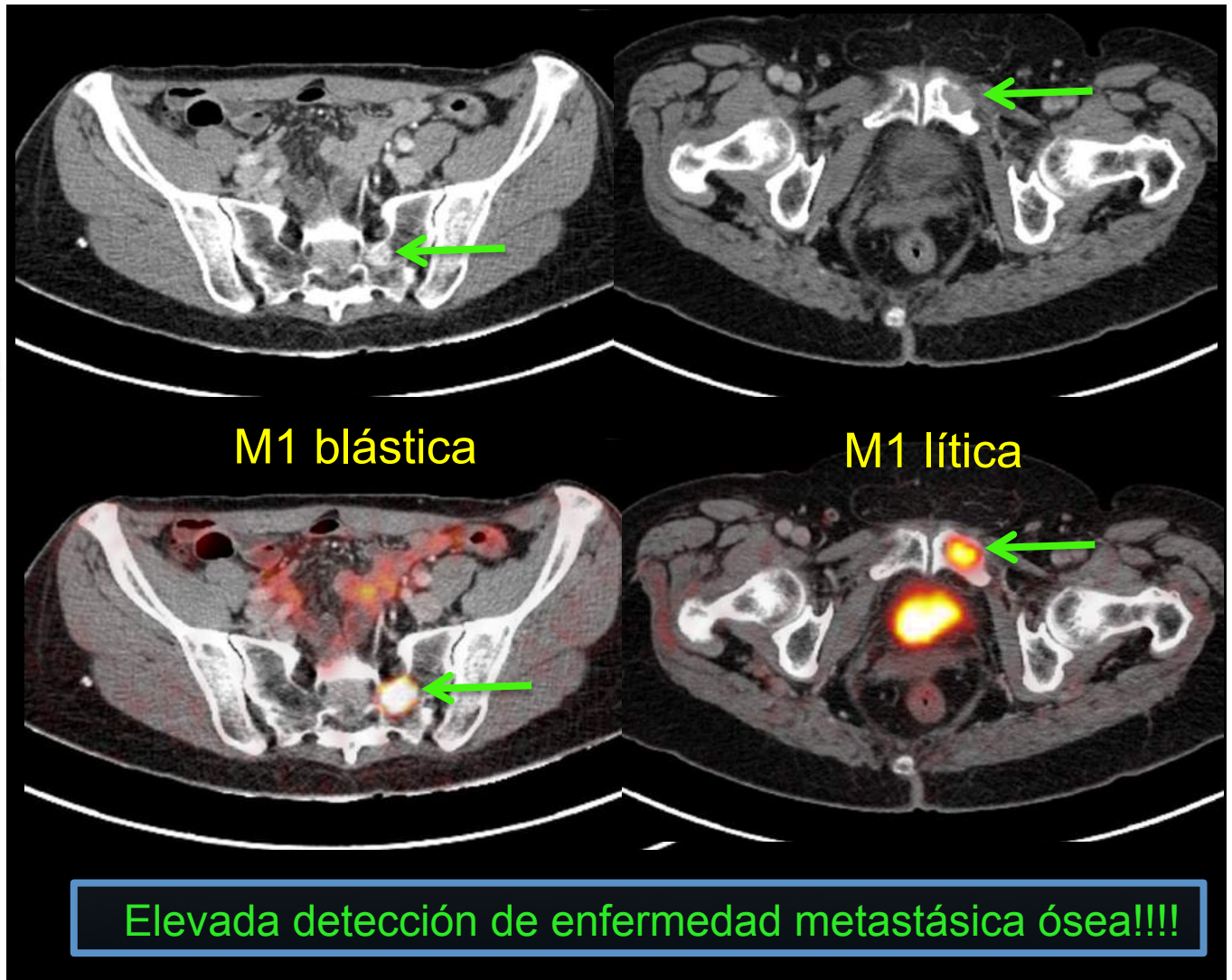
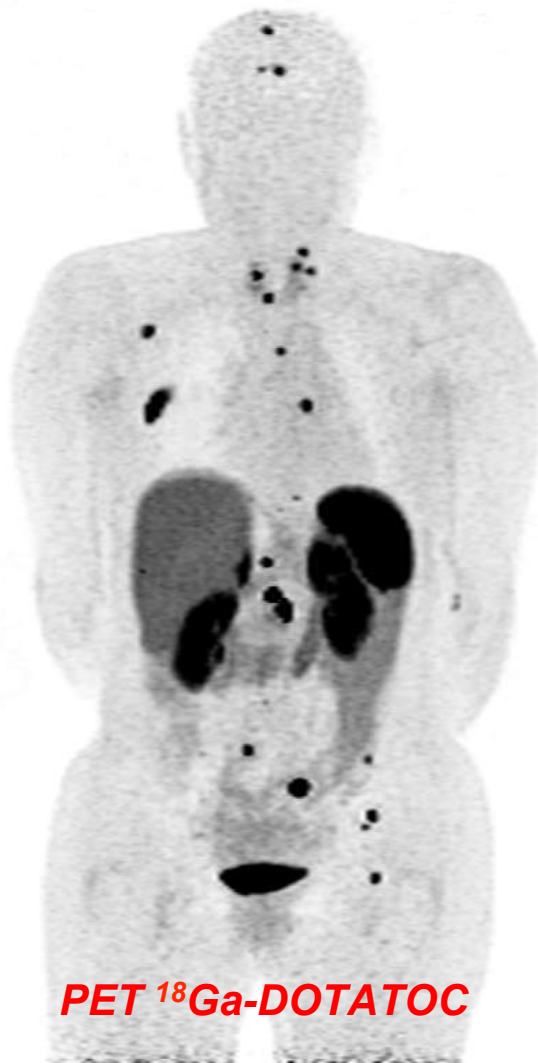
**Table 4**  
Location of newly detected lesions on <sup>68</sup>Ga-DOTATATE PET CT

| Location                     | Number of patients (n = 50) (%) |
|------------------------------|---------------------------------|
| Liver                        | 11 (22)                         |
| Bone                         | 9 (18)                          |
| Mesenteric lymph nodes       | 8 (16)                          |
| Abdominal wall / soft tissue | 6 (12)                          |
| Small intestine              | 3 (6)                           |
| Lung                         | 3 (6)                           |
| Thoracic lymph nodes         | 3 (6)                           |



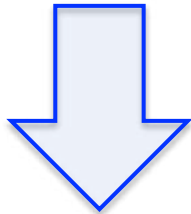
**54% patients !!**

- \* **FP**: Accessory spleen / Dysplasia on biopsy in a stomach polyp
- \* None of the 9 scans performed in patients with biochemical markers or symptoms suggestive of NET were positive



**PET- DOTA (<sup>68</sup>Ga-Dotatoc)**

**COMITÉ MULTIDISCIPLINAR**



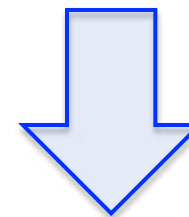
**ESTADIFICACIÓN** ENFERMEDAD

LOCALIZACION **TUMOR PRIMARIO**

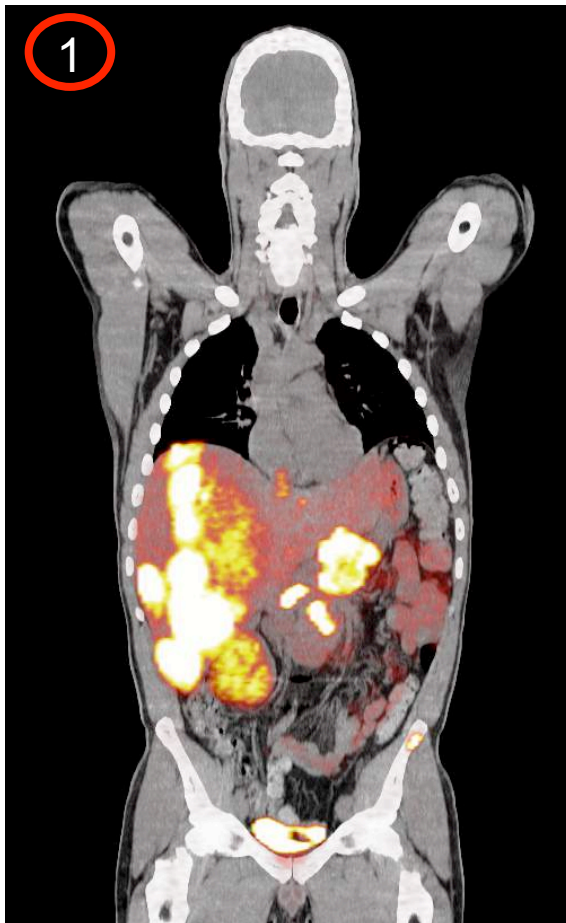
CARACTERIZACIÓN LESIONES SOSPECHOSAS



**POSITIVIDAD** PARA RECEPTOR SOMATOSTATINA



SOSPECHA **PROGRESIÓN**  
(clínica, analítica, radiológica +/-)



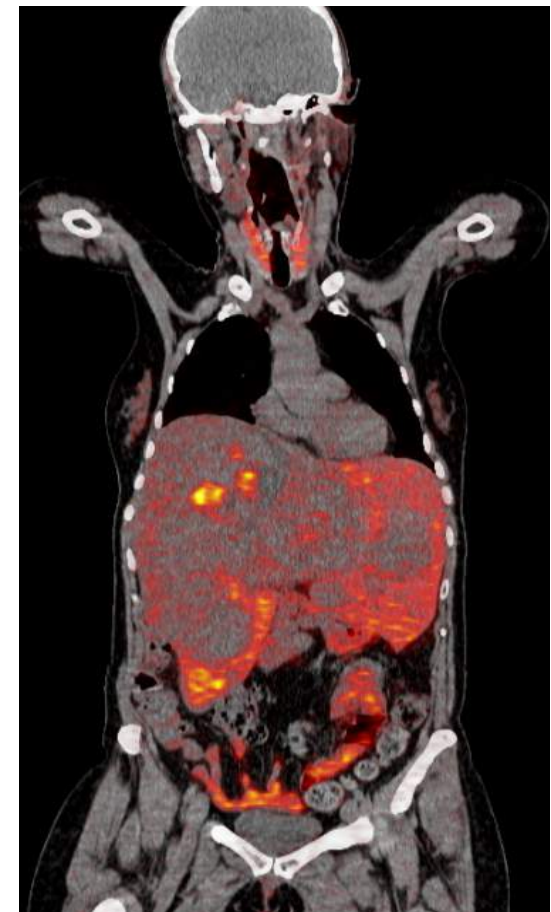
## TNE G2

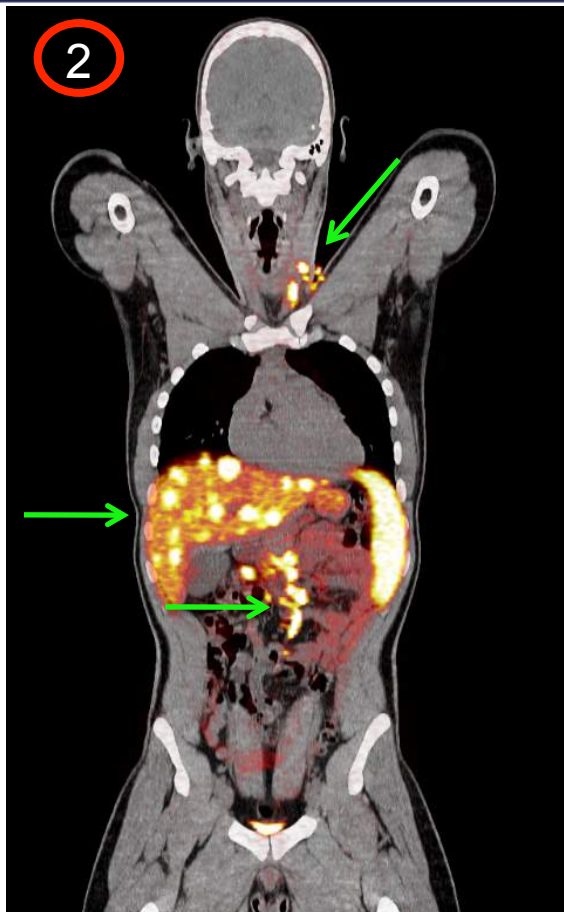
En un subgrupo de pacientes con G2 y en base a los resultados de la PET-DOTA, un **60%** de los pacientes iniciaron Tto con análogos

TNE pancreático no funcionante  
G2 Ki67 18% diseminado →

← TNE pancreático no funcionante  
G2 Ki67 14% diseminado

PET <sup>68</sup>Ga-DOTATOC





**TNE Ki:36%**



**CANDIDATO PRRT**



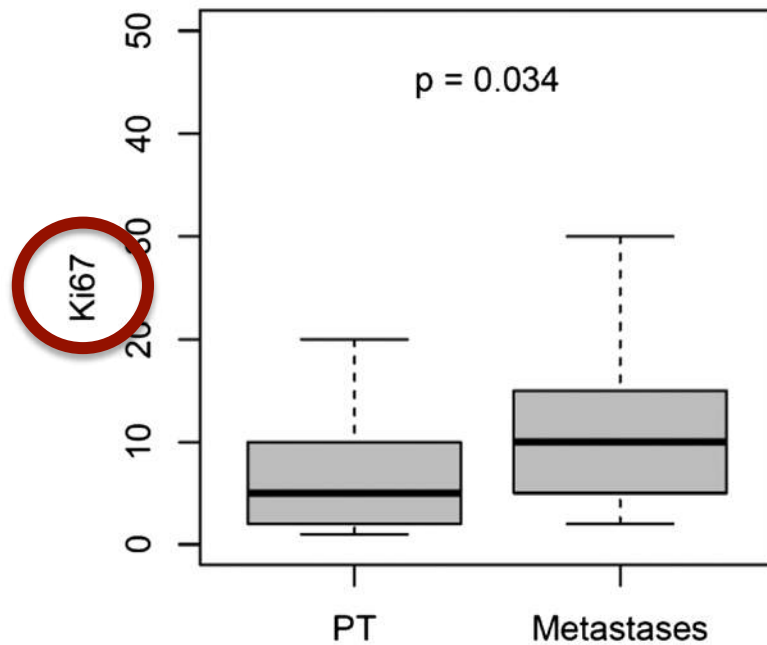
Findings on which management was based

| Grade | <sup>68</sup> Ga-DOTATATE | <sup>18</sup> F-FDG | Both | Total      |
|-------|---------------------------|---------------------|------|------------|
| G1    | 25                        | 1                   | 10   | 36 (34.6%) |
| G2    | 16                        | 10                  | 14   | 40 (38.4%) |
| G3    | 9                         | 11                  | 8    | 28 (27%)   |
| Total | 50                        | 22                  | 32   | 104        |



## Somatostatin receptor PET/CT in restaging of typical and atypical lung carcinoids

Vikas Prasad<sup>1\*</sup>, Ingo G. Steffen<sup>1</sup>, Marianne Pavel<sup>2</sup>, Timm Denecke<sup>3</sup>, Elisabeth Tischer<sup>2</sup>, Konstantina Apostolopoulou<sup>2</sup>, Andreas Pascher<sup>4</sup>, Ruza Arsenic<sup>5</sup> and Winfried Brenner<sup>1</sup>



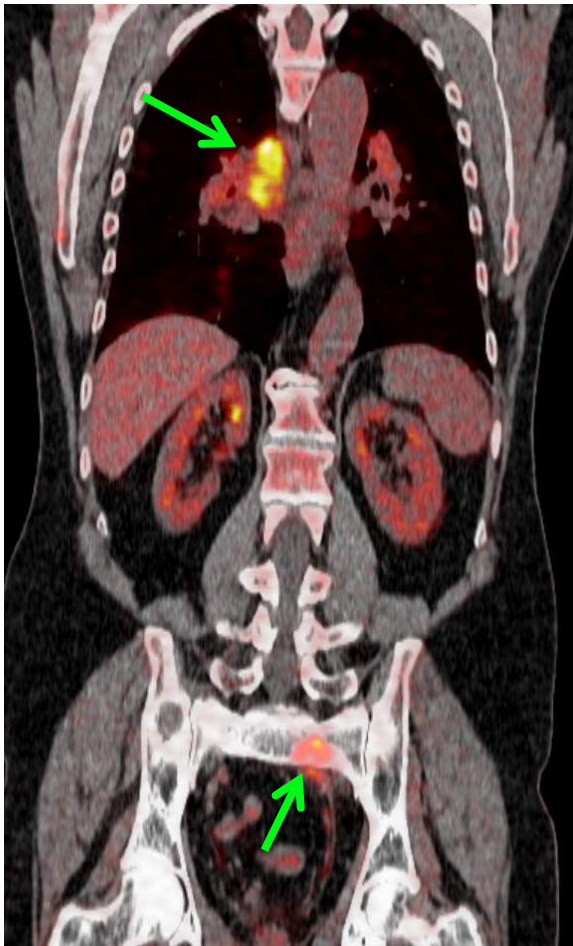
### *Lesiones mixtas (SSTR+/-)*

C. Tipicos 8.3%

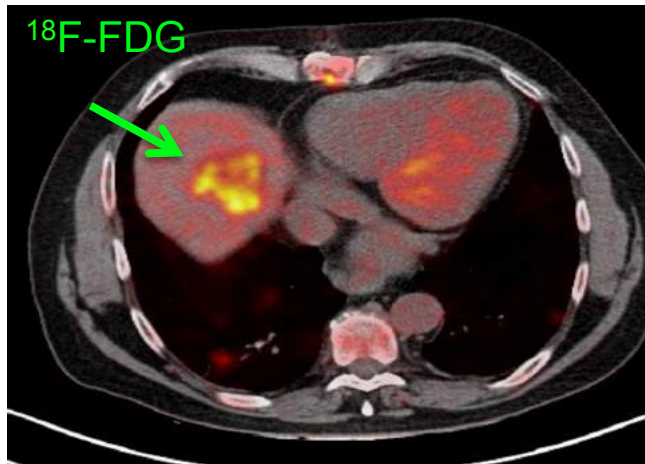
C. Atípicos 26.7%

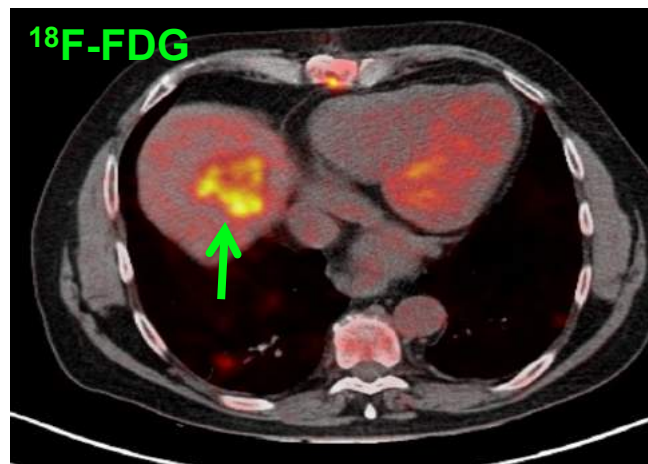
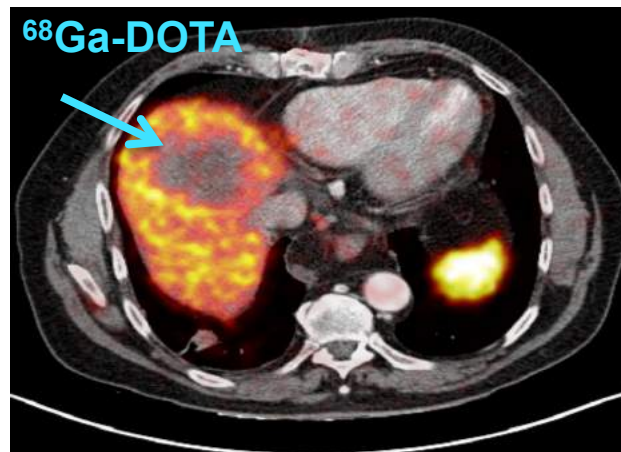
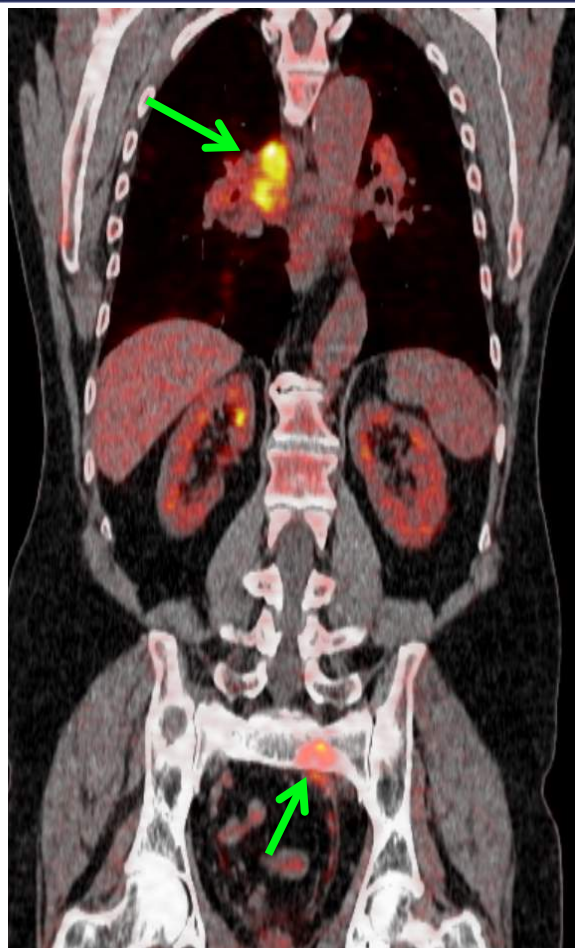
*PT=primary tumor*

3



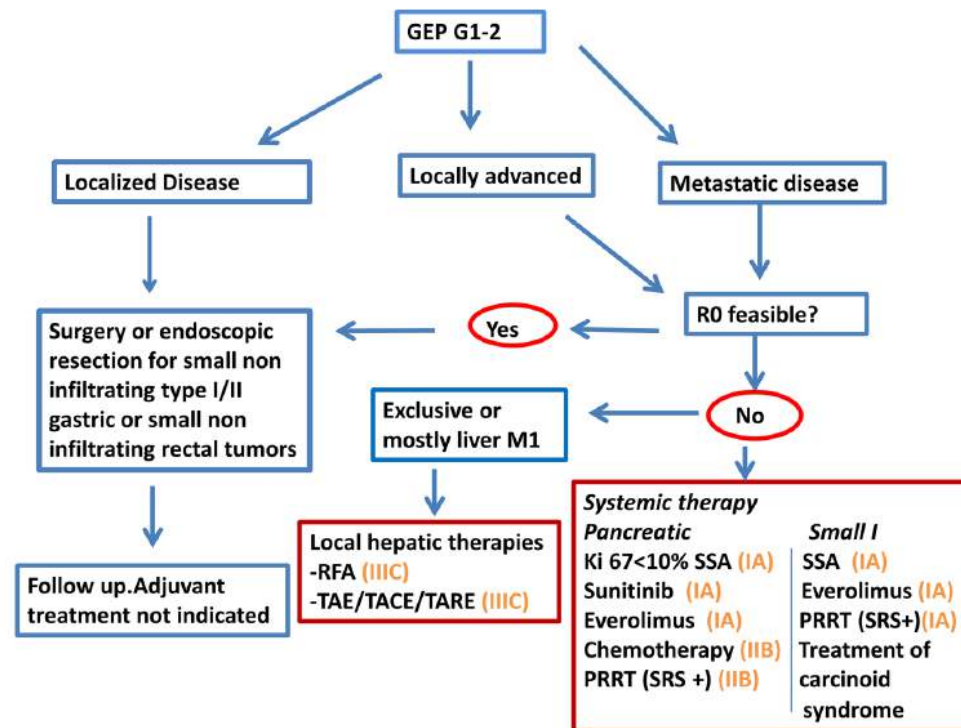
Atypical Pulmonary NET,  
no secretor, Ki<5%





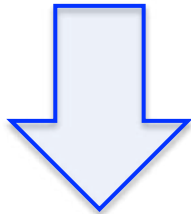
## SEOM: GASTROENTEROPANCREÁTICOS

- Chromogranin A (well-differentiated NETs) (III,B) or neuron-specific enolase (NSE) [poorly differentiated neuroendocrine carcinomas (NECs)] (I, C).
- Urinary 5-hydroxyindoleacetic acid (5-HIAA) (carcinoid syndrome); gastrin ± secretin test (gastrinomas); insulin/glucose ratio, proinsulin, C peptide (insulinomas), glucagon, VIP and others depending upon clinical symptoms (IV, C).
- Histopathological report should include the WHO classification and TNM staging, as well as immunohistochemistry staining including ki67 and general neuroendocrine markers (chromogranin A, synaptophysin and NSE). Specific markers are not mandatory and should only be performed if clinically indicated (insulin, glucagon, etc.) (I, A).
- Somatostatin receptor imaging: <sup>68</sup>Gallium-DOTA-TOC/-NOC/-TATE positron emission tomography (PET) (preferred if available) or somatostatin receptor scintigraphy (octreoscan) [4] (III, B).
- Dynamic CT scan or MRI of the abdomen.
- Chest X-ray. A thoracic CT scan may be considered in poorly differentiated tumors, colon primaries or those in whom surgery of liver metastasis is being considered and is also mandatory in lung NENs.



**PET- DOTA (<sup>68</sup>Ga-Dotatoc)**

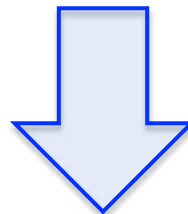
**COMITÉ MULTIDISCIPLINAR**



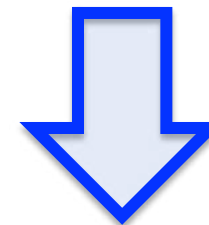
**ESTADIFICACIÓN** ENFERMEDAD

LOCALIZACION **TUMOR PRIMARIO**

CARACTERIZACIÓN LESIONES SOSPECHOSAS



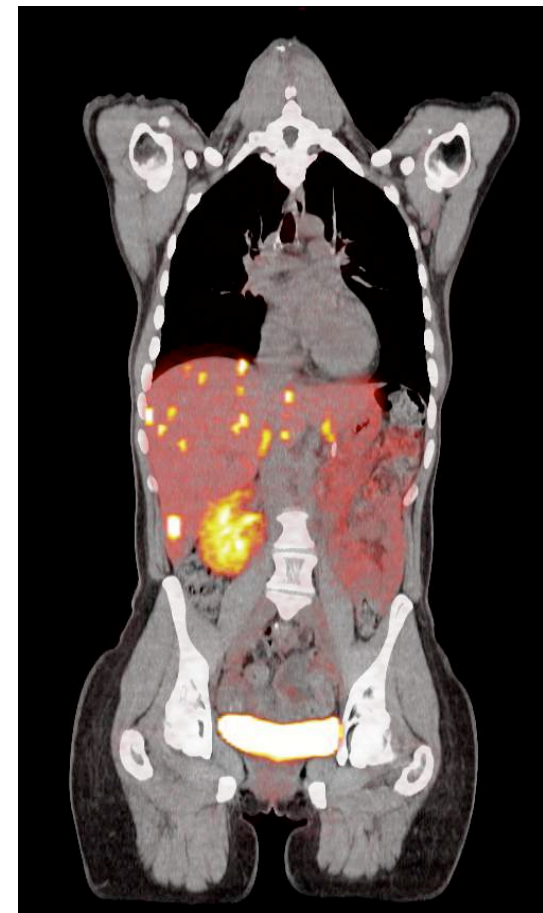
**POSITIVIDAD** PARA RECEP SOMATOSTATINA



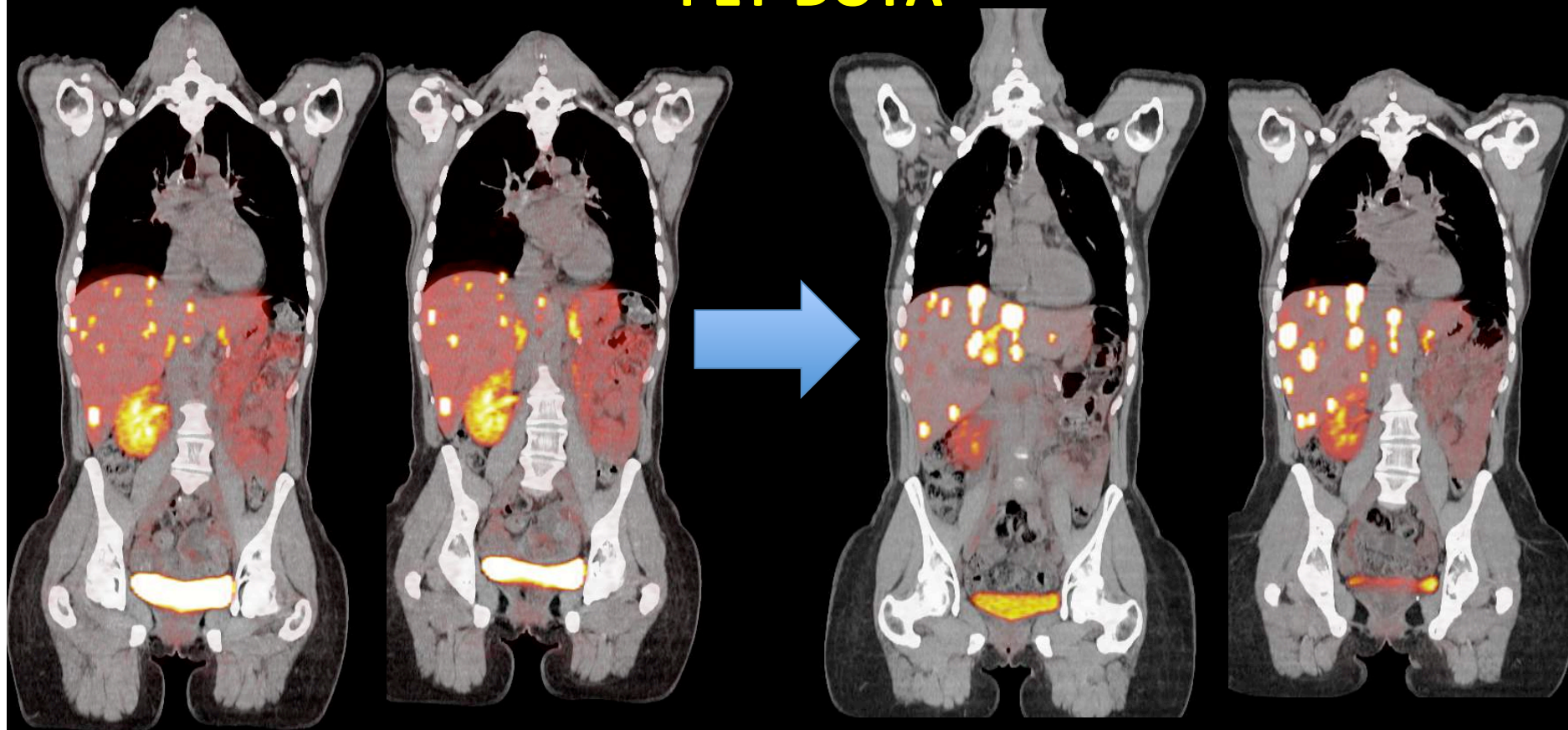
SOSPECHA **PROGRESIÓN**  
(clínica, analítica, radiológica +/-)

Control de la enfermedad...Técnicas morfológicas “TC, RM”

- \* *Scenario 6: **Monitoring of NETs seen predominantly on SSTR-PET** (appropriate)*
- *Sospecha de progresión tumoral en estudios de TC evolutivos*



**PET-DOTA**



**MARZO 2019**

**OCTUBRE 2019**

**Contornos**

Seleccionar una serie para contorno

**MARZO 2019**

Herramientas de modo

PET Edge    Umbral    Cuerpo entero    Crecimiento de región

Lápiz    Pincel 2D    Pincel 3D    Relleno 2D    Mover

Copiar contorno    Contorno puntual

- Lesion (7)
- Lesion (8)
- Lesion (9)
- Lesion (10)
- Lesion (11)
- Lesion (12)
- Lesion (13)
- Lesion (14)
- Lesion (15)
- Lesion (16)
- Lesion (17)
- Lesion (18)
- Lesion (19)
- Lesion (20)
- Lesion (21)
- Lesion (22)
- Lesion (23)
- Lesion (24)
- Lesion (25)

Parámetros de contornos

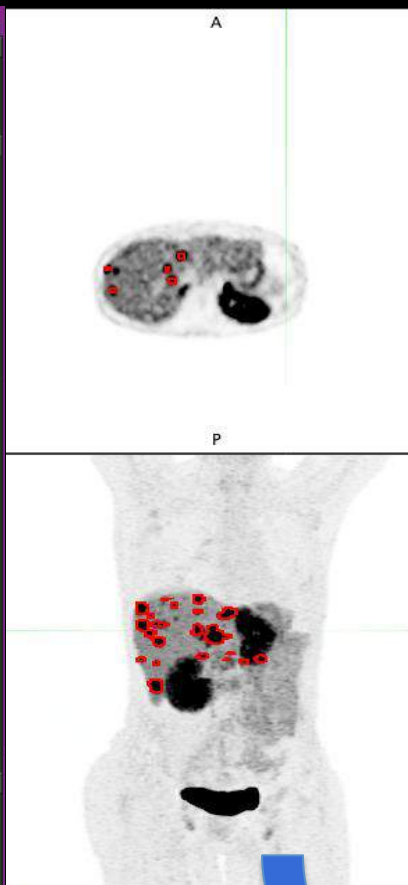
Rojo    Total Tumor Burdi

Ancho de línea 2    Llenar 0%

Tipo Ninguno    Borde nítido

Bloqueo de rango má su; SUVpeso corporal (bw)

Rangos preprogramados: Ninguno



**Contornos**

Seleccionar una serie para contorno

**OCTUBRE 2019**

Herramientas de modo

PET Edge    Umbral    Cuerpo entero    Crecimiento de región

Lápiz    Pincel 2D    Pincel 3D    Relleno 2D    Mover

Copiar contorno    Contorno puntual

- Lesion (11)
- Lesion (12)
- Lesion (13)
- Lesion (14)
- Lesion (15)
- Lesion (16)
- Lesion (17)
- Lesion (18)
- Lesion (19)
- Lesion (20)
- Lesion (21)
- Lesion (22)
- Lesion (23)
- Lesion (24)
- Lesion (25)
- Lesion (26)
- Lesion (27)
- Lesion (28)
- Lesion (29)

Parámetros de contornos

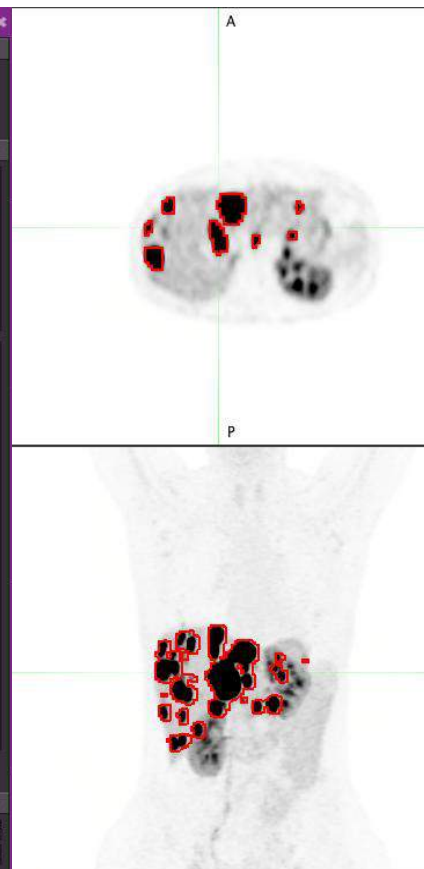
Rojo    Total Tumor Burdi

Ancho de línea 2    Llenar 0%

Tipo Ninguno    Borde nítido

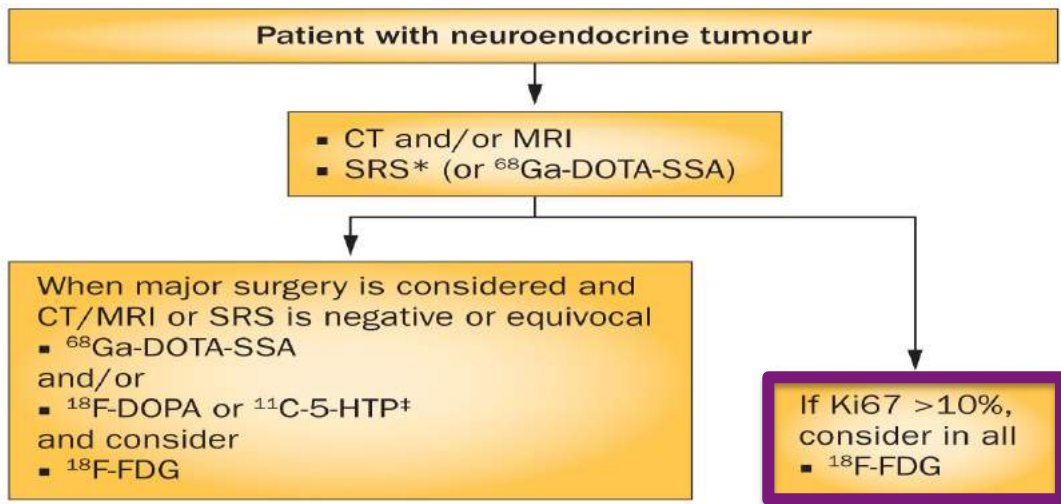
Bloqueo de rango má su; SUVpeso corporal (bw)

Rangos preprogramados: Ninguno



**TOTAL TUMOR BURDEN**

**x4**



van Essen, M. *et al.* (2013)



**In all patients, once (initially) FDG-PET/CT should be done**  
Semin Nucl Med 2012

**Considerations**



|   |
|---|
| <b>Pathological features</b>            |
| • Mitotic count<br>• Ki-67              |
| <b>SSTR expression</b>                  |
| • +/-<br>• Homogeneous +?               |
| <b>Growth rate</b>                      |
| • Slowly, active, or aggressive disease |
| <b>Disease extent</b>                   |

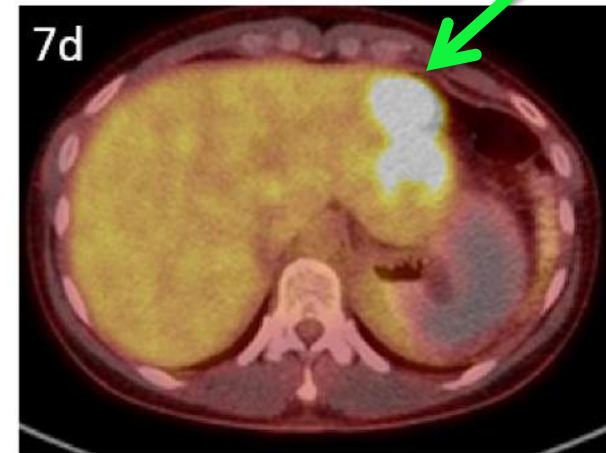
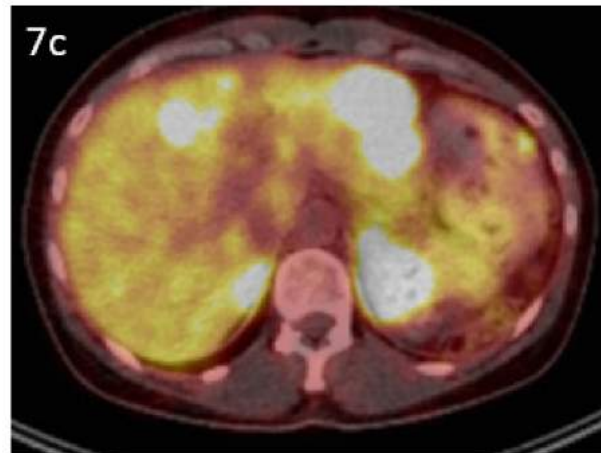
## HETEROGENEIDAD TUMORAL / EVOLUCIÓN DE LA ENFERMEDAD

Paciente de 36 años con tumoración pancreática resecada (Ki<1%). NETG1

**<sup>68</sup>Ga-DOTATOC**

**<sup>18</sup>F-FDG**

40 meses post-IQ



**NET G3 "Ki 30%"**

Predominancia.....

TABLE 3  
 SUVmax of <sup>68</sup>Ga-DOTATATE and <sup>18</sup>F-FDG According to Tumor Grade

|                                    | <sup>68</sup> Ga-DOTATATE | <sup>18</sup> F-FDG | P     |
|------------------------------------|---------------------------|---------------------|-------|
| All NET                            | 16.9 (1.6-50)             | 4.2 (1.4-16.4)      | .005  |
| Low-grade NET Ki67 index ≤2%       | 29 (3.3-45)               | 2.9 (1.5-12)        | <.001 |
| Intermediate NET Ki67 index 3%-20% | 15.5 (1.8-50)             | 10.5 (2.0-13.9)     | NS    |
| High-grade NET Ki67 index >20%     | 4.4 (1.6-8.9)             | 11.7 (4.1-16.4)     | .03   |

SUVmax is the median SUVmax with range in parentheses.  
 SUVmax indicates maximum standardized uptake value; NET, neuroendocrine tumor; <sup>68</sup>Ga-DOTATATE, <sup>68</sup>Ga-DOTA-[SCAP]D[R]Phe<sup>1</sup>,Tyr<sup>3</sup>-octreotate; <sup>18</sup>F-FDG, <sup>18</sup>F-Fluorodeoxyglucose.

TABLE 4  
 Number of Lesions Demonstrating <sup>68</sup>Ga-DOTATATE and/or <sup>18</sup>F-FDG Uptake in High-, Intermediate-, and Low-Grade NET Tumors

|  | High-grade NET | Intermediate-grade NET | Low-grade NET | Total |
|--|----------------|------------------------|---------------|-------|
| Uptake of <sup>68</sup> Ga-DOTATATE and <sup>18</sup> F-FDG          | 5              | 45                     | 21            | 71    |
| Uptake of <sup>68</sup> Ga-DOTATATE but not <sup>18</sup> F-FDG      | 0              | 18                     | 97            | 115   |
| Uptake of <sup>18</sup> F-FDG but not <sup>68</sup> Ga-DOTATATE      | 72             | 33                     | 0             | 105   |
| No uptake of either <sup>68</sup> Ga-DOTATATE or <sup>18</sup> F-FDG | 2              | 5                      | 3             | 10    |
| Total  | 79             | 101                    | 121           | 303   |

- Captación de Ga in low versus high
- Captación FDG in high versus low

Diferencia también en la intensidad!



<sup>18</sup>F-FDG



<sup>68</sup>Ga



The combined approach changed therapy “systemic chemotherapy” in 25% of patients with intermediate or high grade neoplasms

**TABLE 4**  
 Number of Lesions Demonstrating <sup>68</sup>Ga-DOTATATE and/or <sup>18</sup>F-FDG Uptake in High-, Intermediate-, and Low-Grade NET Tumors

|  | High-grade NET | Intermediate-grade NET | Low-grade NET | Total      |
|--|----------------|------------------------|---------------|------------|
| Uptake of <sup>68</sup> Ga-DOTATATE and <sup>18</sup> F-FDG          | 5              | 45                     | 21            | 71         |
| Uptake of <sup>68</sup> Ga-DOTATATE but not <sup>18</sup> F-FDG      | 0              | 18                     | 37            | 115        |
| Uptake of <sup>18</sup> F-FDG but not <sup>68</sup> Ga-DOTATATE      | 72             | 33                     | 0             | 105        |
| No uptake of either <sup>68</sup> Ga-DOTATATE or <sup>18</sup> F-FDG | 2              | 5                      | 3             | 10         |
| <b>Total</b>   | <b>79</b>      | <b>101</b>             | <b>121</b>    | <b>303</b> |

<sup>18</sup>F-FDG

<sup>68</sup>Ga



## USO RACIONAL DE LA PET con $^{18}\text{F}$ -FDG

- Debería realizarse un estudio PET con  $^{18}\text{F}$ -FDG en pacientes con TNE algún momento de la enfermedad.....
- ***Inicial*** “Enfermedad avanzada” o a la ***Progresión*** “rápida”  
(Discrepancias PET-DOTA vs TC)
- >> Impacto en **G2 (moderadamente diferenciados) “> 10%”**  
Análogos/PRRT vs Inhib TK o QT



MUCHAS GRACIAS