VIII EDIZIONE

NEN PRECEPTORSHIP

LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

IEO
Istituto Europeo di Oncologia

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14:15 - 16:15 **NET pancreatico avanzato non funzionante**
SHOOTER: N. Fazio

I SESSIONE
Diagnosi, Stadiazione e Caratterizzazione
PANEL: E. Bertani, G.Bonomo, C. Carnaghi, A. Filice, L. Funicelli, A. Lania, M. Milione, D. Ravizza

16:15 - 16:45 COFFEE BREAK

16:45 - 17:00 **La chirurgia robotica nei NET Pancreatici**
E. Bertani

17:00 - 18:30 **II SESSIONE**
Strategia terapeutica
PANEL: E. Bertani, G.Bonomo, C. Carnaghi, A. Filice, L. Funicelli, A. Lania, M. Milione, D. Ravizza

18:30 - 19:20 **Discussione generale e Conclusioni** - N. Fazio

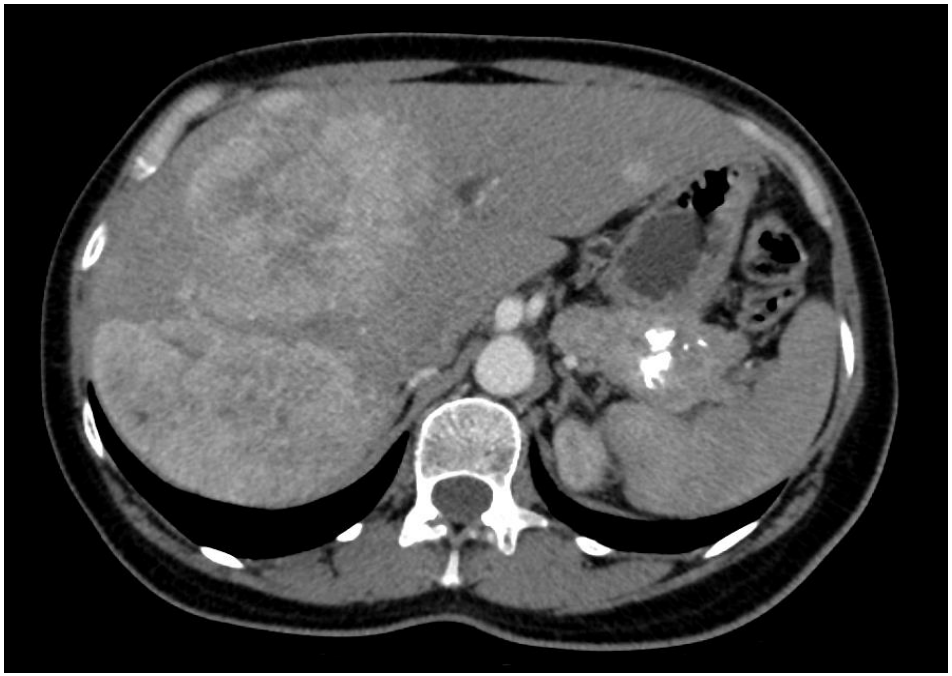
49 aa, F

Astenia, calo ponderale < 5% negli ultimi 3 mesi, dispepsia; picco iperglicemico → ricovero in Medicina Interna e approfondimenti

Comorbidità: pregressa emitiroidectomia per nodulo freddo

Familiarità: sorella operata per timoma a 56 aa, nonna deceduta per mesotelioma pleurico in età avanzata

- **TC addome con mdc**: neoformazione della coda del pancreas + pacchetto adenopatico + lesioni focali epatiche bilobari.



Consulenza oncologica →

Biopsia epatica eco-guidata: “localizzazione epatica di neoplasia neuroendocrina, CgA +”

Paziente

- Femmina 49 aa
- P.S. = 0 (ECOG)
- Paucisintomatica

Tumore

- NEN

1° domanda: cosa proporreste a questo punto?

1. Imaging di medicina nucleare

2. Marcatori circolanti

3. Coinvolgimento di un centro di riferimento

4. Approfondimento istopatologico (es. second opinion da patologo dedicato?)

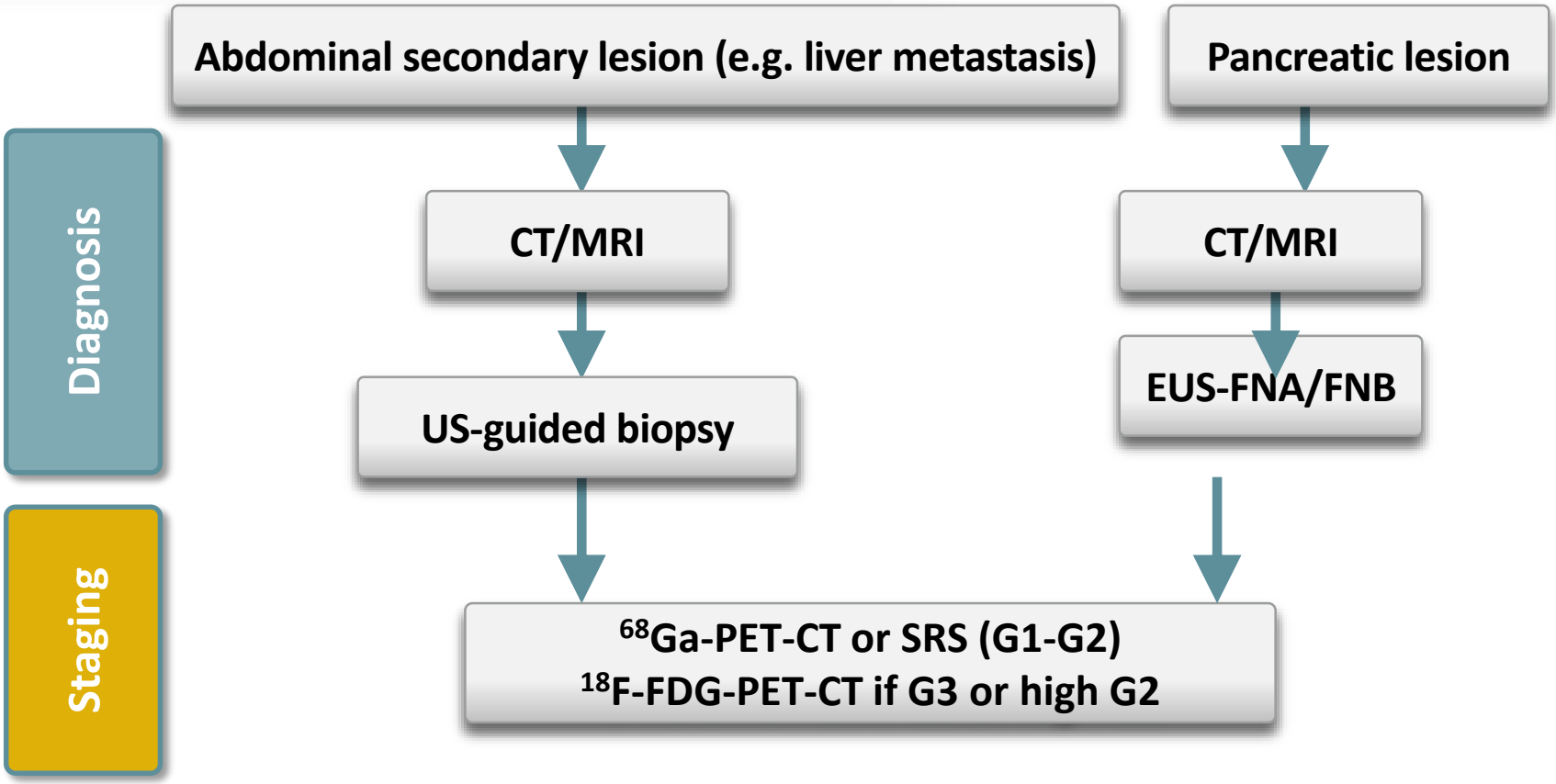
J Endocrinol Invest (2014) 37:875–909
DOI 10.1007/s40618-014-0119-0

POSITION STATEMENT

Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms

Franco Grimaldi · Nicola Fazio · Roberto Attanasio · Andrea Frasoldati · Enrico Papini · Francesco Angelini · Roberto Baldelli · Debora Berretti · Sara Bianchetti · Giancarlo Bizzarri · Marco Caputo · Roberto Castello · Nadia Cremonini · Anna Crescenzi · Maria Vittoria Davì · Angela Valentina D'Elia · Antongiulio Faggiano · Stefano Pizzolitto · Annibale Versari · Michele Zini · Guido Rindi · Kjell Öberg

Filice



Diagnostic flow-chart for GEP-NEN suspected at morphological imaging

ARTICLE IN PRESS
JID: YSONC [mUS5Gb;October 24, 2018;21:51]
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journal homepage: www.elsevier.com/locate/seminoncol

Filice

Peptide receptor radionuclide therapy for patients with advanced pancreatic neuroendocrine tumors

John Ramage[a], Boris G. Naraev[b], Thorvardur R. Halfdanarson[c,*]

[a] Kings Health Partners Neuroendocrine Centre, London, UK
[b] Banner MD Anderson Cancer Center, Gilbert, AZ, USA
[c] Mayo Clinic Cancer Center, Rochester, MN, USA

PET/CT ^{68}Ga-DOTA-peptide

…less uptake occurs on SSTR imaging of G3 tumors, and for this reason G3 NEC are generally imaged with 18F-FDG PET.

Use of 18F-FDG PET has also been proposed alongside Gallium-68 SSTR imaging, in G2 NET with a Ki-67 >10%, for its role in identifying patients with tumors that are more likely to progress.

Marcatori circolanti

Table 1
General and tumour specific markers of neuroendocrine differentiation.

General markers	Tumour specific markers
1. Chromogranins ○ Chromogranin A ○ Chromogranin B ○ Secretogranin II ○ Secretogranin III (1B1075) ○ Secretogranin IV (HISL-19) ○ Secretogranin V (7B2) ○ Secretogranin VI (NESP55) 2. Neuron Specific Enolase 3. Pancreatic polypeptide 4. Chorionic gonadotrophin	1. Carcinoid tumours ○ 24 h Urine 5-hydroxyindole acetic acid ○ 24 h Urine 5-hydroxy-tryptophan ○ Plasma serotonin 2. Insulinoma ○ Fasting insulin ○ Fasting pro-insulin 3. Gastrinoma ○ Fasting/stimulated gastrin 4. Glucagonoma ○ Fasting glucagon 5. VIP-oma ○ Fasting vasoactive intestinal peptide 6. Somatostatinoma ○ Fasting somatostatin

Conditions affecting CgA-circulating levels

Non-oncological		Oncological
Benign diseases	Iatrogenic causes	
Gastrointestinal: chronic atrophic gastritis, Helicobacter pylori infection, liver cirrosi, chronic hepatitis, pancreatitis, inflammatory bowel diseases, irritable bowel	Proton pump inhibitors	Colorectal carcinoma
Cardiovascular: hypertension, heart failure, acute coronary syndromes	Histamine 2 receptor antagonists	Gastric carcinoma
Renal and hepatic dysfunctions	Serotonin reuptake inhibitors	Pancreatic carcinoma
Others: giant cell arteritis, rheumatoid arthritis, systemic lupus erythematosus, pulmonary obstructive disease, hyperthyroidism		Prostate carcinoma
		Breast carcinoma
		Hepatocellular carcinoma
		Ovarian carcinoma

Principal limitations:
CgA measurements are generally nonspecific
No biological CgA standard and evidence
Wide variations in assay measurement between individual laboratories

30-50% NENs present normal CgA levels

Endocrine-Related Cancer (2018) 25, R11–R29

CgA…

…and tumor primary location

The highest values of CgA are observed in small intestine NET (up to 200 times above

…and staging

…as a prognostic factor

3 times above the upper reference range at the time of diagnosis is a significant predictor of shorter survival

basal CgA levels less than 200 ng/mL represents a positive prognostic factor

…to evaluate the esponse to treatment

In assessing NET therapy, a reduction of higher than 50% or at least higher than 25% of a circulating tumor marker is considered to represent a significant effect

…to evaluate the relapse/progression of the disease

In a retrospective study CgA rising above the normal range represented the first indicator of the recurrence

In 2 retrospective studies CgA elevation higher than 25% was a highly sensitive predictor of tumor progression

In a recent prospective study no CgA elevation was seen in subjects developing recurrence who had elevated pre-surgical levels

Three prospective studies demonstrated poor capability of CgA changes in reflecting morphological behavior of NENs

Endocrine-Related Cancer (2018) 25, R11–R29

Associazione Italiana di Oncologia Medica

Linee guida

NEOPLASIE NEUROENDOCRINE

In condivisione con It.a.net
Italian Association for Neuroendocrine Tumours

Edizione 2018
Manuale integrale 2016 (update 2018)

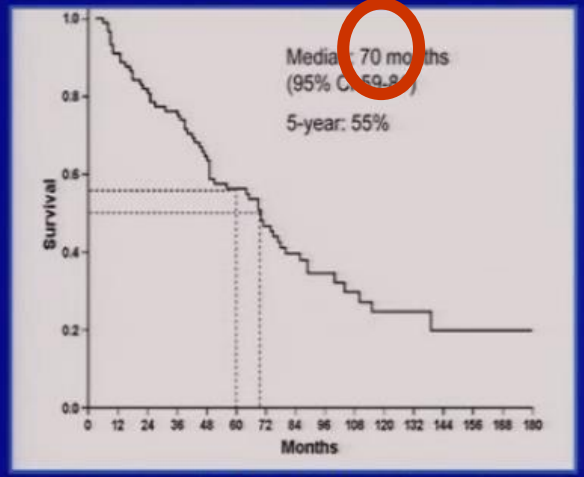
A fronte dei suddetti markers specifici, la Cg-A è considerata il principale marker generico, ovvero utilizzabile indipendentemente dalla presenza di una attività secernente specifica del tumore e dalla eventuale sindrome correlata, essendo valida anche per le NEN non funzionanti.
Si tratta di una glicoproteina presente nei granuli citoplasmatici di tutte le cellule neuroendocrine diffuse nell'organismo, la cui accuratezza diagnostica varia molto in funzione del tipo di tumore, dell' estensione della malattia, e del tipo di metodica utilizzata per il dosaggio.

La sensibilità oscilla tra il 70% e il 90% (2), la specificità varia notevolmente e risente di numerosi possibili falsi positivi, tra i quali la gastrite cronica atrofica del corpo-fondo gastrico, l'infezione da Helicobacter pylori, l'utilizzo di inibitori della pompa protonica, le malattie infiammatorie croniche, l'ipertensione arteriosa non controllata.

A causa dei numerosi e frequenti possibili falsi positivi, e delle diversità metodologiche nella misurazione plasmatica della CgA, questo *marker* non dovrebbe essere utilizzato come *screening* nell'approccio a pazienti che presentano generici sintomi gastrointestinali che solo eccezionalmente sono riferibili alla presenza di una NEN. L'uso della CgA è, infatti, limitato ai pazienti con una diagnosi documentata di NEN per monitorare l'andamento della malattia durante il *follow-up* e la risposta alla terapia medica (3-7).

Metastatic Pancreatic NET: Overall Survival

Median Survival in Single-institution Database (n=90): 5.8 Years



Kaplan-Meier Curve of Overall Survival From Diagnosis of Metastases[1]

Median Survival in SEER: 2 Years

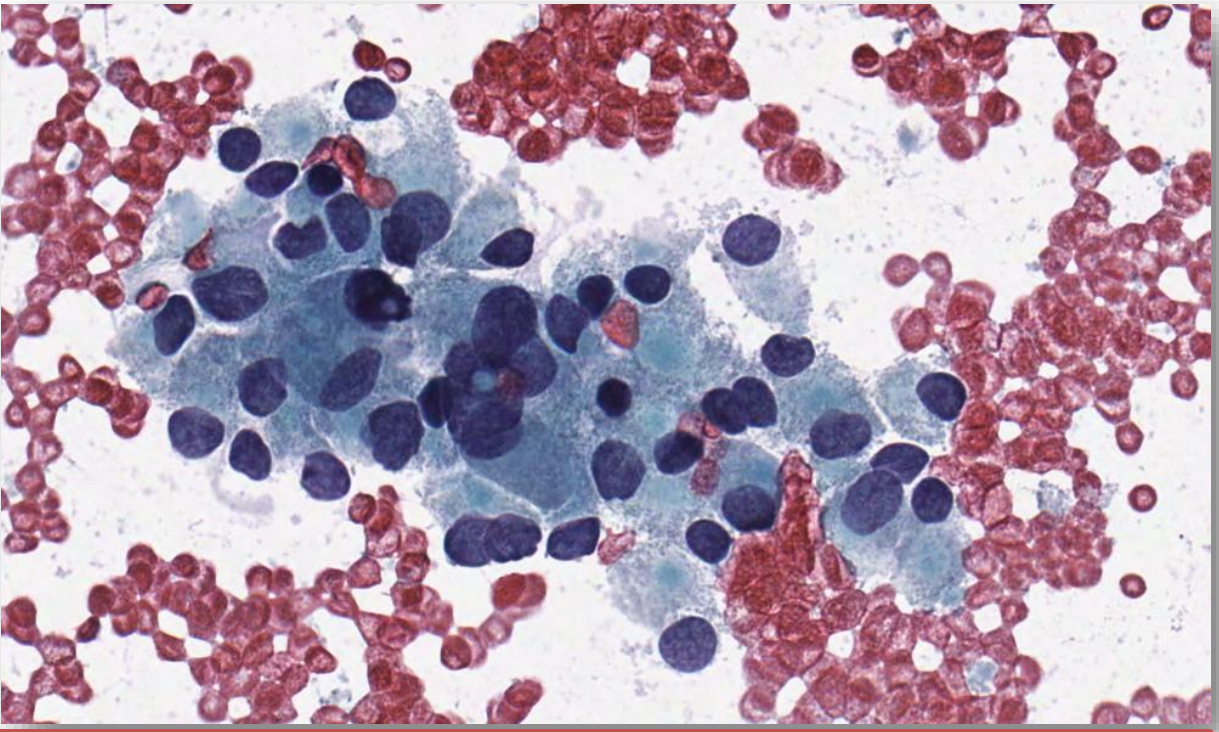
Median Survival (months)[2]

Site	Localized	Regional	Distant
Appendix	>360	>360	27
Cecum	135	107	41
Colon	261	36	5
Duodeum	107	101	57
Gastric	154	71	13
Liver	50	14	12
Lung	227	154	16
Pancreas	136	77	24
Rectum	290	90	22
Small bowel	111	105	56
Thymus	110	68	40

1. Strosberg et al. *Pancreas* 2009; 38: 255-58
2. Yao et al. *J Clin Oncol* 2008; 26: 3063-72

Kulke, ASCO 2011

Fine Needle Aspiration



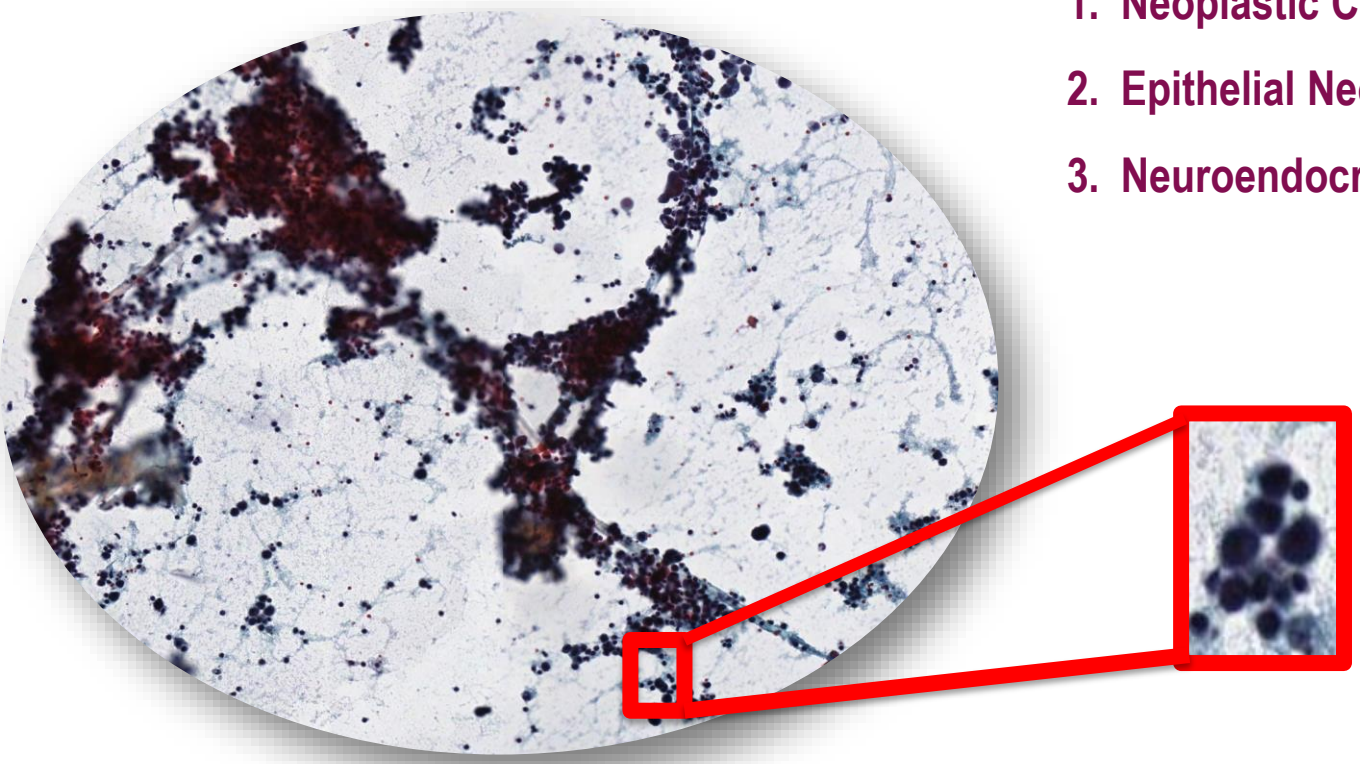
What Pathologist will be able to tell you?

1. **Neoplastic Cells:** Yes or Not
2. **Epithelial Neoplasm:** Yes or Not
3. **Neuroendocrine:** Yes or Not

Cytologic specimen : Only Floating Cells in Ematic Background
Histological Architecture? **NO**
Eligible for Immunohistochemistry? **NO**

Fine Needle Aspiration

(In Well differentiated Neuoroendocrine Neoplasms)



What Pathologist will be able to tell you?

1. **Neoplastic Cells?** Yes or Not
2. **Epithelial Neoplasm?** Yes or Not
3. **Neuroendocrine?** Yes or Not

Cytologic specimen : Only Floating Cells in Ematic Background
Histological Architecture? **NO**
Eligible for Immunohistochemistry? **NO**

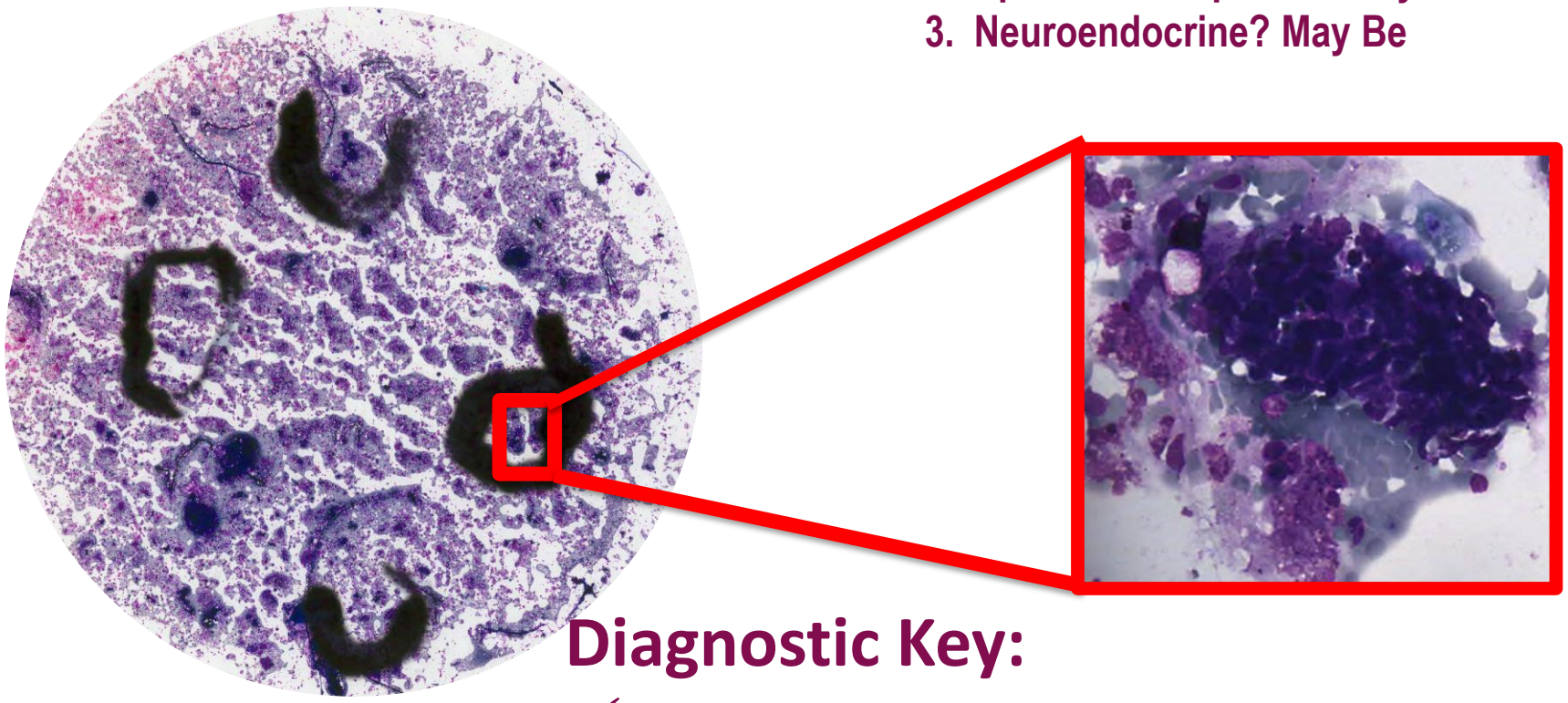
Diagnosis : Well Differentiated Neuroendocrine Neoplasm

Fine Needle Aspiration

(In Poorly differentiated Neuoroendocrine Neoplasms)

What Pathologist will be able to tell you?

1. Neoplastic Cells? Yes
2. Epithelial Neoplasm? May Be
3. Neuroendocrine? May Be



Diagnostic Key:

✓ **Trabeculae: NO**

✓ **Mitosis: YES**

✓ **Atypia: YES**

✓ **Necrosis: YES**

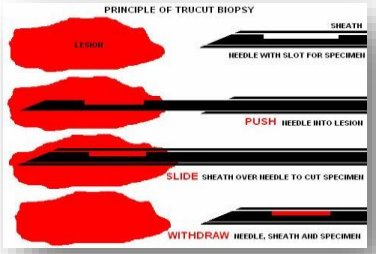
Cytologic specimen : Only Floating Cells in Ematic Background

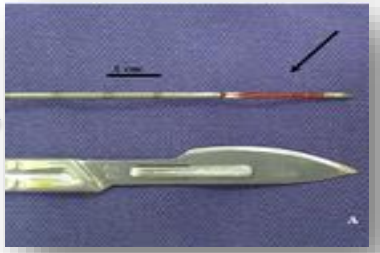
Histological Architecture? **NO**

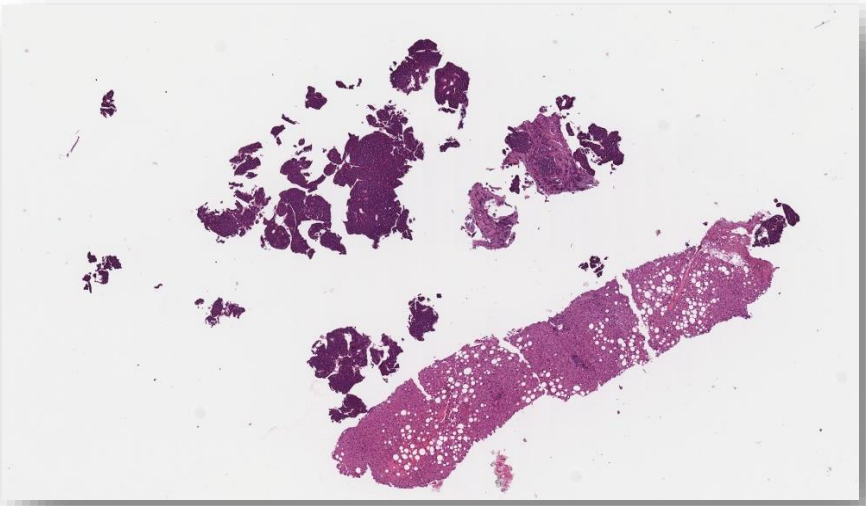
Eligible for Immunohistochemistry? **NO**

Diagnosis : Poorly Differentiated Neoplasm ….may be Neuroendocrine

Biopsy







What Pathologist will be able to tell you?

1. **Tumour : Yes or Not**
2. **Benign *vs* Malignant: Yes or Not**
3. **Neuroendocrine: Yes or Not**
4. **Proliferative Indices (Ki-67/Mitotic Index): May Be**
5. **Tumour Origin (in metastases): May Be**

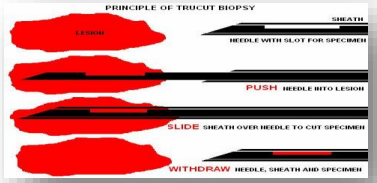
Biopsy

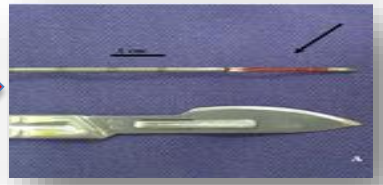
Histological Architecture? **Yes always**

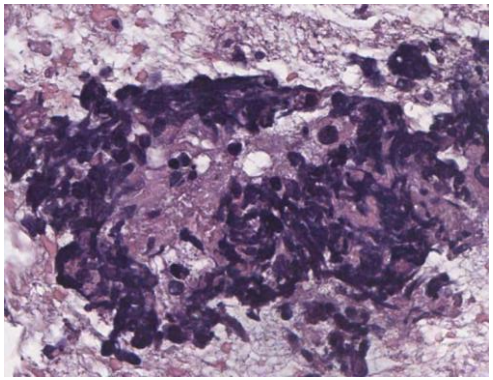
Eligible for Immunohistochemistry: **Yes always**

Could be representative of the original lesion: May Be

Biopsy

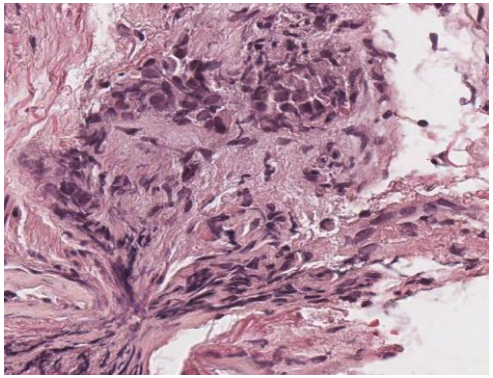


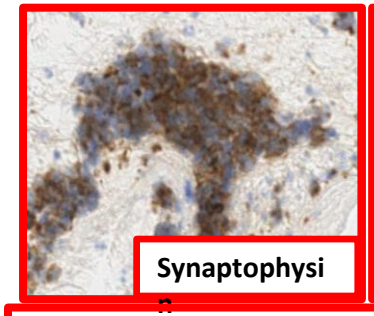


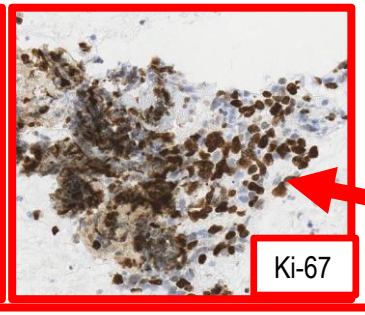


Diagnostic Key:

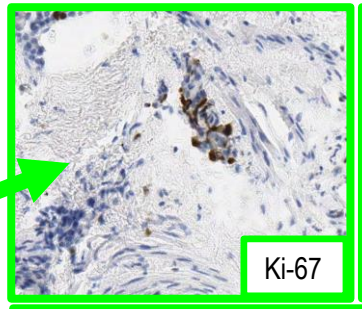
- ✓ **Architecture:** Not Clear
  - ✓ **Mitosis:** may be
  - ✓ **Atypia:** may be
  - ✓ **Necrosis:** may be
  - ✓ **IHC*:** Synaptophysin +

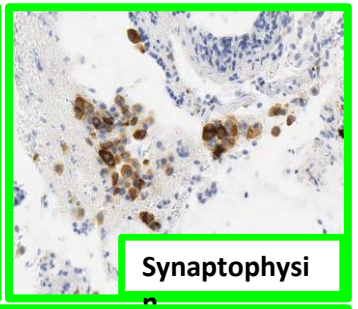






90% ✓**Ki-67** 10%



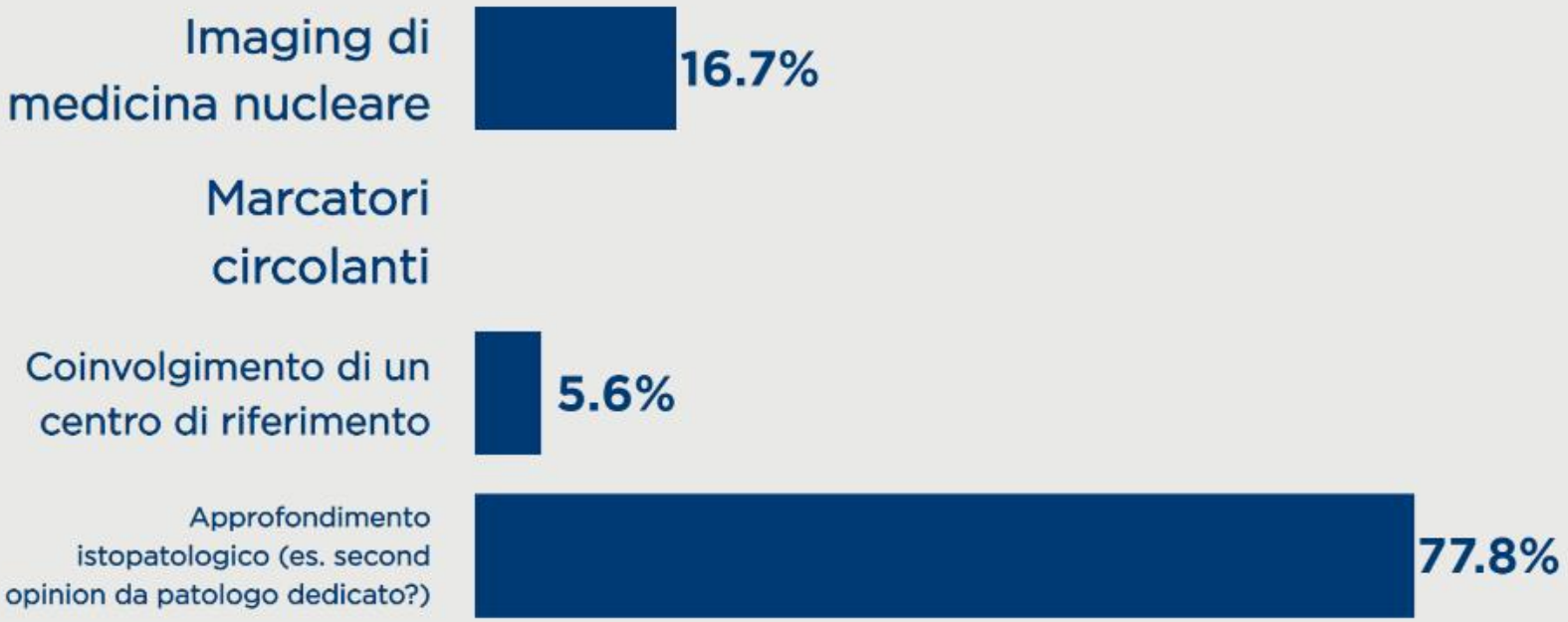


Poorly Differentitated Neuroendocrine carcinoma (NEC)
(microcitoma)

* IHC= Immunohistochemestry

Well Differentitated Neuroendocrine Tumours (NET)
(carcinoid)

Cosa proporreste a questo punto?



Addendum da parte dello stesso patologo che aveva refertato l'esame →

→ NET ben differenziato, Ki-67 < 3%

Paziente

- Femmina 49 aa
- P.S. = 0 (ECOG)
- Paucisintomatica

Tumore

- NET
- Ben differenziato
- Ki-67 < 3%

2° domanda: cosa fareste adesso?

1. PET/TC con Gallio^{68}-DOTA-peptide o Scintigrafia con octreotide marcato

2. Dosaggio ormonale pancreatico specifico

3. Ulteriore imaging radiologico

4. EUS pancreatica +/- FNA

Filice

^{68}Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Metaanalysis

J Nucl Med 2017; 58:1452–1458
DOI: 10.2967/jnumed.117.191197

Michael M. Graham[1], Xiaomei Gu[2], Timothy Ginader[3], Patrick Breheny[3], and John J. Sunderland[1]

1) Sensibilità e specificità

TABLE 2
Sensitivity and Specificity

Reference	*n*	True-positive	False-negative	True-negative	False-positive	Sensitivity	Specificity
Gabriel et al. (*8*)	84	69	2	12	1	97.2%	92.3%
Versari et al. (*9*)	19	12	1	5	1	92.3%	83.3%
Ruf et al. (*10*)	51	32	7	8	4	82.1%	66.7%
Mayerhoefer et al. (*11*)	55	32	1	18	4	97.0%	81.8%
Beiderwellen et al. (*12*)	8	4	1	3	0	80.0%	100.0%
Schraml et al. (*13*)	51	40	1	10	0	97.6%	100.0%
Venkitaraman et al. (*14*)	32	25	1	6	0	96.2%	100.0%
Frilling et al. (*15*)	52	52	0			100.0%	
Poeppel et al. (*19*)	40	40	0			100.0%	
Jindal et al. (*16*)	13	13	0			100.0%	
Kumar et al. (*17*)	20	20	0			100.0%	
Nakamoto et al. (*18*)	46	6	1			85.7%	

Filice

^{68}Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Metaanalysis

J Nucl Med 2017; 58:1452–1458
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Michael M. Graham[1], Xiaomei Gu[2], Timothy Ginader[3], Patrick Breheny[3], and John J. Sunderland[1]

2) Confronto ^{68}Ga-DOTATOC vs ^{111}In Octreotide

The sensitivity of ^{68}Ga-DOTATOC PET is definitely better than ^{111}In-octreotide SPECT imaging. In the 2 papers that directly compared the 2 approaches, the sensitivity for ^{68}Ga-DOTATOC on a per-lesion basis was 100% and for ^{111}In-octreotide 78%. In the

TABLE 5
^{68}Ga-DOTATOC Versus ^{111}In-Octreotide

		DOTATOC		Octreotide	
Reference	*n*	True-positive	False-negative	True-negative	False-positive
Hofmann et al. (*3*)	8	40	0	34	6
Buchman et al. (*24*)	27	70	0	52	18

3) Cambio nel management

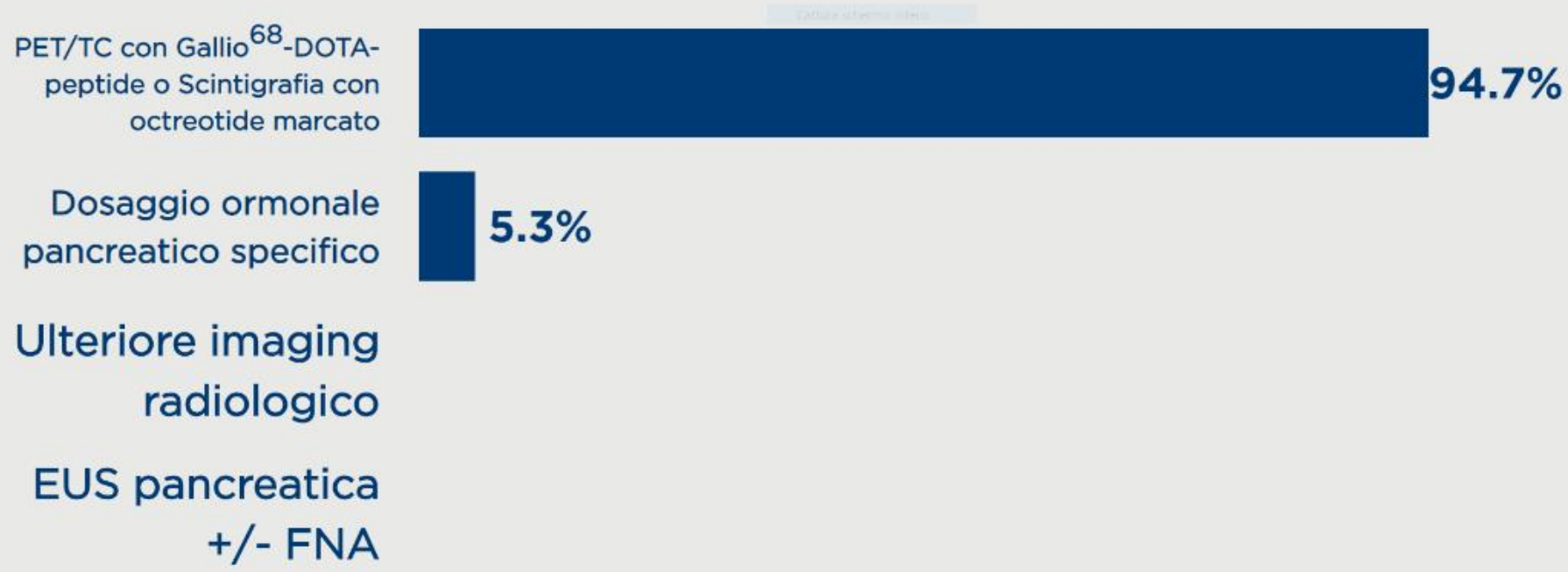
review, 3 papers were found that reported change in management after ^{68}Ga-DOTATOC PET imaging. The pooled result reported change of management in 95 of 188 (51%), which clearly illustrates

Dosaggio ormonale pancreatico specifico ?

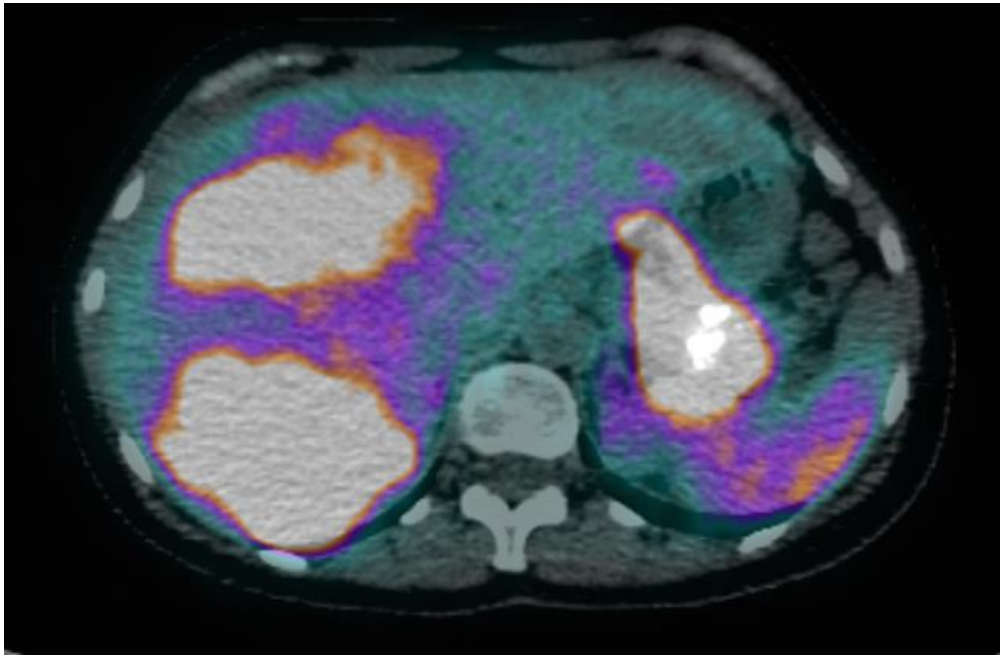
Quadro clinico ?

Name	Biologically active peptide(s) secreted	Incidence (new cases/10^6 population/year)	Tumor location	Malignant %	Associated with MEN-1, %	Main symptoms/signs
A. Most common functional PET syndromes						
Insulinoma	insulin	1–3	pancreas (>99%)	<10	4–5	hypoglycemic symptoms (100%)
Zollinger-Ellison syndrome	gastrin	0.5–2	duodenum (70%); pancreas (25%); other sites (5%)	60–90	20–25	pain (79–100%); diarrhea (30–75%); esophageal symptoms (31–56%)
B. Established rare functional PET syndromes (RFTs)						
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	vasoactive intestinal peptide	0.05–0.2	pancreas (90%, adult); other (10%, neural, adrenal, periganglionic)	40–70	6	diarrhea (90–100%); hypokalemic (80–100%); dehydration (83%)
Glucagonoma	glucagon	0.01–0.1	pancreas (100%)	50–80	1–20	rash (67–90%); glucose intolerance (38–87%); weight loss (66–96%)
Somatostatinoma	somatostatin	rare	pancreas (55%); duodenum/jejunum (44%)	>70	45	diabetes mellitus (63–90%); cholelithiases (65–90%); diarrhea (35–90%)
GRHoma	growth hormone-releasing hormone	unknown	pancreas (30%); lung (54%); jejunum (7%); other (13%)	>60	16	acromegaly (100%)
ACTHoma	ACTH	rare	pancreas (4–16% all ectopic Cushing's)	>95	rare	Cushing's syndrome (100%)
PET causing carcinoid syndrome	serotonin? tachykinins	rare (43 cases)	pancreas (<1% all carcinoids)	60–88	rare	same as carcinoid syndrome above
PET causing hypercalcemia (PTHrp-oma)	PTHrp; others unknown	rare	pancreas (rare cause of hypercalcemia)	84	rare	abdominal pain due to hepatic metastases, symptoms due to hypercalcemia

Cosa fareste adesso?



16-1-2018: PET/TC con Gallio68-DOTATOC



Paziente

- Femmina 49 aa
- P.S. = 0 (ECOG)
- Paucisintomatica
- Sindrome: no

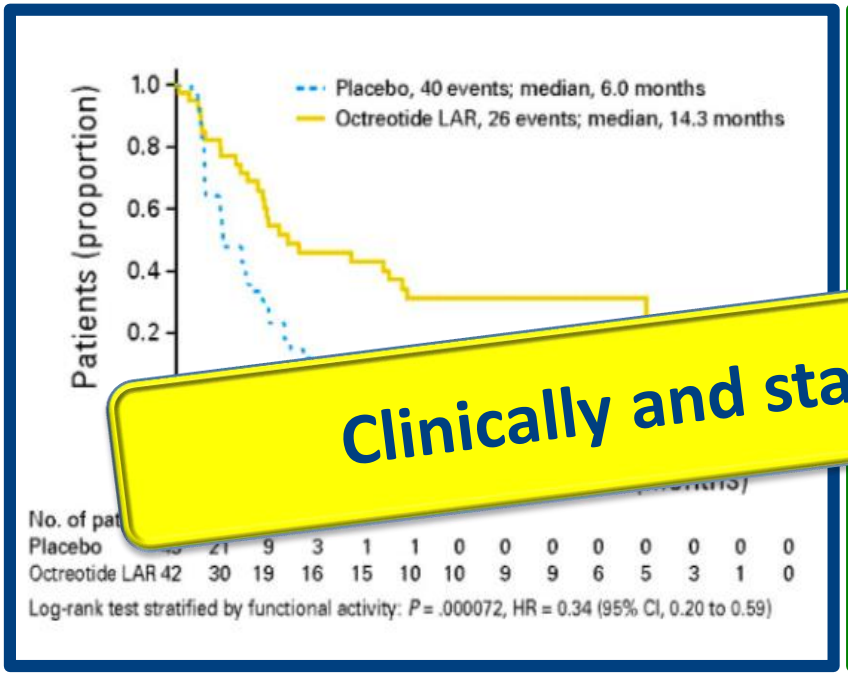
Tumore

- NET
- Ben differenziato
- Ki-67 < 3%
- PET-Gallio +++
- Sporadico

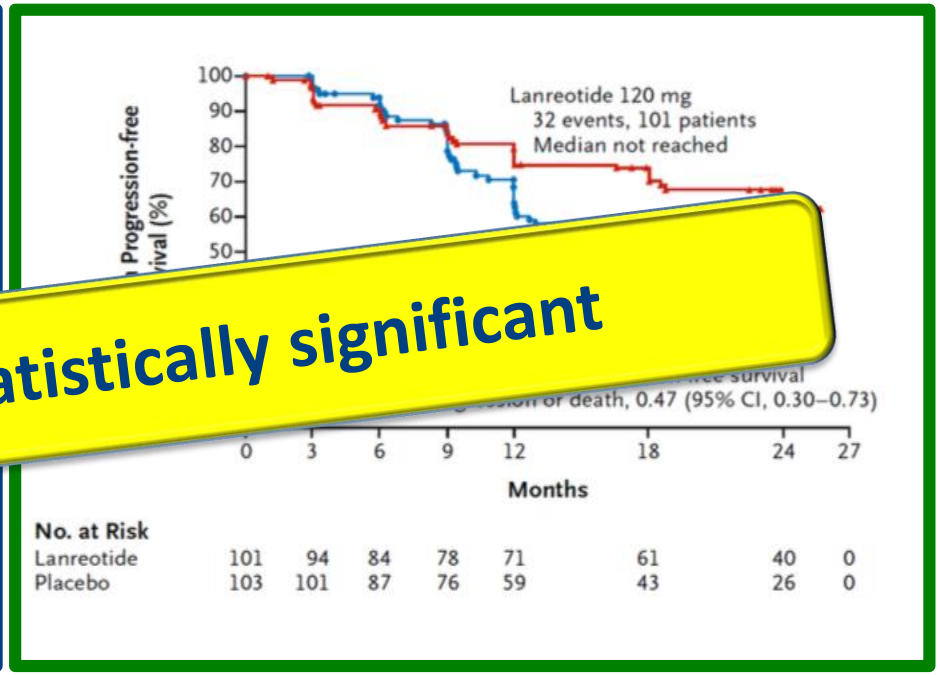
3° domanda: cosa fareste?

1. Inizio SSA
2. Inclusione in studi clinici
3. Watch & wait
4. Terapia sistemica diversa dall’ SSA

PROMID



CLARINET



Clinically and statistically significant

Rinke et al, JCO 2009; Caplin et al NEJM 2014

	PROMID	CLARINET
Type of SSAs used	Octreotide LAR 30 mg/28 d.	Lanreotide 120 mg/28 d.
Primary site	Midgut	Entero-pancreatic
Clinical Status	Functioning/Non-functioning	Non-functioning
Disease Status at baseline	Unknown	Stable disease (96%)
Ki67 (treatment arm)	≤ 2% = 97,6%	< 2% = 68% 3-10% = 32%
Liver involvement (treatment arm)	< 10% = 76% > 25%= 17%	< 10% = 49% > 25% = 39%

Rinke et al, JCO 2009; Caplin et al NEJM 2014

LINEE GUIDA
2018

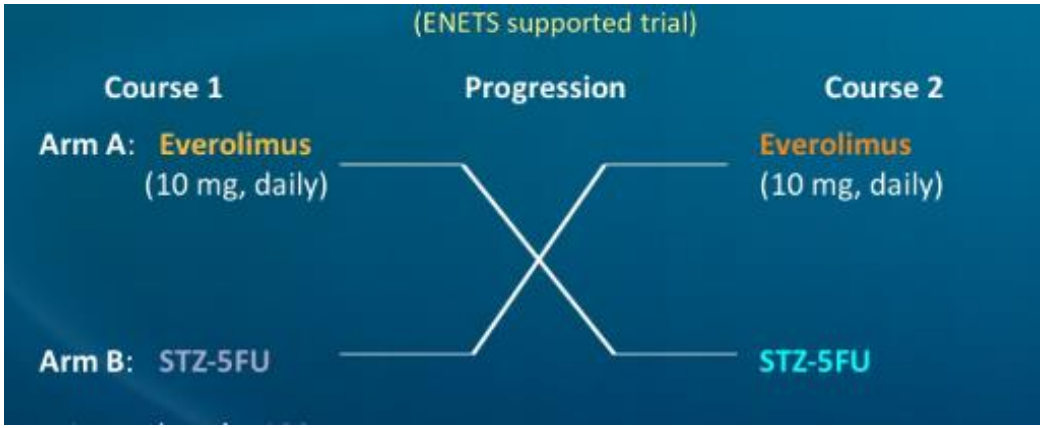
Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione clinica
ALTA	Nei pazienti con NET enteropancreatico, non funzionante, non rapidamente progressivo, con basso Ki67 ed esprimenti i recettori della somatostatina, la terapia con Octreotide e Lanreotide dovrebbe essere presa in considerazione (1,2).	**Positiva forte**

Linee Guida AIOM/ITANET ed. 2018

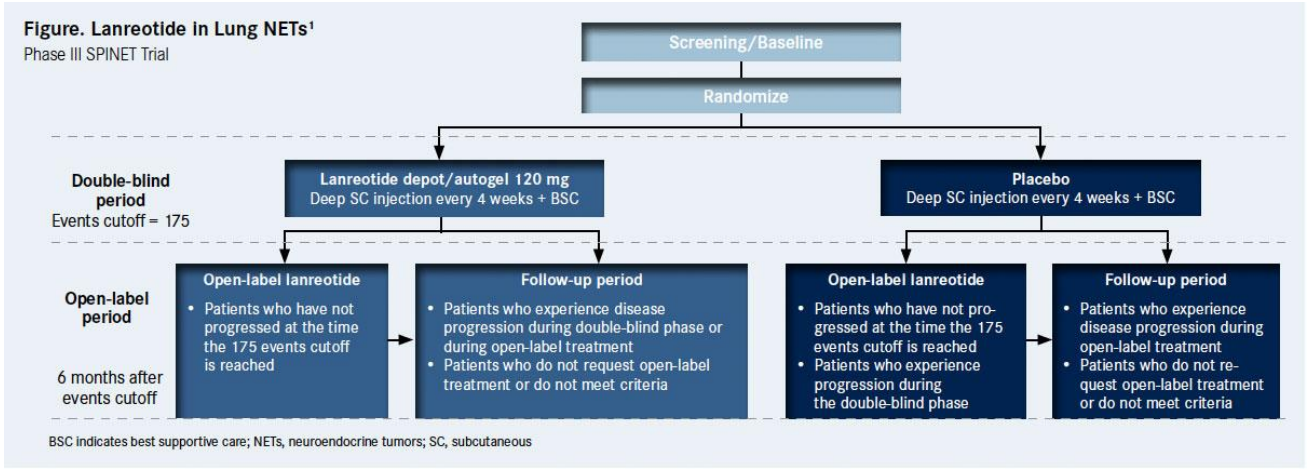
Inclusione in studi clinici

Unmet Needs

SEQTOR



SPINET



European ENETS Neuroendocrine Tumor Society

It.a.net

Centers of Excellence (CoE) Interactive Map

European ENETS Neuroendocrine Tumor Society

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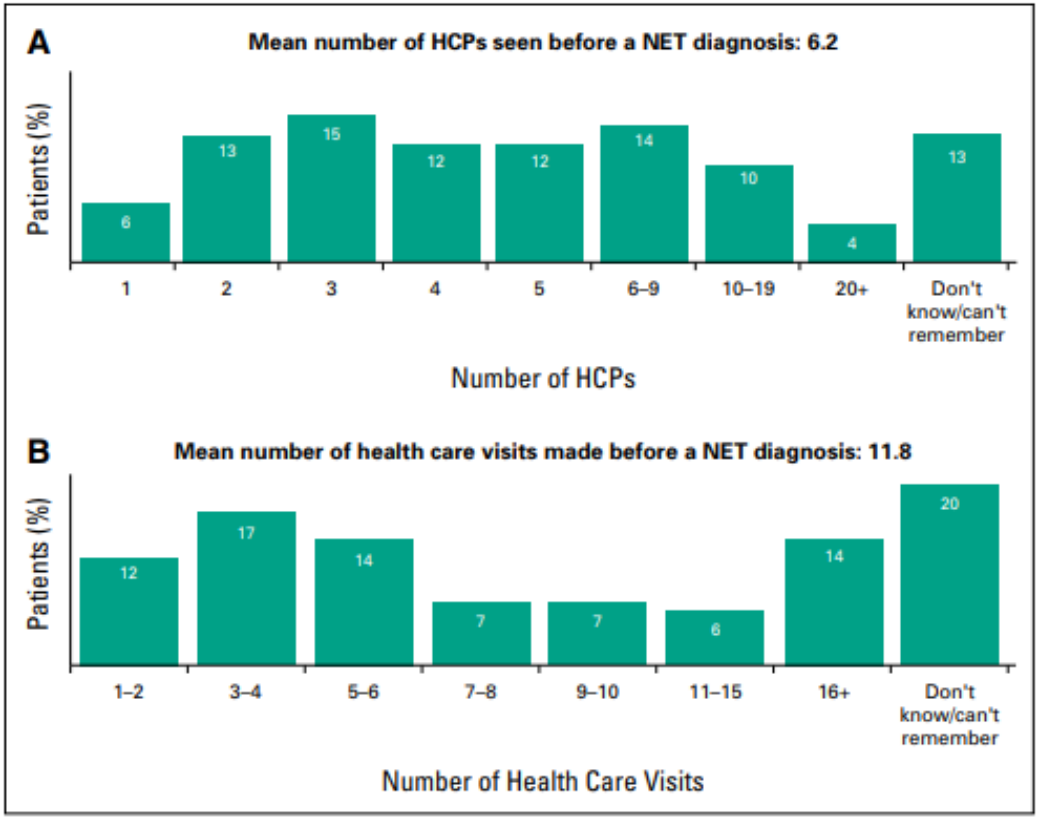


Singh S, et al. Journal of Global Oncology 2017

WJCO World Journal of Clinical Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Clin Oncol 2017 April 10; 8(2): 96-99

DOI: 10.5306/wjco.v8.i2.96

ISSN 2218-4333 (online)

EDITORIAL

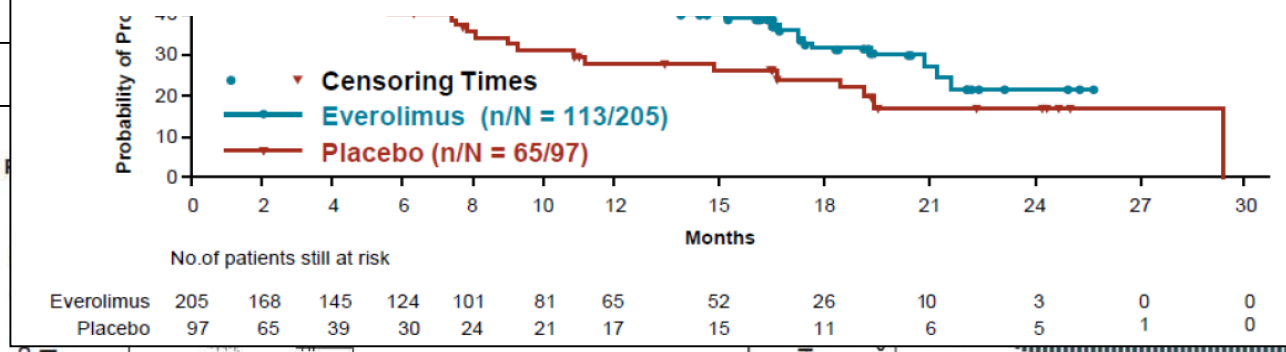
Watch and wait policy in advanced neuroendocrine tumors: What does it mean?

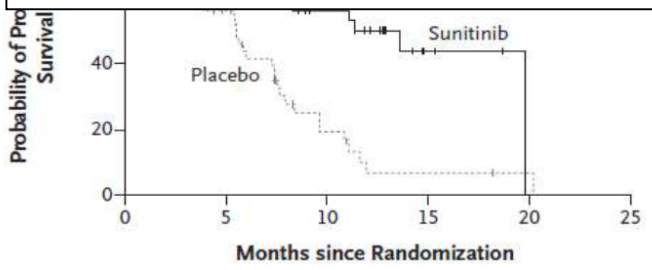
- ✓ Nella maggior parte dei casi W&W sarebbe il piano B per l'analogo della somatostatina
- ✓ In altri tumori W&W è stato proposto come alternativa alla chemioterapia
- ✓ Tipo di esami, timing, costo del follow-up durante W&W non è stato validato
- ✓ I panNET avanzati non trattati progrediscono

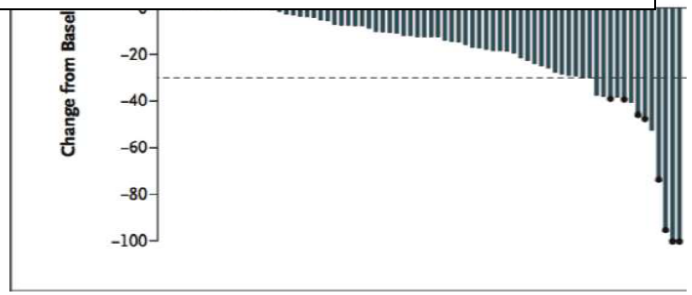
RADIANT-3

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pNEN ben/moderatamente differenziate, avanzate, in progressione, la terapia con everolimus deve essere raccomandata. (20)	**Positiva forte**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pNEN ben differenziate, avanzate, in progressione la terapia con sunitinib deve essere raccomandata (21).	**Positiva forte**







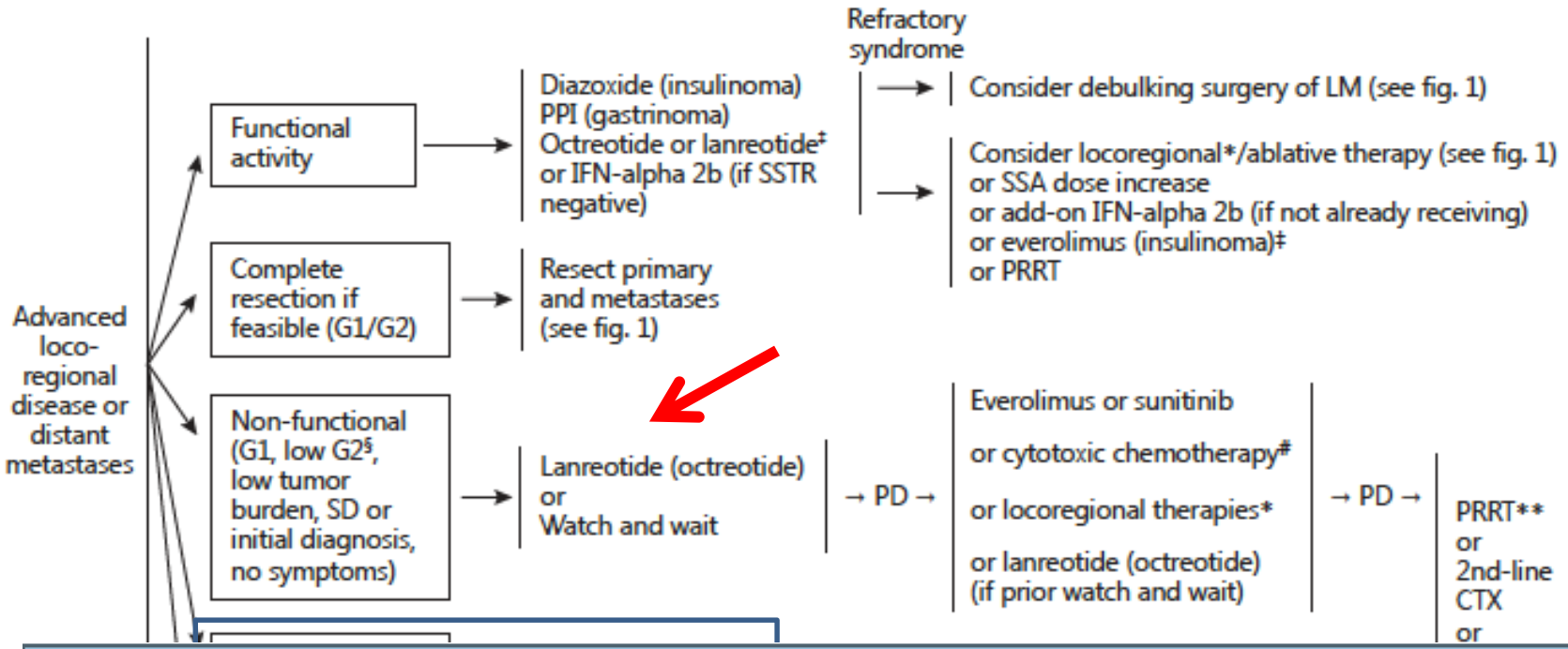
SUN, compared with placebo, significantly improves PFS in patients with advanced progressive pNETs
APPROVED for pancreatic NETs

Raymond et al. NEJM 2011

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site

M. Pavel[a] D. O'Toole[b] F. Costa[c] J. Capdevila[d] D. Gross[e] R. Kianmanesh[f]
E. Krenning[g] U. Knigge[h] R. Salazar[i] U.-F. Pape[a] K. Öberg[j]
all other Vienna Consensus Conference participants

Neuroendocrinology 2016;103:172–185



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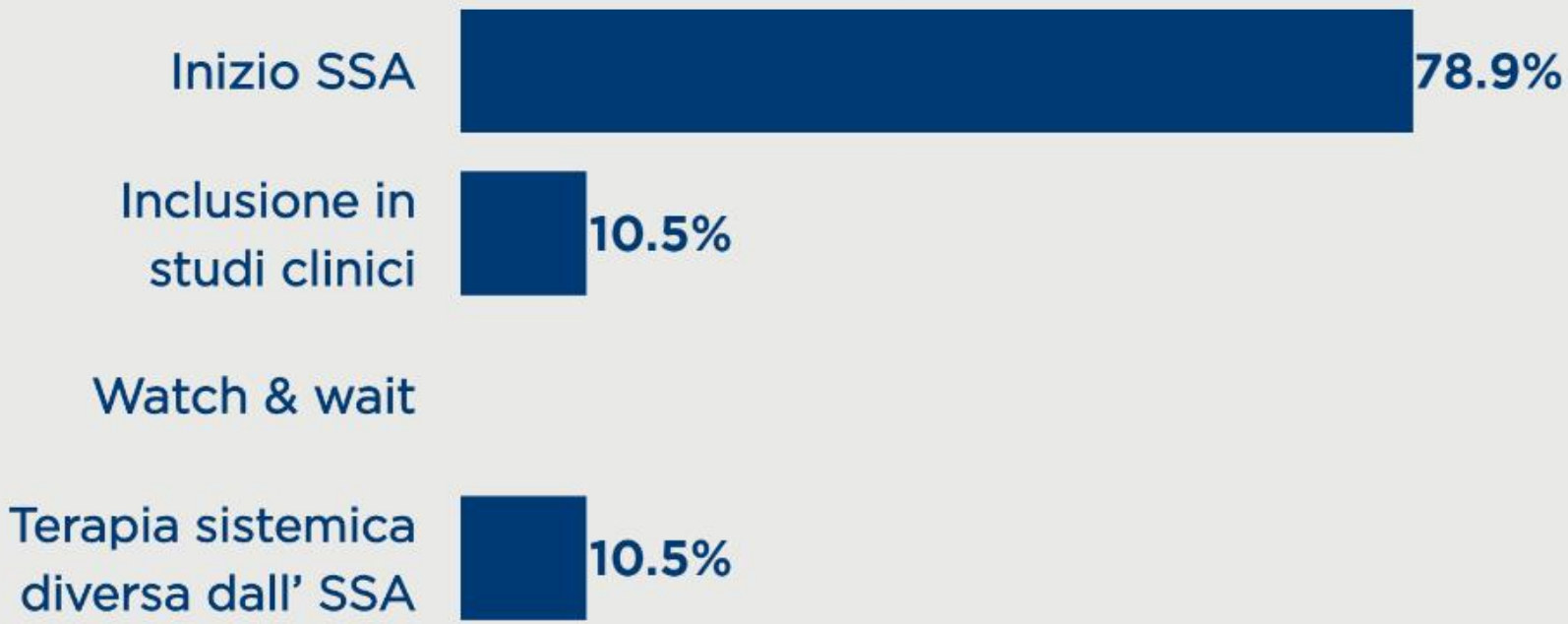
ALTA	Nei pazienti con NET enteropancreatico, non funzionante, non rapidamente progressivo, con basso Ki67 ed esprimenti i recettori della somatostatina, la terapia con Octreotide e Lanreotide dovrebbe essere presa in considerazione (1,2).	**Positiva forte**

Cosa fareste?



Visita oncologica

→ inizia SSA long acting + invio a Centro di riferimento per chirurgia su primitivo

Coffee break

Paziente

- Femmina 49 aa
- P.S. = 0 (ECOG)
- Paucisintomatica
- Sindrome: no

Tumore

- NET
- Ben differenziato
- Ki-67 < 3%
- PET-Gallio +++
- Sporadico

In corso SSA long acting

4° domanda: come proseguireste?

1. Prosegue SSA fino a PD
2. Aggiunge terapia sistemica ad SSA
3. Trattamento locoregionale epatico
4. Chirurgia

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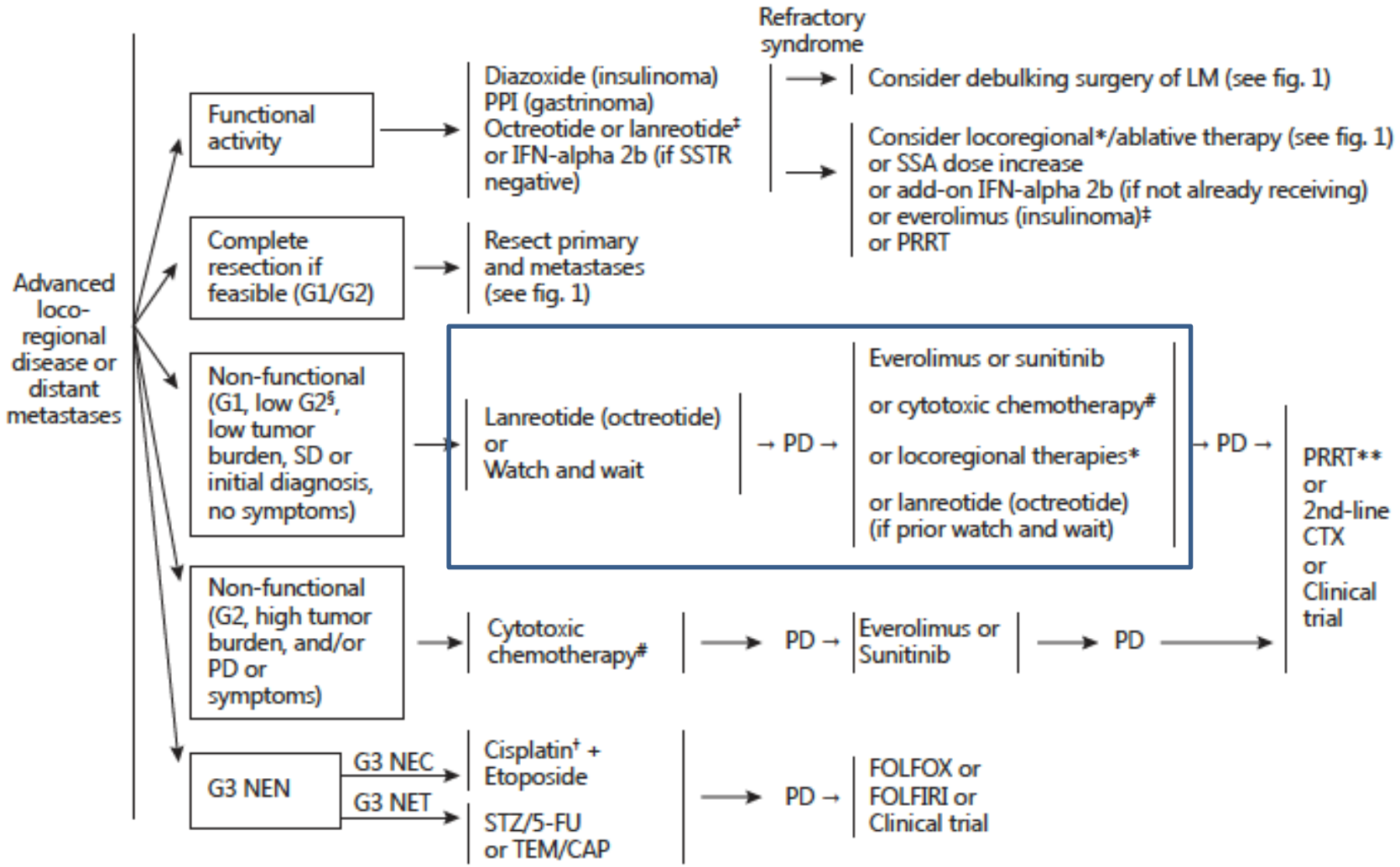
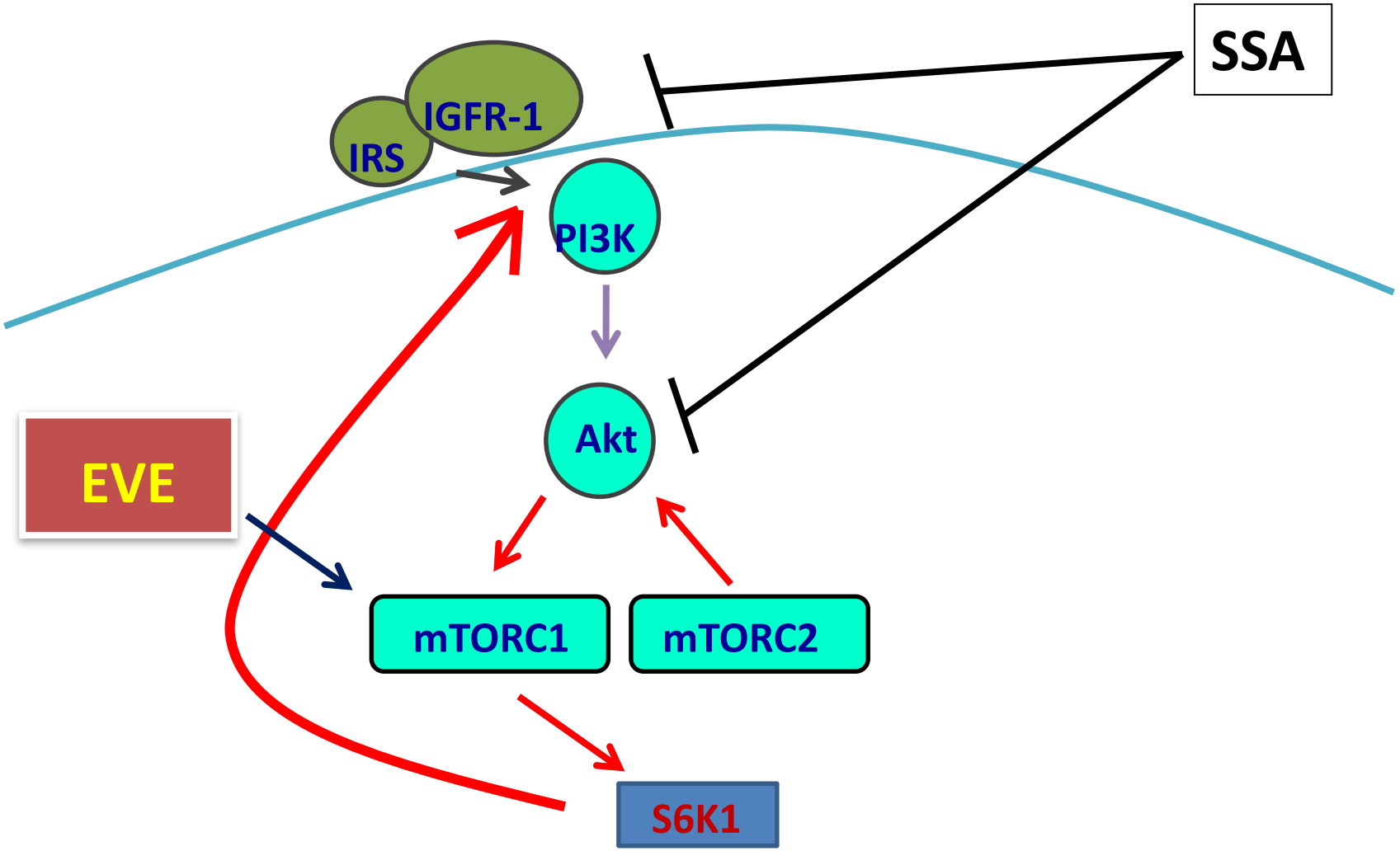
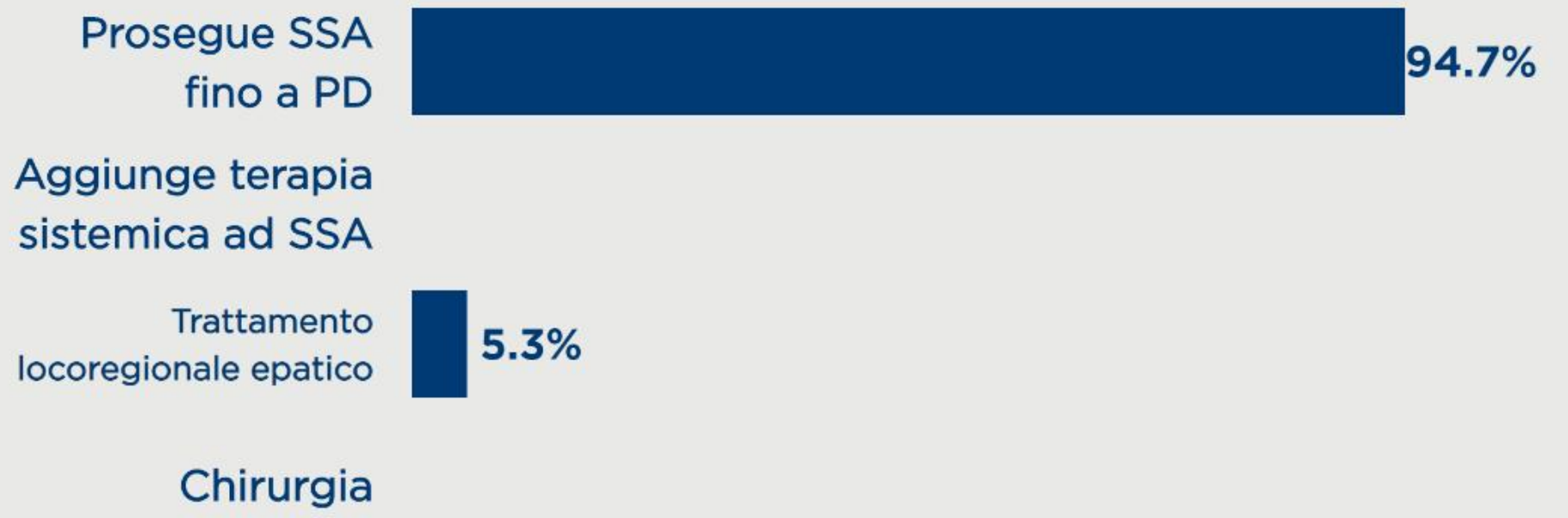


Deconstructing feedback-signaling networks to improve anticancer therapy with mTORC1 inhibitors



Carracedo A, Baselga J, and Pandolfi P.P. Cell Cycle 2008

Come proseguireste?



Discussione multidisciplinare :

Definizione di strategia terapeutica

- **Piano A** → Prosegue SSA e valuta altra terapia sistemica a PD

- **Piano B** → Intensifica terapia sistemica subito a scopo citoriduttivo e valuta chirurgia +/- radiologia interventistca successive → Debulking assoluto

- **Piano C** → Prosegue SSA + Debulking epatico subito, successiva rimozione del primitivo e PRRT dopo

5° domanda: quale terapia sistemica fareste a scopo citoriduttivo?

1. Chemioterapia

2. Terapia radiorecettoriale

3. Sunitinib

4. Everolimus

The longest time spent waiting for a randomized trial…

The New England
Journal of Medicine

Volume 303 NOVEMBER 20, 1980 Number 21

STREPTOZOCIN ALONE COMPARED WITH STREPTOZOCIN PLUS FLUOROURACIL IN THE TREATMENT OF ADVANCED ISLET-CELL CARCINOMA

CHARLES G. MOERTEL, M.D., JAMES A. HANLEY, PH.D., AND LEWIS A. JOHNSON, M.D.

E2211 Study Design

Progressive, G1/G2, metastatic pancreatic NETs

R 1:1

n=72

n=72

ARM A:
Temozolomide 200 mg/m² po QD days 1-5

ARM B:
Capecitabine 750 mg/m² po BID days 1-14
Temozolomide 200 mg/m² QD days 10-14

Cycle length = 28 days; max 13 cycles.
Imaging performed every 12 weeks (RECIST 1.1)

Stratified by:
- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Primary Endpoint:
- PFS (local review)

Secondary Endpoints:
- RR
- OS
- Toxicity

Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

28 YEARS ANNIVERSARY

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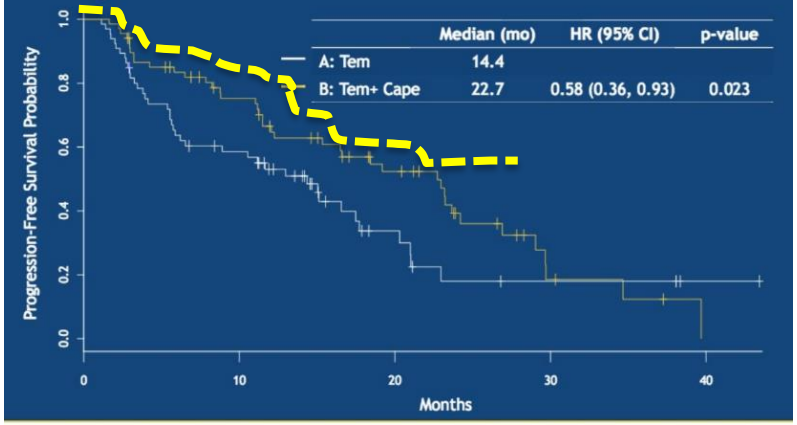
Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

Response Rates

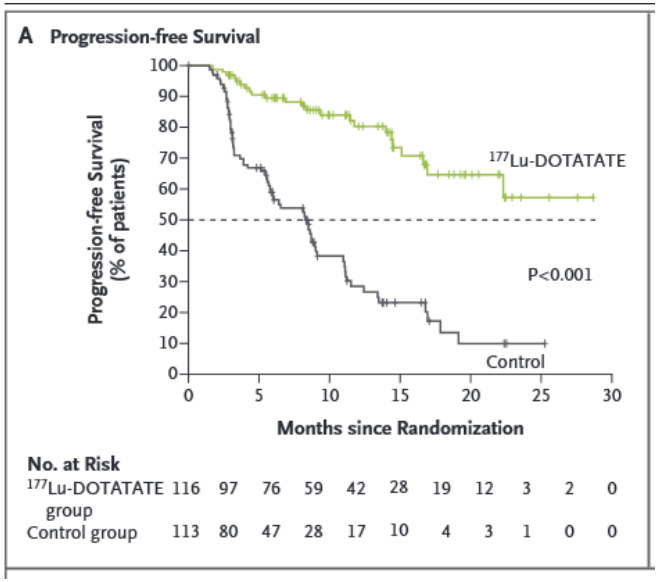
	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)	p-value
Complete response	2.8%	0	
Partial response	25.0%	33.3%	
Stable disease	40.3%	48.6%	
Progressive disease	19.4%	13.9%	
Unevaluable	12.5%	4.2%	
Objective Response Rate (CR+PR)	27.8%	33.3%	0.47
Disease Control Rate (CR+PR+SD)	68.1%	81.9%	
Response Duration (median)	9.7 mo	12.1 mo	

Progression Free Survival



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Pamela L. Kunz, MD Abstract #4004

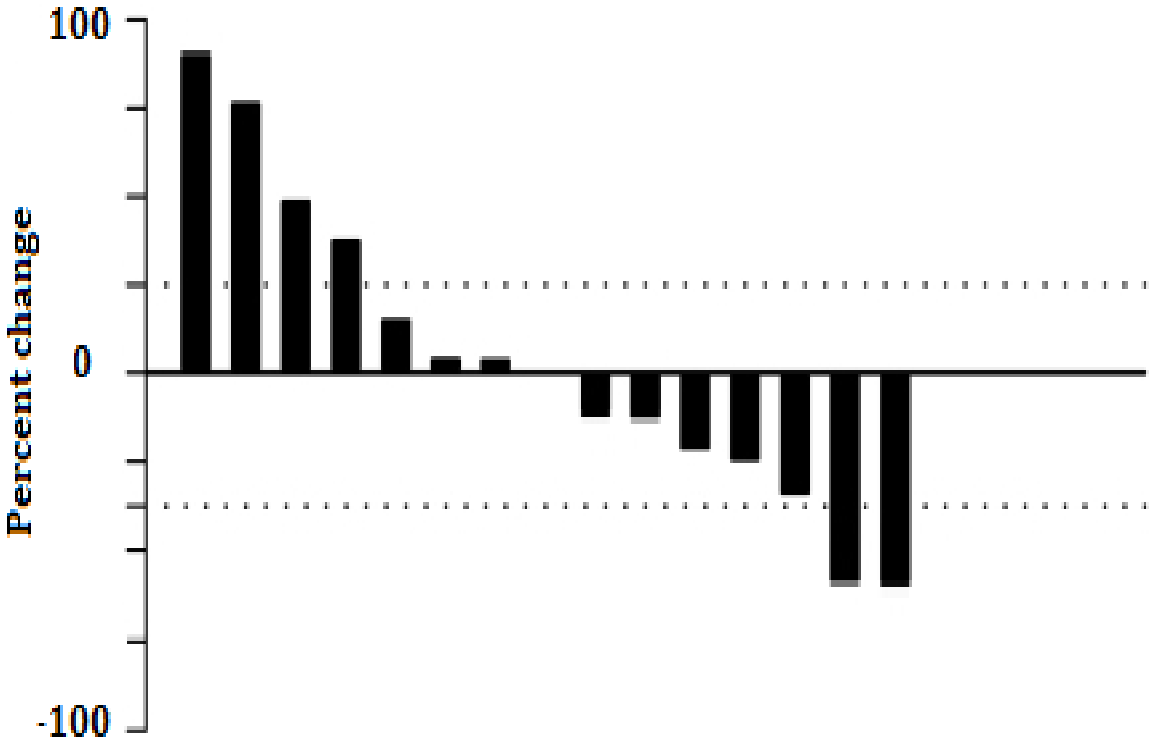


ORR in PanNET phase IV sunitinib trial: RECIST vs. Choi

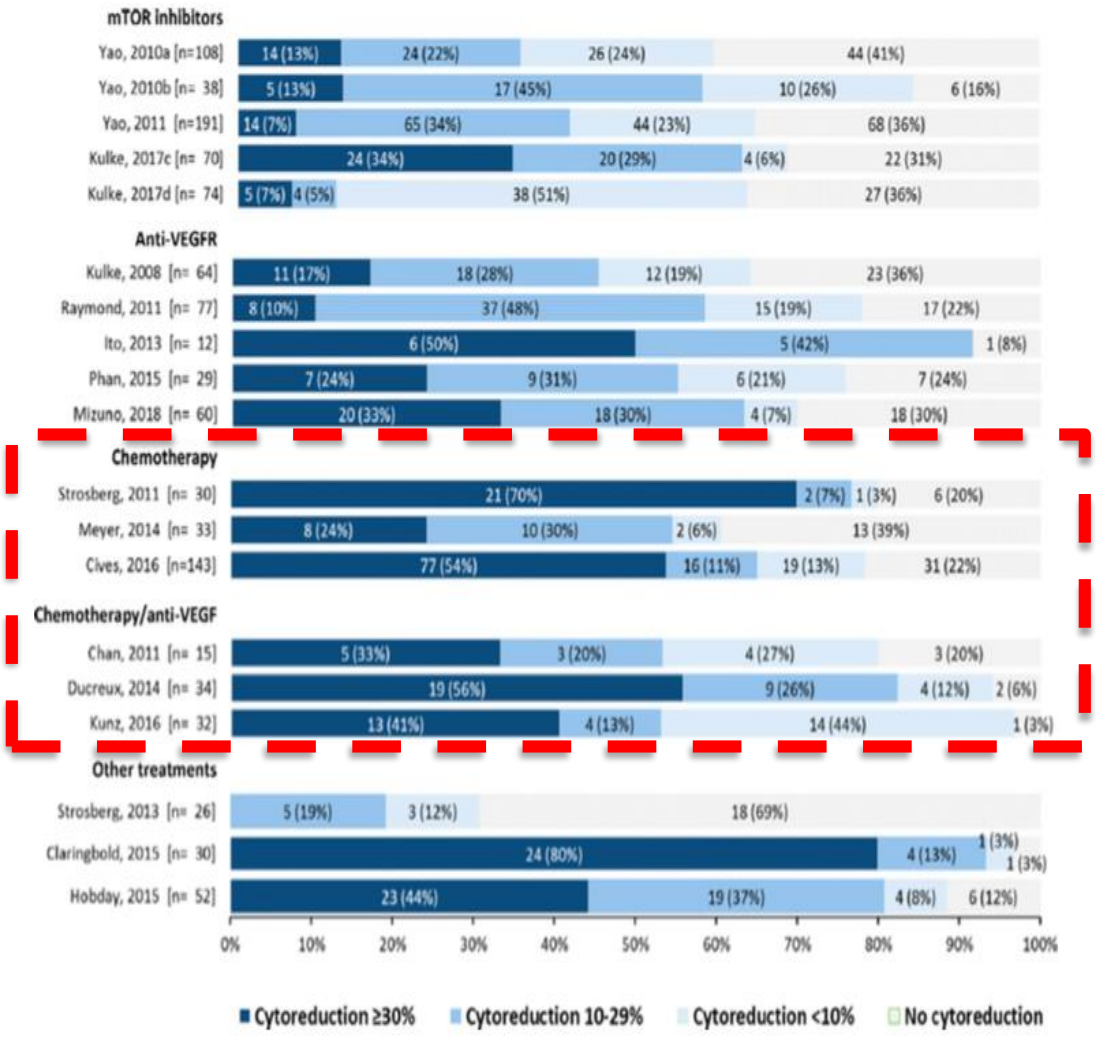
	Treatment-naive cohort (*n* = 61)	Previously treated cohort (*n* = 45)	Total population (*N* = 106)	Treatment-naive cohort (*n* = 61)	Previously treated cohort (*n* = 45)	Total population (*N* = 106)
Objective tumour response per RECIST v1.0 criteria				Objective tumour response per Choi criteria		
Best overall response, *n* (%)	**RECIST**			**Choi**		
Complete response	0	1 (2.2)	1 (<1.0)	0	1 (2.2)	NR
Partial response	14 (23.0)	8 (17.8)	22 (20.8)	32 (52.5)	24 (53.3)	NR
Stable disease	34 (55.7)	34 (75.6)	68 (64.2)	12 (19.7)	17 (37.8)	NR
Progressive disease	10 (16.4)	2 (4.4)	12 (11.3)	9 (14.8)	2 (4.4)	NR

Raymond et al., Neuroendocrinology 2018

Cytoreduction activity in medical research – Waterfall Plot



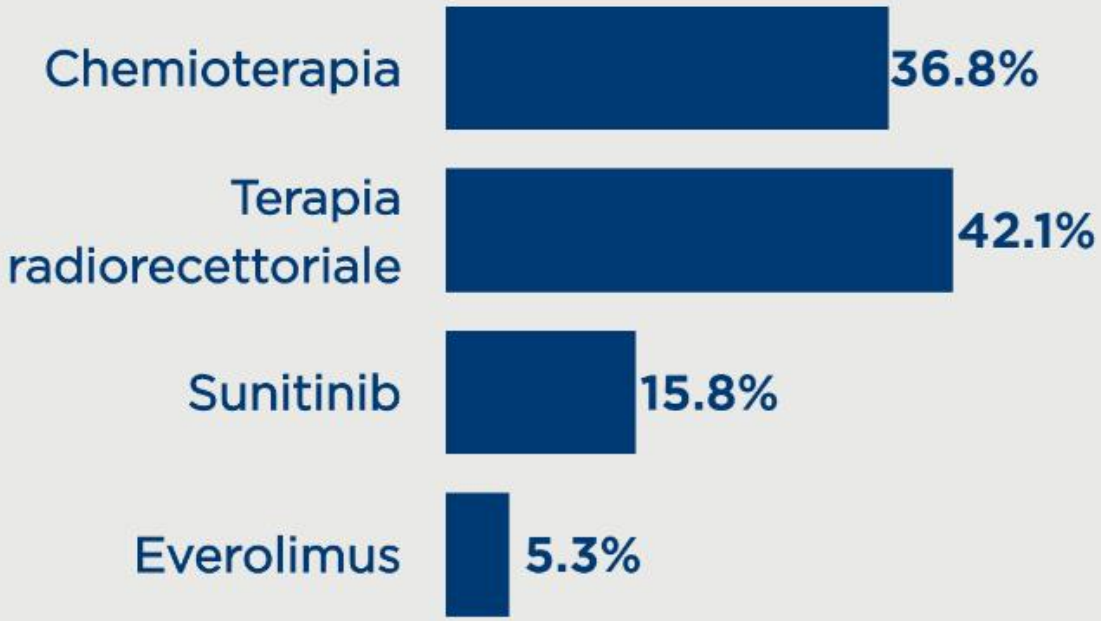
Gillespie TV et al J Adv Pract Oncol 2012



Pozzari M. et al Cancer Treat Rev 2018

VIII EDIZIONE
NEN PRECEPTORSHIP
LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE
16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

Quale terapia sistemica fareste a scopo citoriduttivo?



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- Sindrome: no

Tumore

- NET
- Ben differenziato
- Ki-67 < 3%
- PET-Gallio +++
- Sporadico

Riceve SSA long acting + Sunitinib → dopo sei mesi SD RECIST (con regressione < 30%)

6° domanda: quale scenario valutereste?

1. Proseguo Sunitinib + SSA
2. Chirurgia di primitivo +/- metastasi epatiche
3. Trattamento locoregionale epatico non chirurgico
4. Stop Sunitinib ed inizio di PRRT +/- SSA

VIII EDIZIONE
NEN PRECEPTORSHIP
LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE
16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

Quale scenario valutereste?