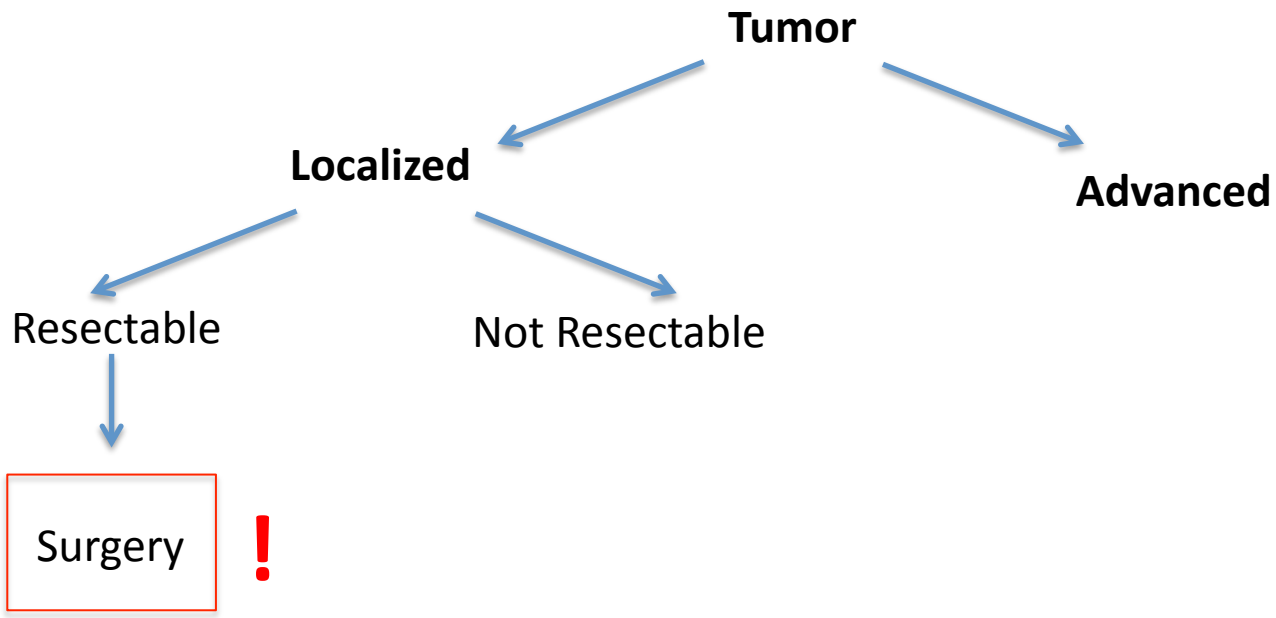
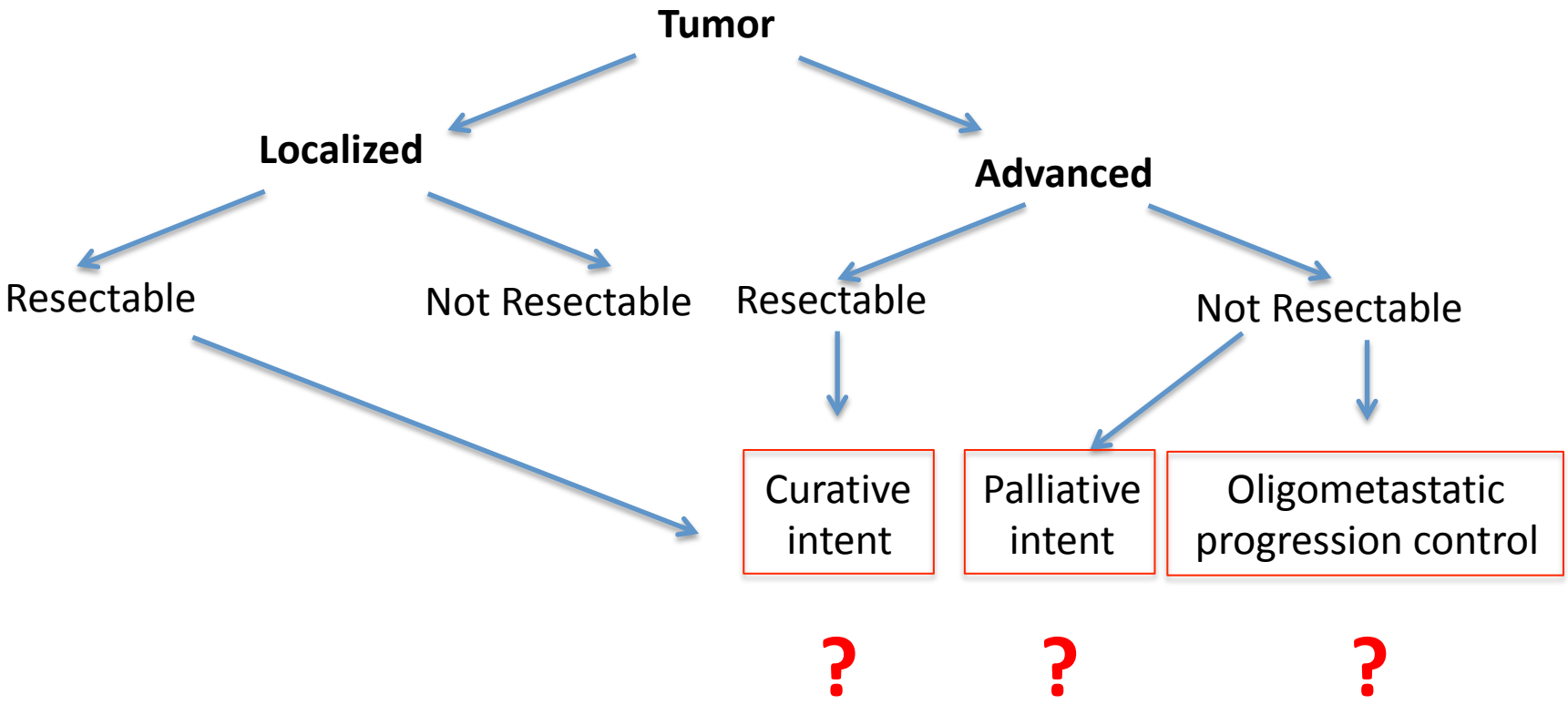
NEN del pancreas: la chirurgia è sempre necessaria?

Stefano Partelli, MD, PhD
Assistant Professor of Surgery
Pancreas Translational & Research Institute
University Vita-Salute,
IRCCS San Raffaele Hospital, Milan

(Typical) Surgical Oncology Paradigm



(NET) Surgical Oncology Paradigm



Is surgery for PanNEN always necessary?

For what?

For localized PanNEN?

For advanced PanNEN?

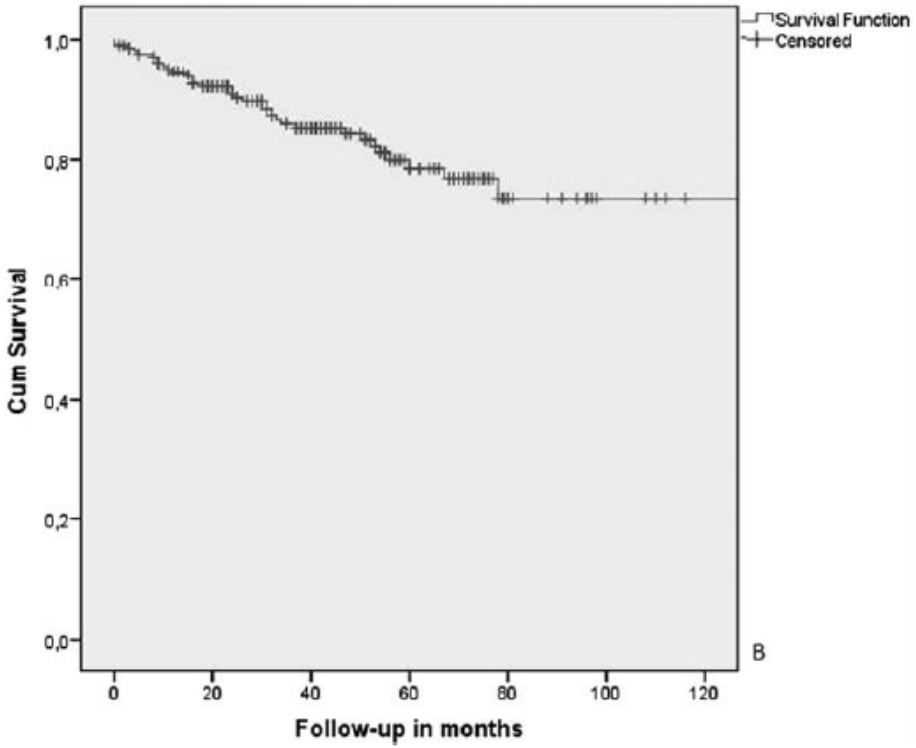
Is surgery for PanNEN always necessary?

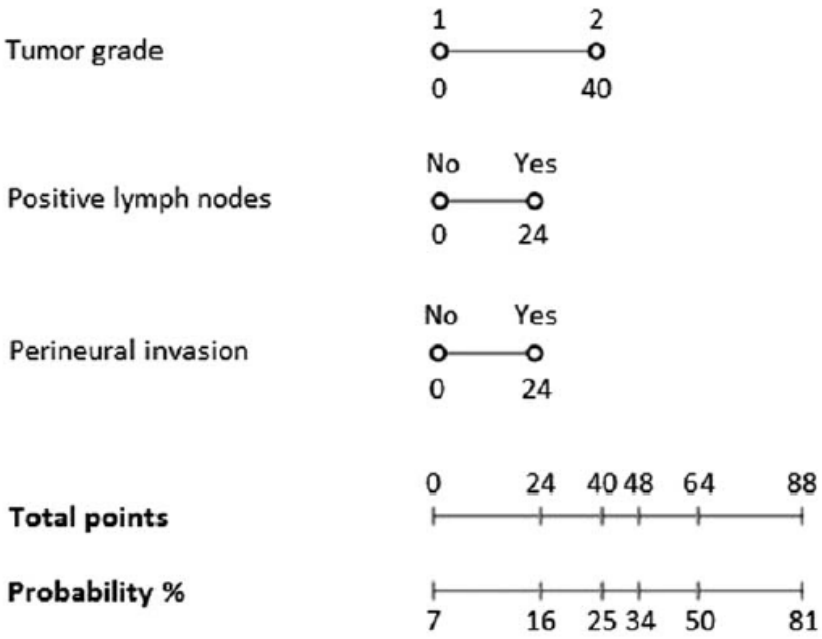
For what?

For localized PanNEN?

For advanced PanNEN?

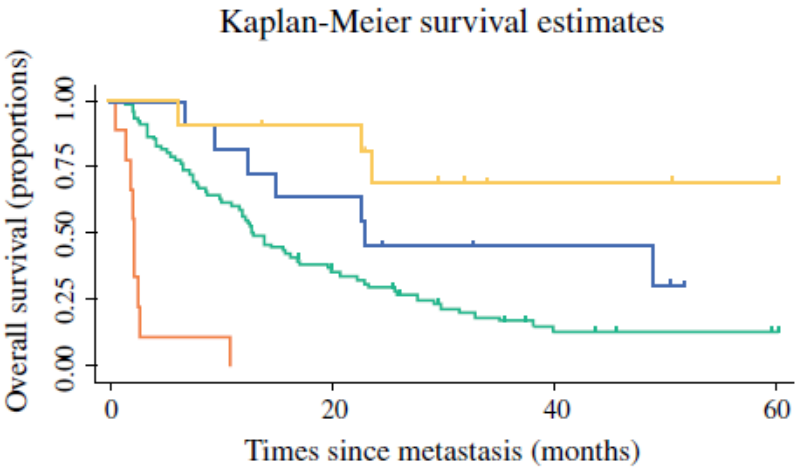
Radical Surgery for localized G1-G2





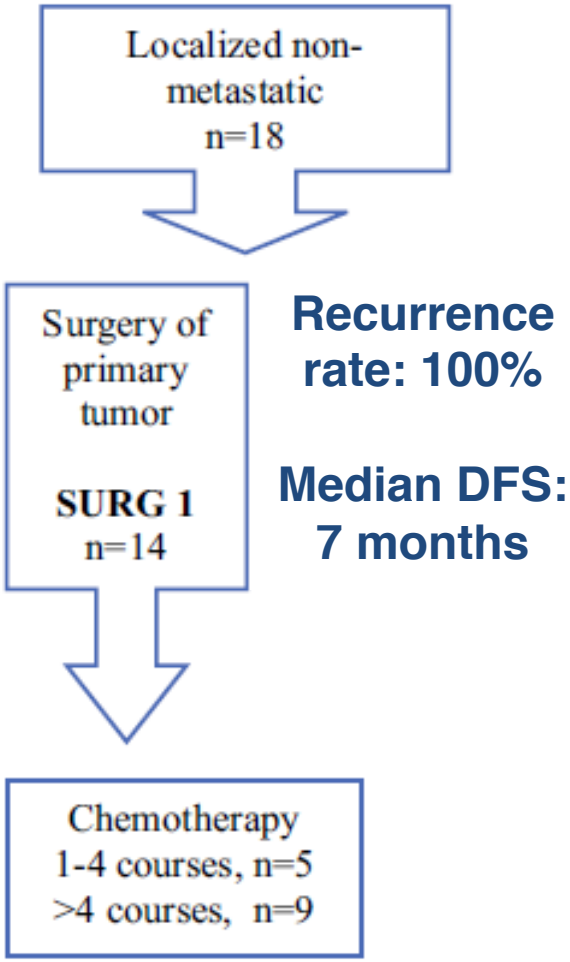
Genc et al. Ann Surg 2018

Radical Surgery for localized G3



Number at risk

SURG1 11	9	5	3	3	0
SURG2 11	10	6	3	3	2
CT2 76	43	21	9	4	3
BSC 9	0	0	0	0	0



Recurrence rate: 100%

Median DFS: 7 months

Haugvik et al. Ann Surg Oncol 2016

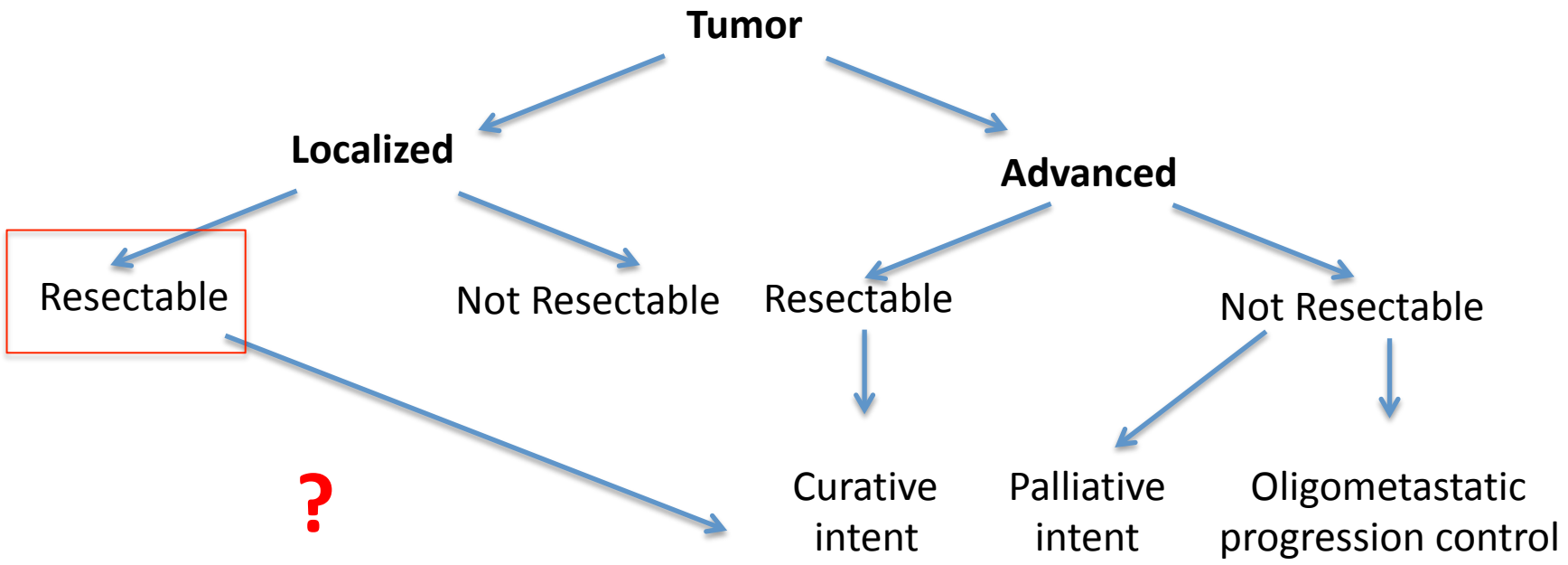
Is surgery always necessary for localized PanNEN?

Yes

But…

Low probability to cure PanNEN-G3

(NET) Surgical Oncology Paradigm



Risk of Overtreatment

Incidence of small PanNET

Variable	*n* (%)
Localization	
Head	24 (58)
Ki67, %	
1	8 (20)
2	1 (2)
Not measured	32 (78)

2,400,000 patients with small PanNET in Italy

An incidental PanNEM/PanNET was found in the pancreatic

The median diameter of incidental PanNEM/PanNET was **3 mm**

Andreasi et al. NANETS meeting, Seattle 2018

Surveillance for small PanNET

REVIEW ARTICLE

Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors – a systematic review and meta-analysis

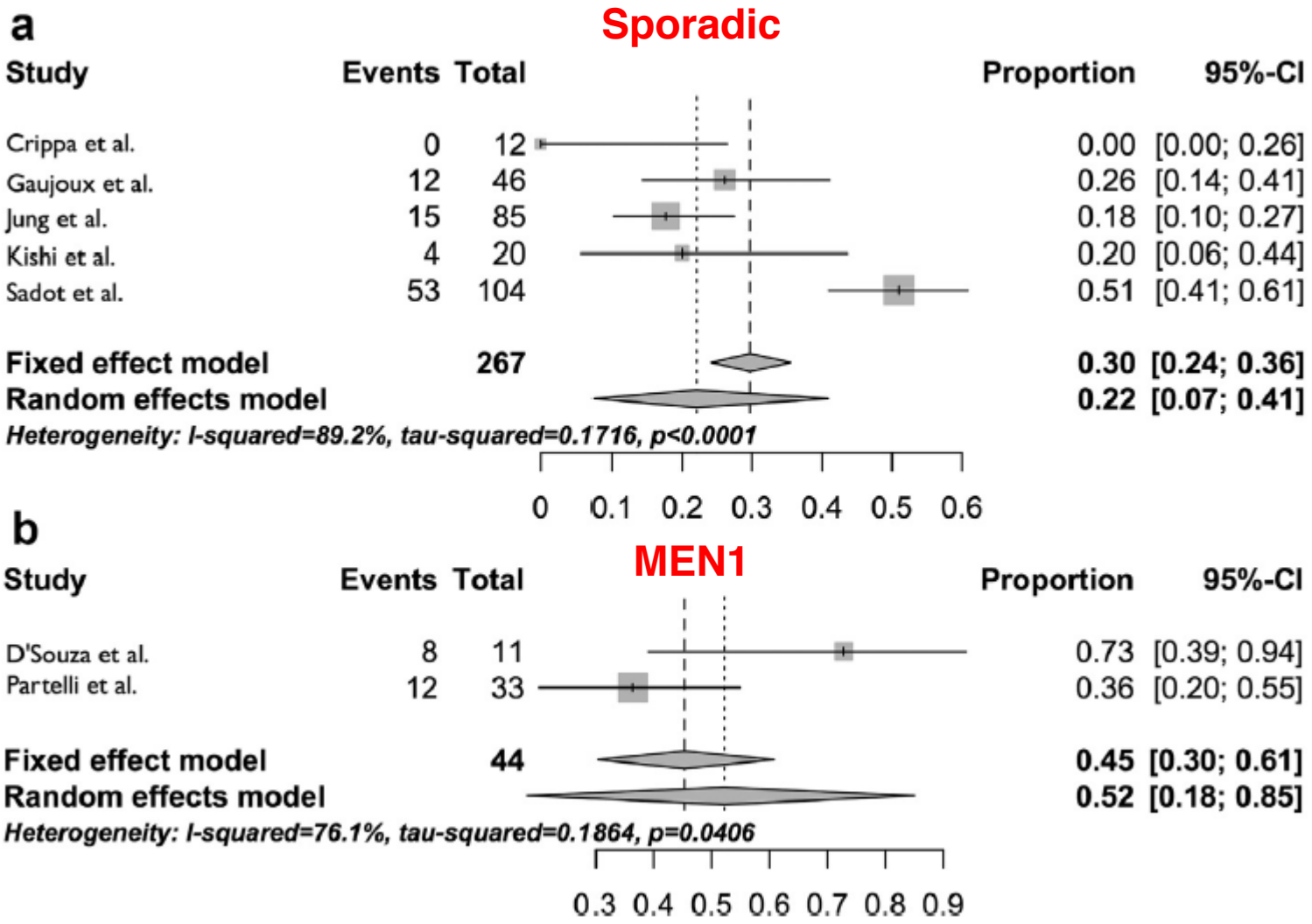
Ville Sallinen[1,2], Tessa Y.S. Le Large[3], Shamil Galeev[4], Zahar Kovalenko[5], Elke Tieftrunk[6], Raphael Araujo[7], Güralp O. Ceyhan[6] & Sebastien Gaujoux[8,9]

Systematic review

Systematic review of active surveillance *versus* surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms

S. Partelli[1], R. Cirocchi[2], S. Crippa[1], L. Cardinali[3], V. Fendrich[4], D. K. Bartsch[4] and M. Falconi[1]

Risk of Tumor Growth in PanNET<2 cm



Chirurgia del Pancreas

Sallinen et al. HPB 2017

Surveillance is safe…

Authors	Type of Management	Disease-specific death n (%)	Lymph-node recurrence n (%)	Distant metastases n (%)	Local recurrence after surgery n (%)
Lee et al.	AS (n=77) SM (n=52)	0 0	NR NR	NR NR	- NR
Gaujoux et al.	AS (n=46) -	0 -	0 (0) -	0 (0) -	- -
Kishi et al.	AS (n=19) SM (n=71)	0 NR	0 (0) 2 (3)	0 (0) 14 (29)	- 1 (1)
Rosenberg et al.	AS (n=15) SM (n=20)	0 2 (10)	0 (0) 0 (0)	3 (7)* 2 (1)*	- 0(0)
Jung et al.	AS (n=85) SM (n=60)	0 0	0 (0) 0 (0)	0 (0) 0 (0)	- 0 (0)
Sadot et al.	AS (n=104) SM (n=77)	0 0	3 (4)	2 (3)	-

*PanNET >2 cm
**Any size

OSPEDALE SAN RAFFAELE
Chirurgia del Pancreas

Partelli et al. Br J Surg 2016

Is surgery always necessary for localized PanNEN?

Yes

But…

Low probability to cure PanNEN-G3

… and excluding from surgery asymptomatic PanNEN <2cm

It sounds easy…

?

but it's not

The Real Life-Our Experience

ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms of the Digestive System: Well-Differentiated Pancreatic Non-Functioning Tumors

Massimo Falconi[a] Detlef Klaus Bartsch[b] Barbro Eriksson[c] Günter Klöppel[d]
José M. Lopes[e] Juan M. O'Connor[f] Ramón Salazar[g] Babs G. Taal[h]
Marie Pierre Vullierme[i] Dermot O'Toole[j]
all other Barcelona Consensus Conference participants[1]

- ✓ Management based on ENETS GL (2012)
- ✓ Conflict of interest (for "wait and see")

Reasons for Surgery

	Active Surveillance n = 73	Surgery n = 28	P value
Age, years *	60 (± 4)	53 (± 13)	0.013
Largest Radiological diameter, mm *	12 (± 4)	16 (± 4)	< 0.0001

OSPEDALE SAN RAFFAELE
Chirurgia del Pancreas

Partelli et al. Submitted Manuscript

Reasons for Surgery

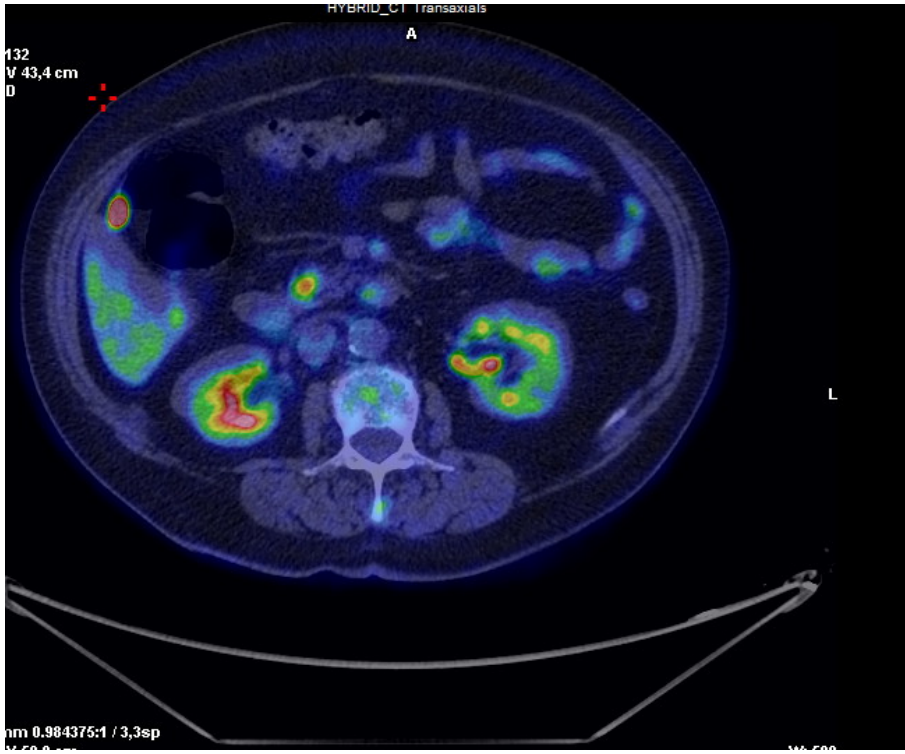
Variable	Active Surveillance N=73 (%)	Surgery N=28 (%)	P value
68-Gallium PET			
Negative	5 (7)	2 (7)	
Positive	46 (63)	17 (60)	
Not performed	22 (30)	9 (32)	1.000
18F-FDG PET			
Negative	16 (22)	2 (7)	
Positive	13 (18)	14 (50)	
Not performed	44 (60)	12 (43)	0.003
FNA			
Diagnostic for NET	35 (48)	12 (43)	
Undetermined/misdiagnosed	9 (12)	7 (25)	
Not performed	29 (40)	9 (32)	0.329
Cytological grading^			
G1	20 (27)	5 (18)	
G2	0 (0)	4 (14)	
Not performed	53 (73)	19 (68)	0.008

OSPEDALE SAN RAFFAELE
Chirurgia del Pancreas

Partelli et al. Submitted Manuscript

Role of 18FDG in small PanNET

Among the cases with a positive 18F-FDG PET (n=14), only 5 had at least one pathological feature of aggressiveness: G2 tumor (n=5), microvascular invasion (n=3), perineural invasion (n=1) or nodal metastasis (n=1).



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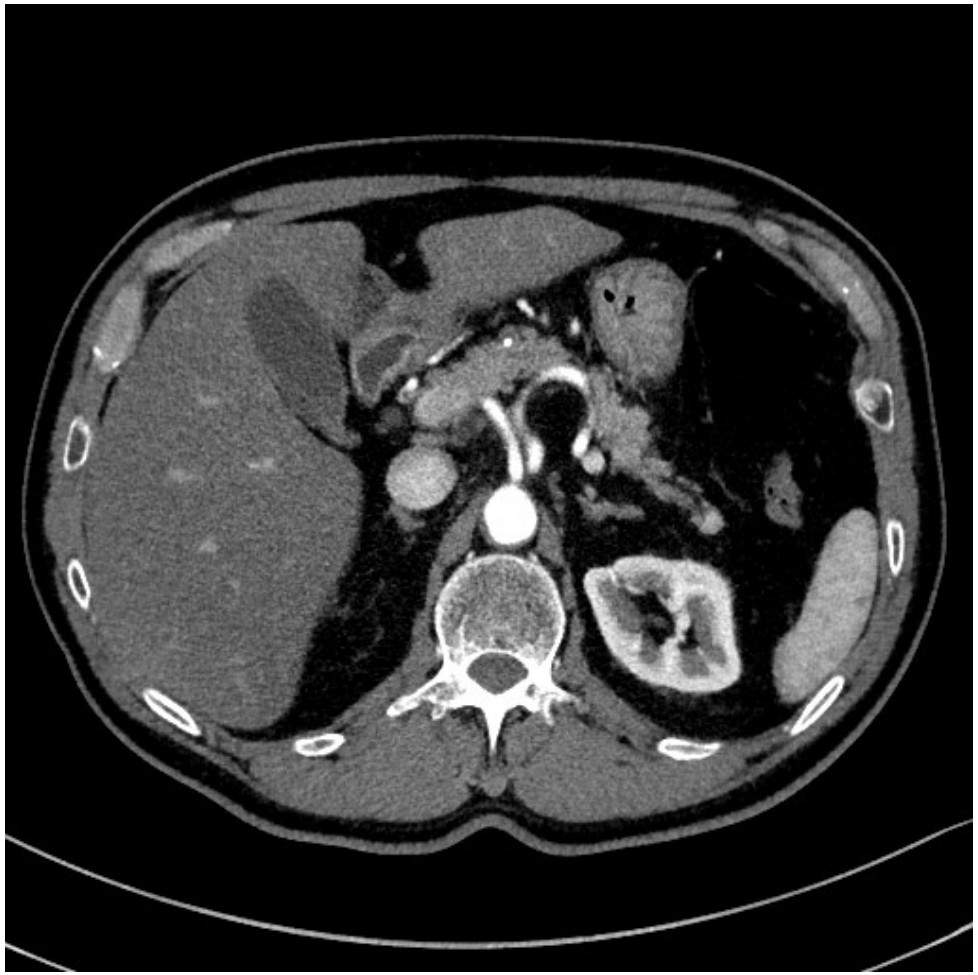
OSPEDALE SAN RAFFAELE
Chirurgia del Pancreas

Partelli et al. Submitted Manuscript



EUS+FNA: G2 (n = 4)

↓

Surgery

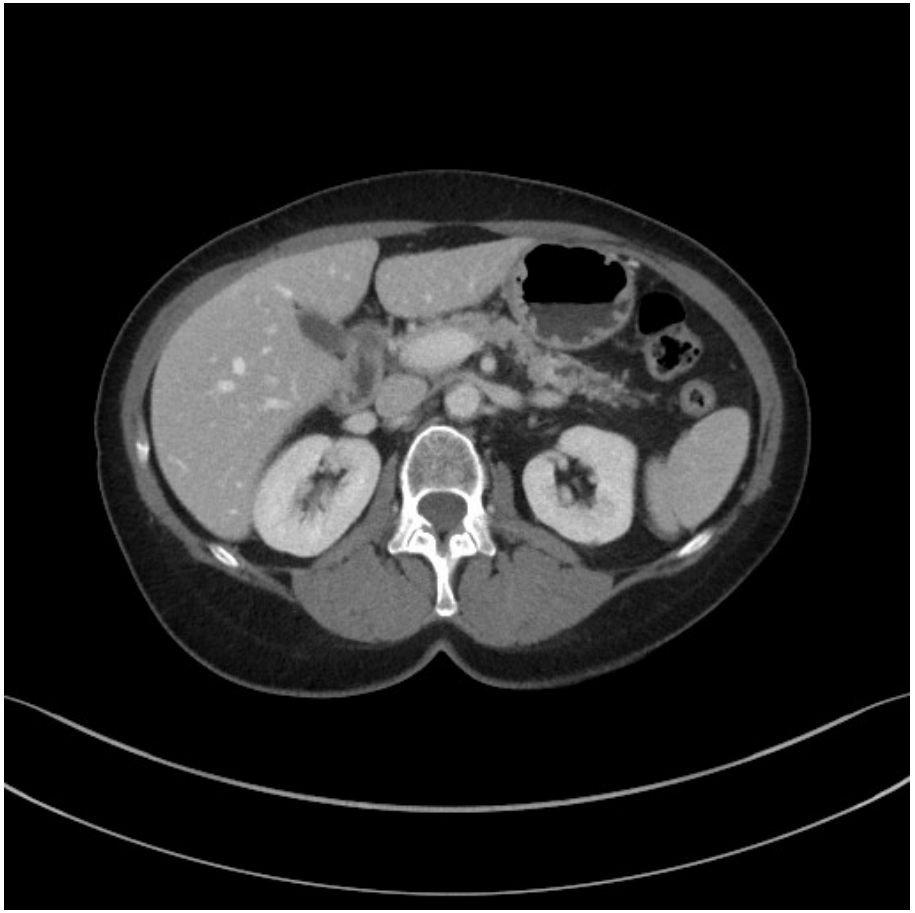
↓

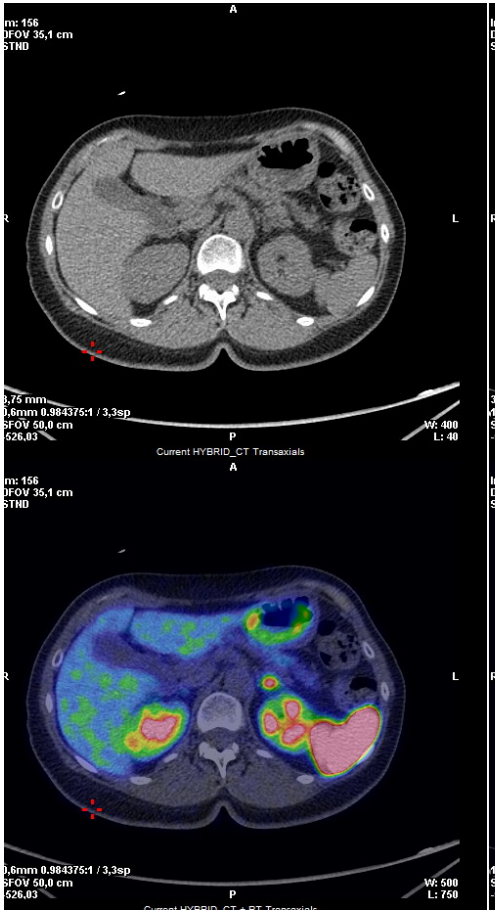
Histology: G2 (n = 1)

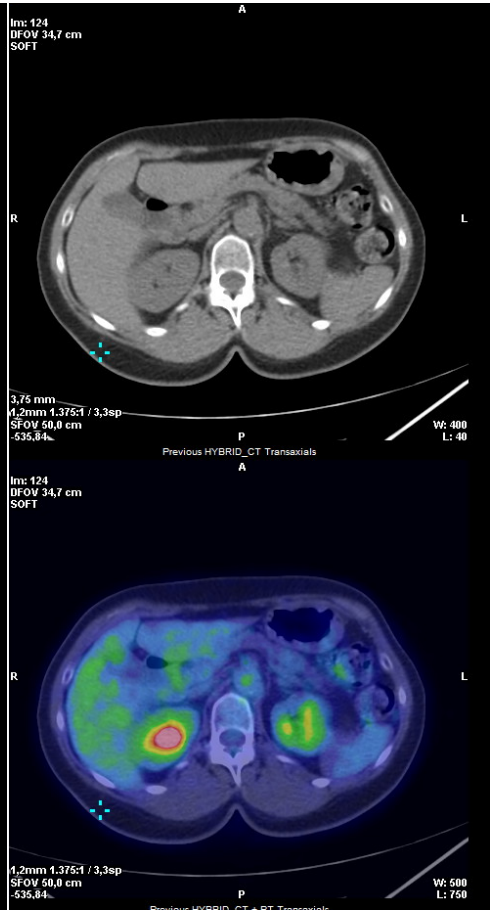
Reasons for Surgery

Variable	Active Surveillance n = 73	Surgery n = 28	P value
Age, years *	60 (± 4)	53 (± 13)	0.013
Largest Radiological diameter, mm *	12 (± 4)	16 (± 4)	< 0.0001
MPD dilatation			
No	73 (100)	22 (79)	
Yes	0 (0)	6 (21)	< 0.0001

Partelli et al. Submitted Manuscript







Ospedale San Raffaele
Chirurgia del Pancreas

Università Vita-Salute San Raffaele

Small and aggressive

#	Serotonin	Symptoms	§TNM	Stage
1	+	Yes	T3N1M1	IV
2	+	Yes	T1NXM1	IV
3	+	Yes	T1N0M0	I
4	+	Yes	T1N0M0	I
5	+	Yes	T1N0M0	I
6	+	No	T2N0M0	IIa
7	+	No	T2N0M0	IIa
8	+	Yes	T1N0M0	I

Massironi et al. Pancreatology 2018

29% operated for patients'preference in our series!

39% in published series!

Reference	Type of follow-up	Follow-up (months)*	No change in tumour size	Tumour growth ≤ 20%	Tumour growth > 20%	Surgery during follow-up	Reason for surgery	Time to surgery (months)*
Lee *et al.*[23]	Clinical and radiological	45	77 (100)	0 (0)	0 (0)	0 (0)	–	–
Gaujoux *et al.*[24]	Clinical and radiological	34 (24–53)	40 (87)	n.r.	6 (13)	8 (17)	Tumour growth 3 Patient choice 5	41 (27–58)
Jung *et al.*[25]	Clinical and radiological (at 3, 6 and 12 months)	n.r.	70 (82)	12 (14)	3 (4)	12 (14)	Tumour growth 8 Patient choice 3 Symptoms 1	34(18)†
Sadot *et al.*[26]	Radiological	44 (4–223)	51 (49·0)	n.r.	n.r.	26 (25·0)	Tumour growth 8 Patient choice 10 Physician preference 7 Pancreatic duct dilatation 1	30 (7–135)
Rosenberg *et al.*[27]	Radiological	28 (19–113)	n.r.	n.r.	n.r.	0 (0)	–	–

OSPEDALE SAN RAFFAELE
Chirurgia del Pancreas

Partelli et al. Br J Surg 2016

Is surgery always necessary for localized PanNEN?

Yes

But…

Low probability to cure PanNEN-G3

… and excluding from surgery asymptomatic PanNEN <2cm

… still in selected cases

Is surgery for PanNEN always necessary?

For what?

For localized PanNEN?

For advanced PanNEN?

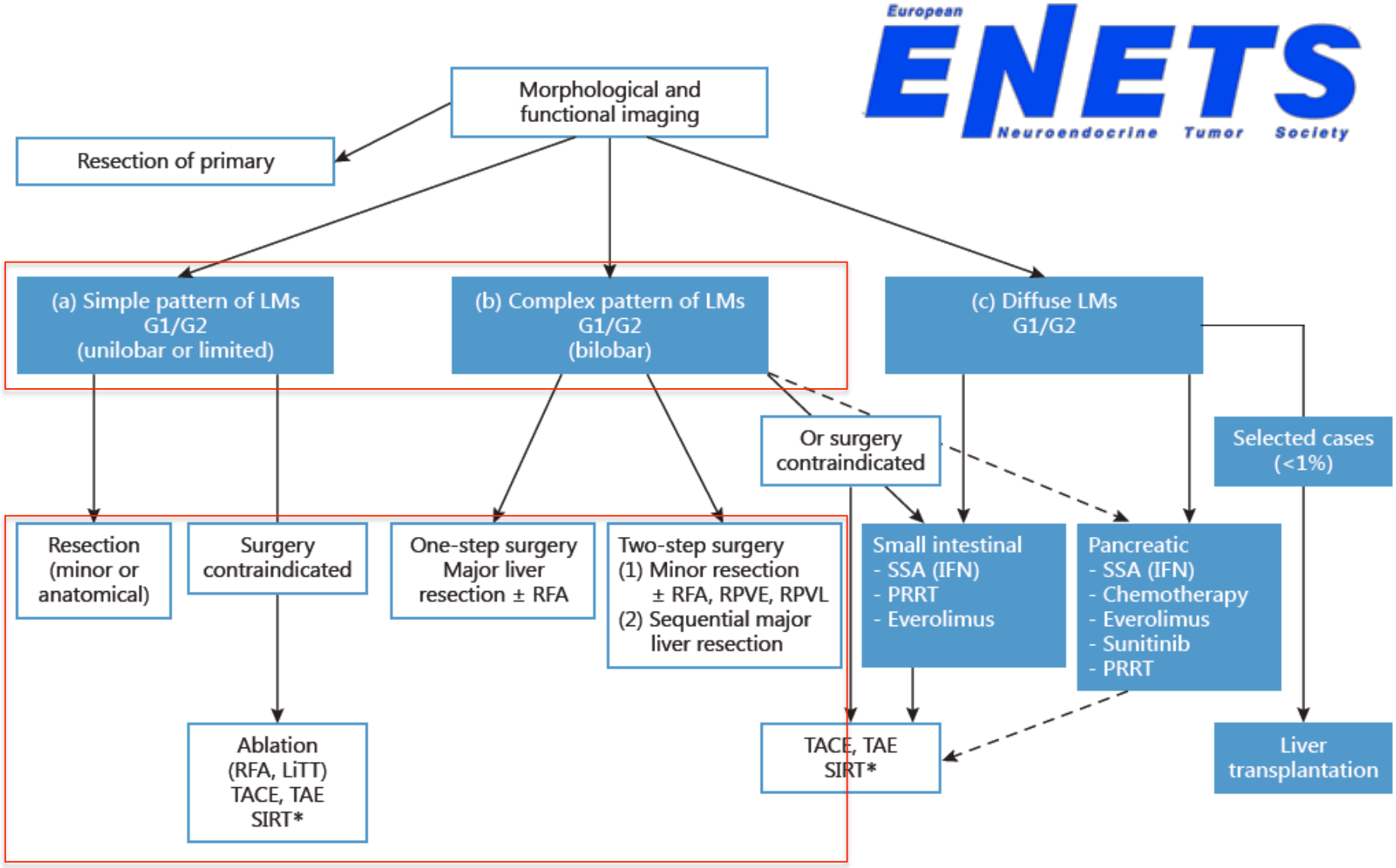
… not necessary but often helpful

WARNING

PanNET G1-G2

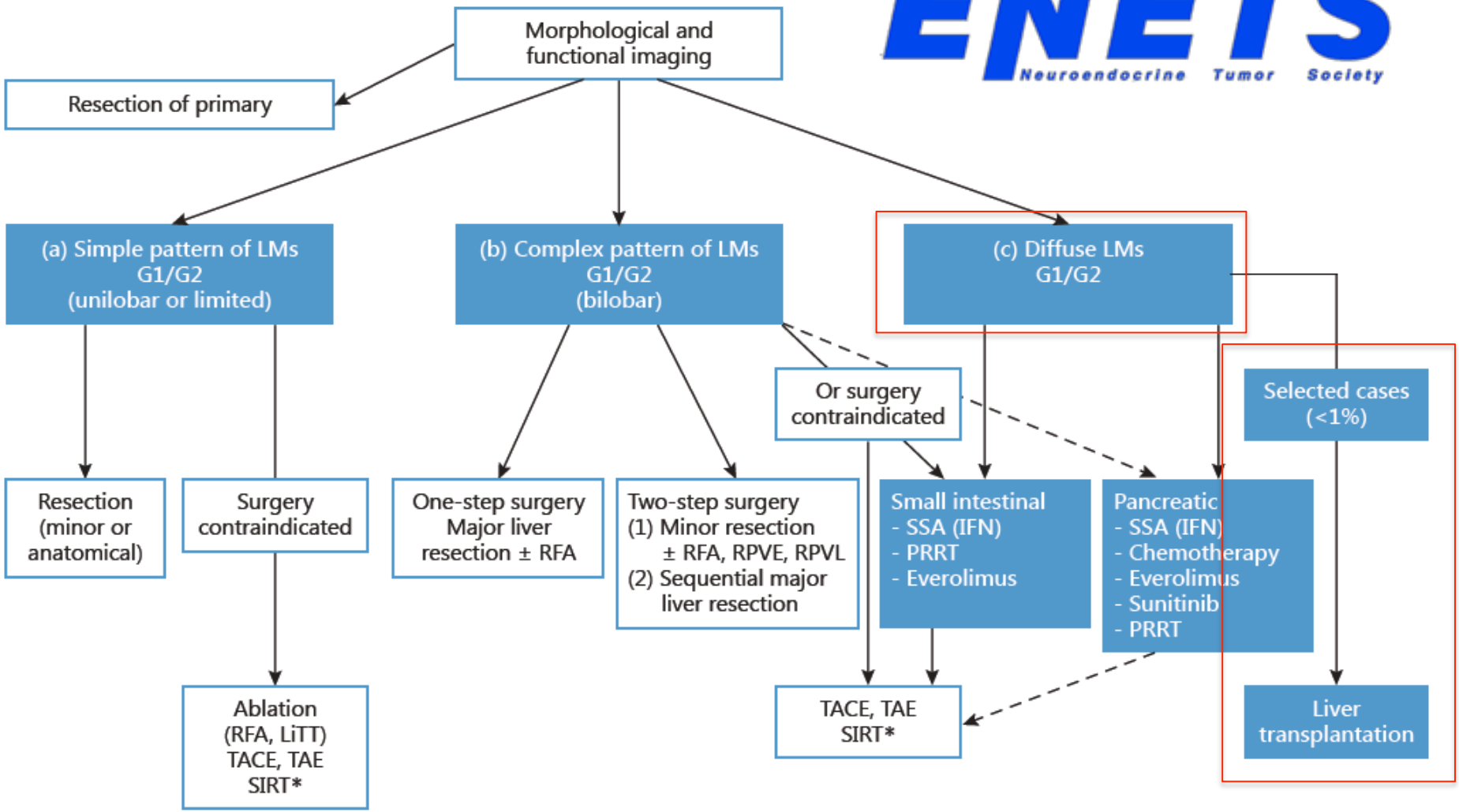
Main localization: body/tail

No extra-abdominal disease



Chirurgia del Pancreas

Pavel et al. Neuroendocrinology 2016



Chirurgia del Pancreas

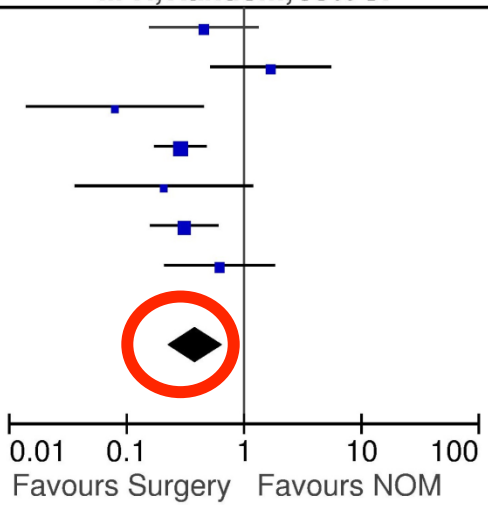
Pavel et al. Neuroendocrinology 2016

Role of palliative pancreatic resection
Overall survival

Study or Subgroup	Surgery Events	Surgery Total	Non operative management Events	Non operative management Total	Weight	Odds Ratio M-H, Random, 95% CI
Bertani 2016	17	30	23	31	13.8%	0.45 [0.15, 1.34]
Bettini 2009	13	19	18	32	12.3%	1.69 [0.51, 5.56]
Citterio 2017	7	18	16	18	7.1%	0.08 [0.01, 0.46]
Hüttner 2015	39	75	290	367	24.8%	0.29 [0.17, 0.48]
Nguyen 2013	15	20	29	31	7.1%	0.21 [0.04, 1.20]
Partelli 2015	30	73	52	75	21.2%	0.31 [0.16, 0.61]
Solorzano 2001	9	16	54	80	13.6%	0.62 [0.21, 1.85]
Total (95% CI)		**251**		**634**	**100.0%**	**0.38 [0.23, 0.65]**
Total events	130		482			

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 11.72$, df = 6 (P = 0.07); $I^2 = 49\%$

Test for overall effect: Z = 3.56 (P = 0.0004)



Partelli S, et al. HPB 2017

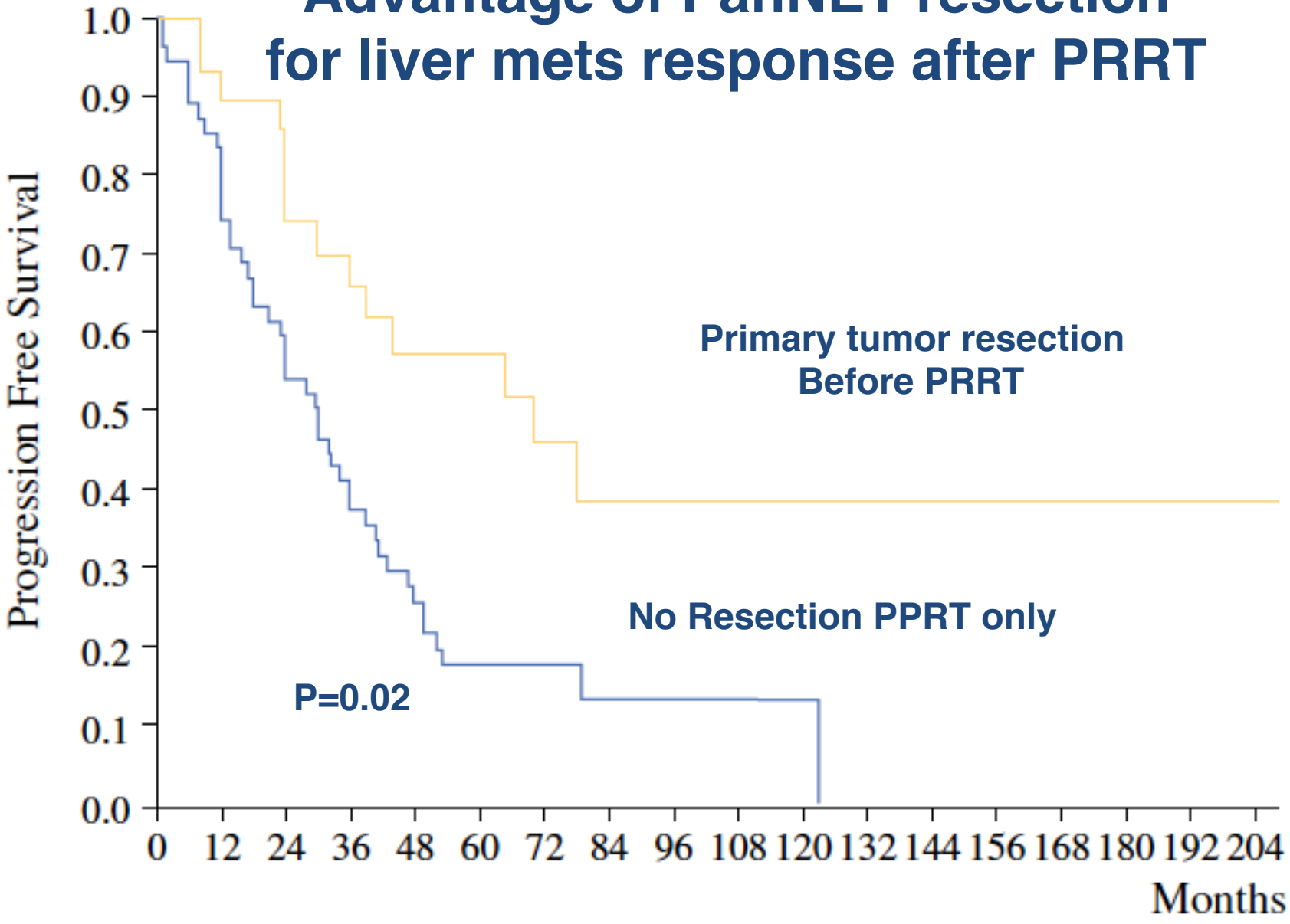
Value of palliative primary resection

To allow treatments only to liver metastases

To reduce the disease burden

To favor further systemic therapy

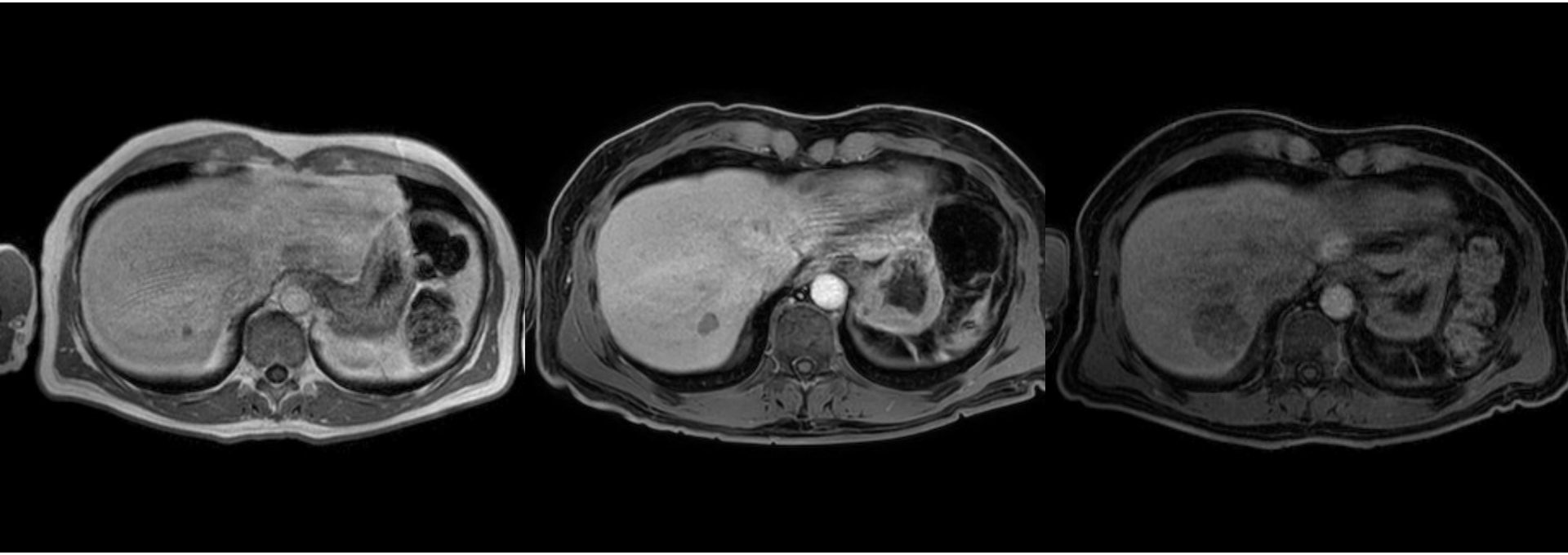
Advantage of PanNET resection for liver mets response after PRRT



Bertani et al. Ann Surg Oncol 2016

Single metastasis progression

2015 2016 2018



Somatostatin Analogs

Everolimus

Surgery

Single metastasis progression

Local treatment can control discrete sites of progression

To allow patients to continue their existing therapy

Is surgery always necessary for advanced PanNEN?

Yes

in VERY selected patients

Conclusions

Surgery is necessary to cure (>70%) localized PanNET G1-G2 >2cm

Surgery is necessary to improve DFS in selected patients with advanced PanNEN G3

Surgery should be avoided in most of asymptomatic PanNET <2cm

Surgery may be necessary to improve PFS in selected patients with advanced PanNEN