

Surgery of GEP-NETs in oligometastatic disease

5th Milan NET Conference

**A live and web multimodal meeting among active Italian
NET Centres**

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State of oligometastases – Definition -

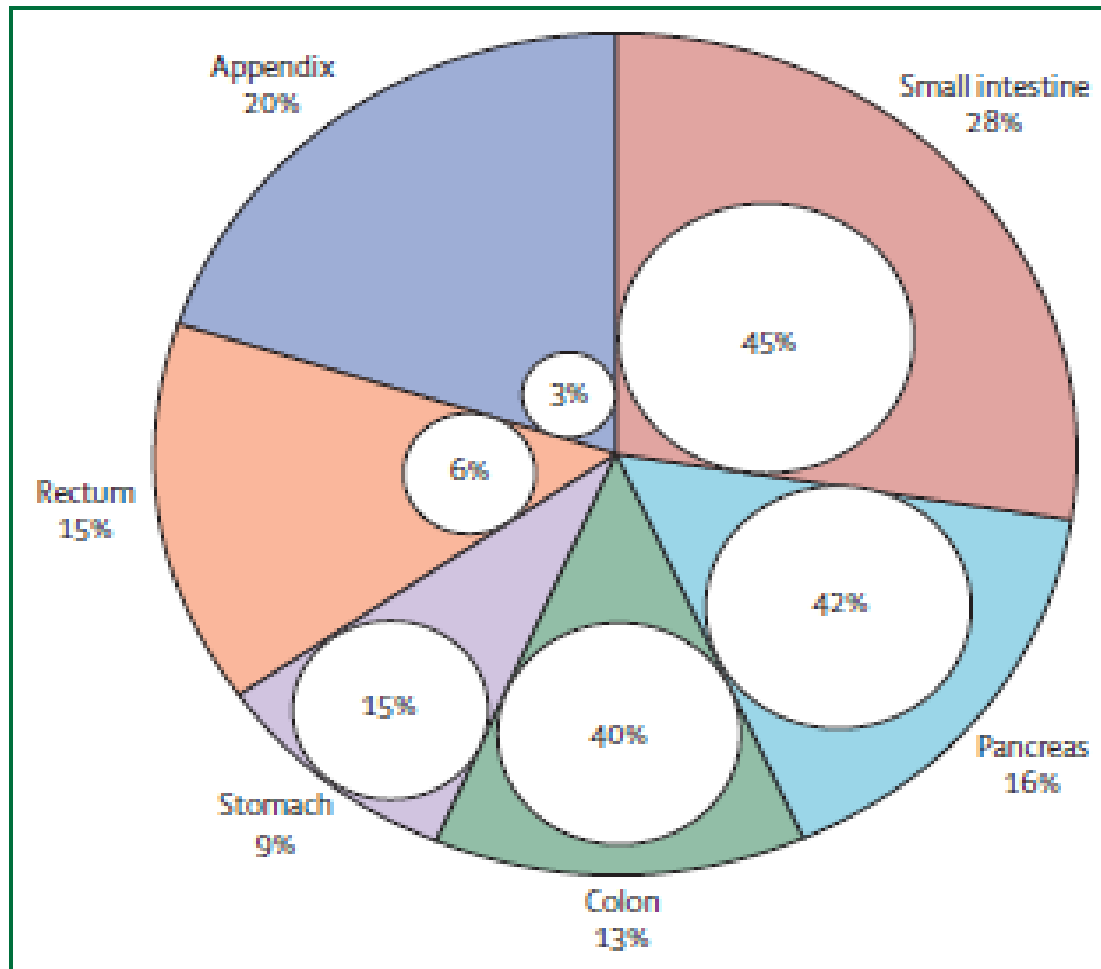
- The extent of disease exists in a transitional stage between localized and widespread systemic disease
- Metastases to a single or a limited number of organs
Clinically evident on radiographic sites
Either 1-3 or 1-5
- No rapidly spreading to more sites
- Some patients so affected should be amenable to a therapeutic surgery
Primary tumour and the metastatic sites
- Local control of oligometastases would have the potential to yield improved systemic control, prolonged disease-free interval , and perhaps even cure

Hellman S and RR Weichselbaum. J Clin Oncol 1995,13 (1); 8-10

Weichselbaum RR and S Hellman. Nature Reviews Clin Oncol 2011, 8:378-382

Reyes DK and KJ Pienta. Oncotarget 2015,6 (11);8491-8524

Incidence of GEP NET LM in relation to the primary tumour site



Small bowel neuroendocrine tumors

n=84 patients
2009-2014

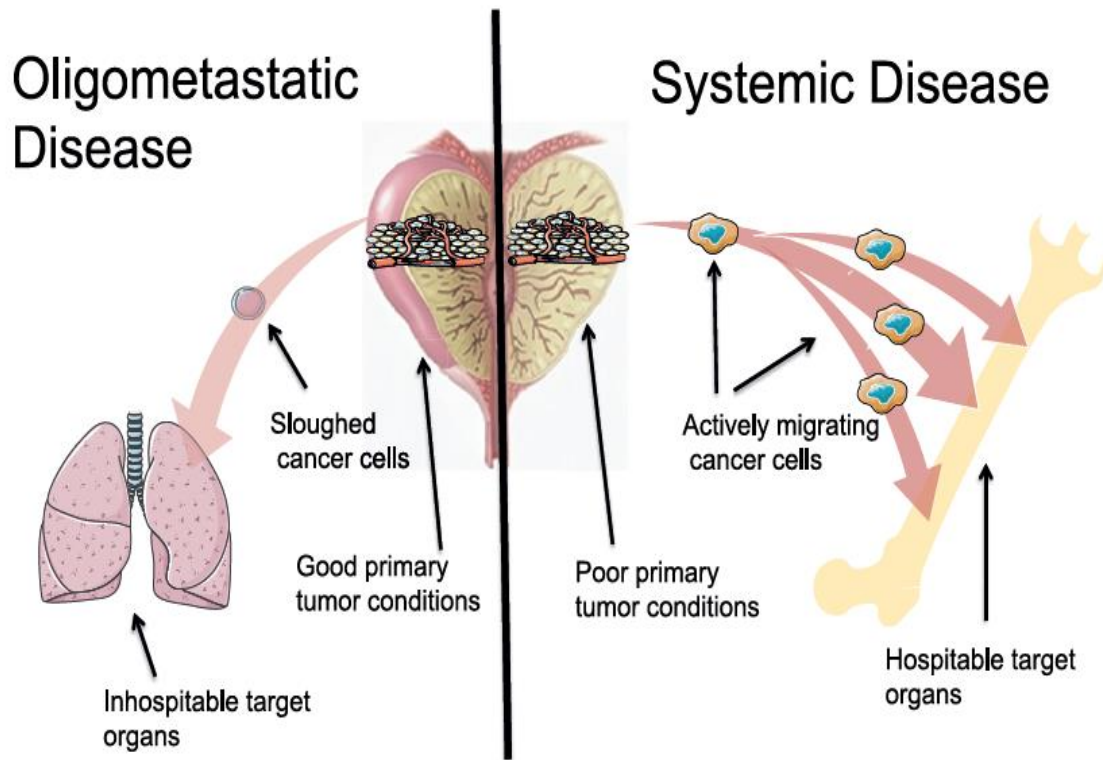
Parameter	N (%)
Total number of patients	84
Mean age (range)	59.6 years (32 to 88)
Gender	
Male	46 (54.8)
Female	38 (45.2)
Tumor functionality	
Functioning	27 (32.1)
Non-functioning	57 (67.9)
Tumor grade	
G1 (Ki67 \leq 2%)	65 (83.3)
G2 (Ki67 3-20%)	11 (14.1)
G3 (Ki67 >20%)	2 (2.6)

Small bowel neuroendocrine tumours - Tumour stage and sites of metastases -

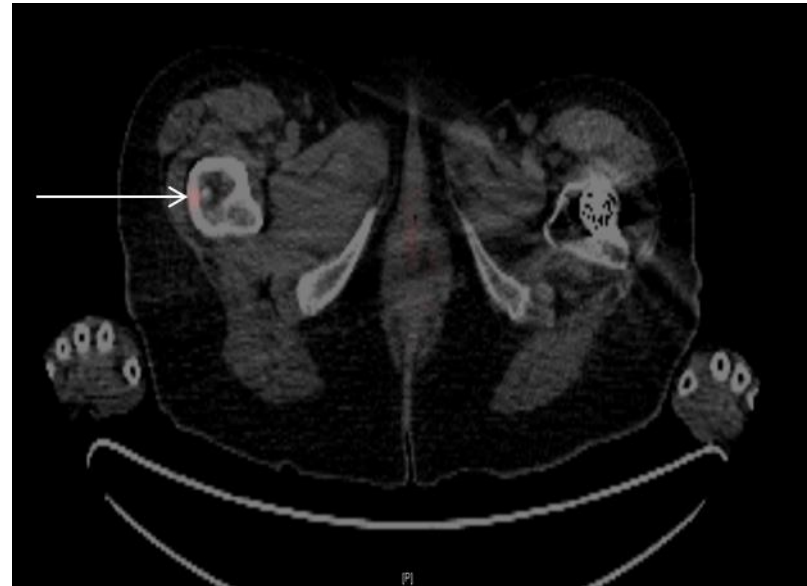
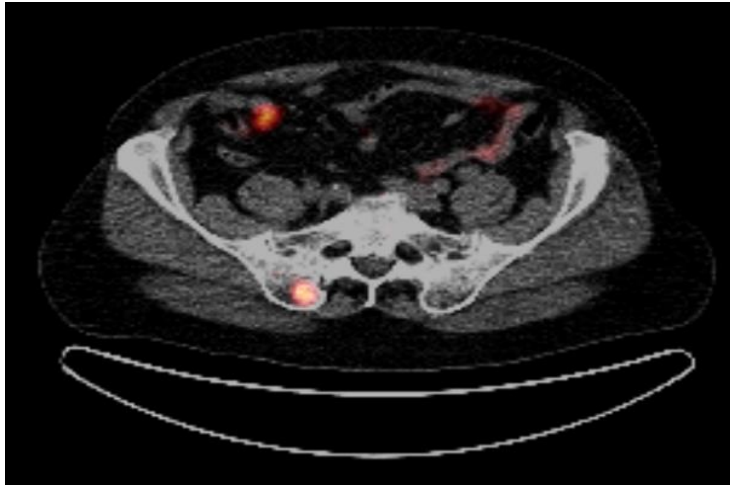
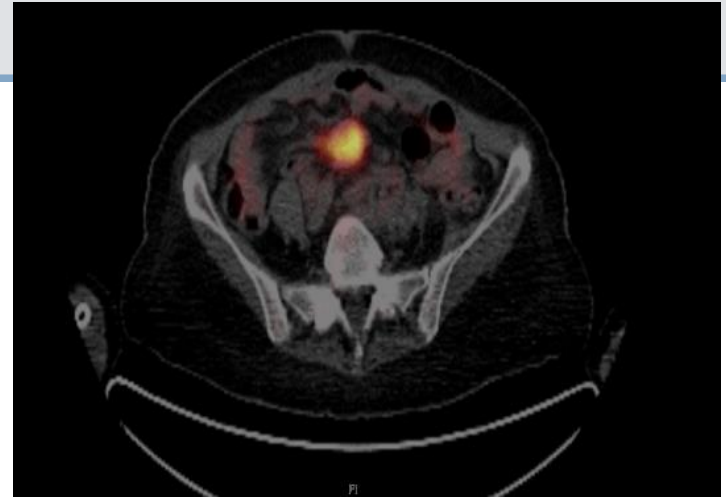
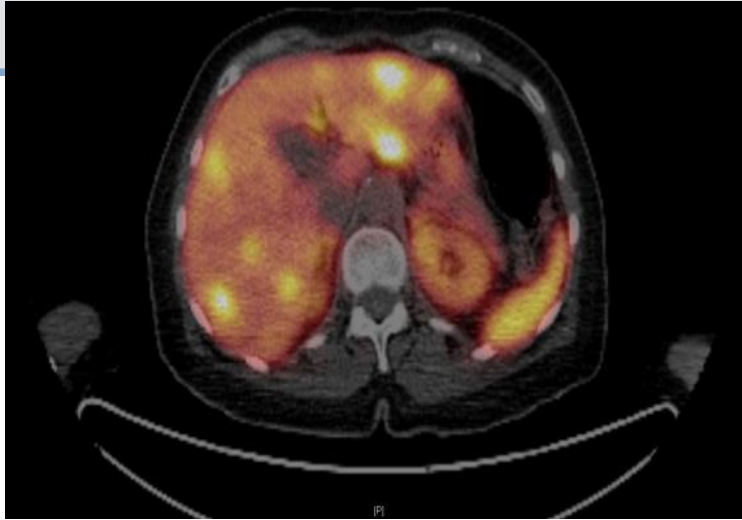
Tumour Stage	N (%)
T ₁₋₄ N ₀ M ₀	9 (10.7)
T ₁₋₄ N ₁ M ₀	24 (28.6)
T ₁₋₄ N ₀ M ₁	1 (1.2)
T ₁₋₄ N ₁ M ₁	50 (59.5)

Locations of distant metastases	N (%)
Liver	45 (53.6)
Bone	1 (1.2)
Peritoneum	2 (2.4)
Liver and bone	2 (2.4)
Liver and peritoneum	1 (1.2)

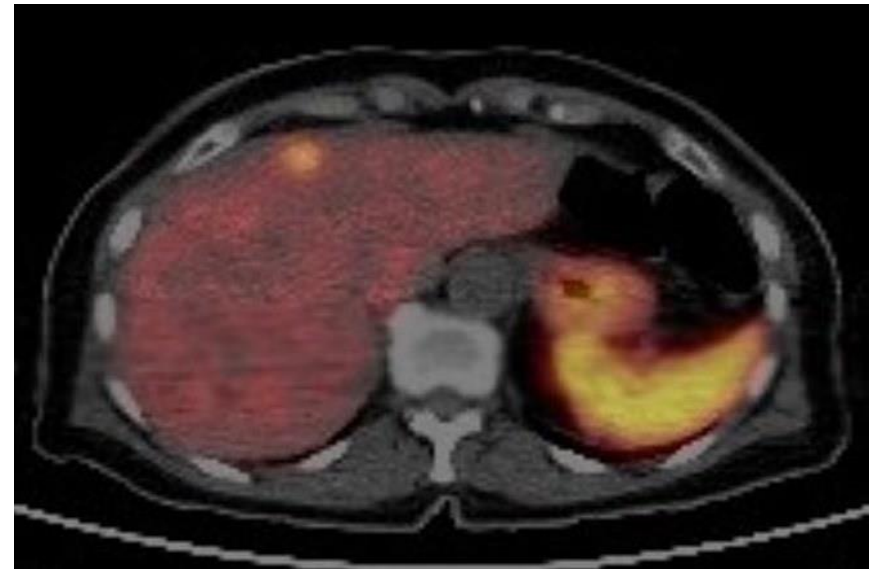
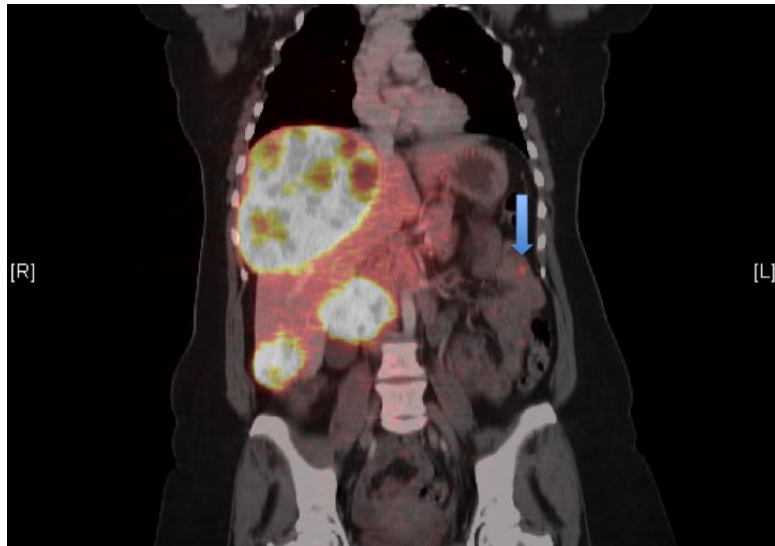
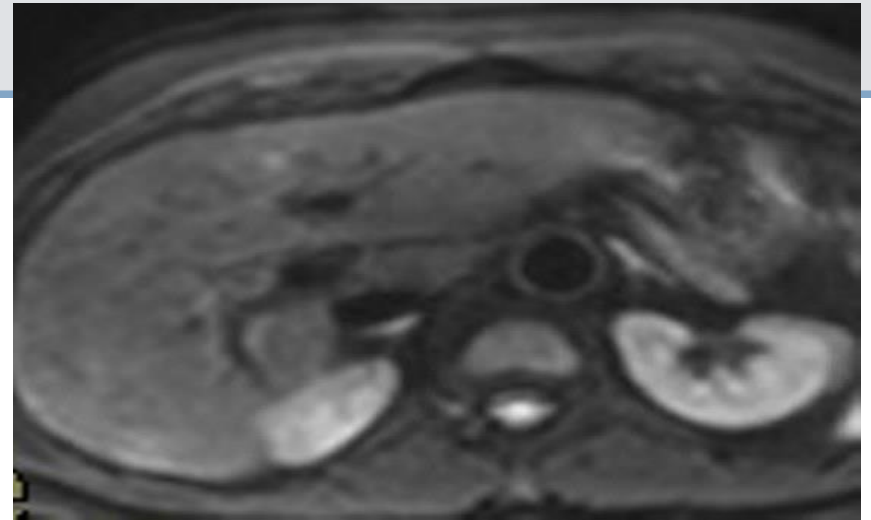
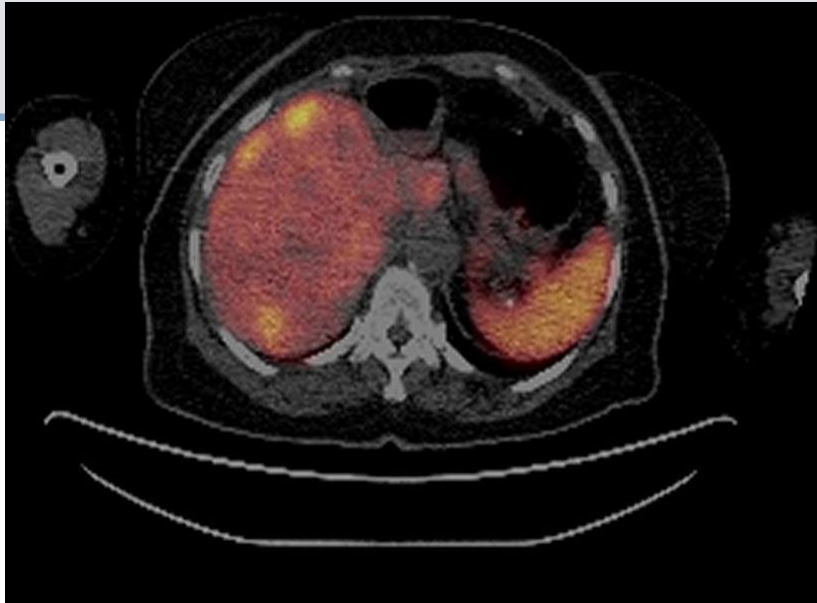
Oligometastatic disease versus systemic disease



Systemic disease versus oligometastatic disease



Systemic disease versus oligometastatic disease

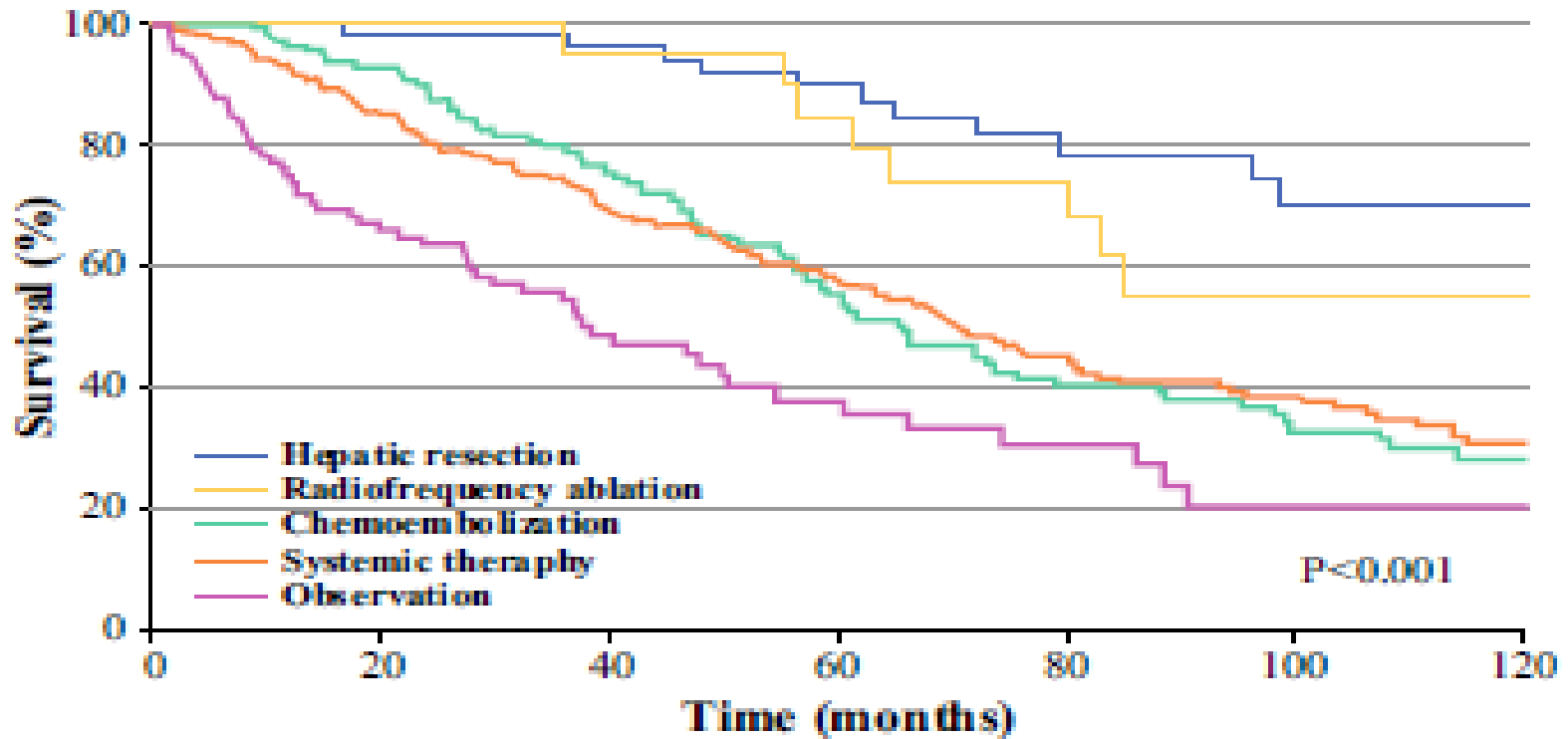


Management of neuroendocrine liver metastases

649 patients

2003-2010

Hepatic resection n=58, 9%



Prognostic factors for OS and PFS after hepatic resection for NELM

Number of metastases

Author	Year	Overall survival Number of metastases	Progression –free survival Number of metastases
Yao	2001	≤ 4	≤4
Elias	2003	<10 vs >10	<10 vs >10
Hibi	2007	Multiple vs solitary	
Durante	2009	<10 vs >10	
Norlen	2012	<5 5-10 >10	<5 5-10 >10
Ruzzenente	2017	1-2 3-9 ≥10	1-2 3-9 ≥10

Yao KA et al. Surgery 2001,130:677-682

Elias D et al. Surgery 2003, 133:375-382

Hibi T et al. Jpn J Clin Oncol 2007,37:102-107

Norlen O et al. World J Surg 2012,36:1419-1431

Ruzzenente A et al. J Gastrointest Surg 2017,21:41-48

Durante C et al. Endocr Relat Cancer 2009,16:585-599

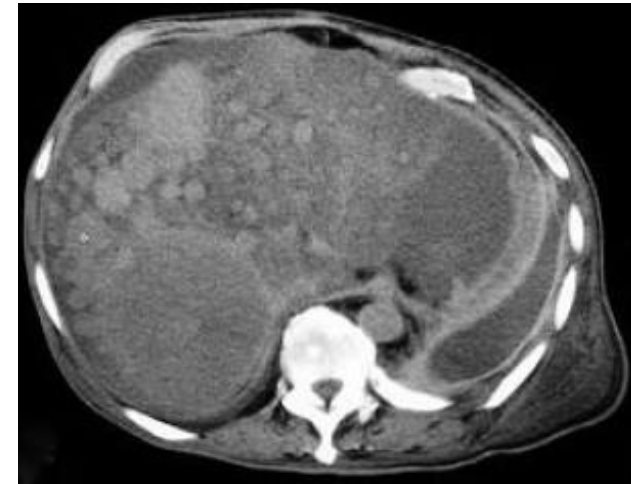
Neuroendocrine liver metastasis – morphologic growth types



Type I: Single metastasis



Type II: isolated metastatic bulk accompanied with smaller deposits



Type III: disseminated metastatic spread

Only 20-30% of the patients with NE LM are potential candidates for R0/R1 (or R2) surgery

Outcomes from liver resection for NE LM

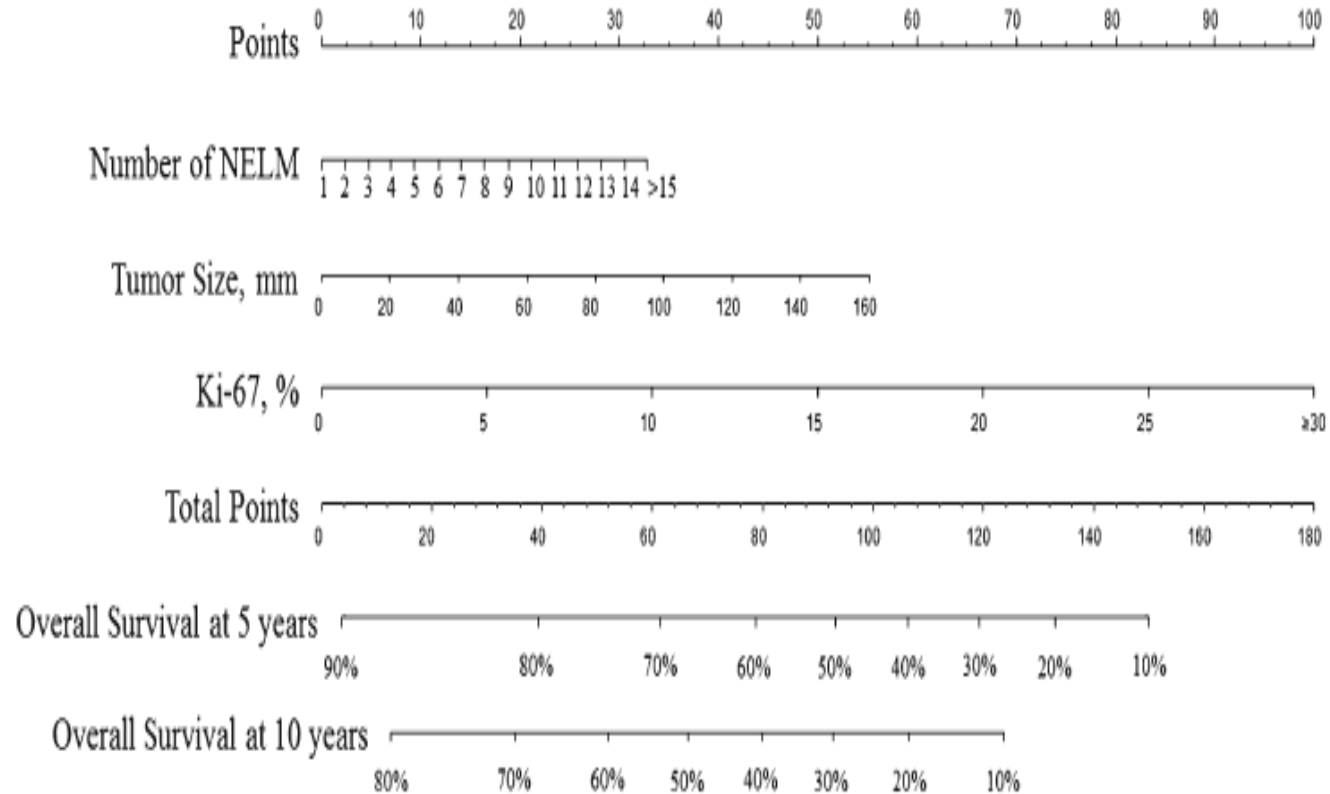
Reference	No. of Patients Undergoing Resection	No. of R0 Resections	5-Year OS, %	5-Year DFS, %	Other Survival Data After R0 Resection	30-Day Morbidity and Mortality
Saxena 2011 ³⁰	74	28	NR	NR	Median OS, 73 mo	Mortality, 1.3% (4% at 60 d)
Scigliano 2009 ³¹	41	26	88	31		Morbidity, 14%; mortality, 0%
Frilling 2009 ²¹	27	23	100	96	Median survival, 70 mo	Morbidity, 7.4%; mortality, 0%
Gomez 2007 ³²	18	15	86	90		Morbidity, 22%; mortality, 5.6%
Elias 2003 ³³	47	25	74	66		Morbidity, 45%; mortality, 5%
Sarmiento 2003 ³⁴	170	75		76		Morbidity, 14%; mortality, 1.2%
Norton 2003 ³⁵	16	16	82			Morbidity, 19%; mortality, 0%
Nave 2001 ³⁶	31	10	86			Morbidity, 13%
Coppa 2001 ³⁷	20	20	67	29		NR
Yao 2001 ³⁸	16	16	70			Morbidity, 12%; mortality, 0%
Chamberlain 2000 ³⁹	34	15	85			Mortality, 6%
Pascher 2000 ⁴⁰	26	13	NR	NR		Mortality, 0%

Abbreviations: DFS, disease-free survival; NR, not reported; OS, overall survival; R0, resection with negative margins.

5-year survival: 67 – 100%

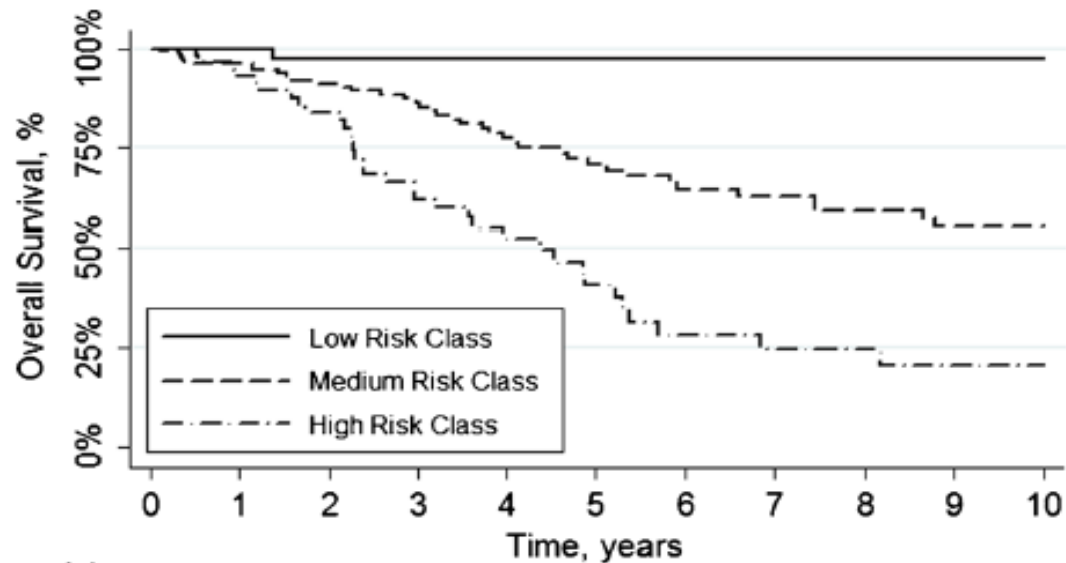
5-year disease-free survival: 29 – 96% (type I-III)

30-day mortality: 0 – 6%



**Nomogram to predict prognosis of patients undergoing
liver resection for NE LM
7 Italian HPB Centres 1990-2014
238 patients**

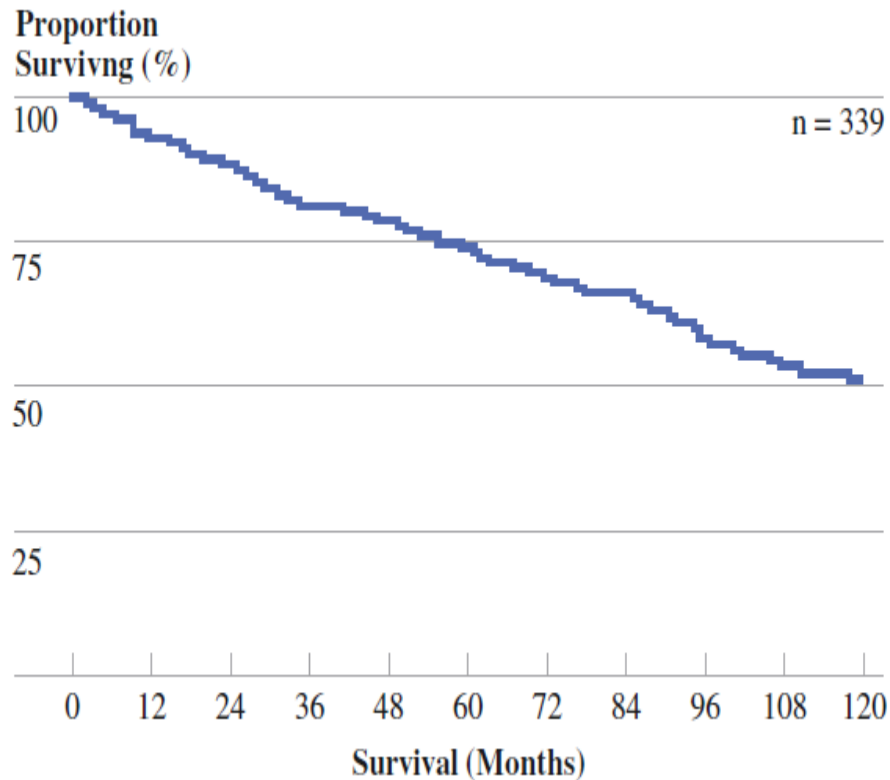
Overall survival stratified by the classification (3 prognostic factors)



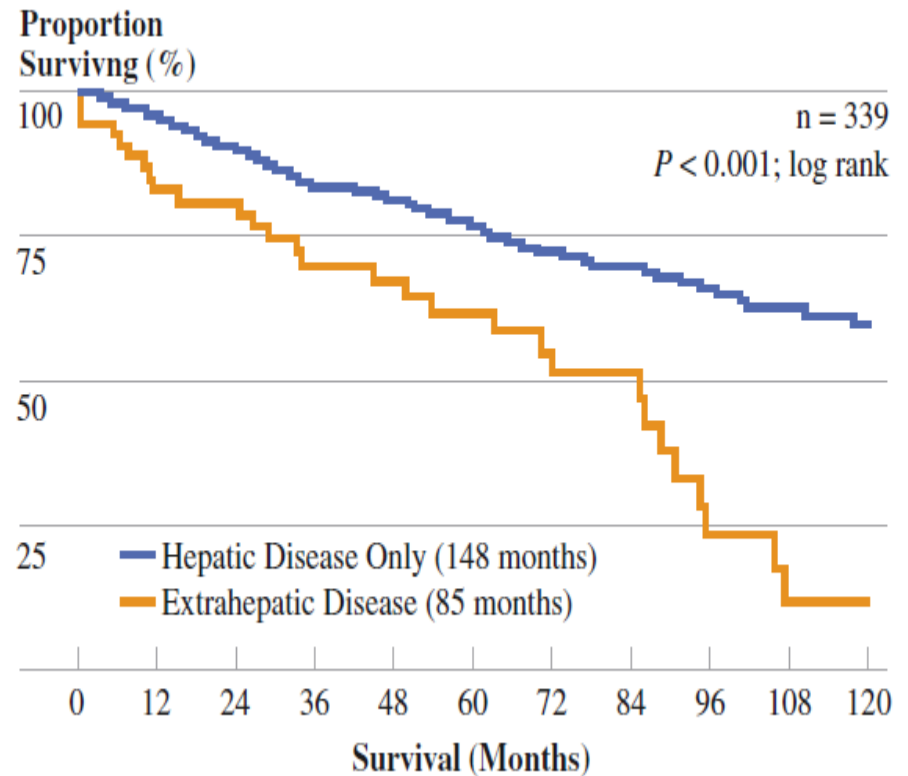
	0	1	2	3	4	5	6	7	8	9	10
Number at risk											
Low Risk Class	46	38	32	27	23	18	17	16	12	10	9
Medium Risk Class	132	122	101	83	65	49	38	35	31	28	23
High Risk Class	60	53	44	30	20	14	9	7	6	5	3

Surgical management of NE LM

- International multi-institutional analysis -
339 patients



5-year survival 74%
10-year survival 51%



5%-year disease recurrence 94%

Hepatic Metastases From Neuroendocrine Tumors With a “Thin Slice” Pathological Examination

They are Many More Than You Think . . .

TABLE 1. Histological, Preoperative Examinations, and Peroperative Exploration Results of 11 Hepatectomies for Neuroendocrine Tumor

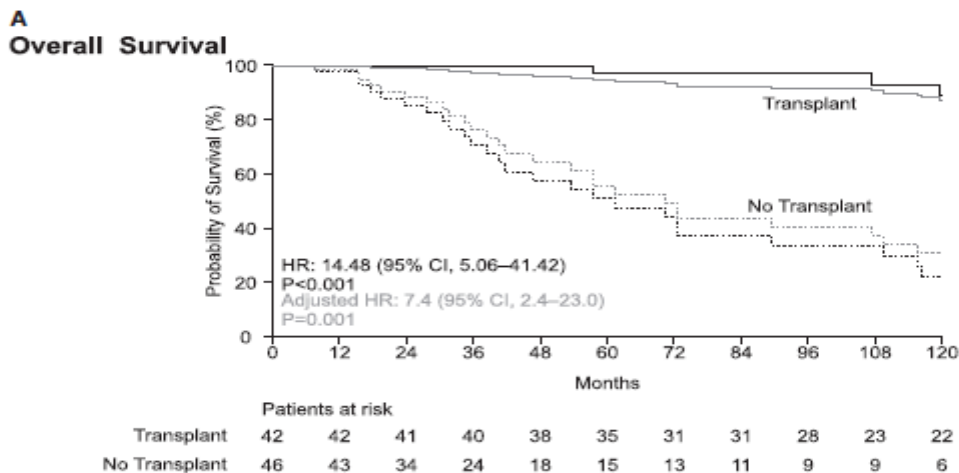
Patient	Primary Tumor	Type of Hepatectomy	No. LM Preoperatively Identified on Imaging							
			Pathologic Findings		Ultrasound Examination		CT-Scan	MRI	Somatostatin Receptor Scintigraphy	Intraoperative Findings
			No. LM	Size cm (min-max)	Normal	Contrast Enhanced				
1	Not identified	Right	13	(0.6–7)	8	8	6	7	0	9
2	Stomach	Left	5	(0.25–1.2)	4	4	4	3	2	5
3	Insulinoma	Right	22	(0.1–2.5)	7	8	5	10	3	10
4	Glucagonoma	Left	59	(0.1–3.5)	4	7	6	13	3	18
5	Insulinoma	Left	9	(0.7–5.5)	4	NA	5	9	0	6
6	Small bowel	Right	16	(0.5–3.5)	7	7	4	7	3	4
7	Small bowel	Right	13	(0.5–5)	6	NA	7	7	10	10
8	Small bowel	Left	12	(0.1–1.4)	2	3	3	2	0	3
9	Lung carcinoma	Right	8	(0.2–5)	3	NA	4	5	3	5
10	Zollinger-Ellison	Left	88	(0.1–5)	0	8	2	6	3	8
11	Glucagonoma	Right	28	(0.2–5)	15	NA	12	20	7	17
Total			273		60	45	58	89	34	95
Mean			24.8 ± 25.7		5.4 ± 3.9	6.4 ± 2.1	5.3 ± 2.7	8.1 ± 5.0	3.1 ± 3.0	8.6 ± 5.0
Median			13		4	7	5	7	3	8

NA indicates non applicable.

Long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumours

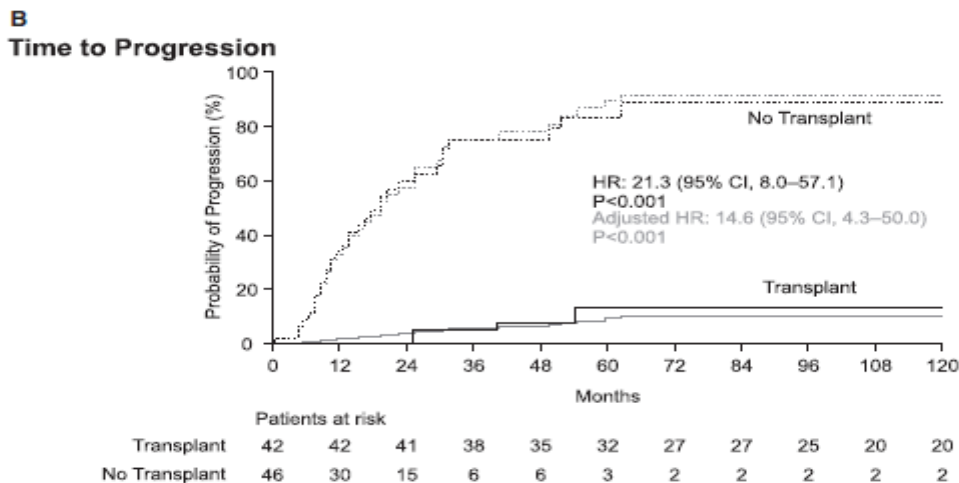
5 and 10 years OS survival 97.2% and 88.8% vs 50.9% and 22.4%

5 and 10 years DF survival 89% and 83.5% vs. 13.1% and 13.1%



Hepatic (H) involvement by NETs metastases, n (%)

H1 (<25%)	17 (40.5)	21 (45.7)
H2 (25-50%)	21 (50.0)	19 (41.3)
H3 (>50%)	4 (9.5)	3 (6.5)
Undetermined	-	3 (6.5)

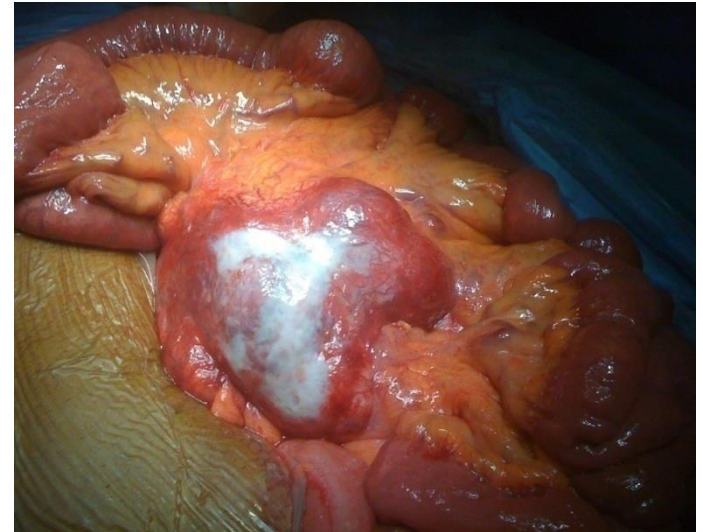
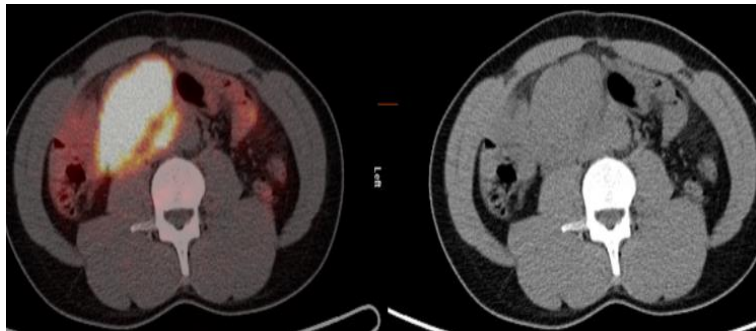
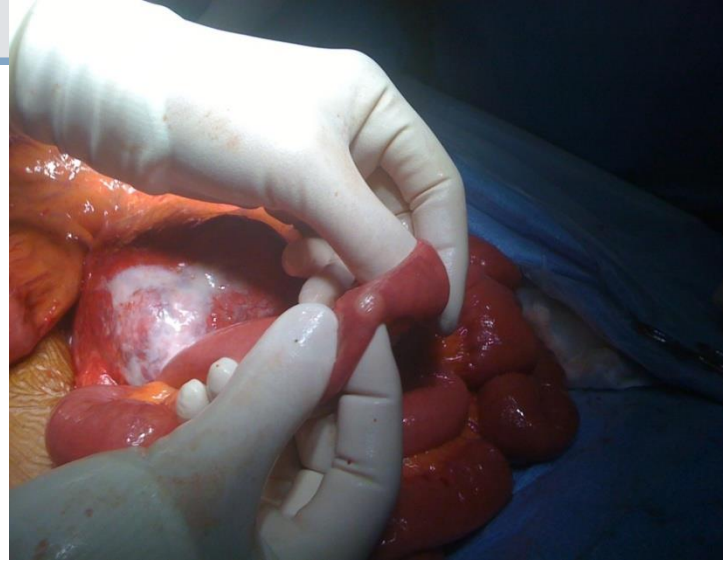
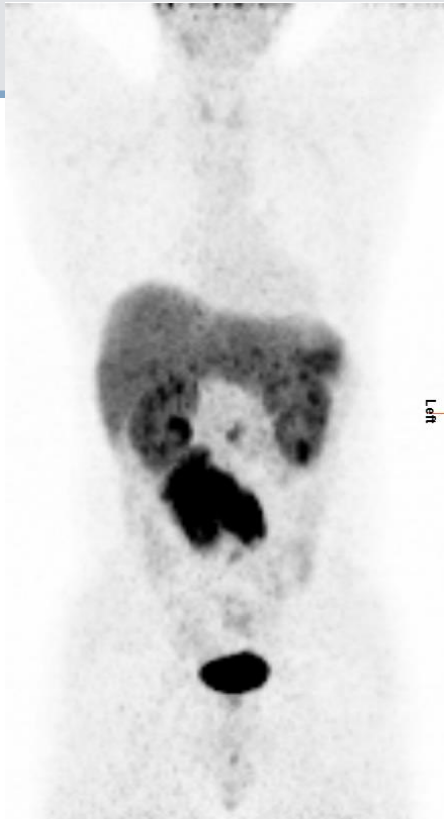


TX patients
5y DFS 89%

vs

Resected patients
(literature)
5y DFS 5%

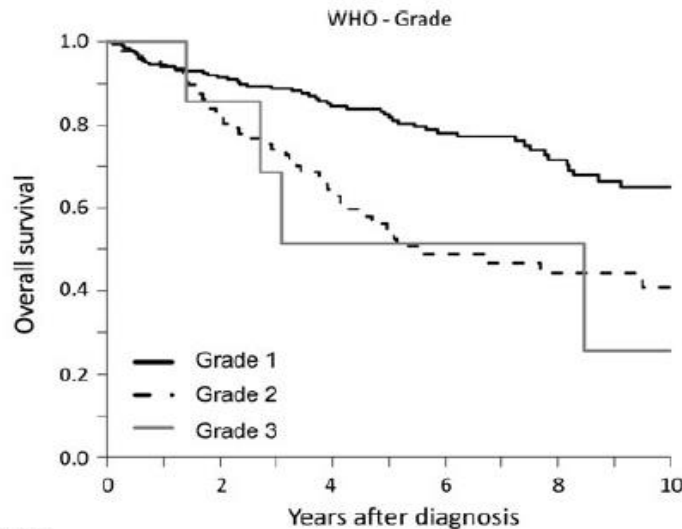
Are there oligometastatic lymph node metastases?



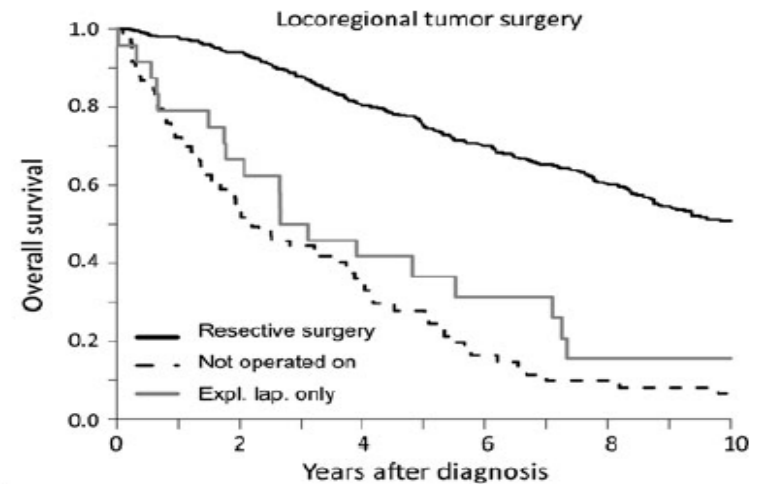
Long term results of surgery for small intestinal NET

603 patients
1985-2010

Median OS 8.4 years, 5-year survival 67%

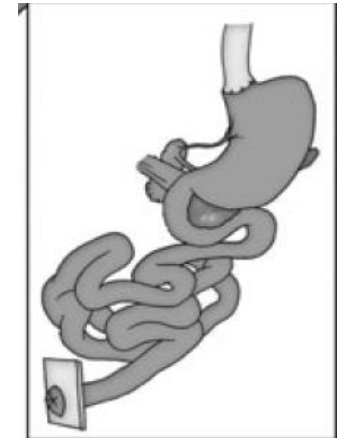
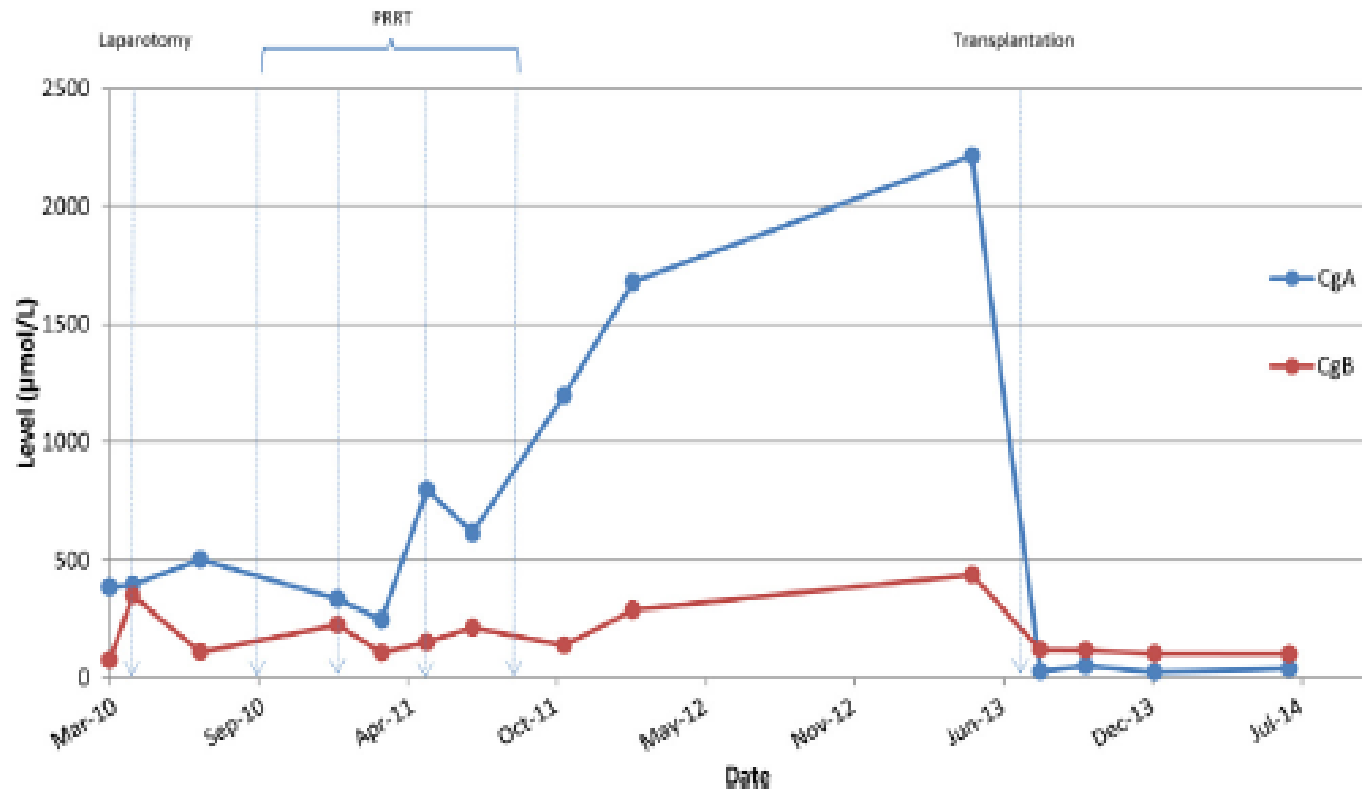


No. At risk	0	2	4	6	8	10
Grade 1	203	176	133	96	59	32
Grade 2	89	68	42	24	17	11
Grade 3	7	6	3	2	2	1



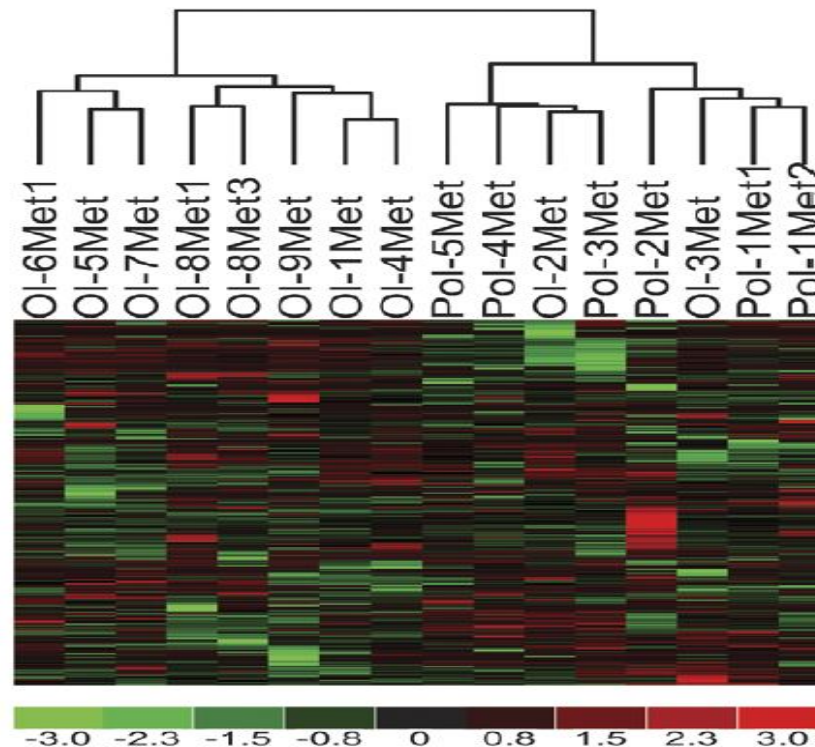
No. At risk	0	2	4	6	8	10
Resective surgery	493	448	349	260	194	132
Not operated on	86	44	22	10	6	4
Expl. lap. only	24	16	9	6	3	3

Multimodal treatment of an advanced small bowel NET



miRNA expression characterizes oligometastasis(es)

Patients who failed to develop polymetastases are characterized by unique prioritized features of miRNA classifier that includes the **miRNA-200 family**



Conclusions

- Oligometastatic disease in NET is not well-defined and the condition not broadly acknowledged in the clinical practice.
- Well-selected patients with G1/G2 NET in oligometastatic stage are candidates for surgery (primary tumour and metastases).
- Precise assessment and confirmation of a diagnosis of oligometastatic stage is pivotal for treatment decision.
- Resection / ablation of oligometastatic disease has an impact on overall survival.
- Adjuvant treatment with an aim to prolong disease-free survival.
- Contemporary molecular markers have the potential to discriminate oligometastatic from polymetastatic disease.