Fondazione IRCCS Istituto Nazionale dei Tumori
Sistema Socio Sanitario Regione Lombardia
UNIVERSITÀ DEGLI STUDI DI MILANO

Preliminary Program

4th Milan NET Conference

A meeting among active Italian Neuroendocrine Tumor Boards

Non-Pharmacologic Liver-Directed Therapies in Hepatic Metastases from NET

A missed opportunity?

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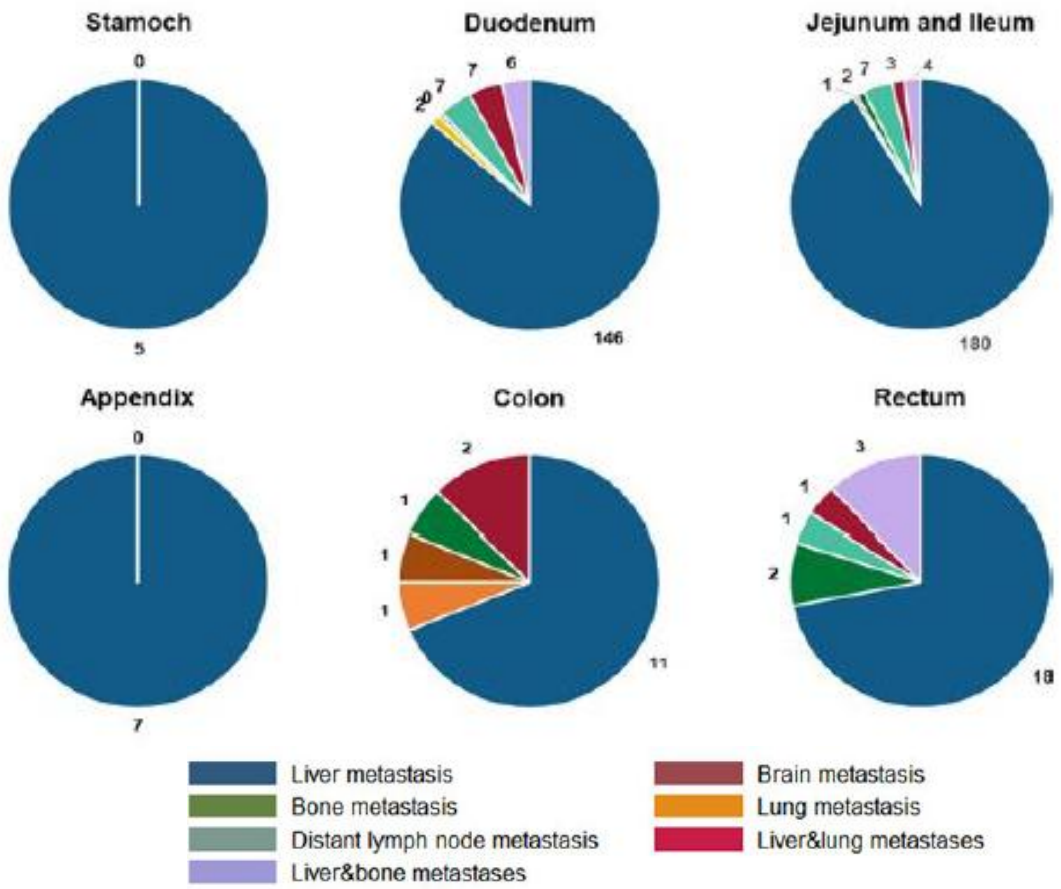
Heterogeneity, rarity and complexity of NET impair treatment comparison through prospective studies



✓ Annual incidence of NET over the last 30 years has increased to 5.25 per 100,000 population

✓ 40-80% of patients present at diagnosis with metastases, being the liver the most involved organ (40–93%)

✓ The slow-growing nature of liver mets are limiting factor for assessing survival outcome

✓ Many tumor and non-tumor variables have influence on results of treatment of liver metastases from NET

Despite the large spectrum of treatments approved for NET, there is a paucity of relevant trials on combined therapies in the specific condition of liver metastases from NET

Hepatic resection			
Orthotopic liver transplant			
Loco-regional therapies*	Ablation	Ethanol injection	
		Radiofrequency	
		Microwave	
		Irreversible Electroporation (IRE)	
		Cryoablation	
		Laser ablation	
	Embolization	Trans-arterial embolization (TAE)	
		Trans-arterial chemoembolization (TACE)	Conventional (cTACE)
			Drug eluting beads (DEB-TACE)
		Trans-arterial radio-embolization (TARE)	Yttrium -90

Metastases from NETs to the liver represent a significant clinical entity, and multiple treatment modalities have been used, engaging multidisciplinary teams

Despite a lot of discussion, not much of interaction

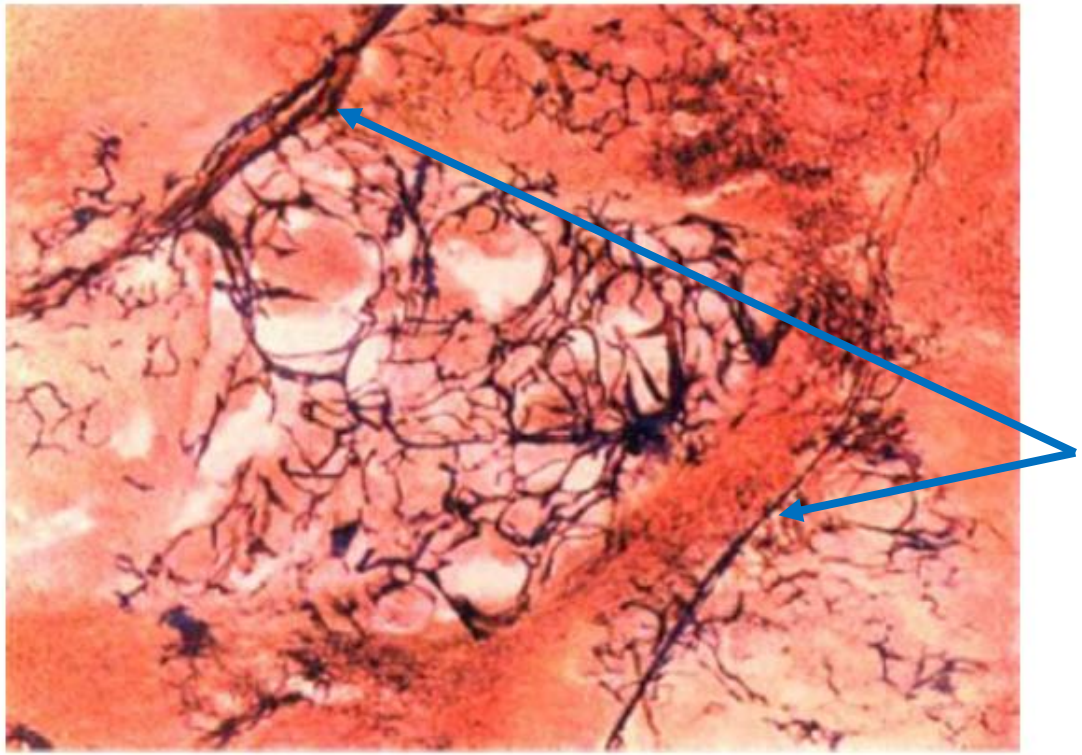


Figure 1 Colour photomicrograph of a liver metastasis. R Douglas Wright developed a way of injecting blue gelatine via the hepatic artery and red gelatine via the portal vein to demonstrate the junction of hepatic artery capillaries and portal venules.[6] Reproduced with permission from the *Journal of Pathology and Bacteriology*.

Livers with metastases were resected from human cadavers with hepatic arteries and portal veins intact and the vessels were subsequently perfused and washed.

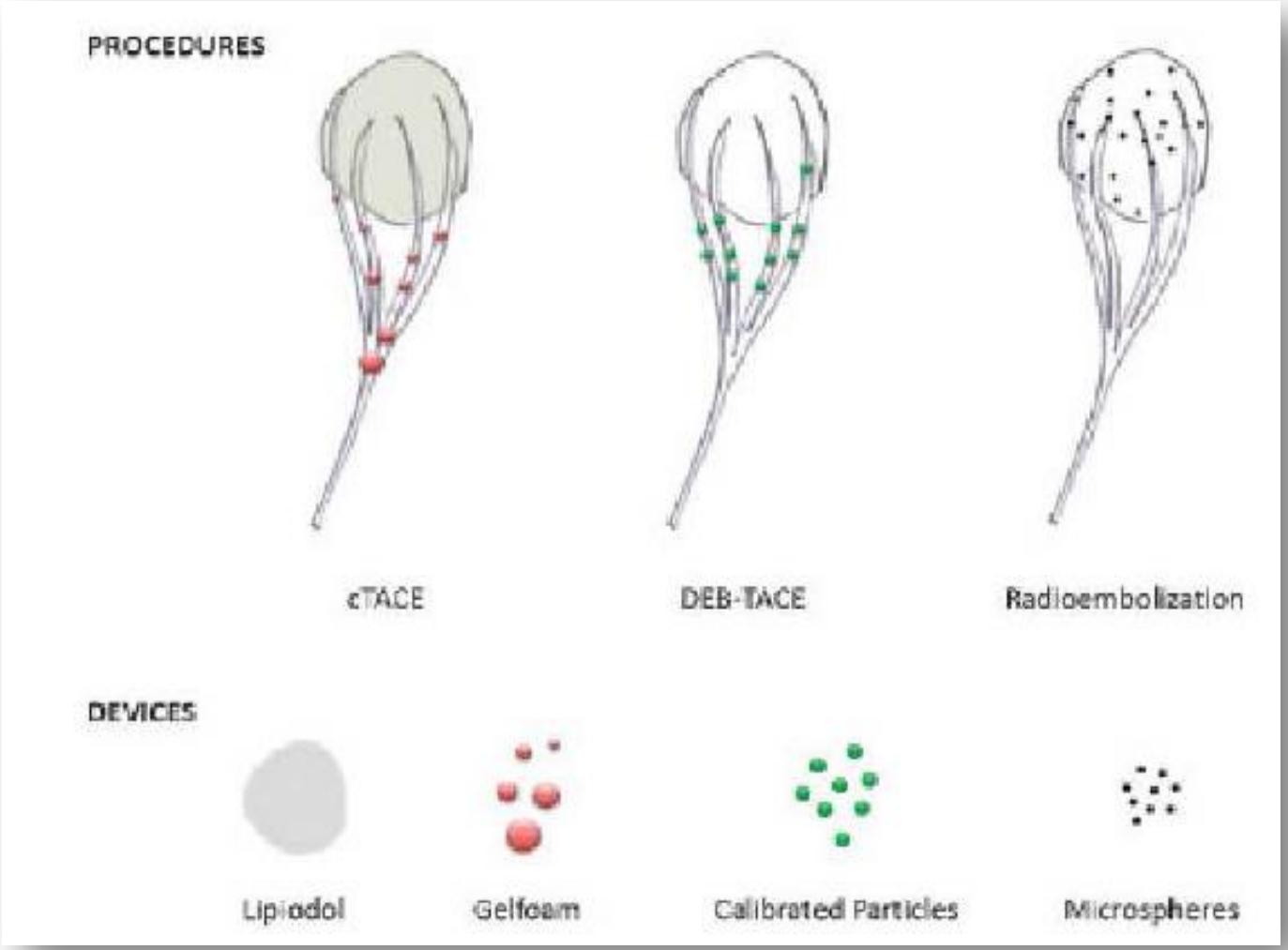
Red gelatine masses were then injected into the portal vein while blue gelatine masses were injected into the hepatic artery, followed by sectioning the next day. Using this method, Wright was able to clearly demonstrate that:

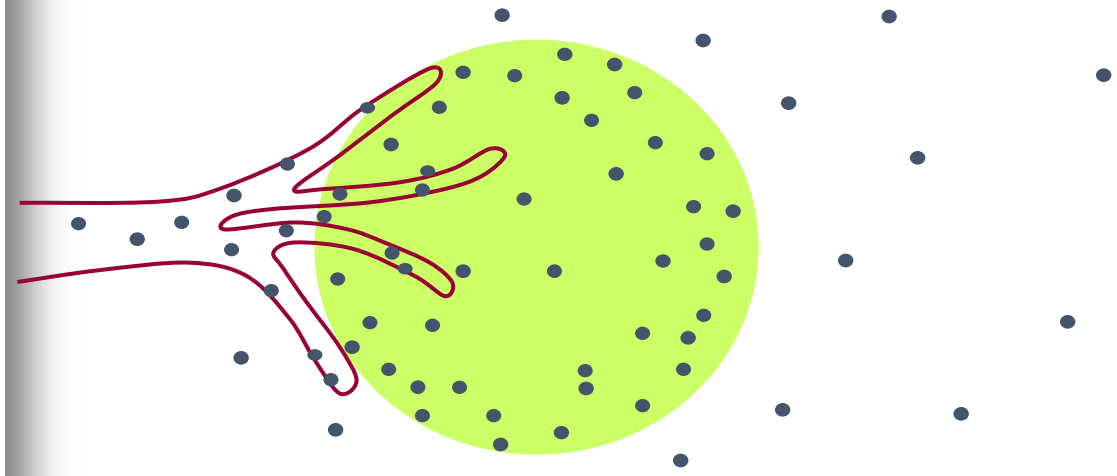
«*When a fibrovascular stroma develops in secondary carcinomata in the liver, the afferent blood supply to these vessels is from the hepatic artery*".

Wright RD J Patholog Bacteriol 1937

The **concept of arterially directed therapy** to selectively target the blood supply of malignancy

Mechanisms of action of c-TACE, DEB-TACE and SIRT ()

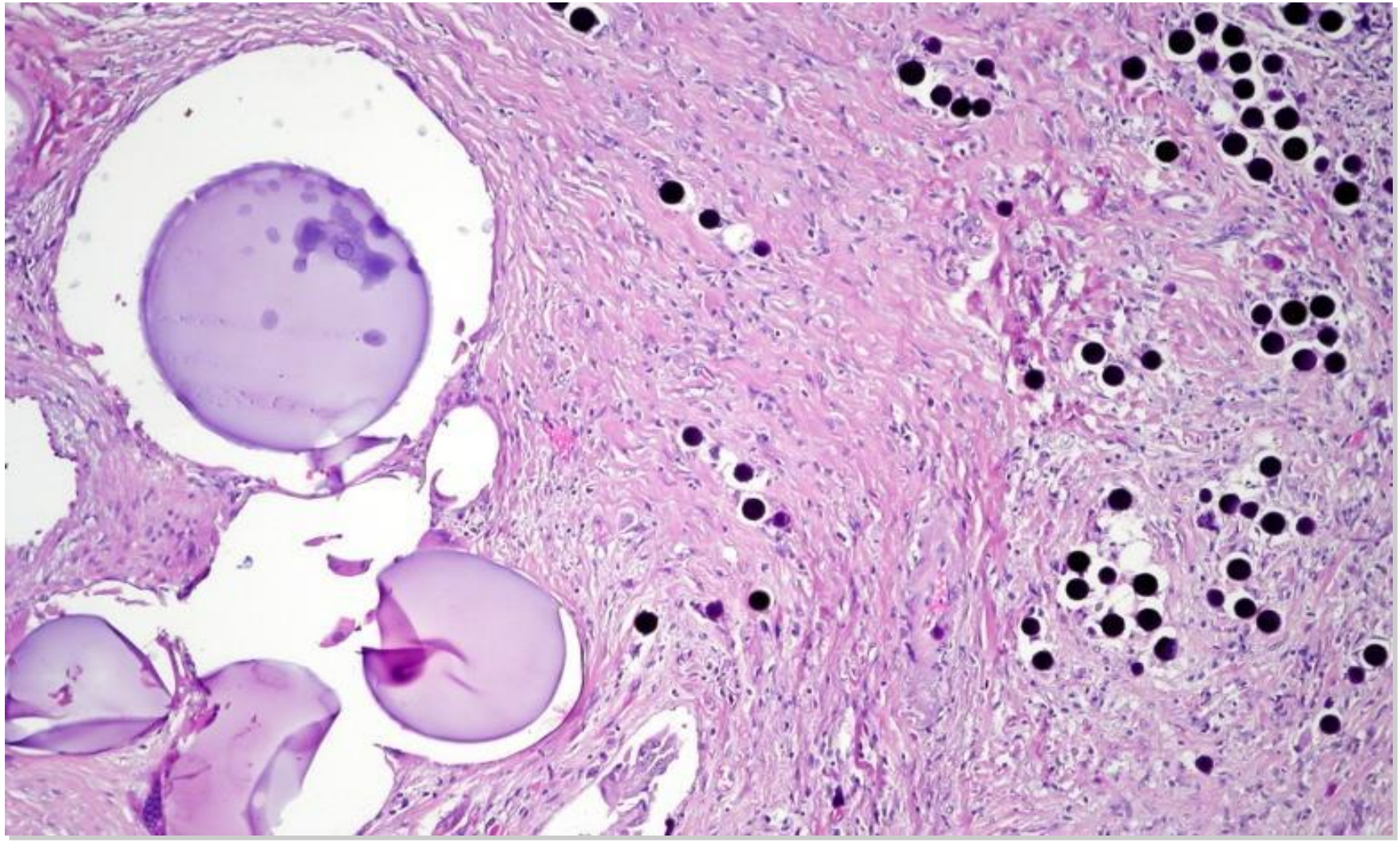




selective internal radiation therapy

Sangro B and Salem R, Sem Liver Dis 2014

TACE



TARE

Response and Survival after TAE or TACE (conventional or DC-Beads)

Study	N	Device Used	Radiologic Response; RECIST 1.0 (%)	Survival Times and Rates
Dong & Carr[53]	123	TACE	62	Mean: 3.3 y 3-y, 5-y, and 10-y survival: 59%, 36%, and 20%
de Baere[59]	20	TACE with doxorubicin-eluting beads	80	Not reported
Vogl[39]	48	TACE with mitomycin C	11.1	Median: 38.6 7 mo 5 y: 11.11%
		TACE with mitomycin C + gemcitabine	23.33	Median: 57.1 5 y: 46.67%
Loewe[30]	23	Bland embolization	73	Median: 69 mo 1-y and 5-y survival: 95.7% and 65.4%
Eriksson[60]	41	Bland embolization	50	Median: 80 mo 5 y: 60%
Pitt[26]	100	Bland[51] vs TACE[49]	NA	Median from dx: TACE, 50.1 mo; bland, 39.1 TACE 1-y, 2-y, 5-y survival: 69%, 52%, 19%. Bland: 19%, 70%, 13%
Ruutiainen[54]	67	Bland[23] vs TACE[44]	TACE: 22 Bland: 38	Survival of 1, 3, and 5 y TACE: 86%, 67%, 50% Bland: 68%, 46%, 33%
Gupta[61]	49	TACE[27] vs bland[42]	TACE: 50 Bland: 25	Median survival for carcinoid tumors: TACE 33.8 vs bland 33.2. Islet TACE 31.5 vs bland 18.2
Maire[62]	26	TACE[12] vs bland[14]	TACE: 100 Bland: 92	2-y survival: TACE, 80%; bland, 100%. Median PFS: TACE, 19.2 mo; bland, 23.6 mo
Guiu[45]	120 NET 88 HCC	DEB-TACE in HCC (cirrhotic) and NETs (noncirrhotic)	NA	NA
Ruszniewski[55]	23	TACE	PR, SD, PD, TTP HACE: 61, 22, 17,14 HAE: 20, 40, 40,12	8 of 23 died median of 12.5 mo after final TACE

Symptomatic responses: 53% to 100% of patients (10–55 mo) - Morphologic responses: 35% to 74% (6–63 mo)
PFS: 14-18 months - OS at 5-year: 40% to 83%
Mortality: 0% to 5% - Morbidity (ie, postembolization syndrome): 28% to 90%.

Response and Survival after TARE

Table 4
Response and survival after radioembolization (TARE)

Study	N	Device Used	Radiologic Response; RECIST 1.0 (%)	Survival
Rhee[51]	42	Yttrium 90 (glass) Yttrium 90 (resin)	54 50	Median: 22 mo Median: 28 mo
Kennedy[8]	148	Yttrium 90 (resin)	63	Median: 70 mo
King[36]	58	Yttrium 90 (resin) plus 5-FU	39	Median: 36 mo 1-y, 2-y, 3-y survival: 86%, 58%, and 47%
Saxena[52]	48	Yttrium 90 (resin)	54	Median: 35 mo 1-y, 2-y, 3-y survival: 87%, 62%, and 42%
Cao[48]	58	Yttrium 90 (resin) plus 5-FU	39.2	Median: 36 mo
Paprottka[50]	42	Yttrium 90 (resin)	22.5	Median: 95% at 16.2 mo
Memon[49]	40	Yttrium 90 (glass)	WHO, 64; EASL, 71.4	Median: 34.4 mo 1-y, 2-y, 3-y survival: 72.5%, 62.5%, 45%

Responses: 20%-71%
Median survival: 22-70 mo

TARE may be advantageous compared with TAE/TACE because of fewer side effects and fewer treatments.
TARE with ^{90}Y is now accepted by all the societies as a suitable replacement for TAE/TACE in liver mNETs

Combination with systemic treatment: a missed opportunity n.1 ?

Because embolization stimulates release of vascular endothelial growth factor (VEGF) into the circulation, sunitinib – an oral VEGF receptor inhibitor – was used after hepatic TAE for mNETs in a phase II clinical trial that observed encouraging median PFS of 15.2 months and OS at 4yrs of 59% (95% CI: 0.38–0.80)

	N	%
Liver tumor burden		
<25%	13	33
25%–50%	12	31
50%–75%	8	21
>75%	6	15

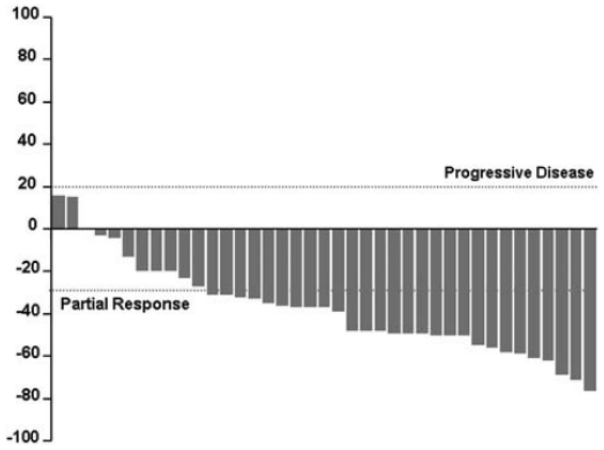


Figure 1. Percentage change from baseline in sum of diameters of target lesions.

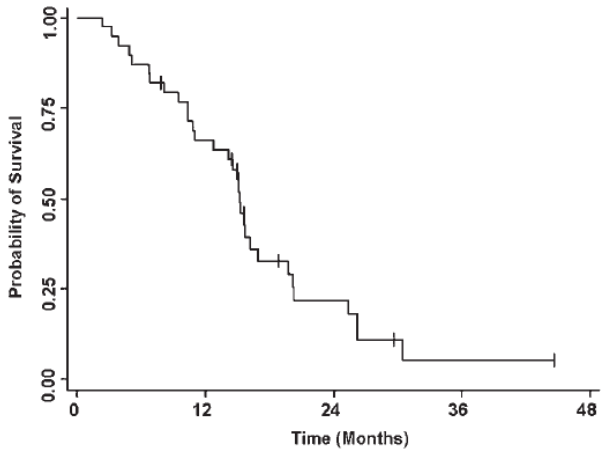
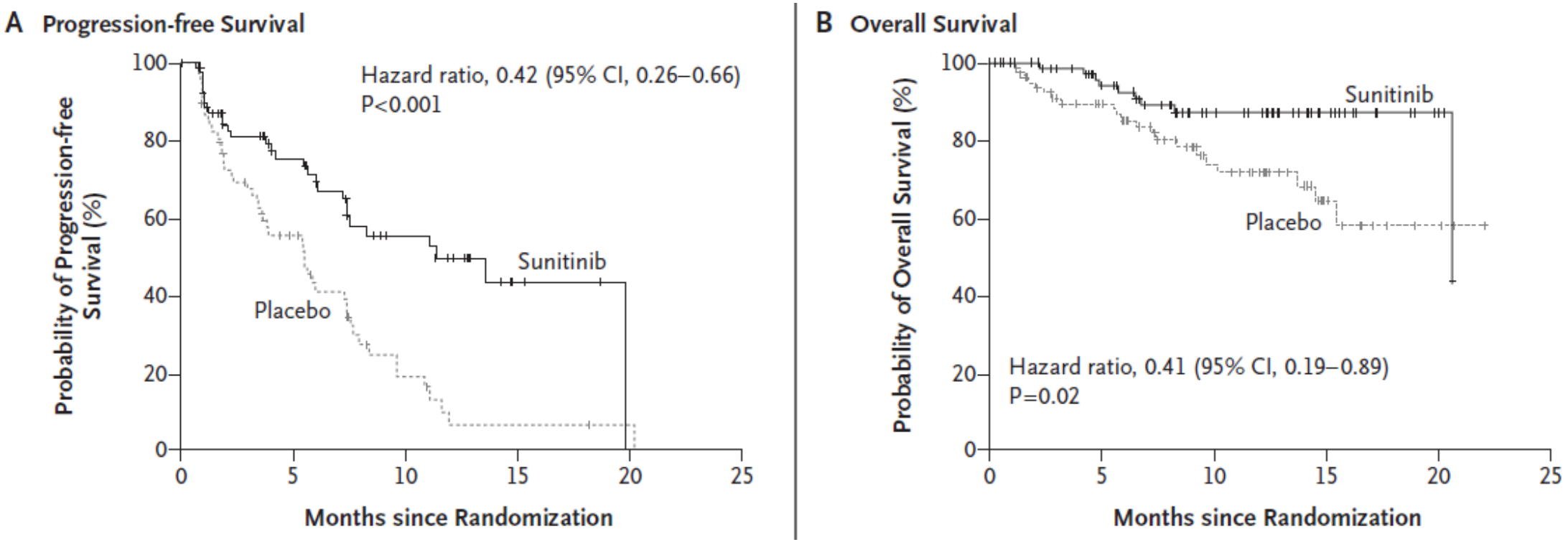


Figure 2. Kaplan–Meier analysis of progression-free survival.

Primary site			
Small intestine			
Pancreas	5.05	1.12–22.8	0.04
Other	2.67	0.27–26.2	0.40
Grade			
Well			
Moderate	2.07	0.25–17.0	0.50
Unspecified	0.97	0.32–2.97	0.96
Hepatic tumor burden			
<50%			
>50%	1.32	0.44–3.96	0.62
Prior progression			
No			
Yes	6.05	1.45–25.2	0.03
Age	0.91	0.84–0.99	0.03

Strosberg et al. Ann Oncol 2012 23: 2335

Combination with systemic treatment: a missed opportunity n.1 ?



Sunitinib improved progression- free survival, overall survival, and the objective response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors

Raymond et al. New Engl J Med 2011 ;364: 501

Combination with radiosensitizer treatment: a missed opportunity n.2 ?

58 patients using 90Y resin microspheres and concurrent 5-fluorouracil (5-FU) in advanced patients with demonstrated progression
Response was at 39%; median survival was 36 months

Characteristics of Patients the With Best Liver Response to Yttrium-90 Radioembolization by Response Evaluation Criteria in Solid Tumors

CT Response in Liver	Primary Site	Prior Liver Treatments	Prior Extrahepatic Disease	% Hepatic Replacement	Follow-up, mo	SIR-Spheres: Dose Delivered, GBq	Yttrium 90 Estimated Tumor Dose, Gy	CgA Fall, %
CR	Pancreas	LR	Nil	30	42	1.9	79	−93
CR	Small bowel	LR	Nil	1	42	1.6	62	−63
CR	Small bowel	Nil			33	2	16	−48
CR	Medullary thyroid	Nil			48	2	46	−60
CR	Small bowel	Nil	Nil	10	28	0.9	19	−70
PR	Small bowel	Nil	Nil	60	26	2.3	18	−23
PR	Small bowel	Nil	Nil	50	4*	1.9	45	Nil baseline
PR	Small bowel	Nil	Nil	40	8*	1.9	60	−31
PR	Unknown	Nil	Nil	50	11*	2.3	40	−14
PR	Small bowel	IV	+	30	24*	1.9	55	−68
PR	Pancreas	LR			45	1.5	65	−77
PR	Glucagonoma	Nil			41	2	125	−63
PR	Unknown	Nil	+	30	41	2.1	36	−20
PR	Unknown	Nil	+	20	35	1.6	55	−25
PR	Somatostatinoma	LR	Nil	10	39	1.8	50	−12.5
PR	Pancreas	Nil	+	25	29	2.1	61	−25
PR	Small bowel	Nil	Nil	40	12*	2	52	Nil baseline
SD	Bronchus	Nil	Nil	10	8	2	105	−55
SD	Small bowel	LR		0	20*	2.3	52	−86
SD	Small bowel	IV		0	39*	2.1	65	−79
SD	Vipoma	LR	+	20	18*	2.1	89	No change
SD	Small bowel	LR	+	25	24*	1.9	40	−75

CR

PR

SD

26.8% ± 9.8%

28.6% ± 4.6%

25% ± 6.7%

King J et al. Cancer 2008 ;113: 921

Tumor burden is an essential component determining result in loco-regional treatments

Characteristics of Patients Without Liver Response to Yttrium-90 Radioembolization by Response Evaluation Criteria in Solid Tumors Criteria

CT Response in Liver	Primary Site	Prior Liver Treatments	Prior Extrahepatic Disease	% Hepatic Replacement	Follow-up, mo	SIR-Spheres: Dose Delivered, GBq	Yttrium 90 Estimated Tumor Dose, Gy	CgA Fall, %
Died at 1 mo	Unknown	Nil	Nil	50	1*	2.2	61	Nil baseline
PD	Small bowel	IV	+	60	28	1.9	12	−72
PD	Small bowel	Nil	+	60	8*	2.8	81	Nil baseline
PD	Medullary thyroid	Nil	+	60	14*	2	48	−65
PD	Small bowel	LR	+	41.2% ± 4%	14*	1.4	40	−38
PD	Unknown	IV	+		15*	1.5	14	−48
PD	Unknown	LR	+	40	28*	2.1	49	−17
PD	Small bowel	Nil	+	40	21	2.3	46	−63
PD	Pancreas	Nil	+	30	28	2.2	51	No change
PD	Pancreas	IV	+	40	30	2.1	42	−7
PD	Unknown	LR	+	40	44	2	40	−41
PD	Unknown	Nil	+	20	44	2	63	−63

CT indicates computed tomography; SIR, selective internal radiation; GBq, gigabecquerel; Gy, grays; CgA chromogranin A; PD, progressive disease; IV, systemic chemotherapy; +, positive; LR, liver resection, *Deceased.

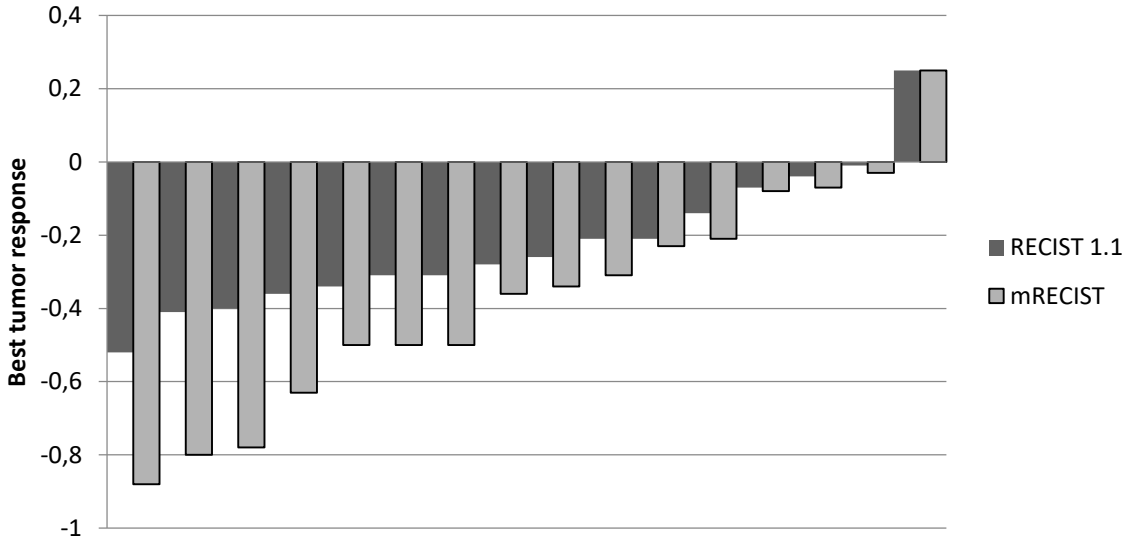
PRO

There was no obvious contributing factor evident that could account for the good to excellent response to ^{90}Y, except perhaps for less hepatic volume replacement

King J et al. Cancer 2008 ;113: 921

Y-90 Radioembolization in patients with oligometastatic NET and measurable tumor burden

Response	RECIST 1.1	mRECIST
CR		
PR	7 (43,7%)	10 (62,5%)
SD	8 (50%)	5 (31,2%)
PD	1 (6,3%)	1 (6,3%)
CR + PR	7 (43,7%)	10 (62,5%)
CR + PR + SD	15 (93,7%)	15 (93,7%)



2011-2016

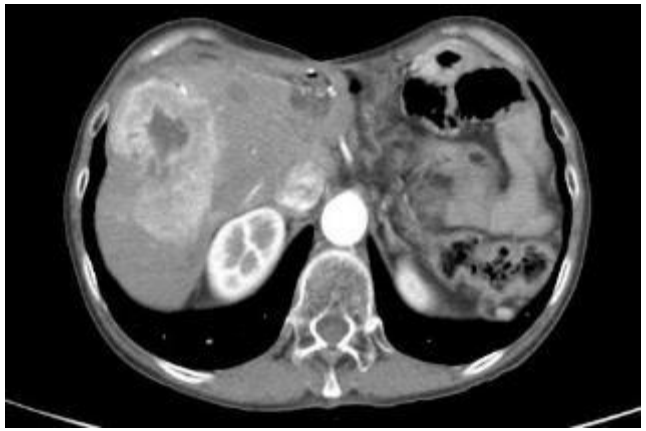
16 Patients

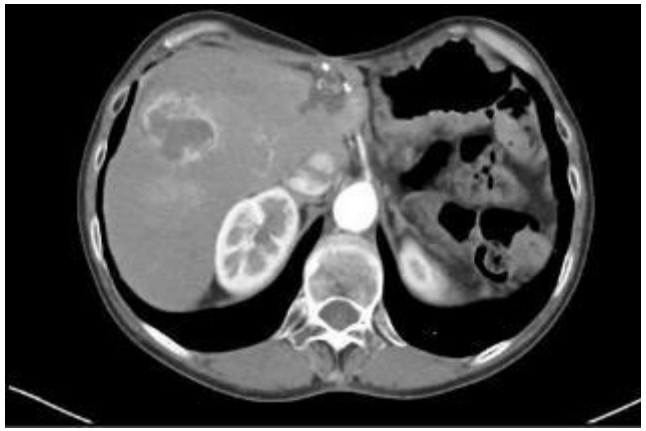
Median follow-up: 34 months.

Best tumor response according to RECIST 1.1 and mRECIST criteria were -52% and -88% respectively.

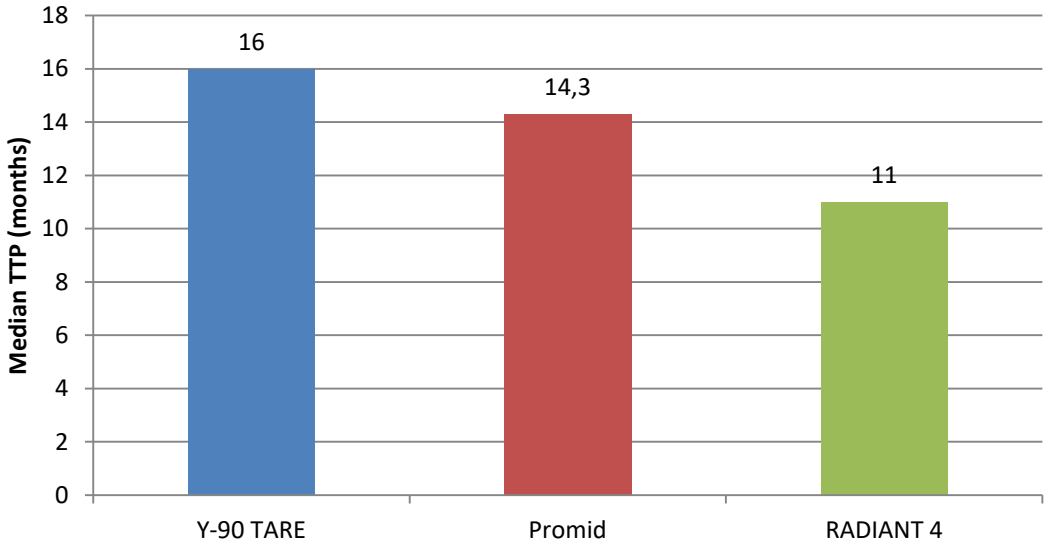
According to RECIST 1.1 and mRECIST

Objective response rate (partial + complete) was 43.7% and 62.5% respectively while the disease control rate (complete + partial response + stable disease) was 93.7%.





Y-90 Radioembolization in patients with oligometastatic NET and measurable tumor burden

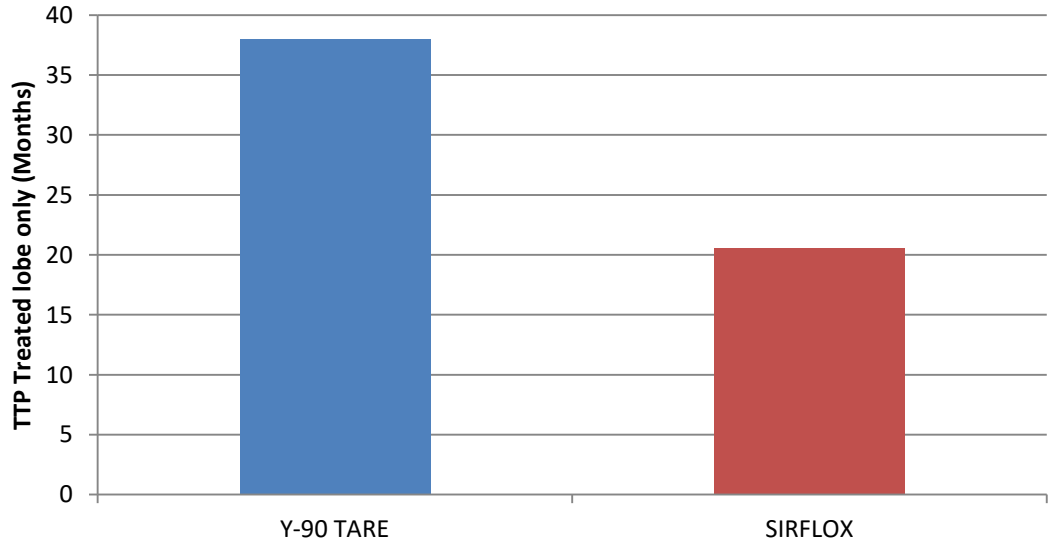


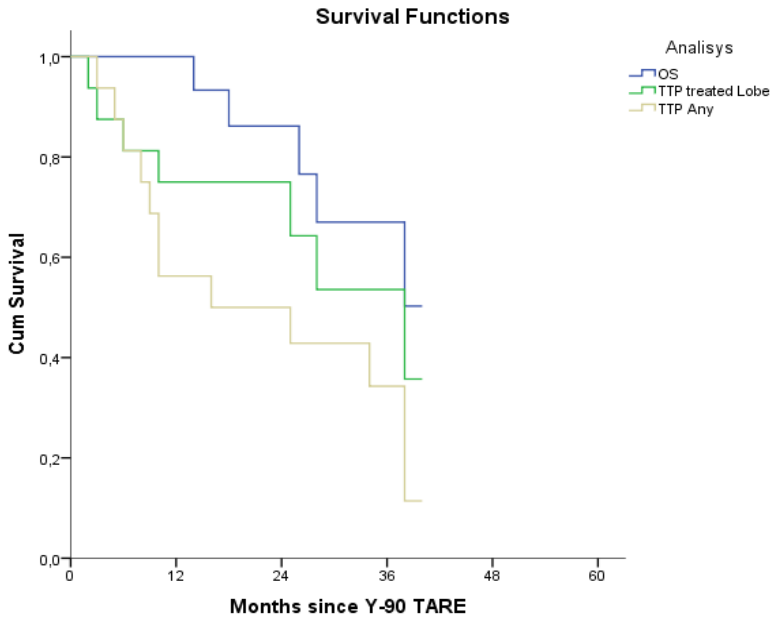
Disease progressed in 12 cases (75%)

Median TTP: 16 months

Only 7 cases (43.7%) progressed in the treated hepatic lobe (Median TTP: 38 months).

OS at 1 and 3 years was 93.3% and 67% respectively





Liver Resection for metastatic NET

								Overall Survival					Disease Free Survival				
First Author	Yr	Patients	Study period	TLV >50%	EHD	G1-G2	Curative	Median (Mts)	1-Yr	3-Yr	5-Yr	10-Yr	Median (Mts)	1-Yr	3-Yr	5-Yr	10-Yr
Mayo	2010	339	1985-2009	87 (26)	55(16)	132/228 (58)	234 (69)	125	92	81	74	51	15	57	24	6	1
Saxena [27]	2010	74	1992-2009	NA	19(26)	53 (70)	48 (65)	95	90	74	63	40	23	68	32	21	0
Glazer [28]	2010	172	1978-2009	NA	NA	85 (49)	144 (84)	116	NA	NA	77	50	NA	NA	NA	NA	NA
Frilling [29]	2009	23	1992-2006	NA	0(0)	23 (100)	23(100)	NR	100	100	100	100	NA	NA	NA	NA	NA
Cho [30]	2008	70	1990-2006	NA	15(21)	37/63 (59)	48 (69)	91	91	74	61	34	17	61	27	17	0
Landry [31]	2008	23	1998-2006	NA	NA	NA	NA	NR	100	100	75	NR	NA	NA	NA	NA	NA
Gomez [31]	2007	18	1994-2006	NA	NA	11(61)	15(83)	NR	92	86	86	NA	NA	NA	NA	66	NA
Hibi [33]	2007	21	1976-2004	2(19)	7(33)	NA	14(67)	54	94	75	41	25	NA	NA	NA	NA	NA
Reddy [34]	2007	33	1995-2005	NA	7(21)	NA	21 (64)	NR	93	75	68	NA	13	50	32	NA	NA
Musunuru [36]	2006	13	1996-2004	3(20)	0(0)	NA	12(92)	NR	100	83	60	NA	NA	NA	NA	NA	NA
Touzios [37]	2005	19	1990-2004	3(16)	9(47)	NA	NA	96	79	72	72	NA	NA	NA	NA	NA	NA
Knox [38]	2004	13	1980-2001	NA	NA	NA	10(77)	107	85	85	85	44	19	C:67	C:50	C:33	NA
Sarmiento [26]	2003	170	1977-1998	NA	0(0)	NA	75(44)	81	95	74	61	35	21	71	32	16	6
Norton [39]	2003	16	1995-2003	NA	NA	NA	16(100)	75	100	82	82	0	NA	NA	NA	NA	NA
Gulec [53]	2002	30	1998-2001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Elias [40]	2001	47	1985-2000	2(4)	20 (32)	47(100)	37(79)	91	91	82	71	35	46	80	55	45	11
Chung[41]	2001	31	1992-2000	NA	11(35)	NA	2(6)	NA	NA	NA	31	NA	NA	NA	NA	NA	NA
Coppa[42]	2001	20	1987-1999	1(5)	NA	NA	20(100)	57	100	100	67	NA	24	63	44	29	NA
Yao [43]	2001	16	1992-2000	NA	NA	NA	16(100)	NR	100	86	70	NA	29	NA	NA	NA	NA
Nave [44]	2001	31	1983-1995	NA	20 (65)	NA	10(32)	NA	NA	NA	47	NA	NA	NA	NA	NA	NA
Chamberlain [2]	2000	34	1992-1998	15(44)	15(44)	NA	15(44)	NR	94	83	76	NA	NA	NA	NA	34	NA
Grazi [45]	2000	25	1981-1997	NA	NA	NA	21 (84)	NR	100	93	79	79	NA	NA	NA	NA	NA
Jaeck [46]	1999	13	1986-1998	NA	NA	NA	NA	NA	100	91	68	NA	NA	NA	69	NA	NA
Chen [47]	1998	15	1984-1995	NA	0(0)	NA	15(100)	NR	NA	NA	73	NA	21	NA	NA	NA	NA
Ahlman/Wangberg	1996	14	1985-1992	NA	NA	NA	14(100)	NR	100	100	100	100	NA	NA	NA	NA	NA
Dousset [50]	1996	17	1986-1994	NA	NA	NA	12(71)	48	94	87	46	NA	21	63	36	36	NA
Que[51]	1995	74	1984-1992	NA	NA	45(61)	28 (38)	NR	93	83	NA	NA	NA	NA	NA	NA	NA
McEntee [52]	1990	37	1970-1989	NA	NA	NA	17(46)	65	93	80	59	NA	NA	NA	NA	NA	NA
Median				**19**	**23.5**	**61**	**71**	**NA**	**94**	**83**	**70.5**	**42**	**21**	**63**	**32**	**29**	**1**
Range				**4-44**	**0 65**	**49 100**	**6 100**	**NA**	**79 100**	**63 100**	**31 100**	**0 100**	**13 46**	**50 80**	**24 69**	**6 66**	**0 11**
Total (all patients)				**113/493**	**178/897**	**433/699**	**905/1384**	**1364**	**1190**	**1190**	**1365**	**1022**	**814**	**780**	**793**	**799**	**700**
Overall weighted average				**23**	**20**	**62**	**65**	**NA**	**93**	**81**	**69**	**47**	**20**	**63**	**31**	**17**	**3**

Statistical Cure is said to occur when the mortality of patients treated for a specific disease returns to the same level as that of the general population.

The probability of being cured by liver surgery is 43.9%
The time to cure is 5.1 years
The median survival of uncured patients is 1.7 years

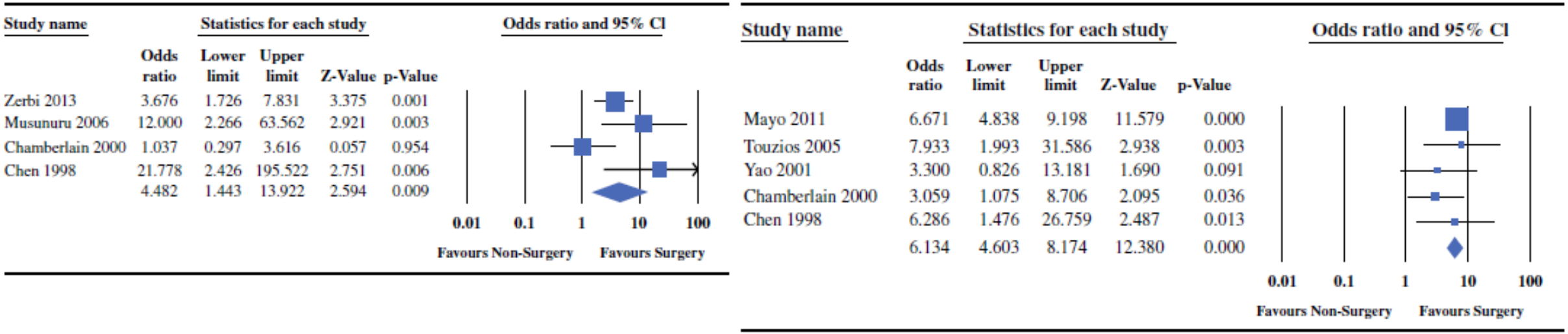
TABLE 4 Multivariable cure-fraction calculation stratified by baseline characteristics

Variable	Coefficient (95%CI)	P
Constant	95.4% (82.7 to 99.9)	-
Liver involvement, >50%	−34.2% (−49.6 to −18.8)	<0.001
Grade, moderate/poorly differentiation	−24.8% (−38.2 to −11.4)	<0.001
Type of NET, pancreatic non-functional	−28.1% (−41.7 to −14.4)	<0.001

In a multivariable cure model only **type of NET**, grade of **tumor differentiation**, and **degree of liver involvement** remained independent predictors of cure of liver metastases from NET undergoing resection.

Tumor burden >50% is able to decrease of more than a third the chances to be cured with surgery if compared to the best scenario of a patient resected for a G1 gastrointestinal NET who had <50% of liver involvement.

Bagante F et al. J Surg Oncol. 2017;115:687–695.



Forest plot for the aggregate survival of liver resection or nonsurgical treatment in patients with pancreatic neuroendocrine tumor liver metastases. **a** 2- or 3-year survival; **b** 5-year survival

Liver resection demonstrated favorable prognostic outcomes with higher postoperative symptom relief rates, longer median survival as well as 2-, 3-, and 5-year survival with respect to non-surgical therapies

Yuan C-h et al. Ann Surg Oncol 2016);23:244–249

Allocation to treatment (resection vs. intra-arterial treatment): a Markov model

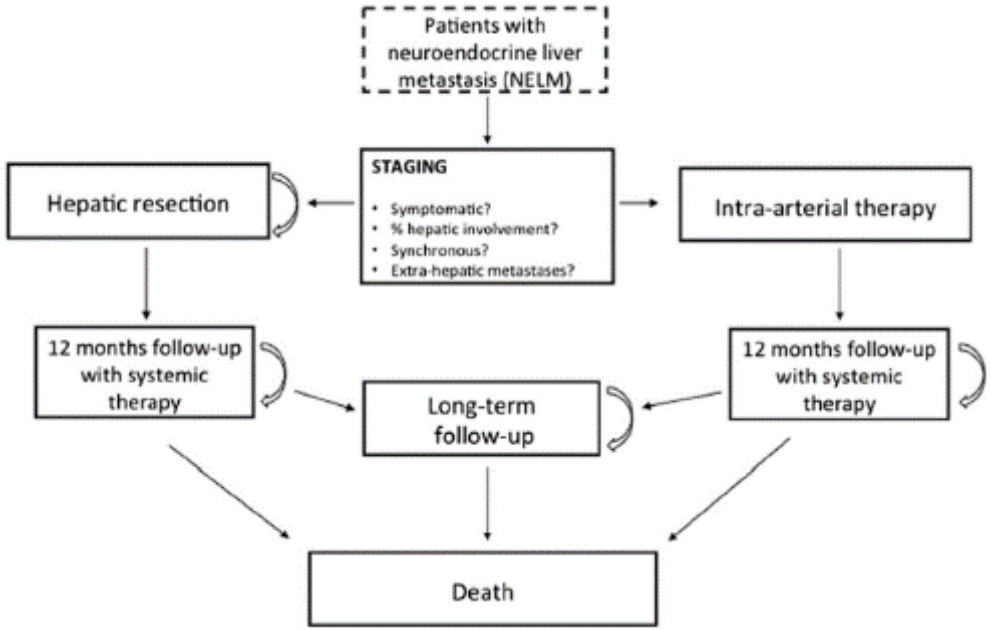


Table II. Multivariate analysis including variables with a significant impact on NHB of HR versus IAT

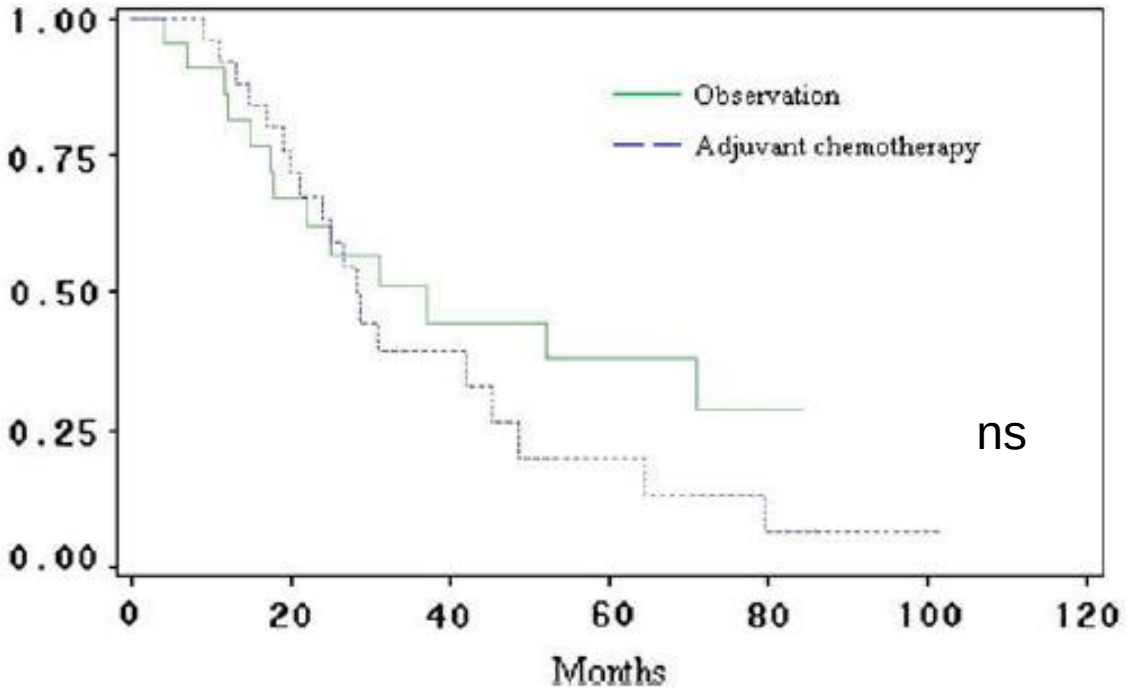
	Symptomatic			*Asymptomatic*		
Covariates	*Estimate*	*SE*	P *value*	*Estimate*	*SE*	P *value*
Constant	26.51	0.63	<.0001	20.87	1.46	<.0001
Extrahepatic disease	−19.54	0.71	<.0001	−11.19	1.80	<.0001
Synchronous disease	−5.78	0.53	<.0001	0.54	1.21	.6555
Hepatic involvement of ≥25%	−0.05	0.55	.9254	−25.62	1.24	<.0001
Male gender	1.61	0.53	.0025	−0.07	1.20	.9539
Age > 60 y	−7.59	0.56	<.0001	−1.72	1.25	.1716
QOL after resection	12.70	0.60	<.0001	8.98	1.45	<.0001
QOL after IAT	−2.25	0.62	.0003	0.39	1.36	.7740

The constant term of the final model represents the estimated survival benefit for patients without risk factors for surgery. The covariates effects for the estimated survival benefit are assumed to be additional to the constant term.
Multivariate models in the subgroups of patients symptomatic or asymptomatic showed an interaction between symptoms and other covariates.
IAT, Intraarterial therapy; *NHB*, net health benefit; *QOL*, quality of life; *SE*, standard error.

In both symptomatic and asymptomatic patients with **low disease burden**, hepatic resection should be considered as first-line therapy.
Among asymptomatic patients with **extensive liver disease**, IAT provides a comparable survival benefit and is more cost effective.

Spolverato G et al. Surgery 2015

Combination with post-surgical adjuvant treatment: a missed opportunity n.3 ?



ns

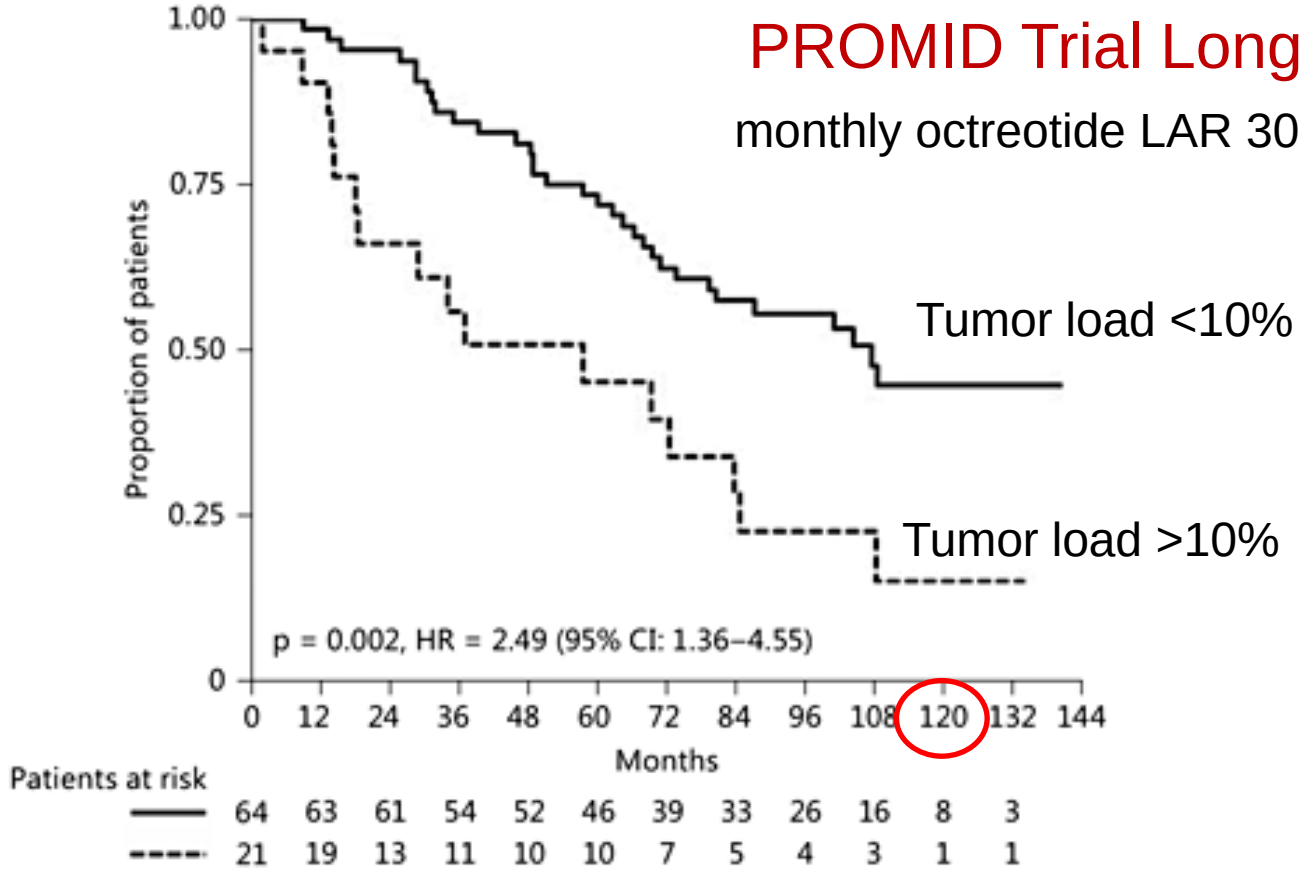
1996-2006
52 consecutive patients (median age 54 years [21--69])
R0 resection for LM from well-differentiated NET. The primary tumor was resected.
Patients were considered for adjuvant chemo if the primary tumor was pancreatic, if LM was ≥10, or if the patient was <50 years old.
29 patients received adjuvant CT and 23 were in the observation group.
Adjuvant CT included streptozotocin and 5-FU

RFS in patients receiving adjuvant CT was similar to that reported in the observation group and in historical cohorts without adjuvant CT. Thus, administration of streptozotocin+5-FU cannot be recommended in this indication.

Maire F et al. Surgery 2009; 145:69

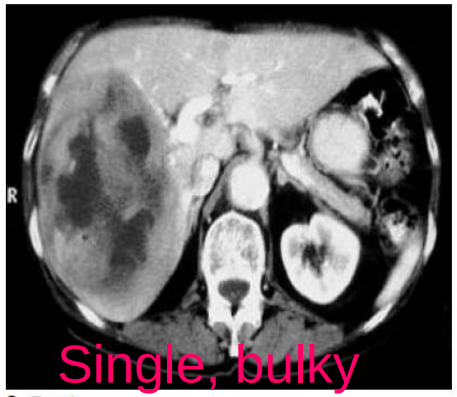
PROMID Trial Long-Term Data

monthly octreotide LAR 30 mg vs. placebo

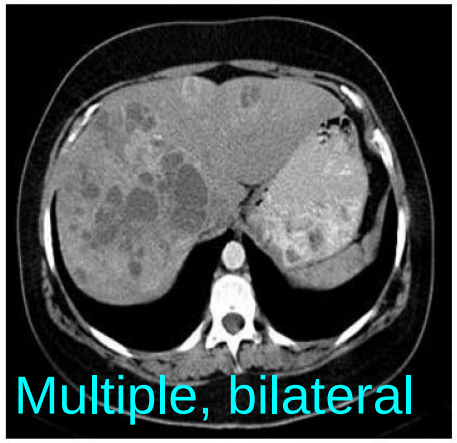


The extent of tumor burden is a predictor of shorter survival in octreotide-treated patients with metastatic NET

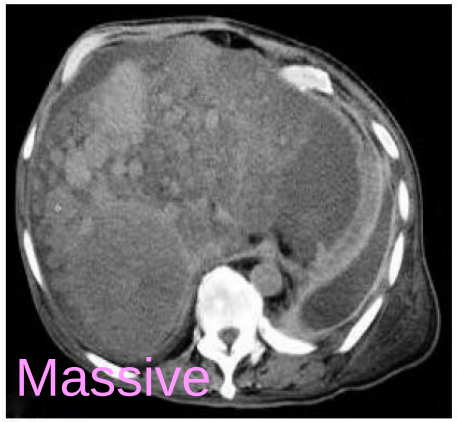
Rinke A et al. Neuroendocrinology 2016



a Type I



b Type II



c Type III

Resectable = No transplant

Transplant for cure

Transplant for palliation

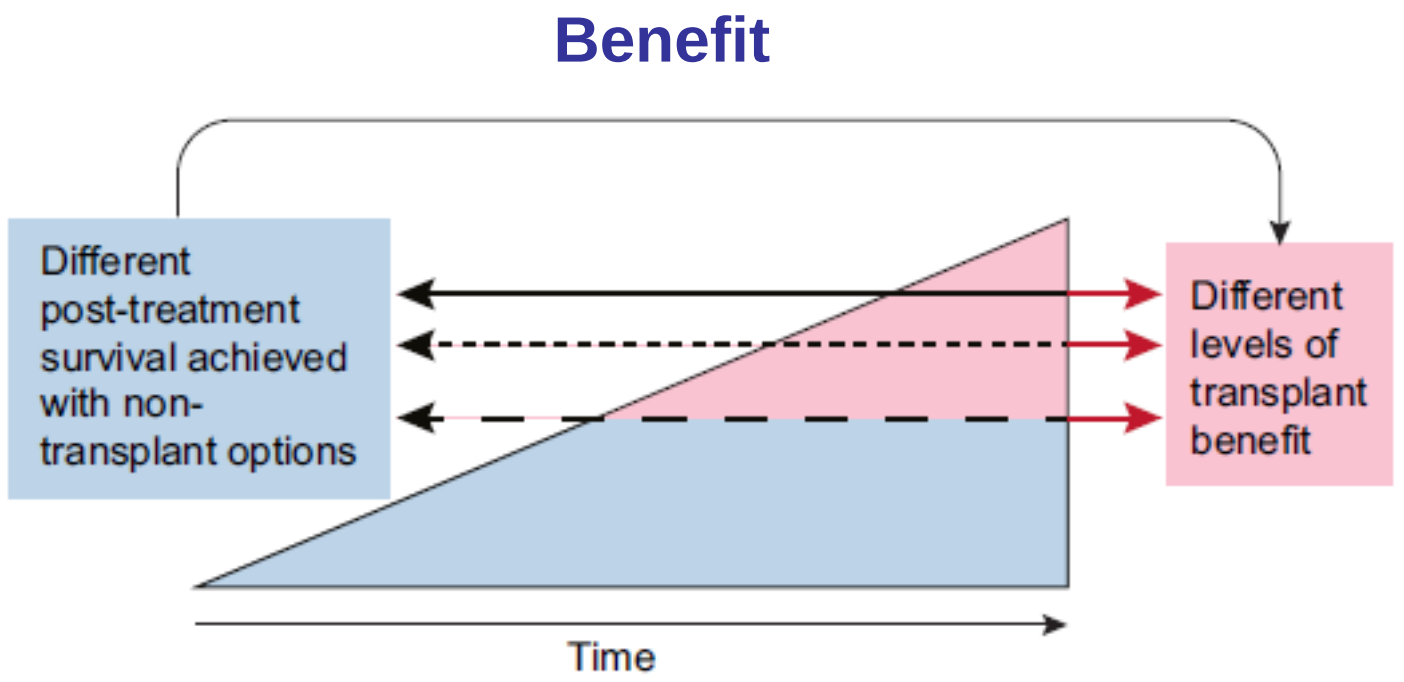
Combined Therapies

These patients are cirrhosis free, carry a very low risk of death in the midterm, and have very good chances of long-term post-transplant survival.
This is a patient subset in which the utility principle of transplantation could be maximized

Urgency

Utility

Mazzaferro V et al, Am J Transpl 2016



EASL 2018 Guidelines, J Hepatol 2018

Milan selection criteria [1-3] for patients with liver mets from NETs

1. **Confirmed histology of low-grade (G1-G2) neuroendocrine tumors**

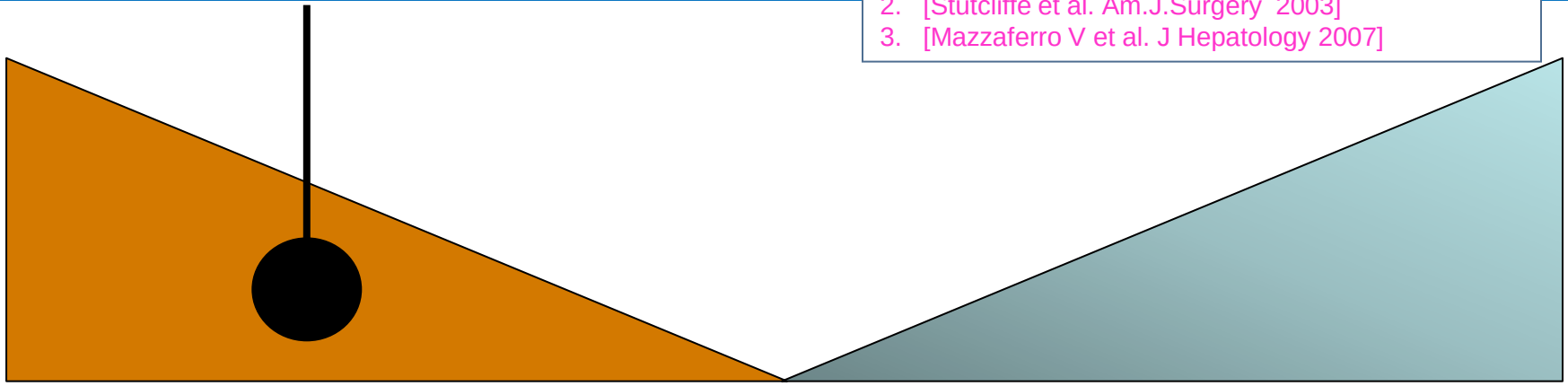
2. **Primary tumor drained by the portal system removed with all extrahepatic deposits in a separated pre-transplant curative resection**

3. **Metastatic diffusion to liver parenchyma < 50%**

4. **Response / stable disease for at least 6 months during the pre-LT period**

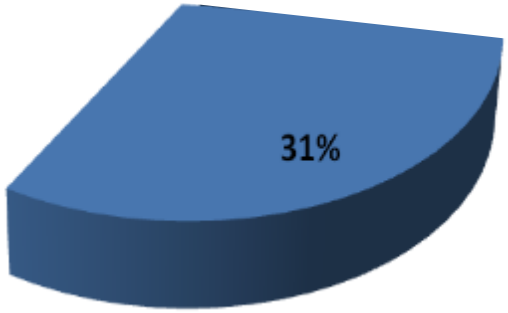
5. *Age < 65 years*

1. [Coppa JC et al, Transpl Proc 2001]
2. [Stutcliffe et al. Am.J.Surgery 2003]
3. [Mazzaferro V et al. J Hepatology 2007]



Reduce tumor burden and subtract adverse prognostic factors

Improve patients outcome



Study design

Liver mets from GEP-NET eligible to LT (n=88)

GROUP 1 Liver transplant (n=42)	GROUP 2 Non-Transplant (n=46)

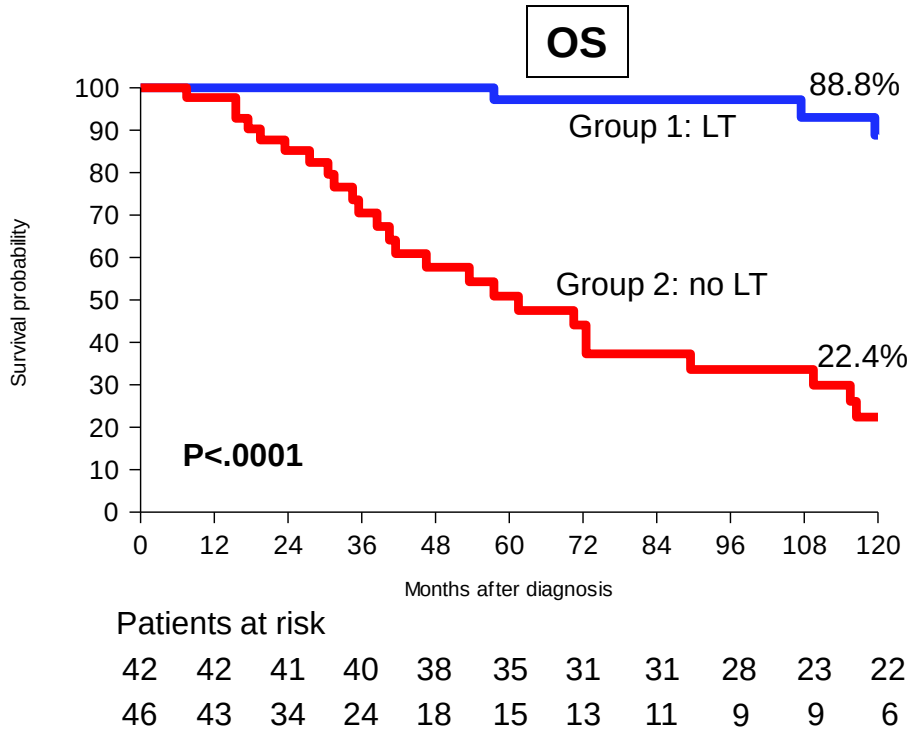
- Non compliance/refusal (n=22)
- Waiting list unavailability (n=24)

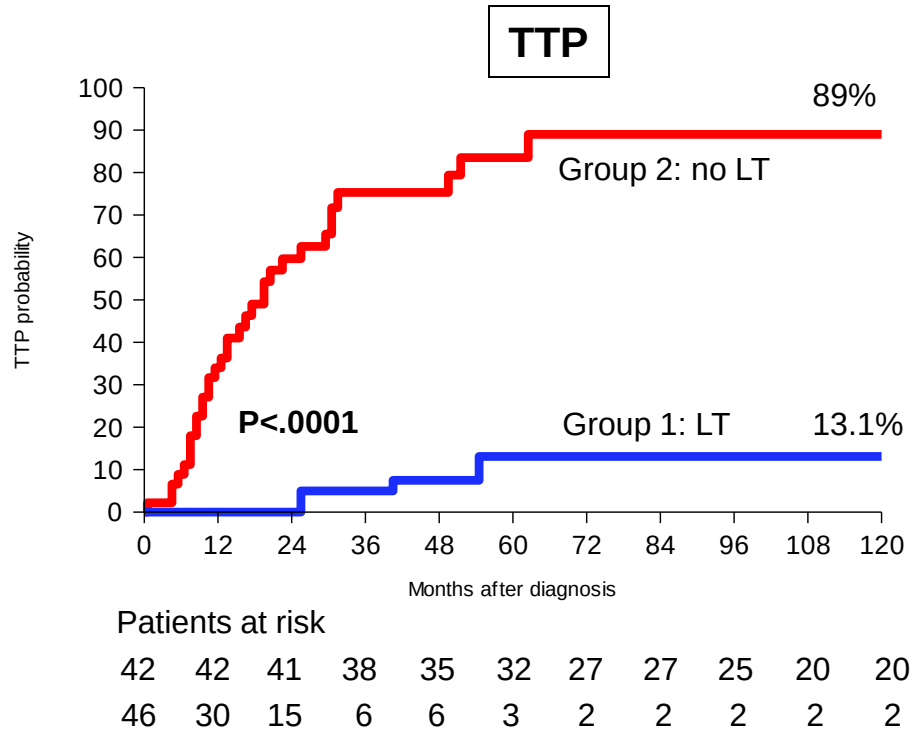
Mazzaferro V et al Am J Transpl 2016

RESULTS: Characteristics of the Study Population

	Group 1: LT (42 pts)	Group 2: no LT (46 pts)	p
Octreotide analogs at any time			**0.0003**
No	19 (45.2)	5 (10.9)	
Yes	23 (54.8)	41 (89.1)	
Syndrome			1
No	27 (65.9)	27 (64.3)	
Yes	14 (34.1)	15 (35.7)	
Serum chromogranin	163.5 (82, 382)	207 (97, 909)	0.170
Liver involvement			0.718
H1 (<25%)	17 (40.5)	21 (48.8)	
H2 (25-50%)	21 (50.0)	19 (44.2)	
H3 (>50%)	4 (9.5)	3 (7.0)	
WHO 2000 grading			0.360
well diff.	39 (97.5)	39 (90.7)	
poorly diff.	1 (2.5)	4 (9.3)	
WHO 2010 grading (pathology revision)			**0.032**
G1 (MIB1 ≤ 2%)	33 (82.5)	24 (61.5)	
G2 (MIB1 3-20%)	7 (17.5)	11 (28.2)	
G3 (MIB1 >20%)	-	4 (10.3)	
Previous Loco-regional treatments			**0.003**
No	25 (59.5)	36 (78.3)	
TACE	17 (40.5)	6 (13.0)	
PRRT	-	4 (8.7)	

Outcomes: Overall Survival and Time to Progression

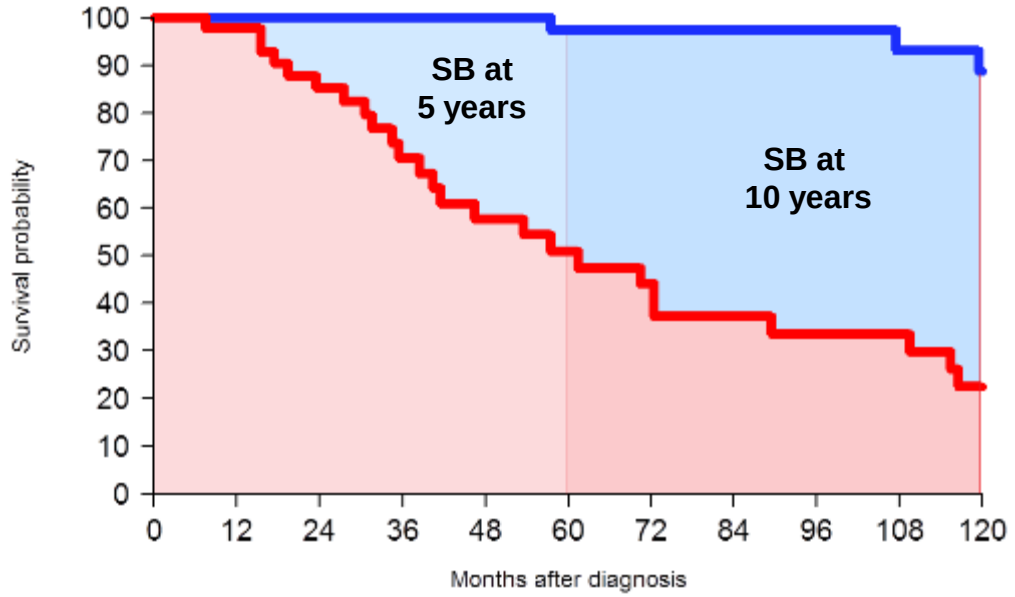




	GROUP 1: LT	GROUP 2: no LT
5-yr OS	97.2%	50.9%
10-yr OS	88.8%	22.4%
Median OS	NR	62 months
Median TTP	NR	20 months

Mazzaferro V et al Am J Transpl 2016

Survival Benefit estimation according to treatment (with/without adjustment for propensity score)

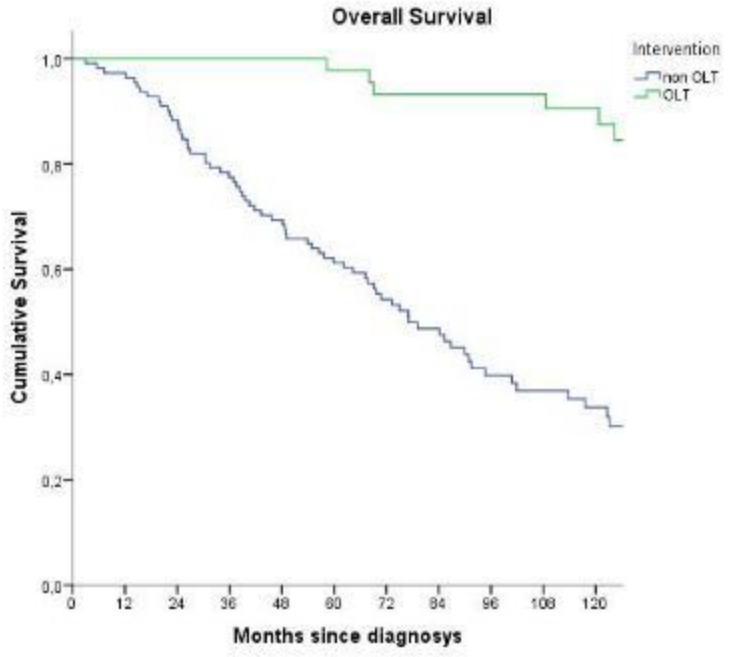


	SURVIVAL BENEFIT ESTIMATION			
	Univariable model		*Multivariable model (adjusted for propensity score)*	
	D-MST (CI)	**p**	**D-MST (CI)**	**p**
At 5 years Group1 vs Group 2	12.79 (7.95,17.63)	**<0.0001**	6.82 (1.10,12.54)	**0.019**
At 10 years Group1 vs Group 2	48.62 (35.49,61.75)	**<0.0001**	38.43 (21.41,55.45)	**<0.0001**

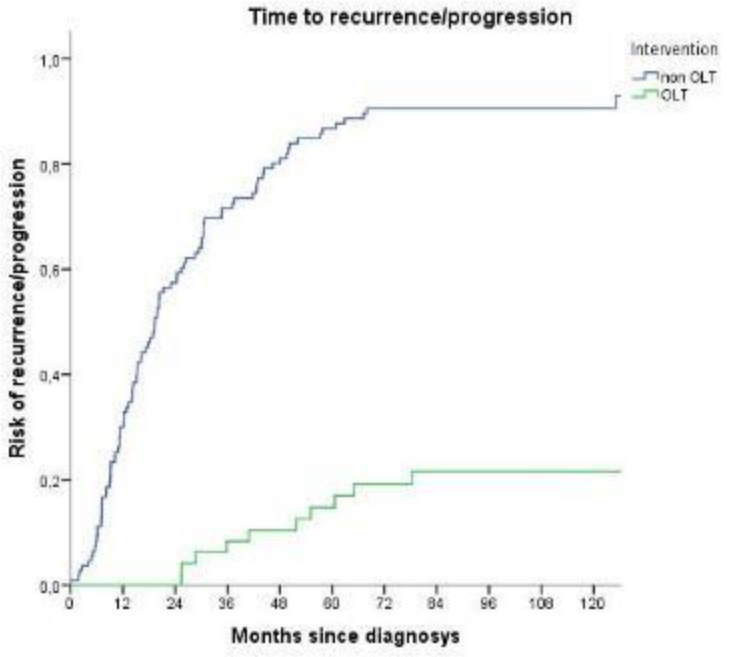
Mazzaferro V et al Am J Transpl 2016

Outcomes: Overall Survival and Time to Progression

OS



TTP



	OS 5 Yrs	OS 10 Yrs	Mean survival 5 Yrs	Mean survival 10 Yrs
OLT	97.8	90.6	59.96 mo	115.98 mo
Non OLT	61.2	32.0	49.16 mo	76.39 mo
Survival Benefit			10.8 mo	39.59 mo

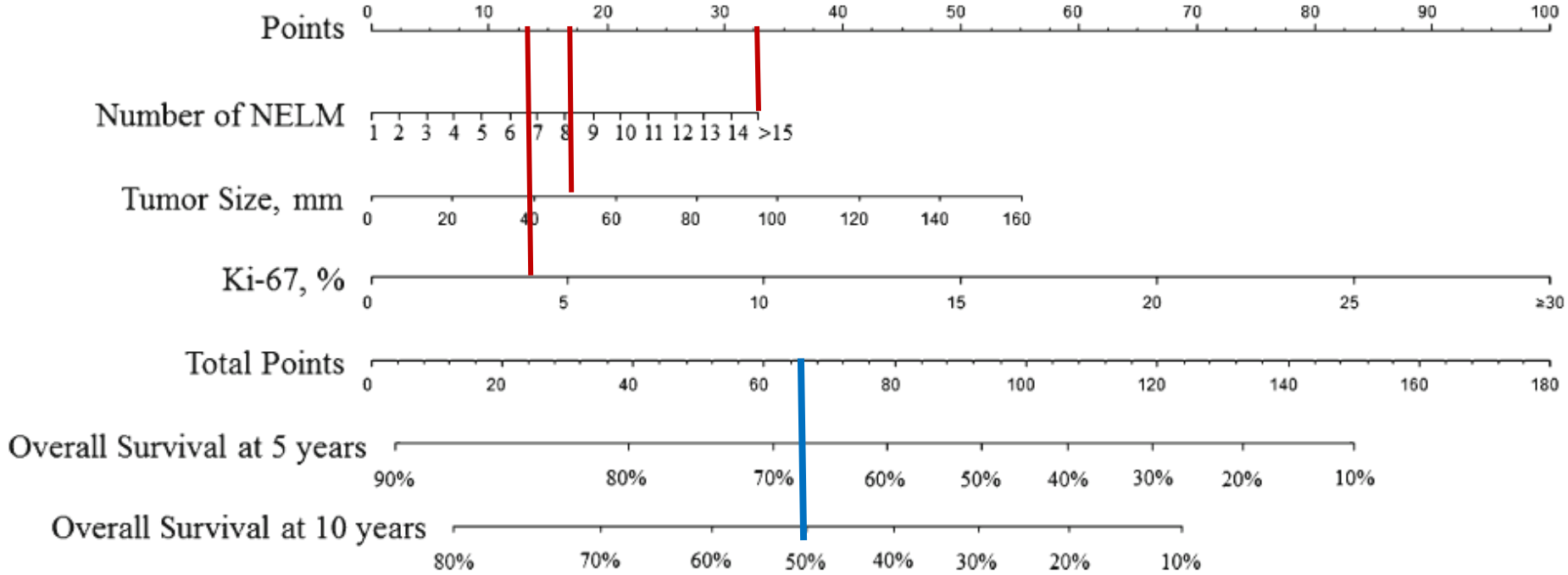
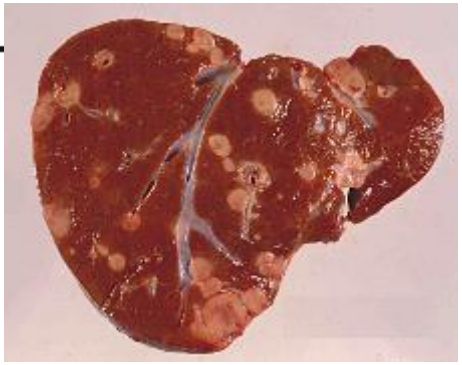


Fig. 1 The novel nomogram for predicting patient prognosis



Ruzzenente A et al J Gastroint Surg 2017

238 curative liver resections for metastatic NET (1990-2014)

Three different risk classes were identified according to predicted survival:
Low risk (>80 % predicted 5-year OS),
Medium risk (40–80 % predicted 5-year OS),
High risk (<40 % predicted 5-year OS) risk classes.
10-year OS was 97.0, 55.9, and 20.0 % in the low, medium, and high-risk classes, respectively ($p < 0.001$)

Conclusions

There is a lot of space for reconsidering systemic therapies in combination with intra-arterial and surgical treatment. Opportunities should not be missed and trial result should be interpreted in a proactive way

Surgical resection, when feasible offer the best long-term outcome, although recurrence rate is high and statistical cure may occur only after 5 yrs free of recurrences

Intra-arterial therapies are safe and effective. TARE in selected liver-only disease may offer competitive outcome with respect to conventional medical therapies

Liver transplantation offer the highest benefit in selected candidates (Milan criteria). The transplant benefit is maximized at long-time intervals (10 yrs)

In absence of OS studies (unfeasible due to the bias of treatment crossovers) QoL becomes of significant interest.

Patient-reported tolerance in treatments approved in neuroendocrine tumors

54 patients received 258 treatments

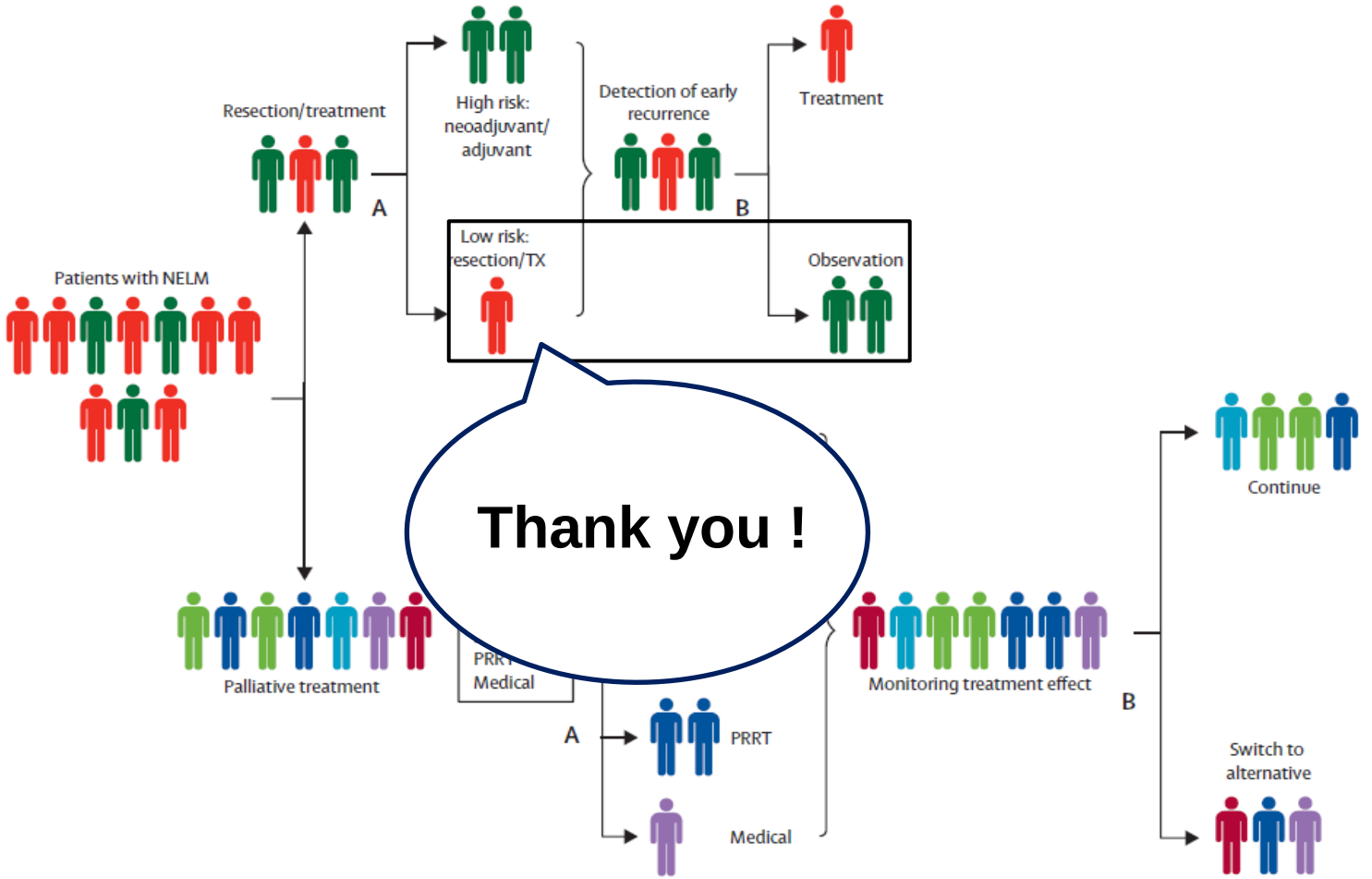
Table 3 Poor perceived tolerance of treatments in comparison with somatostatin analogs as reference.

	n	Toxicity Odds ratio [95%CI]	*P*
Somatostatin analogs	44	1	
Primary tumor surgery	46	2.23 [0.94–5.29]	0.055
Metastases surgery	18	2.85 [1.11–7.32]	0.027
Radiofrequency ablation	6	2.44 [0.63–9.47]	0.217
TAE/TACE	24	3.67 [1.58–8.53]	0.001
Interferon	8	< 1[a]	0.267
Everolimus	26	3.39 [1.44–7.93]	0.003
Sunitinib	10	5.87 [2.62–13.13]	< 0.001
Oral chemotherapy	21	1.75 [0.60–5.08]	0.306
Intravenous chemotherapy	30	4.89 [2.23–10.72]	< 0.001
Peptide receptor radionuclide therapy	9	< 1[a]	0.239

CI: confident interval; TAE: transarterial embolization; TACE: transarterial chemoembolization.
[a] Odd ratio was not calculated because no patient reported poor perceived tolerance as defined in the Methods section (score 4 or 5) with interferon as well as with peptide receptor radionuclide.

Compared to SSA, odd ratios of this **poor perceived tolerance were between 1 and 3 for surgeries** (both, of primary tumor or metastases), RFA and oral chemotherapy; **between 3 and 4 for TAE/TACE and everolimus**; and **more than 4 for sunitinib and intravenous chemotherapy**

Plante A et al. Clin Res Hepatol Gastroenterol 2018

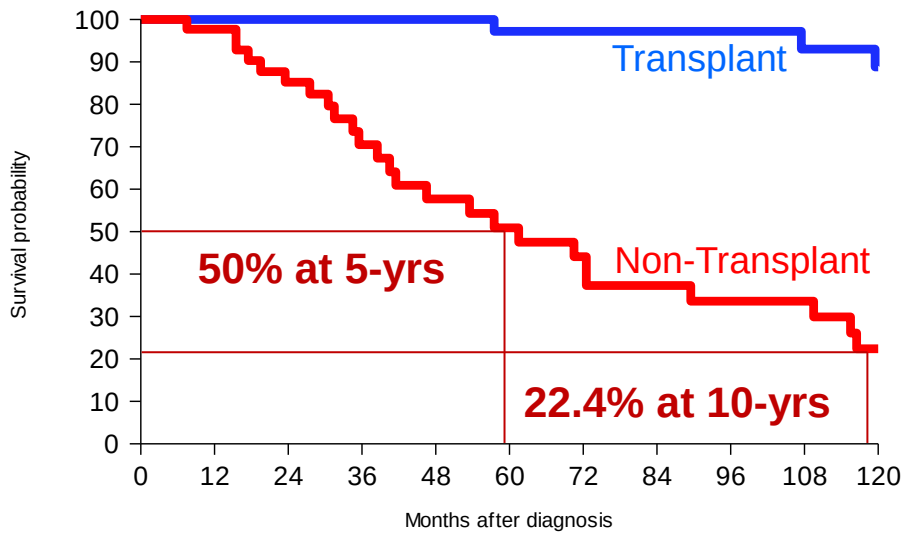


igure 5: Potential strategies for neuroendocrine liver metastases management in the era of personalised medicine

vincenzo.mazzaferro@istitutotumori.mi.it

… who should be transplanted ?

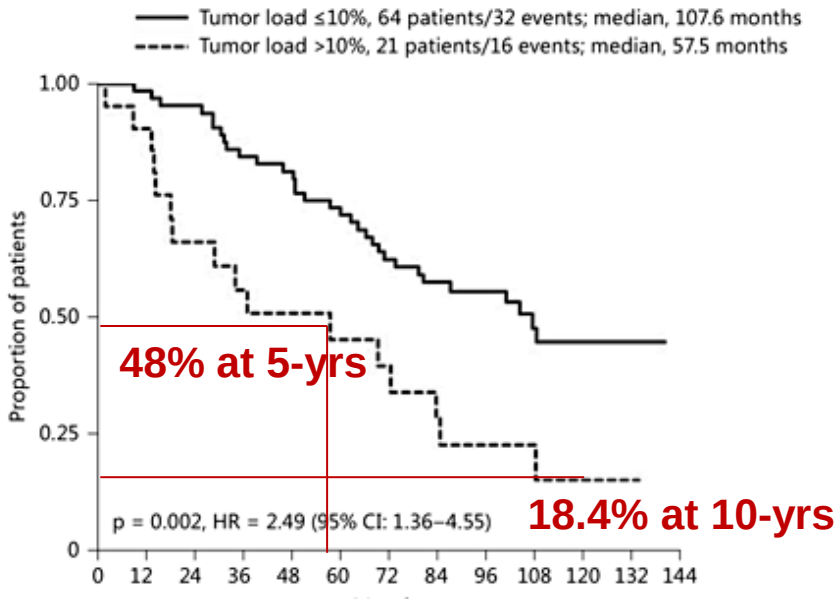
Milan trial
(midgut: 57%, pNET: 36%, 7% other;
G1: 78%; G2: 18%)
(Am J Transpl 2016)



<50% of liver involved: 90%

Median survival: 62 mo

PROMID trial long-term results
(G1 midgut 100%)
Rinke A et al. Neuroend. 2016



>10% of liver involved: 32%

Median survival: 57.5 mo

Features associated with the PROMID study cohort – enriched of higher tumor load and moderately expanded inclusion criteria – **showed a long-term outcome similar to the Milan non-transplant series**