Liver directed therapies for liver metastases of NET

ESMO 16th World Congress on Gastrointestinal Cancer
Barcelona June 26, 2014

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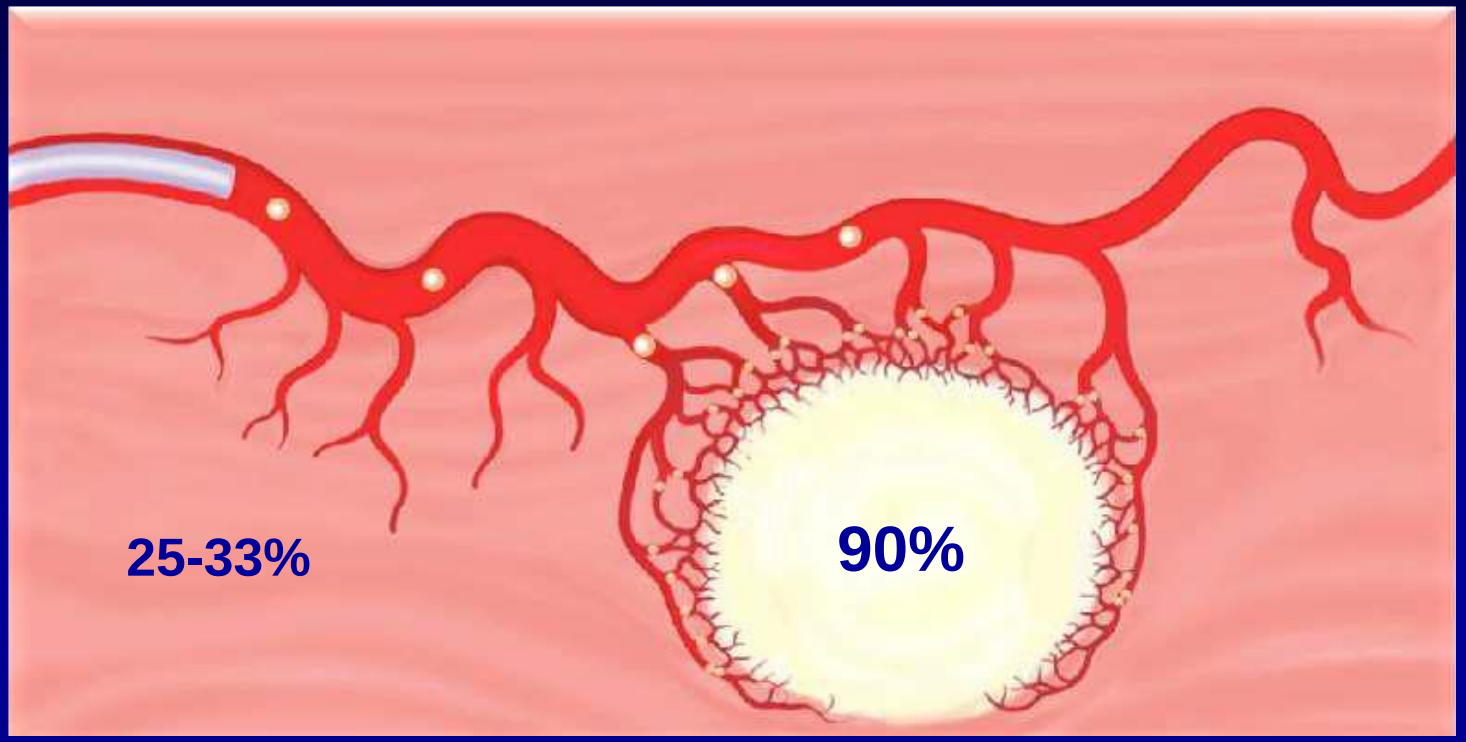
DISCLOSURES

- Advisory Board
  - Ipsen
  - Novartis
- Research Grant
  - Pfizer
  - Keocyt

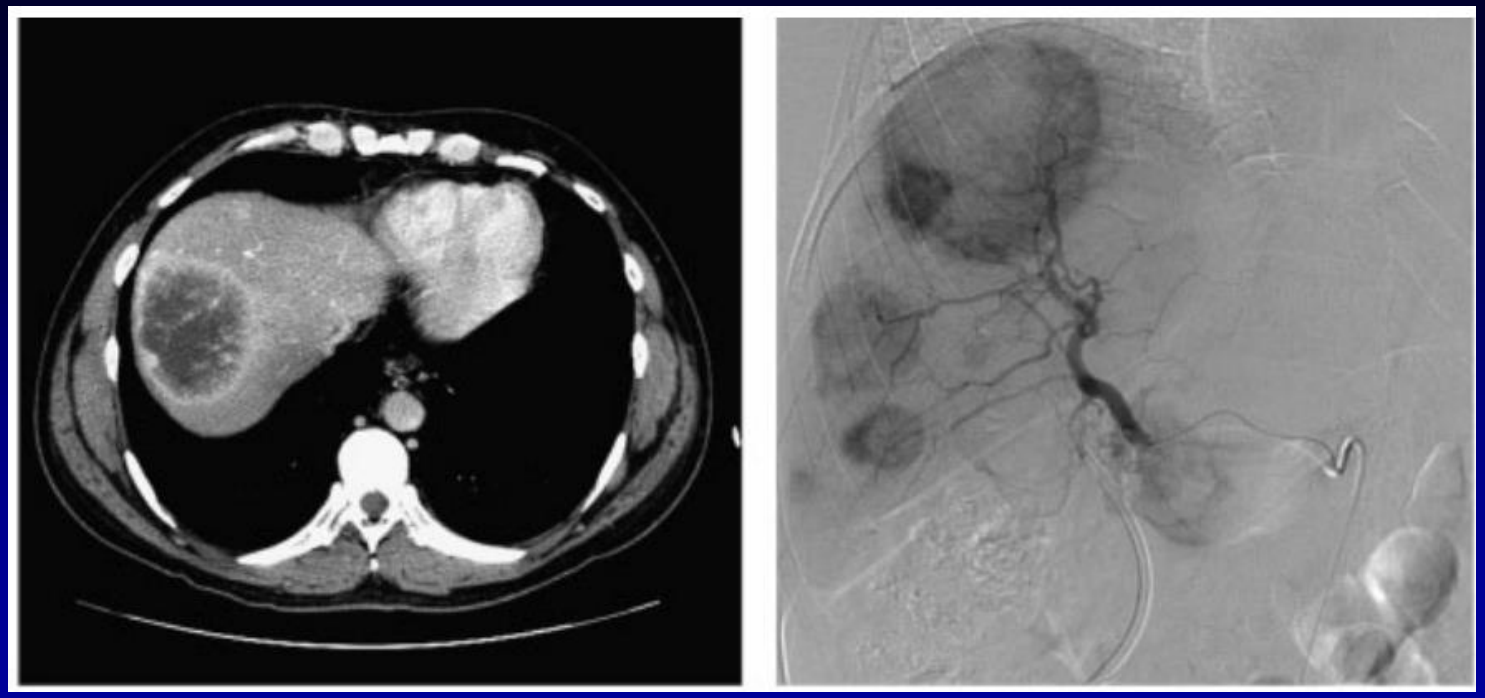
Rationale

- Liver metastases of GEP-ET
  - frequent (25-90 %)
  - often isolated
  - obvious prognostic implications
- Surgery seldom feasible
- Systemic chemotherapy « disappointing »
- Liver metastases are hypervascular
  - blood supply from the hepatic artery

Rationale



Intra arterial injection followed by embolisation

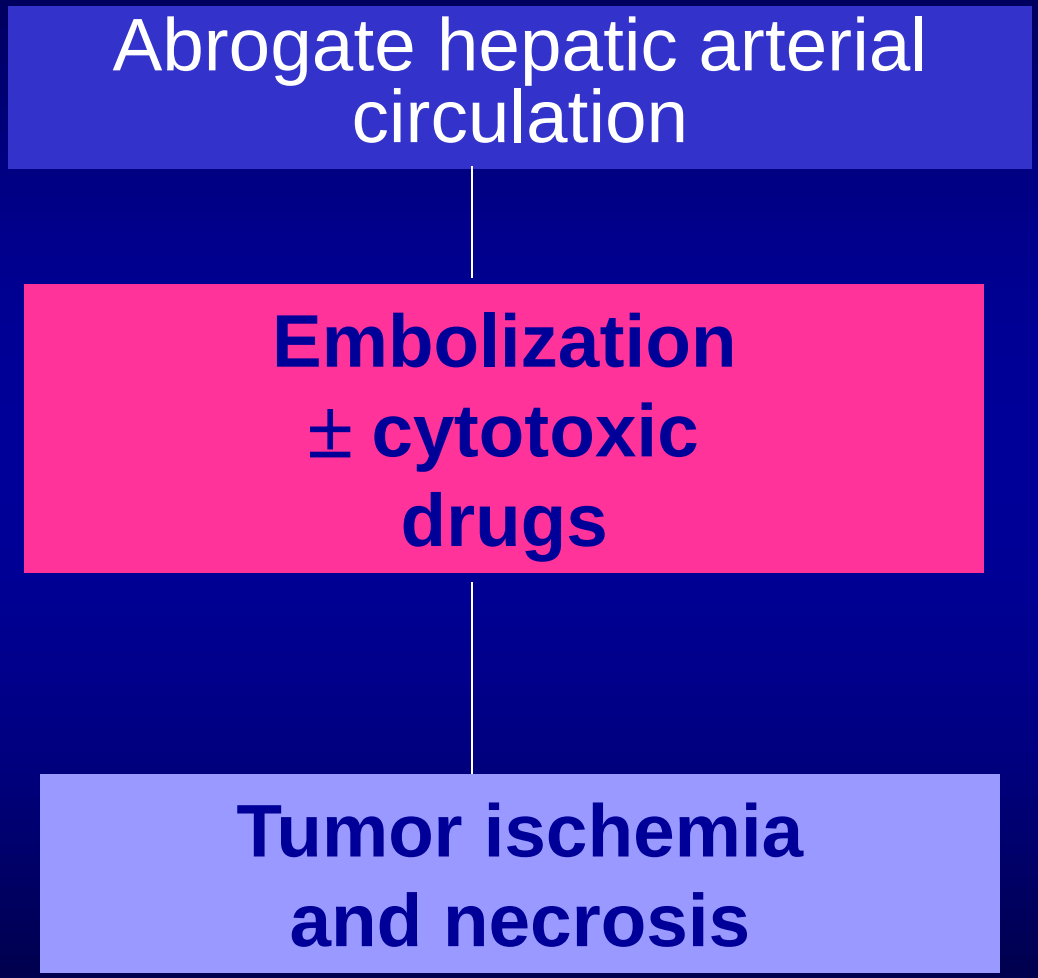


Vectors

ultra fluid Ethiodized Oil

DC Beads

Vascular occlusion : LM of GEP-ET



Chemoembolization : methods (1)

- Arteriography
  - Distribution of the hepatic arteries, portal blood flow, number and location of LM
- Emulsion of the cytotoxic drug
  - Adriamycin 50 mg/m^2 or Streptozotocin 1.5 g/ m^2 in 10 ml iodized oil, injected in the branches of the HA supplying the tumors
- Embolization
  - Gelatin sponge 2-3 mm particles or microspheres, until marked decrease in arterial blood flow

Chemoembolization : methods (2)

- Courses every ~ 3 months

  - slow natural history, intervals adapted to tumoral response and tolerability

- IV hydration ; antibiotics (H-3 for H72) ; analgesics & antiemetics
- Octreotide in pts with the carcinoid syndrome
- General anaesthesia if streptozotocin
- Contra-indications

  - total portal vein obstruction, hepatic insufficiency, biliary anastomosis

Results : Symptoms & Hormones

	Drug	N	Clinical response - %	Biological Response* - %
Ruszniewski Cancer 1993	ADR (50 mg)	18:Carc 5:ICC	73 (8/11)	57
Therasse Radiology 1993	ADR (40-80 mg)	23 : Carc	100 (10/10)	91
Tomassetti 1994	ADR (40-80)	15:Carc 12:ICC	90	---
Diaco **Am J Surg** 1995	ADR-MMC-CDDP Octreotide 5-FU IA	10:Carc	100	---
Ruszniewski Eur J Gastroenterol Hepatol 2000	STZ 1.5 g/m^2	8:Carc 7: ICC	67 (6/9)	46 (6/13)
Kress Digestion 2003	ADR (20-40 mg)	10: Carc 16: Other	0/9	66 (6/9)
Roche Hepatogastroenterol 2004	ADR 25-120 mg)	15: Carc 49: Other	93 (42/45) DR : 16 mo	51 (19/37)
Ruszniewski 2007	ADR 50 mg : n=23 STZ : 1.5: n=44	27: Carc 40 : Other	91 (21/23)	66 (25/38)

Carc: carcinoid tumours; ICC: islet-cell carcinoma. * >50% decrease in tumor marker

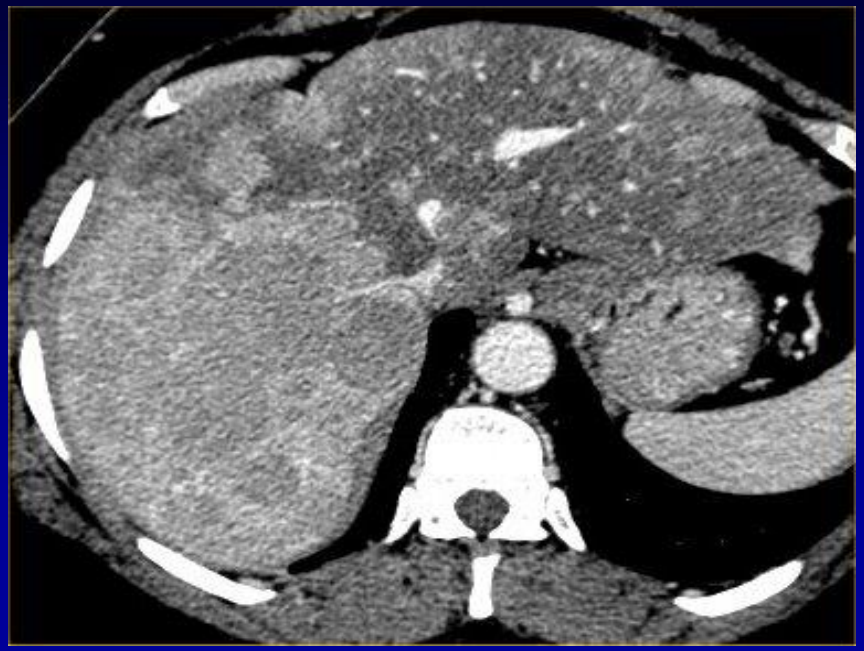
Transarterial Chemoembolization Results on Tumor Load

		N	OR (%)	Duration (mo)
Dominguez	2000	15	53	11
Gupta*	2003	81	67	17
Loewe	2003	23	73	-
Roche	2004	64	74	18
Strosberg	2006	23	48	-
Marrache	2007	67	37	14
Granberg*	2007	15	40	6
Ho*	2007	46	30	-
Dong	2010	123	62	-
Whitney	2011	28	100 at 3 mo.	-

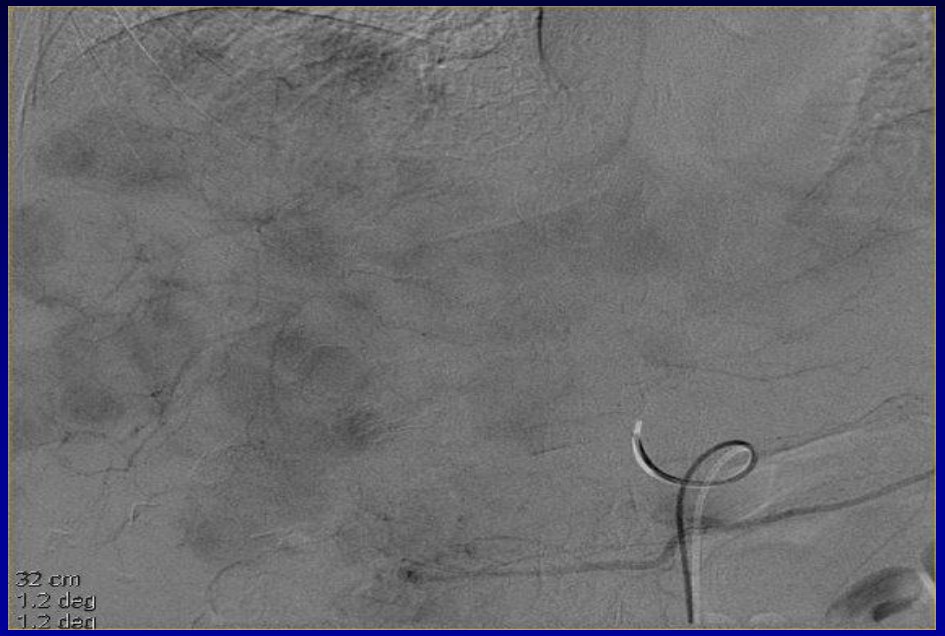
* TACE or TAE

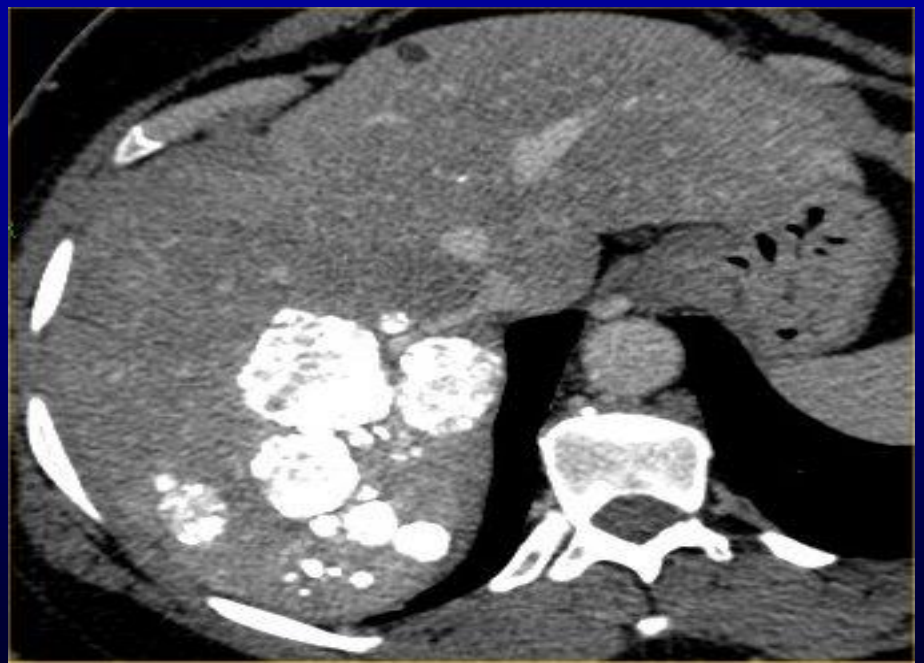
All but 2 studies included small bowel and pancreatic primaries

CT arterial phase



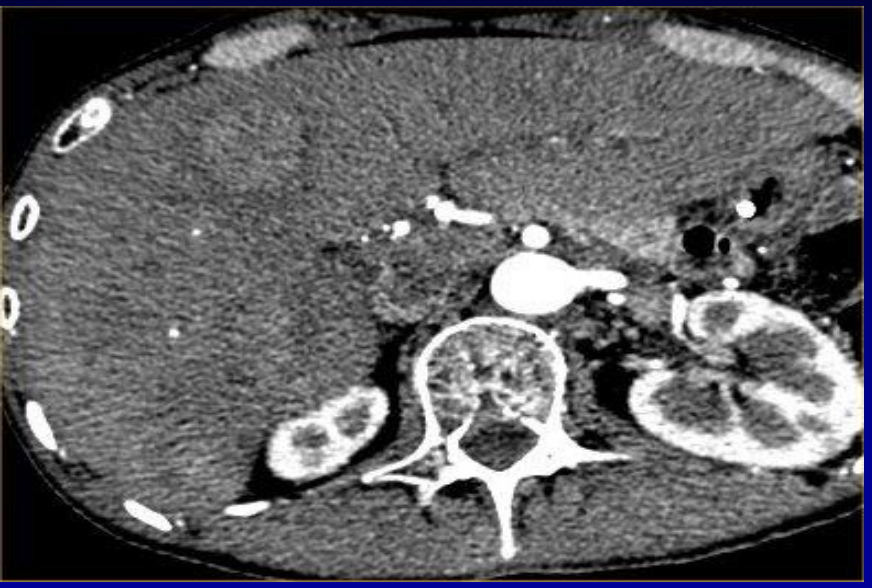
Tumor blushes during arteriography



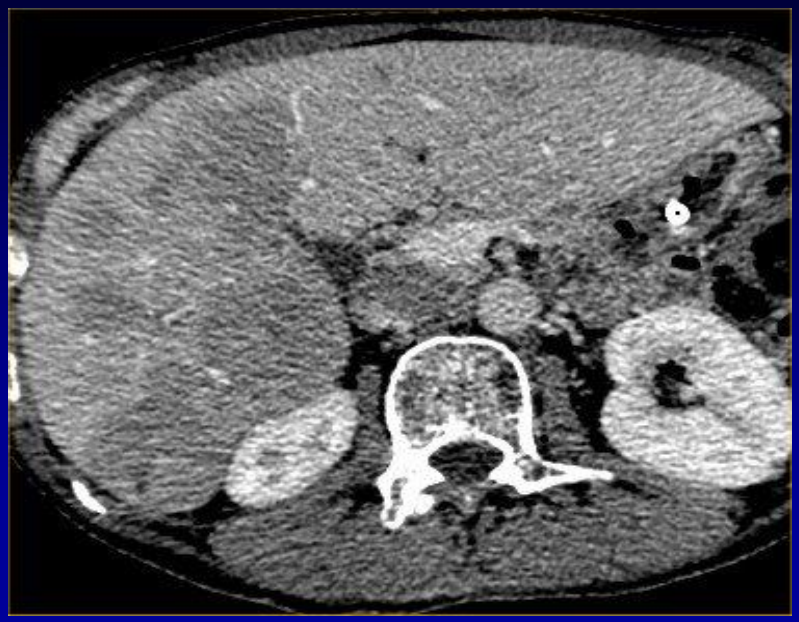


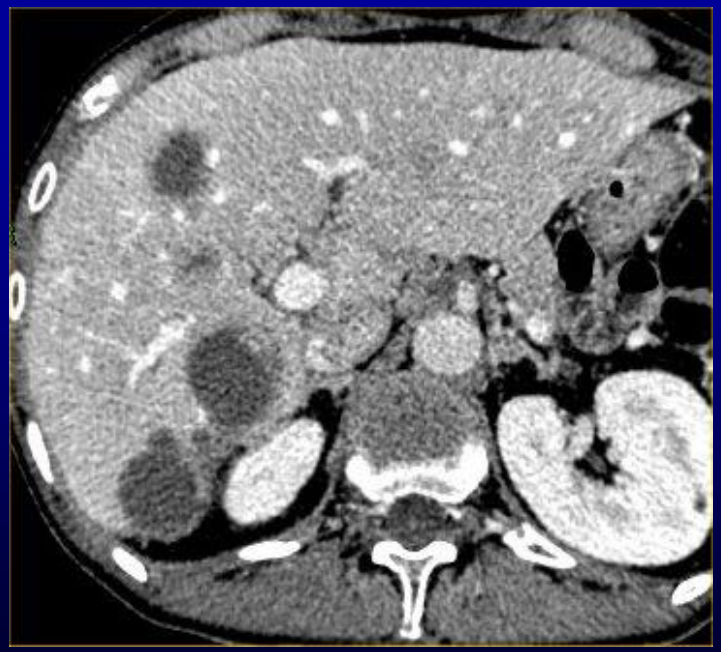
3 months after CE
with STZ and ethiodized oil

CT arterial phase



CT portal phase





3 months after
E alone with embospheres

Predictive factors for tumour response - 1

Liver involvement	Response rate, %	P multivariate
< 30%	53	0.016
30-60%	23	
> 60%	27	
primary, differentiation, size of metastases, previous treatments		NS

Roche, *Hepatogastroenterology*, 2003

CT vascular pattern	Tumor shrinkage
Hypervascular	60 %
Isovascular	27 %

Perry, Surgery, 1994

Predictive factors for tumour response - 2

Tumor response predictors (multivariate)			
	OR	CI 95 %	p
Arterial phase enhancement	8.11	1.06-42	0.044
Body mass index	1.3	1.04–1.63	0.022
Functioning tumour	7.31	1.26-42.5	0.027
Streptozotocin vs ADR	21.3	1.48-306	0.025

ns : primary, differentiation, size of metastases, previous chemotherapy, % of liver replacement, MIB-1?

Ruszniewski, Br J Cancer, 2007

When do patients respond ?

AFTER 1 CYCLE	25%
AFTER 2 CYCLE	56%
AFTER 3 CYCLES…	19%

Roche, Hepatogastroenterology, 2003

Predictive factors for morbidity

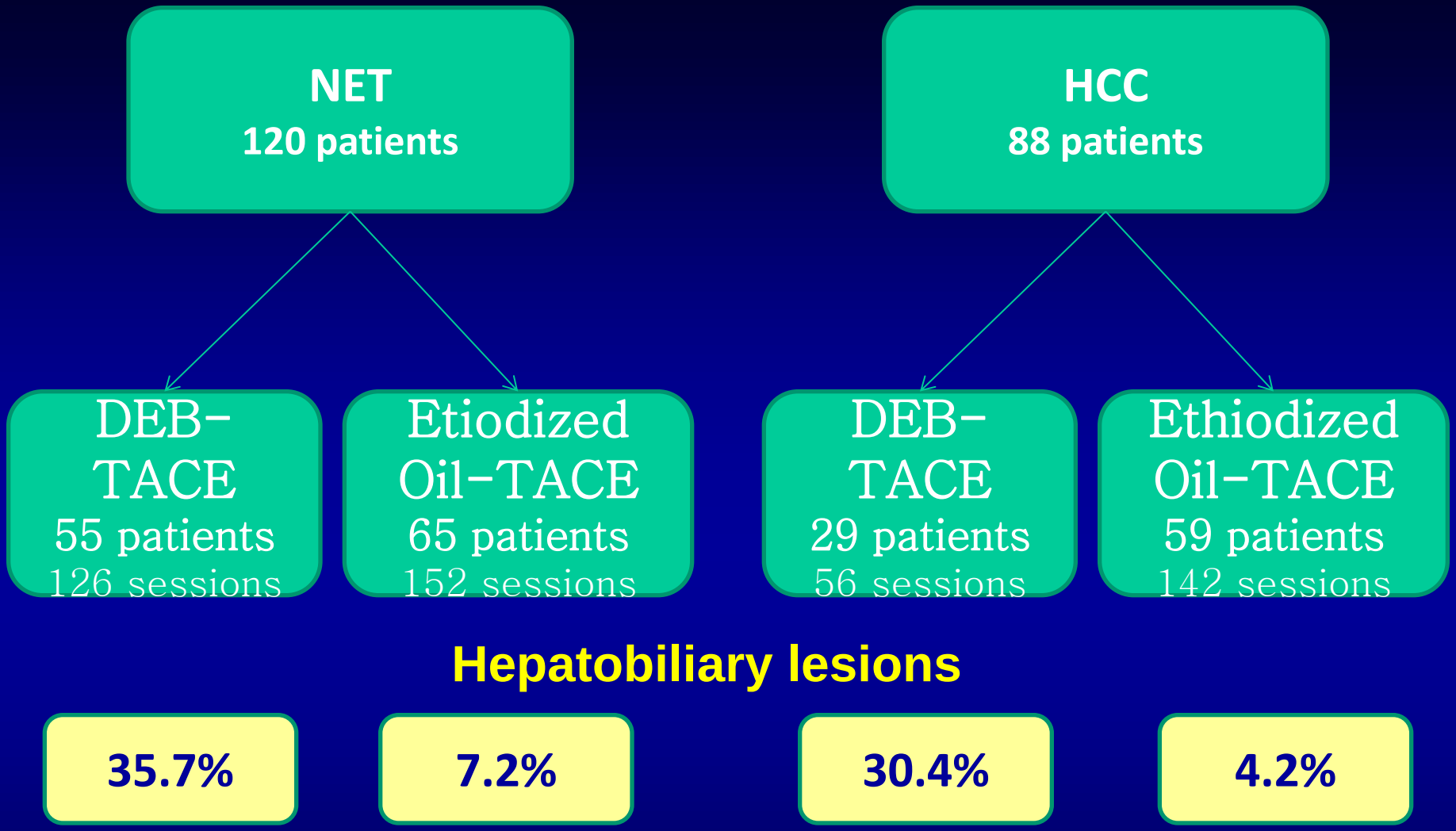
- Liver involvement > 70% : 0.029
- CE vs CIAH alone : 0.03
- Treatment in both lobes : 0.001
- Carinoid heart disease: NS

Roche, Hepatogastroenterology, 2003 / Ruszniewski 2007

Side effects

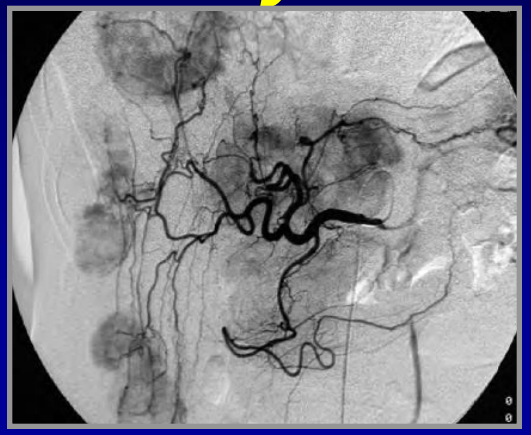
- Minor side-effects : post-embolization syndrome
  - abdominal pain 50 % - 60 %
  - fever up to 38°5 30 % - 60 %
  - nausea, vomiting 50 % - 70 %
  - raised transaminases always
  - vagal reaction

- Major complications (rare)
  - acute renal failure
  - liver failure
  - liver abscess
  - bleeding peptic ulcer
  - cholecystitis
  - carcinoid crisis



Guiu J Hepatol, 2012

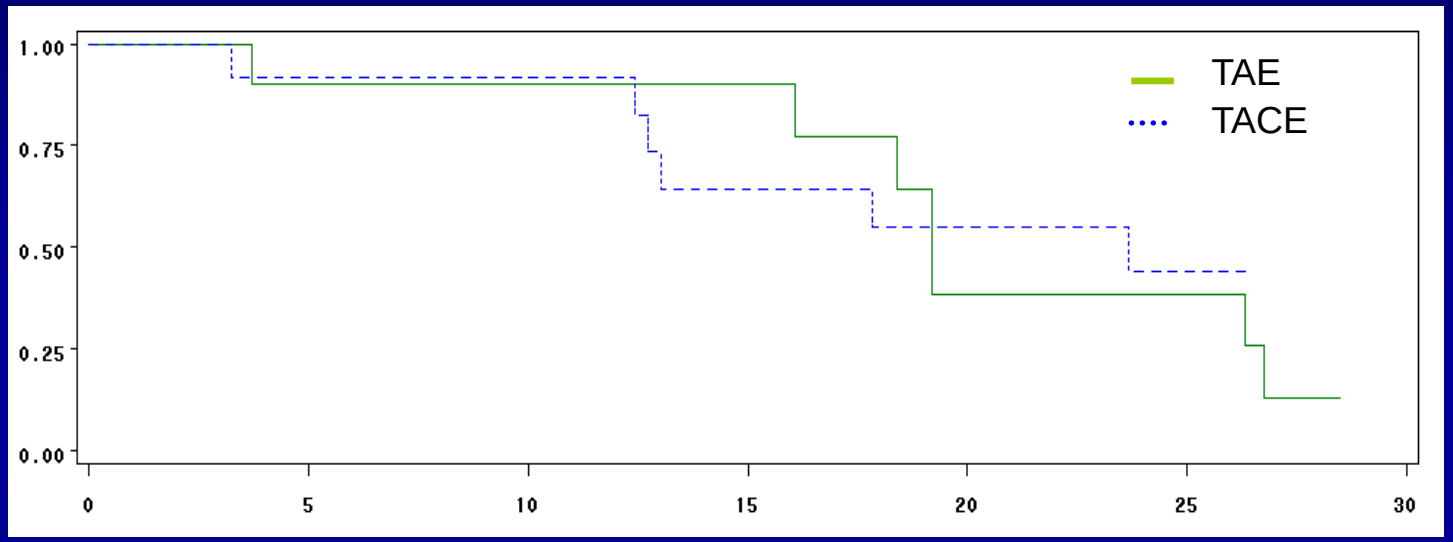
Hepatic arterial embolization vs chemoembolization
A prospective randomized study



- 2 procedures at 3-month interval
- Premedication with intravenous hydration, antibiotics and octreotide
- Embolization with gelatin sponge particles *(Gelitaspon, Gelita Medical, Amsterdam, The Netherlands)*
- Doxorubicin 50 mg/m^2 dissolved in normal saline and combined with 10-15 mL of iodized oil *(Ethiodized Oil Ultra Fluid; Guerbet, Aulnay-sous-Bois, France)* in the TACE arm

Maire et al Neuroendocrinology 2012

Progression free survival rates



	TACE	TAE	P
median PFS	19.2 [16.1-26.8]	23.6 [12.7-NA]	
2-year PFS rates	38%	44%	0.90

Maire et al Neuroendocrinology 2012

Treatment side effects

	TACE n = 12	TAE N = 14	P
Treatment-related death	0	0	-
Adverse events			
post-embolization syndrome	10	10	
carcinoid crisis	2	0	
acute liver failure	1	2	
neutropenia	2	0	
Total adverse events			0.30
any grade	11	12	
grade 3	3 *	2 **	

* Neutropenia n = 2, acute liver failure n =1

** Acute liver failure n= 2

Maire et al Neuroendocrinology 2012

Selective internal radiation therapy (SIRT) with ^{90}Y microspheres

		N	OR(%)	Duration (mo)
King	2008	34	50	-
Kennedy	2008	148	63	-
Rhee	2008	42	51	-
Paxena	2010	48	54	-
Whitney	2011	15	100 at 3 mo	-
Prapottka	2011	42	225	-

Ethiodized Oil or DC beads?

---------- NO RANDOMIZED CONTROLLED TRIAL ----------

DEBDOX-TACE

→ **82% tumor control** PR: 43% SD: 39%
TTP: 14 months

Gaur CVIR 2011

→ **95% tumor control** PR: 80% SD: 15%
TTP: 15 months

De Baere JVIR 2008

Ethiodized Oil-TACE

→ **89% tumor control**
TTP: 18 months

Roche Hepatogastro 2004

→ **91.7% tumor control**
TTP: 19 months

Gupta Cancer 2005

Conclusions

- *Selective TAE or TACE may be used to treat LM when surgery not faisible regardless of the origin of the primary tumor*
- *Control symptoms, decrease in biochemical markers, control tumor growth (50 %)*
- *TACE ~ TAE*
- *To be performed in specialized centers (side effects)*
- *Beware of contra-indications*
- *SIRT still investigational*

Pavel M et al, Neuroendocrinology 2012;95:157-76