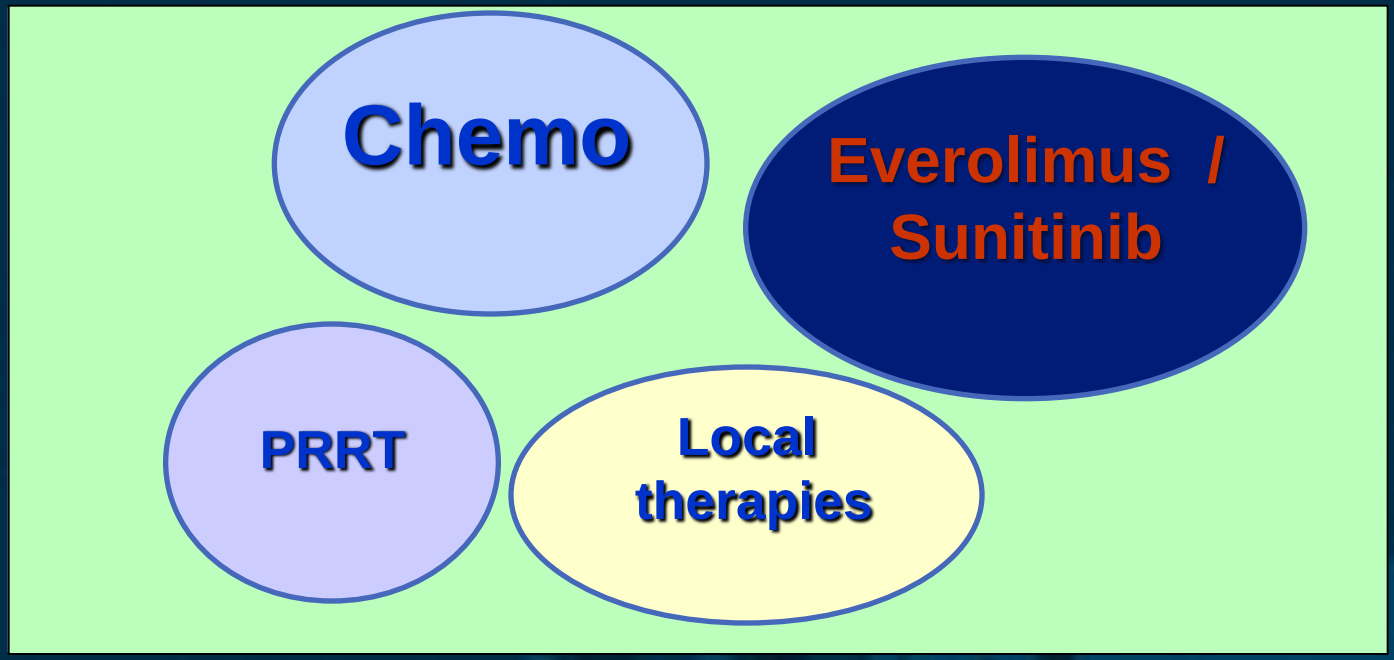
Terapie locoregionali epatiche

Guido Bonomo

Divisione di Radiologia Interventistica

GEP NET: WHO 2010



CHEMOTHERAPY

Bosman F, Carneiro F, Hruban R, Theise N. WHO Classification of Tumours of the Digestive System. Lyon, France: IARC Press; 2010.

- La maggior parte dei NET ha una progressione lenta e metastatica

- Sopravvivenza a 5 anni nel metastatico **40 %**

0163-769X/04/$20.00/0
Printed in U.S.A.

Endocrine Reviews 25(3):458–511
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doi: 10.1210/er.2003-0014

The Diagnosis and Medical Management of Advanced Neuroendocrine Tumors

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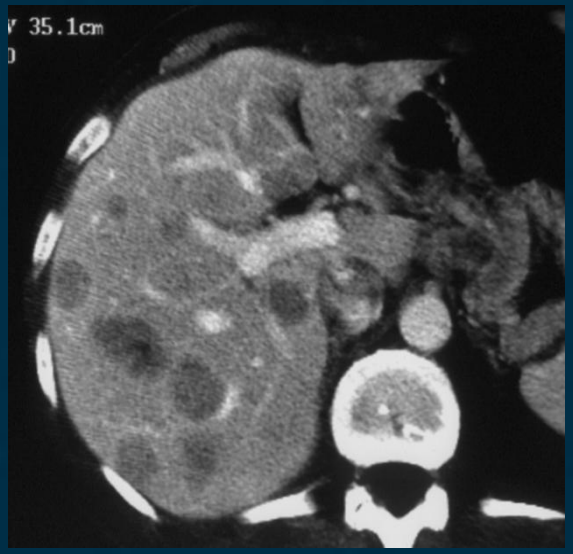
Razionale per trattamenti locoregionali

- Palliazione dei sintomi (tumori funzionanti)
- Riduzione della massa tumorale (**debulking**)
- Progressione monofocale

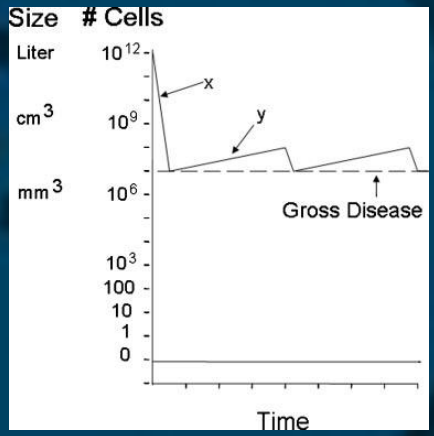
Background

- La prognosi dipende dal coinvolgimento epatico e i sintomi sono spesso correlati con le metastasi epatiche



RAZIONALE PER LA CITORIDUZIONE

Le procedure di citoriduzione sono efficaci per la lenta crescita dei tumori Neuroendocrini con lunghi periodi di benessere, e potenziale ripetibilità



Cytoreduction is depicted by line x.
A long period may pass before regrowth of the tumor (y) to significant levels.

Maithel and Fong J. Surg. Oncol. 2009;100:635–638

NET

HIA CT

RF

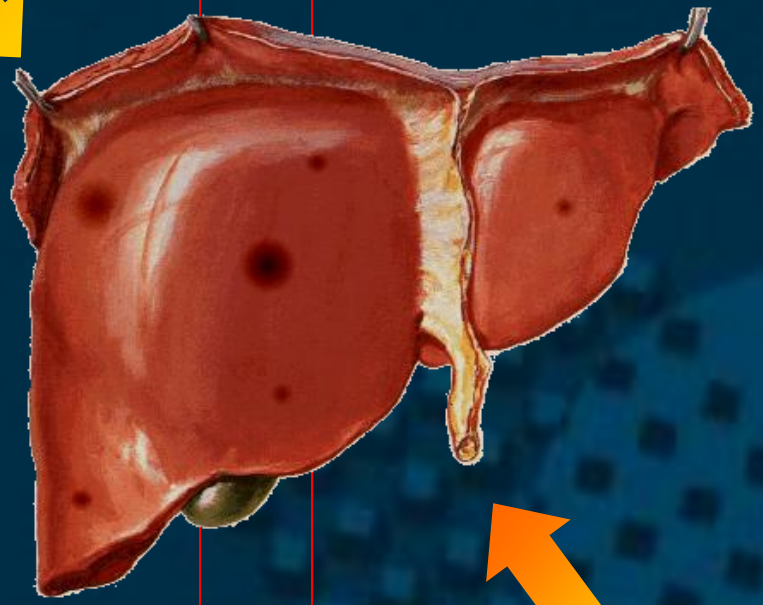
TACE /TAE

$Y^{90}RE$

OLT

Resection

IMRT



PRRT

Somatostatin Analogue

IFN

systemic CT

Anti-angiogenetics (Thalidomid)

Targeted therapy

Hyperthermia

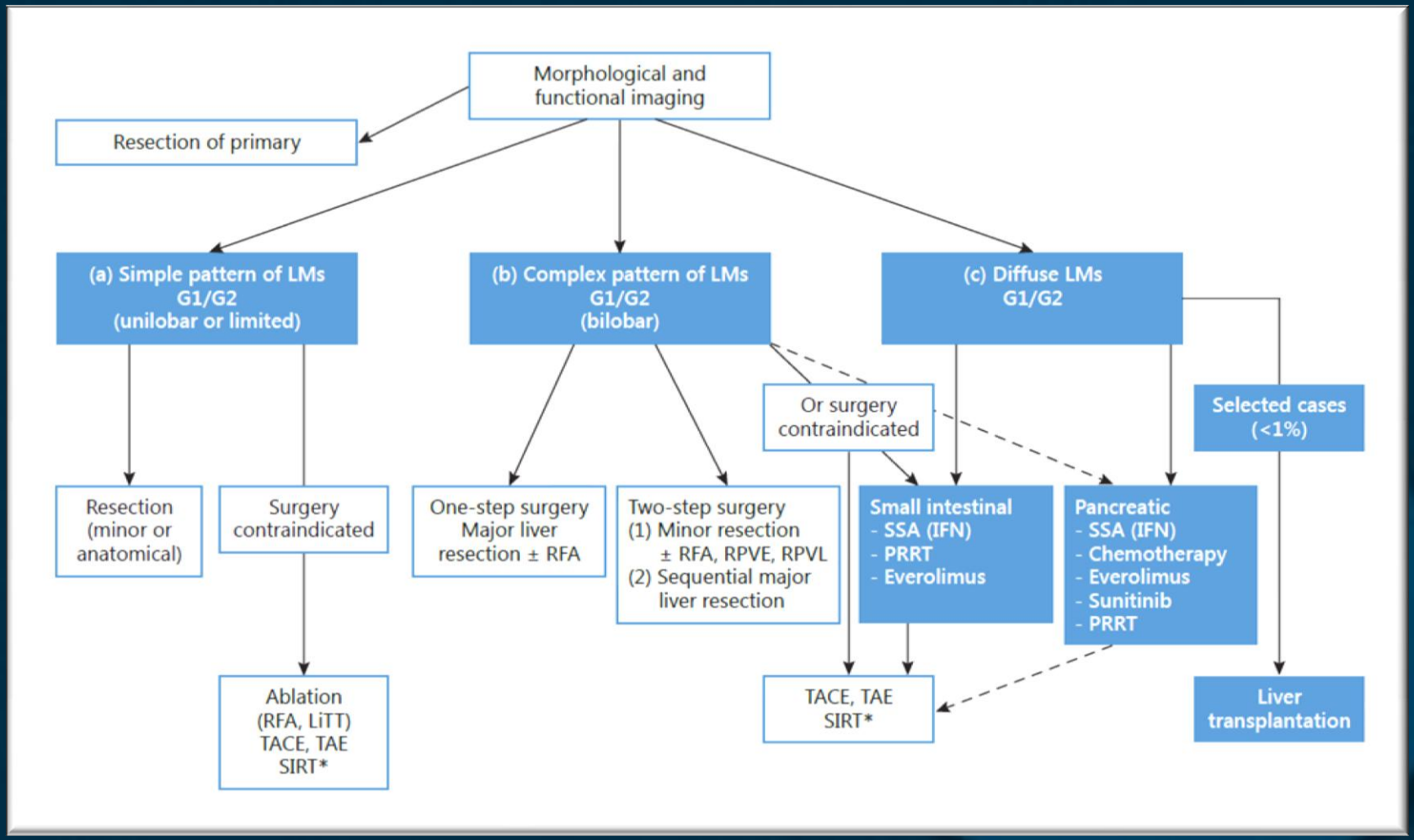
NET

Quando i trattamenti locregionali (fegato)

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
DOI: 10.1159/000443167



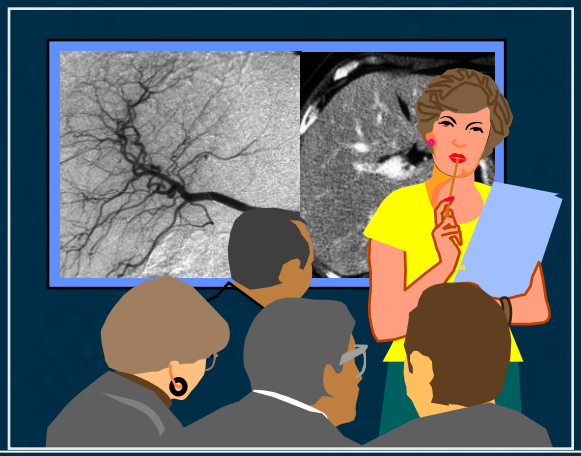
NET

Fondamentale un approccio multidisciplinare e multimodale…

Consenso nella strategia di trattamento

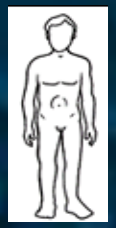
Qualità nella gestione del paziente

Gestione del paziente vs la patologia



Task force multidisciplinare

Trattamento locoregionale



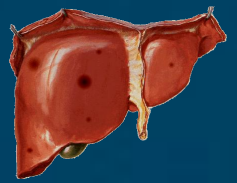
- *Primo* : indicazione clinica

Well-differentiated
Slow-growing

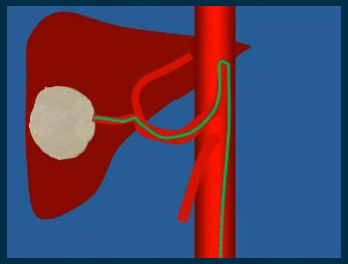
- *Secondo* : indicazione tecnica

primitivo

secondario



Terapie mini-invasive

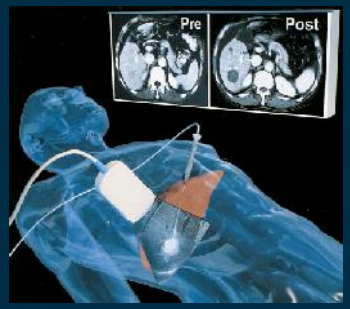


Intrarteriose

TAE (nuove particelle)

TACE

Radioembolizzazione (SIRT)



Percutanee

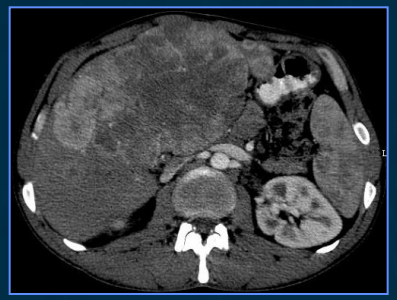
RFA- MWA

Tecniche combinate

NET

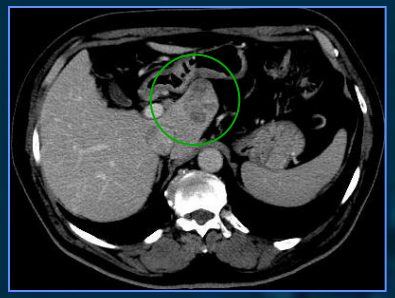
Terapie mini-invasive

Prima domanda:



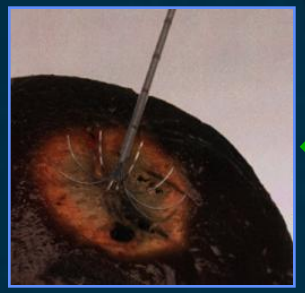
è clinicamente indicato?

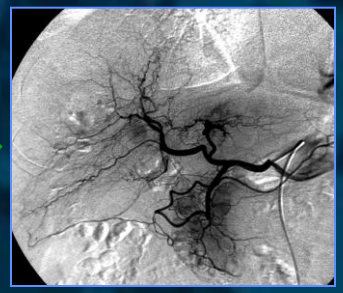
Seconda domanda:



è tecnicamente fattibile?

Terza domanda:





quale approccio?

NET

Trattamenti locali

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
DOI: 10.1159/000443167

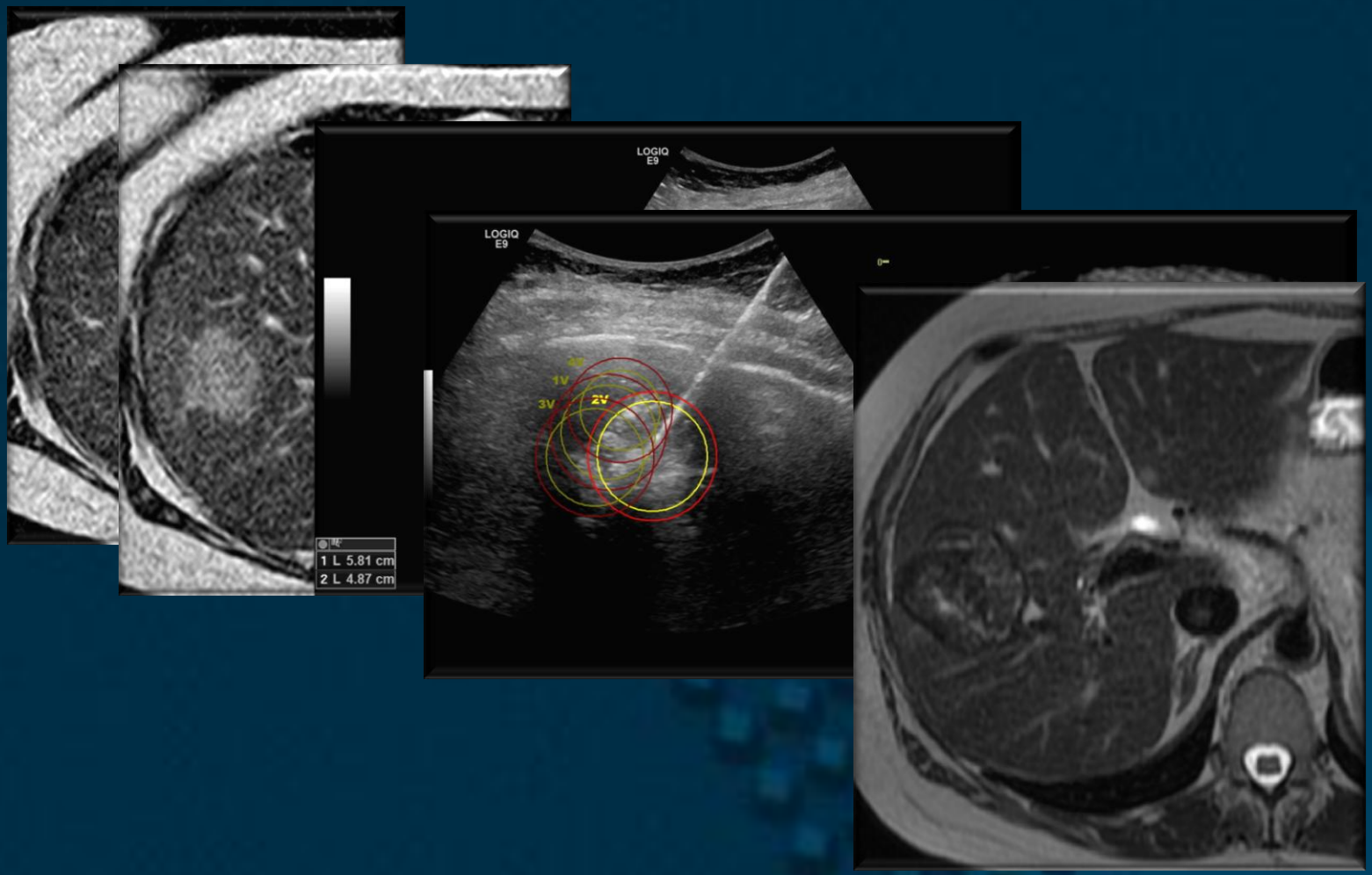
Locoregional Therapies

In the absence of any large comparative trials of different locoregional or ablative therapies (bland embolization, chemoembolization, radioembolization, radiofrequency ablation or microwave destruction) or systemic treatment, the choice of treatment is based on individual patient features (e.g. size, distribution and number of liver lesions, vascularization, proliferative index) and local physicians' expertise [14]. Locoregional therapies should be exploited early, following SSA therapy, to prevent carcinoid crisis in functionally active NET (especially midgut NET with classical carcinoid syndrome), and they may be an alternative option to systemic therapies in patients with non-functional tumors if the disease is limited to the liver. Locoregional therapies may be considered repetitively during the course of the disease. There is consensus that SIRT is still investigational, and that a comparative trial of SIRT to bland embolization is required, as well as more safety data on long-term tolerability of SIRT to establish this procedure for the management of NEN [14–18].

NET

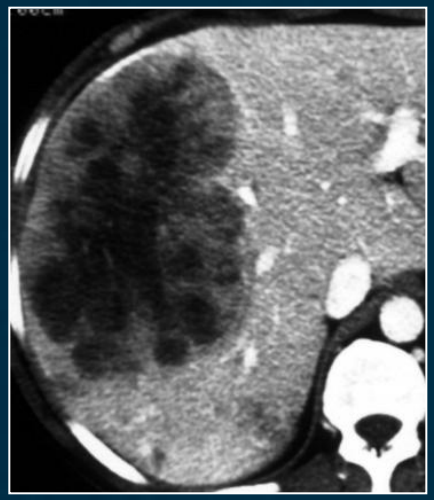
Termoablazione

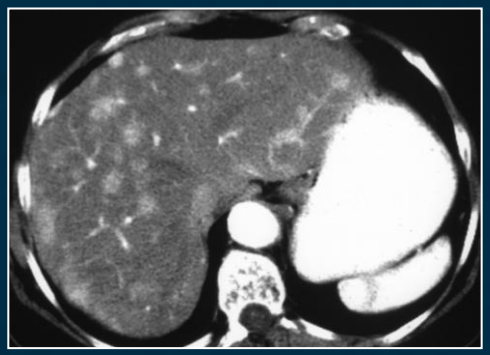
GT, 54 aa; NET ignoto, M+ fegato, Ki67=20%

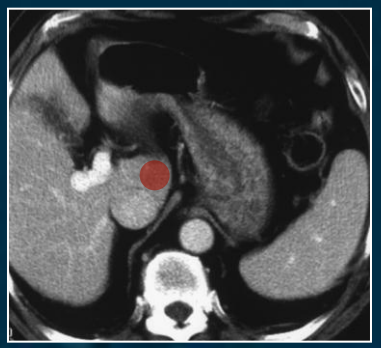


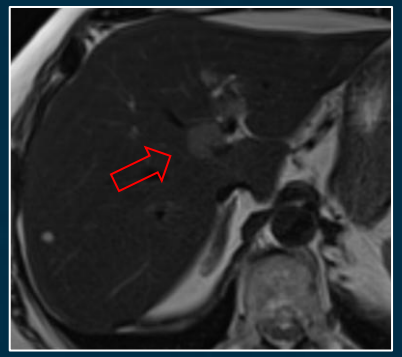
Trattamenti endovascolari

Lesioni *grandi, multiple* ed in *sedi difficili* possono essere trattate con approccio vascolare super-selettivo ripetuto









- **Razionale**: **le metastasi epatiche da NET sono tipicamente "ipervascolari" poiché vascolarizzate per l'80-90% da sangue arterioso**

THE BLOOD SUPPLY OF NEOPLASMS IN THE LIVER *

CHARLES BREEDIS, M.D., and GANG YOUNG, M.D.

(From the Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia, Pa., and the Pathology Research Institute, Medical College, National Sun Yat Sen University, Canton, China)

... whereas normal liver tissue is mainly vascularized by the portal vein blood flow

NET considerazioni Trattamenti endovascolari

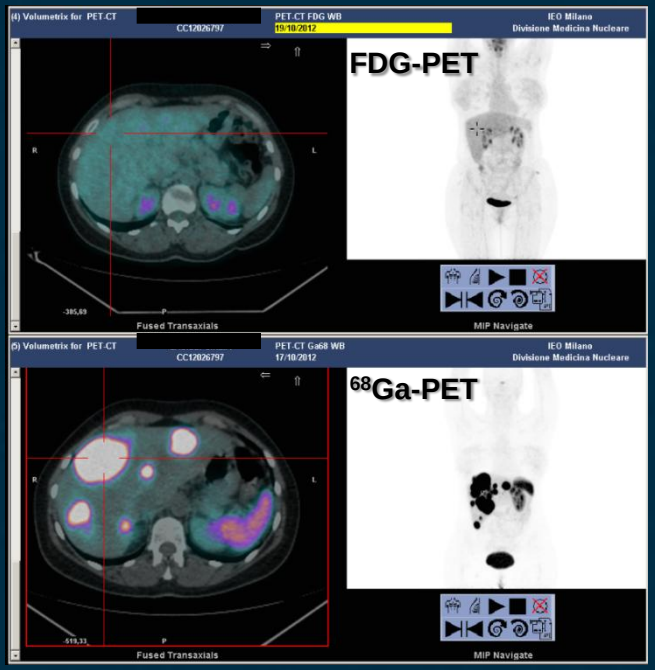
- TACE: il farmaco è rilasciato nella metastasi, con maggior concentrazione (fino a 20 volte maggiore) rispetto alla chemioterapia sistemica

- A fronte di questo vantaggio teorico, non c'è evidenza di significative differenze nel risultato clinico fra TACE e TAE

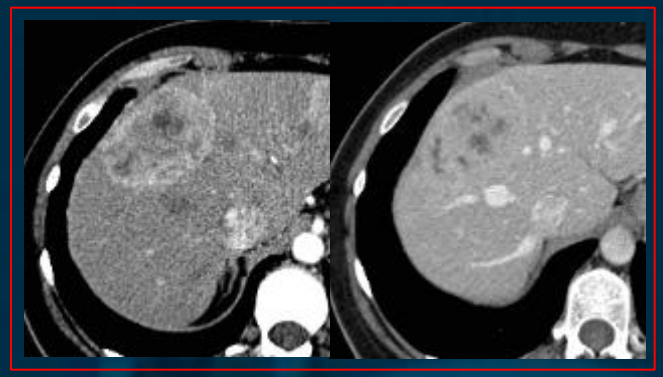
- Al fine di evitare complicanze nel trattamento di grosse masse epatiche, è opportuno trattare piccole porzioni di malattia per ogni trattamento

NET

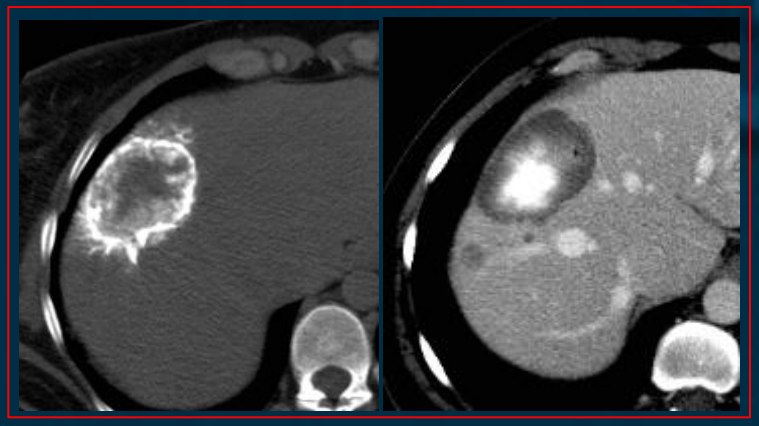
TAE



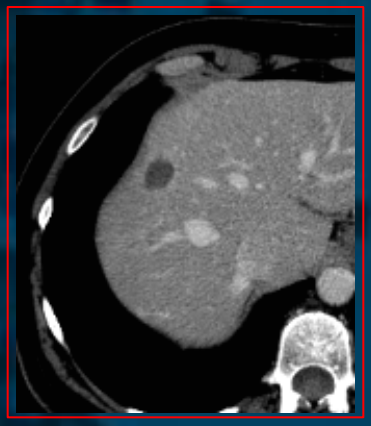
NET pancreas, M+ fegato
Ki67=5%
^{68}Ga-PET+ (funzionante)



TAE



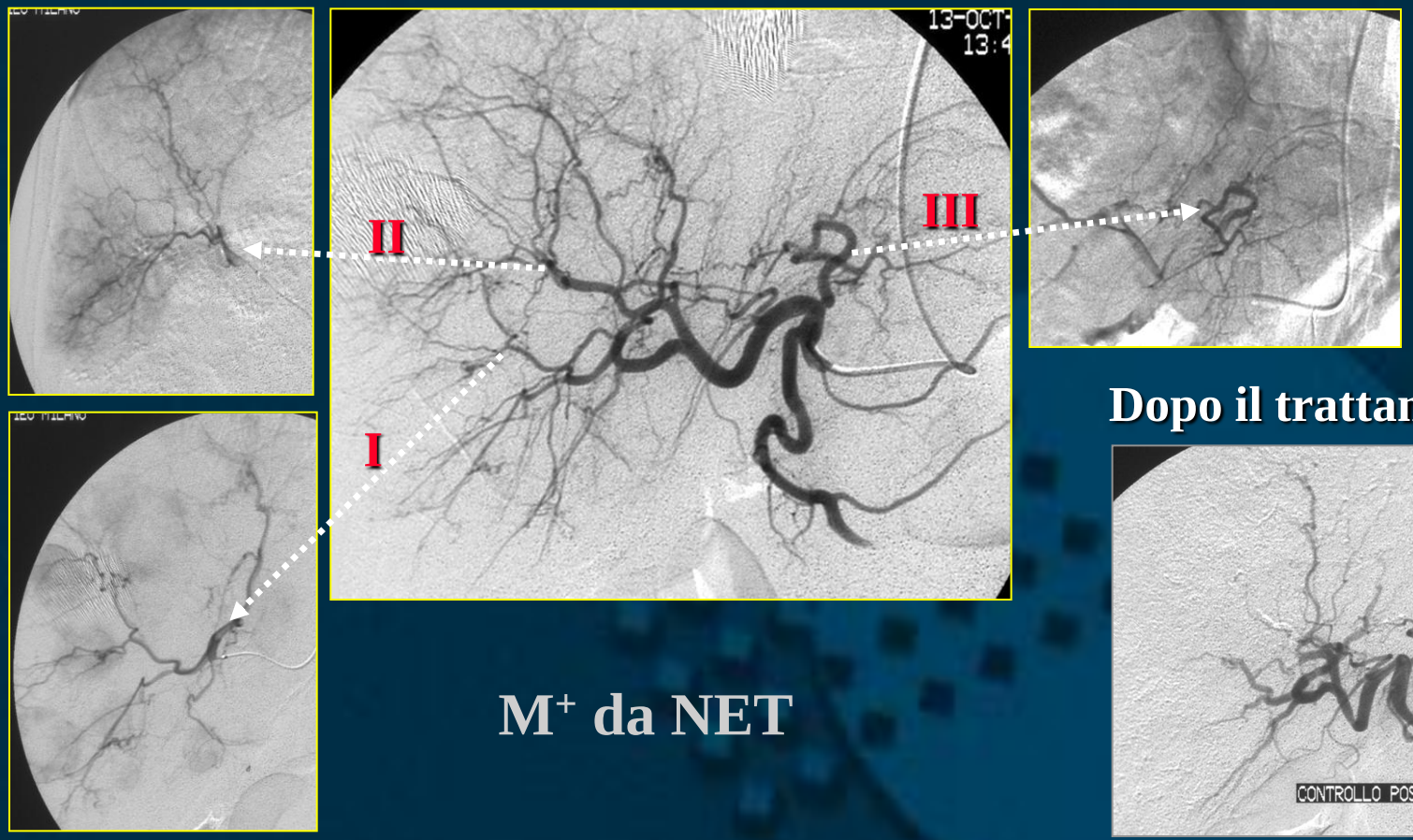
9 mesi



PRRT

Trattamenti endovascolari

- **In caso di multiple lesioni possono essere efficaci multipli trattamenti superselettivi**



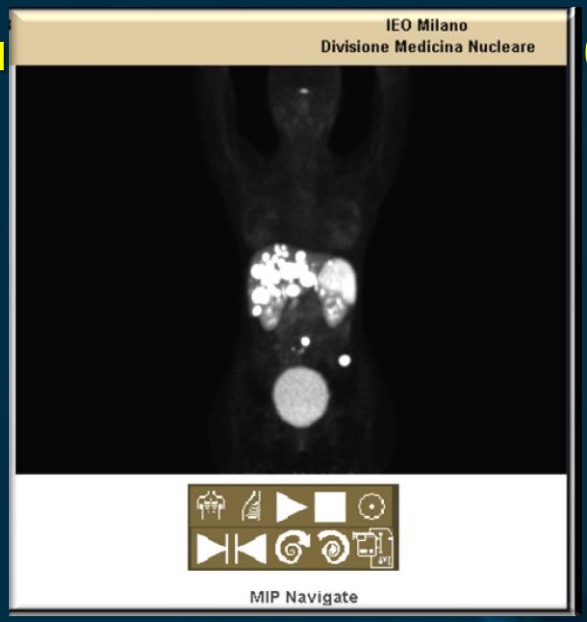
M⁺ da NET

Dopo il trattamento

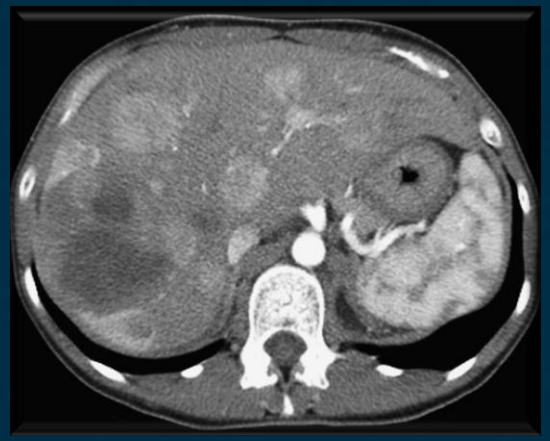
NET

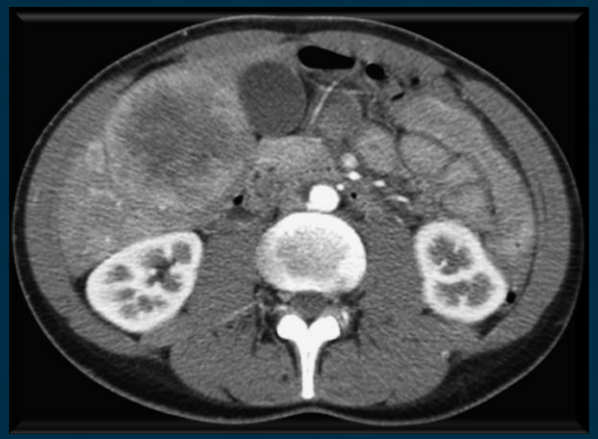
TAE sequenziale

GM, 31 aa; NET ileale fu

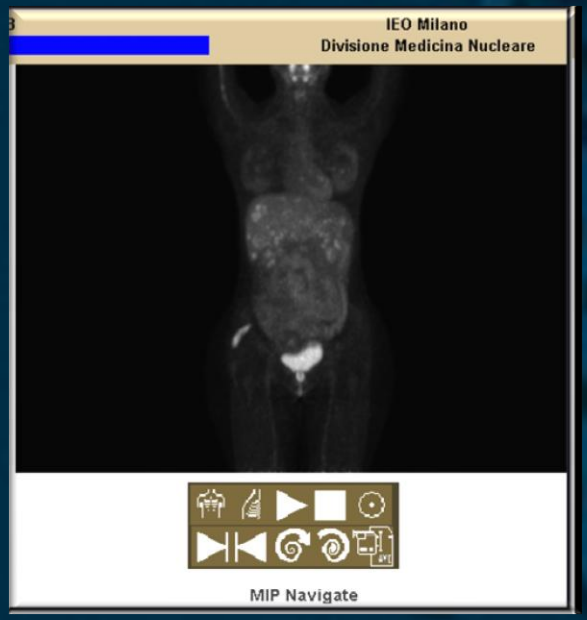


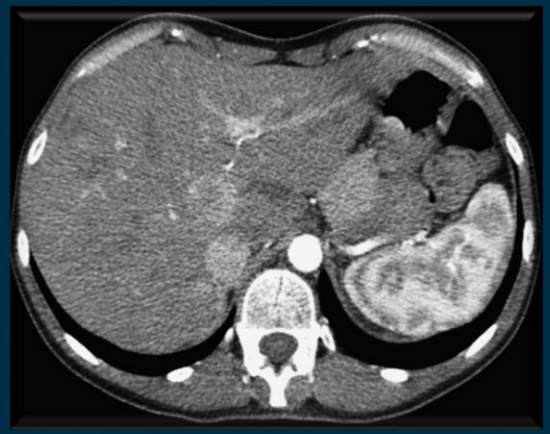
67=7%

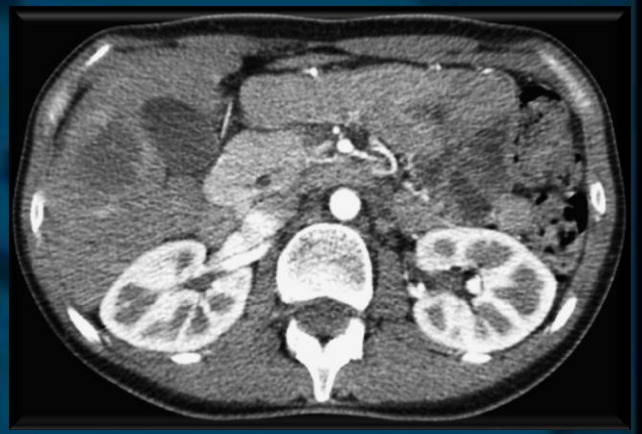




pre





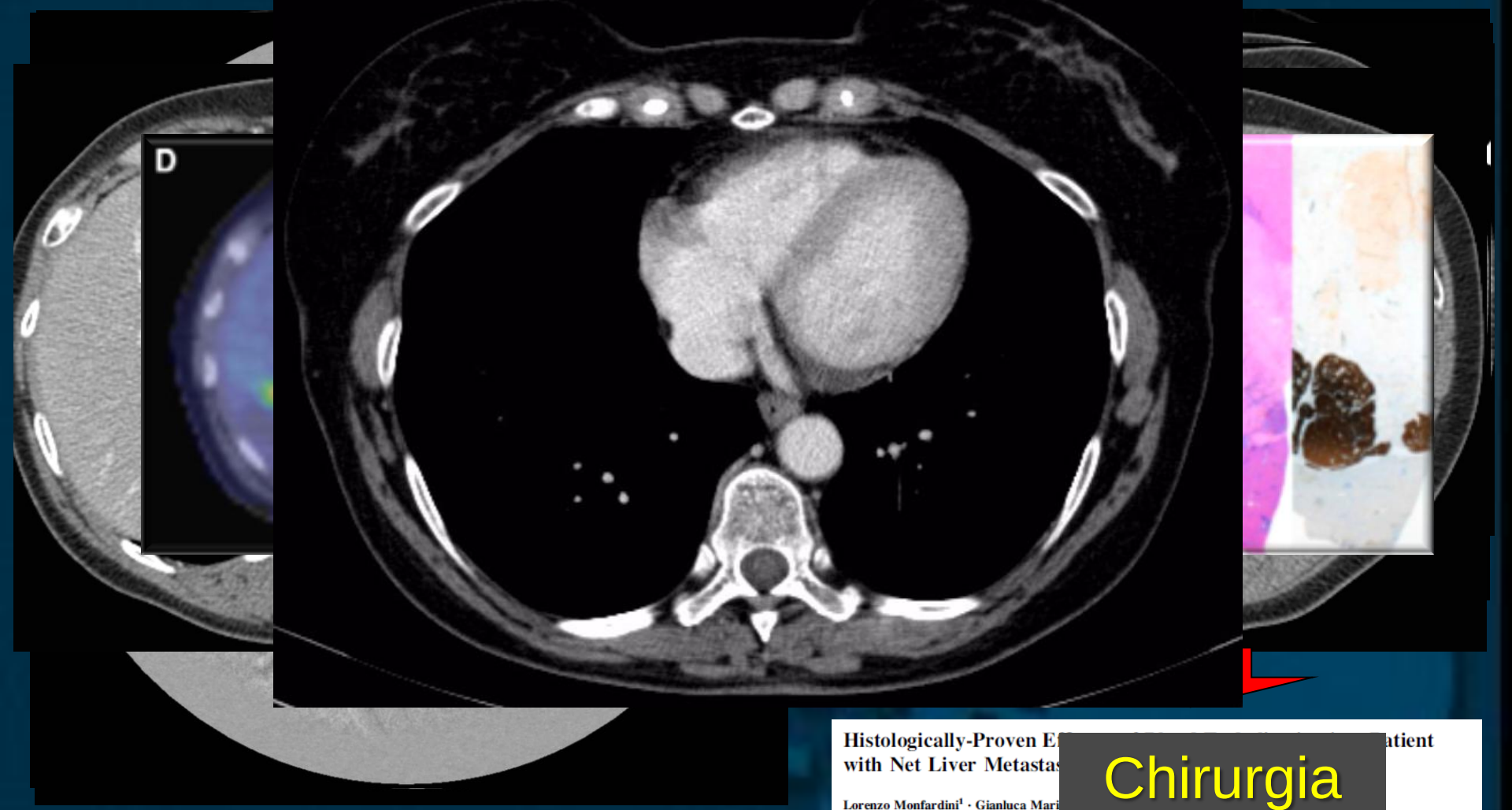


post

NET

TAE sequenziale

VV, 58 aa; NET duodeno funzionante, M+ fegato, Ki67=5%
Dic '13→ Mar '14



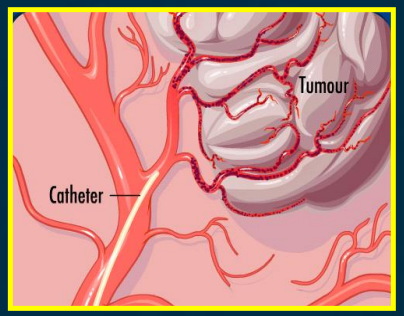
Histologically-Proven E… …atient
with Net Liver Metastas…

Lorenzo Monfardini[1] · Gianluca Mari…
Guido Bonomo[1] · Emilio Bertani[2] · El…
Franco Orsi[1]

Chirurgia
17/11/2014

Trattamenti endovascolari

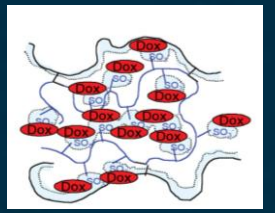
Chemioembolizzazione



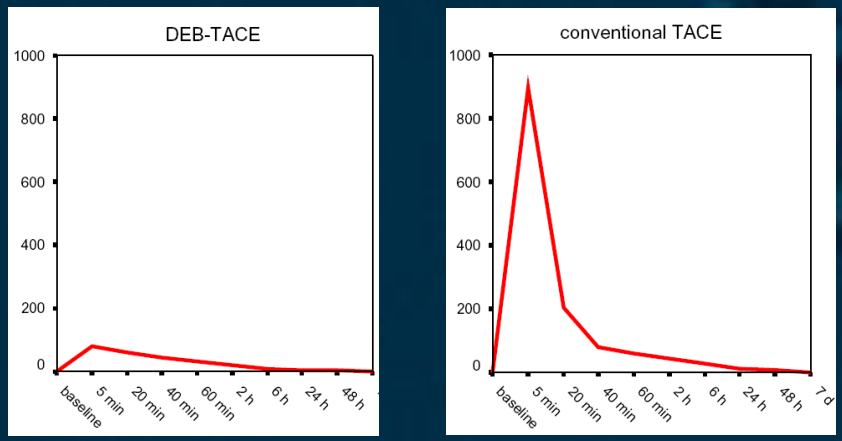
DRUG  +  Lipiodol ▶ C-TACE

Conventional Chemoembolization

 -DCBead ▶ DEB-TACE



Serum doxorubicin levels at different time in patients receiving TACE with DC Bead or C-TACE



"..Beads sequester doxorubicin hydrochloride from solution and release it in a controlled and sustained fashion.."

Varela M et al. BCLC. J Hepatol 2007;100:698-711

TAE risultati nei NET

Author	Year	#	Embolic	PR+SD	Symptom Response	OS
Carrasco	1986	25	sponge	94%	87%	16
Ajani	1988	22	PVA	60%	60%	34
Eriksson	1998	41	Sponge	81%	52%	80
Brown	1999	35	PVA	NR	89%	21
Loewe	2003	33	Cyano	96%	56%	NR
Strosberg	2006	84	PVA, Embo	100%	80%	36
Granberg	2007	15	Embo	91%	42%	NR
Sward	2009	107	Sponge, PVA	NR	71%	56

TACE risultati nei NET

Author	Year	#	Drugs	PR+SD	Symptom Response	OS
Ruszniewskj	1993	23	Dox	83%	73%	NR
Therasse	1993	28	Dox	59%	100%	24
Diamandidou	1998	20	Cis	100%	67%	NR
Dominguez	2000	15	STZ	53%	60%	NR
Roche	2004	64	Dox	74%	93%	NR
Bloomston	2007	122	Dox/Cis/Mito	94%	92%	33
Marrache	2007	67	Dox/STZ	73%	91%	NR
Dong	2011	123	Dox/STZ	86%	NR	39
Arrese	2013	192	Dox/Cis/Mito	78%	72%	30

DEB TACE in NET

Year	Author	#	Outcome
2008	De Baere	20	PFS 15m
2011	Whitney	28	PFS 18m
2011	Gaur	18	PFS 14m
2013	Bhagat	13	Biloma in 54%

Vantaggi potenziali rispetto alla c-TACE:

- Rilascio di farmaco più consistente
- Facilità d'impiego
- Maggiore chiarezza nei controlli strumentali

Aumentato rischio di danno biliare/ascesso

NET TACE

Published in final edited form as:
Cardiovasc Intervent Radiol. 2013 April ; 36(2): 449–459. doi:10.1007/s00270-012-0424-y.

Phase II Study of Chemoembolization With Drug-Eluting Beads in Patients With Hepatic Neuroendocrine Metastases: High Incidence of Biliary Injury

Results—DEB-TACE was successfully performed in all 13 patients. At 1 month follow-up, there was a mean 12 % decrease in tumor size (p <0.0003) and a 56 % decrease in tumor enhancement (p <0.0001). By EASL criteria, the targeted lesion objective response rate was 78 %. Grade 3 to 4 toxicities were fatigue (23 %), increased alanine amino transferase (15 %), hyperglycemia (15 %), and abdominal pain (8 %). Seven patients developed bilomas (54 %); all of these patients had multiple small (<4 cm) lesions. Subsequently, four underwent percutaneous drainage, three for abscess formation and one for symptoms related to mass effect.

Conclusions—Although biloma and liver abscess are known risks after TACE, the high incidence in our study population was unexpected and forced interruption of the trial. Although this occurred in a small group of patients, we have changed our technique and patient selection as a result of these findings, thus allowing resumption of the trial.

Recommendations

On the basis of the safety findings of our interim analysis, we modified our patient selection criteria and changed our DEB-TACE technique. We decided to include only patients with multiple large lesions (smallest lesion >4 cm) and extensive tumor burden. After the interim analysis, we no longer consider small multifocal disease (largest lesion <4 cm) for DEB-TACE treatment. The DEB-TACE procedure was also modified. The DEBs are now mixed with four times the amount of contrast to improve visualization of the DEBs, thereby preventing potential misadministration of the DEBs. We understand that these changes in

Cardiovasc Intervent Radiol (2015) 38:372–380
DOI 10.1007/s00270-014-0914-1

Predisposing Factors of Liver Necrosis after Transcatheter Arterial Chemoembolization in Liver Metastases from Neuroendocrine Tumor

Julien Joskin · Thierry de Baere · Anne Auperin · Lambros Tselikas · Boris Guiu · Geoffroy Farouil · Valérie Boige · David Malka · Sophie Leboulleux · Michel Ducreux · Eric Baudin · Frédéric Deschamps

Results Liver necrosis developed after 23 (6.1 %) of 374 TACE. In multivariate analysis, DEB > 300 µm in size induced more liver necrosis compared to Lipiodol (odds ratio [OR] 35.20; $p < 0.0001$) or with DEB < 300 µm in size (OR 19.95; $p < 0.010$). Pretreatment BDD (OR 119.64; $p < 0.0001$) and PVT (OR 9.83; $p = 0.030$) were predictive of liver necrosis. BDD or PVT responsible for liver necrosis were present before TACE in 59 % (13 of 22) and were induced by a previous TACE in 41 % (9 of 22) of cases.

Conclusion DEB > 300 µm in size, BDD, and PVT are responsible for increased rate of liver necrosis after TACE. Careful analysis of BDD or PVT on pretreatment images as well as images taken between two courses can help avoid TACE complications.

Table 2 Characteristics of the TACE ($n = 374$)

TACE characteristic	Lipiodol-TACE ($n = 209$)	DEB-TACE ($n = 165$)	p
Treatment location			
Segmental/subsegmental	42	49	
Lobar	167 (80 %)	116 (70 %)	0.03
Session			
1	88 (42 %)	76 (46 %)	
2	67 (32 %)	57 (35 %)	
3	32 (15 %)	23 (14 %)	
4	17 (8 %)	9 (15 %)	
5	5 (2 %)	0 (0 %)	0.25
Dose of doxorubicin			
<70 mg	75	40	
≥70 mg	132 (64 %)	124 (76 %)	0.01
DEB size			
100–300 µm		46 (28 %)	
300–500 µm		24 (16 %)	
500–700 µm		95 (58 %)	
Complementary embolization			
No	33	165	
Yes	175 (84 %)	0	

Data are presented as *n* (%)

DEB drug-eluting beads, *TACE* transarterial chemoembolization

Table 3 Characteristics of complications after TACE ($n = 374$)

Complication	Lipiodol-TACE ($n = 209$)	DEB-TACE ($n = 165$)
Liver necrosis	3 (1 %)	20 (12 %)
Liver necrosis by TACE session number		
1 ($n = 164$)	1/88 (1 %)	10/76 (13 %)
2 ($n = 124$)	1/67 (1 %)	7/57 (12 %)
3 ($n = 55$)	1/32 (3 %)	2/23 (9 %)
4 ($n = 26$)	0/17 (0 %)	1/9 (11 %)
5 ($n = 5$)	0/5 (0 %)	0/0
Liver necrosis size, cm	6; 10; 19	3.8 (SD 1.2) (range 2–5.7)
Liver necrosis extension ($n = 23$)		
Lobar	1 (33 %)	2 (10 %)
Sectorial	0	6 (30 %)
Segmental	2 (66 %)	12 (60 %)
Liver necrosis occurrence in patients with		
No biliary/portal damage	0	1
Biliary/portal damage at baseline imaging	2 (1 necrosis at first session)	11 (9 necrosis at first session)
Biliary/portal damage at intermediate imaging before session[a]	3	19
Posttreatment biliary/portal damage		
Bile duct dilatation	23 (12 %)	35 (21 %)
Portal vein narrowing	10 (5 %)	25 (15 %)
Portal vein thrombosis	4 (2 %)	18 (11 %)

Data are presented as *n* (%) unless otherwise indicated

TACE transcatheter arterial chemoembolization, *DEB* drug-eluting beads

[a] Baseline imaging when we study the first session

NET TACE

Haemodynamic events and localised parenchymal changes following transcatheter arterial chemoembolisation for hepatic malignancy: interpretation of imaging findings

J CHUNG, MD, J-S YU, MD, J-J CHUNG, MD, J H KIM, MD and K W KIM, MD

The British Journal of Radiology, 83 (2010), 71–81

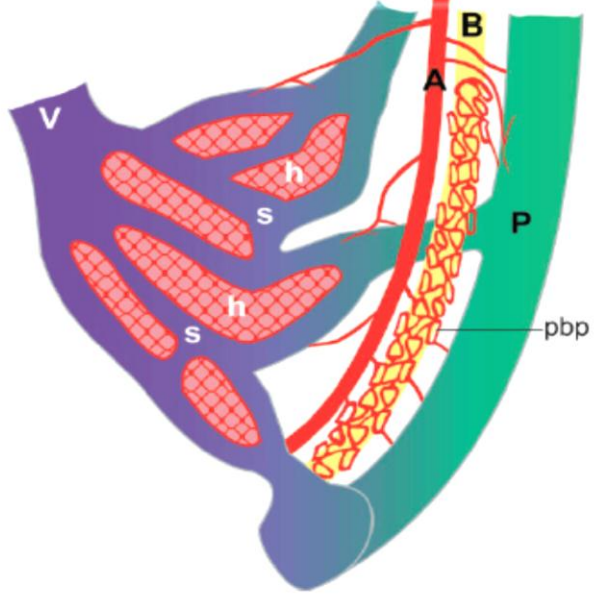


Figure 1. Schematic anatomy of normal hepatic vessels. The hepatic artery (A) primarily supplies the hepatic framework of the portal tract, which consists of the portal vein (P), bile duct (B) and hepatic artery. There are capillary networks between the hepatic artery (A) and portal vein (P), which is called the peribiliary plexus (pbp), and the portal venous flow affords sinusoidal (s) perfusion, supplying the hepatocytes (h). V, hepatic vein.

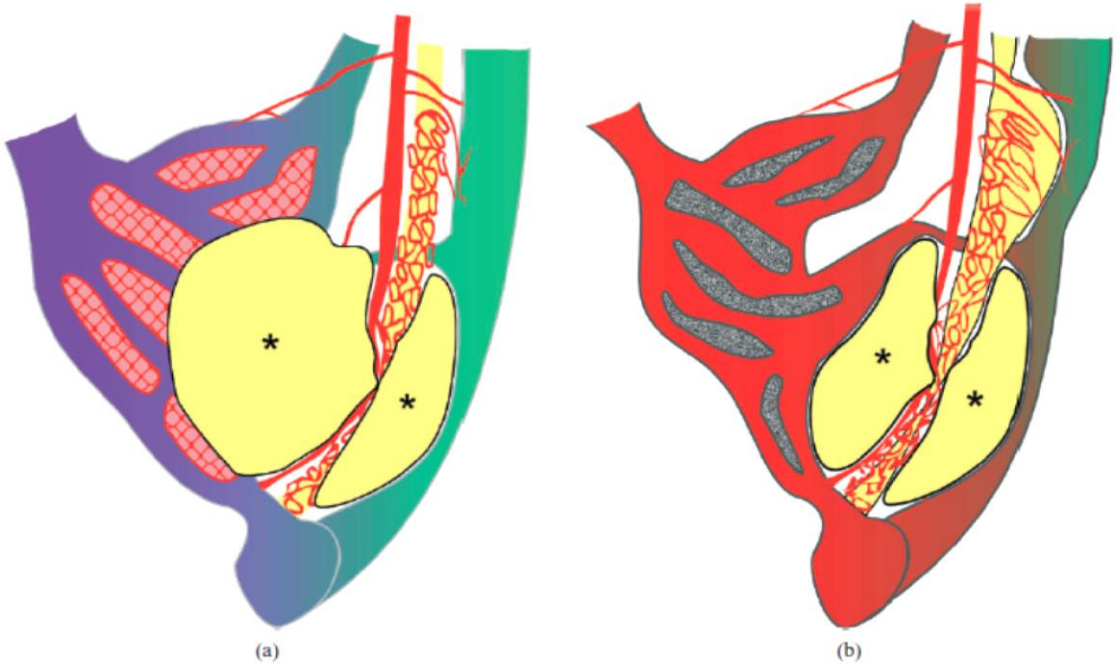
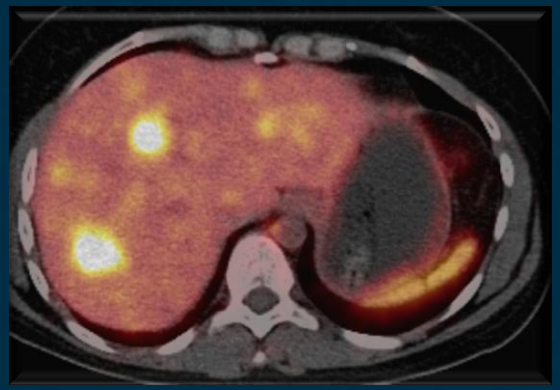


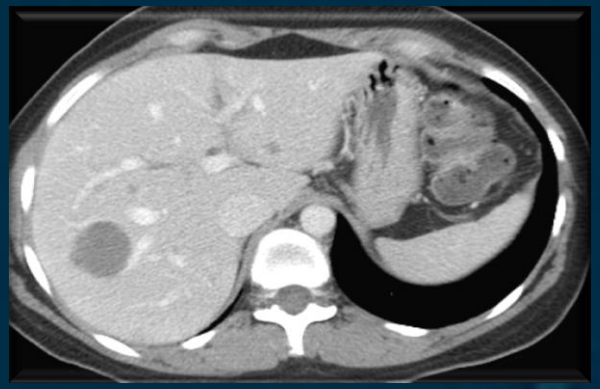
Figure 3. Schemata of acute and chronic transcatheter arterial chemoembolisation (TACE)-induced bile duct injury and portal vein obliteration, with or without parenchymal infarct. (a) In the acute stage, necrosis of the bile duct induces rupture of the bile duct and biloma formation (asterisks) along the portal tract. A large cystic biloma can occupy the space of the acutely infarcted parenchyma. (b) In the chronic stage, the portal tract injury with stricture and dilatation of the bile ducts is accompanied by gradual portal vein obliteration, resulting in parenchymal atrophy.

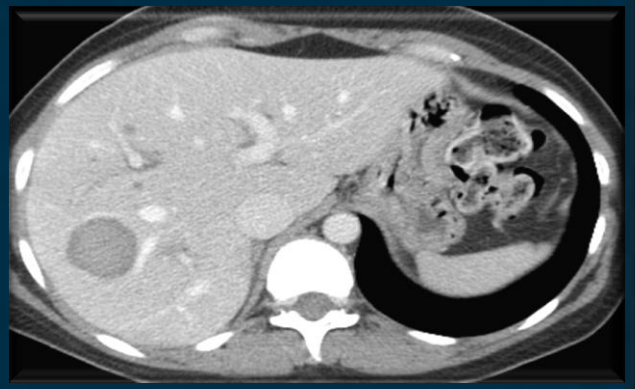
NET

Deb-TACE

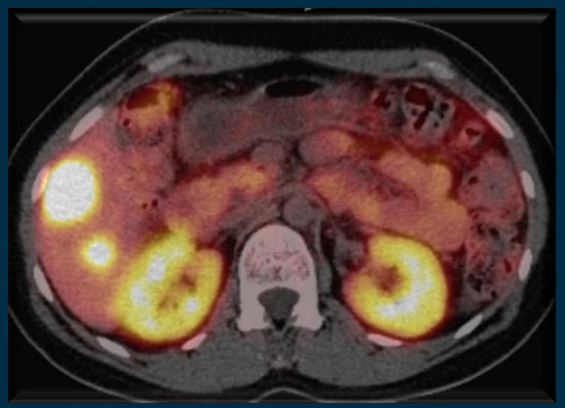
GBC, 38 aa; NET duodeno, M+ fegato, Ki 67= 4%
Trattamento: Tandem 40μm x 2,5ml+Doxo 125mg



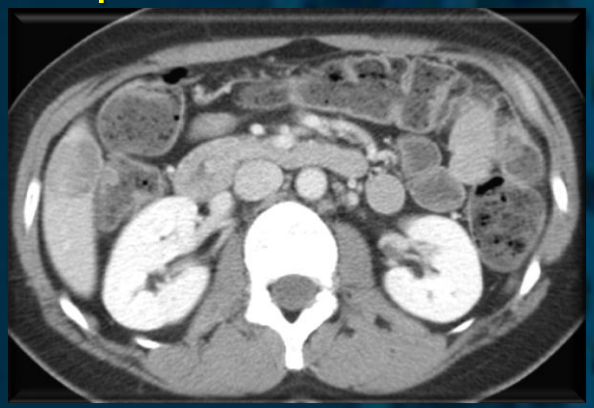




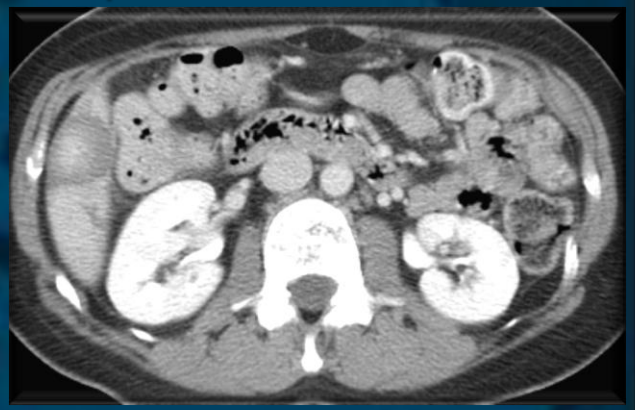
^{68}Ga-PET+



TC-pre



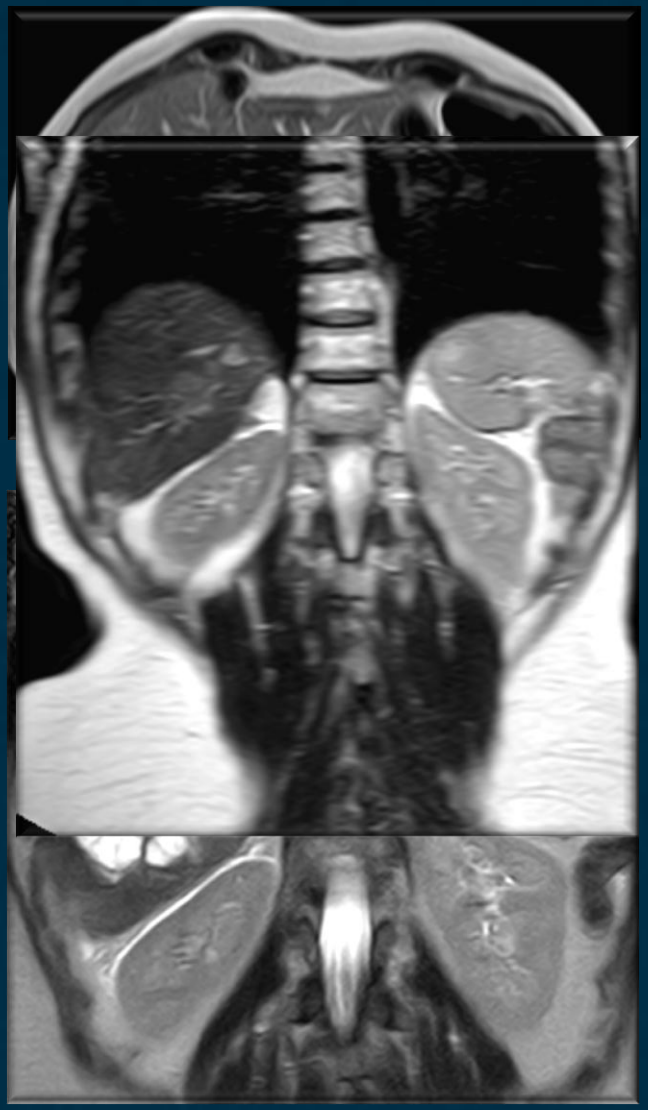
TC-post



NET

Deb-TACE

GBC, 38 aa; NET duodeno, M+ fegato, Ki 67= 4%
Trattamento: Tandem 40μm x 2,5ml+Doxo 125mg



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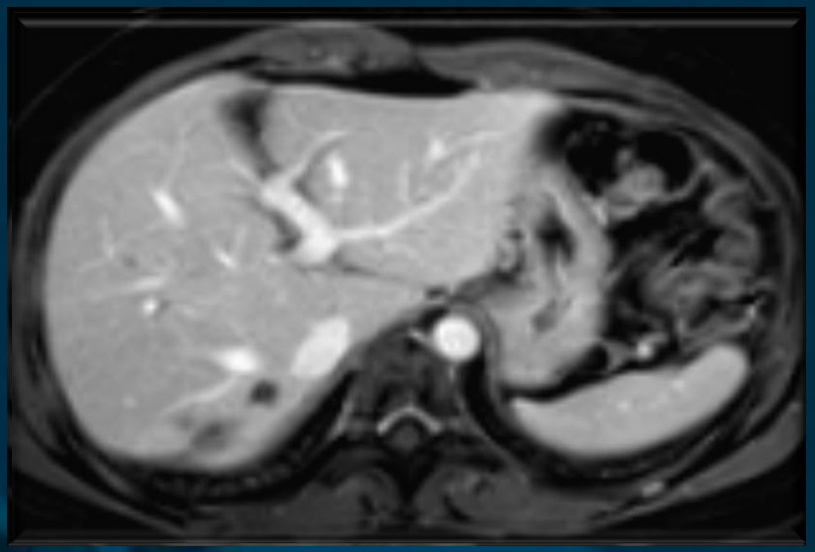
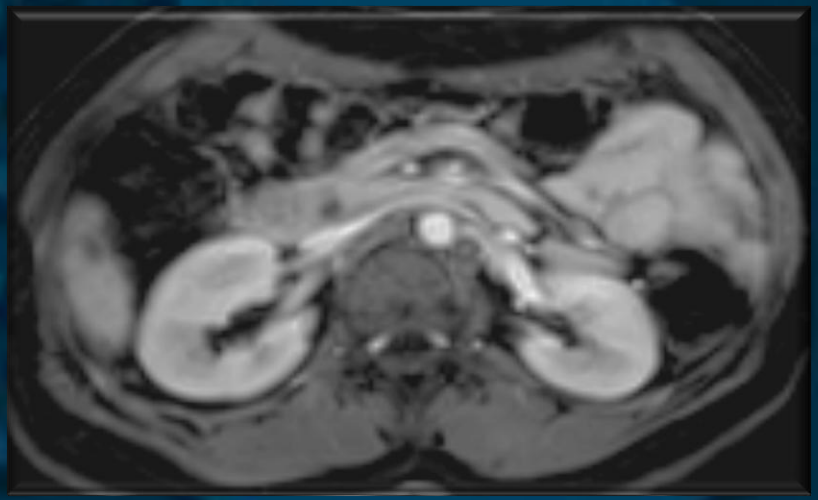




Endocrine (2014) 47:177–182
DOI 10.1007/s12020-013-0130-9

ORIGINAL ARTICLE

Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors

Francesco Fiore · Michela Del Prete · Renato Franco · Vincenzo Marotta · Valeria Ramundo · Francesca Marciello · Antonella Di Sarno · Anna Chiara Carratù · Chiara de Luca di Roseto · Annamaria Colao · Antongiulio Faggiano

as possible when delivering the agent. In TAE procedure, Lipiodol administration (5 ml) is followed by the administration of embolizing agents (75–150 μm) without the administration of chemotherapeutic agents. In TACE procedure, 50 mg Epirubicin combined with a contrast medium agent (Lipiodol R) was used, followed by the administration of embolizing agents (75–150 μm). Some

A post-embolization syndrome was observed in 41 % of patients treated with TAE, and 61 % of those treated with TACE ($p = 0.40$). The post-embolization syndrome was

TAE and TACE are quite similar in terms of effectiveness and safety, with only a slight lower rate of side effects for TAE than for TACE, it is reasonable to prefer TAE to TACE in NET patients with liver metastases because of the potential cumulative toxicity that chemotherapy could determine. This aspect is still more relevant, if we consider that NET patients are long-time survivors who receive many different therapeutic approaches during their life, also including systemic chemotherapy and peptide radioreceptorial therapy.

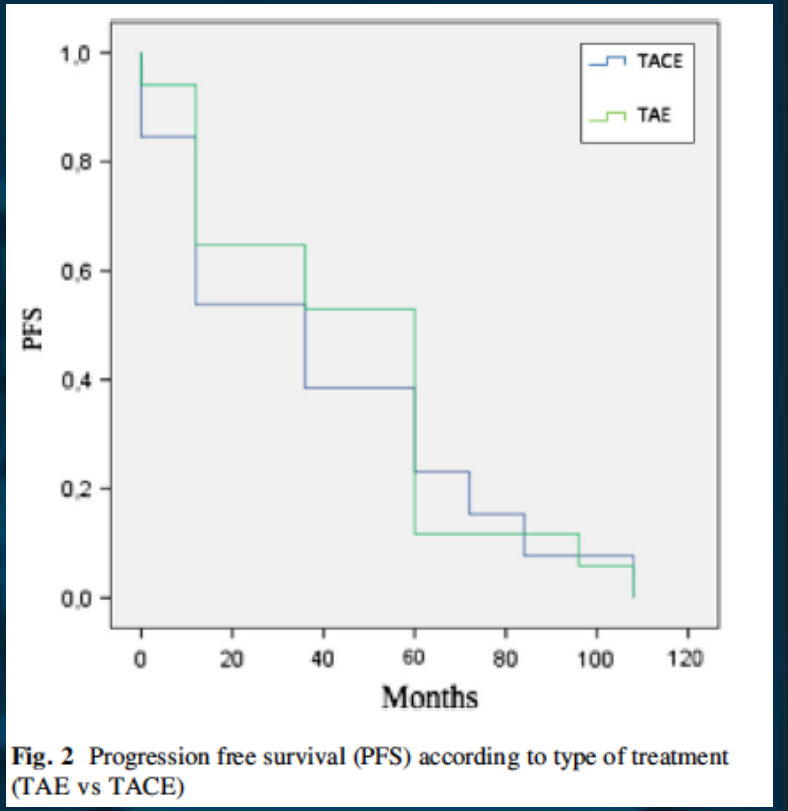


Fig. 2 Progression free survival (PFS) according to type of treatment (TAE vs TACE)

Prima e dopo le procedure endovascolari

Terapia

- Iperidratazione
- Analogo SS(octreotide)
- Metoclopramide

Per evitare

- Sindrome da carcinoide
- Insufficienza epatica e renale
- Nausea & dolore

Nei 3 giorni dal trattamento abbiamo osservato:

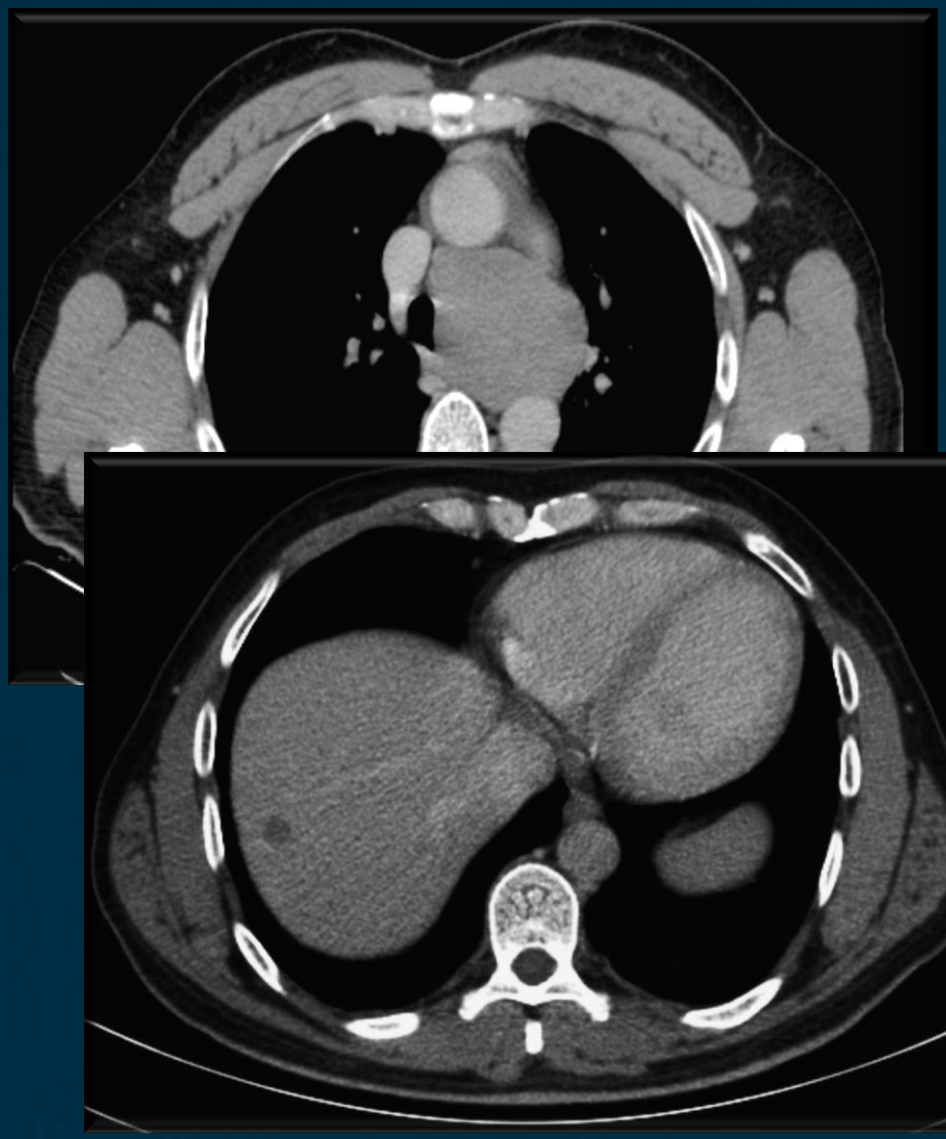
•Nausea e vomito	72%
•Dolore addominale	64%
•Febbre	3%

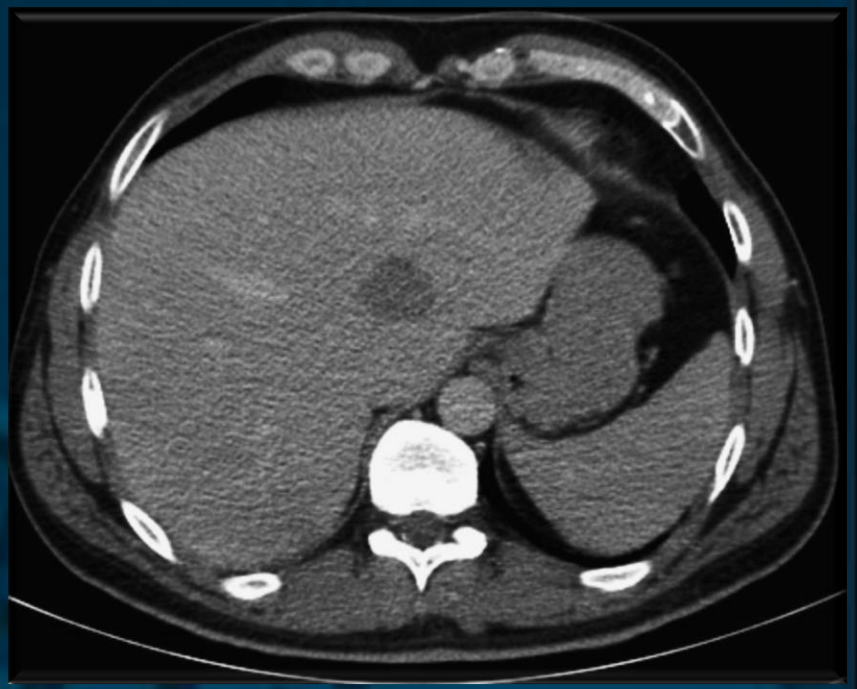
•Alterazione biochimica	100%
•Sindorme da carcinoide	1%
•Complicanze maggiori*	1%

NET

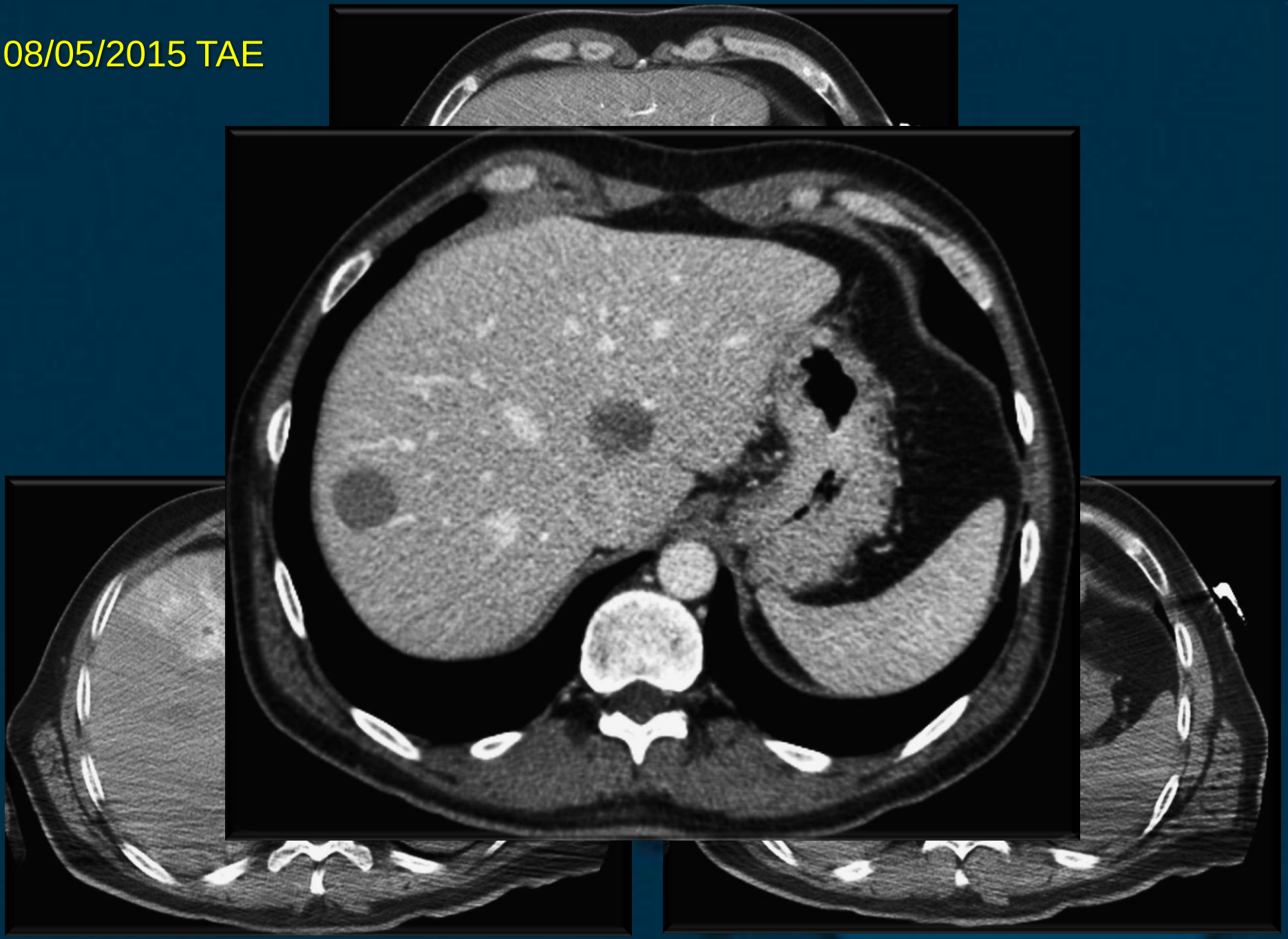
Trattamenti combinati

DSV, 47 aa; NET ignoto, M+ fegato, Ki67=19%

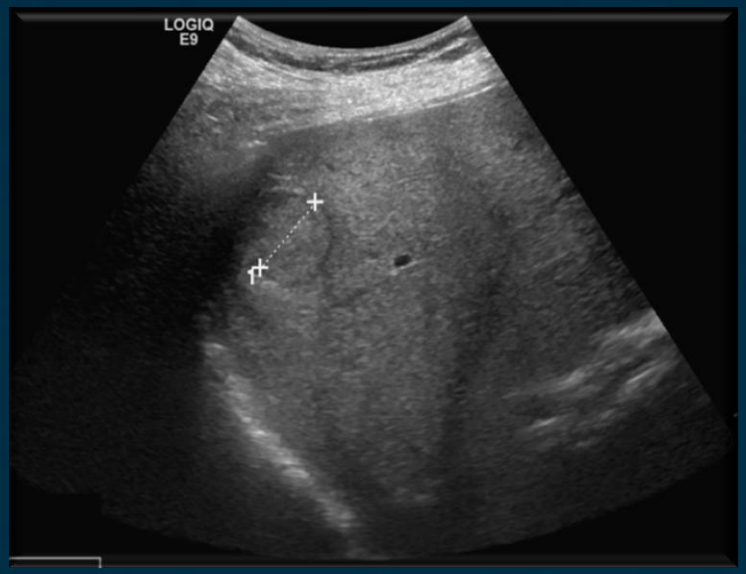


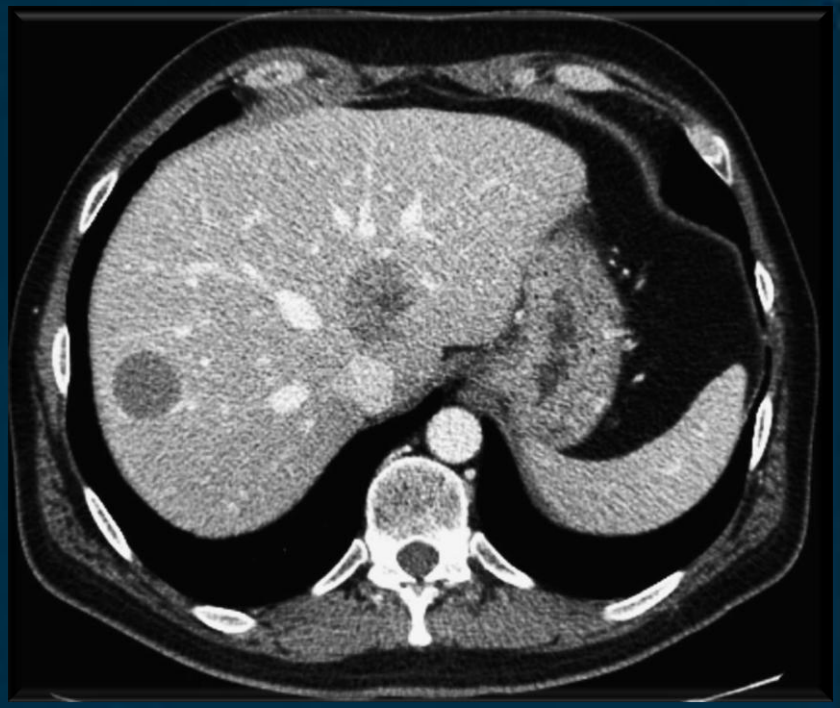


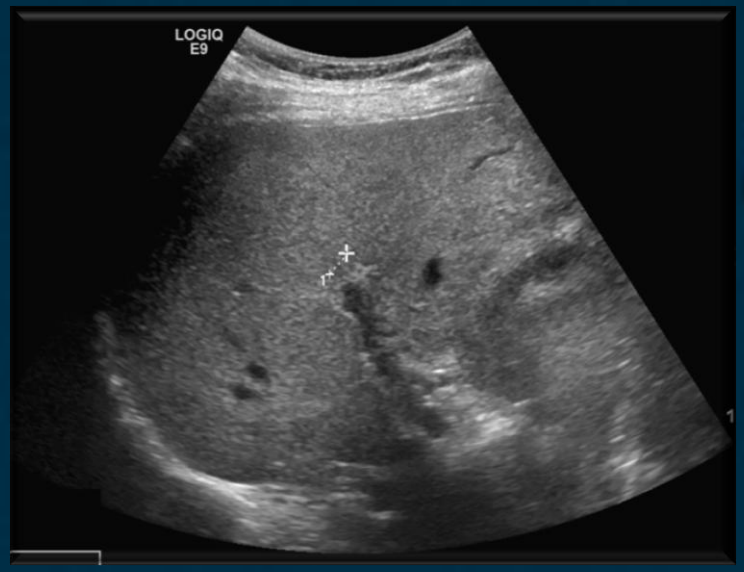
08/05/2015 TAE

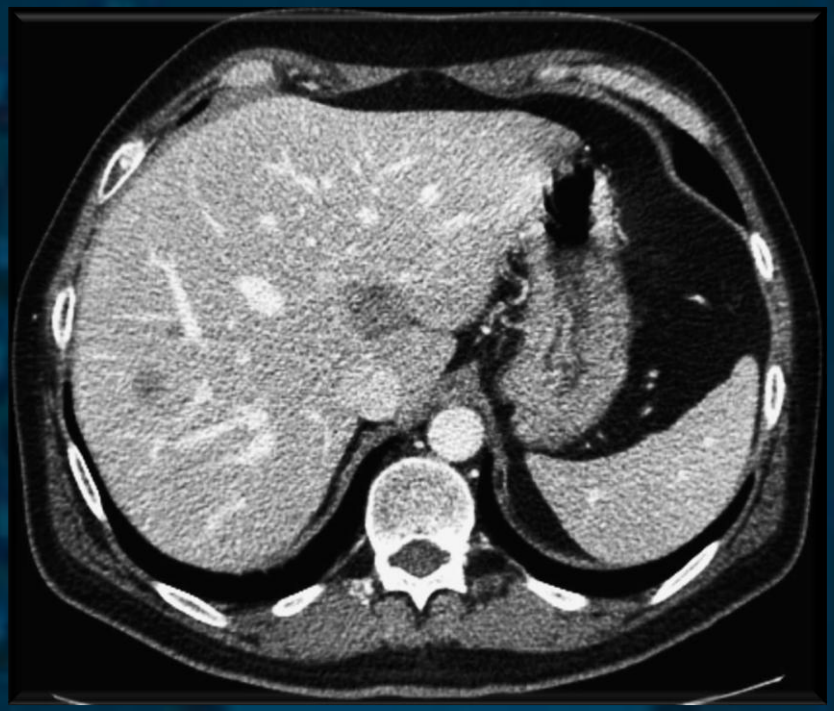


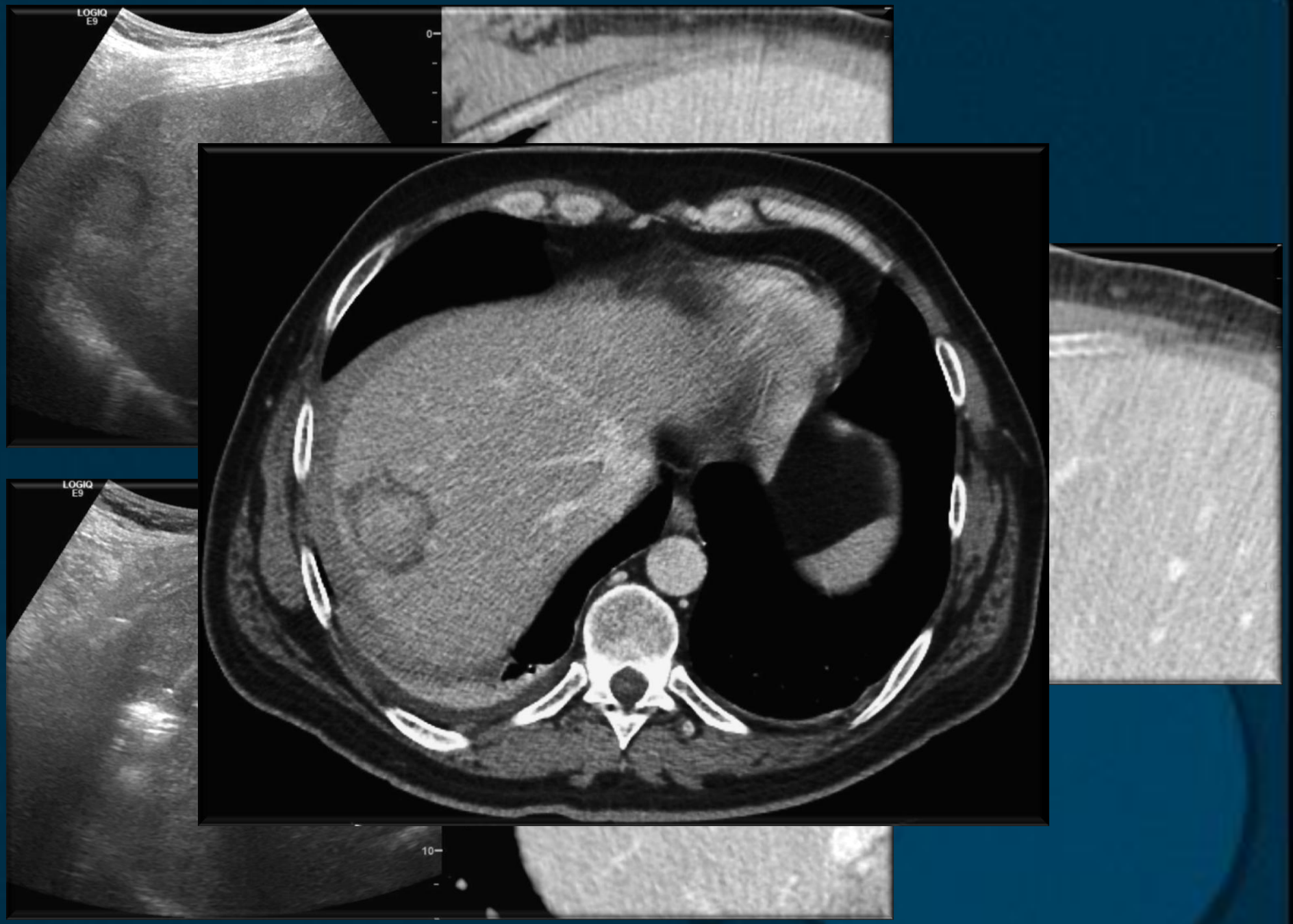
11/03/2016 MWA







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Conclusioni

- La multidisciplinarietà e la multimodalità sono mandatorie per la migliore gestione dei NET

  ☞ Gruppo multidisciplinare

- La maggior parte dei clinici è d'accordo con l'idea di un trattamento disegnato per ogni singolo paziente

- E' importante, nell'ambito dei trattamenti locoregionali, scegliere quello più efficace, senza trascurare la tossicità d'organo, in considerazione della lunga spettanza di vita dei pazienti affetti da NET

Ki67- differenziazione !!!