Società Medico Chirurgica di Ferrara dal 1846

Il Percorso del paziente con neoplasia neuroendocrina nella provincia di Ferrara

Sabato 12 Ottobre 2019

Aula Magna Nuovo Arcispedale S. Anna
Cona, Ferrara

Terapia loco-regionale: la radiologia interventistica

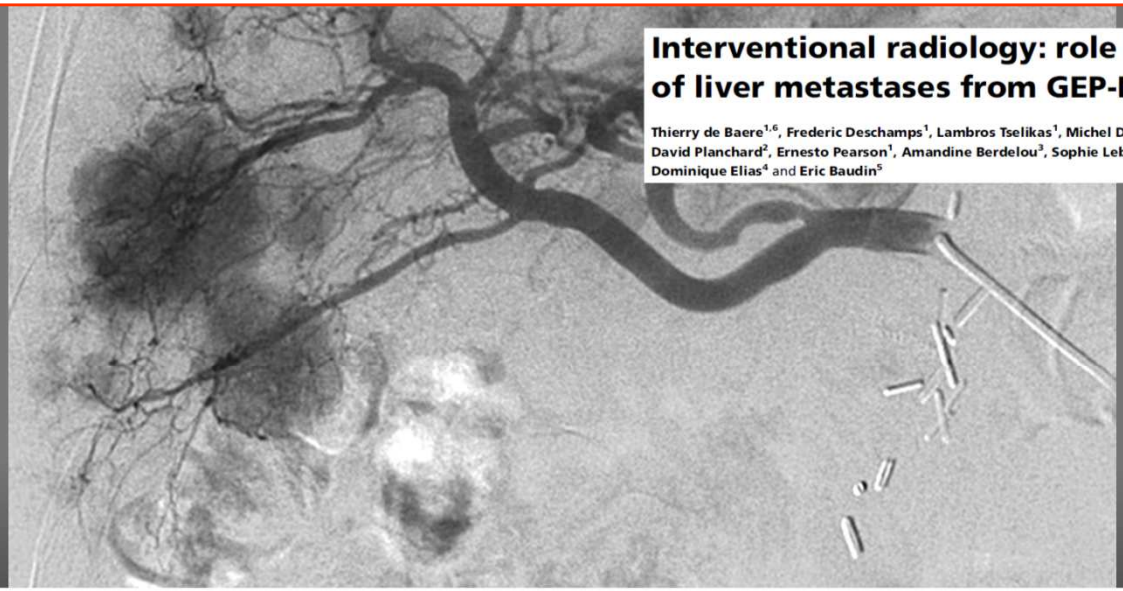
R. Galeotti

Roberto Galeotti
Azienda Ospedaliero-Universitaria "Arcispedale S.Anna" di Ferrara
Dipartimento di Radiologia
U.O.S. Radiologia Vascolare ed Interventistica

TERAPIA TRANSARTERIOSA METASTASI EPATICHE DA NET

Indications

Non-surgical candidates with liver predominant disease or major uncontrolled symptoms are best candidates for hepatic intra-arterial therapies



Interventional radiology: role in the treatment of liver metastases from GEP-NETs

Thierry de Baere[1,6], Frederic Deschamps[1], Lambros Tselikas[1], Michel Ducreux[2,6], David Planchard[2], Ernesto Pearson[1], Amandine Berdelou[3], Sophie Leboulleux[3], Dominique Elias[4] and Eric Baudin[5]

European Journal of Endocrinology (2015) 172, R151–R166

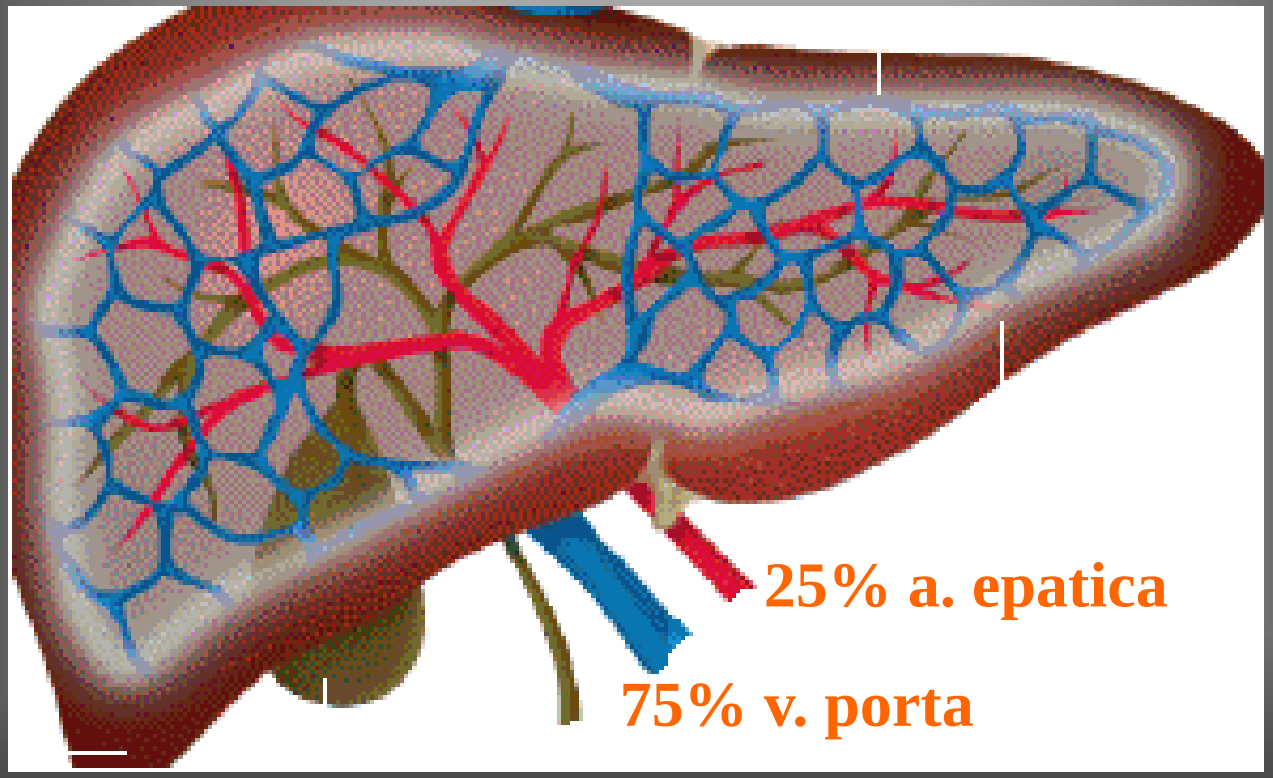
Terapia loco-regionale: la radiologia interventistica

R. Galeotti

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

- PRESUPPOSTI -

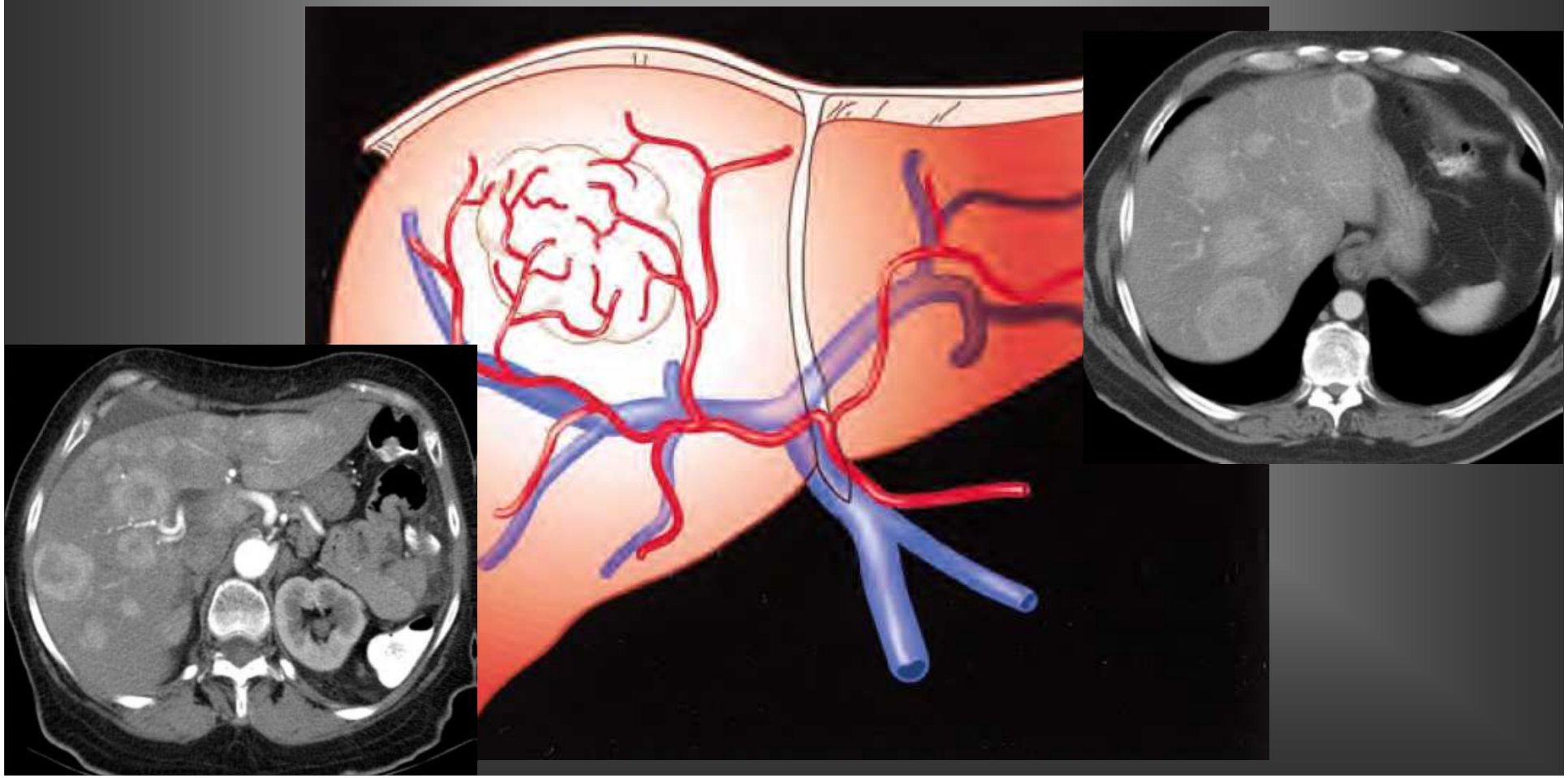
1 – Doppia vascolarizzazione epatica



TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

- PRESUPPOSTI -

2 – Vascolarizzazione arteriosa delle metastasi epatiche da neoplasie neuroendocrine



TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

TECNICHE

- **BLAND EMBOLIZATION (TAE)**
- **CHEMOEMBOLIZATION (cTACE)**
- **DRUG ELUTING BEADS (DEB TACE)**
- **RADIOEMBOLIZATION (RE)**

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

BLAND EMBOLIZATION (TAE)

Microsfere

Spugna gelatinica

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

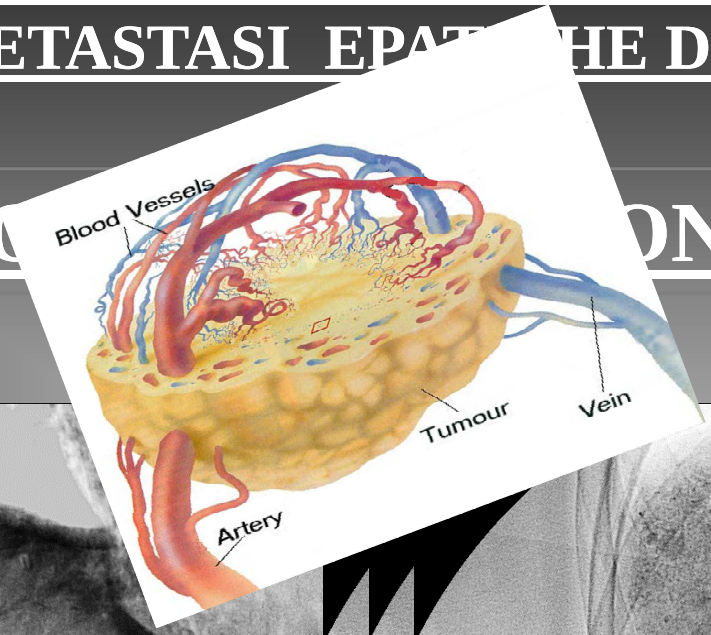
CHEMOEMBOLIZATION (cTACE)

Tropismo del Lipiodol Ultrafluid (LUF) per i tumori vascolarizzati dall'arteria epatica

Kanematsu T., Inokuchi K.
Treatment of liver cancer and concomitant esophageal varices
Nippon Geka Gakkai Zasshi 1983;84(9) :923-6

TERAPIA TRANSARTERIOSA
METASTASI EPA HE DA NET

CHEMO ON (cTACE)

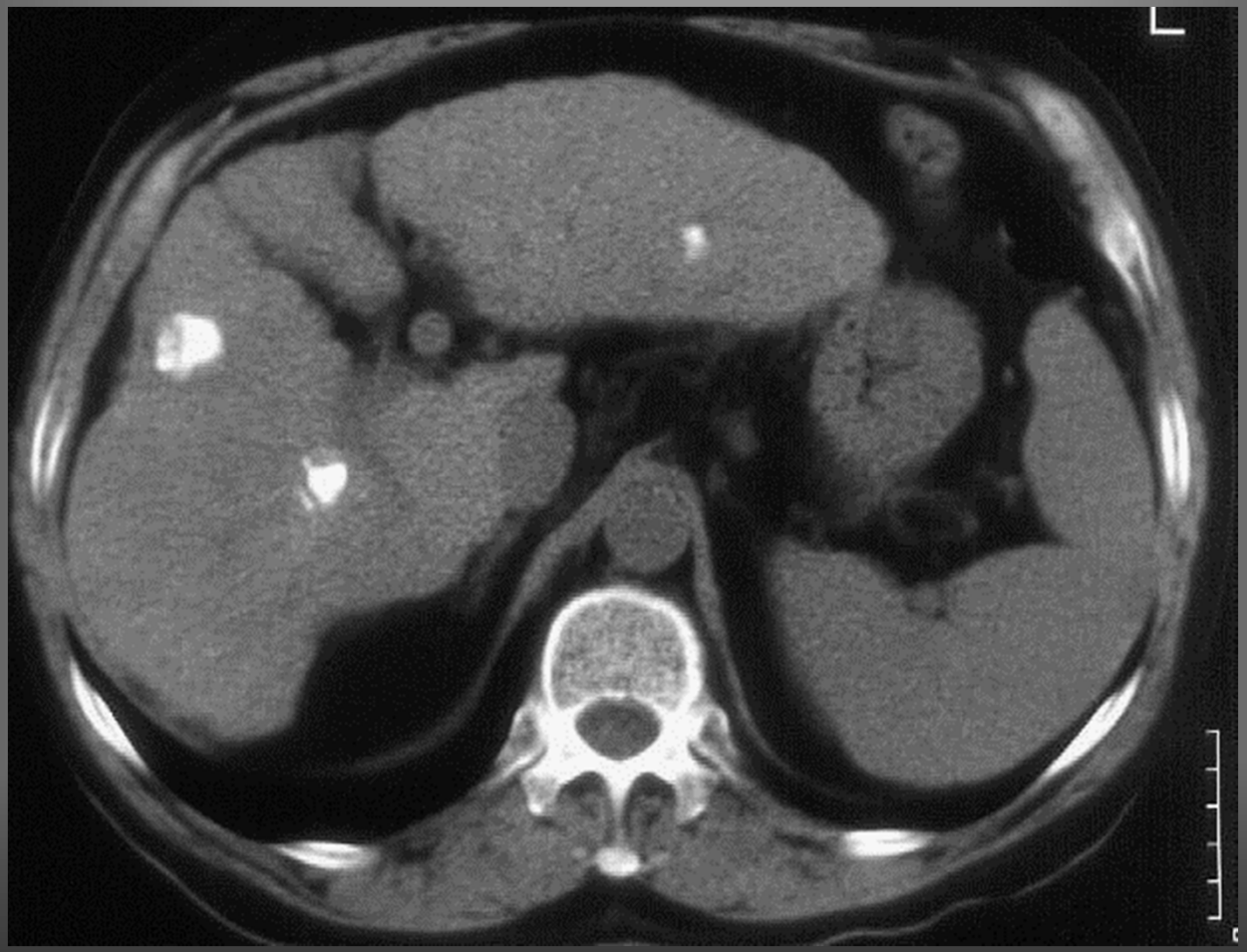


Arteriografia epatica

Chemioembolizzazione

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

CHEMOEMBOLIZATION (cTACE)



TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

•DRUG ELUTING BEADS (DEB TACE)

Microsfere a rilascio di farmaco

Razionale di Utilizzo

- Prolungato rilascio di farmaco all'interno dei rami arteriosi tumorali
- Incremento dell'effetto citotossico sulle cellule neoplastiche senza incremento della tossicità d'organo
- Decremento della dispersione sistemica del chemioterapico con conseguente riduzione degli effetti collaterali

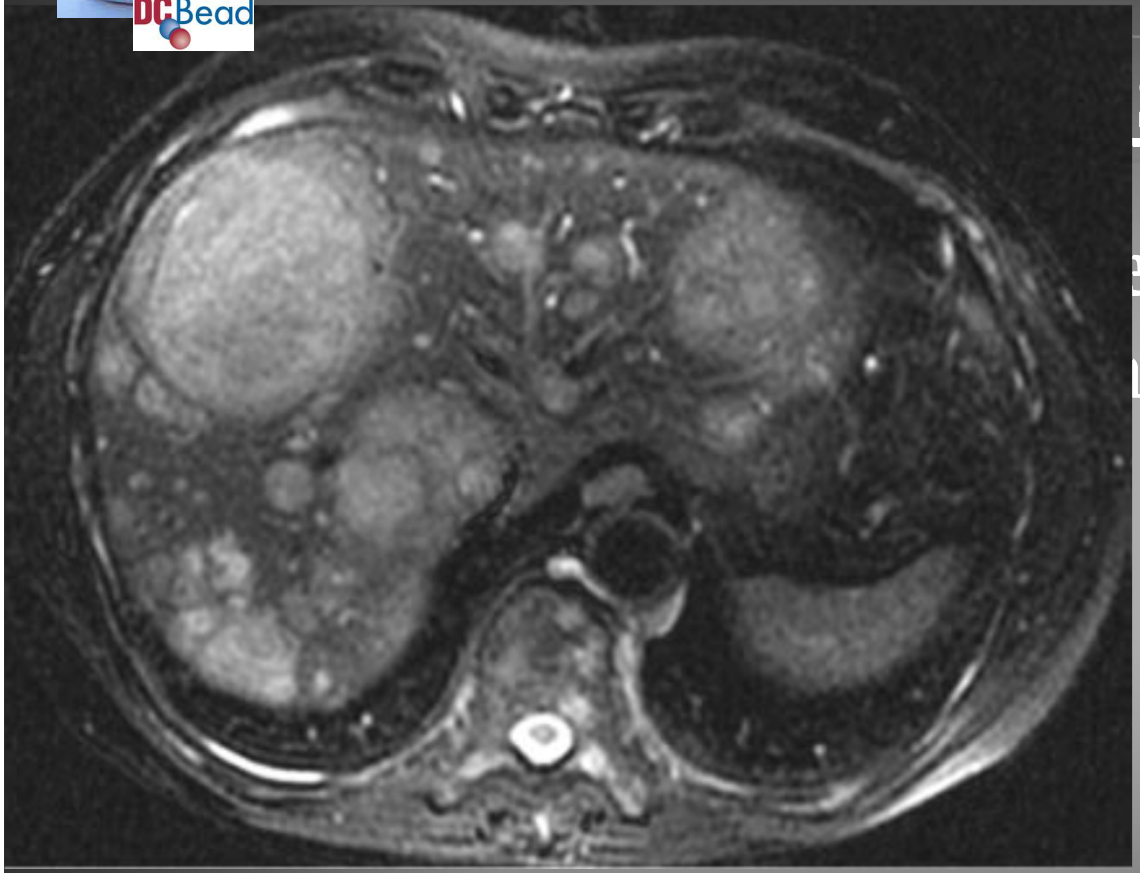
TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

S (DEB TACE)

e con microsfere

ne superselettiva

(Precision TACE)



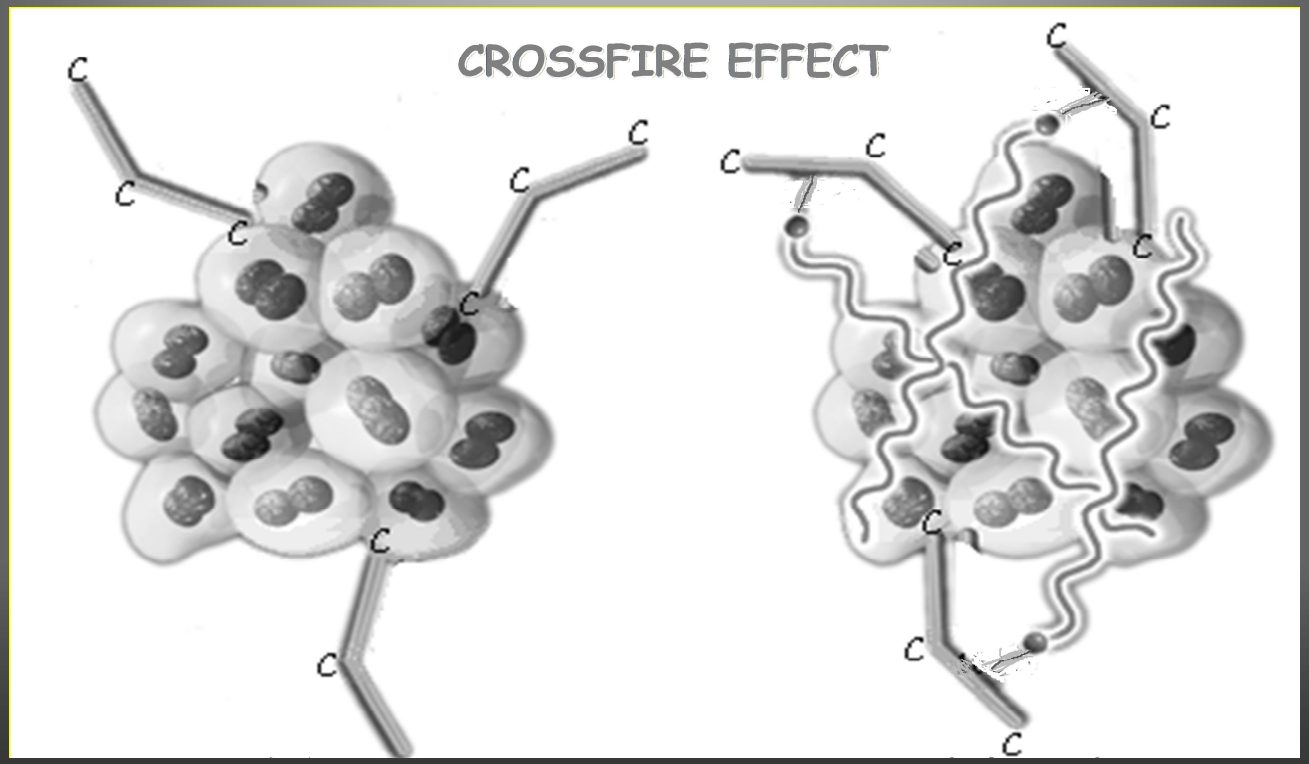
Sulla base dell'estensione tumorale intraepatica (grandezza e numero delle lesioni, estensione mono o bilobare) può essere necessario modulare il trattamento in più sessioni ad intervalli di 30-60 gg

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

•RADIOEMBOLIZATION (RE)

SIR-Spheres®
Yttrium-90 microspheres
Tomorrow's standard practice in the treatment of Liver Cancer

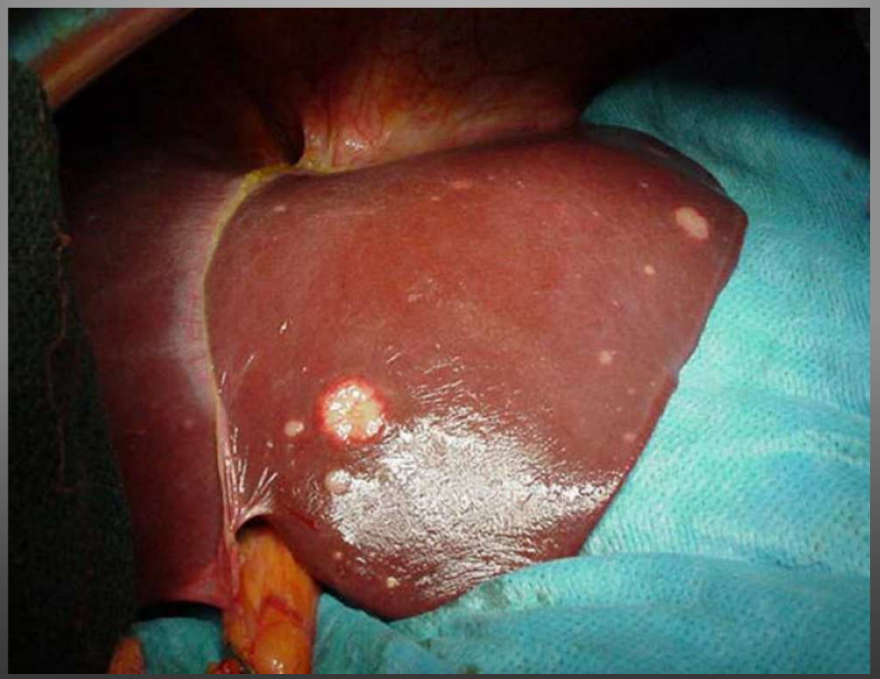
Lipiodol Radioattivo



TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

CRITERI DI INCLUSIONE

Controindicazione alla chirurgia e/o
alle procedure ablative locoregionali ecoguidate



TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

CONTROINDICAZIONI

- **Trombosi portale**
- **Bilirubinemia >2-3 ml/dL**
- **Estensione tumorale epatica >75%**

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

COMPLICANZE

-Sindrome post-embolizzazione (dolore, febbre, nausea, ileo) — 70%

- Colecistite
- Arterite
- Ascesso epatico
- Stenosi biliari
- Insufficienza epatica
- Sindrome epato-renale
- Pancreatite

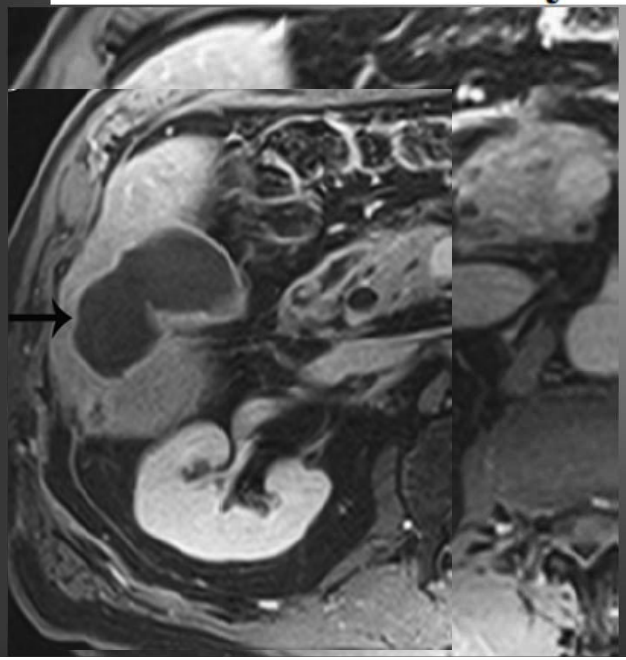
— 4%

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

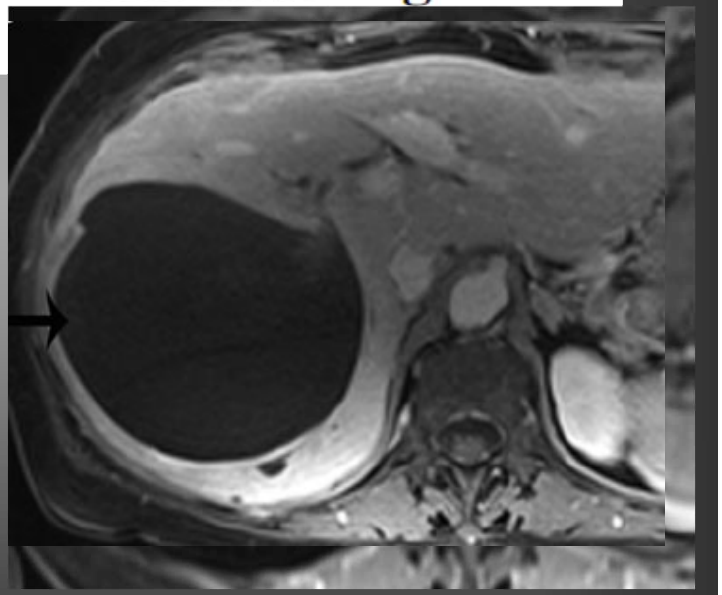
COMPLICANZE

Nikhil Bhagat · Diane K. Reyes · Mingde Lin · Ihab Kamel · Timothy M. Pawlik · Constantine Frangakis · J. F. Geschwind

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



Bilomas 54%



Cardiovasc Intervent Radiol (2013) 36:449–459

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

COMPLICANZE

Nikhil Bhagat · Diane K. Reyes · Mingde Lin · Ihab Kamel · Timothy M. Pawlik · Constantine Frangakis · J. F. Geschwind

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

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.

Cardiovasc Intervent Radiol (2013) 36:449–459

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

COMPLICANZE

Our institution reported a series of 120 patients with GEP-NET liver metastasis treated with either DEB–TACE or Lipiodol–TACE.
In this patient cohort, the occurrence of liver/biliary injury in non-tumoral territories was strongly and independently associated with DEB–TACE (odds ratio (OR)Z6.63; P!0.001), and more serious complications such as bilomas and parenchymal infarcts were as well both significantly associated with DEB–TACE vs Lipiodol–TACE (ORZ9.78; PZ0.002)

Interventional radiology: role in the treatment of liver metastases from GEP-NETs

Thierry de Baere[1,6], Frederic Deschamps[1], Lambros Tselikas[1], Michel Ducreux[2,6], David Planchard[2], Ernesto Pearson[1], Amandine Berdelou[3], Sophie Leboulleux[3], Dominique Elias[4] and Eric Baudin[5]

European Journal of Endocrinology
(2015) 172, R151–R166

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

RISULTATI

EFFETTO SULLA SINTOMATOLOGIA

EFFETTO SULLA MASSA TUMORALE

EFFETTO SULLA SOPRAVVIVENZA

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

EFFETTO SULLA SINTOMATOLOGIA

Remissione dei sintomi nel 60% - 100% dei pazienti trattati

Table 1 Symptoms and hormonal secretion

Reference	No./Type	Chemotherapy	Sustained relief (%) (in symptomatic pts)	5-HIAA decrease > 50% (results only for CT)
Therasse *et al.* (1993)	23/CT	ADR	100	91
Ruszniewski *et al.* (1993)	18/CT 5/ICC	ADR	73	57
Clouse *et al.* (1994)	14/CT*	ADR	90	69
Diaco *et al.* (1995)	10/CT	CDDP, MMC, ADR**	100	—
Rusniewski & Malka (2000)	8/CT 7/ICC	STZ (1.5 g/m²)	67	50
Roche *et al.* (2003)	10/CT 4/other	ADR	70	75

ICC, islet cell tumor; CT, patients with carcinoid syndrome mostly from midgut origin; ADR, adriamycin; MMC, mitomycin; CCDP, cisplatin.
*Mostly CT; all 14 tumors were functionally active; ** sequential intra-arterial 5-fluorouracil also administered.

D O'Toole, F Marie and P Ruszniewski.
Ablative therapies for liver metastases of endocrine tumors Endocrine-Related Cancer (2003) 10 463-468

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

EFFETTO SULLA MASSA TUMORALE

Risposta oggettiva 33% – 86 %

Table 2 Variations in tumor size (according to WHO criteria)

Reference	No./Type	Objective response (%)	Mean duration (months)	Progression rate (%)
Therasse *et al.* (1993)	23/CT	35	—	12
Ruszniewski *et al.* (1993)	18/CT 5/ICC	33	21	17
Mavligit *et al.* (1993)	5/ICC	80	18.5	—
Clouse *et al.* (1994)	20/CTor ICC	78	6–8.5	—
Diaco *et al.* (1995)	10/CT	60	42.5	—
Ruzniewski & Malka (2000)	8/CT 7/ICC	53	10.5	26
Roche *et al.* (2003)	10/CT 4/other	86	—	14

D O'Toole, F Marie and P Ruszniewski.
Ablative therapies for liver metastases of endocrine tumors Endocrine-Related Cancer (2003) 10 463-468

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

EFFETTO SULLA SINTOMATOLOGIA

EFFETTO SULLA MASSA TUMORALE

Results:

Symptomatic improvement was observed in 75% of patients .
Radiological response was observed following 73% of embolization treatments delivered

Hepatic artery embolization in advanced neuroendocrine tumors: Efficacy and long-term outcomes

Marinos PERICLEOUS,[1] Martyn E CAPLIN,[1] Emmanuel TSOCHATZIS,[3] Dominic YU,[2] Luke MORGAN-ROWE[2] and Christos TOUMPANAKIS[1]

Asia-Pacific Journal of Clinical Oncology 2016; 12: 61–69

TERAPIA TRANSARTERIOSA METASTASI EPATICHE DA NET

EFFETTO SULLA SOPRAVVIVENZA

Studies have demonstrated efficacy of these liver-directed embolotherapies for tumor growth reduction and NET symptom relief, with current 5-year survival rates of over 60% and response rates between 70% and 90%

Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial

James X. Chen[1], E. Paul Wileyto[2,3] and Michael C. Soulen[1,3,4*]

Trials (2018) 19:390

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

RISULTATI

QUALE TECNICA ?

Which intra-arterial therapies?

There is no strong argument today to choose between available intra-arterial therapies, and further randomized studies would help rule out some of the therapies based on efficacy, safety, or pharmacoeconomic outcomes. At present, Lipiodol–TACE is the intra-arterial therapy with the largest volume of data, followed by TAE, while DEB–TACE and RE are more recent and consequently have much less data, namely on long-term toxicity

In the absence of such randomized clinical trials favoring DEB–TACE, it is advisable to use Lipiodol-TACE especially when the total liver is treated

RE carries the advantage of minimal side effects in the early post-treatment period, but irradiation delivered to the healthy liver makes the treatment less repeatable than TACE because of the risk of RILD.

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European Journal of Endocrinology
(2015) 172, R151–R166

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

RISULTATI

QUALE TECNICA ?

***Conclusions*:**

TAE/TACE are beneficial treatments for control of symptoms as well as tumor growth, with acceptable morbidity and mortality rates. No significant efficacy and survival differences were shown between TAE and TACE.

Hepatic artery embolization in advanced neuroendocrine tumors: Efficacy and long-term outcomes

Marinos PERICLEOUS,[1] Martyn E CAPLIN,[1] Emmanuel TSOCHATZIS,[3] Dominic YU,[2] Luke MORGAN-ROWE[2] and Christos TOUMPANAKIS[1]

Asia-Pacific Journal of Clinical Oncology 2016; 12: 61–69

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

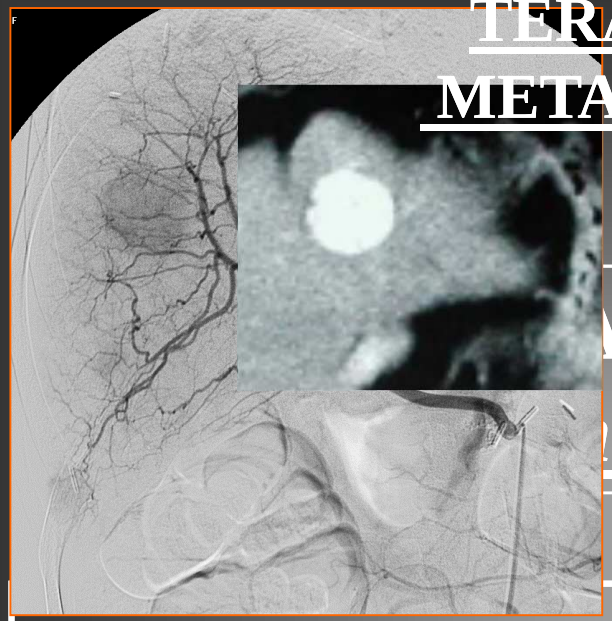
META-ANALISI della LETTERATURA
Informazioni tecniche

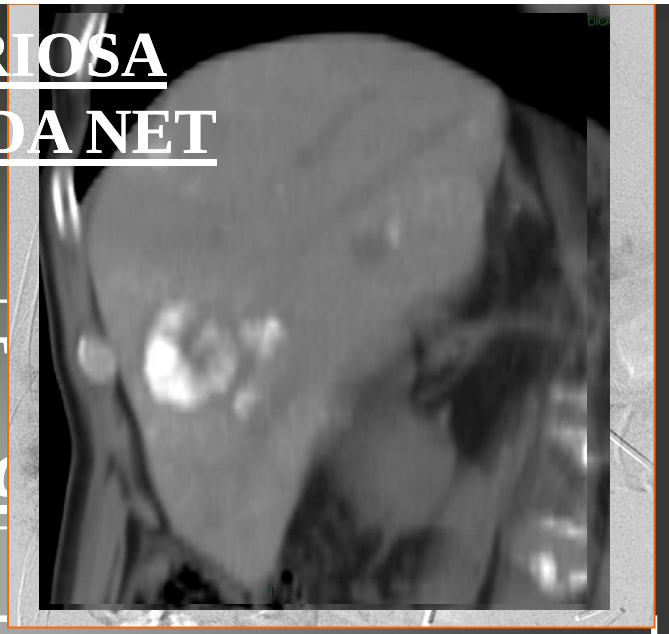
***Cicli ripetuti di trattamento**, modulati sulla risposta morfologica e sulla tolleranza clinica, aumentano l'efficacia terapeutica.*

Steward M.J., et al.
Neuroendocrine Tumors: Role of Interventionale Radioogy in Therapy
RadioGraphics 17:1235-1250 (2008)

Madoff D C, et al.
Update in the Management of Neuroendocrine Hepatic Metastases
JVIR 17:1235-1250 (2006)

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET





ALISI della LET
formazioni tecni

*I pazienti con **coinvolgimento del parenchima epatico superiore al 50% - 75%** hanno un outcome peggiore*

Steward M.J., et al.
Neuroendocrine Tumors: Role of Interventionale Radioogy in Therapy
RadioGraphics 17:1235-1250 (2008)

Touzios, et al.
Neuroendocrine Hepatic Metestases: Does Aggressive Management improve survival?
Ann Surg 241: 776-785 (2005)

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

META-ANALISI della LETTERATURA
Informazioni tecniche

L'Associazione con altre terapie aumenta l'efficacia terapeutica :

- -Chirurgia
- - PEI
- - RF
- - Radioterapia interna
- - Immunoterapia
- - Terapia genica
- - Terapia antiangiogenetica

Madoff D C, et al.
Update in the Management of Neuroendocrine Hepatic Metastases
JVIR 17:1235-1250 (2006)

TERAPIA TRANSARTERIOSA METASTASI EPATICHE DA NET

SVILUPPI

12.15 La terapia radiometabolica *M. Bartolomei*

Terapia radiorecettoriale con analoghi radiomarcati della somatostatina in tumori con elevata espressione dei recettori per la somatostatina

Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases

Clemens Kratochwil, Ruben López-Benítez[1], Walter Mier, Sabine Haufe, Berend Isermann[2], Hans-Ulrich Kauczor[1], Peter L Choyke[3], Uwe Haberkorn and Frederik L Giesel

Endocrine-Related Cancer (2011) **18** 595–602

TERAPIA TRANSARTERIOSA METASTASI EPATICHE DA NET

SVILUPPI

Abstract

Intravenously administered radiolabeled peptides targeting somatostatin receptors are used for the treatment of unresectable gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Recently, we demonstrated a high first-pass effect during intra-arterial (i.a.) administration of positron emission tomography (PET) labeled ^{68}Ga-DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC). In this pilot study, we investigated the therapeutic effectiveness of arterial administered DOTATOC, labeled with the therapeutic β emitters ^{90}Y and ^{177}Lu. ^{90}Y- and/or ^{177}Lu-DOTATOC were infused into the hepatic artery of 15 patients with liver metastases arising from GEP-NETs. Response was assessed using DOTATOC-PET, multiphase contrast enhanced computed tomography, magnetic resonance imaging, and the serum tumor marker chromogranin A. Pharmacokinetic data of the arterial approach were assessed using ^{111}In-DOTATOC scans. With the treatment regime of this pilot study, complete remission was achieved in one (7%) patient and partial remission was observed in eight (53%) patients, six patients were classified as stable (40%; response evaluation criteria in solid tumors criteria). The concomitant decrease of elevated serum tumor marker confirmed the radiologic response. Median time to progression was not reached within a mean follow-up period of 20 months. Receptor saturation and redistribution effects were identified as limiting factors for i.a. DOTATOC therapy. The high rate of objective radiologic response in NET patients treated with arterial infusion of ^{90}Y-/^{177}Lu-DOTATOC compares favorably with systemic chemotherapy and intravenous radio-peptide therapy. While i.a. DOTATOC therapy is only applicable to patients with tumors of limited anatomic distribution, the results of this pilot study are a promising development in the treatment of GEP-NET and warrants further investigation of this novel approach.

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

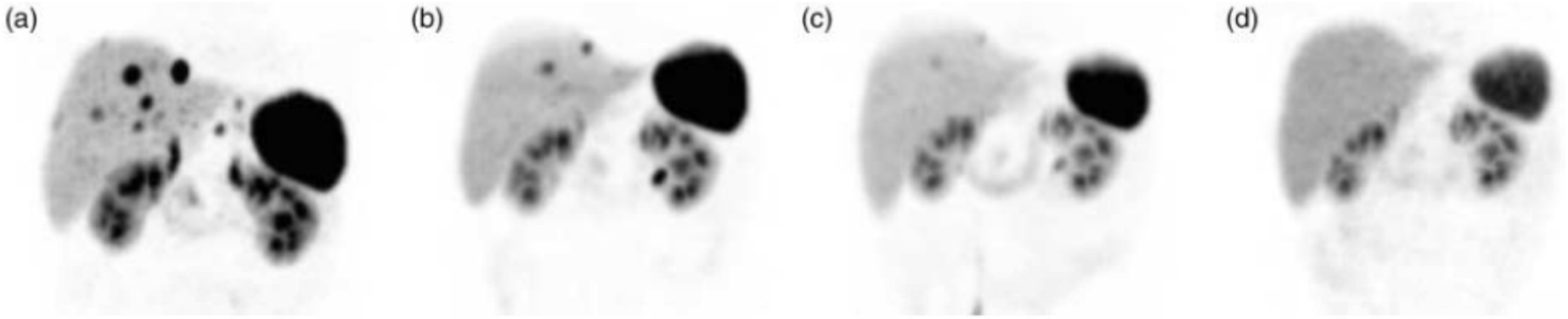


Figure 1 Complete remission. Maximum intensity projections of initial and follow-up examinations with ^{68}Ga-DOTATOC (DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide) positron emission tomography (PET). A patient presented with 12 neuroendocrine liver metastases as diagnosed with magnetic resonance imaging (MRI) and ^{68}Ga-DOTATOC-PET. (a) After each cycle of intra-arterial radiopeptide therapy regression of the metastases was observed (b and c). After three cycles complete remission was demonstrated both in MRI and DOTATOC-PET (d). A fourth cycle was performed for consolidation and the complete remission is still present with 27 months of follow-up.

Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases

Clemens Kratochwil, Ruben López-Benítez[1], Walter Mier, Sabine Haufe, Berend Isermann[2], Hans-Ulrich Kauczor[1], Peter L Choyke[3], Uwe Haberkorn and Frederik L Giesel

Endocrine-Related Cancer (2011) **18** 595–602

Intra-Arterial Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumor Liver Metastases

Sander C. Ebbers, MD[1] Maarten W. Barentsz, MD, PhD[2] Arthur J.A.T. Braat, MD[3] Marnix G.E.H. Lam, MD, PhD[4]

[1] Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
[3] Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
[4] Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Address for correspondence Sander C. Ebbers, MD, PhD, Candidate, Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA, Utrecht, The Netherlands (e-mail: S.C.Ebbers-2@umcutrecht.nl).

Dig Dis Interv 2019;3:81–90.

Abstract

Purpose Currently, peptide receptor radionuclide therapy (PRRT) with lutetium-177 (^{177}Lu)-DOTATATE is used in patients with progressive neuroendocrine neoplasms (NEN) as salvage therapy. The standard treatment schedule consists of multiple cycles of intravenous (IV) administration. However, patients with liver metastases suffer from reduced tumor targeting and worse response and survival. This review provides an overview of the available evidence on the intra-arterial (IA) administration of radionuclide-labeled somatostatin analogues.

Methods Databases of PubMed and Embase were searched systematically in May 2018 for studies that addressed IA PRRT. Included studies were original research publications focusing on absorbed tumor dose or tumor response after IA administration of PRRT for NEN. Publications on combined PRRT with other therapies or treatment of nonhepatic sites were excluded. Included publications were critically appraised on quality and their results reported accordingly.

Results Seven publications were included in this review, including a total of 114 patients treated IA with different types of radiopeptides. Objective response was seen in 13 to 69% of the patients and disease stabilization in 18 to 52%. Disease progression occurred in 0 to 29% of the patients. IA administration resulted in a 1.06 to 9.2-fold increase in tumor-to-nontumor dose ratios in liver tumors, while normal liver and kidney doses remained within expected ranges. The incidence of adverse events was comparable to IV administration.

Conclusion There is limited evidence that IA application of PRRT results in higher tumor-to-non-tumor dose ratios compared with IV infusion. IA administration of ^{177}Lu-DOTATATE seems to be a promising new improvement in current clinical practice, achieving a higher absorbed tumor dose in patients with hepatic metastases of NEN.

Keywords

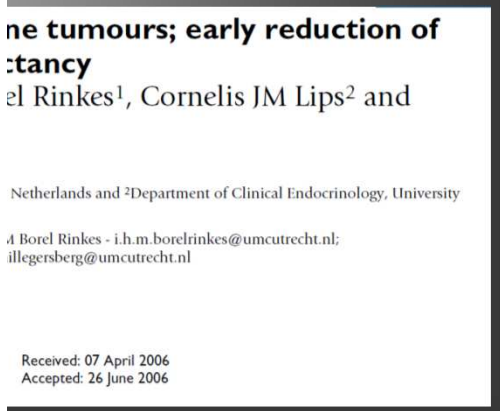
- intra-arterial
- peptide receptor radionuclide therapy
- neuroendocrine neoplasm
- liver metastases
- lutetium-177-DOTA-octreotate

TERAPIA TRANSARTERIOSA METASTASI EPATICHE DA NET

CONCLUSIONI

Conclusion:

Treatment for patients with neuroendocrine hepatic metastases **must be tailored for each individual patient.** When local ablative therapies are used early in the course of the disease, the occurrence of carcinoid syndrome with end stage hepatic disease can be postponed or prevented.


ne tumours; early reduction of
tancy
el Rinkes[1], Cornelis JM Lips[2] and

Netherlands and [2]Department of Clinical Endocrinology, University

M Borel Rinkes - i.h.m.borelrinkes@umcutrecht.nl;
illegersberg@umcutrecht.nl

Received: 07 April 2006
Accepted: 26 June 2006

TERAPIA TRANSARTERIOSA
METASTASI EPATICHE DA NET

Azienda Ospedaliero-Universitaria , Ferrara, Italy - VASCULAR AND INTERVENTIONAL RADIOLOGY UNIT

GRAZIE PER L'ATTENZIONE