

VIII EDIZIONE
NEN PRECEPTORSHIP
**LA PRATICA CLINICA NELLE
NEOPLASIE NEUROENDOCRINE**

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN  **Preceptorship**

 **IEO**
Istituto Europeo di Oncologia



Terapie locoregionali epatiche

Guido Bonomo

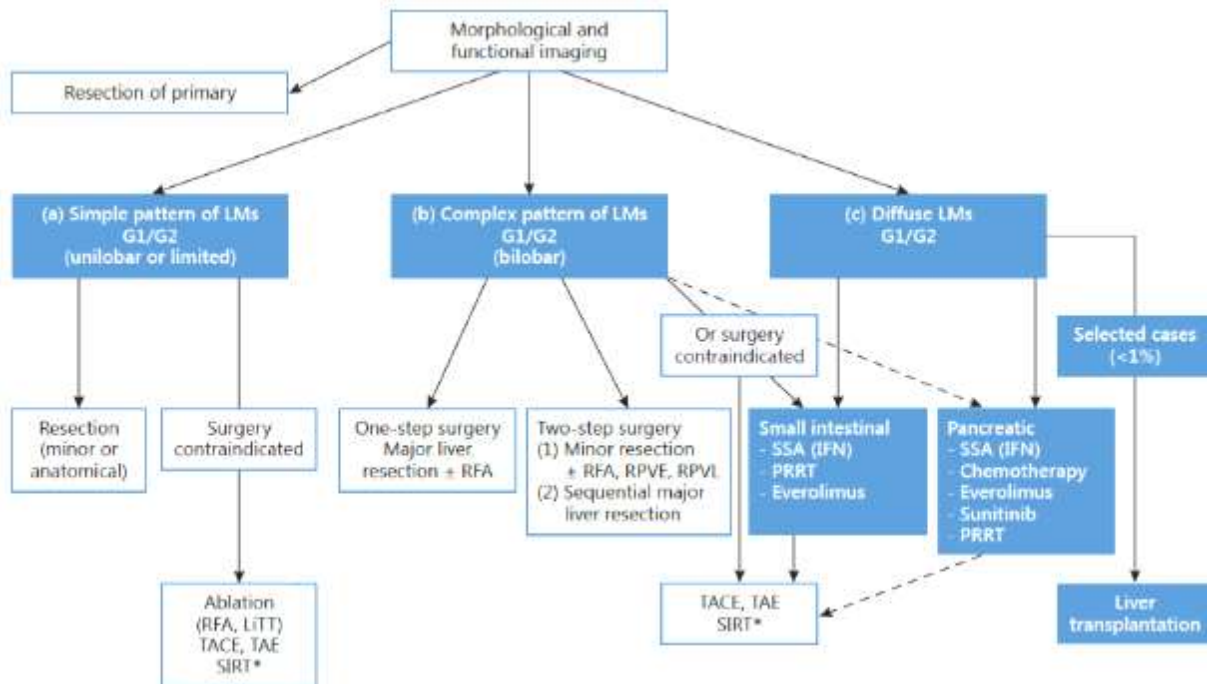
Divisione di Radiologia Interventistica



Nen

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. Pavel¹, D. O'Toole², F. Costa³, J. Capdevila⁴, D. Gross⁵, R. Kianmanesh⁶,
E. Krenning⁷, U. Knigge⁸, R. Salazar⁹, U.-F. Pape¹⁰, K. Oberg¹¹,
all other Vienna Consensus Conference participants



Indicazioni

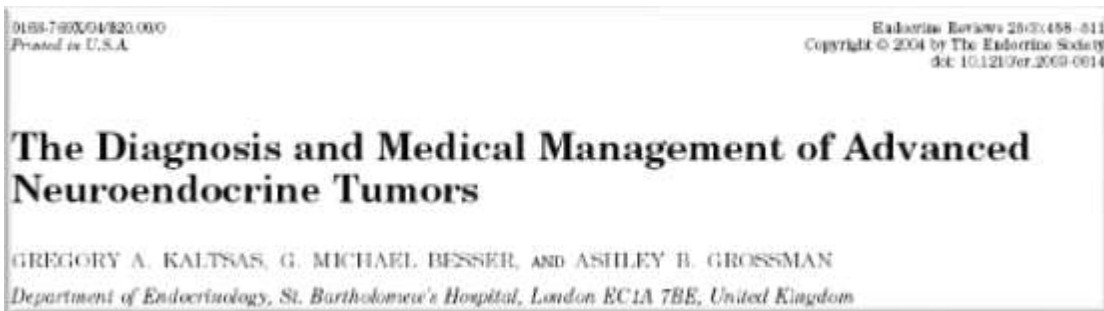
Locoregional Therapies

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].

Nen

Indicazioni

- La maggior parte dei NET ha una progressione lenta e metastatica
- Sopravvivenza a 5 anni nel metastatico **40 %**



Razionale per trattamenti locoregionali

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

Nen

Indicazioni

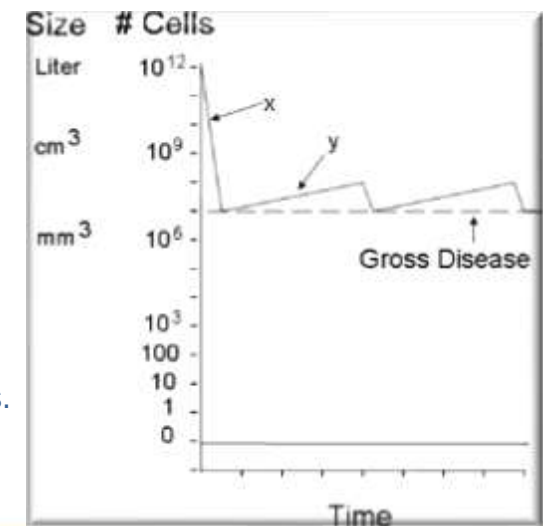
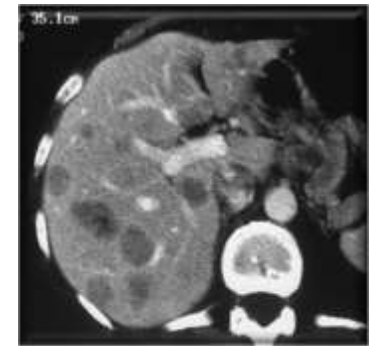
- La prognosi dipende dal coinvolgimento epatico e i sintomi sono spesso correlati con le metastasi epatiche

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

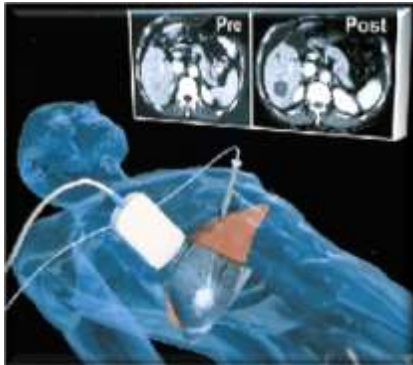
Cytoreduction is depicted by line x.
A long period may pass before regrowth of the tumor (y) to significant levels.

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



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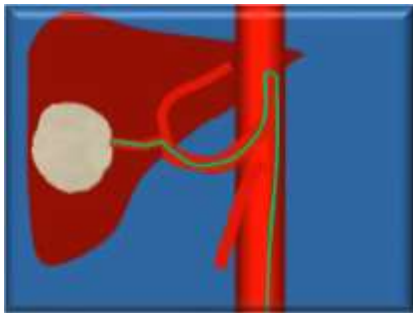
Indicazioni



● Percutanee

RFA- MWA

Tecniche combinate



● Intrarteriose

TAE (nuove particelle)

TACE

TARE

Nen

Review	T de Baere and others	Interventional radiology in GEP-NET treatment	172-4	R151-R166
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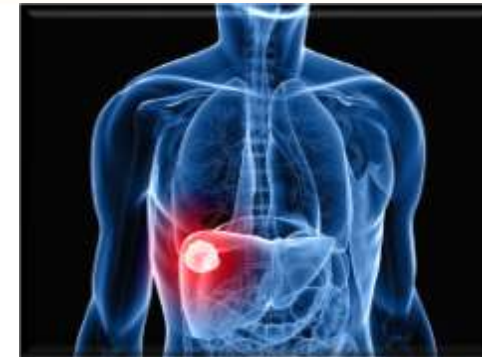
GEP-NETS UPDATE

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

Thierry de Baere^{1,2}, Frederic Deschamps¹, Lambros Tselikas¹, Michel Ducreux^{3,4},
David Planchard⁵, Ernesto Pearson⁶, Amandine Berdelou⁷, Sophie Leboulleux⁸,
Dominique Elias⁹ and Eric Baudin⁵

¹Interventional Radiology, ²Medical Oncology, ³Nuclear Medicine and Endocrine Oncology, ⁴Oncology Surgery,
⁵Endocrinology, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France and
⁶Université Paris-Saclay, Le Kremlin-Bicêtre, France

Correspondence
should be addressed
to T de Baere
Email:
tdeb@igro.fr



Abstract

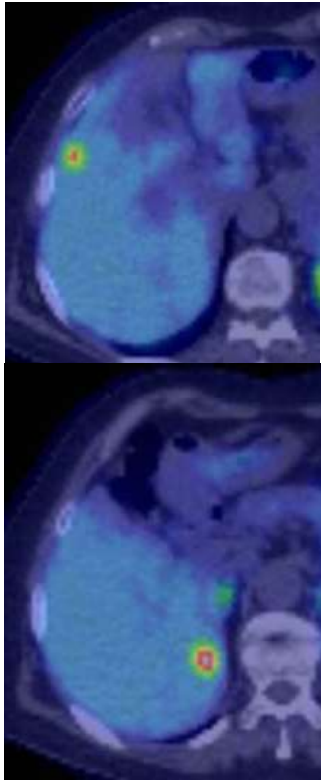
Neuroendocrine tumors from gastro-pancreatic origin (GEP-NET) can be responsible for liver metastases. Such metastases can be the dominant part of the disease as well due to the tumor burden itself or the symptoms related to such liver metastases. Intra-arterial therapies are commonly used in liver only or liver-dominant disease and encompass trans-arterial chemoembolization (TACE), trans-arterial embolization (TAE), and radioembolization (RE). TACE performed with drug emulsified in Lipiodol has been used for the past 20 years with reported overall survival in the range of 3–4 years, with objective response up to 75%. Response to TACE is higher when treatment is used as a first-line therapy and degree of liver involvement is lower. Benefit of TACE over TAE is unproven in randomized study, but reported in retrospective studies namely in pancreatic NETs. RE provides early interesting results that need to be further evaluated in terms of benefit and toxicity. Radiofrequency ablation allows control of small size and numbered liver metastases, with low invasiveness. Ideal metastases to target are one metastasis <5 cm, or three metastases <3 cm, or a sum of diameter of all metastases below 8 cm. Ablation therapies can be applied in the lung or in the bones when needed, and more invasive surgery should be probably saved for large-size metastases. Even if the indication of image-guided therapy in the treatment of GEP-NET liver metastases needs to be refined, such therapies allow for manageable invasive set of treatments able to address oligometastatic patients in liver, lung, and bones. These treatments applied locally will save the benefit and the toxicity of systemic therapy for more advanced stage of the disease.

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

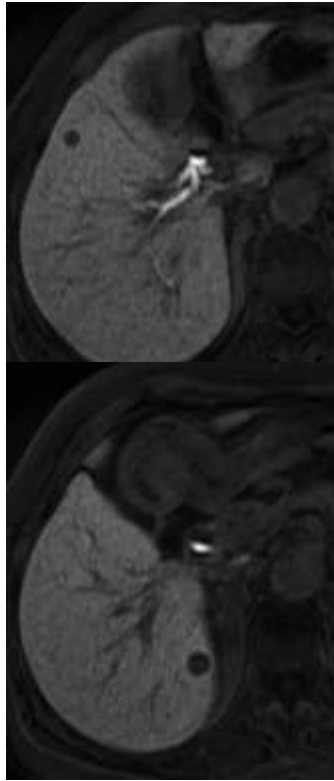
Nen

Termoablazione

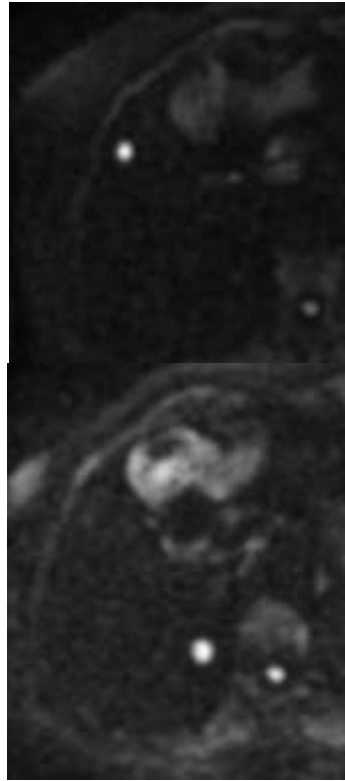
NEN ileo G1 , Ki67=1%, M+ fegato → emicolectomia dx + analogo → SD → intolleranza all'analogo



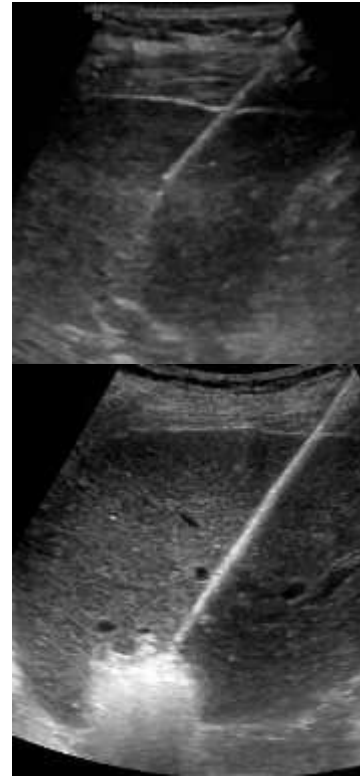
Pet Ga68



RMN +C



RMN diff



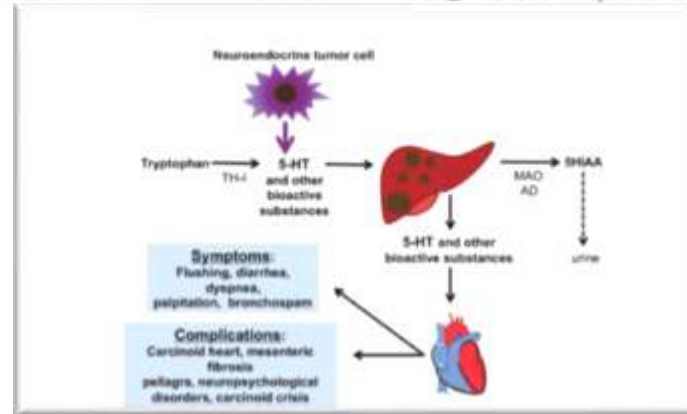
MWA



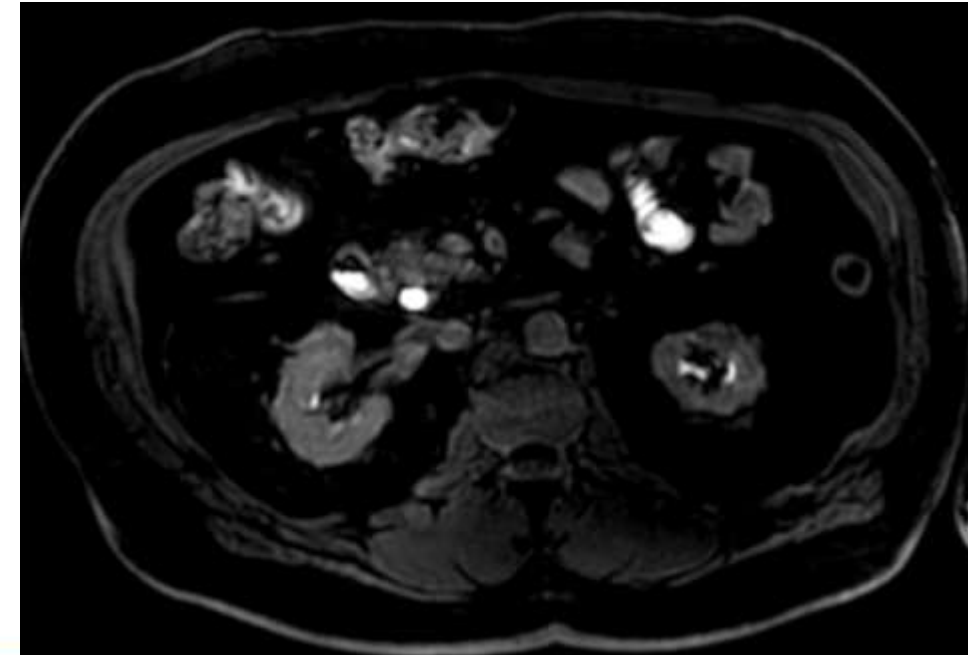
TC 24 hr

Nen

NEN ileale G2-3 , Ki67=30% ileo, 15%
M+ fegato, funzionante.
Programma : debulking per sindrome



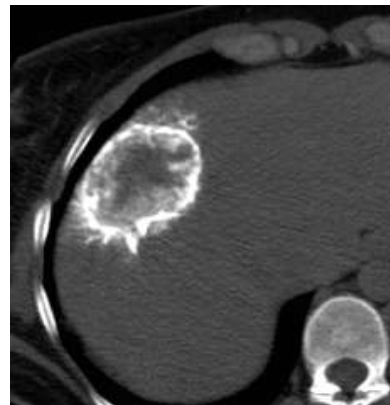
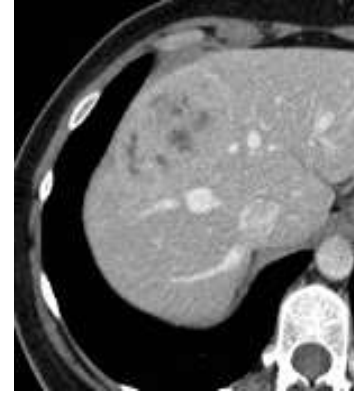
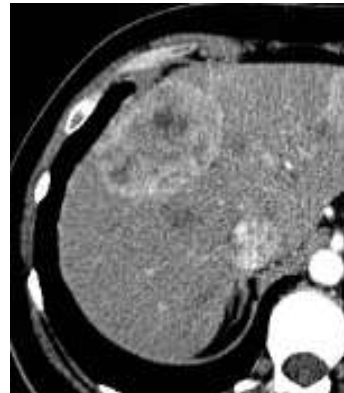
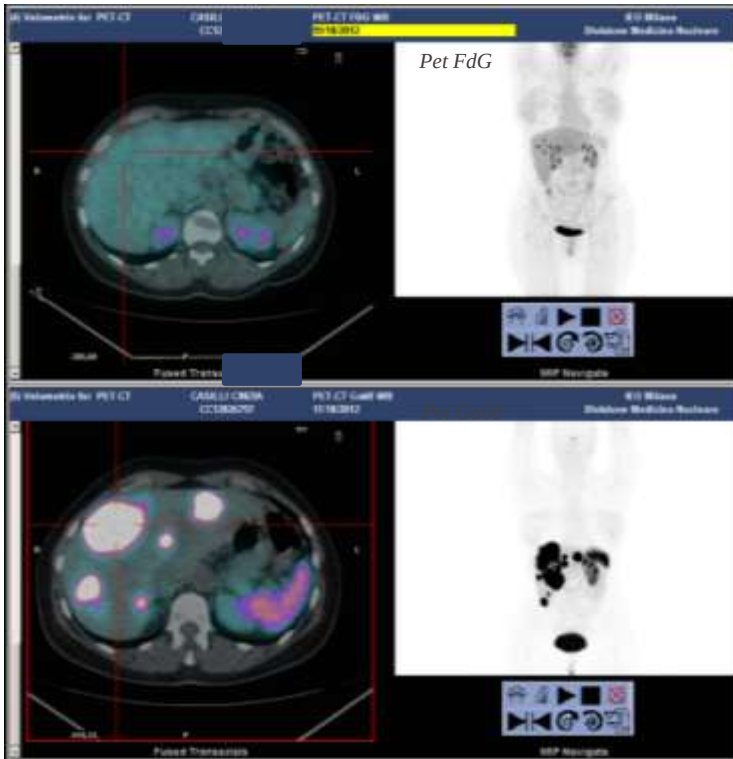
TAE



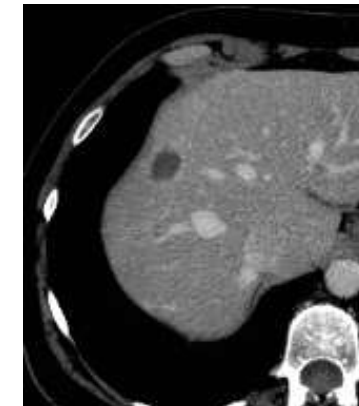
Nen

TAE

NEN pancreas G2 , Ki67=5%, M+ fegato, funzionante. Programma : debulkig + PRRT



9 mesi



PRRT

Nen

ORIGINAL ARTICLE

Safety and Effectiveness of ^{177}Lu -DOTATATE Peptide Receptor Radionuclide Therapy After Regional Hepatic Embolization in Patients With Somatostatin-Expressing Neuroendocrine Tumors

Mohammadali Hamiditabar, MD,* Muzammil Ali, MD,* Luke Bolek, MD,* Gelareh Vahdati, MD,* Izabela Tworowska, PhD,† and Ebrahim S. Delpassand, MD*†

DOTATATE ($r = -0.59$ to 0.17). In our analysis, the average time interval between CHE and PRRT was 32.4 months (4.2–134.8 months) and between RHE and PRRT was 30.5 months (4.8–93.6 months). Based on these data, it is advisable to perform PRRT 4 to 6 months after any HE procedure. This assessment may help answer the “safe time interval” concern before starting PRRT following HE.

TAE & PRRT

Purpose: Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu -DOTATATE is shown to be an effective therapeutic option for somatostatin-expressing neuroendocrine neoplasms. Some concerns are raised over safety of this modality in patients with a history of regional chemoembolization and radionuclide hepatic embolization (CRHE) and is cause of reluctance among some physicians for suggesting ^{177}Lu -DOTATATE in this patient population.

Methods: We retrospectively reviewed 143 patients with somatostatin-expressing neuroendocrine tumors who underwent ^{177}Lu -DOTATATE PRRT. Statistical analysis was performed on effect of ^{177}Lu -DOTATATE in patients with and without prior CRHE using resampling procedures and correlation coefficient (r).

Results: Proportion of toxicity in patients with and without CRHE was comparable ($P = 0.246$). No statistically significant correlation (r) found between any toxicity and prior CRHE ($r = -0.3$ to -0.03) or time elapsed between embolization and the first cycle of PRRT ($r = -0.59$ to 0.17). Following PRRT, 76.5% of patients with CRHE experienced benefit (partial response + stable disease), whereas 23.4% experienced progressive disease. Patients with CRHE showed more stable disease ($P = 0.048$) and less progressive disease ($P = 0.046$) following PRRT compared with no CRHE. The CRHE and no-CRHE status shared same probability for developing partial response/complete response following PRRT ($P = 0.50$).

Conclusions: Treatment with ^{177}Lu -DOTATATE did not show clinically or statistically significant toxicity in CRHE patients regardless of frequency of embolization or time interval between embolization and first PRRT. Results suggested a statistically significant higher response rate in patients with a history of CRHE. A prior history of CRHE is not a contraindication to subsequent PRRT.

Nen

TAE & Sunitinib

A phase II clinical trial of sunitinib following hepatic transarterial embolization for metastatic neuroendocrine tumors

J. R. Strosberg^{1*}, J. M. Weber¹, J. Choi², T. L. Campos¹, T. L. Valone¹, G. Han³, M. J. Schell³ & L. K. Kvols¹

Departments of ¹Gastrointestinal Oncology; ²Interventional Radiology; ³Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA

Received 13 October 2011; revised 12 December 2011; accepted 13 December 2011

Background: The liver is the predominant site of metastases among patients with advanced neuroendocrine tumors (NETs). Prior retrospective studies have reported high response rates in patients treated with transarterial embolization (TAE). NETs are highly vascular and are known to express vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR). We hypothesized that administration of sunitinib, a VEGFR inhibitor, following TAE would extend progression-free survival (PFS).

Patients and methods: Patients with metastatic NETs to the liver underwent a series of selective TAEs followed by sunitinib (until disease progression or maximum of 12 months). Radiographic response (by RECIST), survival, and safety parameters were monitored.

Results: Thirty-nine patients were enrolled. The overall response rate was 72% [95% confidence interval (CI), 0.58–0.86]. Median PFS was 15.2 months. Rates of overall survival (OS) at 1 and 4 years were 95% (95% CI, 0.88–1.00) and 59% (95% CI, 0.38–0.80), respectively. A significant 34% rise in serum VEGF was observed following the initial TAE ($P = 0.03$).

Conclusions: Hepatic TAE is a highly active treatment option for patients with metastatic NETs to the liver. Embolization stimulates release of VEGF into the circulation. Sunitinib, an oral VEGFR inhibitor, can be safely administered following embolization. The high rates of PFS and OS associated with this sequence of therapies are encouraging.

TACE

Nen

Drug



+



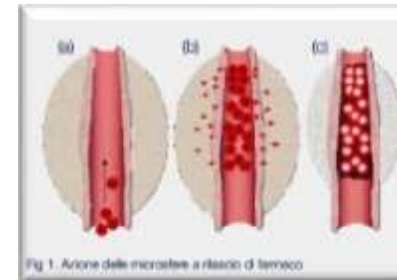
Lipiodol



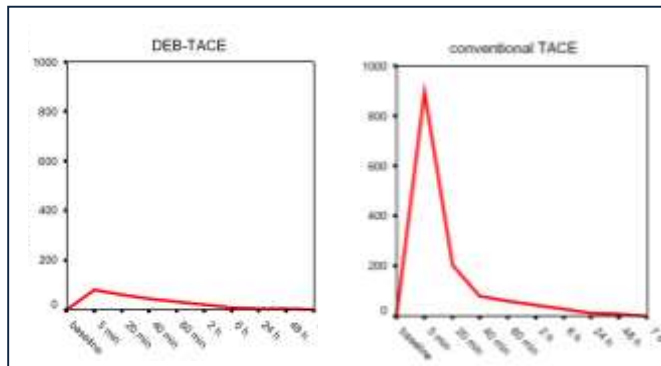
Conventional chemoembolization



-DCBead



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..”

Nen

TACE

 NIH Public Access
Author Manuscript
Published in final edited form as:
Carcinoma 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

Research Article



**Liver/biliary injuries following chemoembolisation
of endocrine tumours and hepatocellular carcinoma:
Lipiodol vs. drug-eluting beads**

Boris Guin^{1,2,*}, Frédéric Deschamps¹, Serge Aho³, Flore Munck¹, Clarisse Dromain⁴, Valérie Boige⁵,
David Malka⁶, Sophie Leboulleux⁸, Michel Ducreux⁹, Martin Schlumberger⁷, Eric Baudin⁶,
Thierry de Baere¹

Journal of Hepatology 2012 vol. 56 | 609–617

Background & Aims: Transarterial chemoembolisation (TACE) is usually performed by injecting an emulsion of a drug and iodised oil. Drug-eluting beads (DEBs) have undeniable pharmacological advantages by offering simultaneous embolisation and sustained release of the drug to the tumour. No data are currently available on liver/biliary injury following DEB-TACE. This study describes and compares liver/biliary injuries encountered with TACE in tumours developed in cirrhotic (hepatocellular carcinoma (HCC)) and non-cirrhotic (endocrine tumours (NETs)) livers.

Methods: In consecutive patients treated for a well-differentiated metastatic NET (n = 120) or a HCC (n = 88), 684 CT- and MR-scans were analysed. Liver/biliary injuries were classified as follows: dilated bile duct, portal vein narrowing, portal venous thrombosis and biloma/liver infarct. A generalised estimating equation logistic regression model was used.

Results: A liver/biliary injury followed 17.2% (82/476) of sessions in 30.8% (64/208) of patients. The occurrence of liver/biliary injury was associated with DEB-TACE (OR = 6.63; $p < 0.001$) irrespectively of the tumour type. Biloma/parenchymal infarct was strongly associated with both DEB-TACE (OR = 9.78; $p = 0.002$) and NETs (OR: 8.13; $p = 0.04$). Biloma/liver infarcts were managed conservatively but were associated with an increase in

serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatases, and gamma glutamyl transpeptidase ($p = 0.005$, $p = 0.005$, $p = 0.012$, and $p = 0.006$, respectively).

Conclusions: Liver/biliary injuries are independently associated with DEB-TACE. Biloma/liver infarct, the most serious injury, is independently associated with both DEB-TACE and NETs. The absence of such an association in TACE of HCC may be explained by the hypertrophied peribiliary plexus observed in cirrhosis, which protects against the ischemic/chemical insult of bile ducts. We suggest caution when using DEB-TACE in the non-cirrhotic liver.

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Introduction

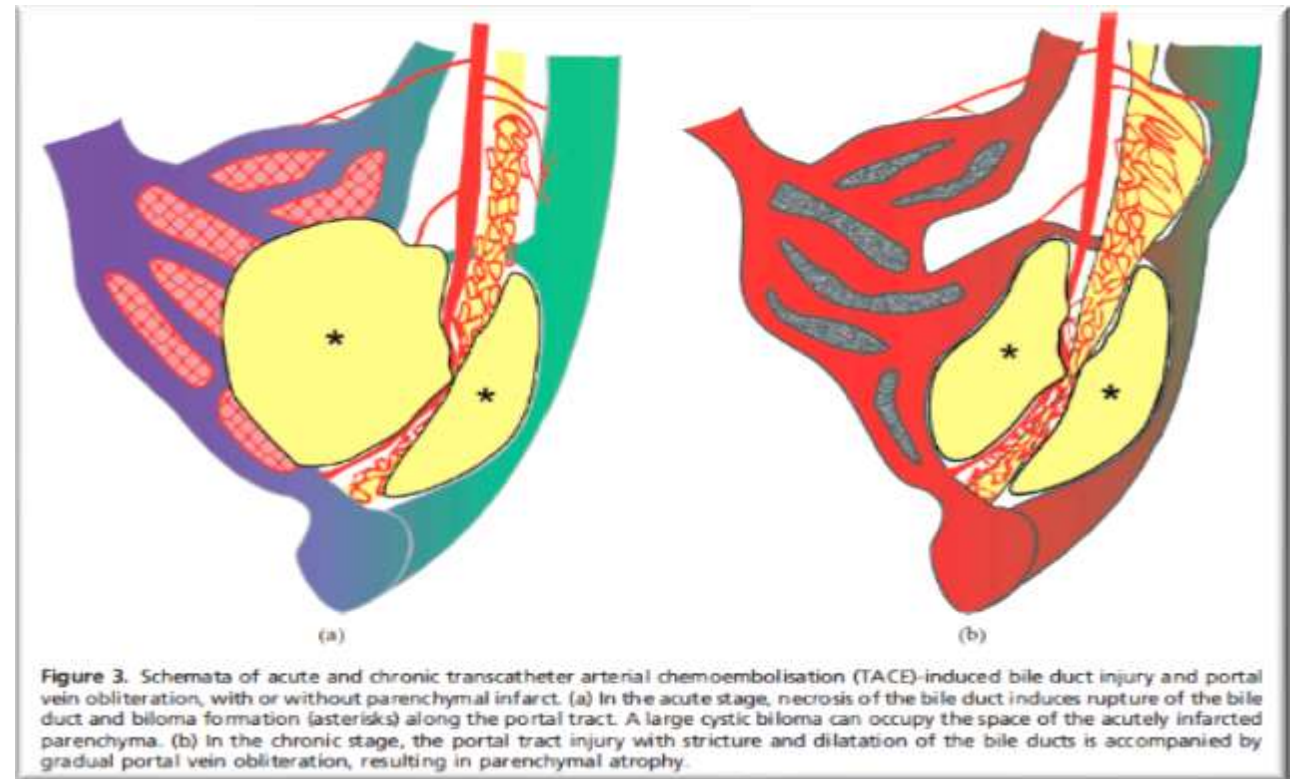
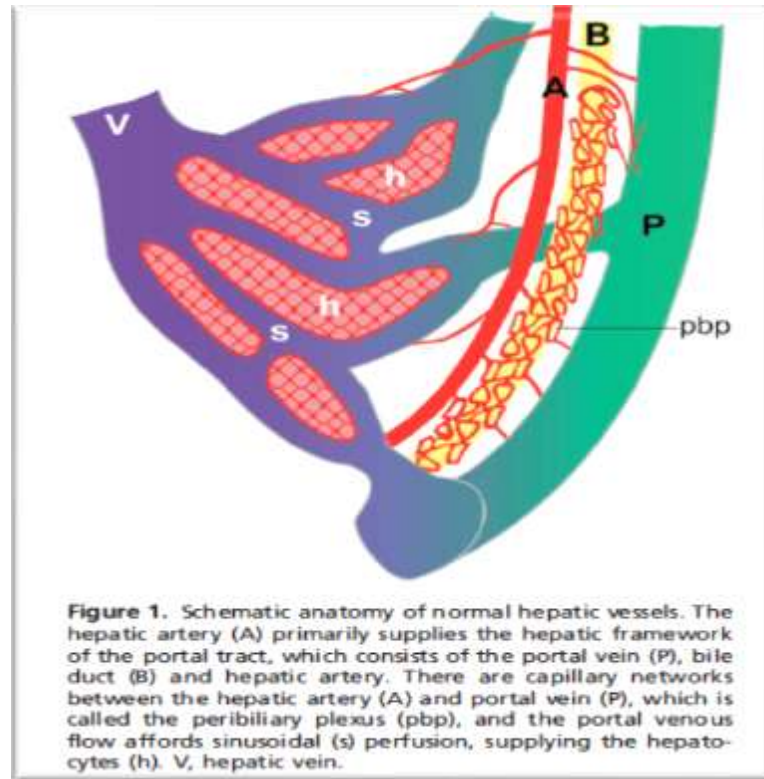
Transcatheter arterial chemoembolisation (TACE) combines the cytotoxic action of selectively-injected intra-arterial chemotherapy and the ischemic effects of embolising agents. TACE has been widely used to treat hepatic malignancies including liver metastases from endocrine tumours (NETs) and hepatocellular carcinoma.

Nen

TACE

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

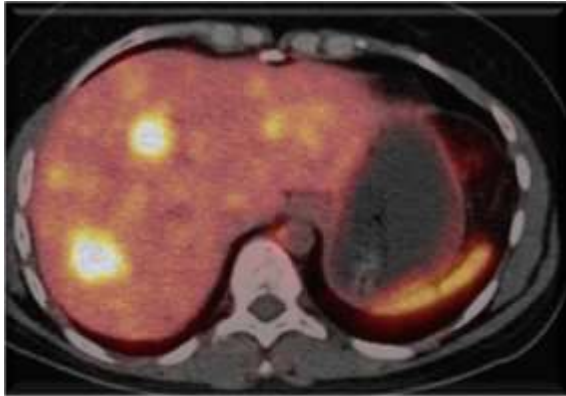
J CHUNG, MD, J-S YU, MD, J-J CHUNG, MD, J H KIM, MD and K W KIM, MD



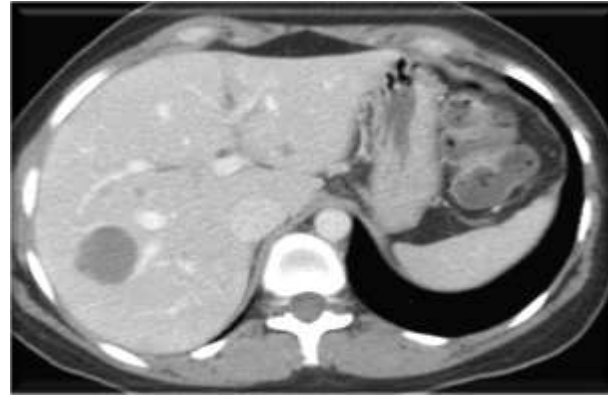
Nen

NEN duodeno, M+ fegato, Ki 67= 4% Tandem 40mm x 2,5ml+Doxo 125mg

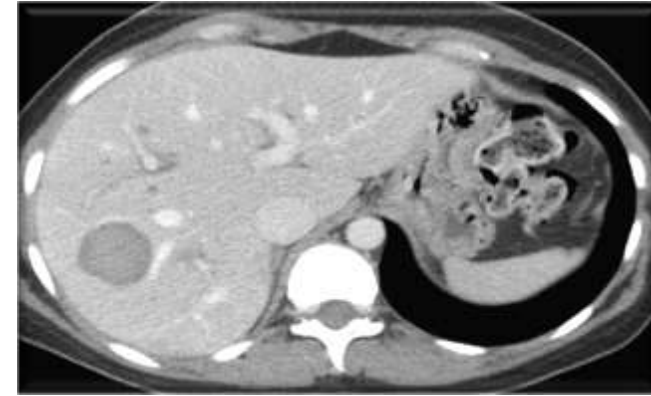
TACE



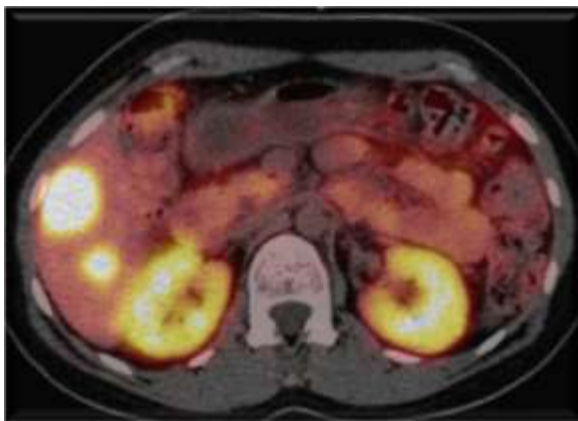
⁶⁸Ga-PET+



CT-pre

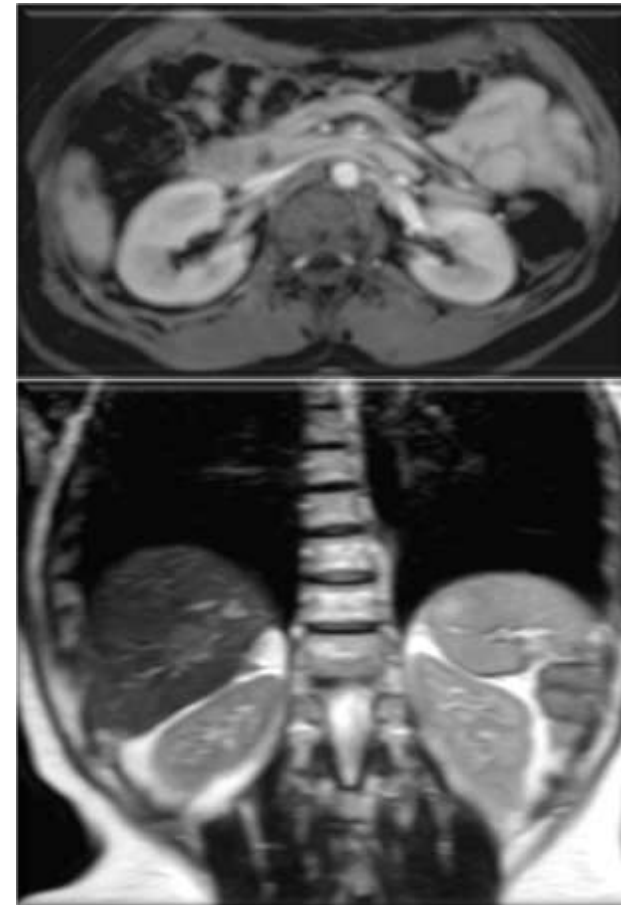
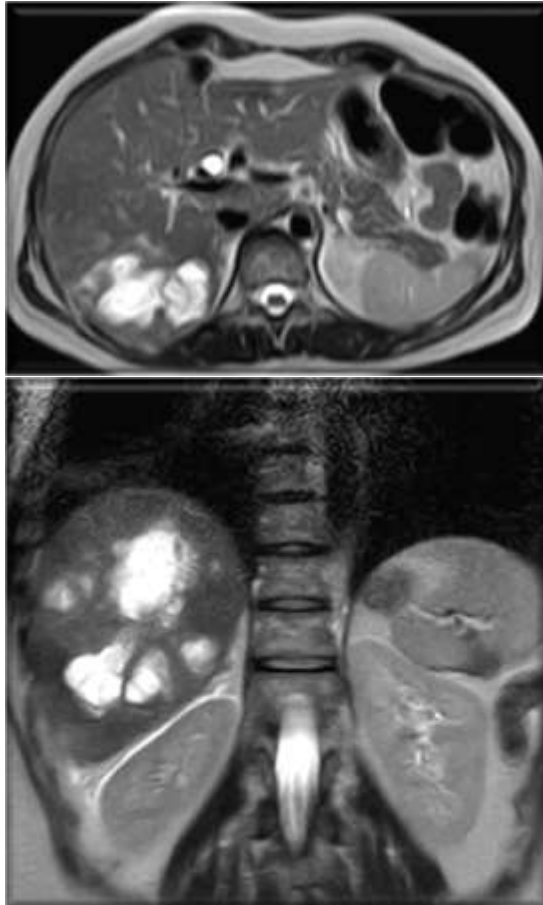


CT-post



Nen

TACE



Nen

TARE

It is defined as the injection of embolic particles loaded with a radioisotope through the percutaneous transarterial technique.



- (^{90}Y)-loaded microspheres is an alternative treatment for patients with unresectable primary or secondary liver tumours

- Whole liver
- Lobar
- Segmental

Radioembolization Versus Bland Embolization for Hepatic Metastases from Small Intestinal Neuroendocrine Tumors: Short-Term Results of a Randomized Clinical Trial

Anna-Karin Elf¹ · Mats Andersson² · Olof Henrikson² · Oscar Jalnefjord³ · Maria Ljungberg³ · Johanna Svensson⁴ · Bo Wängberg¹ · Viktor Johanson¹

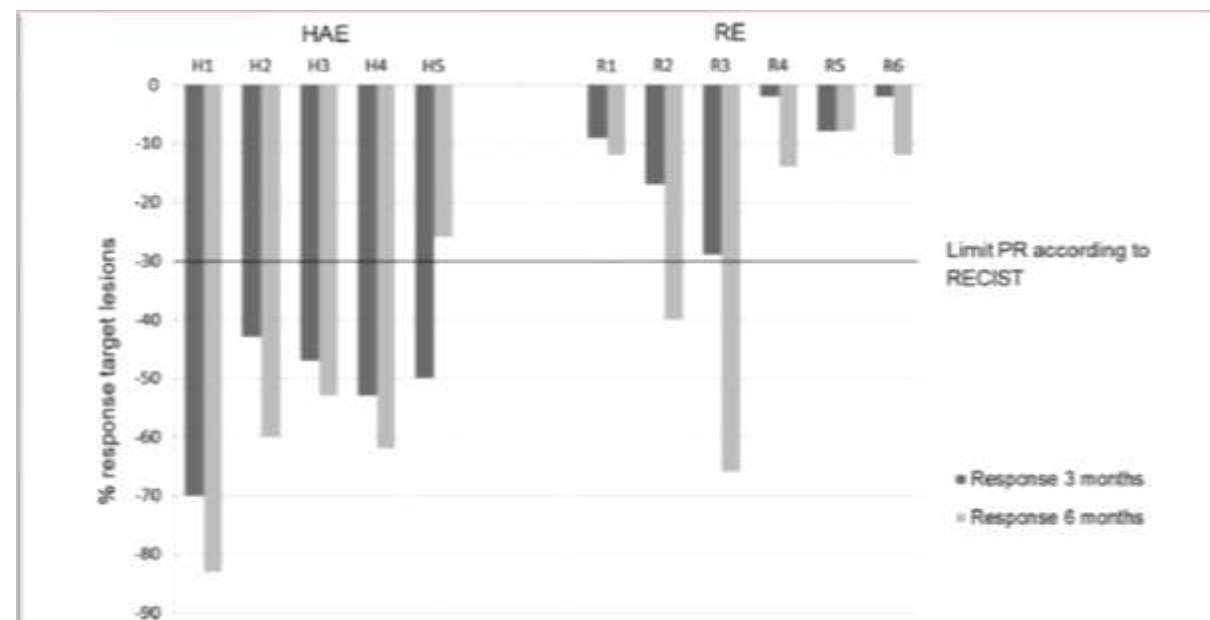


Fig. 1 RECIST response in target lesions in the treated liver at 3 months (dark gray staples) and 6 months (light gray staples) post-treatment. Solid black line indicates threshold for partial response (PR). At 3 months, no responders were seen in the RE group while all patients in the HAE group showed PR ($p = 0.0022$)

Radioembolization-induced liver disease: a systematic review

Marion N.G.J.A. Braat¹, Karel J. van Erpecum², Bernard A. Zonnenberg³, Maurice A.J. van den Bosch⁴ and Maria G.E.H. Lam¹

Radioembolization is embedded with a β -arteries and some injury, with intra RE-RE-related hepatitis REILD. A systematic screened for definite abnormalities occur 0 and 31%, although presentation of hep established in the of hepatotoxicity is a of precluding reliable of Hepatol 20:144-152 Copyright © 2017 V

Liver Disease Induced by Radioembolization of Liver Tumors

Description and Possible Risk Factors

Bruno Sangro, MD, PhD¹
Belen Gil-Alzugaray, MD¹
Javier Rodriguez, MD, PhD²
Iosu Solà, MD, PhD³
Antonio Martínez-Cuesta, MD, MSc, PhD⁴
Antonio Viudez, MD²
Ana Chopitea, MD²
Mercedes Iharraraigui, MD, PhD¹
Javier Arbizu, MD, PhD⁵
Jose I. Bilbao, MD, PhD⁴

BACKGROUND. To the authors' knowledge, liver damage after liver radioembolization with yttrium90-labeled microspheres has never been studied specifically.

METHODS. Using a complete set of data recorded prospectively among all patients without previous chronic liver disease treated by radioembolization at the authors' institution from September 2003 to July 2006, patterns of liver damage were identified and possible risk factors were analyzed.

RESULTS. In all, 20% of patients developed a distinct clinical picture that appeared 4 to 8 weeks after treatment and was characterized by jaundice and ascites. Veno-occlusive disease was the histologic hallmark observed in the most severe cases. This form of sinusoidal obstruction syndrome was not observed among patients who never received chemotherapy or in those in whom a single hepatic lobe was treated. Relevant to treatment planning, a possible risk factor was a higher treatment dose in relation to the targeted liver volume. A transjugular intrahepatic stent shunt improved liver function in 2 patients with impending liver failure, although 1 of them eventually died from it.

CONCLUSIONS. Radioembolization of liver tumors, particularly after antineoplastic chemotherapy, may result in an uncommon but potentially life-threatening form of hepatic sinusoidal obstruction syndrome that presents clinically with jaundice and ascites. *Cancer* 2008;112:1538-46. © 2008 American Cancer Society.

Available definitions of radioembolization-induced liver disease

n	Definition of REILD
al [14]	45 Potentially life-threatening liver damage characterized by jaundice and ascites developing 4-8 weeks after treatment, with pathologic changes consistent with VOD in the most severe cases
[20]	12 REILD is characterized by jaundice and ascites as a form of sinusoidal obstruction syndrome. Definition according to Sangro et al [14]
al [13]	13 A syndrome characterized by ascites with an onset ~ 2-4 weeks after irradiation. This may be accompanied by hyperbilirubinemia and tender hepatomegaly
al [22]	515 REILD has been described after external beam radiation and is widely acknowledged to be a clinical entity that can present with ascites 2 weeks to 4 months after hepatic irradiation. Clinically, patients develop rapid weight gain, increased abdominal girth, liver enlargement, jaundice, and increased transaminase levels, particularly alkaline phosphatase
er et al [30]	34 REILD was diagnosed by clinical presentation of jaundice and ascites and a bilirubin increase of > 50 μ mol/L (2.9 mg/dL). Definition according to the definition by Sangro et al [14]
ly et al [17]	260 REILD was defined as the appearance of a serum total bilirubin of 3 mg/dL or higher and ascites clinically or by imaging 1-2 months after RE in the absence of tumor progression or bile duct obstruction
[25]	247 REILD was suspected in the presence of signs and symptoms including jaundice, fatigue, ascites, and changes in laboratory values (elevated serum bilirubin, AST, ALT, alkaline phosphatase and ammonia; decreased albumin) in the absence of hepatic tumor progression
Roa et al [16]	14 Definition according to Sangro et al [14]
[36]	21 Definition according to Sangro et al [14]
[24]	30 REILD was defined as the appearance of a serum total bilirubin of 3 mg/dL (51 μ mol/L) or higher, plus new appearance of ascites within 3 months after RE, which could not be explained by tumor progression or bile duct obstruction. Definition according to Gil-Alzugaray et al [17]
[15]	427 REILD has a typical onset of 4-8 weeks after radioembolization and patients present with jaundice and ascites in the absence of tumor progression or bile duct dilatation

Radioembolization; REILD, radioembolization-induced liver disease; RILD, radiation-induced liver disease.
al REILD in a study solely analyzing RE treatments, consistent with the authors' definition of REILD.

¹ Liver Unit, Department of Internal Medicine, University Clinic and OBERMO, Pamplona, Spain

² Department of Medical Oncology, University Clinic, Pamplona, Spain

³ Department of Pathology, University Clinic, Pamplona, Spain

⁴ Department of Interventional Radiology, University Clinic, Pamplona, Spain



CLINICAL STUDY

Long-Term Hepatotoxicity of Yttrium-90 Radioembolization as Treatment of Metastatic Neuroendocrine Tumor to the Liver

Yu-Kai Su, MD, Rosewell V. Mackey, MD, Ahsun Riaz, MD, Vanessa L. Gates, MS, Al B. Benson, III, MD, Frank H. Miller, MD, Vahid Yaghmai, MD, Ahmed Gabr, MD, Riad Salem, MD, and Robert J. Lewandowski, MD

ABSTRACT

Purpose: To determine long-term hepatotoxicity of yttrium-90 (⁹⁰Y) radioembolization in patients treated for metastatic neuroendocrine tumor (mNET) and evaluate if imaging and laboratory findings of cirrhosis-like morphology are associated with clinical symptoms.

Materials and Methods: Retrospective review from 2003 to 2016 was performed for patients with mNET treated with ⁹⁰Y glass microspheres. Fifty-four patients with > 2 year follow-up were stratified into unilobar (n = 15) vs whole-liver (n = 39) treatment. The most common primary mNET sites were small bowel (19 of 54), pancreas (19 of 54), and unknown (8 of 54). Pre-radioembolization imaging and laboratory findings were compared with most recent follow-up for indications of worsening portal hypertension and decline in hepatic function.

Results: Among patients who underwent unilobar radioembolization, imaging follow-up at a mean of 4.1 years (range, 2.0-15.2 y) revealed cirrhosis-like morphology in 26.7% (4 of 15), ascites in 13.3% (2 of 15), varices in 6.7% (1 of 15), and a 21.9% increase in splenic volume. The respective incidences in patients treated with whole-liver ⁹⁰Y radioembolization were 56.4% (22 of 39), 41.0% (16 of 39), and 15.4% (6 of 39), with a 64.7% increase in splenic volume. Patients treated with whole-liver radioembolization exhibited significantly decreased platelet counts ($P = .023$) and lower albumin levels ($P = .0002$). Eight patients (20.5%) treated with whole-liver radioembolization who exhibited cirrhosis-like morphology showed clinical signs of hepatic decompensation; only 2 of 39 patients (5.1%) had no other causes of hepatotoxicity.

Conclusions: Whole-liver ⁹⁰Y radioembolization for patients with mNET results in long-term imaging findings of cirrhosis-like morphology and portal hypertension in > 50% of treated patients, but the majority remain clinically asymptomatic. Long-term hepatotoxicity solely attributable to ⁹⁰Y develops in a small percentage of patients.

ABBREVIATIONS

mNET = metastatic neuroendocrine tumor, ⁹⁰Y = yttrium-90

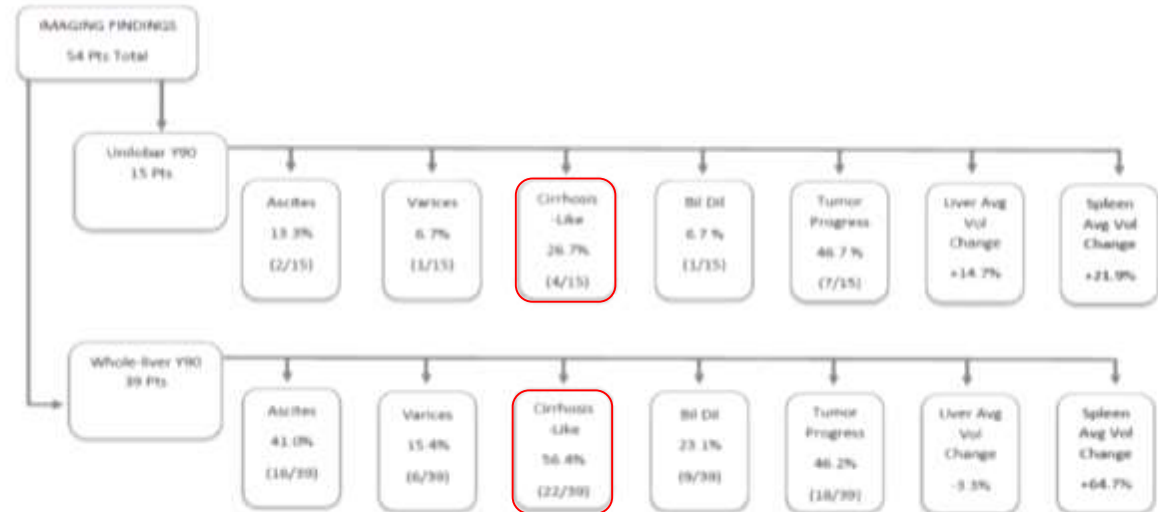
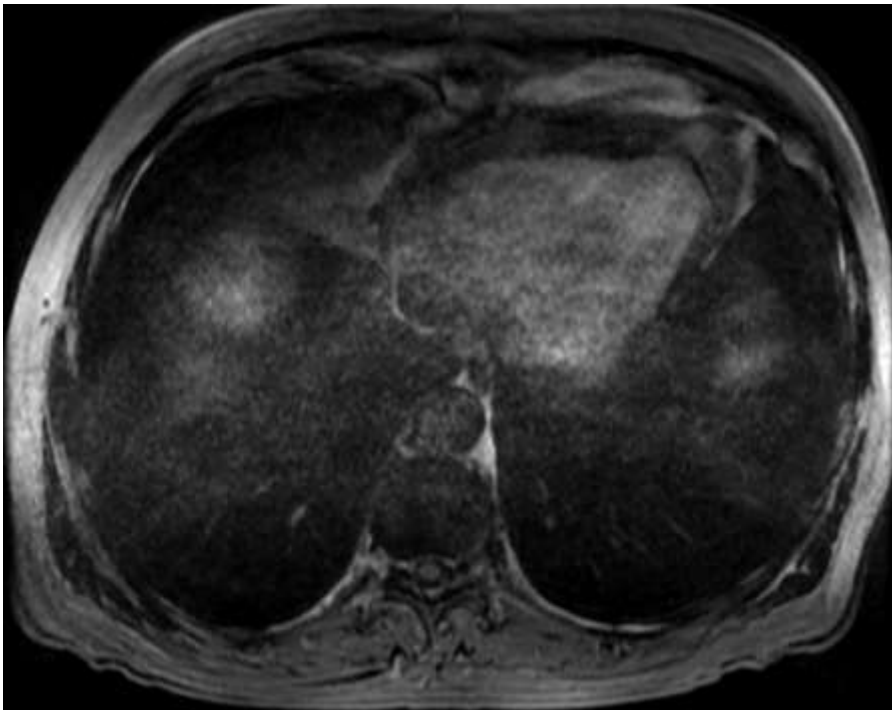


Figure. Imaging findings before and after ⁹⁰Y radioembolization in patients who underwent whole-liver versus unilobar treatment (bold text indicates $P < .05$; Table 1).

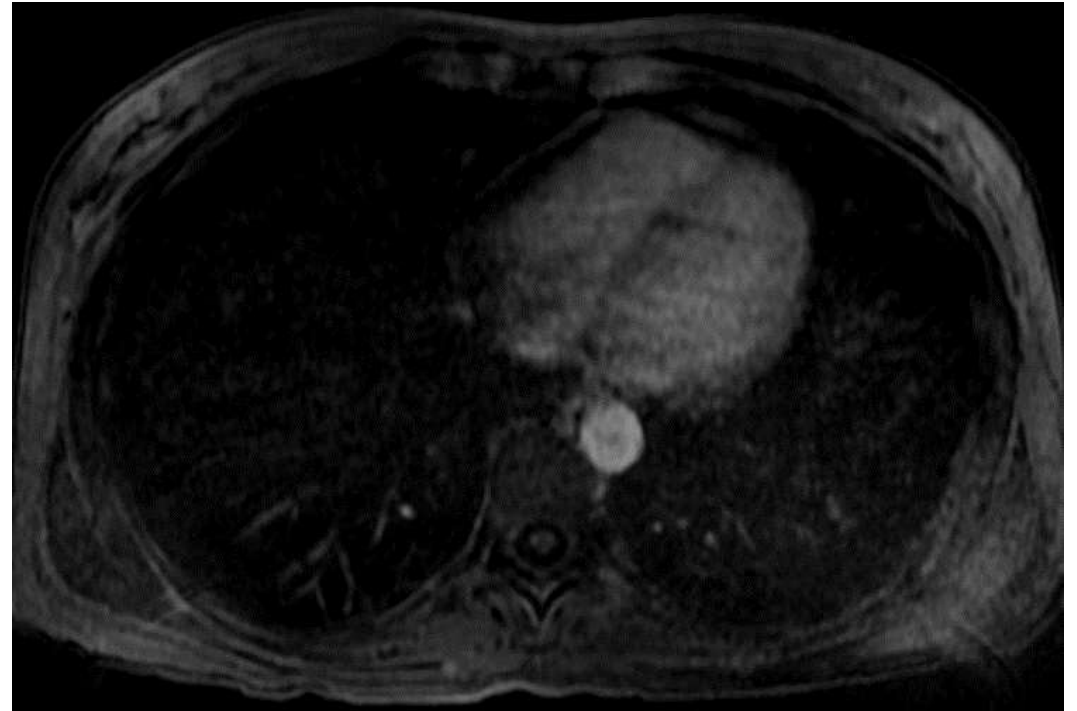
Nen

NET colon dx , M+ fegato, Ki 67= 7%
Trattamento: C-TACE 11/2002;
TAE 01-04-09/2015, 11/2017



TARE

Melanoma uveale, M+ fegato (9/2016 → 4/2018 AVASTIN
bimestrale)
Trattamento: TARE lobo dx 6/2018; lobo sin 9/2018



VIII EDIZIONE
NEN PRECEPTORSHIP
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