



XXIV CONGRESSO NAZIONALE

AIRO 2014

Padova 8-11 Novembre



La Malattia Metastatica Epatica

Il Ruolo della radiologia Interventistica

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Locoregional Therapies

•Thermo-Ablation

–Radiofrequency (RFA)

–Laser

–Microwave, Cryo, HIFU

•Chemo-Ablation

–Chemoembolization (TACE)

•Radio-Ablation

–Stereotactic RTx

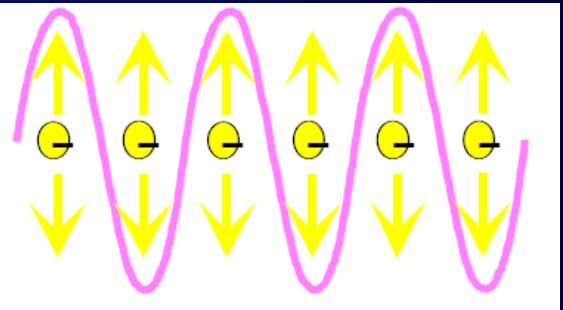
–Selective internal radiotherapy (SIRT)

RF History



Mono-and bipolar HF devices
—Standard in surgery

- Principles behind Radiofrequency**
Alternating current of high frequency
- Movement of ions—heat by friction
 - Heat source = tissue near electrode (antenna)
 - Heating limited to small volume around electrode
 - Heating beyond this only by conduction (McGahan JP et al., Invest Radiol, 1990; 25:167-270)



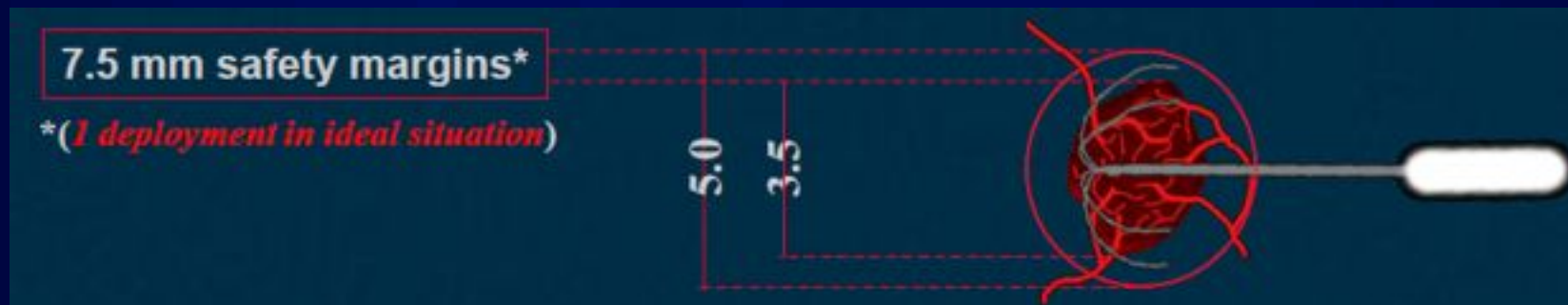


$$\frac{\text{post-RFA zone max diameter} - \text{pre-RFA tumor max diameter}}{2} = \text{safety free margins}$$

Cady B, Jenkins RL, Steele GD et al (1998) Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. Ann Surg 227:566-571

Cady et al. recommended a surgical standard of a 2-cm margin but settled for at least 1-cm hepatic resection margin for crc liver metastases to prevent local progression.

Needles diameter available ≤ 5 cm



Microwave ablation



Microwave for tumor ablation –same principle as microwave oven

Microwaves cause movement / oscillation of water molecules –heat generated by friction of those water molecules

Difference:

- **Microwave oven –energy deposition inside**
- **Ablation –energy deposition towards surrounding tissue**

MW Ablation: Potential Advantages

- **Bigger ablation = Deeper penetration of energy**
- **Hotter = applicator temps. 120 -140°C**
- **Faster ablation time**

Results in literature

Patients	Number	Diameter	median survival	overall survival		
				1 yr	3 yrs	5 yrs
2344	3.2	2.9 cm	32 months	- 96%	71%	55%

Gunette and Dupuy J Surg Oncol 2010

Patients	Number	Diameter	median survival	overall survival		
				1 yr	3 yrs	5 yrs
1833	NA	2.9 cm	NA	- 95%	81%	68%

Boutros et al. Surg Oncol 2011

Indications

Resection still gold standard

- No resectability
- Diameter < 3.5 -5 cm

Complications

- Peritoneal pain (analgo-sedation)
- Postinterventional pain/fever
- Pleural effusion

Other ~ puncture related

- Hematoma/bleeding
- Thrombosis
- Superinfection, abscess
- Bowel necrosis
- Pneumothorax
- Tumor seeding

Total ~ 2.5 -6 %



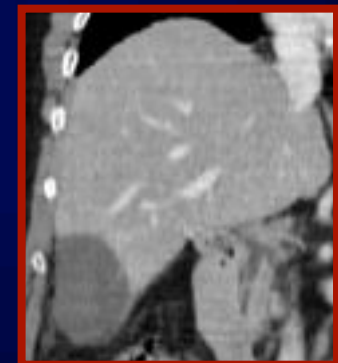
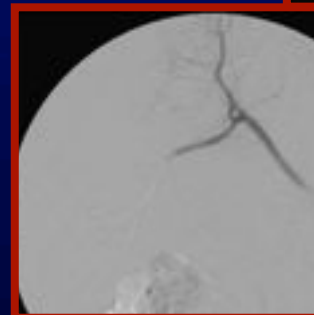
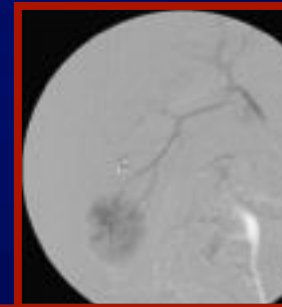
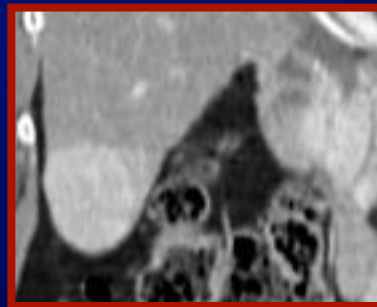
- **RFA is very effective in small tumors (up to 3 cm)**
- **...but high rate of local recurrence is reported: up to 40% with percutaneous placement**
- **1.8% to 12% in surgical open approach**

EJSO 2007

Combined Therapy: RFA+TACE

“For lesions bigger than 3.0 cm, multiple delivery technique or RFA combined with TACE/TAE is recommended “

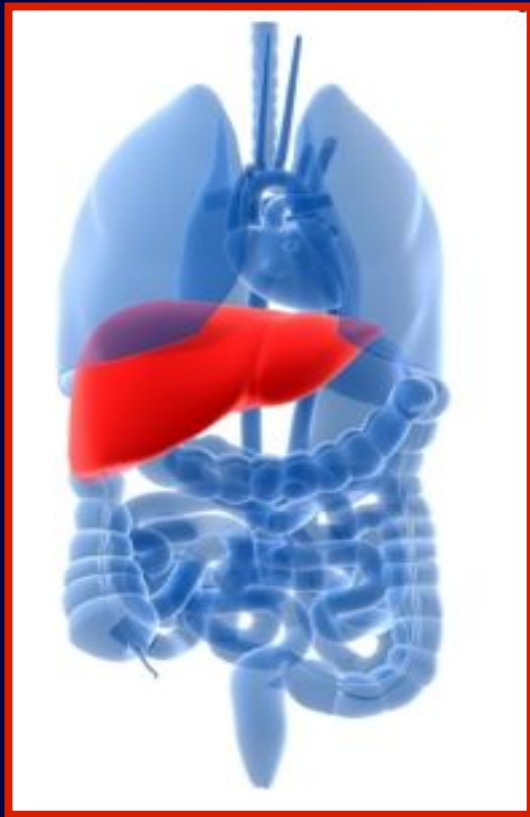
G.S.Liao et al . EJSO 2007



INTRA ARTERIAL HEPATIC INFUSION

The advantage of delivering chemotherapy by hepatic arterial infusion is the administration of high-dose of the drug in the target

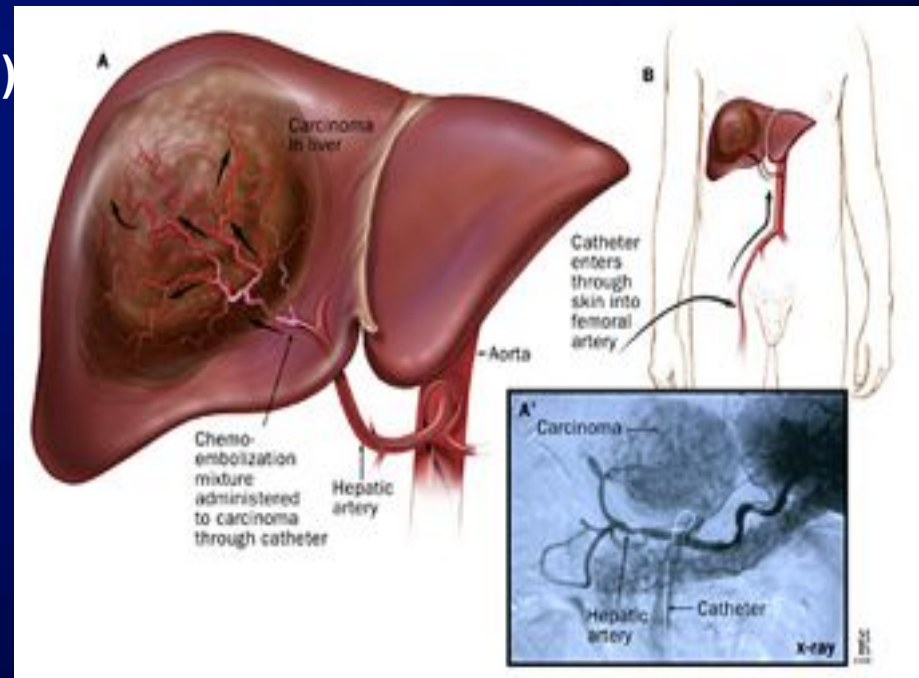
What is locoregional therapy?



Locoregional therapy delivers a concentrated dose of chemotherapeutic agents to a target organ or region of the body while limiting systemic toxicities.

Current Intraarterial Locoregional Therapies for Metastatic Disease to Liver

- Conventional Transcatheter Arterial Chemoembolization (TACE)
- Transarterial Bland Embolization
- Drug Eluting Transarterial Chemoembolization
- **Radio-Embolization**
- Hepatic Arterial Infusion



Radioembolization using ^{90}Y microspheres in colorectal cancer liver metastases

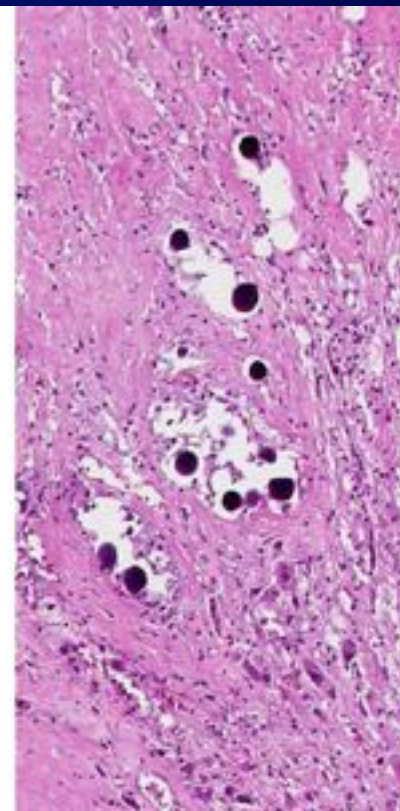
Microspheres for Y90-RE

	Resin	Glass
Mean Diameter	35 μ	25 μ
Activity/sphere	50 Bq	2,500 Bq
Spheres / dose	$40 \cdot 10^6$	$1.5 \cdot 10^6$

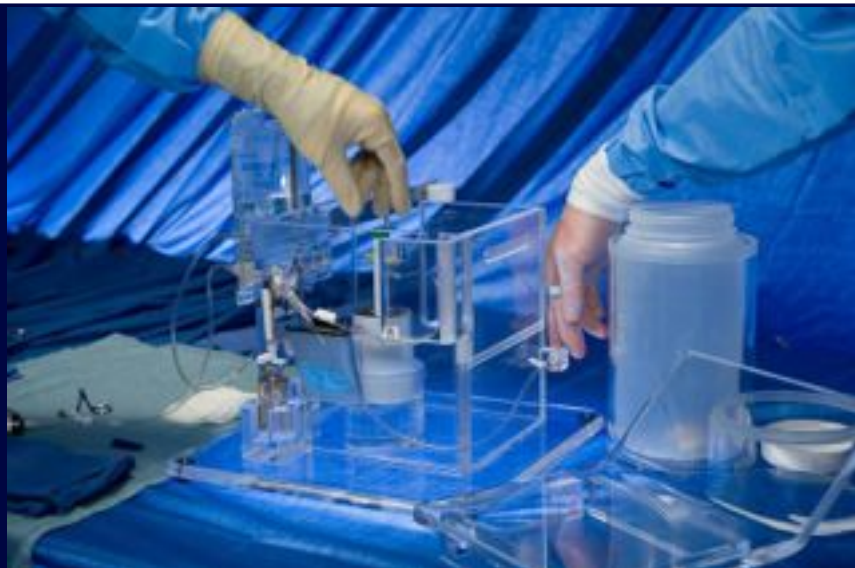
Yttrium-90: Beta Emitter.

Mean Penetration: 2.5 mm

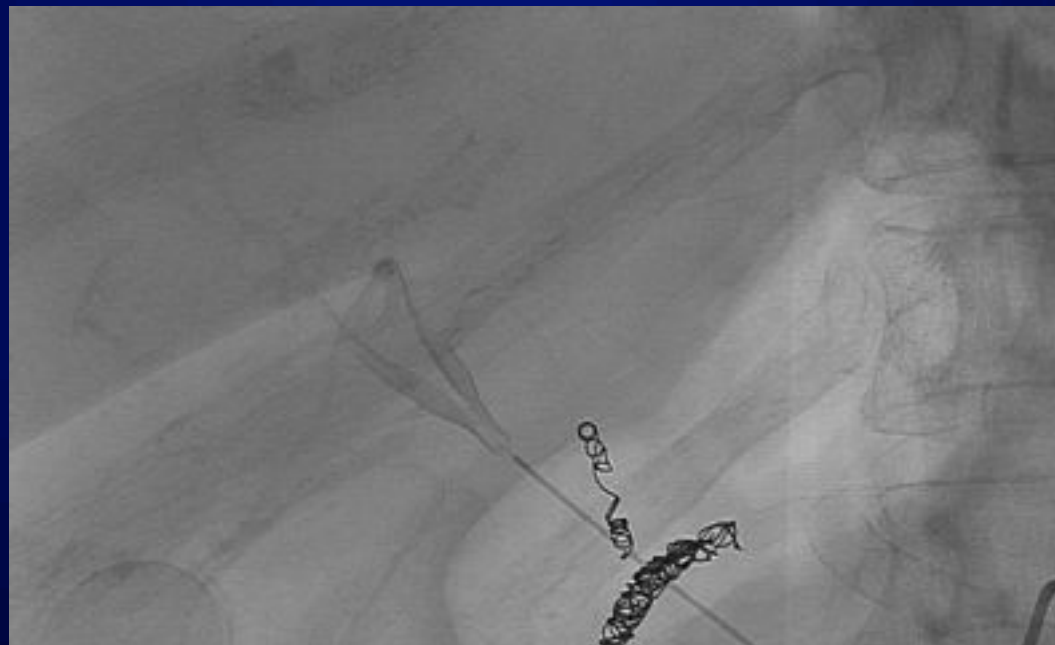
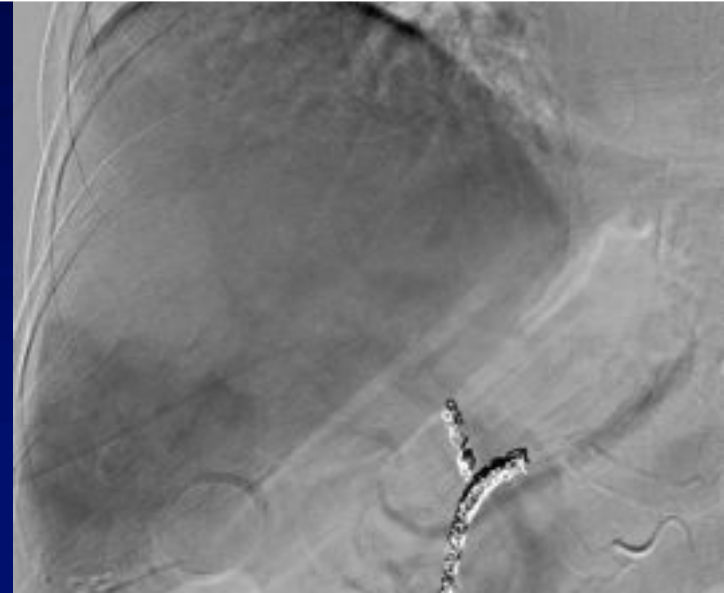
Half life: 64.2 h (95% of dose delivered by day 11)



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Retrospective study of SIR-Spheres as treatment of chemorefractory tumors

All failed 1st and 2nd line chemotherapy

Group 1 = MCRC; Group 2 = all other primaries

208 patients, 223 Y90 procedures

OS = 7.9 mo for MCRC, 8.7 mo for others

Evans et al. JVIR 2010; 21:1521-1526

Prospective multicenter phase III RCT comparing IV FU alone to IV FU + Y90

–Primary endpoint was time to liver progression (TTLP), with crossover to Y90 thereafter allowed

–Data for 44 of 46 randomized patients analyzed

•Median f/u of 24.8 months

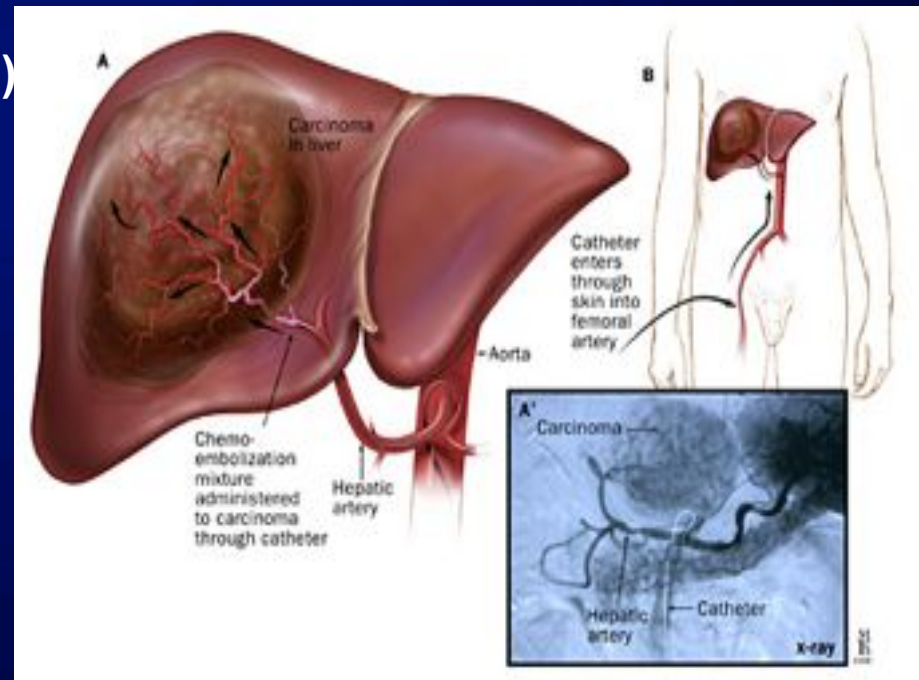
•Median TTLP 2.1 (FU alone) and 5.5 months (FU + Y90; $p=0.003$)

•**Median OS 7.3 and 10 months respectively ($p=0.8$)**

Hendlisz et al. J Clin Oncol 2010; 28:3687-3694

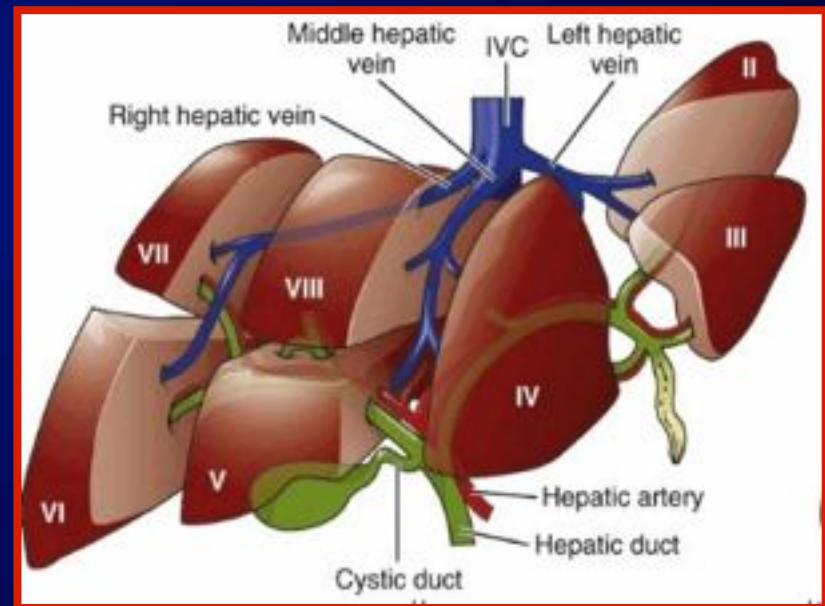
Current Intraarterial Locoregional Therapies for Metastatic Disease to Liver

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- Radio-Embolization
- Hepatic Arterial Infusion



Rationale for whole organ therapy to the liver

- Treats both visible and non-visible metastases in the liver
- Permits increased tumour exposure to a chemotherapeutic agent no matter where it is in the liver
- Permits reduction in systemic exposure, allowing dose escalation



TACE AND DEBIRI: The Same or Different?

TACE

- **Performed Selectively**
- **Stasis Preferred Endpoint**
- **Aqueous Chmeotherapy**
- **Great Systemic exopusure**

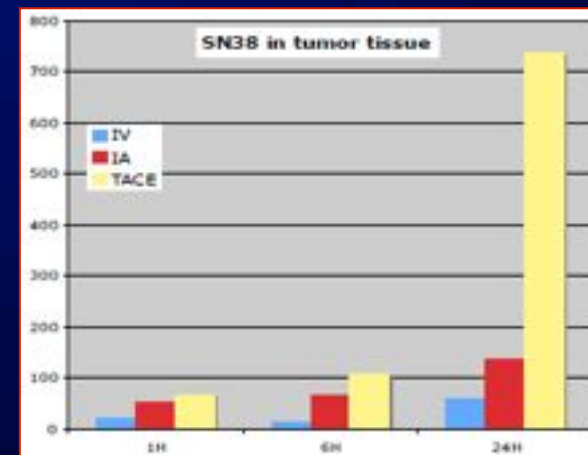
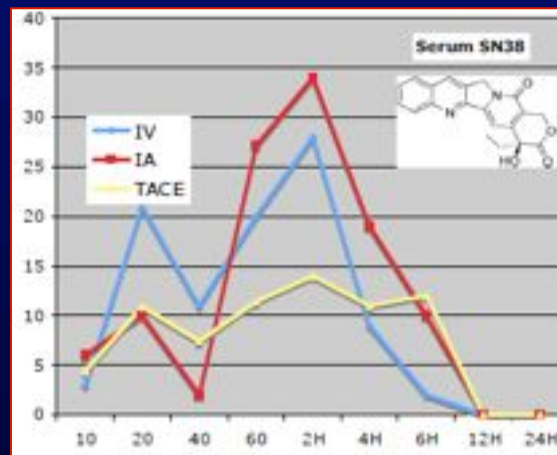
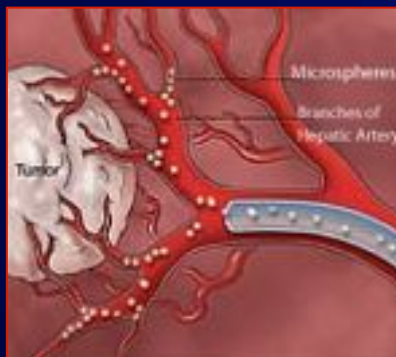
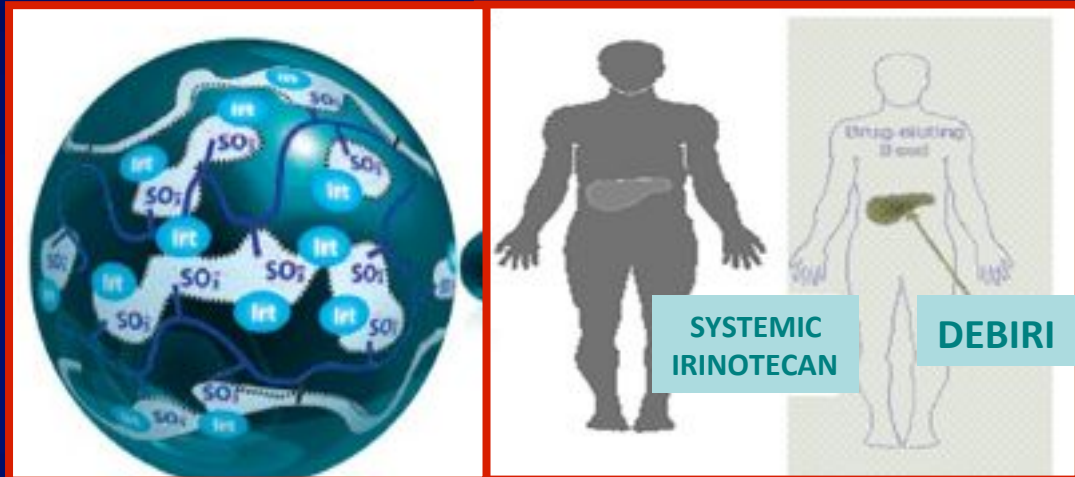
DEBIRI

- **Lobar Infusion**
- **Drug Delivery Endpoint**
- **Chemotherapy loaded PVA Particle**
- **Minimal to No Systemic Exposure**

Device

Irinotecan Drug Eluting Bead (DEBIRI) TACE

- PVA microspheres
- Loaded with Irinotecan
- Intra-arterial delivery
- Reduced first pass metabolism
- Reduced off-target side-effects



PHASE I FEASIBILITY STUDY

Dr. Martin, Surgical Oncology, University Hospital
Louisville

10 patients: lobar treatment 100 mg irinotecan

	Mambrini et al., ²⁵ i.v.	Mambrini et al., ²⁵ i.a. (ng/ml)	de Jonge et al., ²³ i.v.	van Riel et al., ²⁴ i.v.	Current study
CPT-11	6799±1055	5462±696	3842.7±1114.7	76.27±39.89	18.6±4.2
SN-38	60.9±24.1	87.5±29	29.42±18.05	5.57±2.39	1.55±0.64

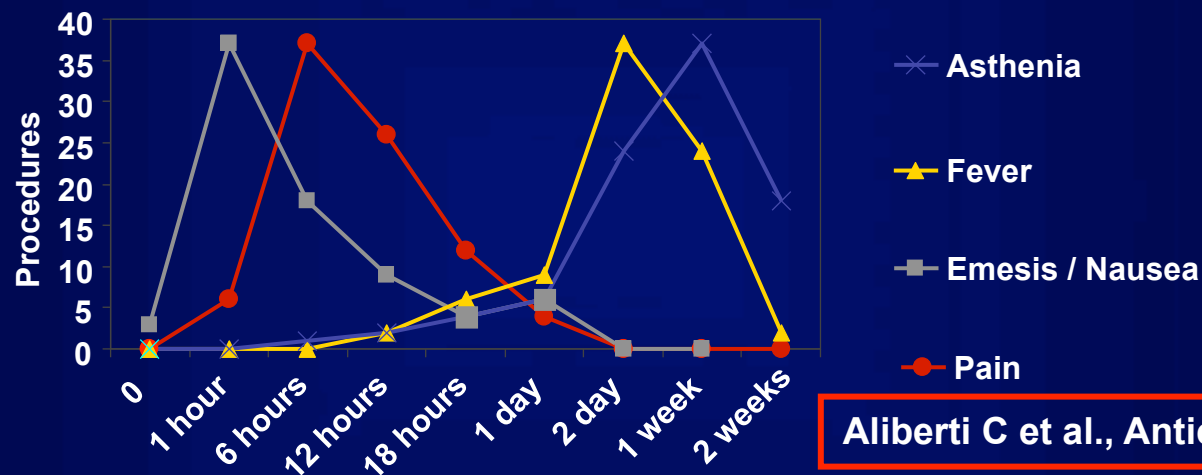
Martin RC et al. J GI Surg 2012

DEBIRI => LESS IRINOTECAN IN SYSTEMIC CIRCULATION

REGISTRY

Dr. Aliberti, Radiology, AUSL Ferrara

Dr. Fiorentini, Oncology, General Hospital San Giuseppe, Empoli



Aliberti C et al., Anticancer Res. 2011

•185 procedures 100% technical success (81 with 100mg, 104 with 200mg of Irinotecan)

- most common AE was post-embolisation syndrome
- 1 case of Acute Pancreatitis due to non-target embolisation of cystic artery

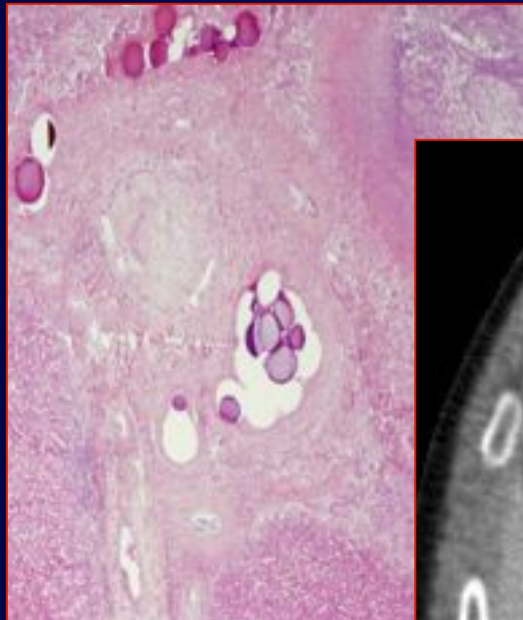
REGISTRY**Dr. Martin, Surgical Oncology, University of Louisville****5 centers USA, Serbia, 4 centers Czech Republic, Russia**

Adverse Event Description	# events	Adverse Event Grade	Adverse Event Outcome
Anorexia (n = 3 patients)	3	Grade 2	Resolved
	1	Grade 3	Resolved
Hypertension (N = 1 patient)	4	1-2	Resolved
Liver dysfunction/failure (n = 4 patients)	3	1-2	Resolved
	2	3	Ongoing
	1	5	Resolved
Nausea (n = 4 patients)	5	1-2	Resolved
Vomiting (n = 3 patients)	5	1-2	Resolved
Other: Gastritis, Dehydration, Anemia, Pneumonia (n = 4 patients) Cholecystitis (n = 1 patient)	5	1-2	Resolved
	1	3	Resolved

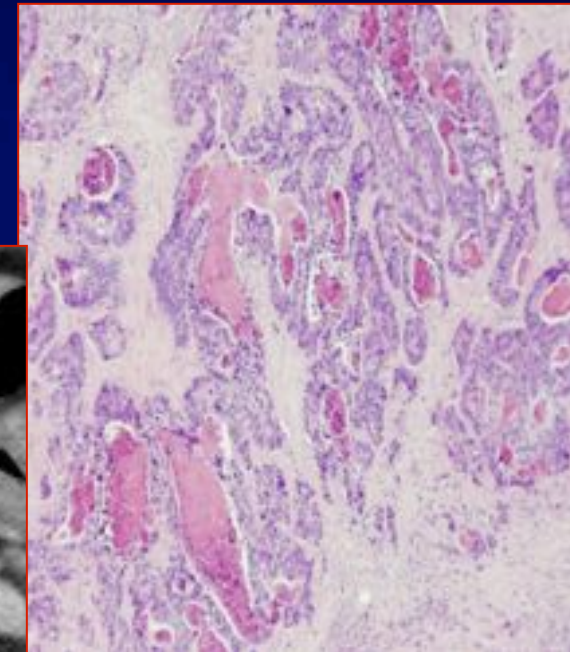
**55 patients – 99
treatments**

- Prophylactic treatment for pain, nausea and infection
- 16 patients w/ 30 AEs
- most common AE was post-embolisation syndrome
- 1 SAE = 1 death
- 6/55 downstaged to resection

Result of DEBIRI

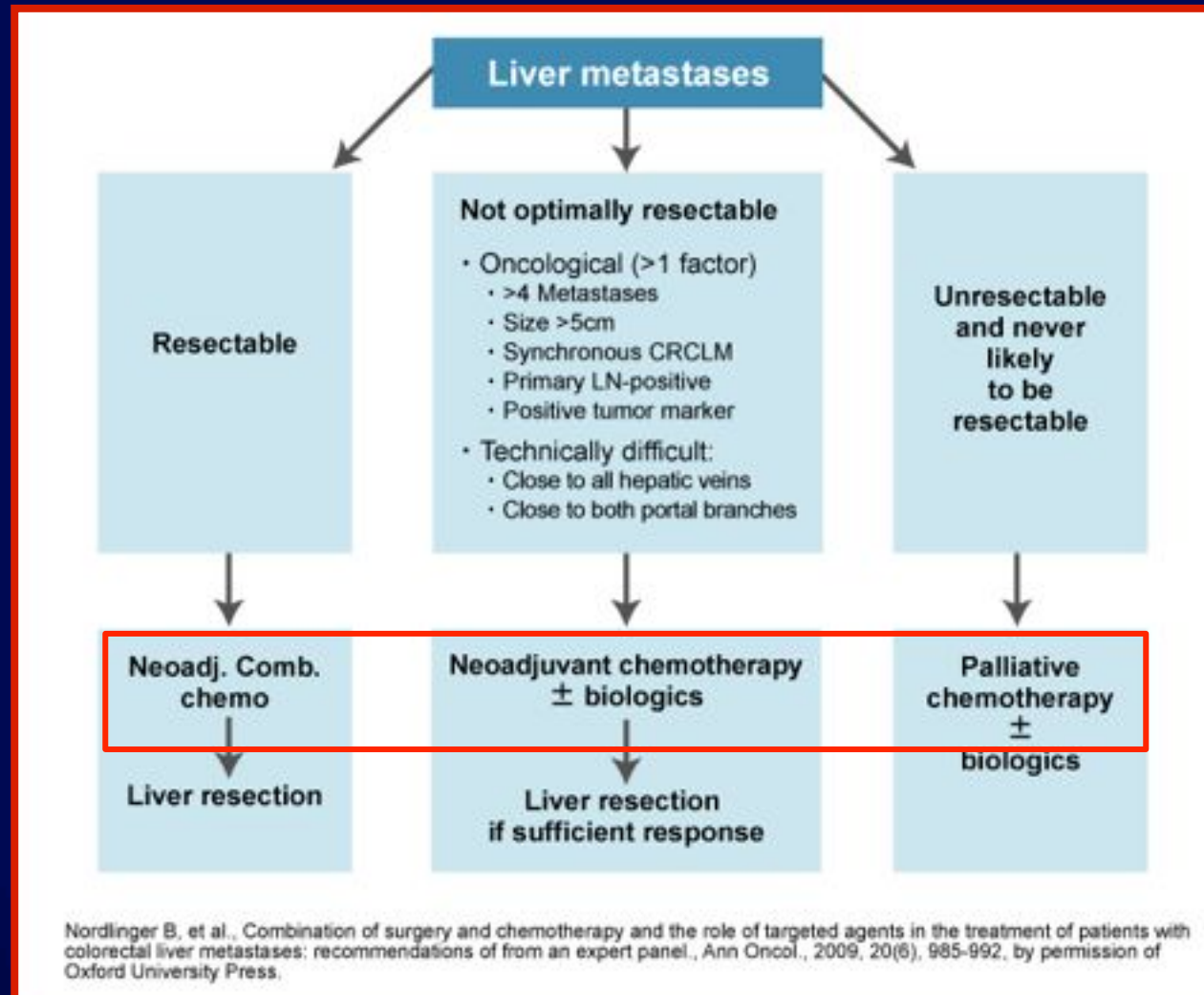


Treated metastasis



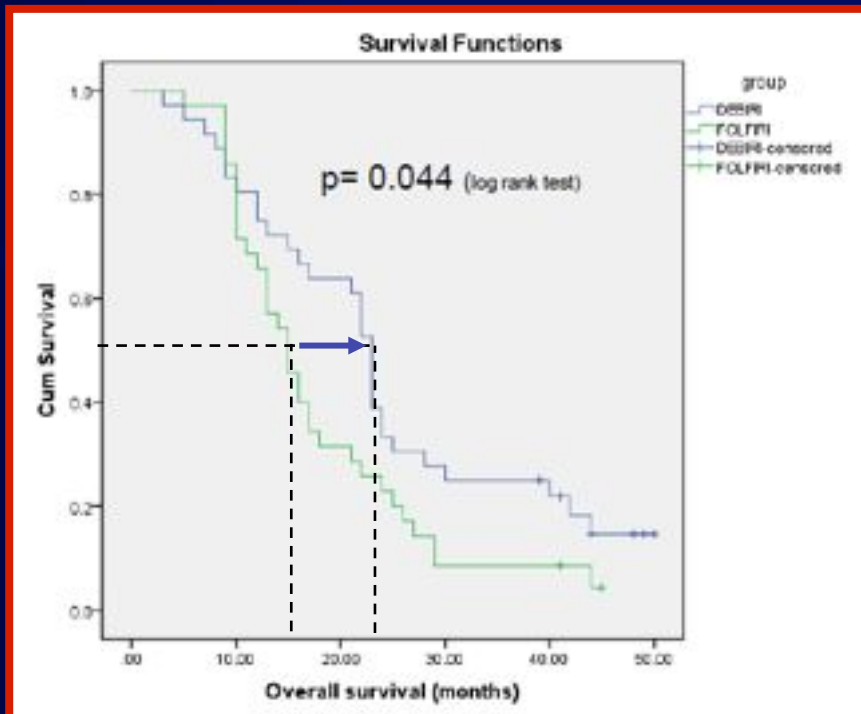
Untreated metastasis

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CLINICAL EVIDENCE – UNRESECTABLE CRLM

PHASE III – RCT – DEBIRI vs FOLFIRI 3/4 LINE - Completed
Pesaro, Ferrara, Carrara, L'Aquila



N=74
Only metachronous disease
Primary tu resected
No extrahepatic metastasis
Avg 4 LM (3-10)

68/74: Previously 2 or 3 lines ChT
FUFA, FOLFOX, IFL
FOLFOX + BEVACIZUMAB
FU + CETUXIMAB

Fiorentini G et al., Anticancer Res. 2012

7 months

DEBIRI => INCREASED SURVIVAL

CLINICAL EVIDENCE – UNRESECTABLE CRLM

Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review.

Richardson AJ, Laurence JM, Lam VW.J Vasc Interv Radiol. 2013 Aug;24(8):1209-17.

Five observational studies and one randomized controlled trial (RCT) were reviewed.

235 patients included in the descriptive analysis of observational studies.

The median survival time ranged from 15.2 months to 25 months.

For patients with unresectable CRLM, particularly after failure to respond to first-line regimens, DEBIRI represents a novel alternative to systemic chemotherapy alone, transarterial embolization with other agents, or other local treatments (eg, microwave or radiofrequency ablation).

DEBIRI was safe and effective in the in the treatment of unresectable CRLM.

Further RCTs comparing DEBIRI with alternative management strategies are required to define the optimal role for this treatment.

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Rank	Status	Study
1	Completed	Drug-Eluting Bead, Irinotecan (DEBIRI) Therapy of Liver Metastasis From Colon Cancer With Systemic FOLFOX6 Condition: Colon Cancer With Metastases to the Liver Interventions: Device: LC bead loaded with Irinotecan, Drug: FOLFOX6 and Avastin
2	Recruiting	Observational Study on Second Line Treatment of Hepatic Metastases With Intra-arterial Infusion of Irinotecan-loaded Drug-eluting Beads (DEBIRI) and Cetuximab Condition: Liver Metastases From Colon Cancer Carcinoma Intervention:
3	Not yet recruiting	Intra-arterial Hepatic Beads Loaded With Irinotecan With Concomitant Chemotherapy With FOLFOX in Patients With Colorectal Cancer With Unresectable Liver Metastases: a Phase II Multicenter Study Condition: Colorectal Cancer With Non Resectable Hepatic Metastasis Intervention: Drug: HIA DEBIRI + systemic FOLFOX

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4 Recruiting [Chemotherapy and Maximal Tumor Debulking of Multi-organ Colorectal Cancer Metastases](#)

Condition: Multi-organ Metastatic Colorectal Cancer

Interventions: Drug: XELOX regimen according to standard procedures; Drug: FOLFOX regimen according to standard procedures; Procedure: Surgery; Other: radiofrequency ablation (RFA); Other: transarterial chemo-embolization using irinotecan drug-eluted beads ((DEBIRI-)TACE); Radiation: stereotactic body radiation therapy (SBRT); Drug: Bevacizumab; Procedure: tumor biopsy

5 Completed [Chemoembolization Using Irinotecan in Treating Patients With Liver Metastases From Metastatic Colon or Rectal Cancer](#)

Conditions: Liver Metastases; Mucinous Adenocarcinoma of the Colon; Mucinous Adenocarcinoma of the Rectum; Recurrent Colon Cancer; Recurrent Rectal Cancer; Signet Ring Adenocarcinoma of the Colon; Signet Ring Adenocarcinoma of the Rectum; Stage IV Colon Cancer; Stage IV Rectal Cancer

Interventions: Device: irinotecan-eluting beads; Procedure: hepatic artery embolization

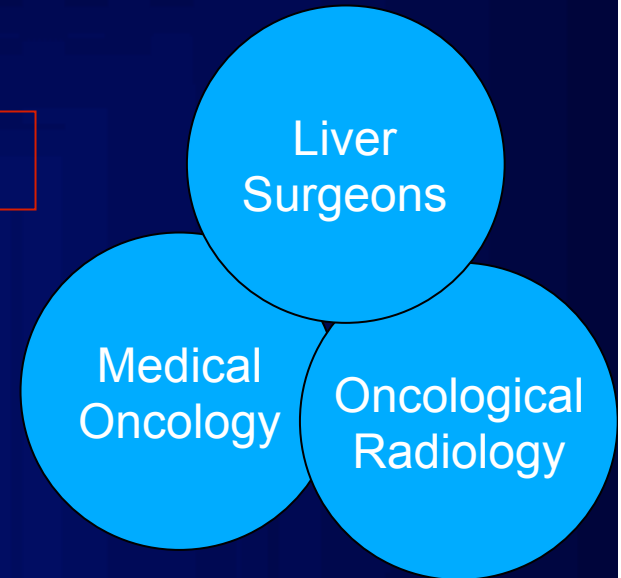
6 Not yet recruiting [Chemoembolisation With CPT11 Loaded DC Bead With Cetuximab and 5FU/LV in First Line in Patients With KRAS Wildtype mCRC](#)

Conditions: Liver Metastases; Colorectal Cancer

Interventions: Device: DC Bead™; Drug: Cetuximab; Drug: 5 FU; Drug: Irinotecan

[↑ TO TOP](#)

Multidisciplinary therapy team

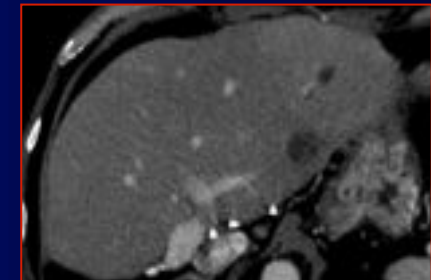
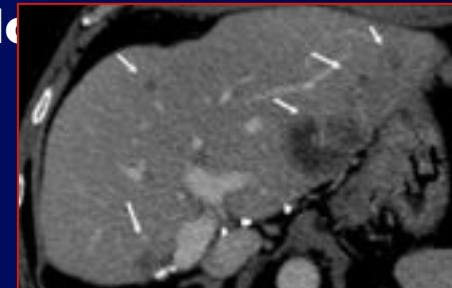


Indication

- **Alternative to best supportive care**
- **Prevalence of liver disease progression, not fast, after 2 lines of Cht.**

Summary

- **Minimally Invasive and Repeatable procedure and will require close coordination with referring Oncologist**
- **Whole organ therapy**
- **Is effective**
- **Expands patient population beyond focal therapy or resection**
- **Has Phase 3 Clinical Trial Supporting Data**
- **New promising regional hepatic therapy that will expand the DEBIRI role in Oncology.**



1) J of Oncology 2009 2) World J of Surg Onc 2009 3) HPB 2009 4) HPB 2010 5) Ann Surg Onc 2010
6) Anticancer Res. 7) J Gastrointest Surg. 2012 8) HPB (Oxford). 2013 9) Anticancer Res. 2013
10) J Vasc Interv Radiol. 2013 11) Anticancer Research 2014

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Scientific Knowledge' speed



Technological Knowledge' speed

LEVELS OF EVIDENCE



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Radiology

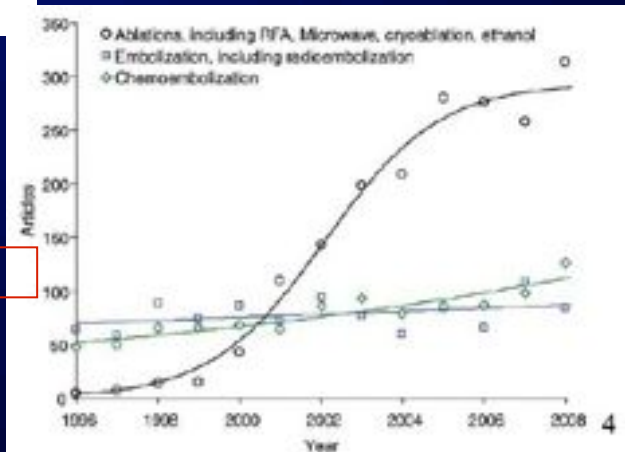
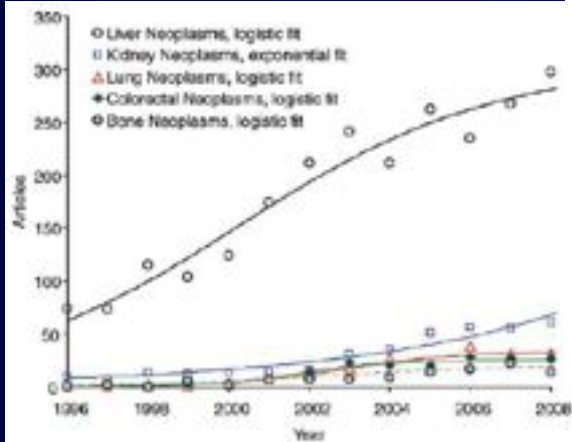
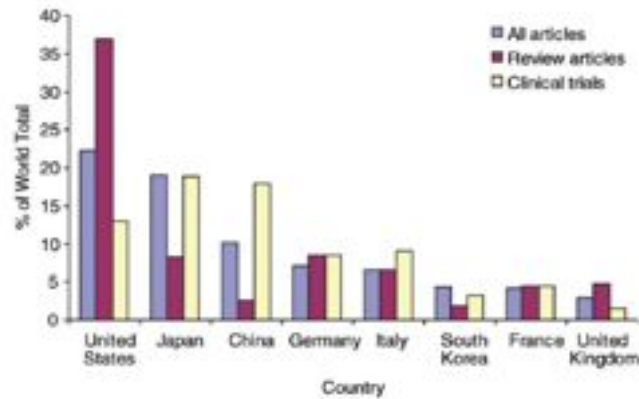
Interventional Oncology Research in the United States: Slowing Growth, Limited Focus, and a Low Level of Funding¹

Daniel S. Chow, MD
Michael W. Itagaki, MD, MBA

Purpose: To establish the characteristics of published interventional oncology (IO) research, including the volume, growth,

410

radiology.rns.org • Radiology: Volume 257: Number 2—November 2010



Sappiamo bene che ciò che facciamo
non è che una goccia nell'oceano.
Ma se questa goccia non ci fosse,
all'oceano mancherebbe.

Madre Teresa di Calcutta

camillo.aliberti@ioveneto.it