



# TRATTAMENTO NON CHIRURGICO DELLE OLIGOMETASTASI

## CHEMIOEMBOLIZZAZIONE

**Terni, 21 Giugno 2013**

*Dott. Massimiliano Allegritti*

# Introduzione

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- **Patologia metastatica epatica rappresenta la causa di morte piu' comune nei pz oncologici**
- **Resezione chirurgica curativa solo nel 25% dei casi**
- **Differenti procedure interventistiche sono state sviluppate per il trattamento delle lesioni epatiche**

*H.Mahnken et al; Radiology; Feb. 2013 ,266: 407-30.*

# Introduzione

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## INTERVENTISTICA ONCOLOGICA EPATICA

PVE (portal vein embolization)

HAIC (hepatic artery infusion chemotherapy)

TACE (Trans arterial chemoembolization)

TARE (Trans arterial radioembolization)

RF (Radiofrequency)

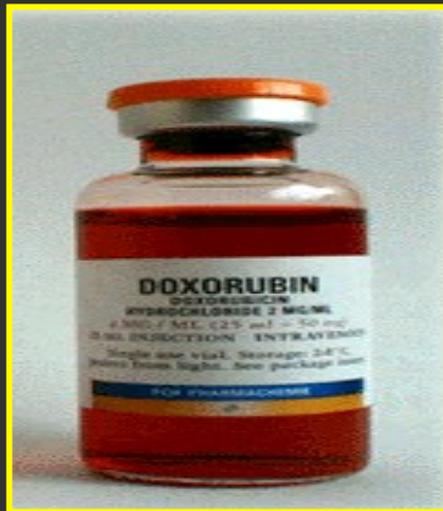
# COSA E' LA TACE?

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# COSA E' LA TACE?

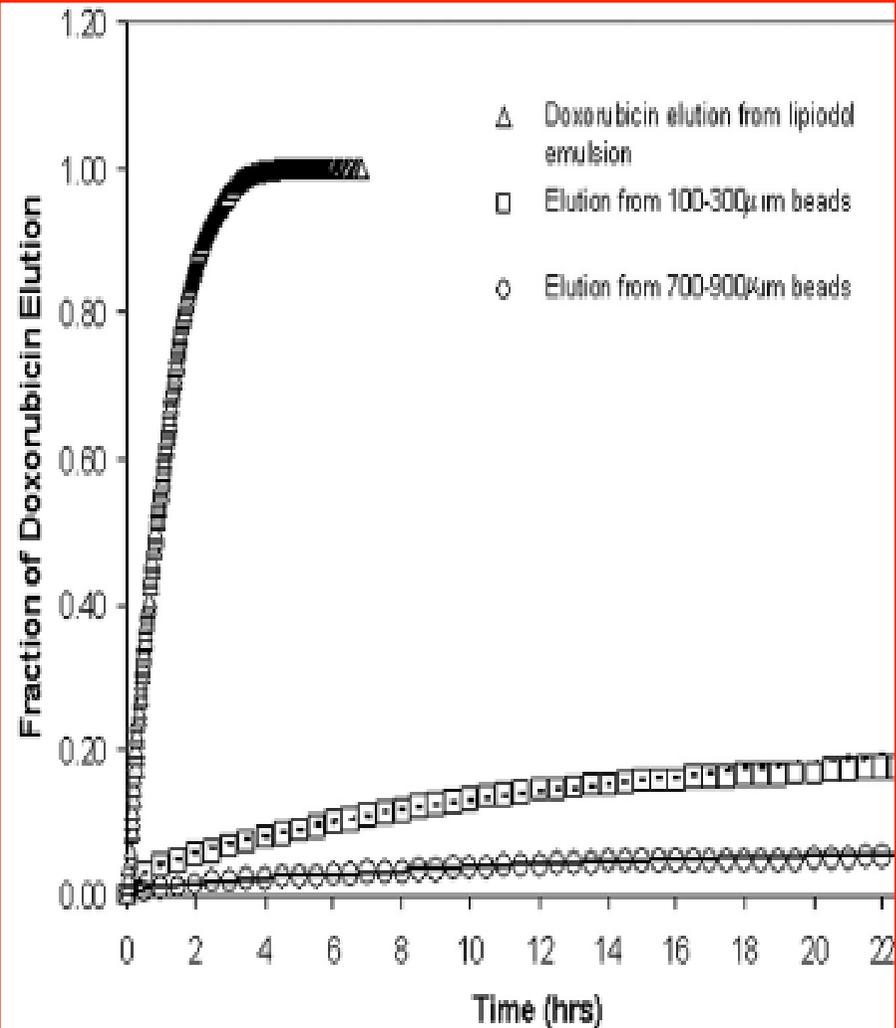
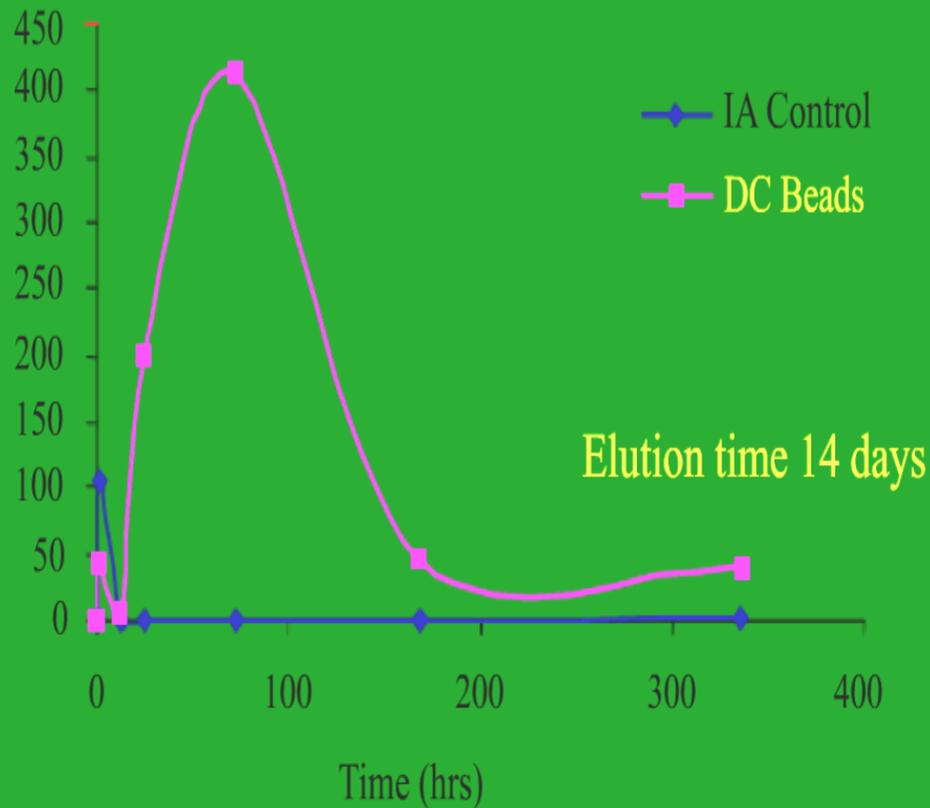
Procedura di radiologia interventistica consistente, previo accesso percutaneo transfemorale, nell'infusione intrarteriosa di microparticelle embolizzanti pre-caricate con chemioterapico



# DEB-TACE

## Rabbit VX-2 Tumor Results

Doxorubicin Concentration in the Tumour



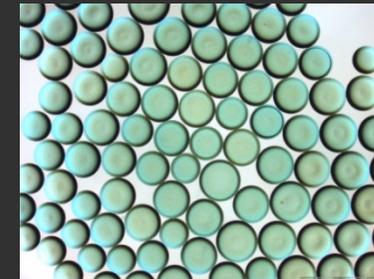
700 - 900 µm

verve

# DEB-TACE

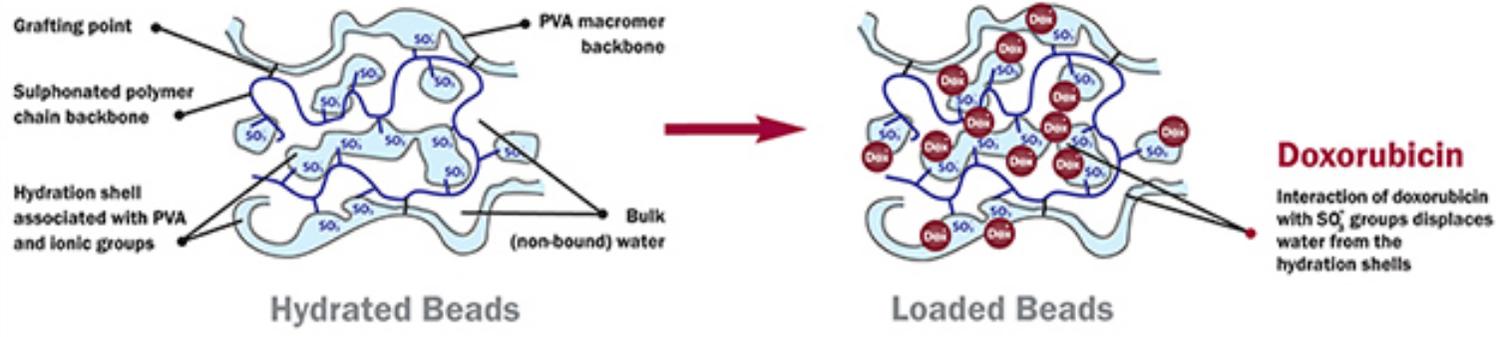


DC Bead prima di essere caricate



DC Bead dopo caricamento CHT

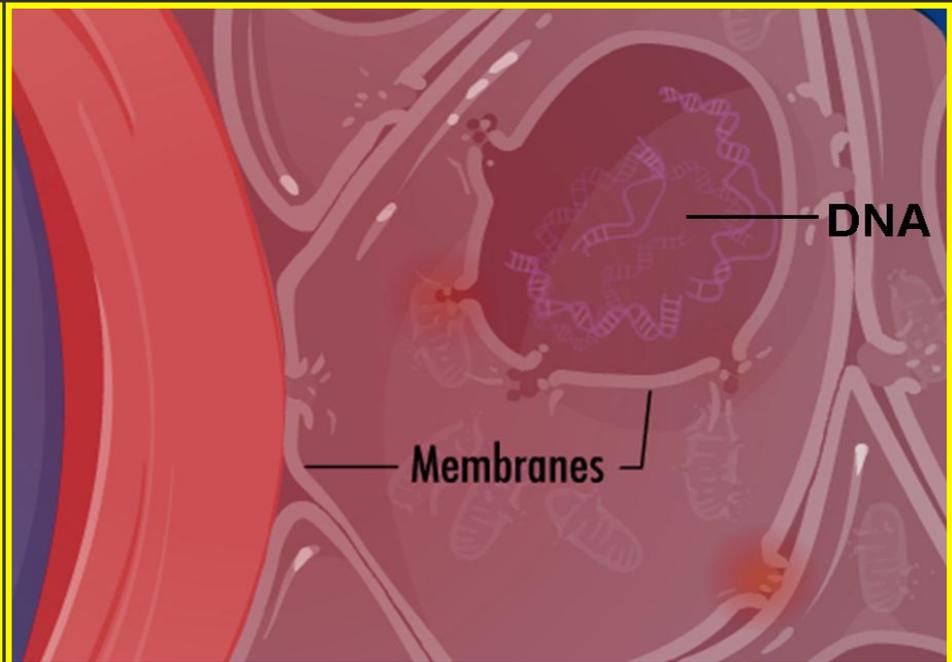
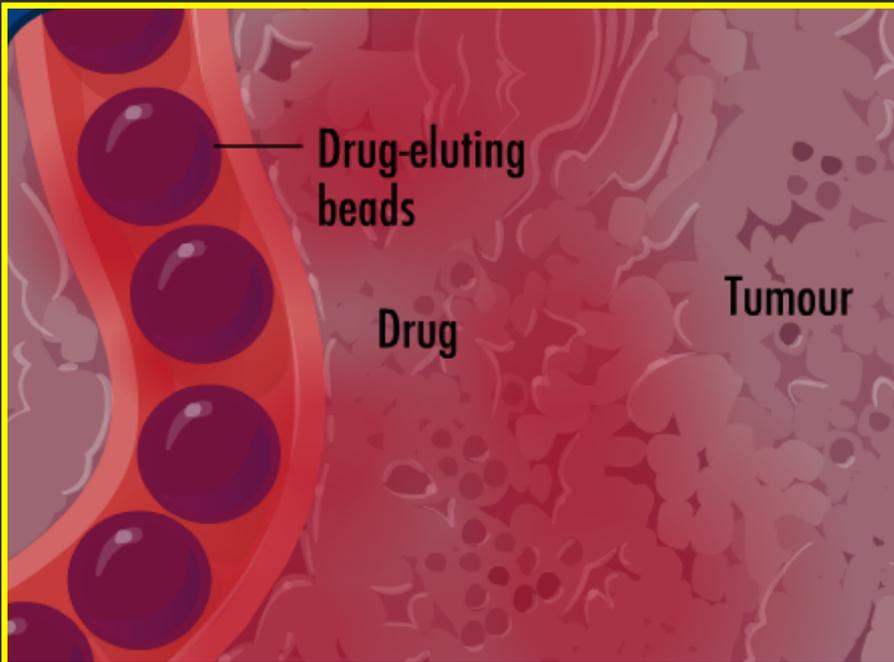
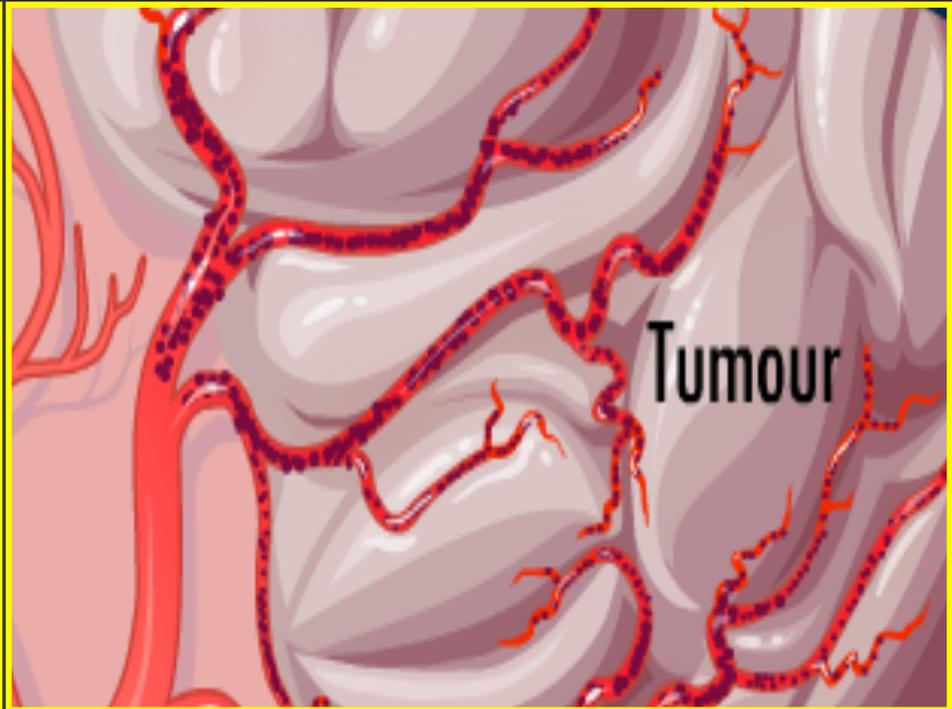
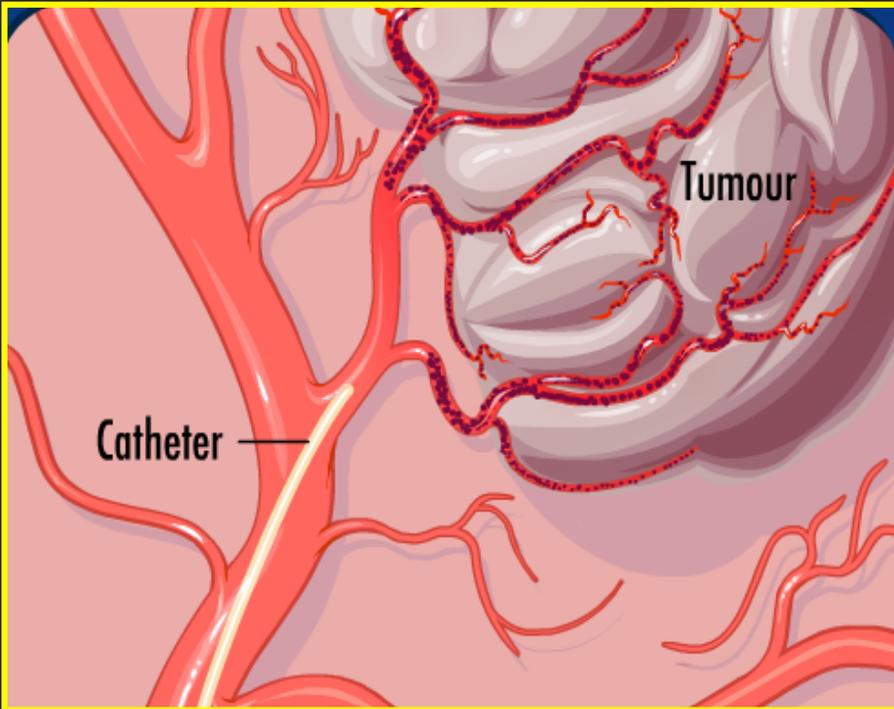
## DC Bead<sup>™</sup> Mode of Loading



# RAZIONALE DELLA TACE

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- Vascolarizzazione metastasi 100% arteriosa
- Riduzione della concentrazione sistemica CHT
- L'effetto embolico aumenta l'uptake del chemioterapico e produce necrosi tumorale

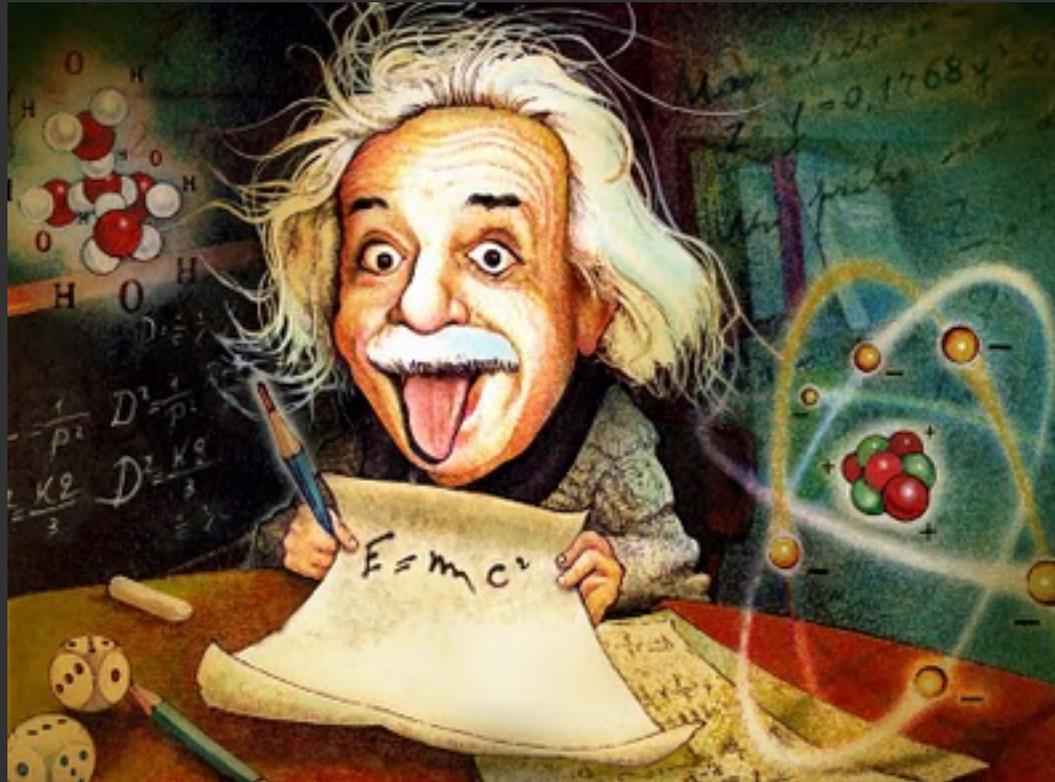


# RAZIONALE DELLA TACE

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- **Aumento della concentrazione del farmaco entro il tumore attraverso l'iniezione arteriosa selettiva da 10 a 100 volte rispetto all'infusione sistemica**
- **L'ischemia prodotta nella regione tumorale aumenta l'effetto di alcuni farmaci, che potenziano la loro efficacia in condizioni di ipossia (doxorubicina e cisplatino )**
- **Tossicità sistemica minimizzata e risparmio del tessuto epatico circostante**

# RAZIONALE DELLA TACE



# INDICAZIONI TACE

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- **NEO-ADIUVANTE (CHIRURGIA O RF)**

- **PALLIATIVA**

# INDICAZIONI TACE

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- Paziente con metastasi epatiche non candidabile a trattamento radicale (chirurgia/ RF)
- Progressione malattia dopo CHT (CRC)
- Funzionalità epatica conservata
- Assenza di invasione vascolare



# INDICAZIONI TACE

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- COLON RETTO
- MELANOMA
- NET
- COLANGIOCARCINOMA
- MAMMELLA
- ALTRI

# CONTROINDICAZIONI TACE

## -Alterata funzionalità epatica

- Bilirubina > 3 mg/dl
- Albumina < 3 g/dl
- INR > 1.6



## -Ostruzione Biliare (se non correggibile)

## -Trombosi portale (relativa)

## -Insufficienza renale

## -Disordini coagulativi

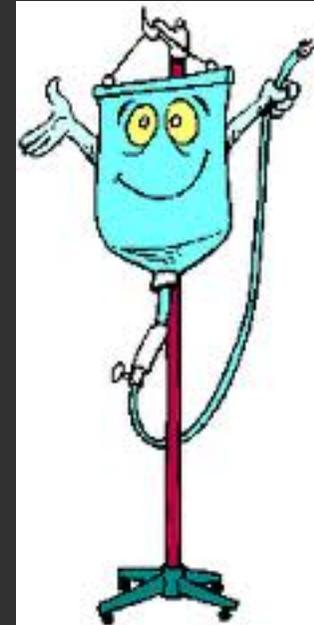
## -Allergia mdc

# TACE- PROTOCOLLO

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## -Premedicazione:

- Idratazione
- Antiemetici
- Antibiotici (pz con alterazioni biliari)



# TACE- PROTOCOLLO

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- Antibiotici (pz con alterazioni biliari)

## -Accesso Femorale



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## -Arteriografia t. celiaco



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## -Arteriografia t. celiaco

## -Arteriografia selettiva/ s. selettiva epatica



# TACE- PROTOCOLLO

## -Premedicazione:

- Idratazione
- Antiemetici
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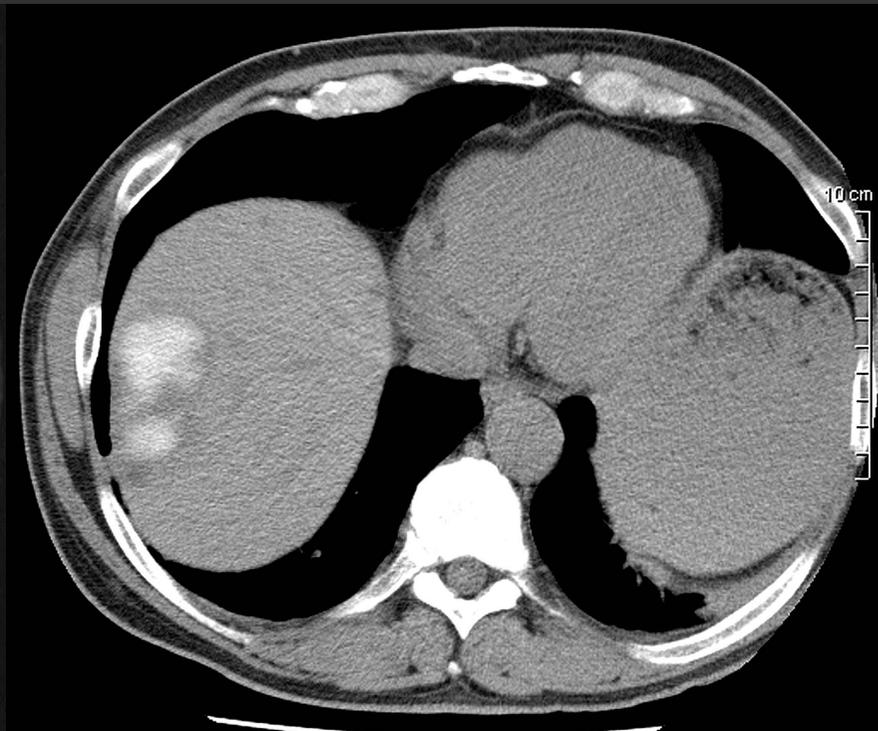
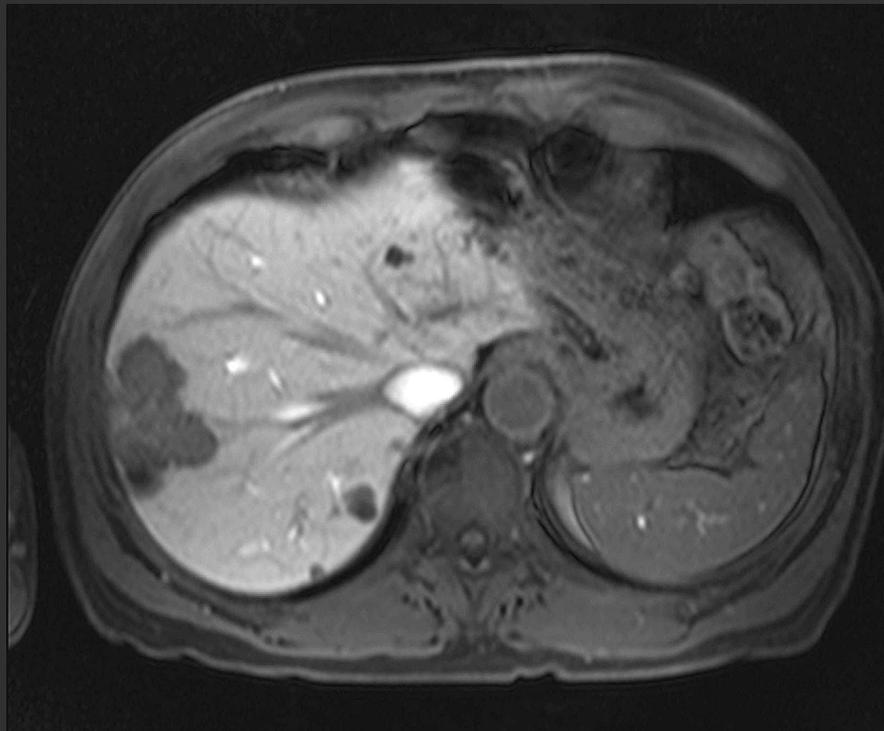
## -Arteriografia t. celiaco

## -Arteriografia selettiva/ s. selettiva epatica

## -Embolizzazione



# Controllo RM/TC



# TACE

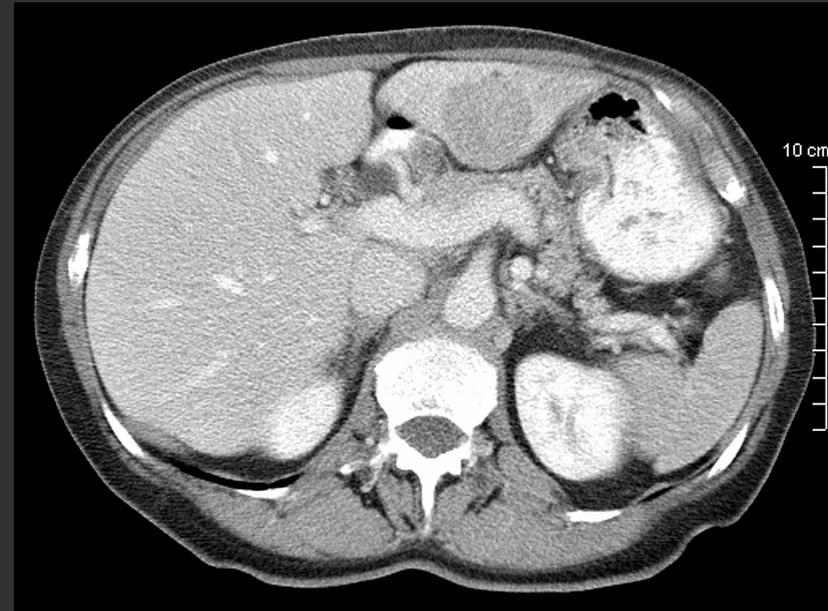
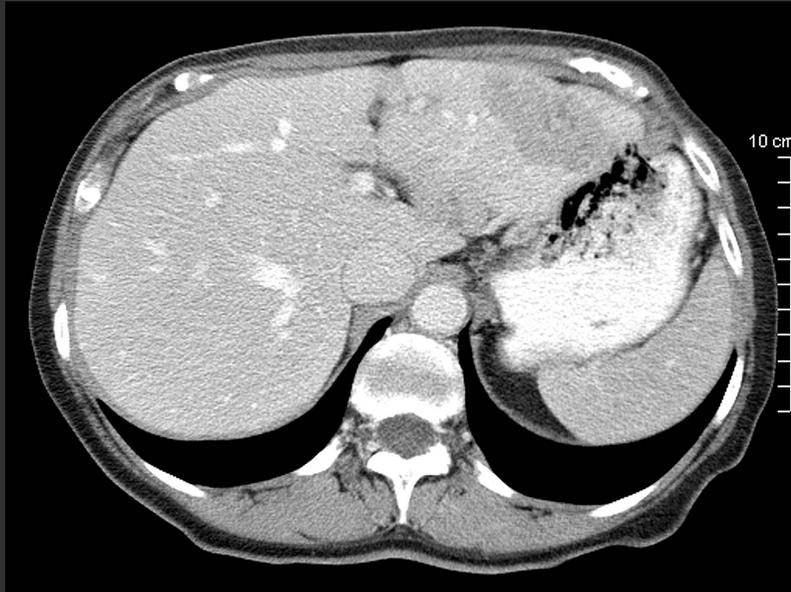
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## Agenti chemioterapici:

IRINOTECAN, CISPLATINO, DOXORUBICINA,  
MITOMICINA C

# Caso Clinico n.1

Age/sex	LMts	Syst. Trx.	TACE	Irinotc	DEB	EASL	RECIST	SV
58y/f	Sx	2						



# DC Beads 100-300 $\mu\text{m}$ CR/PR

Age/sex	LMts	Syst. Trx.	TACE	Irinotc	DEB	EASL	RECIST	SV
58y/f	Sx	2	11.11.12	100 mg	2 cc			
			23.11.12	100 mg	2 cc			



# DC Beads 100-300 $\mu$ m CR/PR

Age/sex	LMts	Syst. Trx.	TACE	Irinotc	DEB	EASL	RECIST	SV
58y/f	Sx	2	11.11.12 23.11.12	100 mg 100 mg	2 cc 2 cc	PR (70%)	PR (3mo)	al.



baseline



2 mesi

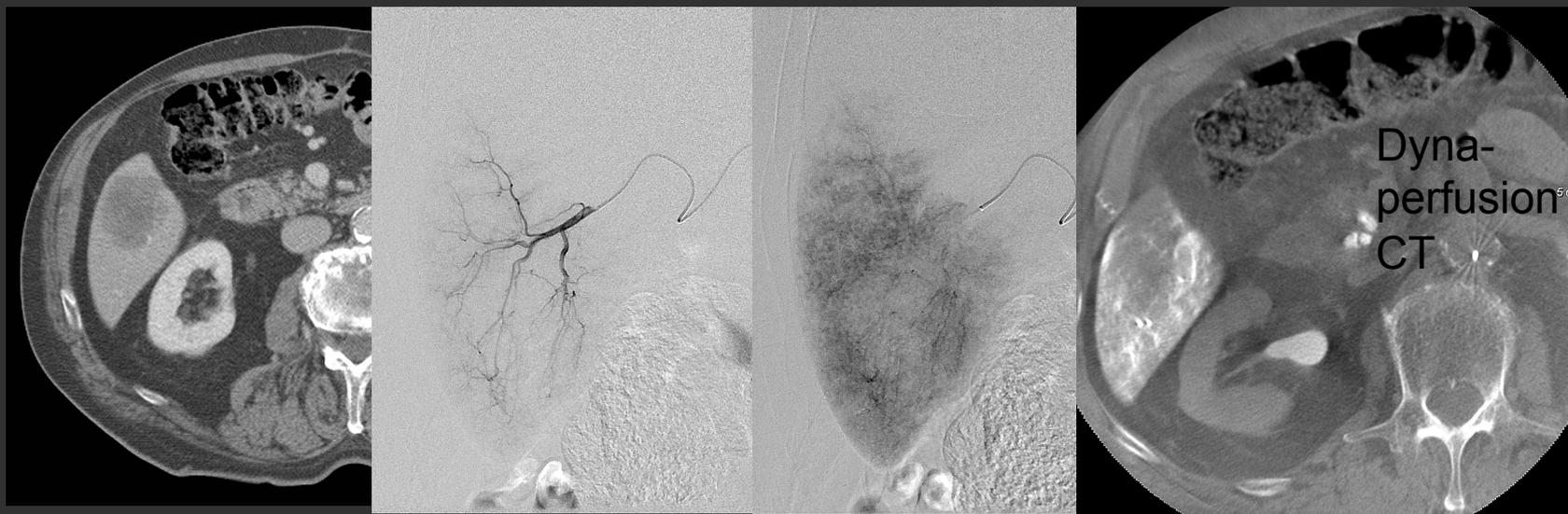


3 mesi



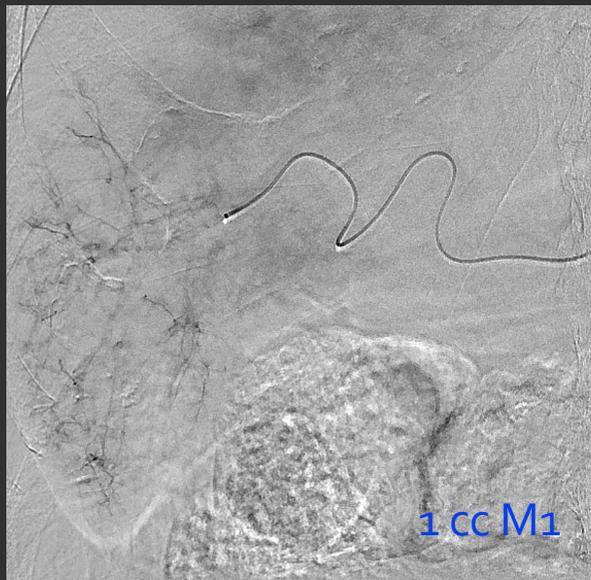
# C. Clinico n.2- T. Ipovascolare

Age/sex	LMts	Chth	TACE	Irinotc	M1 Beads	EASL	RECIST	SV
78Y / m	Dx	2	28/09/11	100 mg	2CC (70-150 $\mu$ m)			



28/09/10

Age/sex	LMts	Chth	TACE	Irinotc	M1 Beads	EASL	RECIST	SV
78Y / m	Dx	2	28/09/11	100 mg	2CC (70-150 $\mu$ m)			

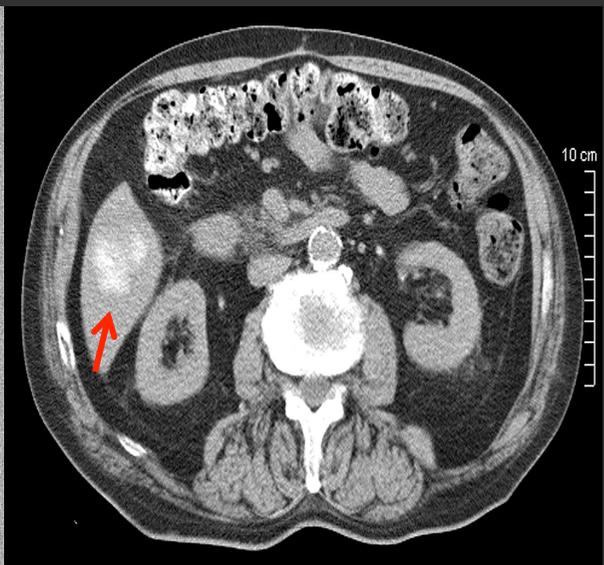
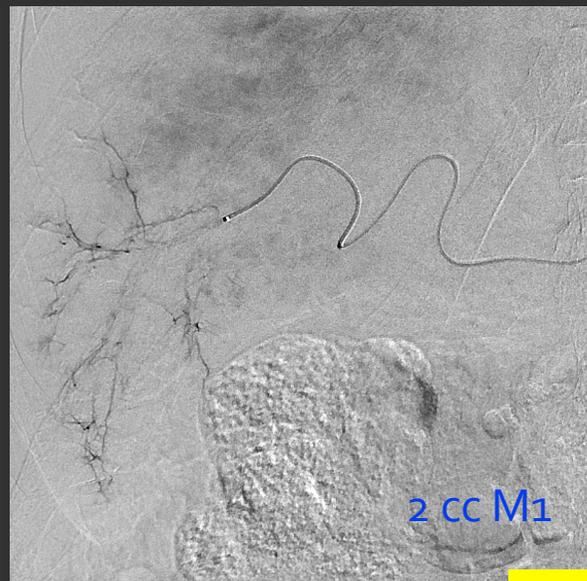
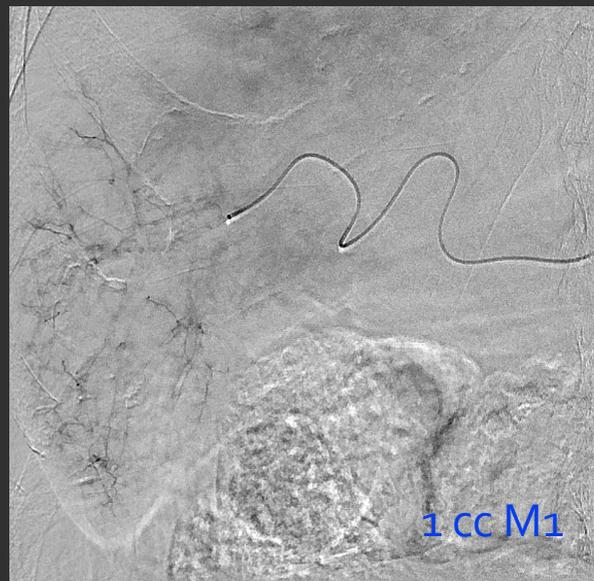


Durante/dopo TACE

28/09/10

29/09/10

Age/sex	LMts	Chth	TACE	Irinotc	M1 Beads	EASL	RECIST	SV
78Y / m	Dx	2	28/09/10	100 mg	2CC (70-150 $\mu$ m)			



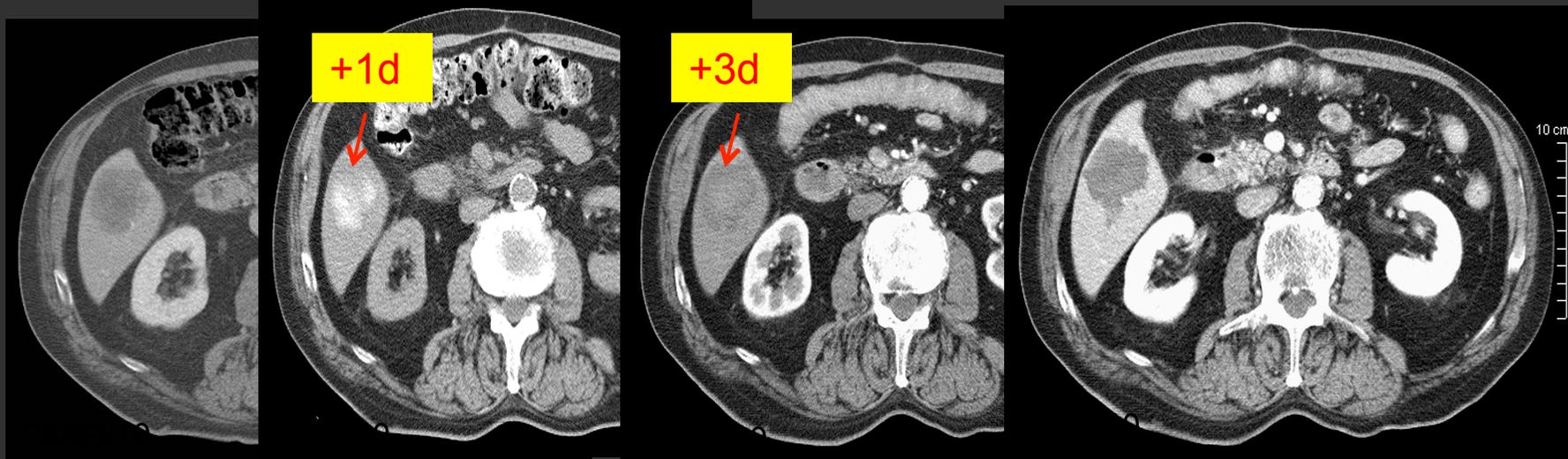
Durante/dopo TACE

Uptake Beads/CM

28/09/10

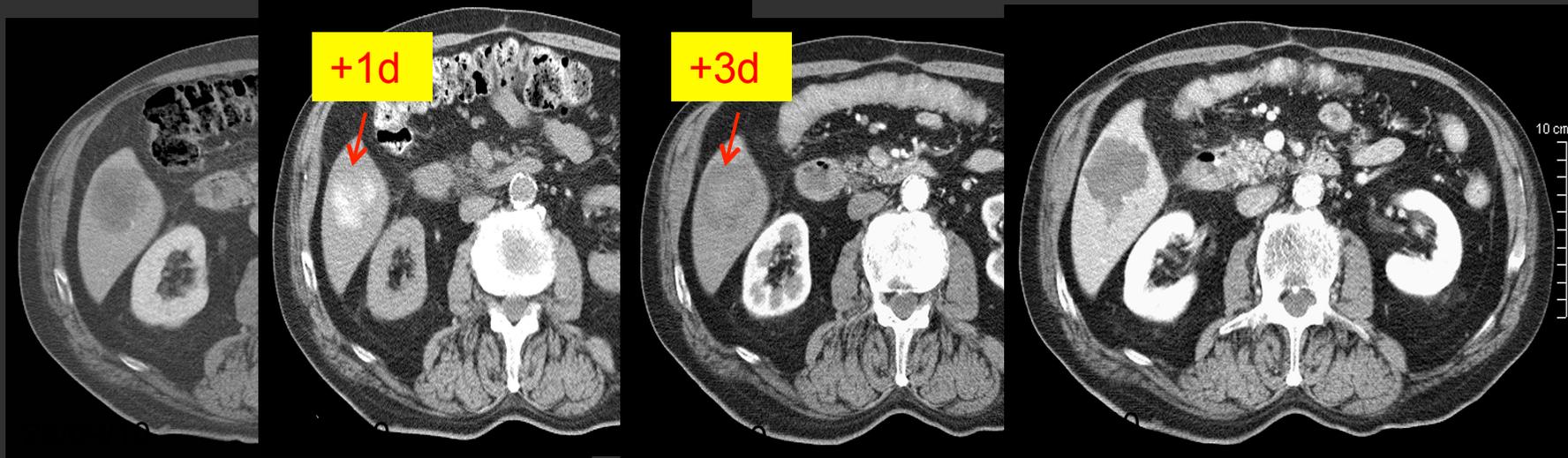
29/09/10

Age/sex	LMts	Chth	TACE	Irinotc	M1 Beads	EASL	RECIST	SV
78Y / m	Dx	2	28/09/11	100 mg	2CC (70-150 $\mu$ m)			



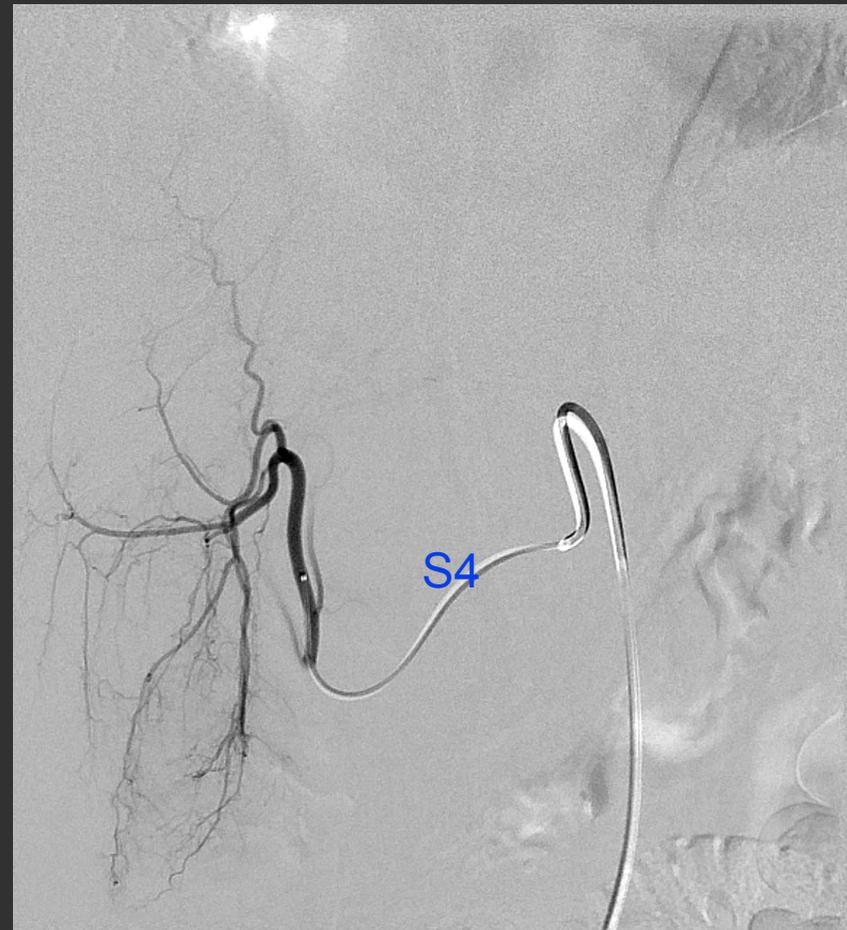
Intenso Uptake di DC Beads® : necrosi completa tumore

Age/sex	LMts	Chth	TACE	Irinotc	M1 Beads	EASL	RECIST	SV
78Y / m	Dx	2	28/09/11	100 mg	2CC (70-150 $\mu$ m)			

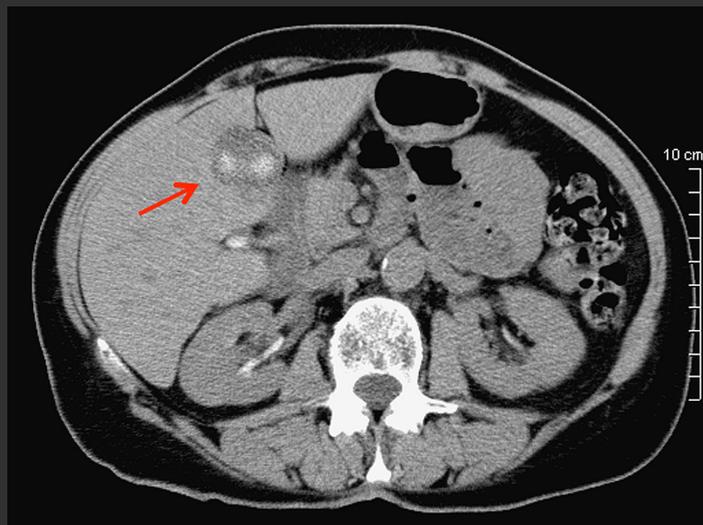


DC-Beads hanno la potenzialità di penetrazione profonda all'interno della vascolarizzazione inducendo necrosi completa  
Anche nei tumori ipovascolari

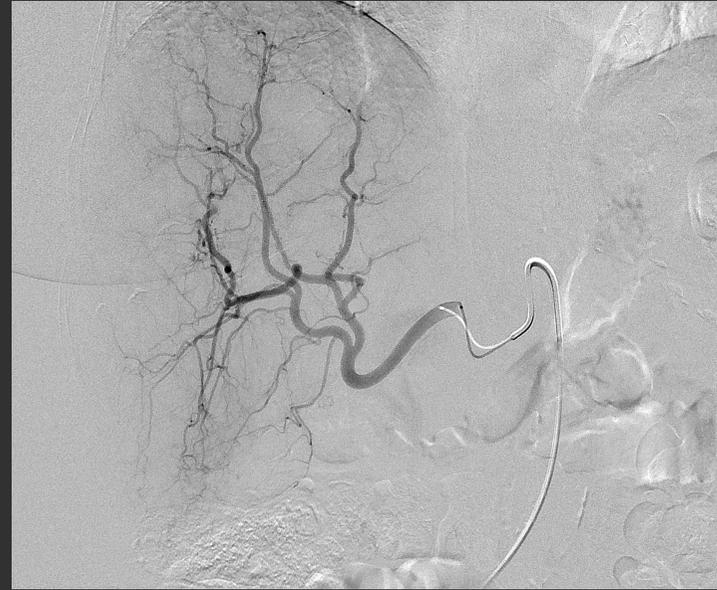
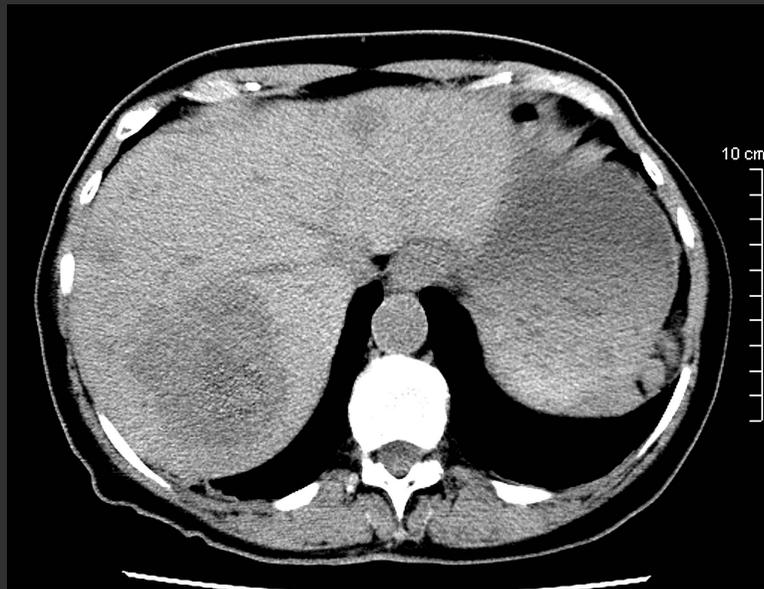
# Singolo „feeder“ arterioso



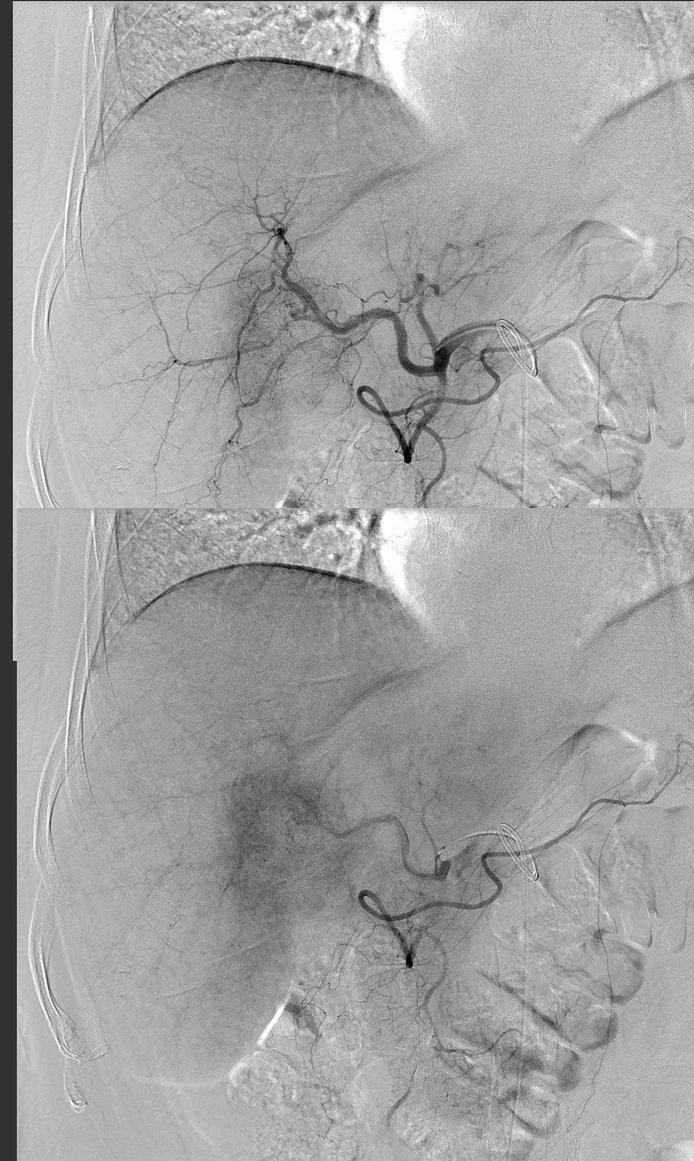
# Singolo „feeder“ arterioso



# Multipli „ feeders“ arteriosi



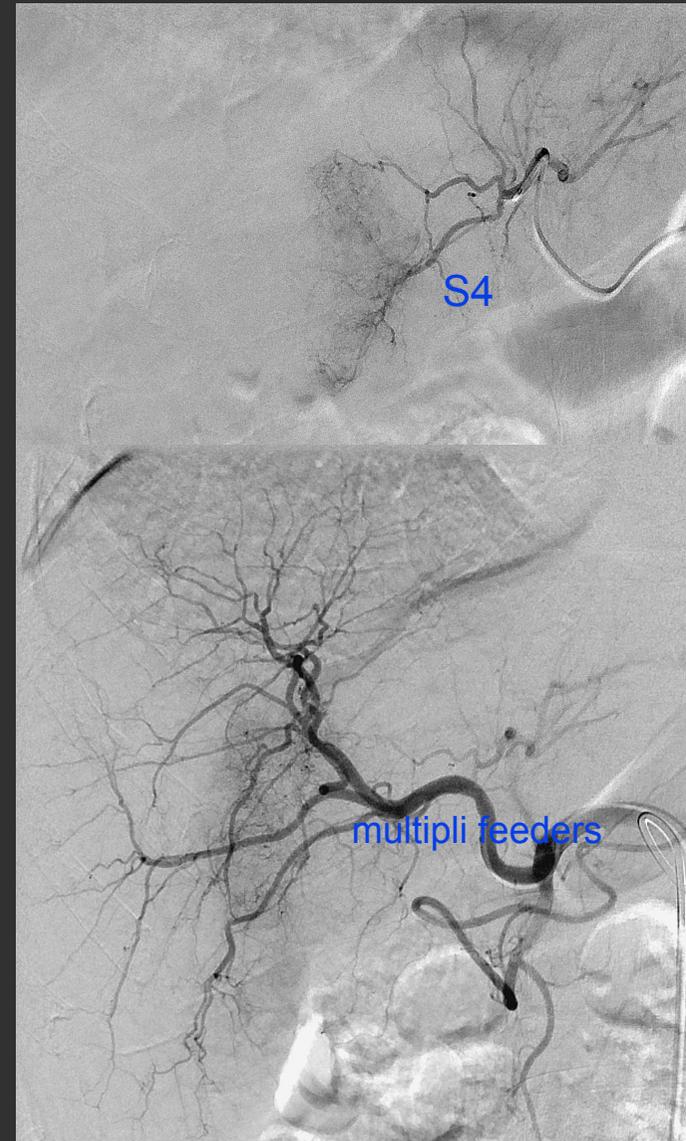
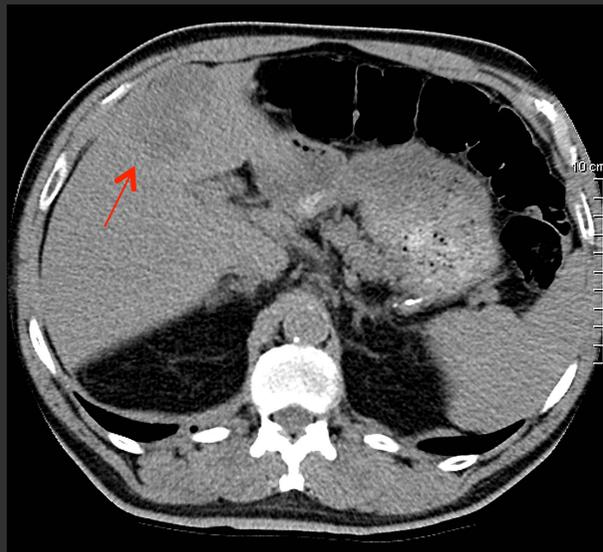
# Multipli „ feeders“ arteriosi



# Multipli „ feeders“ arteriosi



# Multipli „ feeders“ arteriosi



# TACE- COMPLICANZE

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**Intra-procedurali**

**Post-procedurali**

# TACE- COMPLICANZE

**Table 5** Changes in biochemical parameters after TACE

Biochemical change	Average frequency (%)
>50 % increase in ALT	74
>50 % increase in AST	1.5
>50 % increase in creatinine	45.2
>3-second increase in prothrombin time	58.9
Bilirubin >38 $\mu\text{mol/L}$	6.5
If pre-TACE level was normal or $\geq$ twice the basal level	1
If pre-TACE level was abnormal	3
$\geq 25$ % decrease in AFP	0.5
$\geq 50$ % decrease in AFP	0.5

*CIRSE guidelines for TACE-2012*

# TACE- COMPLICANZE

**Table 6** Complications of TACE and their management

Complication	Management
Postembolization syndrome (nausea, vomiting, pain, fever)	Self-limited supportively (acetaminophen, nonsteroidal antirheumatics, etc.)
Hemorrhage	Embolization
Liver abscess	Drainage + antibiotics
Acute hepatic decompensation	Precaution measures: patient selection, superselective treatment
Embolism (pulmonary, cerebral)	Precaution measures: patient selection, (exclusion of relevant tumor AV shunt)
Side effects of chemotherapeutic agents (toxicity)	Supportive medication

*CIRSE guidelines for TACE-2012*

# TACE- COMPLICANZE

**Table 4** List of GI complications after c-TACE

Complication	Reported rate (%)	Threshold (%)
Liver failure	2.3	4
Abscess with functional sphincter of Oddi	<1	2
Postembolization syndrome requiring extended stay or readmission	4.6	10
Abscess with biliary-enteric anastomosis/ biliary stent/sphincterotomy	25	25
Surgical cholecystitis	<1	1
Biloma requiring percutaneous drainage	<1	2
Pulmonary arterial embolus	<1	1
GI bleeding/ulceration	<1	1
Iatrogenic dissection preventing treatment	<1	1
Death within 30days	1	2

*CIRSE guidelines for TACE-2012*

# TACE-RISULTATI

**Table 5**

**Summary of Major Studies on Chemoembolization in Metastatic NETs, Breast Cancer, and Uveal Melanoma**

Study and Year	No. of Patients	Embolic Agent	Chemotherapeutic Agent	Type of Cancer	Design	Overall Survival				Median Survival (mo)
						1 Year (%)	2 Year (%)	3 Year (%)	5 Year (%)	
Gupta et al, 2005 (202)	69	Polyvinyl alcohol or gelatin sponges	Not reported	Carcinoid	Retrospective	95.3	68.8	NA	28.6	33.8
Gupta et al, 2005 (202)	54	Polyvinyl alcohol or gelatin sponges	Not reported	Islet cell	Retrospective	68.8	48.7	NA	13.7	23.7
Christante et al, 2008 (203)	77	Lipiodol	Mitomycin C, cisplatin, doxorubicin	NET	Retrospective	79	NA	NA	27	39
Vogl et al, 2007 (204)	12	Lipiodol plus starch microspheres	Mitomycin C	Uveal melanoma	Retrospective	NA	NA	NA	NA	21
Huppert et al, 2010 (205)	14	Polyvinyl alcohol	Cisplatin	Uveal melanoma	Retrospective	40	14	NA	NA	11.5
Vogl et al, 2010 (206)	208	Starch microspheres	Mitomycin C; mitomycin C plus gemcitabine; mitomycin C plus irinotecan	Breast	Prospective	69	40	33	NA	18.5

Note.—Table includes only studies published since 2005. NA = not available.

**Radiology:** Volume 266: Number 2—February 2013 ■ [radiology.rsna.org](http://radiology.rsna.org)

# TACE-RISULTATI

**Table 4**

**Summary of Studies on Chemoembolization in Colorectal Liver Metastases**

Study and Year	No. of Patients	Embolic Agent	Chemotherapeutic Agent	Study Design	Overall Survival			Median Survival (mo)
					1 Year (%)	2 Year (%)	3 Year (%)	
Müller et al, 2003 (199)	66	Lipiodol or gelatin sponges	5-FU, GM-CSF, melphalan	Prospective	NA	66	NA	NR
Pohlen et al, 2004 (200)	95	Starch microspheres	5-FU, interferon $\alpha$ , folinic acid (arterial pump)	Prospective	NA	NA	NA	24
Vogl et al, 2009 (136)	463	Starch microspheres	Mitomycin C; mitomycin C plus gemcitabine; mitomycin C plus irinotecan	Retrospective	68	28	NA	14
Martin et al, 2011 (144)	95	Drug-eluting beads	Irinotecan	Prospective	75	NA	NA	19
Albert et al, 2011 (201)	121	Lipiodol plus polyvinyl alcohol	Cisplatin plus doxorubicin plus mitomycin C	Retrospective	36	13	4	9

Note.—Studies in this table included more than 50 patients each. GM-CSF = granulocyte-macrophage colony-stimulating factor, NA = not available, NR = not reached.

**Radiology:** Volume 266: Number 2—February 2013 ■ [radiology.rsna.org](http://radiology.rsna.org)



*Struttura Semplice di Radiologia Interventistica  
Az. Ospedaliera S. Maria, Terni*

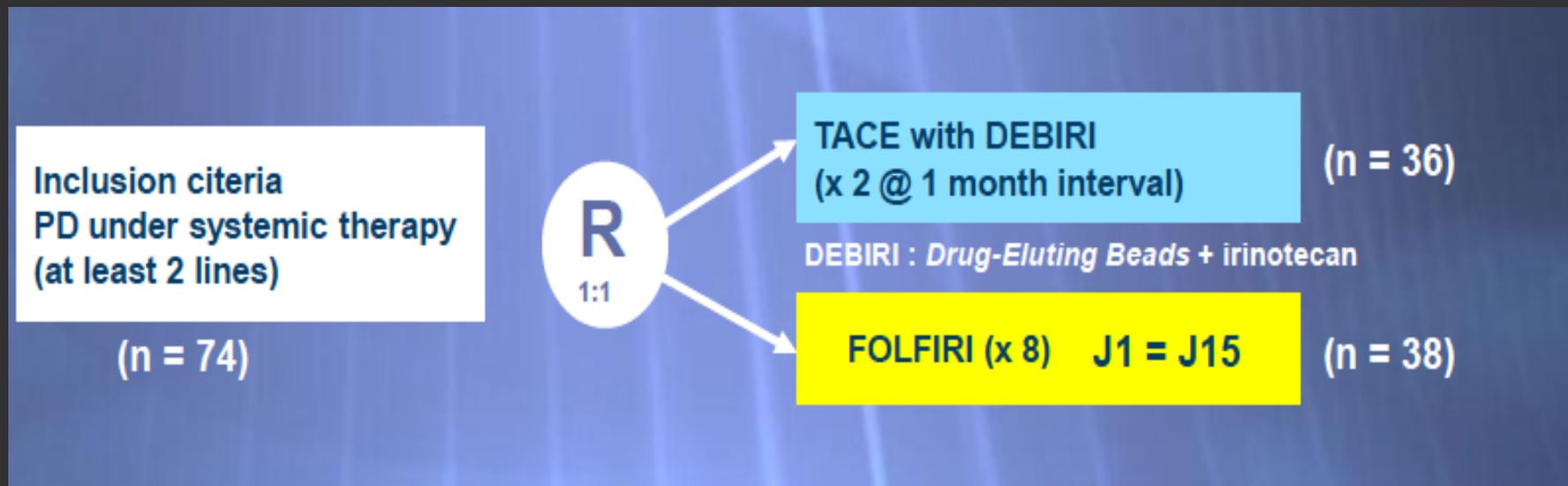
# TACE-RISULTATI

*Anticancer Res.* 2012 Apr;32(4):1387-95.

**Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study.**

Florentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani E, Alessandrini P, Catalano V, Coschiera P.

Department of Oncology-Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro, Italy. g.florentini@alice.it



# TACE-RISULTATI

PATIENTS CHARACTERISTICS	DEBIRI (D)	FOLFIRI (CT)
NUMBER OF PATIENTS	36	38
SEX (M – F)	20-16	24-14
AGE	64 (range 44-74)	63 (range 42-73)
LIVER INVOLVEMENT ( $\leq 25\%$ - $\leq 50\%$ )	26 - 10	26 - 12
SYNCHRONOUS/METACHRONOUS DISEASE	0/36	0/38
NUMBER OF METASTASES	4 (range 3 – 10)	4 (range 3 – 10)
LARGEST DIAMETER (cm)	4.5 ( range 2.5 -8)	4 ( range 2.5 – 8)
PERFORMANCE STATUS (0 – 1 and 2)	32 and 4	34 and 4
EXTRAHEPATIC METASTASES	0	0
PREVIOUS CHEMO (2–3 LINES)	23 - 13	25 - 14
TYPES OF PREVIOUS CHEMO	13 FUFA, 18 FOLFOX, 13 IFL, 3 FOLFOX+BEVACIZUMAB 3 FU+CETUXIMAB	12 FUFA, 20 FOLFOX, 14 IFL, 5 FOLFOX+BEVACIZUMAB 3 FU+CETUXIMAB
WEIGHT LOSS (-1 to 3 Kg) IN 2 MONTHS	20 (60%)	24 (63%)
ALBUMIN, g/dl (median)	4	3.9
CEA ng/mL	69 (range 3.5-473)	77 (range 2.5-611)
K-RAS (WT-M)	22 - 14	26 - 12
P53 (positive-negative)	22-12	20-18

Fiorentini et al;2012

# TACE-RISULTATI

Toxicity (all procedures)	70 DEBIRI	272 FOLFIRI
Pain	30%	0%
Vomiting	25%	25%
Diarrhoea	2%	35%
Asthenia	20%	50%
Leukopenia	5%	35%
Anaemia	5%	35%
Fever	15%	3%
Alopecia	5%	35%

Fiorentini et al;2012

# TACE-RISULTATI

	<b>DEBIRI</b> 35 pts	<b>FOLFIRI</b> 35 pts
<b>COMPLETE &amp; PARTIAL RESPONSES</b>	<b>24 (68.6%)</b>	<b>7 (20%)</b>
<b>STABLE DISEASE</b>	<b>4 (11.4%)</b>	<b>12 ( 34,3%)</b>
<b>PROGRESSION</b>	<b>7 (20%)</b>	<b>16 (45,7%)</b>

Fiorentini et al;2012

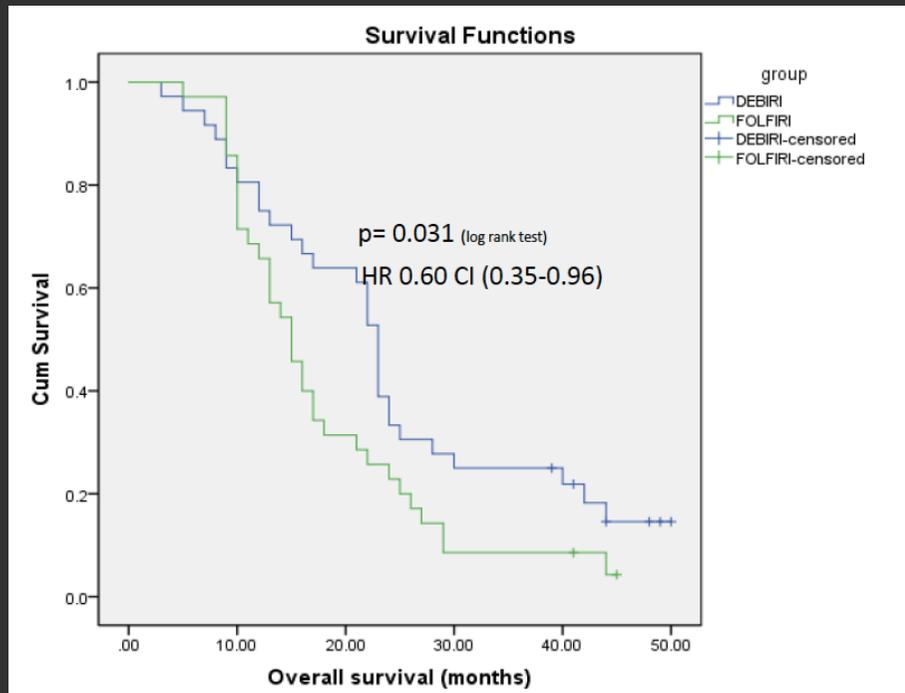
# TACE-RISULTATI

Arm	Median Overall Survival (Months)	PFS (Months)	Acute Toxicity (G2-G3)	Late Toxicity (G2)	Edmonton Score Improvement (from baseline)	Cost per Patient (Euros)
DEBIRI (D) (n=35)	22	7	70%	20%	60%	5,000 (2 D)
FOLFIRI (CT) (n=35)	15	4	25%	80%	22%	18,000 (8 CT)

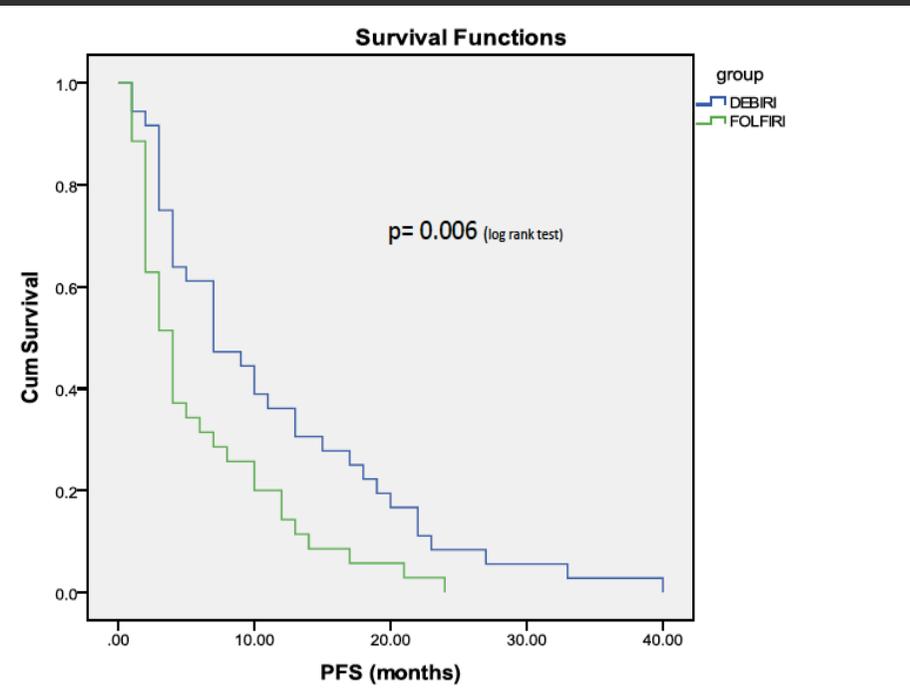
Fiorentini et al;2012

# TACE-RISULTATI

## OVERALL SURVIVAL



## PROGRESSION FREE SURVIVAL



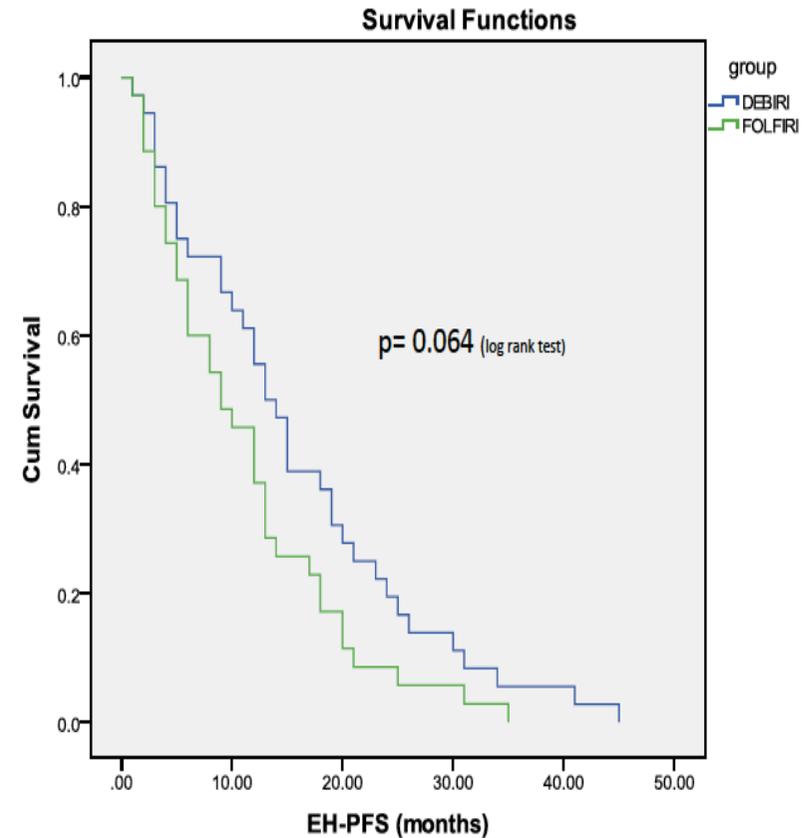
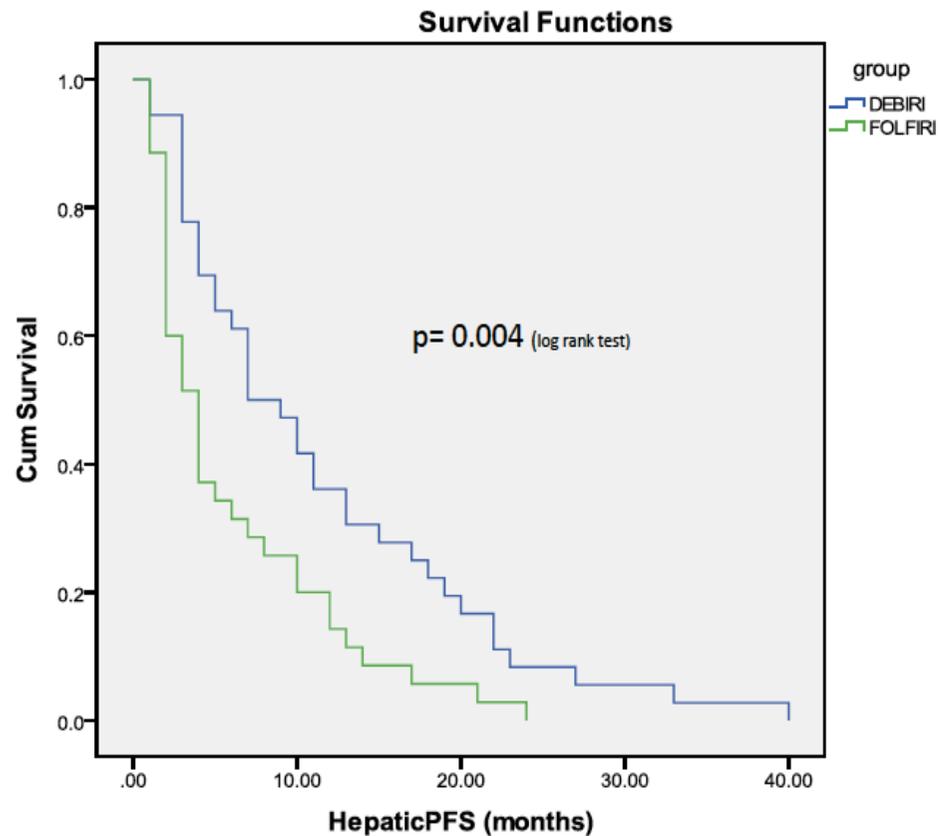
Fiorentini et al;2012

**SOPRAVVIVENZA 56% vs 32 % A 2 ANNI**

# TACE-RISULTATI

TIME TO HEPATIC PROGRESSION

TIME TO EXTRAHEPATIC PROGRESSION



Fiorentini et al;2012



AZIENDA  
OSPEDALIERA  
SANTA MARIA  
TERNI

Struttura Semplice di Radiologia Interventistica  
Az. Ospedaliera S. Maria, Terni

# CONCLUSIONI

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- TACE è un trattamento palliativo sicuro ed efficace nei pazienti con metastasi epatiche
- Studi con numero maggiore di pz
- Necessaria un'attenta selezione dei pazienti
- Fondamentale una valutazione multidisciplinare

[massimiliano.allegritti@gmail.com](mailto:massimiliano.allegritti@gmail.com)



*Struttura Semplice di Radiologia Interventistica  
Az. Ospedaliera S. Maria, Terni*