



The dark side of the guidelines

2nd Interventional Radiologist under 40 Meeting

Interventional Oncology

8-10 Maggio 2017

Bologna

Società Medica Chirurgica - Palazzo dell'Archiginnasio



TACE convenzionale e DEB-TACE

Orsola Perrone

U.O. Radiologia Interventistica

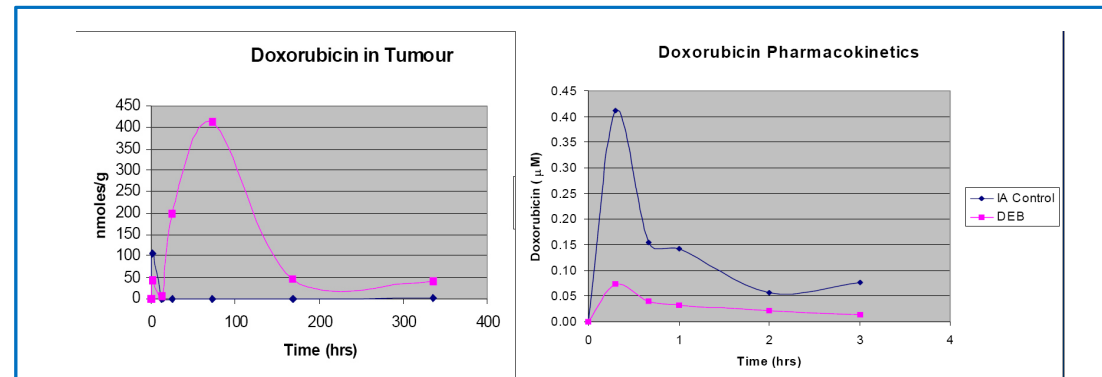
Azienda Ospedaliero Universitaria Pisana



2nd Interventional Radiologist under 40 Meeting
Interventional Oncology

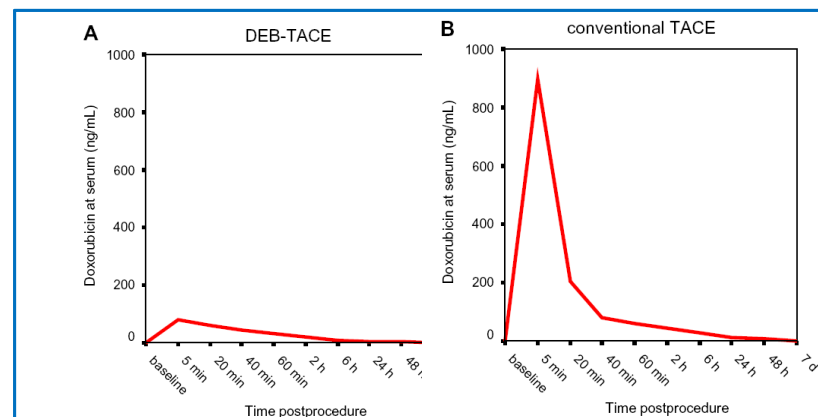
2005: The beginning of the story

Preclinical model



Hong K et al. Clin Cancer Res 2006

Preliminary experience



Well tolerated and safe
Response rate : 75%

Varela M et al. J Hepatol 2007

Drug eluting beads

CLINICAL INVESTIGATION

Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: Results of the PRECISION V Study

Lammer J et al. Cardiovasc Intervent Radiol 2010

**Improved tolerability
Reduced toxicity**

Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design

Burrel M et al. J Hepatol 2012

Chemoembolization With Doxorubicin-Eluting Beads for Unresectable Hepatocellular Carcinoma: Five-Year Survival Analysis

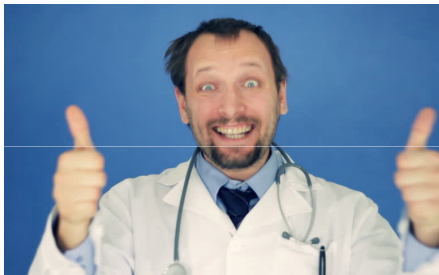
Malagari K et al. Cardiovasc Intervent Radiol 2012

**Median survival
> 40 months**

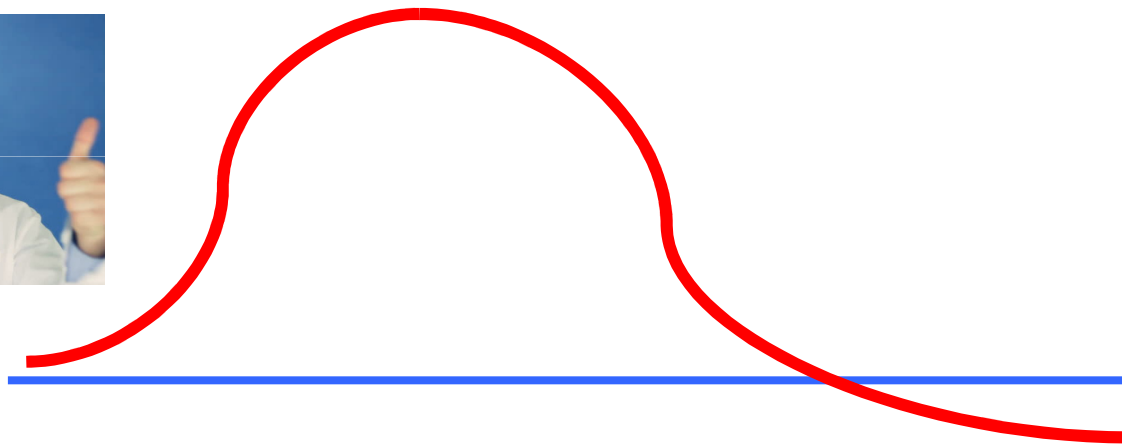
The “BEADS” generation



The last decade in literature



2006

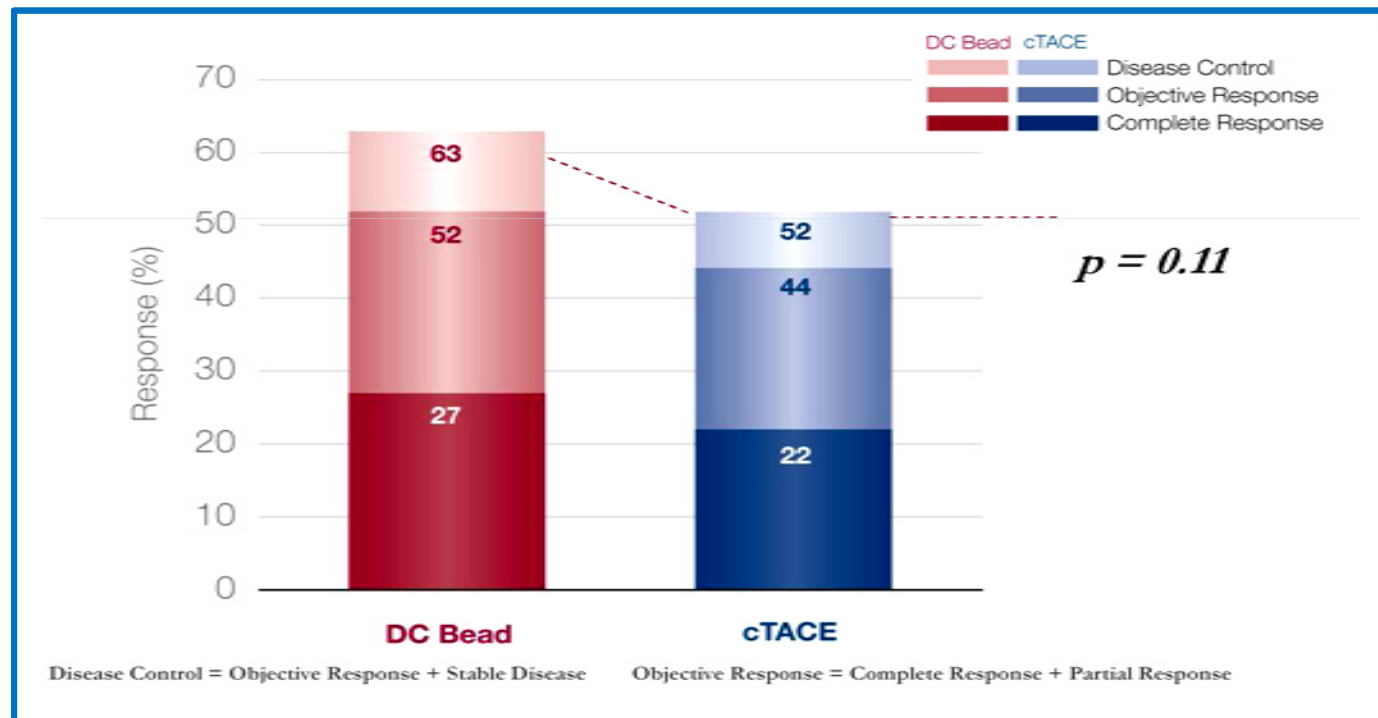


2016



DEB-TACE or Lipiodol™-TACE?

**No difference
in radiological
response**



Lammer J et al. Cardiovasc Intervent Radiol 2010

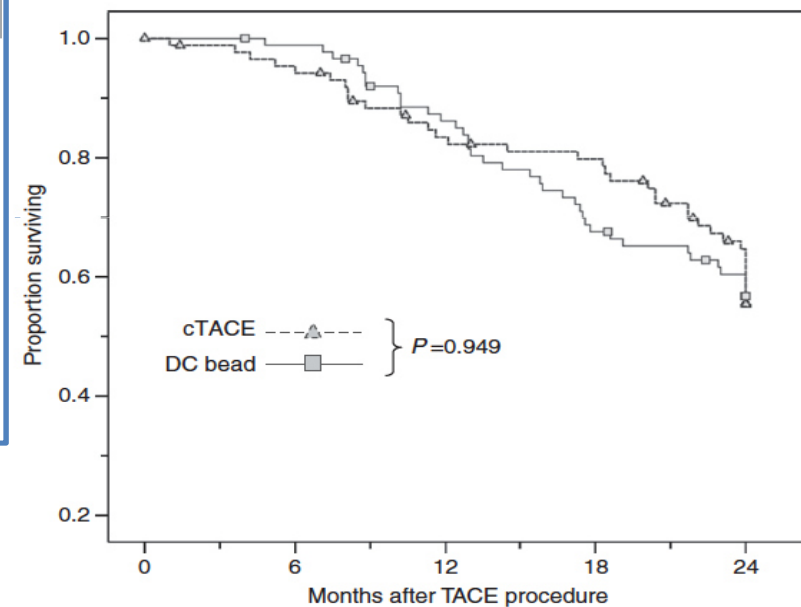
DEB-TACE or Lipiodol™-TACE?

BJC FULL PAPER
British Journal of Cancer (2014) 111, 255–264 | doi: 10.1038/bjc.2014.199

Keywords: liver cancer; intra-arterial hepatic therapy; mRECIST; survival

Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma

R Golfieri¹, E Giampalma¹, M Renzulli^{*,1}, R Cioni², I Bargellini², C Bartolozzi², A D Breatta³, G Gandini³, R Nani⁴, D Gasparini⁵, A Cucchetti⁶, L Bolondi⁶ and F Trevisani⁶ on behalf of the PRECISION ITALIA STUDY GROUP⁷



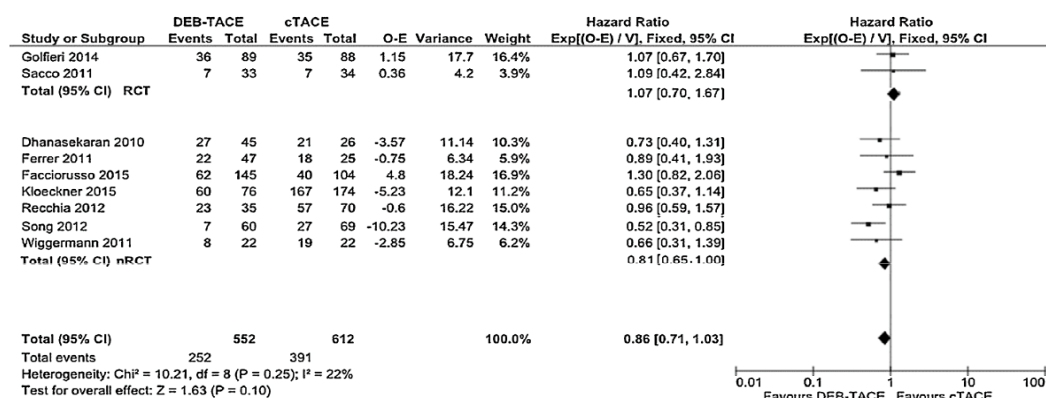
At risk	0	3	6	9	12	18	24
cTACE	88	85	82	74	69	65	42
DC bead	89	88	87	79	74	58	47

No difference in survival

Golfieri R et al. British Journal of Cancer 2014

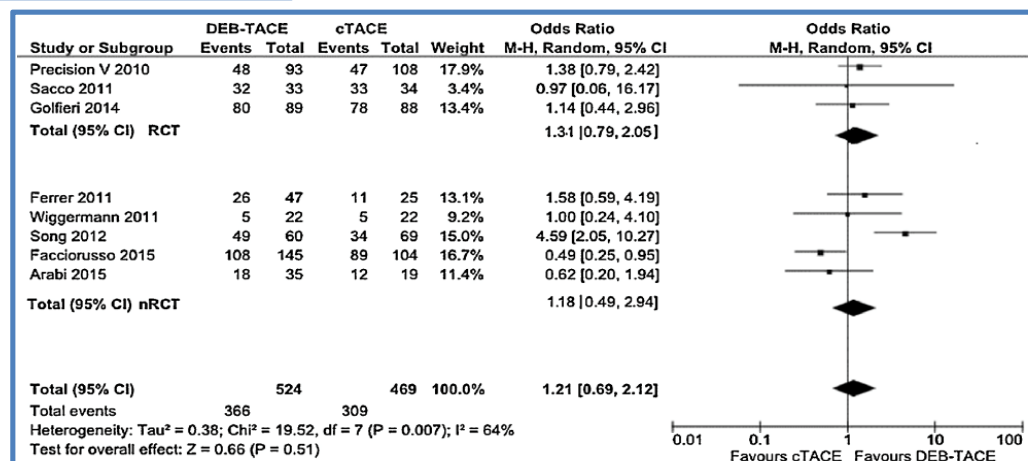
Review Article

Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis

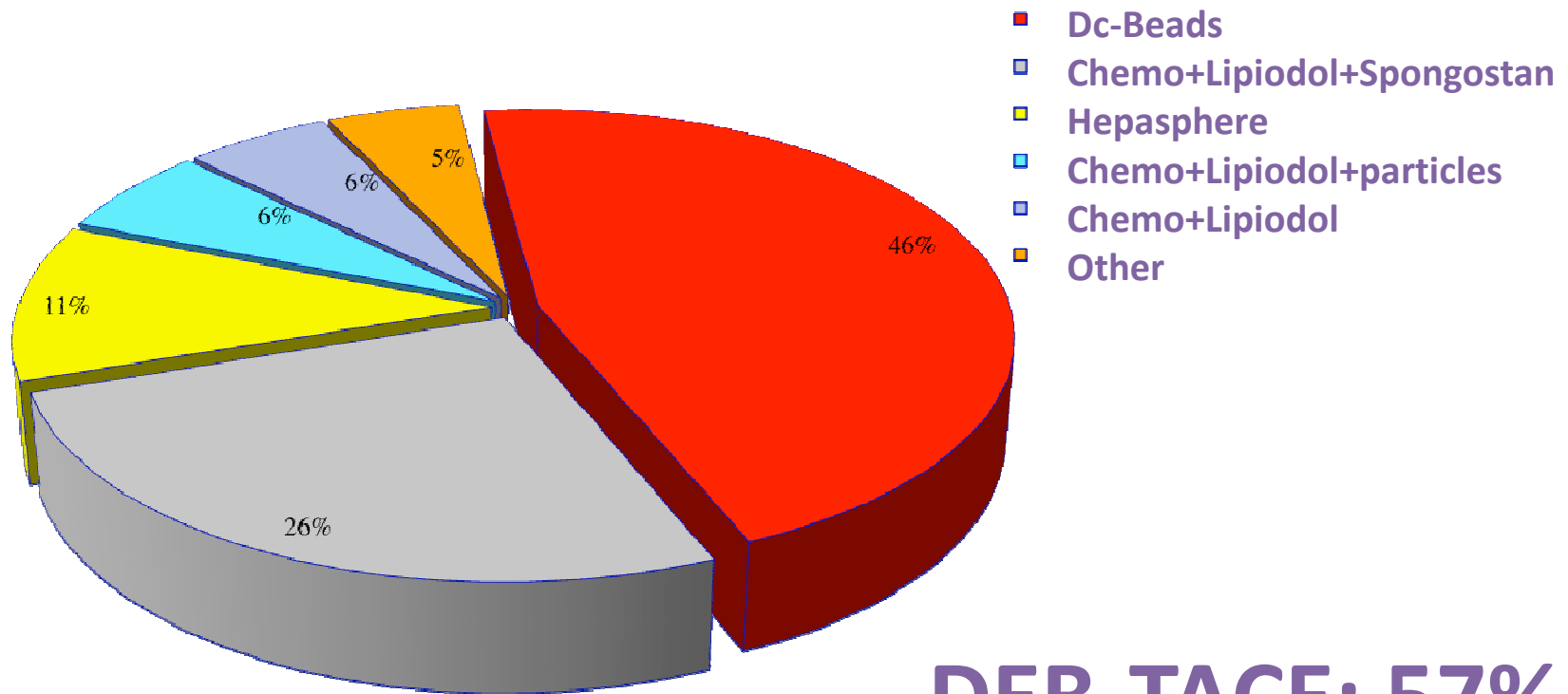


Survival

Obj response



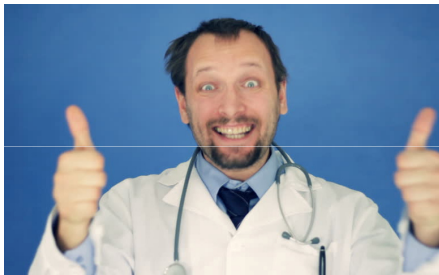
TACE in Italy in 2012



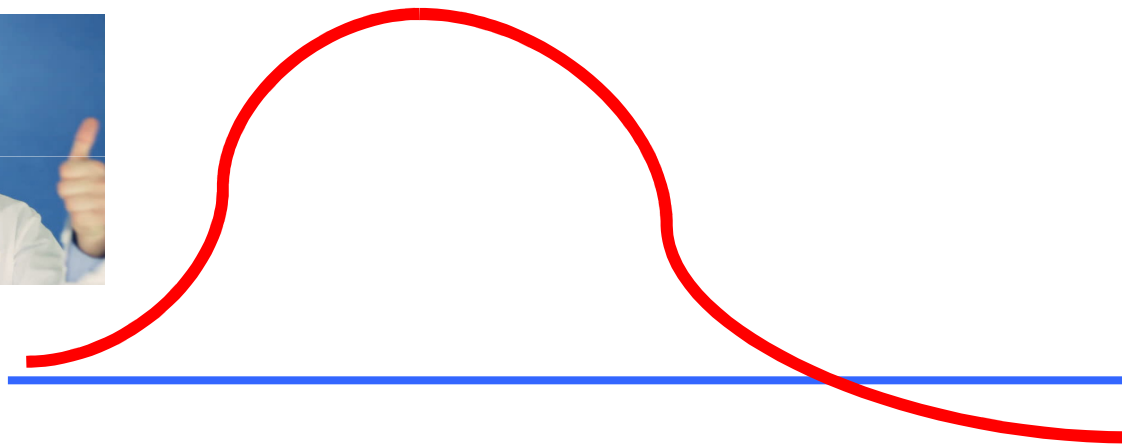
DEB-TACE: 57%

Bargellini I et al. Cardiovasc Intervent Radiol 2013

The last decade in literature



2006

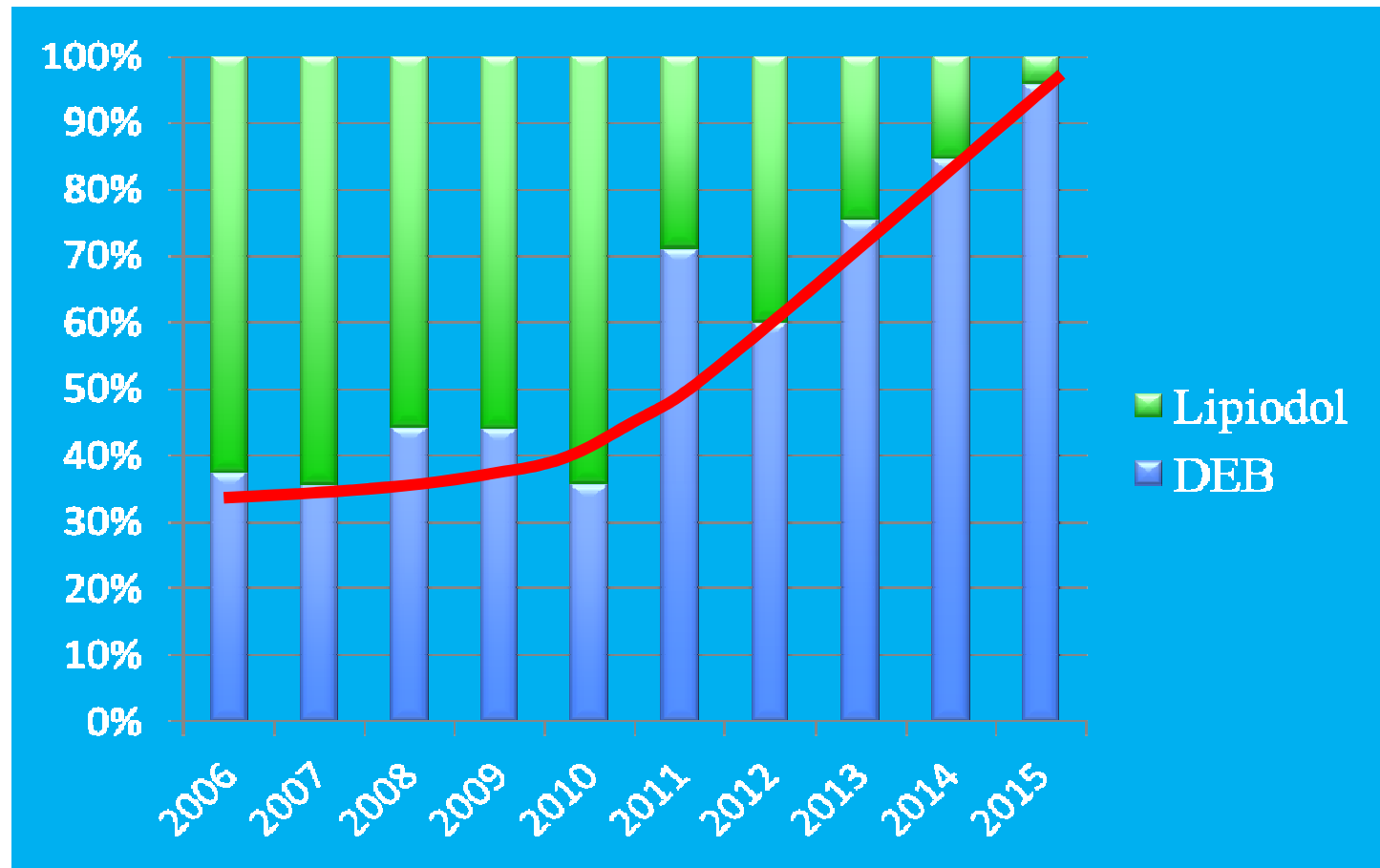


2016



The last decade in PISA

TACE in 813
naive HCC
pts



DEB-TACE or Lipiodol™-TACE?

486 naive HCC pts treated with TACE from 2006 to 2011

Mean hospitalization

- Lipiodol-TACE (n=271): 3.8 ± 3.5 days
- DEB-TACE (n=215): 2.7 ± 2.6 days

**P= 0.0004*

Personal series

Clinical and economic impact of drug eluting beads in transarterial**Table 4.** Overall cost of a TACE strategy valued by the official tariffs from the DRG prospective payment system

Valuation	Period 1 without DEBs (<i>n</i> = 118)		Period 2 with the possibility of using DEBs (<i>n</i> = 296)		<i>P</i> Value
	Median	Mean ± SD	Median	Mean ± SD	
TACE courses	10 685	10 628 ± 5719	6749	7159 ± 4375	<10 ⁻³
Management of TACE-related toxicity	0	808 ± 2528	0	300 ± 1441	0.03
Medical products financed in addition to the DRG	0	37 ± 68	177	197 ± 231	10 ⁻⁴
Overall strategy	11 825	11 472 ± 5901	7379	7654 ± 4626	<10 ⁻⁴
Overall strategy including cost of DEBs	11 983	11 600 ± 5855	7720	8278 ± 4917	10 ⁻³

**No difference in clinical outcomes but
significantly lower rate of rehospitalizations
for the management of TACE-related toxicities**

Oncology

Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma



Table 4
Results of Markov simulation model over 2000 patients submitted wither to cTACE or DEB-TACE.

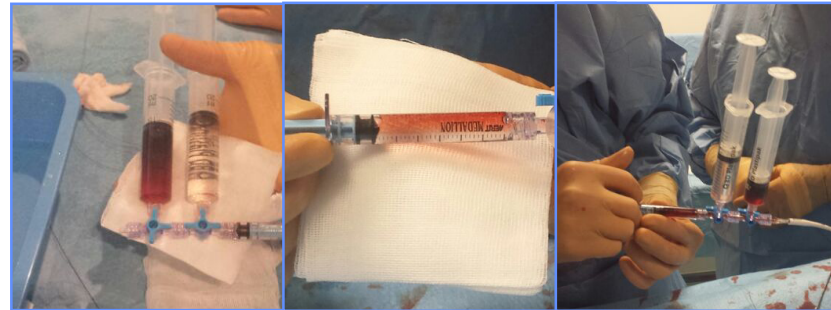
	DEB-TACE (n = 1000)	cTACE (n = 1000)	Effect size
Base-case scenario			
Costs (€)	10,460 ± 1252	9435 ± 1518	0.737
Life-expectancy (years)	3.1 ± 0.5	2.8 ± 0.5	0.605
Quality-adjusted life-expectancy (QALY)	2.4 ± 0.4	2.0 ± 0.4	0.911
Cost-effectiveness (€/QALY)	4705 ± 858	4821 ± 1149	0.114
Proportion optimal strategy (%) ^a	68.4	31.6	0.791
Cost-per-year (€/year)	3371 ± 547	3469 ± 783	0.145
RCTs scenario			
Costs (€)	11,656 ± 1321	10,389 ± 1554	0.879
Life-expectancy (years)	5.2 ± 0.8	4.6 ± 0.6	0.849
Quality-adjusted life-expectancy (QALY)	4.0 ± 0.6	3.3 ± 0.5	1.288
Cost-effectiveness (€/QALY)	3089 ± 523	3246 ± 649	0.266
Proportion optimal strategy (%) ^a	78.2	21.8	1.366
Cost-per-year (€/year)	2211 ± 325	2330 ± 428	0.313

Results are reported as mean and standard deviation; QALY = quality-adjusted life-years.
Effect size values are reported in absolute values: <0.3 indicate small differences; between 0.3 and 0.5 indicate moderate differences, and >0.5 indicate large differences.
^a The percentage of cases in which one treatment resulted in longer quality-adjusted life-expectancy than the other.

Metanalysis on 5 RCTs and 11 observational studies, including 1860 patients

“DEB-TACE was found more cost-effective than cTACE when a minimum willingness-to-pay of about € 2000–3500/QALY was accepted, mainly depending on shorter in-hospital stay and better quality of life”

Cucchetti A et al. Dig Liver Dis 2016



1-month target tumor response after DEB-TACE in BCLC A naïve pts



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
pts (n)	13	23	16	17	15	19	39	42	39	46
CR (%)	38.5	82.6	81.2	76.5	33.3	63.1	51.3	69.1	69.2	69.6
PR (%)	30.8	13	12.5	11.8	33.3	31.6	28.2	26.1	25.6	17.4

Personal series

RCTs : too eager to start?

Cardiovasc Intervent Radiol (2010) 33:41–52
DOI 10.1007/s00270-009-9711-7

CLINICAL INVESTIGATION

Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: Results of the PRECISION V Study

Johannes Lammer · Katarina Malagari · Thomas Vogl · Frank Pilleul · Alban Denys · Anthony Watkinson · Michael Pitton · Geraldine Sergent · Thomas Pfammatter · Sylvain Terraz · Yves Benhamou · Yves Avajon · Thomas Gruenberger · Maria Pomoni · Herbert Langenberger · Marcus Schuchmann · Jerome Dumortier · Christian Mueller · Patrick Chevallier · Riccardo Lencioni · On Behalf of the PRECISION V Investigators

**Enrollment period:
November 2005 - June 2007**

BJC

FULL PAPER

British Journal of Cancer (2014) 111, 255–264 | doi: 10.1038/bjc.2014.199

Keywords: liver cancer; intra-arterial hepatic therapy; mRECIST; survival

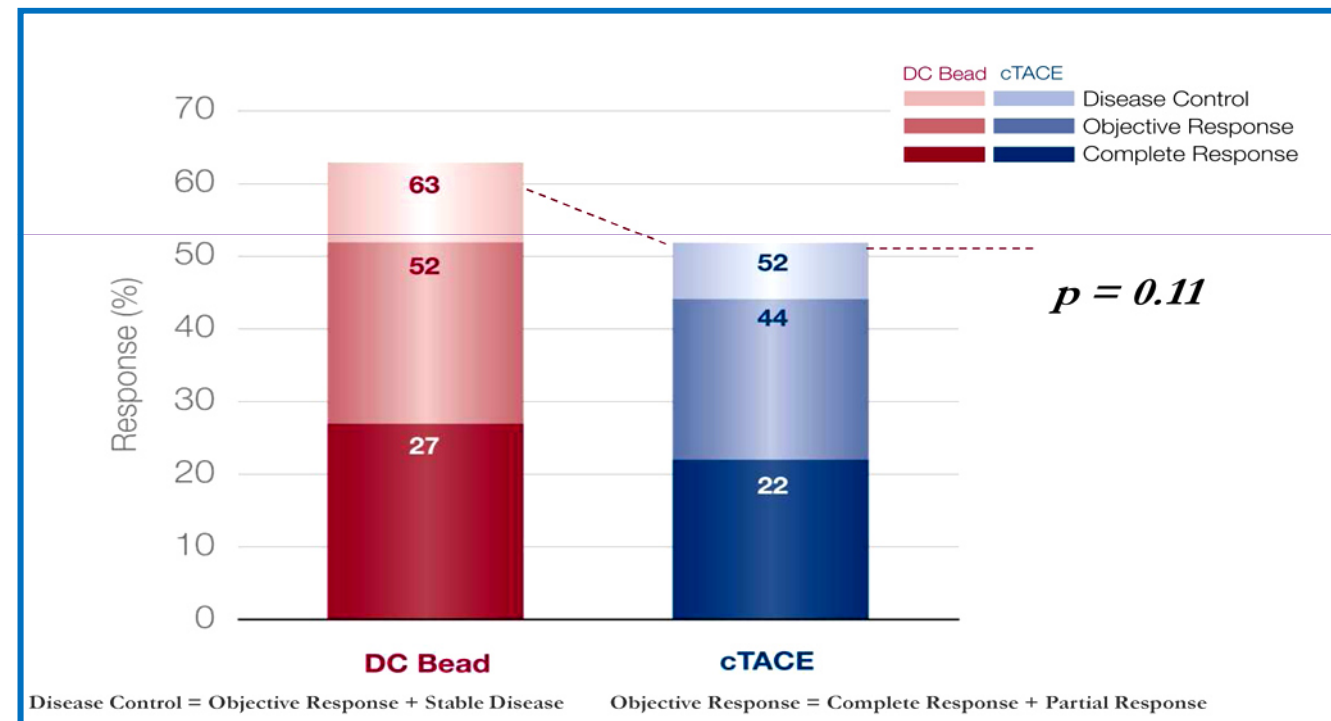
Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma

R Golfieri¹, E Giampalma¹, M Renzulli^{1*}, R Cioni², I Bargellini², C Bartolozzi², A D Breatta³, G Gandini³, R Nani⁴, D Gasparini⁵, A Cucchetti⁶, L Bolondi⁶ and F Trevisani⁶ on behalf of the PRECISION ITALIA STUDY GROUP⁷

**Enrollment period:
March 2008 - December 2010**

TACE in 2016: are we missing something?

**Poor tumor
response**

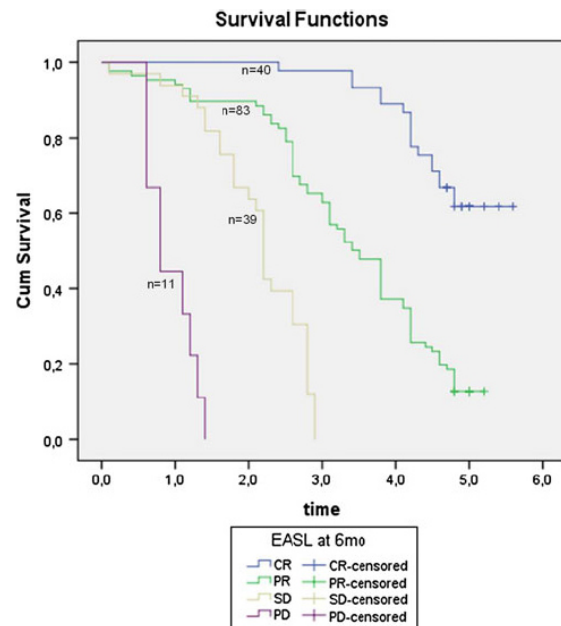


Lammer J et al. Cardiovasc Intervent Radiol 2010

TACE in 2016: are we missing something?

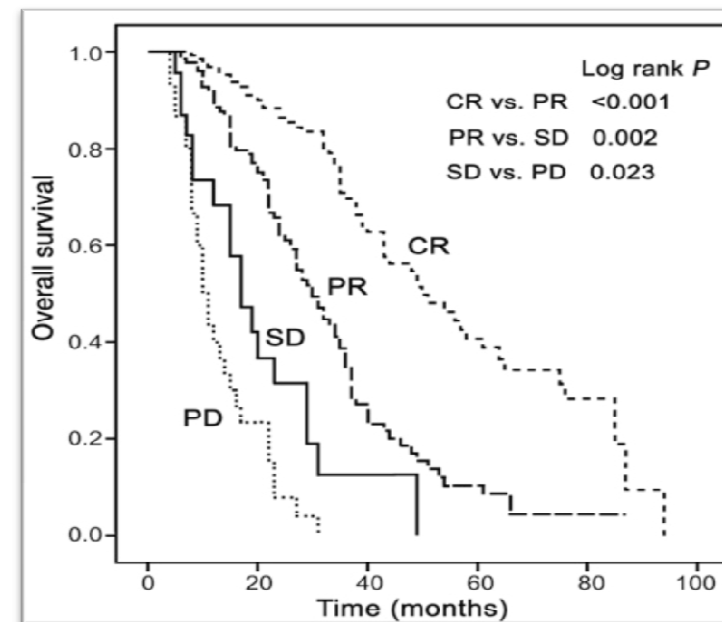
Tumor response affects survival

EASL



Malagari K et al.
Cardiovasc Intervent Radiol 2012

mRECIST



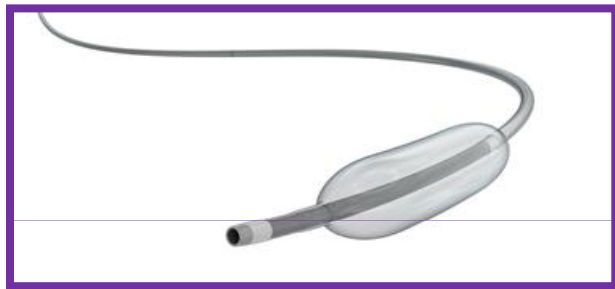
Shim JH et al.
Radiology 2012

TACE: the next generation...

- **Balloon-occluded TACE (BO-TACE)**
- **Smaller size particles**
- **Degradable starch microspheres (DSM)**
- **Radiopaque particles**
- **Loading with new agents**

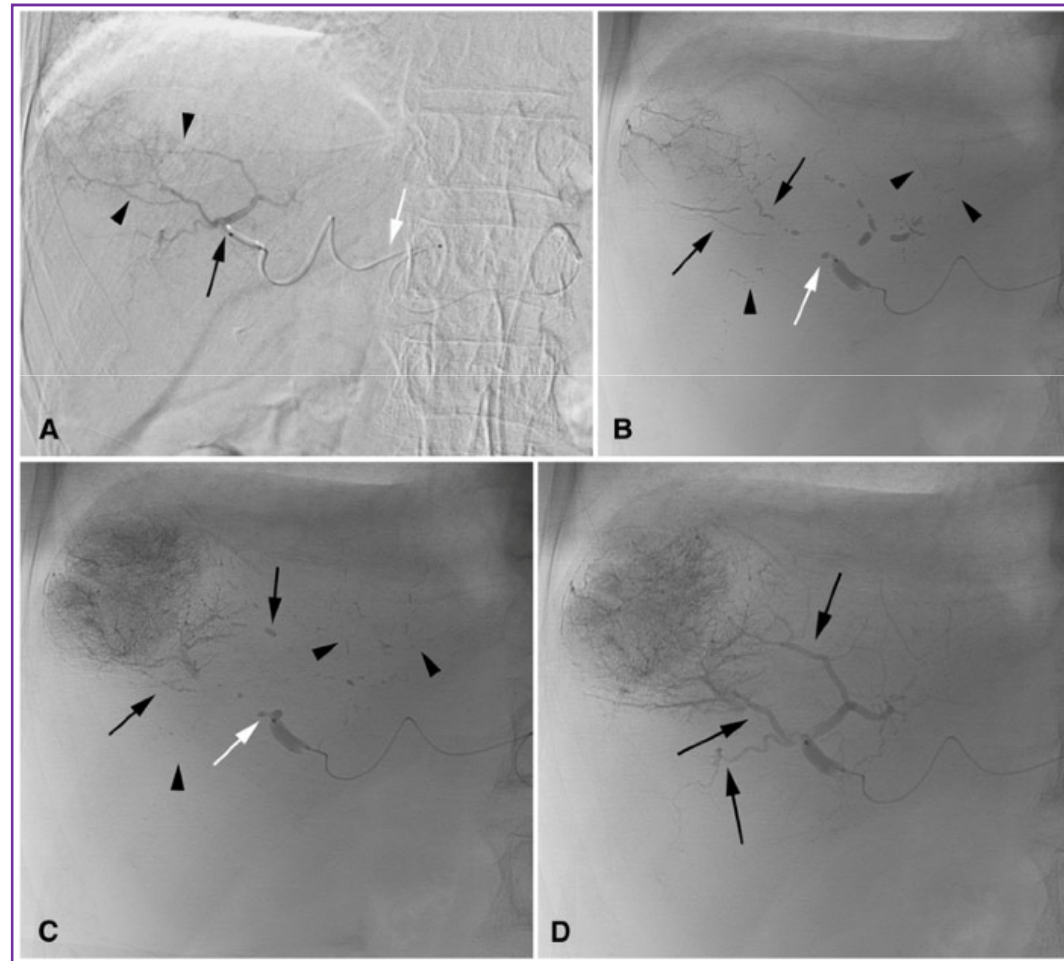
Balloon-occluded TACE

Micro-balloon



The reduced intravascular pressure may increase drug flow into cancer nodules by reducing portal vein uptake

Irie T et al. CVIR 2013



Original Article

Safety and efficacy of balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma

Table 1 Patient and tumor characteristics

		B-TACE (n = 49)	C-TACE (n = 48)	
Age	Median (range)	71.9 (62–84)	69.9 (54–91)	n.s.
Sex	(M/F)	33/16	34/14	n.s.
Etiology	(HBV/HCV/NBNC)	1/41/7	4/36/8	n.s.
Child–Pugh grade	(A/B/C)	36/13/0	37/11/0	n.s.
Stage	(I/II/III)	16/33/0	22/26/0	n.s.
Tumor size (mm)	Median (range)	29 (8–73)	24.5 (14–90)	n.s.
Portal vein invasion		0	0	n.s.
Miriplatin dose (mg)	Median (range)	40 (10–120)	20 (5–120)	P < 0.01

Increased drug dose

Table 2 Treatment effect of TACE using miriplatin

	B-TACE (n = 49), n	C-TACE (n = 48), n
TE4	27 (55.1%)	19 (39.6%)
TE3	19 (38.8%)	16 (33.3%)
TE2	2 (4.1%)	12 (25.0%)
TE1	1 (2.0%)	1 (2.1%)





Better tumor response

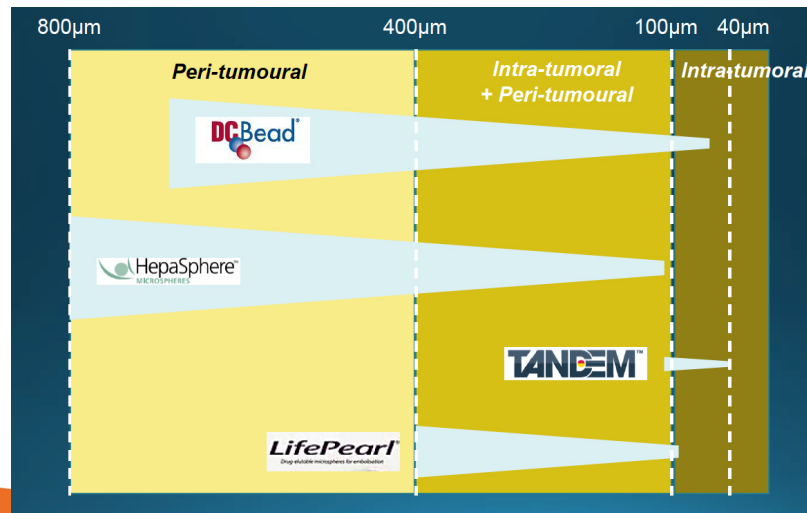
P<0.05

Arai H et al. Hepatol Res 2015

Drug-eluting beads platforms

smaller sizes, higher doses

				
Size (µm)	45-700	120-800	100-400	40-100
Loading (mg/mL)	37.5	37.5	50	50



*Modified from Namur J.
Presented at ECIO 2016*

Drug-eluting beads platforms *smaller sizes*

Hepasphere 120-240 μ m

45 pts

mRECIST	Overall response <i>n</i> (%)	Target lesion response <i>n</i> (%)	Nontarget lesion response <i>n</i> = 40
CR	8 (17.8)	10 (22.2)	5 (12.5)
PR	23 (51.1)	21 (46.6)	
SD	9 (20)	10 (22.2)	
PD	5 (11.1)	4 (8.8)	4 (10)
Non-PD			32 (80)

OR: 68.9 %

Safe and well tolerated

Malagari K et al. CVIR 2014

DCBeads M1 75-150 μ m

45 pts

Diameter of nodules	No. of modules	CR	PR	SD	PD
<3 cm	72	31	25	12	4
3–5 cm	21	10	7	4	0
>5 cm	10	2	5	3	0
		43	37	19	4
Overall response	103	42 %	36 %	18 %	4 %

OR: 77.7 %

Safe and well tolerated

Spreafico C et al. CVIR 2015

Degradable starch microspheres

The starch microspheres consist of a three-dimensional, cross linked hydrophilic starch matrix, which swells heavily in a water suspension environment and are completely degradable by amylase.

Potential advantages:

- No embolization-related side effects
- Preserved arterial access to the tumor (repeated treatments)
- No stimulation of neoangiogenesis (reduced recurrence rate)
- Combination with different agents (chemotherapeutics, cytokines, gene therapy products)



DSM-TACE MULTICENTER STUDY IN HCC TREATMENT, PLACED IN THE TRIVENETO AREA (North-East Italy)

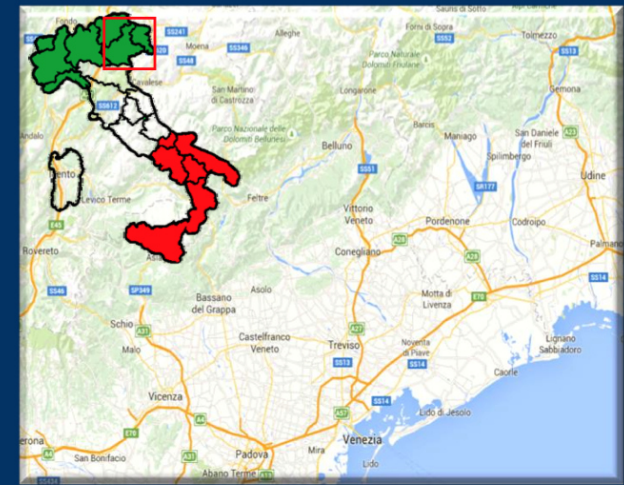
*Silvia Dal Bello
Castelfranco Veneto*

Cesari Stefano(1), Biscosi Mauro(2), Romanzi Francesco(3), Berletti Riccardo(4), Avventi Paolo(1), Dal Bello Silvia(1), Sponza Massimo(5), Vit Alessandro (5), Iurilli Vincenzo(6), Miotto Diego(6)

Presented at
ECIO 2016

This trial started June, 1, 2013 in 5 Interventional Radiology Centers, situated in the Triveneto Area (North-East , Italy).

- Castelfranco Veneto
- Tolmezzo
- Vittorio Veneto
- Trento
- Udine
- Padova



Degradable starch microspheres

BCLB B patients, with HCC in at least 4 liver segments

PATIENTS	63
dsm-TACE	177
TACE per patient (average)	2,8
TACE per patient (min/max)	1-8

Dal Bello S et al. Presented at ECIO 2016

Degradable starch microspheres

Safety

No. of procedures	177	100,0
SIDE EFFECTS	N	%
post-ischemic syndrome	2	1,13
gangrenous cholecystitis	1	0,56
pancytopenia	1	0,56
Pain (6-8 h)	109	61,58
Asymptomatic	18	10,17
Nausea and vomiting	10	5,65
Liver enzyme alteration (24h)	4	2,26

mRECIST

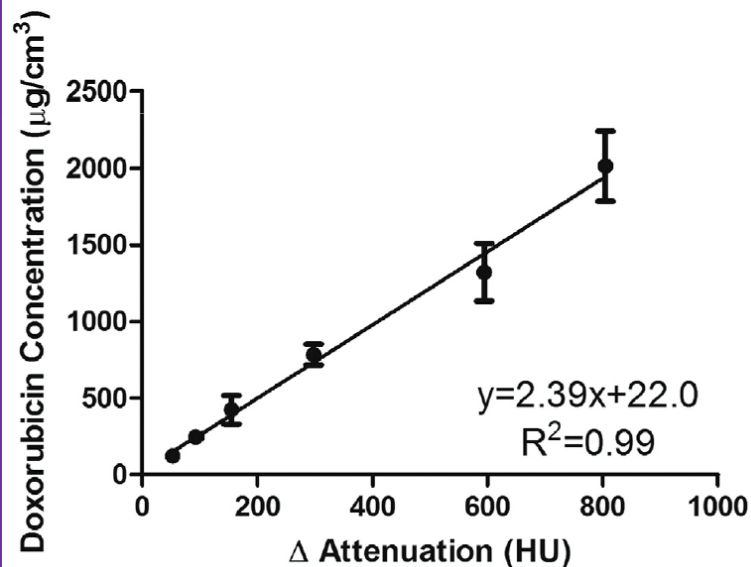
PAZIENTS	n.(63) With follow up (56)	%
Complete response	21	37,50
Partial response	23	41,07
OBJECTIVE RESPONSE Complete + partial response	44	78,57
Non-responders (stable disease or progression)	12	21,43
Waiting for the follow-up	7	

Dal Bello S et al. Presented at ECIO 2016



LABORATORY INVESTIGATION

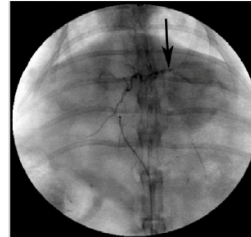
Preparation of Radiopaque Drug-Eluting Beads for Transcatheter Chemoembolization



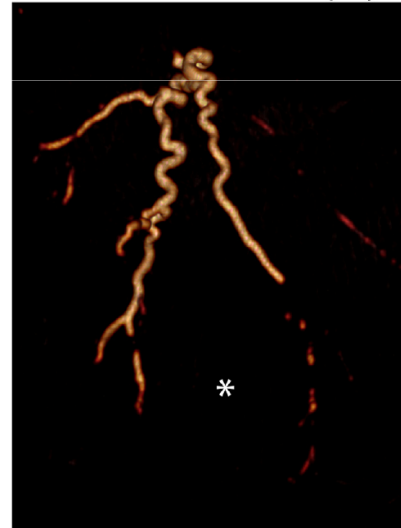
Pre embolization



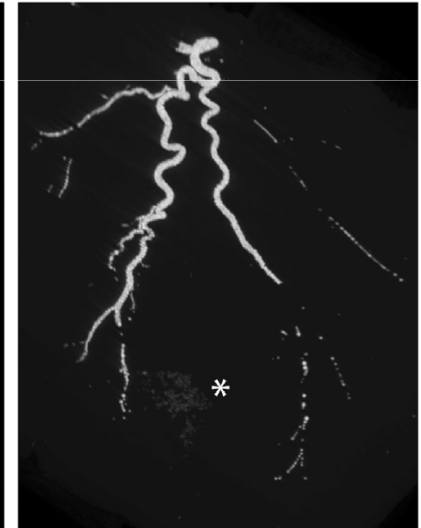
Post embolization



CT - surface shaded display



microCT - MIP



Johnson CG et al. J Vasc Interv Radiol 2016

Newer platforms for newer drugs

AP&T Alimentary Pharmacology and Therapeutics

Idarubicin-loaded beads for chemoembolisation of hepatocellular carcinoma: results of the IDASPHERE phase I trial

M. Boulin^{*,†}, P. Hillon^{*,‡}, J. P. Cercueil^{*,§}, F. Bonnetain[†], S. Dabakuyo^{*,*}, A. Minello^{*,‡}, J. L. Jouve^{*,‡}, C. Lepage^{*,‡}, M. Bardou^{†,††}, M. Wendremaire^{†,†}, P. Guerard^{†,†}, A. Denys^{§§}, A. Grandvillain^{¶¶}, B. Chauffert^{***}, L. Bedenne^{*,†‡} & B. Guio^{*,†‡}



Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Sunitinib-eluting beads for chemoembolization: Methods for in vitro evaluation of drug release

Katrin Fuchs^{a,*}, Pierre E. Bize^b, Alban Denys^b, Gerrit Borchard^a, Olivier Jordan^a

J Biomater Sci Polym Ed. 2015;26(2):77-91. doi: 10.1080/09205063.2014.982242. Epub 2014 Nov 26.

Preparation and structure of drug-carrying biodegradable microspheres designed for transarterial chemoembolization therapy.

Wang Y¹, Benzina A, Molin DG, Akker Nv, Gagliardi M, Koole LH.

Hepat Oncol. 2016 January 1; 3(1): 19–28. doi:10.2217/hep.15.36.

Targeting glucose metabolism in cancer: new class of agents for loco-regional and systemic therapy of liver cancer and beyond?

Lynn Jeanette Savic^{1,2}, Julius Chapiro^{1,2}, Gregor Duwe², and Jean-François Geschwind^{*,1}

ACS Appl Mater Interfaces. 2016 May 9. [Epub ahead of print]

Acidic pH-Triggered Drug Eluting Nanocomposites for MRI Monitored Intra-Arterial Drug Delivery to Hepatocellular Carcinoma.

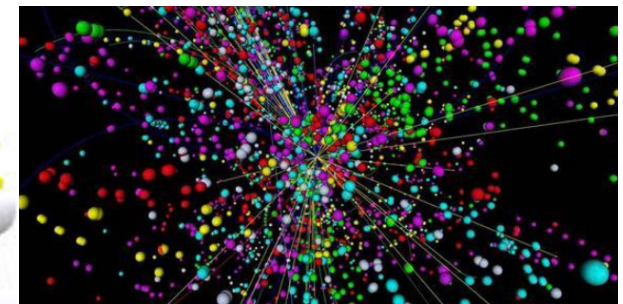
Park W, Chen J, Cho S, Park SJ, Larson AC, Na K, Kim DH.

Lipiodol-TACE or DEB-TACE: which and when

**No difference
in radiological
response**



*Yesterday, I didn't know,
Today, I know I don't know,
Tomorrow, who knows?!*



The dark side of the guidelines



2nd Interventional Radiologist under 40 Meeting
Interventional Oncology