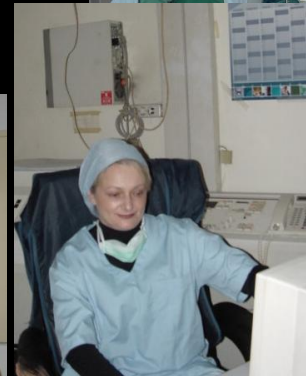


FIVE YEAR SURVIVAL OF HCC PATIENTS TREATED WITH DOXORUBICIN ELUTING DC BEAD™



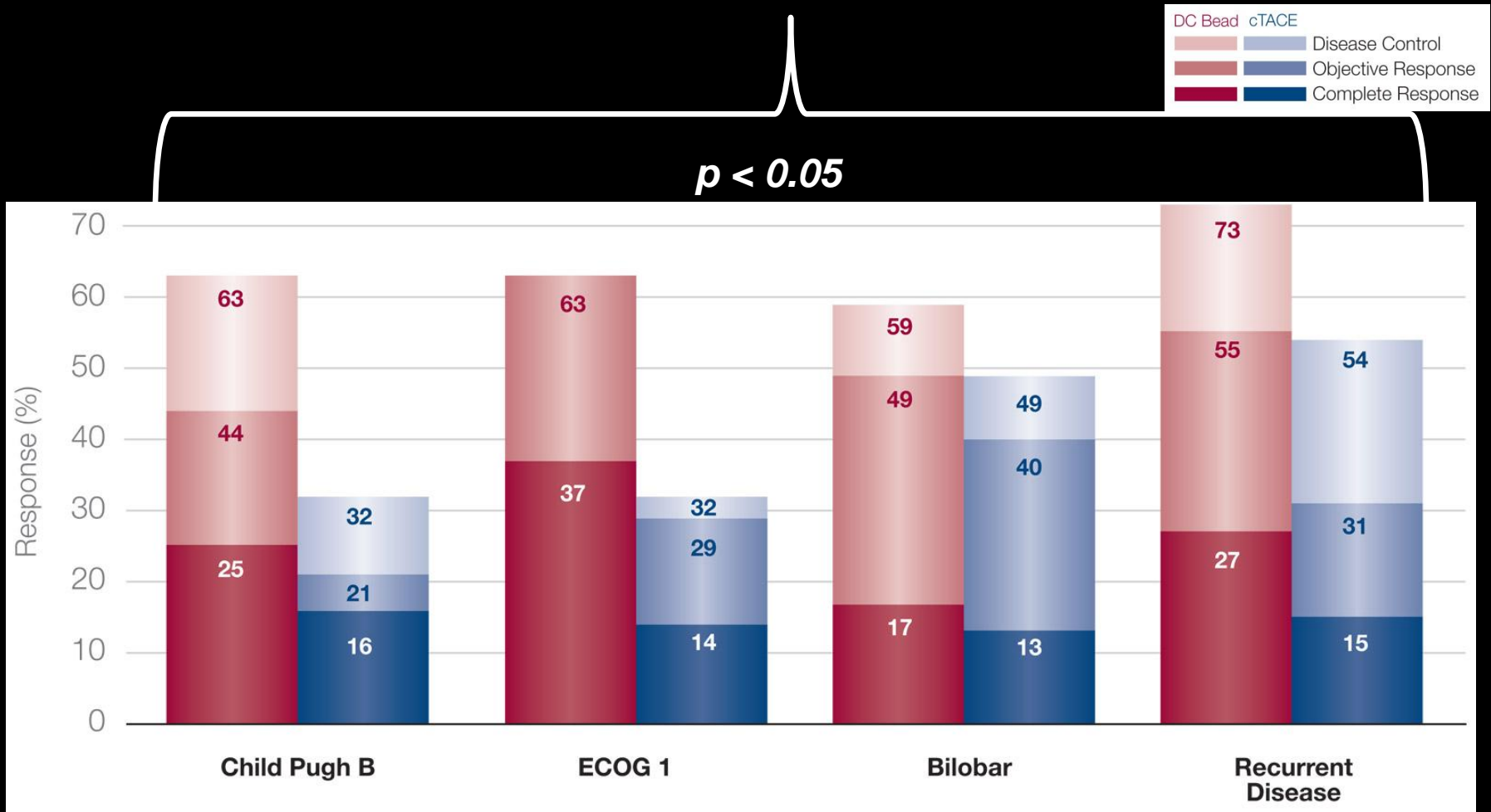
Giannis Kornezos
Bana Bouma
Efi Alexopoulou
Manolis Emmanouil
Aggelos Harokopakis
Pandora Papandoniou
Savas Tandeles
Georgia Economou
Matina Kampanarou
Dimitra Letsou
Hrisovalandis Vergadis
Giannis Probonas

FIVE -YEAR SURVIVAL OF HCC PATIENTS TREATED WITH DOXORUBICIN ELUTING DC BEAD

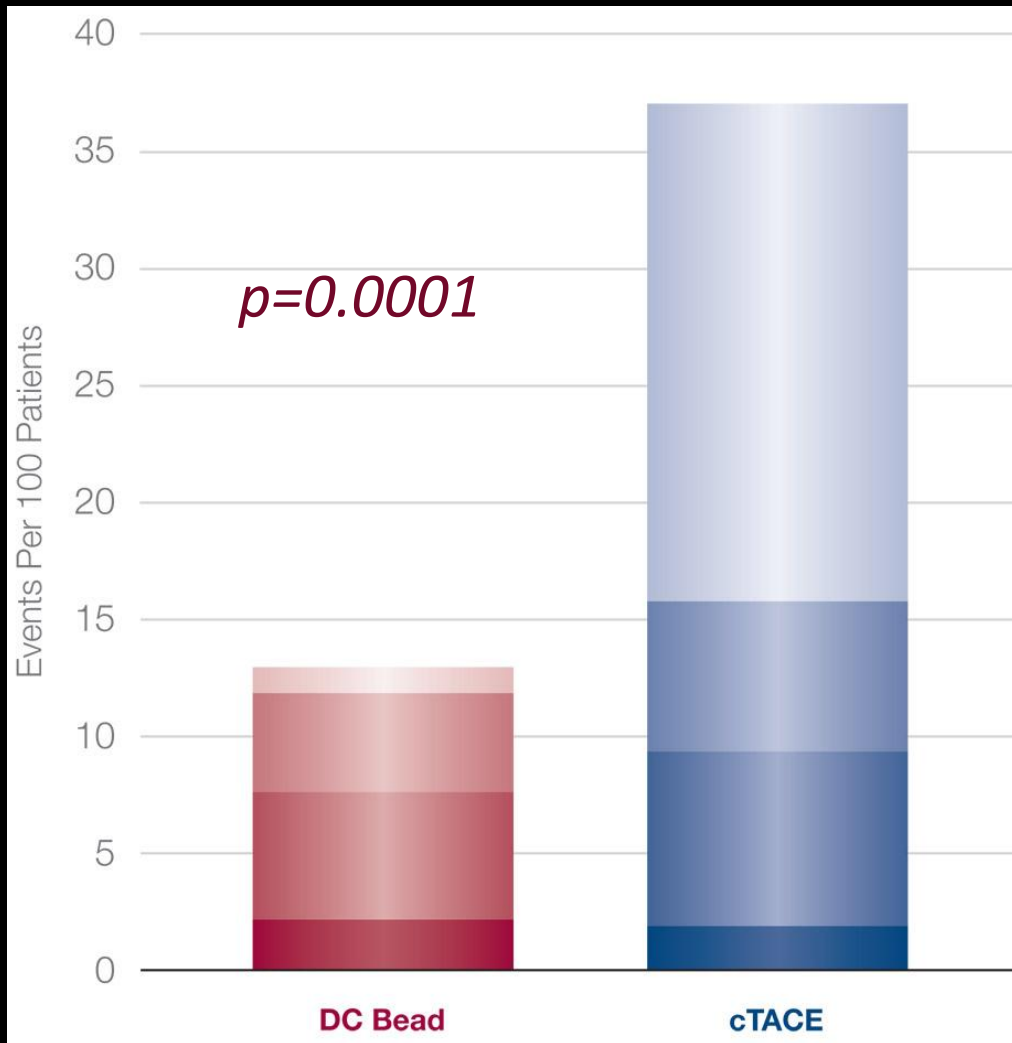
K. Malagari, M. Pomoni, H. Moschouris, A. Kelekis, A. Stefaniotou, E. Alexopoulou, A. Chatziioannou, I. Hadjimarkou, A. Pomoni, K. Chatzimichail, J. Koskinas, L.Thanos, S. Dourakis, N. Kelekis, D.A. Kelekis.

6-Month Response in More Advanced Patients

DC Bead™ demonstrated statistically significant advantage in advanced patients Objective Response (p=0.038) and Disease Control (p=0.026)



Doxorubicin-Related Side Effects



There is a highly significant ($p < 0.01$) reduction in drug related toxicity with DC Bead

CLINICAL FEATURES OF PATIENTS

Multiinstitutional study

Multidisciplinary group : hepatologist, liver surgeon, interventional radiologist

Age (yrs)	70.4±7.4
Sex (M/F)	(132/41)
Cause of cirrhosis (n)	173
HBV	80 (46.2%)
HCV	5 (2.9%)
HBV+HCV	44 (25.4%)
Other	44 (25.4%)
AFP (ng/ ml)	1725±4692
Child Pugh class A/B	102/71 (59% / 41%)
Child score	6.2±1.2
5	67 (39.4)
6	33 (19.4%)
7	44 (25.9%)
8	22 (12.9%)
9	4 (2.4%)
Radiological ascitis (yes)	16 (9.2%)
ECOG 0/1	154/19 (89% / 11%)
Okuda	
0	91 (53.2%)
1	61 (35.7%)
2	19 (11.1%)
Performance Status (%)	97.7±5.5
Sum lesion diameter (cm)	7.6±2.1
Lesion morphology	
One dominant ≤ 5cm±0-2 satellites	38 (22%)
One dominant >5cm ±0-2 satellites	72 (41.6%)
Multifocal ≤5	45 (26%)
Multifocal >5	18 (10.4%)

BCLC B :(n= 135)

BCLC A : (n= 38)

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

ECOG: Eastern Cooperative Oncology Group performance status

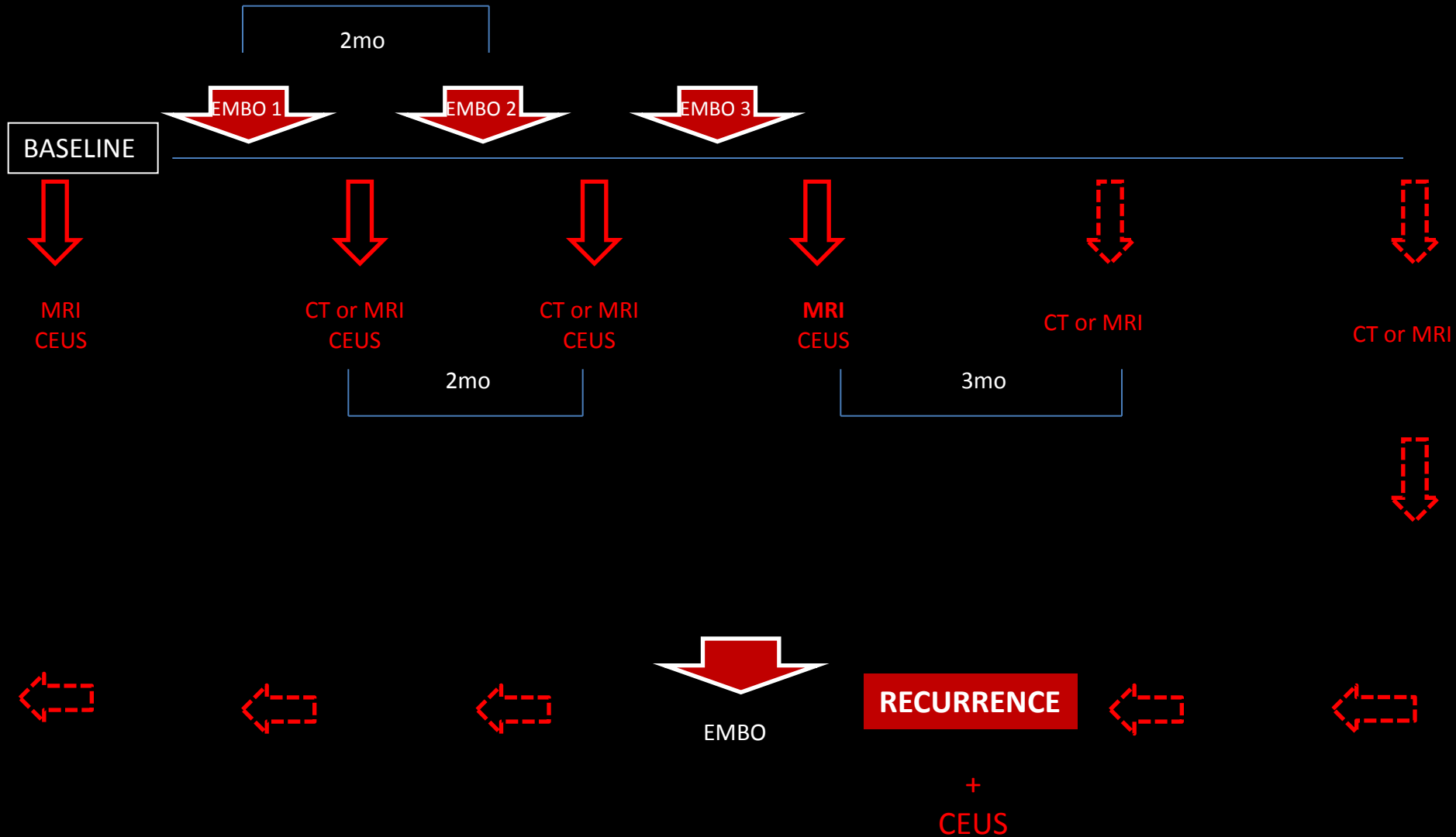
ELIGIBILITY

- BCLC B
- BCLC A not amenable to curative treatments (RFA, surgery)
- function :bilirubin < 3mg/dl, AST, ALT < 270 IU/l
- chemo-naive
- previous treatment with local ablation or surgery was not criteria for exclusion
- arteriovenous shunts, thrombus within main portal vein
- extrahepatic disease



exclusion

TREATMENT PROTOCOL



FOLLOW UP AND ADDITIONAL TREATMENTS

- **additional embolizations** (embolization on demand): consistently DEB-DOX / interval between sessions were recorded
- additional **RFA** or MW when suitable/number recorded
- **antiangiogenesis** treatment at some point during the course of f-u: sorafenib 400mg x2
- Sorafenib indications in this population:
 - development of multiple new lesions or diffuse disease
 - need to re-embolize more frequently than 4 months (after the initial 3 scheduled sessions)
 - inability to perform DEB-DOX due to progression to BCLC C or D disease or liver functional impairment

assessed as variables in the statistical analysis

Follow up period ranged between 2-68 months i.e. until time of death or time of the analysis

Embolization procedure

- Embolization : as selectively as possible (microcatheters 2.7 or 2.4 F (Progreat, Terumo)).
 - for lesions >6cm : of 100-300 μ m and/or 300-500 μ m
 - for lesions \leq 6cm : 100-300 μ m ONLY
- Bead loading : at 37.5mg of doxorubicin per ml of reconstituted beads (max 150mg per patient): much less in multi- repeat -embo
- Contrast mixture: per vial of reconstituted beads + diluted in 15 ml of contrast
- Endpoint of embolization : obliteration of neovascularity (assessed at angiography) / administration of complete dose
-
- Relatively avascular tumors- or repeat post many DEB-DOX: intraarterial/ intraprocedural CEUS

RESULTS

Mean AFP levels : 1725±4692 ng/ml

137 had hypervascular lesions at angiography at baseline (79.2%)

mean number of embolizations was 5.6 (1-9)

44 received local ablation of a local recurrence (if accessible) or a new lesion (mean number of ablations in the 44 patients: 1.4; range 1-3)

sorafenib was given in 51 patients as an adjunct to DEB-DOX or eventually as a sole treatment.

LOCAL RESPONSE (EASL) PER SCHEDULED SESSION

	Local response	Number of embolization session (scheduled)		
		1 st (%)	2 nd (%)	3 rd (%)
Child A (n= 102)	CR	8 (7.8)	15 (14.7)	24 (23.5)
	PR	31 (30.4)	42 (41.2)	50 (49)
	SD	61 (59.8)	41 (40.2)	23 (22.5)
	PD	2 (2)	4 (3.9)	5 (4.9)
Child B (n=71)	CR	5 (7)	12 (16.9)	16 (22.5)
	PR	17 (23.9)	26 (36.6)	33 (46.5)
	SD	46 (64.8)	28 (39.4)	16 (22.5)
	PD	3 (4.2)	5 (7)	6 (8.4)

CR (100% necrosis), Partial response:PR (decrease \geq 50%), Progressive disease: PD (increase \geq 25% increase or new lesions), Stable disease:SD (decrease <50% or increase <25%) (15)

1.5T PM2H-Z8P403M90X
Ex: 225305546
LIVER THRIVE_SPAIR
Se: 501/38
Im: 50/80
Ax: 820.4 (000)
192 x 192

2nd DPT RAD UO
PHIOS OBO RGMS
1954 Aug 01 M 3147607
Acc: 55471
2007 Feb 23
Acq Tm: 12:01:12.33



ET: 60
TR: 3.5
TE: 1.7

baseline

LIVER THRIVE 1.5H

1954 Aug

Se: 2301/38

Im: 57/80

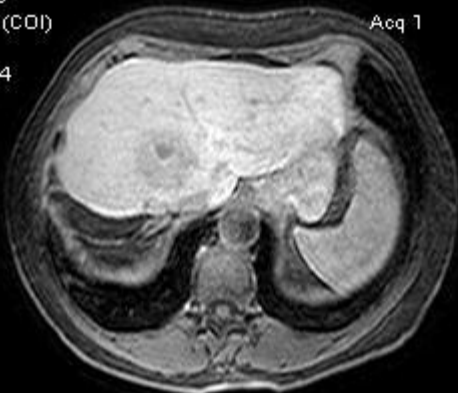
Ax: 53.3 (COI)

Acq 1

240 x 214

R.

ET: 60



3MoPOST

1.5T PM2H-Z8P403M90X
Ex: 23000952
LIVER THRIVE_SM
Se: 1201/38
Im: 95/80
Ax: 884.6 (000)
256 x 225

2nd DPT RAD UO
PHIOS OBO RGMS
1954 Dec 11 M 3147607
Acc: 55471
2007 Apr 17
Acq Tm: 10:00:56.79



ET: 60
TR: 3.5
TE: 1.7

1.5T PM2H-Z8P403M90X

Ex: 235478482

LIVER THRIVE_SM

Se: 1401/38

Im: 53/80

Ax: 853.2 (000)

224 x 224

ZZ+ x ZZ+

ET: 60

TR: 3.5

TE: 1.8

SENSE-body

+DfW-2.0sp

Un:DCM / Un:DCM / M:10

WV:1525 L277

ET: 60

TR: 3.5

TE: 1.8

SENSE-body

+DfW-2.0sp

Un:DCM / Un:DCM / M:10

WV:1525 L277

ET: 60

TR: 3.5

TE: 1.8

SENSE-body

+DfW-2.0sp

Un:DCM / Un:DCM / M:10

WV:1525 L277

6MoPOST

ET: 60

TR: 3.5

TE: 1.8

SENSE-body

+DfW-2.0sp

Un:DCM / Un:DCM / M:10

WV:1525 L277

P.

DFOV: 45.5 x 45.5cm

CR

1.5T PMSM-Z8P 403MSQX
Ex: Z20011762
PRECISION THRIVE_SPAIR
Se: 801/10
Im: 55/100
Ax: 850.1 (000)

A

2nd DPT RAD UO A
KARPENISOTIS KONINOS
1944 Mar 05 M ATT846
Acc:
2006 Dec 22
Acq Tm: 10:43:03.07

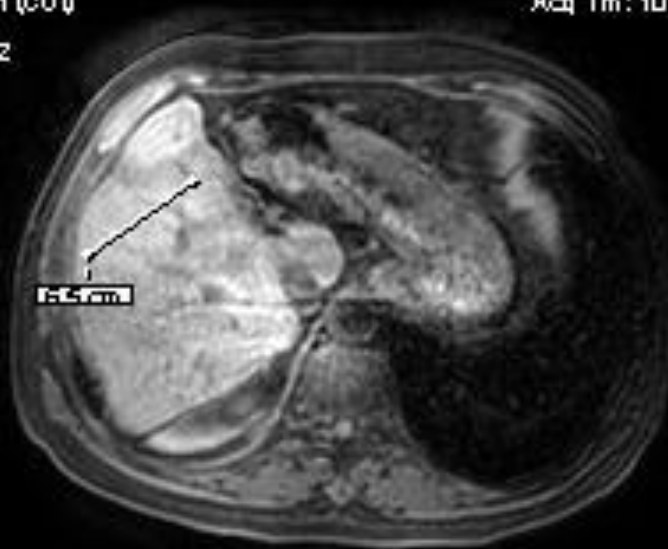
1.5T PMSM-Z8P 403MSQX
Ex: Z24765791
LIVER THRIVE_SPSM
Se: 1401/10
Im: 70/100
Ax: 16.6

A

2nd DPT RAD UO A
KARPENISOTIS KONINOS
1944 Mar 05 M 3129468
Acc:
2007 Feb 15
Acq Tm: 11:25:54.37

192 x 192

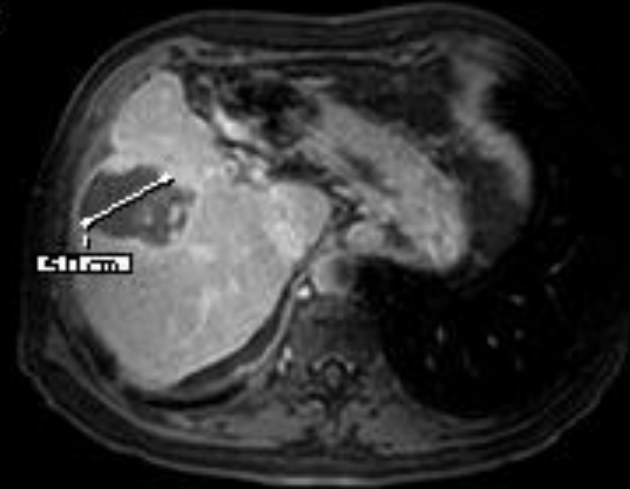
R



ET: 60
TR: 3.5
TE: 1.7
SENSEbody
4.0FW-2.0sp

192 x 192

L



ET: 60
TR: 3.5
TE: 1.7
SENSEbody
4.0FW-2.0sp

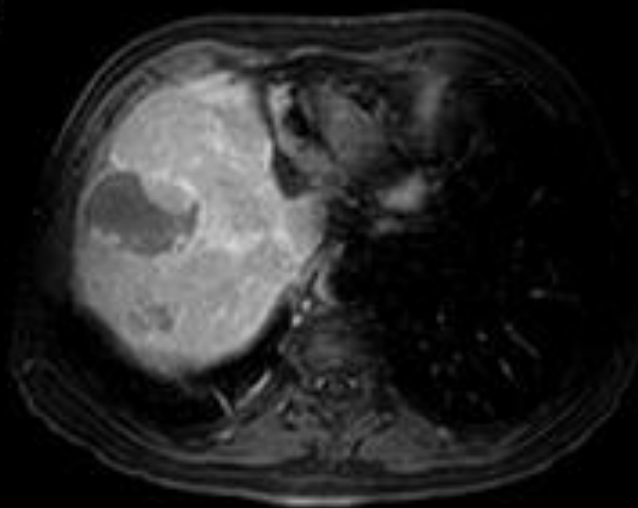
PRE embolization
embolization

POST 3rd

1.5T PMSN-ZBP403M9QX
Ex: 224765791
LIVER_THRIVE_SPSM
Se: 1401/10
Im: 78/100
Ax: 89.4

192 x 192

R



ET: 60
TR: 3.5
TE: 1.7
SENSE-body
+Dhw-2.0sp
Un:DCM / Un:DCM / M:10
W:2001 L:1077

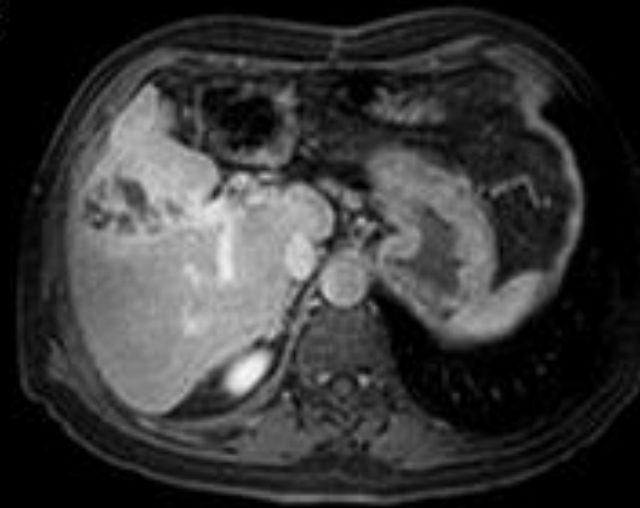
P

2nd DPT RAD UOA
KARPENISOTIS KONINOS
1944 Mar 05 M 3129468
Acc: 2007 Feb 15
Acq Tm: 11:25:54.37

1.5T PMSN-ZBP403M9QX
Ex: 224765791
LIVER_THRIVE_SPSM
Se: 1401/10
Im: 63/100
Ax: 89.4

192 x 192

L



ET: 60
TR: 3.5
TE: 1.7
SENSE-body
+Dhw-2.0sp
Un:DCM / Un:DCM / M:10
W:2001 L:1077

P

2nd DPT RAD UOA
KARPENISOTIS KONINOS
1944 Mar 05 M 3129468
Acc: 2007 Feb 15
Acq Tm: 11:25:54.37

DFOV: 48.5 x 48.5cm

POST 2nd EMBO

POST 3rd EMBO

1.5T PMSB-28P403N90X
Ex: 224508515
LIVER_THRIVE_SM
Se: 140125
In: 47310
Ac: 826.0

A

2nd DPT RAD UOA
KOUTSIBOS KONSTADIMOS
1943 May 12 M 3137366
Acc: 6257.1
2007 Sep 04
Acq Tm: 11:45:51.32

192 x 152



ET: 60
TR: 3.6
TE: 1.7
SENSEbody
+DfW-2.0sp
Un:DCM / Un:DCM / M:10
W:1989 L:1100

P

DFOV: 45.5 x 45.5cm

1.5T PMSB-28P403N90X
Ex: 242127381
PRECESSION_THRIVE_DYN
Se: 1001/15
In: 144240
Ac: 822.7 (0.0)

A

2nd DPT RAD UOA
KOUTSIBOS KONSTADIMOS
1943 May 12 M 3137366
Acc: 6257.1
2007 Sep 04
Acq Tm: 09:54:13.76

256 x 229



ET: 50
TR: 3.6
TE: 1.2
SENSEbody
+DfW-2.0sp
Un:DCM / Un:DCM / M:10
W:1527 L:878

P

DFOV: 49.5 x 49.5cm

1.5T PMSB-28P403N90X
Ex: 242127381
PRECESSION_THRIVE_SM
Se: 1301/15
In: 51630
Ac: 828.7 (0.0)

A

2nd DPT RAD UOA
KOUTSIBOS KONSTADIMOS
1943 May 12 M 3137366
Acc: 6257.1
2007 Sep 04
Acq Tm: 09:58:58.26

256 x 229



ET: 50
TR: 3.6
TE: 1.8
SENSEbody
+DfW-2.0sp
Un:DCM / Un:DCM / M:10
W:1767 L:1016

P

DFOV: 49.5 x 49.5cm

COMPLICATIONS

- Thirty day mortality :1.2%
- Complications:
 - abscess (2.9%)
 - irreversible liver failure (1.7%)
 - transient liver decompensation (4.6%)
 - cholecystitis (5.8%)
 - pleural effusion (0.6%)
 - post embolization syndrome (73.9%)
- Grade 5 :2.3%
- Grade 4: 1.2%
- Grade 3 : abscess formation (2.9%), and pleural effusion (4%)

SURVIVAL

Table 3. Rates of survival overall and in patient subgroups

Child A (n)		1yr (%)	2yrs (%)	3yrs (%)	4yrs (%)	5yrs (%)
21	One dominant ≤ 5 cm	100	95.2	71.4	66.6	47.6
37	One Dominant > 5 cm	97.3	89.1	85.1	43.3	32.4
31	Multinodular ≤ 5	93.5	90.3	61.3	41.9	25.8
13	Multinodular > 5	84.6	69.2	46.1	15.3	0
102	overall	95	88.2	61.7	45	29.4
Child B						
17	One dominant ≤ 5 cm	94.1	88.2	58.8	41.2	23.5
35	One Dominant > 5 cm	91.4	71.4	54.2	37.1	11.4
14	Multinodular ≤ 5	85.7	75	25	14.3	0
5	Multinodular > 5	100	60	20	0	0
71	overall	91.5	75	50.7	35.2	12.8
TOTAL		93.6	83.8	62	41.04	22.5

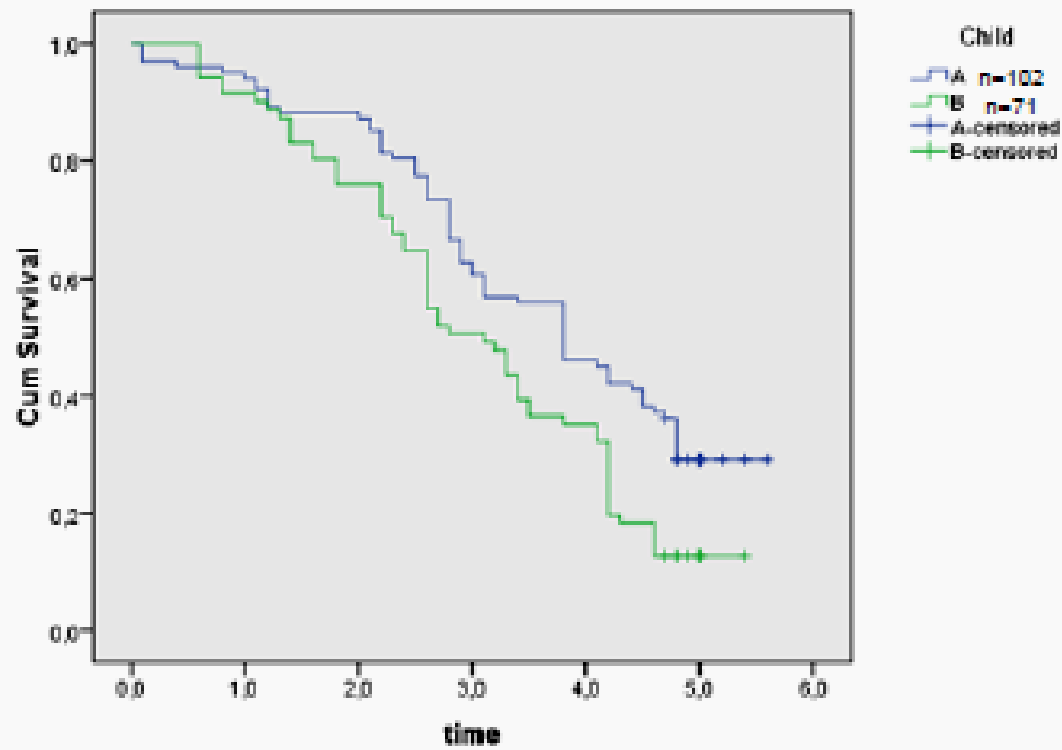
Mean overall survival : 43.8 months (1.2-64.8)

48.7 months for Child A

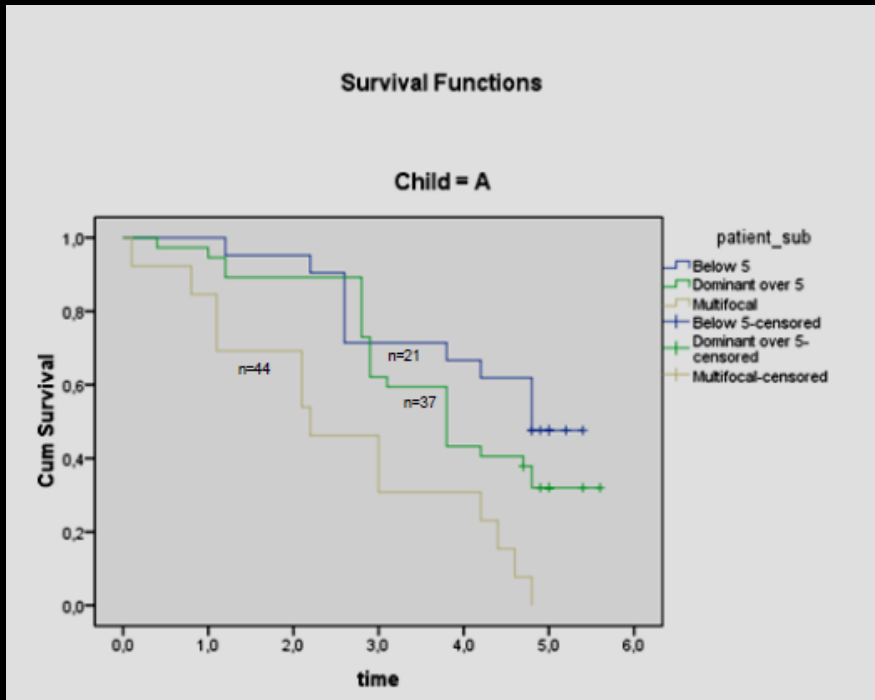
36.7 months for Child B

Twenty seven patients were alive at the time of the analysis.

Survival Functions

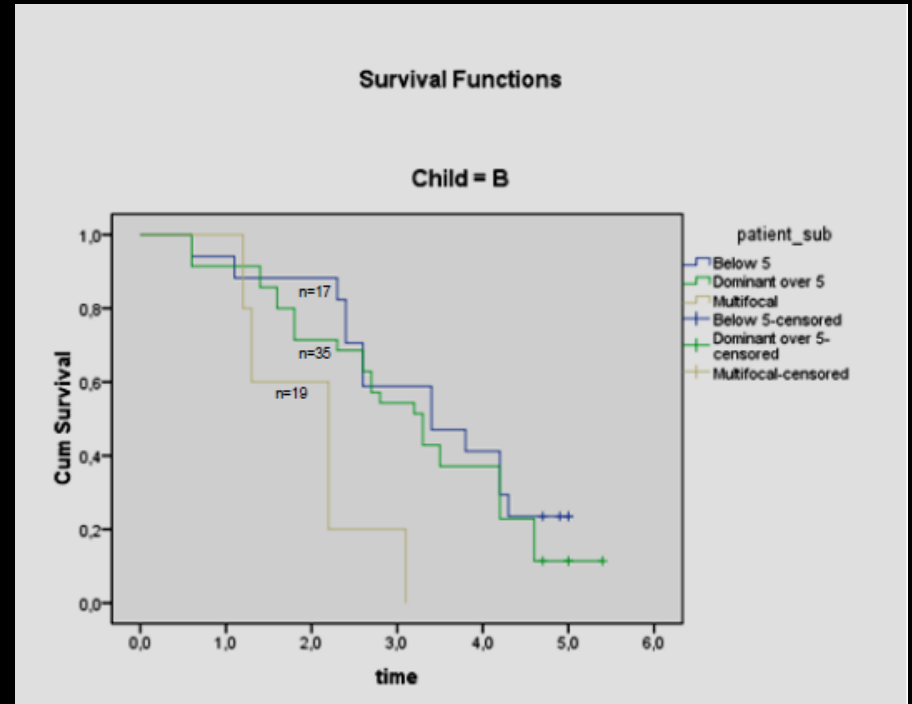


log-rank test: $p=0.029$



One dominant lesion vs multifocal :
One dominant > 5 vs ≤5 cm :

(log-rank test: $p < 0.0001$)
(log-rank test: $p = 0.041$)



One dominant lesion vs multifocal :
One dominant > 5 vs ≤5 cm :

(log-rank test: $p < 0.0001$)
(log-rank test: $p = 0.86$)

Survival Functions

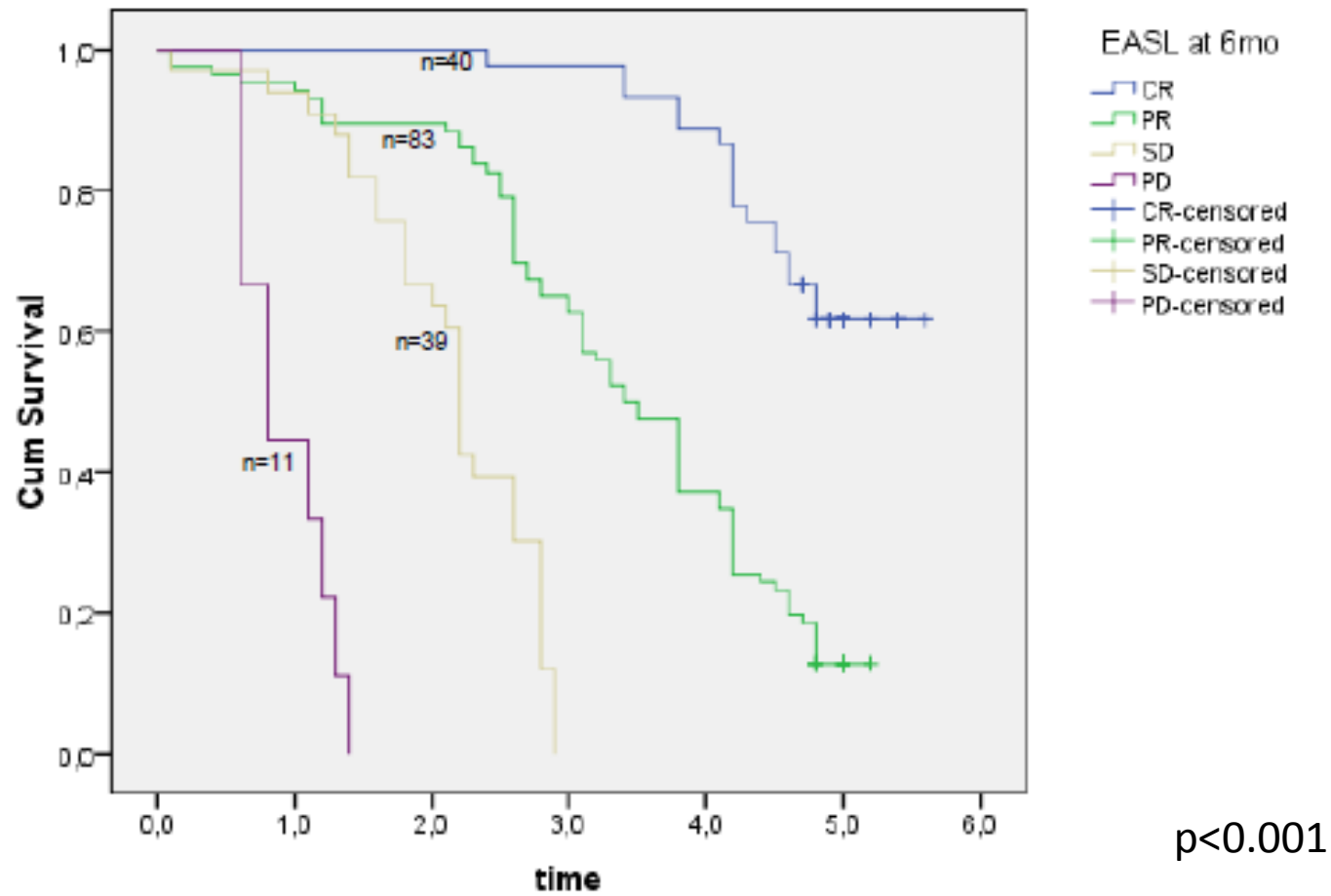


Table 4. Results of Univariate and multivariate analysis

Parameter/ risk factors	Univariate Analysis (Log – rank test)	Multivariate Analysis (Cox Proportional Hazard Model)		
	P value	Hazard Ratio	95% CI	P value
Sex (M vs F)	0.414	1.108	0.672-0.825	0,688
AFP (≤500 vs >500 ng/ml)*	0.019	1.468	0.965-2.232	0.073
Child Pugh class (B vs A)	0.003	1.024	0.365-2.868	0.965
Radiological ascitis (yes vs no)	0.000	1.494	0.446-5.002	0.515
ECOG (1 vs 0)	0.000	1.633	0.616-4.331	0.325
Okuda (2 vs 1)	0.000	2.193	0.816-5.894	0.119
Lesion morphology (Multifocal vs one dominant)	0.014	1.662	1.042-2.651	0.033
Lesion vascularity (hypervascular vs hypovascular)	0.000	0.290	0.149-0.564	0.000
Additional local ablation** (yes vs no)	0.000	0.326	0.202-0.526	0.000
Additional Sorafenib*** (yes vs no)	0.004	0.316	0.188-0.531	0.000
Number of embolizations (1-6 vs >6) *	0.455	0.900	0.493-1.646	0.733
Extent of embolization (s vs >2s) *	0.000	1.508	0.869-2.615	0.144
Initial CR	0.000	0.134	0.059-0.303	0.000
Initial OR (CR+PR)	0.000	0.534	0.267-1.067	0.046

(*): *Cut-off value*

(**) *Local ablation was used after the initial 6 months (of the scheduled treatments) only complementary to “on demand” embolization during the follow up to treat new lesions – if in suitable locations.*

*** *Sorafenib was given in a few patients in addition to on demand embolization in patients with short time to progression.*

SURVIVAL

Child A (n)		1yr (%)	2yrs (%)	3yrs (%)	4yrs (%)	5yrs (%)
21	One dominant ≤5cm	100	95.2	71.4	66.6	47.6
37	One Dominant >5cm	97.3	89.1	85.1	43.3	32.4
31	Multinodular ≤5	93.5	90.3	61.3	41.9	25.8
13	Multinodular >5	84.6	69.2	46.1	15.3	0
102	overall	95	88.2	61.7	45	29.4
Child B						
17	One dominant ≤5cm	94.1	88.2	58.8	41.2	23.5
35	One Dominant >5cm	91.4	71.4	54.2	37.1	11.4
14	Multinodular ≤5	85.7	75	25	14.3	0
5	Multinodular >5	100	60	20	0	0
71	overall	91.5	75	50.7	35.2	12.8
TOTAL		93.6	83.8	62	41.04	22.5

REPORT OF 5-YR SURVIVAL SMALL DIAMETERS OF BEADS

Marelli et al :	71±18%	48±16%		34±13%	14±10%
Lo et al mean :	57%	31%	26%		
Llovet et :	82%	63%	29		
Molinari et al :	76.6%	55.5%	50%		
Suilleabha et al:					8%
Saccheri et al :			39% Child A		
			8% Child B		
Takayasu et al :	82%		47%		26%
Hatanaka et al :					26%
Ikeda et al :					25%
Lencioni et al :	100%		76%		51%
	89%		46%		31%

7cm (42.5% solitary) / mdn :4.7 courses
 4.9cm (solitary : 32% ; Child class A :in 77.5%)
 6.8±3.2 cm i/only Child class A
 9cm ; 81% Child A survival
 (≤5 in 38%; >5 in 16% and multiple in 36%)
 16% (7 yrs) class A :51% ; ≤5cm in 75%
 Child class A, lesions ≤5cm
 Child class B, lesions ≤5cm

CONCLUSIONS

- a) reports high survival rates achieved with sequential sessions of DEB-DOX in HCC patients not amenable to curative treatments
- b) shows that DEB-DOX cannot be classified among the curative treatments such as RFA and surgery even for single lesions ≤ 5 cm. However if these patients are not suitable for local ablation DEB-DOX achieves the next best results