# **Discussion for abstract 3570**

The tumor vascularity and lipiodol deposition predicts risk of disease progression after TACE in patients with unresectable HCC. Hai –Liang Li et al.

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# Disclosure

- Research fund, material: Lilly, Merck, GSK
- Advisor: Merck, Lilly, Celltrion, Taiho, Quintiles



# Aim of the study

- BCLC stage B HCC is treated with TACE.
- Early studies did not support the hypothesis that lipiodol deposition is a predictor of overall survival (OS)
- In this study, the **prognostic value** of **tumor vascularity and lipiodol deposition** as well as other risk factors on **OS and TTP** were evaluated in BCLC B and C patients.
  - Single institution, retrospective study



- **cTACE**: standard of care with level 1 evidence
  - TACE + embolization > TACE in OS
  - No other technology of TACE is superior to cTACE

## **Discordance in data:**

- Difference in patient population
- Difference in cTACE technology
- Difference in efficacy evaluation
- Small number of patients
- Short follow-up duration
- Retrospective study

# **Baseline characteristics of subjects**

	Subjects with good blood supply (n=101)	Subjects with poor lipiodol deposition (n=73)
Gender		
Male	88(87.13%)	62(84.93%)
Female	13(12.87%)	11(15.07%)
Age (years) Median	57.35±11.71	57.01±12.01
Tumor size (cm)	8.2±4.63	8.41±5.11
Number of nodules	3.05±3.66	3±2.75
Child Pugh score	5.54±0.88	5.44±0.86
AFP	614.74±561.79	598.82±534.36
ECOG performance G	roup % 0.45±0.5	0.52±0.5
No. of TACE procedures	2.74±1.19	2.49±0.97
BCLC stage		
В	63(62.38%)	40(54.79%)
С	38(37.62%)	33(45.21%)
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## Intermediate/advanced HCC

	<b>Tumor size (cm)</b>	8.2±4.63 cm	8.41±5.11 cm
,	Complete necrosis by size: •	2 TACEs for co	mplete necrosis
	< 2 cm: 69%	single session	$-4.6 \pm 1.8$ cm
	4~5 cm: 68%	subsequent sessi	$6.3 \pm 2.6 \mathrm{cm}$
	>6 cm : 13%	non-response	$7.4 \pm 4.4 \text{ cm}$

> 5cm : rarely achieved compact lipiodolization
 → combined with RT, RFA
 5-7 cm: TACE + RT vs TACE → 2-yr OS: 63% vs 42%

Peng et al. JC0 2013



# Multiplicity

#### Number of nodules

#### 3.05±3.66



#### **Retrospective study (n=490)**

single HCC 33.7% multiple HCC 14.6%

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Kim et al. AP & T 2012

# Inclusion criteria and Exclusion criteria

**Inclusion criteria** 

- (1) Diagnosis of HCC (BCLC stage B or C)
- (2) Child-Pugh grade A or B
- (3) ECOG score of 0 or 1
- (4) Received at least two cycles of TACE



- (1) Previous treatment with microwave ablation, radiofrequency ablation, surgical resection or liver transplantation after TACE
- (2) Platelet count  $< 50 \times 10^9/L$



# **Multiple TACEs**

No. of TA procedu	ACE res	<b>2.74</b> ±1	1.19		2.49±0.97	
• Georgia	• Georgiades et al. Re		trospective study (n=116), at least		at least 2 TACE	
		EAS		n	nRECIST	
1 <sup>st</sup> No responder		45%			50%	
2 <sup>nd</sup> resp	oonder	44%	)		47%	
Group	1-year OS	2-year OS	3-year	OS		
R1	66 ± 6	41 ± 6	25 ±	6		
N1	53 ± 7	31 ± 7	19 ±	6		
P value	.16	.28	.49		0.4 - ', '''''''''''''''''''''''''''''''''	
N1R2	68 ± 10	50 ± 11	37 ±	11		
N1N2	<b>39 ± 10</b>	14 ± 7	.0*			
P value	.036	.006	<.00	5†	0 500 1000 1500 2000	



# **TACE effect evaluation**

- after 24 hours : by non-enhanced multi-slice detect CT (MDCT) homogenous **lipiodol retention**
- after 4 weeks: : by contrast enhancement CT non-enhancing area + oil retension area: necrosis residual tumor vascularization
- Pre-treatment : vascularity evaluation post-treatment : degree of lipiodol uptake





# **Angiography:** golden standard for tumor vascularity evaluation

- Intra-procedure imaging
- mesenteric celiac angio: detect branch to extra-hepatic structure detect extra-hepatic collaterals
- 3D angio combined with MDCT
- Delivery of treatment by continuous visualization
  - targeting and distribution
  - non-target distribution

confirm by CT(after 24 hours)



## **Follow-up TACE (> 4 weeks)**

- gelatin sponge: re-cannalisation within 1-2 weeks, absorbed after 1 month
- lipiodol is gradually washed out in neovascularized tumor portion (  $\approx$  4 weeks)
- Resuming of normal attenuation value in surrounding normal tissue: 1 month
- viable tumor re-growth: after 3-4 months



### Vascularity evaluation

- hypervascularity : enhance than adjacent liver tissue or more than 50% hypervascularity
- hypovascularity : equal to adjacent liver or

less than 50% hypervascularity

### Response criteria:

- decrease to < 25%: successful
- decrease to > 25%: partial

Wober et al. Clin Hemorheo Microcirc 2014



# **Golden standard: hepatic angiography**

- Dynamic MRI : prospective (n=37) <u>Yamashita et al. Acra Radiol 1993</u>
- Power doppler sonography (PDS): prospective (n=43), depth < 7cm

Hosoki et al. Acta Radiol 1999

• Dynamic susceptibility contrast enhanced MRI (DSC-MRI): prospective (n=17) heterogenous enhancement

Tsui et al. Clinical Imaging 2000

• Multiphase helical CT: prospective (n=72)

Ebied et al. Cancer 2002

• Levovist power dopper U/S (Levovist US): prospective (n=46)

Vallone et al. Anticancer Res 2003

• Contrast enhanced U/S: prospective (n=29)

Kim et al. J Ultrasound Med 2006

- Contrast enhanced U/S (CEUS) with multi-slice detection CT (MDCT) prospective (n=40) <u>Wober et al Clin Hemorheo Microcirc 2014</u>
- First-pass perfusion-weighted MRI (FP-MRI)

# Dynamic CT (MDCT) and MRI: preferred as the golden standard for response evaluation after TACE

## **Tumor response evaluation**

**EASL** : surface of viable part of tumor

mRECIST: arterially enhanced part (devascularization)



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Ronot et al The Oncologist, 2014

# **Tumor necrosis and size change**

- reduction of diameter (>30%, PR) or SD with necrosis (>50%)

Kim et al. Radiol 2010

• 1997-2009: retrospective study (n=50): Response depends on vascularity

- hypervascular tumor : 85% responsive hypovascular tumor : 10% responsive

#### • Lipiodol uptake: Survival depends on lipiodol uptake

	1-yr OS	2-yr OS	5-ys OS
compact	92.7%	70.7%	52.4%
incompact	60.8%	28.0%	16.9%

Kim et al. AP & T 2012





### • Ebied et al:

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#### based on both vascularity and responsiveness

OS (Mo)	Hypervascular responders (n = 34) (%)	Hypervascular nonresponders (n = 28) (%)	Hypovascular responders (n = 4) (%)	Hypovascular nonresponders (n = 6) (%)
6	34(100)	25(89)	4(100)	5(83)
12	28(82)	18(44)	2(50)	0(0)
18	16(47)	4(14)	2(50)	0(0)
24	9(27)	3(11)	1(25)	0(0)









- Absence of lipiodol deposition
  - missing feeding vessel
  - extra-hepatic collaterals
    - radioembolization
    - systemic therapy
    - supportive care

 Hypervascular tumor: TACE is effective
 Hypovascular tumor: RFA, ethanol
 → Combination with TACE



# **Stopping rules** (shift to other treatment)

#### Number of TACE correlated with decreased risk of progression

- Most common causes of stopping sequential TACE:
- diminished hepatic function reserve
- marked reduction of general health status

### Stopping rule

- absence of response in 2 TACE
- inability to reach all main tumor vessels
- functional deterioration

ECOG  $\geq 2$ ,

hepatic decompensation (Child-Pough C)

LDH > 425 UI/ml AST > 100 UI/ml bilirubin > 2.0 mg/dl tumor volume > 50%



# Conclusion

- Combined lipiodol retention and tumor vascularity should be considered as predictors of disease progression after TACE
- Poor lipiodol retention may predict a poor TTP and OS despite the blood supply status.

## Response predictor

- TNM: tumor size < 7.0cm
- nodules: < 5
- Child-Pough class
- tumor vascularity
- portal vein occlusion
- initial compact lipiodolization (complete necrosis)

- aFP SINGAPORE ESTO ASIA 2015 18-21 DECEMBER SINGAPORE

# No agreement points on cTACE

- Lipiodol:
  - preparation: 10ml (<15ml per session, water-in-lipid)
  - administration
- Anti-cancer agent: cisplatin = adriamycin/epirubicin
- Embolic material: gelatin sponge particle (100~300 microns)
  - resorvable embolisation is recommended
  - lipiodol + particulates
    main tumor necrosis: 13% → 83%
    satellite necrosis : 6% → 53%
- Intervention technical details and device
- Treatment schedule
- Tumor response criteria
- Combination of treatment
- Subsequent treatment

Response end-points:

- imaging response (CT)
- biologic response (aFP)
- degree of tumor necrosis
- patient survival

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- QoL
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