ECIO 2013
Fourth European Conference on Interventional Oncology
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Budapest | Hungary

New IO Approaches for HCC: An Update on Clinical Trials

Riccardo Lencioni, MD, FSIR, EBIR

Phase III Trials Investigating New Systemic Targeted Therapies in HCC

Experimental agent or combination (trial name)	Control	Molecular targets of experimental agent(s)	Primary endpoint	Identifier
Unresectable/advanced HCC: first-line therapy				
Sorafenib SHARP Asia Pacific	Placebo	VEGFR, PDGFR, Raf, c-kit	OS	[illegible]43
Sunitinib	Sorafenib	VEGFR, PDGFR, FLT3, KIT, RE		
Brivanib (BRISK-FL)	Sorafenib	VEGFR and FGFR		[illegible]971
Linifanib (ABT-869)	Sorafenib	VEGFR and [illegible]		[illegible]009539
Sorafenib (BOOST) Child-Pugh B only	Placebo	VEGFR		NCT01405573
Erlotinib/sorafenib (SEARCH)	Sorafenib	EG[illegible]	OS	NCT00901901
Sorafenib/doxorubicin (CALGB-80802)	Sorafenib		OS	NCT01015833
Unresectable/advanced HCC: second-line therapy				
Brivanib (BRISK-PS)	[illegible]		OS	NCT00825955
Brivanib (BRISK-APS)	[illegible]	[illegible]FR	OS	NCT01108705
Ramucirumab	[illegible]	[illegible]2	OS	NCT01140347
Everolimus (EVOLVE-1)	[illegible]	mTOR	OS	NCT01035229
Adjuvant therapy after or [illegible]				
Brivanib (TACE TA[illegible]	[illegible]	VEGFR and FGFR	OS	NCT00908752
Sorafenib ECOG	[illegible]	VEGFR, PDGFR, Raf, c-kit	PFS	NCT01004978 NCT01324076 NCT00855218 NCT01217034
[illegible]	Placebo	bFGF and VEGF	OS	NCT00921531
[illegible] [illegible]ENTAL)	Placebo	VEGFR, PDGFR, FGFR	OS	NCT01465464
Early [illegible] [illegible]djuvant therapy after surgery or RFA				
Sor[illegible] STORM)	Placebo	VEGFR, PDGFR, Raf, c-kit	RFS	NCT00692770

6 trials completed, all of them failed

Colombo M et al. Eur J Gastroenterol Hepatol 2013;25:639-651

Loco-Regional Interventional Oncology Therapies for HCC

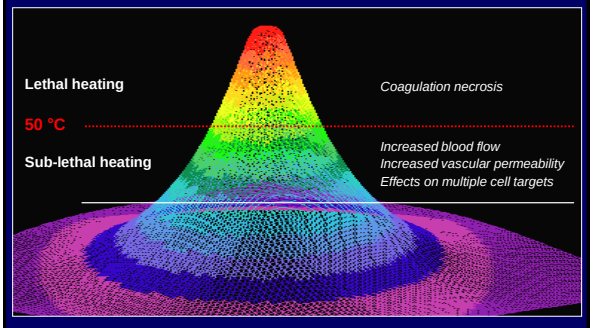
PERCUTANEOUS APPROACH

- ✓ Ethanol injection
- ✓ Acetic acid injection
- ✓ Radiofrequency ablation
- ✓ Laser ablation
- ✓ Cryoablation
- ✓ Microwave ablation
- ✓ Light activated therapy
- ✓ Irreversible electroporation

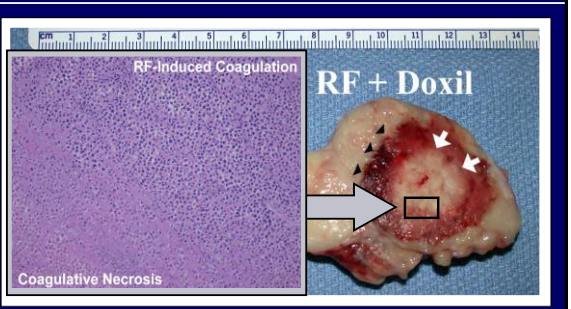
TRANSCATHETER APPROACH

- ✓ Transarterial embolization
- ✓ Transarterial chemotherapy
- ✓ Transarterial lipiodolization
- ✓ Intraarterial chemoinfusion
- ✓ I-131 lipiodolization
- ✓ Chemoembolization
- ✓ Y-90 Radioembolization
- ✓ Drug-eluting bead

Percutaneous Image-Guided Thermal Ablation: Temperature-Tissue Interactions



RFA plus IV Injection of Liposomal Doxorubicin in Animal Tumor Models



Ahmed et al. Radiology 2005;235:469–477

RFA plus IV Injection of Liposomal Doxorubicin in Animal Tumor Models

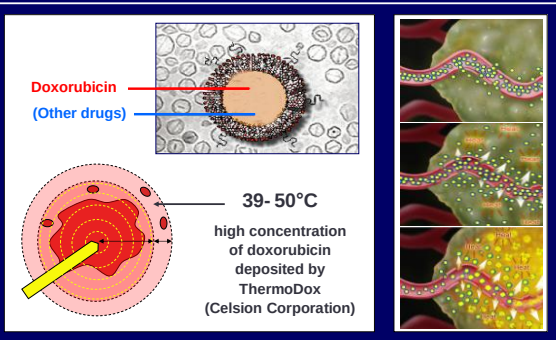
Treatment	Tumor Size (mm)	Size of Central Region of Coagulation (mm)	Size of Hyperemic Rim of Coagulation (mm)	Overall Size of Coagulation (mm)
RF ablation + doxorubicin	50.1 ± 1.8	20.9 ± 1.7	15.6 ± 7.4	36.5 ± 5.9
RF ablation alone	51.8 ± 0.2	15.3 ± 2.2	7.3 ± 1.1	22.7 ± 1.4

Note.—Data are means ± standard errors of the mean. *P* values for differences in values between the combined therapy and RF ablation–only treatment groups are as follows: .683 for tumor size, .006 for size of central region of coagulation (ie, white zone), .015 for size of hyperemic rim of coagulation (ie, red zone), and .037 for size of overall coagulation (ie, red and white zones combined). Significant increases in overall tumor tissue coagulation were achieved with combination therapy compared with the coagulation achieved with RF ablation alone.

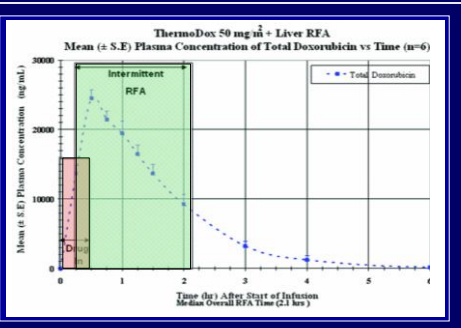
+ 415 %
in ablation volume

Ahmed et al. Radiology 2005;235:469–477

RFA in Combination with IV Heat-Activated Liposomal Encapsulation of Doxorubicin



A Phase I Study of Heat Deployed Liposomal Doxorubicin during RFA for Liver Malignancies



Wood B et al. J Vasc Interv Radiol 2012;23:248-255

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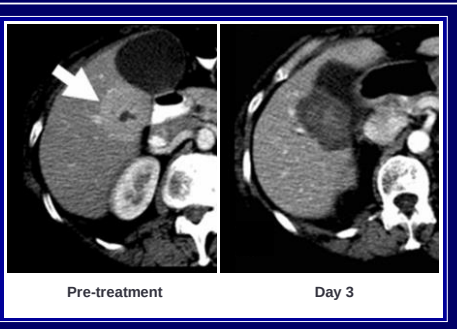
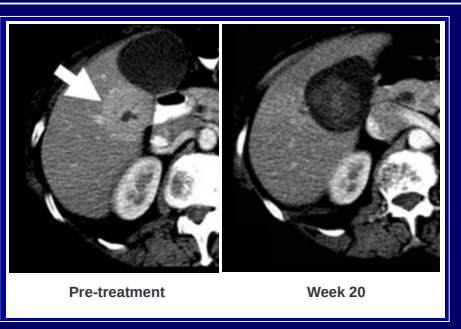


Pre-treatment Day 3

Wood B et al. J Vasc Interv Radiol 2012;23:248-255

A Phase I Study of Heat Deployed Liposomal Doxorubicin during RFA for Liver Malignancies



Pre-treatment Week 20

Wood B et al. J Vasc Interv Radiol 2012;23:248-255

HEAT: A Phase III Randomized Controlled Study of RFA + ThermoDox vs RFA Alone for HCC

HEAT

A Phase III, Randomized, Double-Blinded, Dummy-Controlled Study of the Efficacy and Safety of ThermoDox® in Combination with RFA Compared to RFA Alone in the Treatment of HCC

PIs: R. Lencioni, R. T. Poon

Main eligibility criteria:
- HCC 3-7 cm
- ≤ 4 tumors
- Candidate for RFA
- Child - Pugh A-B
- No prior treatment

Target enrollment:
- 700 patients

Randomization

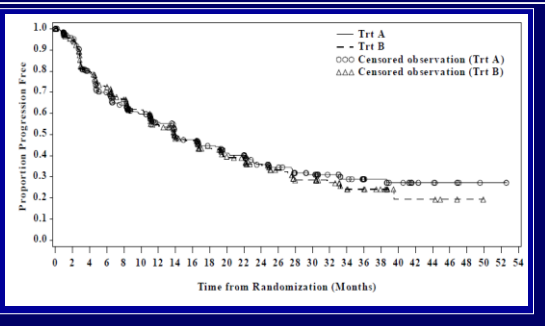
- 50 mg/m² ThermoDox
- Dummy infusion

Primary endpoint:
- PFS

Secondary endpoints:
- OS
- TTLR
- Safety
- Other

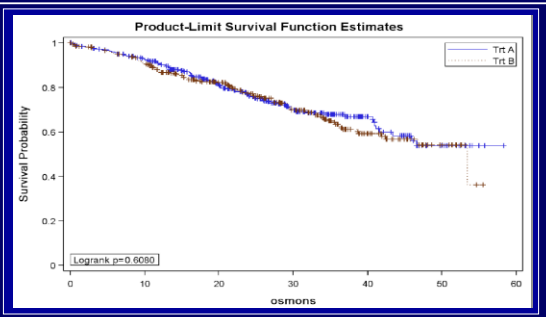
www.clinicaltrials.gov; NCT 00617981

HEAT Trial: Progression-Free Survival Analysis (Primary Endpoint)



Lencioni R and Poon RT. Presented at WCIO 2013, New York, NY, May 16-19.

HEAT Trial: Overall Survival Analysis (Secondary Endpoint)



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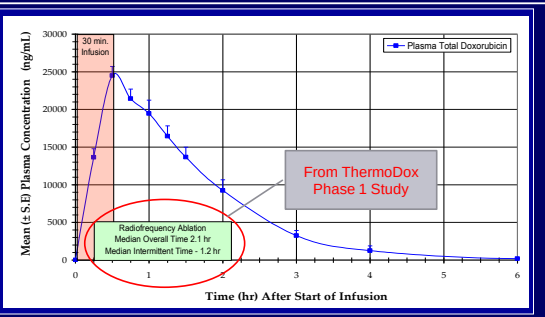
HEAT Trial: Overall Survival by RFA Heating Time in Single Lesions (Post-Hoc Analysis)



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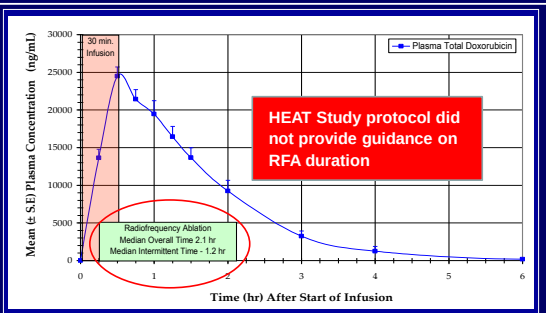

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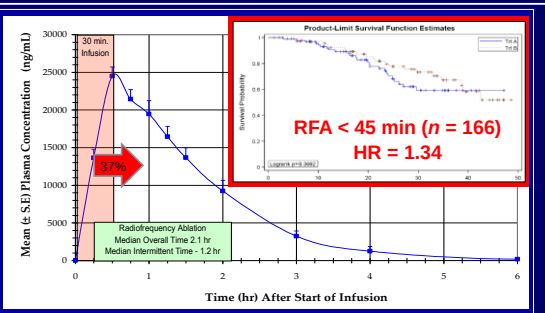

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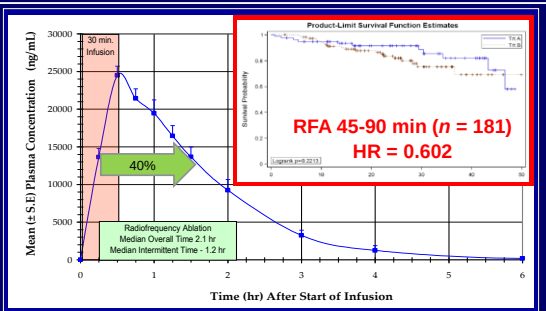

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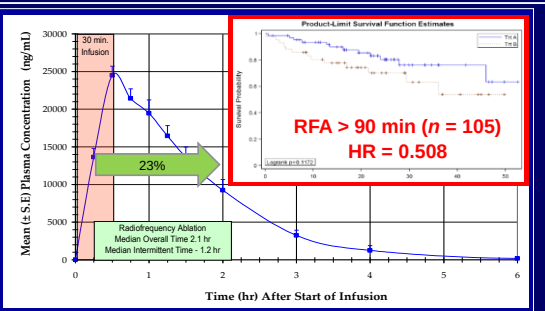

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HEAT Trial: RFA plus Heat Deployed Liposomal Doxorubicin – Where Do We Stand?

- The HEAT study shows that ThermoDox is well-tolerated with no unexpected serious adverse events
- The data did not provide sufficient evidence of clinical effectiveness, as measured by the trial's primary endpoint of progression-free survival
- Post-hoc findings suggest that optimized heating cycles could improve RFA plus ThermoDox's potential for clinically relevant improved survival outcomes: however these data should be viewed with caution since they are not statistically significant and the HEAT study has not reached its median point for overall survival analysis

Oncolytic Immunotherapy

Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer

Jeong Heo[1,2,17], Tony Reid[2,3,17], Leyo Ruo[4], Caroline J Breitbach[5], Steven Rose[3], Mark Bloomston[6], Mong Cho[1], Ho Yeong Lim[7], Hyun Cheol Chung[8], Chang Won Kim[1], James Burke[5], Riccardo Lencioni[9], Theresa Hickman[5], Anne Moon[5], Yeon Sook Lee[10], Mi Kyeong Kim[10], Manijeh Daneshmand[11], Kara Dubois[5], Lara Longpre[5], Minhtran Ngo[12,13], Cliona Rooney[12–14], John C Bell[5,11], Byung-Geon Rhee[15], Richard Patt[16], Tae-Ho Hwang[1,10,18] & David H Kirn[5,18]

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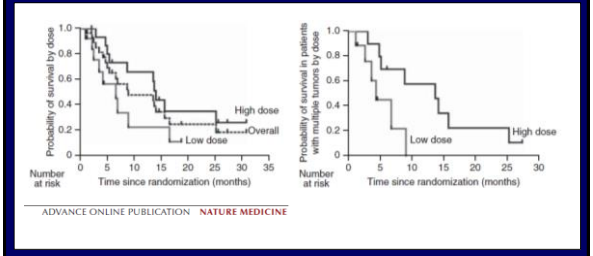
nature medicine

Oncolytic Immunotherapy



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✓ *First RCT showing that an oncolytic virus or gene therapy agent was associated with improved overall survival*

Image-Guided Oncolytic Immunotherapy

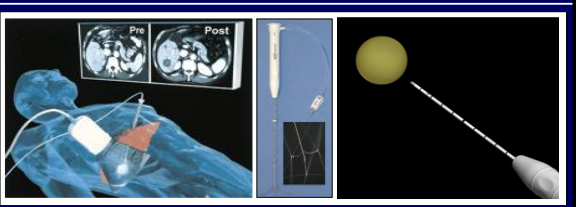
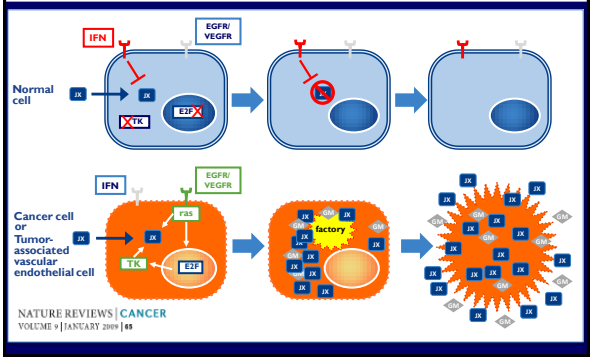
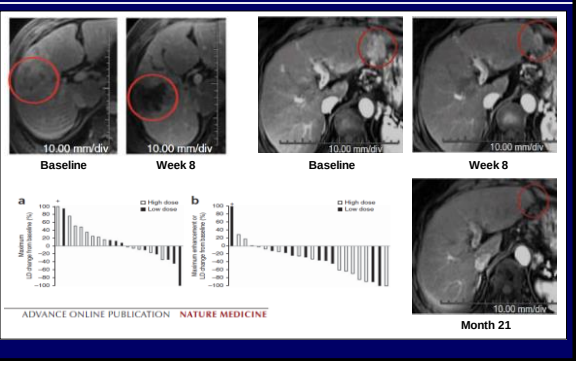


Image-Guided Oncolytic Immunotherapy



NATURE REVIEWS | CANCER
VOLUME 9 | JANUARY 2009 | 65

Image-Guided Oncolytic Immunotherapy



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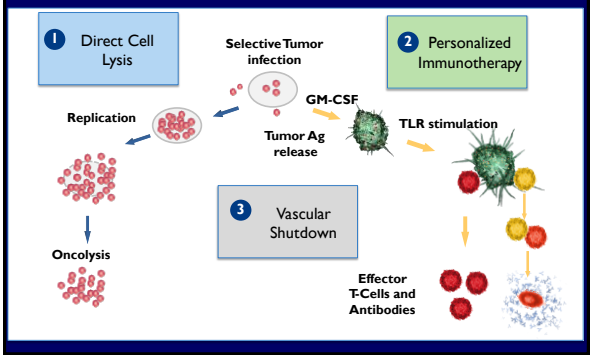
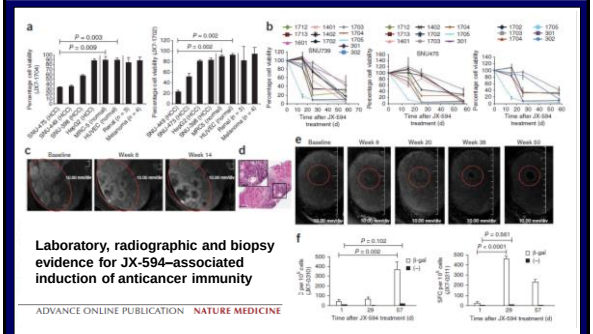
Oncolytic Immunotherapy: Mechanisms of Action



Intratumoral Injection, Systemic Effect



Laboratory, radiographic and biopsy evidence for JX-594–associated induction of anticancer immunity

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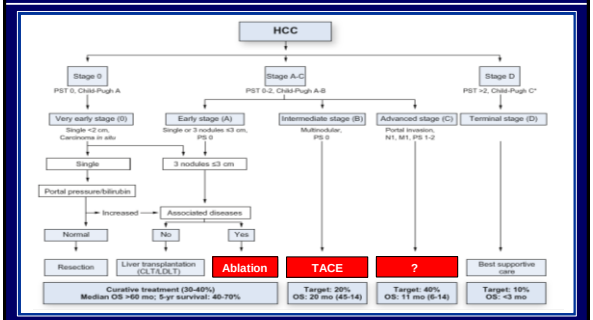
EASL-EORTC Clinical Practice Guidelines: Management of HCC



EASL-EORTC Guidelines. J Hepatol 2012 & Eur J Cancer 2012