

ILCA

International Liver Cancer Association

Priming Knowledge in
Liver Cancer across Disciplines



OPTIMA Phase III Clinical Trial: Study Design and Protocols

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Frequency and Distribution of Microsatellites According to HCC Tumor Size

46% of patients with single HCC < 5 cm show microsatellites on histology

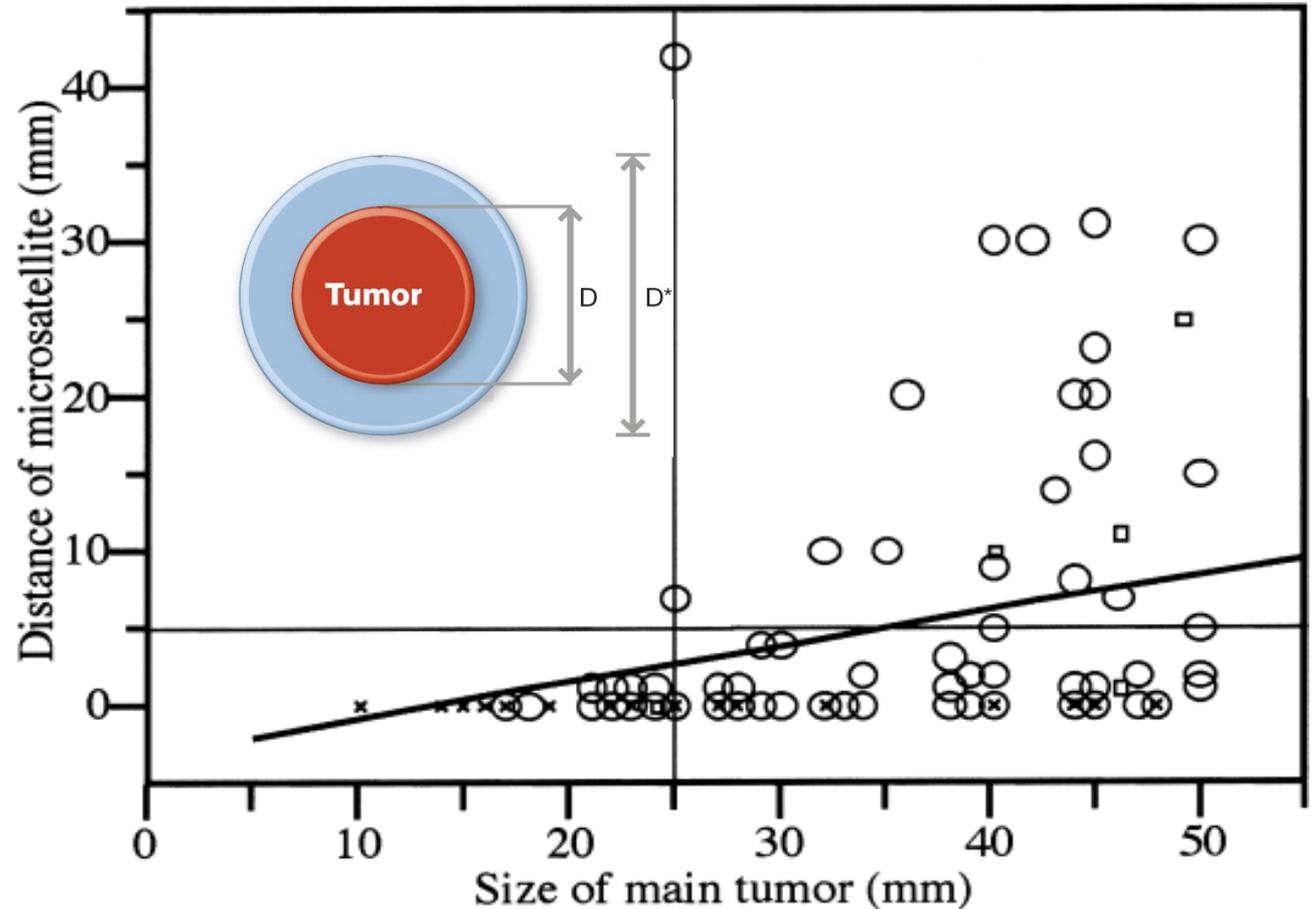
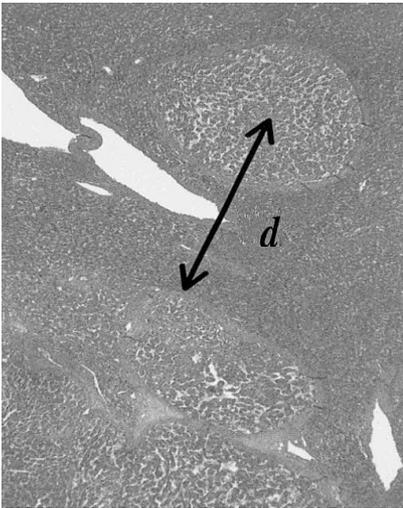
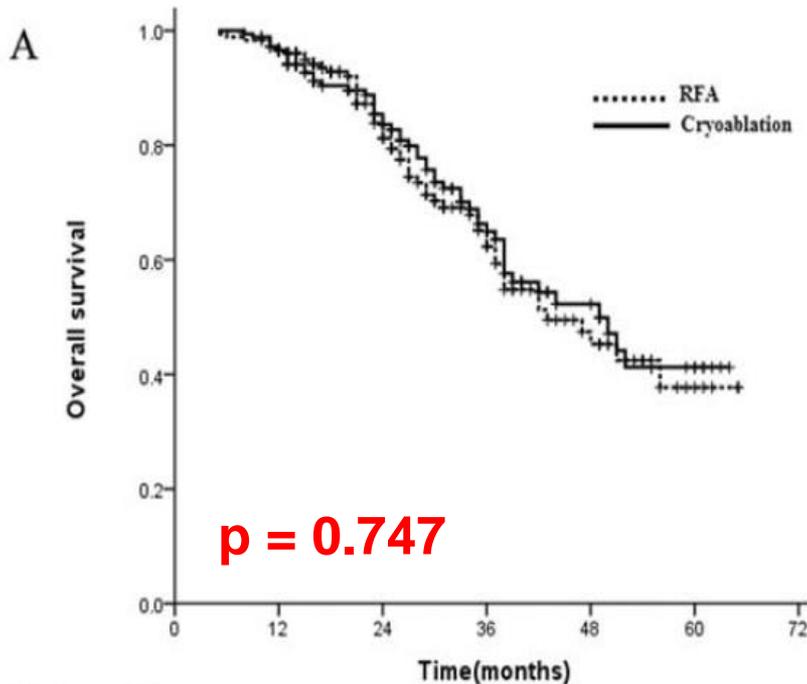


Image-Guided Tumor Ablation: Evolving Methods and Technologies

Technology	Potential advantages	Potential disadvantages
RFA	<ul style="list-style-type: none"> • High rates of local control in tumors 3 cm or smaller • Established safety profile • Known limitations • Experience in combination treatments (TACE + RFA) • Widely available 	<ul style="list-style-type: none"> • High rates of incomplete ablation in tumors >3 cm • Heat sink effect in perivascular tumors • Potential risk of thermal injury to critical structures • Variability in RFA devices
MWA	<ul style="list-style-type: none"> • Potential to treat tumors larger than 3 cm more effectively • Less impacted by heat sink effect • Ability to activate multiple probes at the same time • No grounding pads required 	<ul style="list-style-type: none"> • Limited efficacy data (predictability and reproducibility) • Limited safety data • Potential risk of thermal injury to critical structures / vessels • Variability in MWA devices
CRYO	<ul style="list-style-type: none"> • Ability to activate multiple probes at the same time • Ability to image the ice-ball formation 	<ul style="list-style-type: none"> • Insufficient clinical data • Risk of bleeding • Risk of cryoshock
IRE	<ul style="list-style-type: none"> • Potential to treat tumors located in the vicinity of critical structures • Heat sink effect not relevant 	<ul style="list-style-type: none"> • Insufficient clinical data • Neuromuscular blockage and cardiac gating required

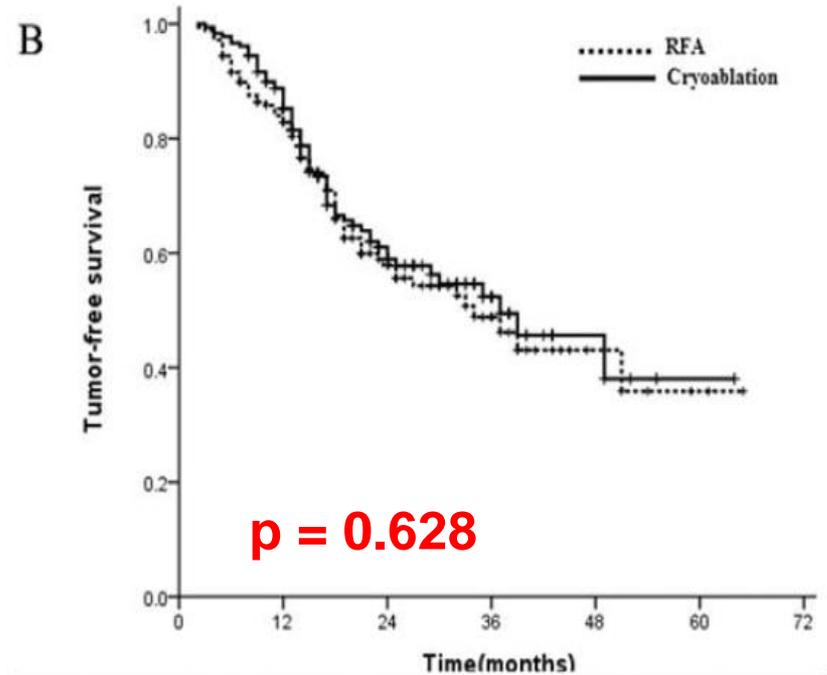
Cryo vs. RFA: A Multicenter Randomized Controlled Trial in HCC Tumors ≤ 4 cm

Overall Survival



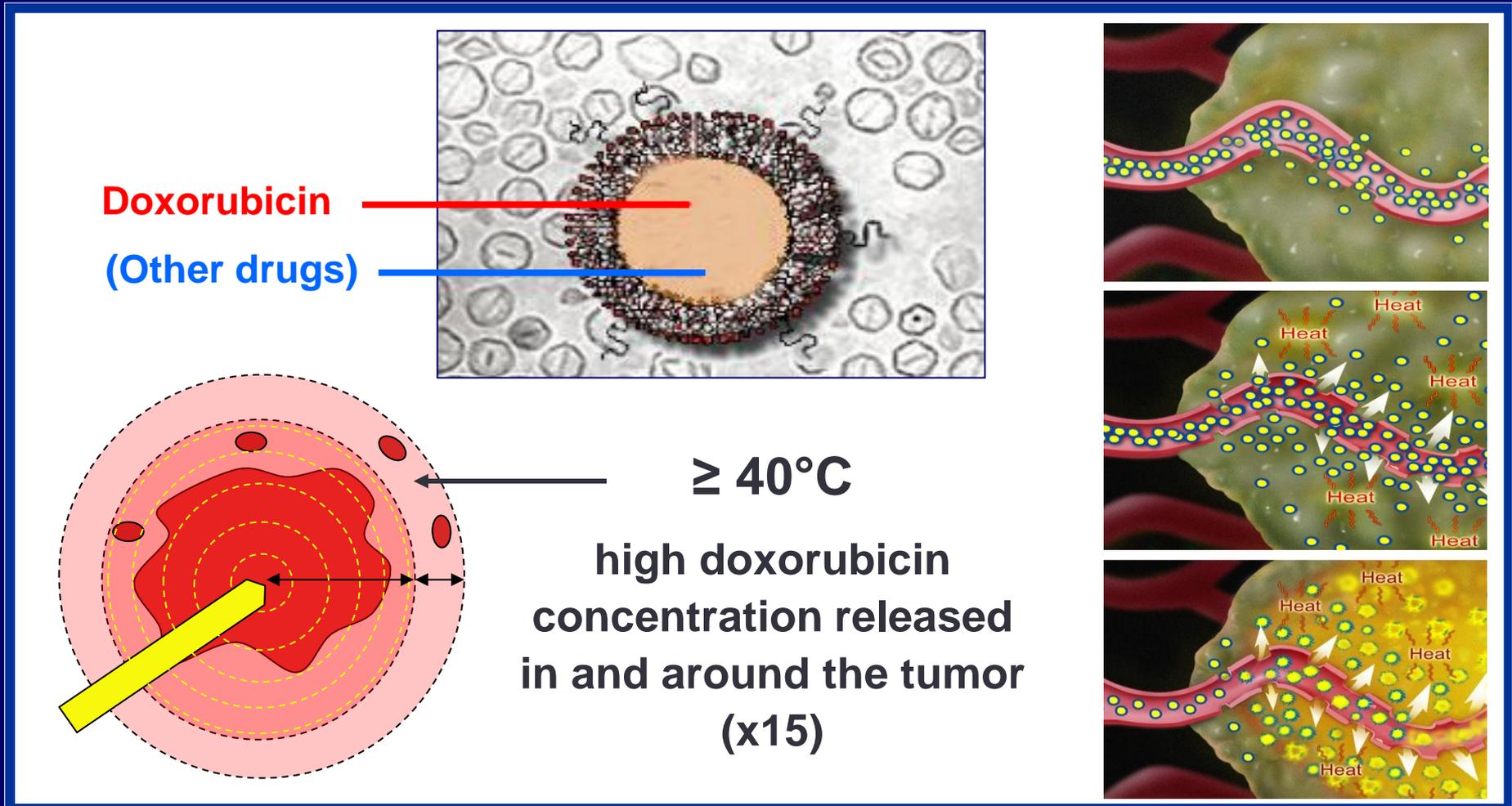
Patients at risk						
Cryoablation	180	156	93	46	22	6
RFA	180	172	88	42	21	4

Tumor-Free Survival



Patients at risk						
Cryoablation	180	135	51	18	6	1
RFA	180	137	51	18	5	1

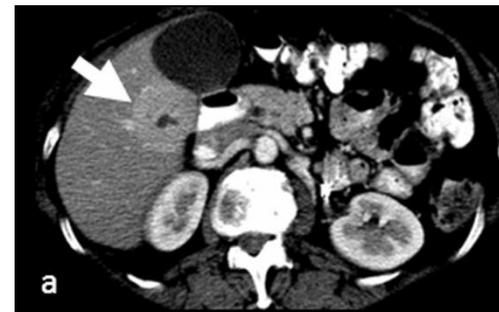
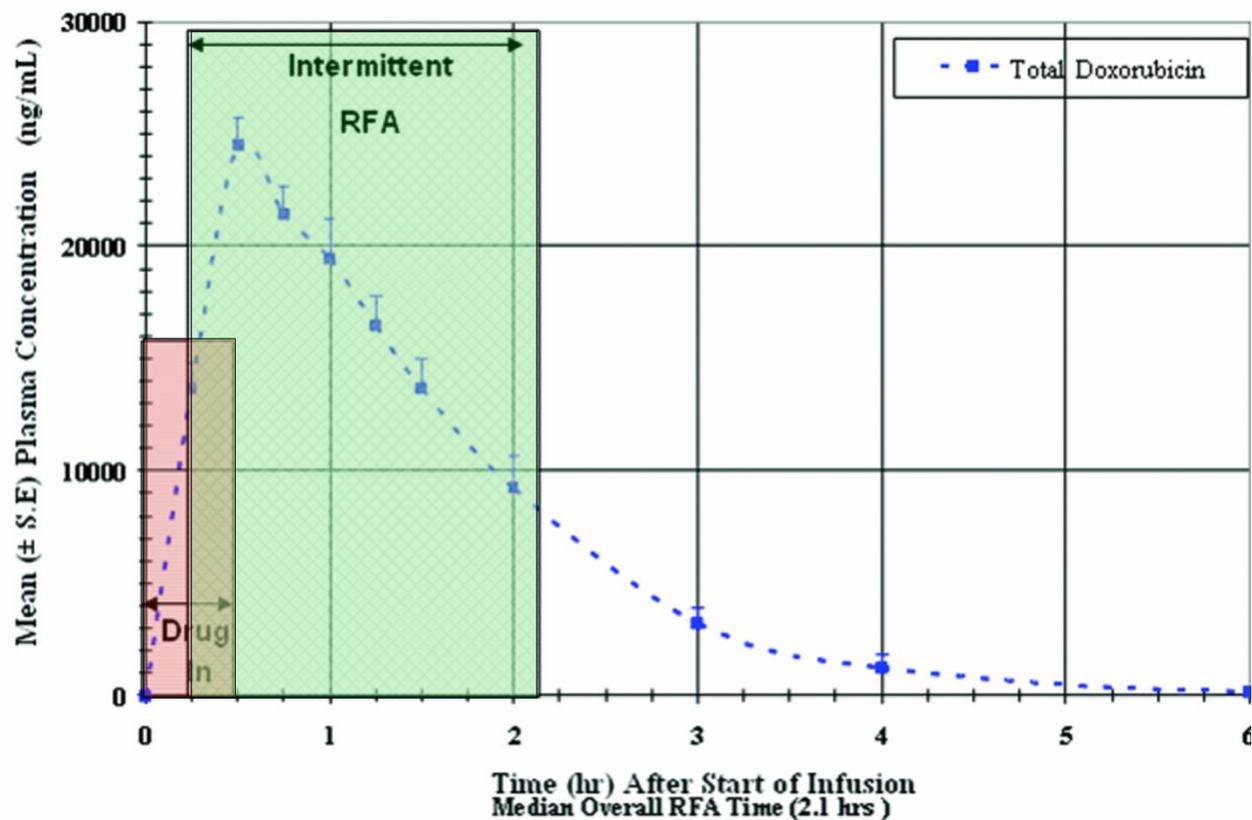
Lyso-Thermosensitive Liposomal Doxorubicin (LTLD): Mechanism of Action



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

ThermoDox 50 mg/m² + Liver RFA

Mean (\pm S.E) Plasma Concentration of Total Doxorubicin vs Time (n=6)



The HEAT Study: A Phase III Randomized Trial of RFA plus LTLD vs RFA Alone in HCC Treatment

In HCC

The logo for the HEAT study, featuring the word "HEAT" in a bold, black, sans-serif font. A yellow swoosh underline is positioned beneath the letters "E" and "A".

The HEAT Study: A Phase III, Randomized, Double-Blinded, Dummy-Controlled Study of LTLD (ThermoDox[®]) in Combination with RFA Compared to RFA Alone in the Treatment of HCC

Inclusion Criteria

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

Randomization

50 mg/m² LTLD

Dummy infusion

Primary Endpoint
- PFS

Secondary Endpoints
- OS
- TTLR
- Safety
- Others

n = 701

The HEAT Study - RFA plus LTLD vs RFA Alone: Baseline Patient Characteristics

In HCC

Parameter	RFA + LDLT (n = 354)	RFA (n = 347)	p-value
Male	267 (75.4%)	263 (75.8%)	NS
Female	87 (24.6%)	84 (24.2%)	
Age > 65	149 (42.1%)	138 (39.8%)	NS
Hepatitis B	207 (58.5%)	203 (58.5%)	NS
Hepatitis C	92 (26.0%)	89 (25.6%)	NS
Child class A	329 (92.9%)	329 (94.8%)	NS
Single tumor	234 (66.1%)	219 (63.1%)	NS
Max. size 3-5 cm	289 (81.6%)	286 (82.4%)	NS
Percutaneous route	321 (90.7%)	315 (90.8%)	NS

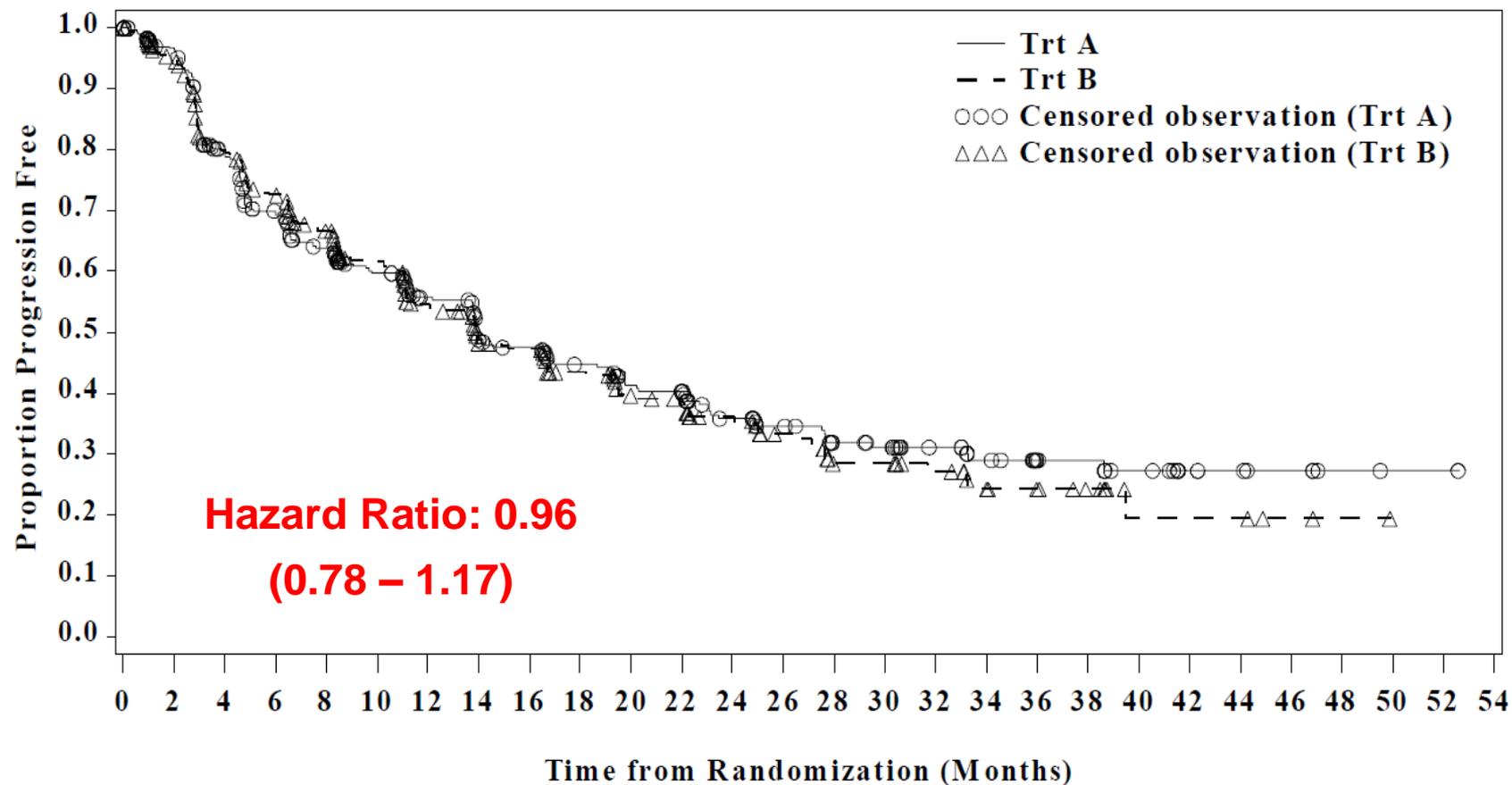
The HEAT Study - RFA plus LTLD vs RFA Alone: Treatment-Emergent AEs (\geq Grade 3, \geq 1%)

In HCC

Parameter	RFA + LDLT	RFA
Hematologic		
Neutropenia	162 (47.2%)	7 (2.1%)
Thrombocytopenia	18 (5.2%)	7 (2.1%)
Anemia	4 (1.2%)	1 (0.3%)
Non-hematologic		
AST increased	33 (9.6%)	35 (10.5%)
ALT increased	22 (6.4%)	18 (5.4%)
Bilirubin increased	7 (2.0%)	8 (2.4%)
Alopecia	13 (3.8%)	0 (0.0%)

The HEAT Study - RFA plus LTLD vs RFA Alone: Progression-Free Survival (Primary Endpoint)

In HCC



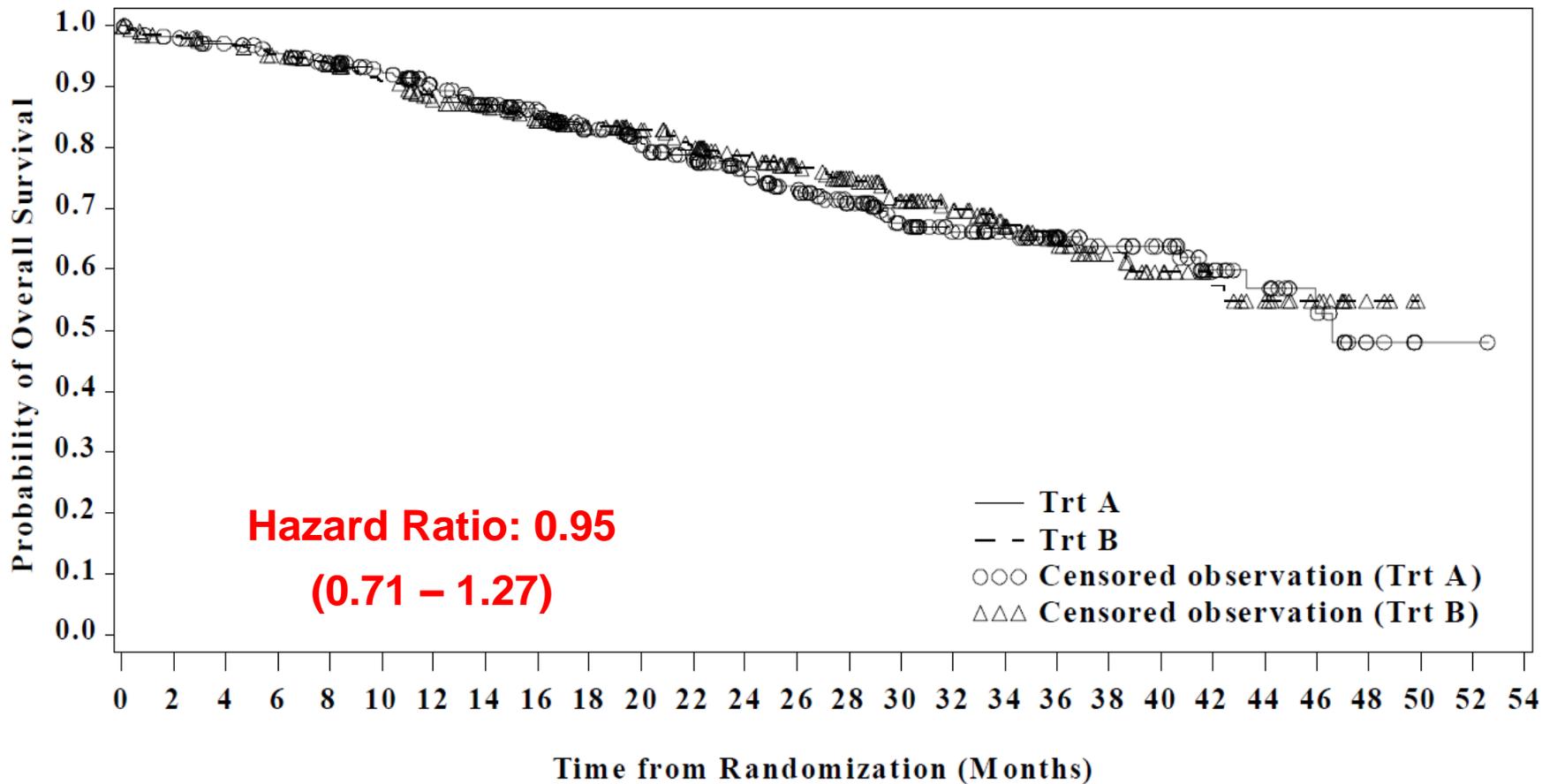
The HEAT Study - RFA plus LTLD vs RFA Alone: Progression-Free Survival (Primary Endpoint)

In HCC

Type of Event	RFA + LTLD (n=185)	RFA (n=186)	Total (n=371)
Local Recurrence	41 (22.2%)	37 (19.9%)	78 (21%)
New Distant Hepatic Lesion	78 (42.2%)	95 (51.1%)	173 (46.6%)
New Extrahepatic Lesion	13 (7.0%)	10 (5.4%)	23 (6.2%)
Combination	7 (3.8%)	8 (4.3%)	15 (4.0%)
Death	17 (9.2%)	17 (9.1%)	34 (9.2%)
Treatment Failure	29 (15.7%)	19 (10.2%)	48 (12.9%)

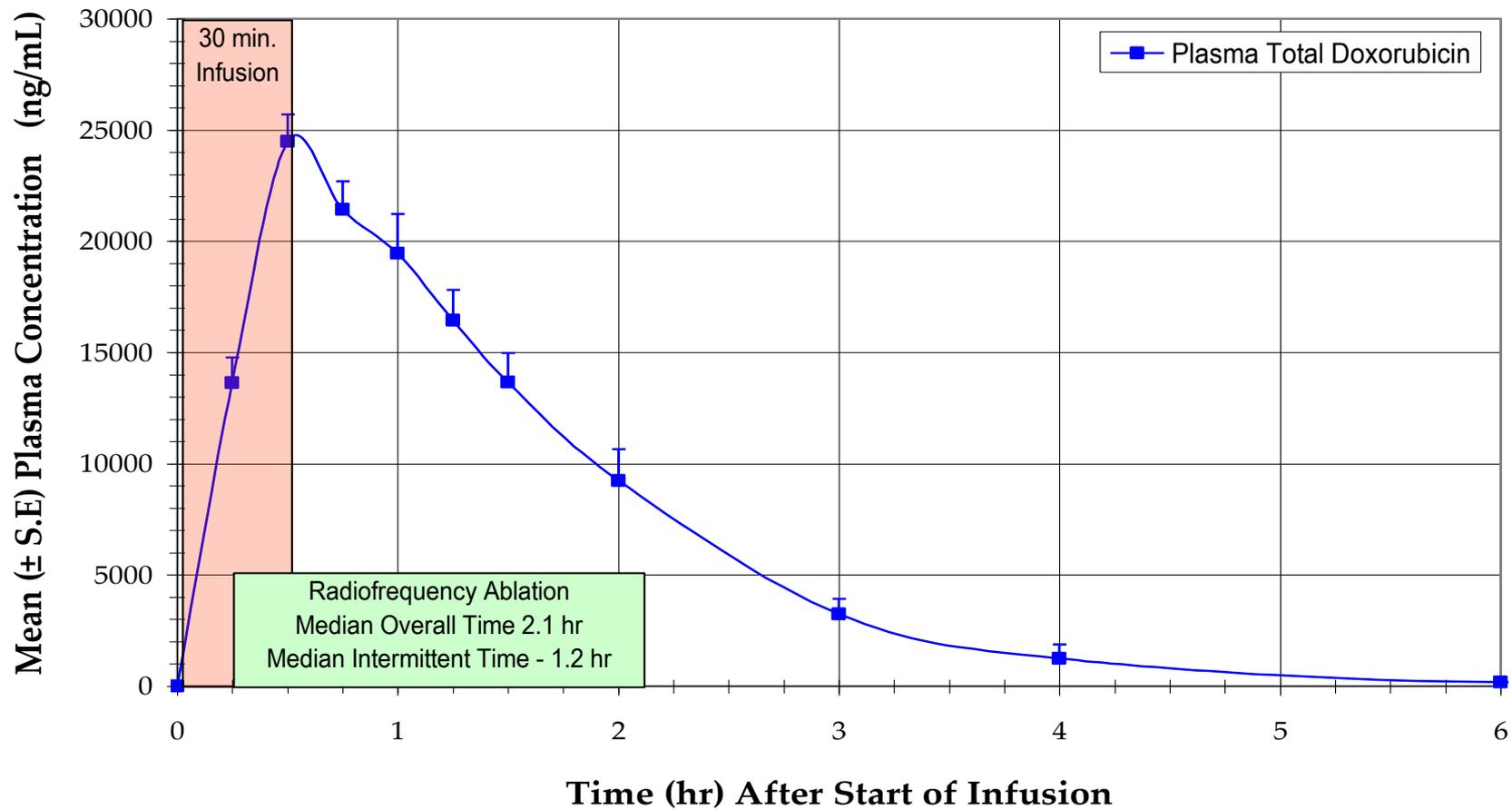
The HEAT Study - RFA plus LTLD vs RFA Alone: Overall Survival (Secondary Endpoint)

In HCC



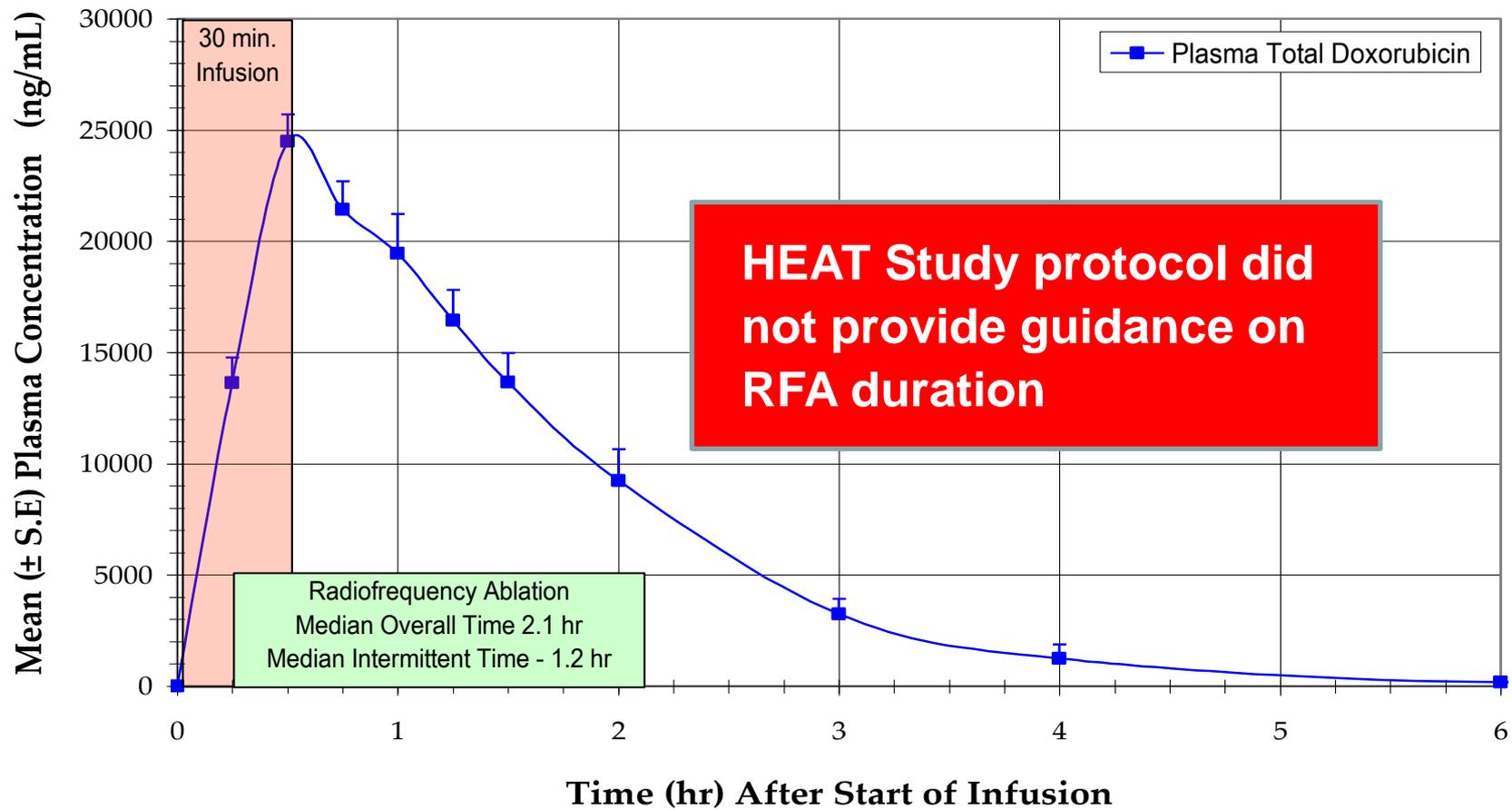
A Phase I Study of Heat Deployed Liposomal Doxorubicin during RFA for Liver Malignancies

In HCC



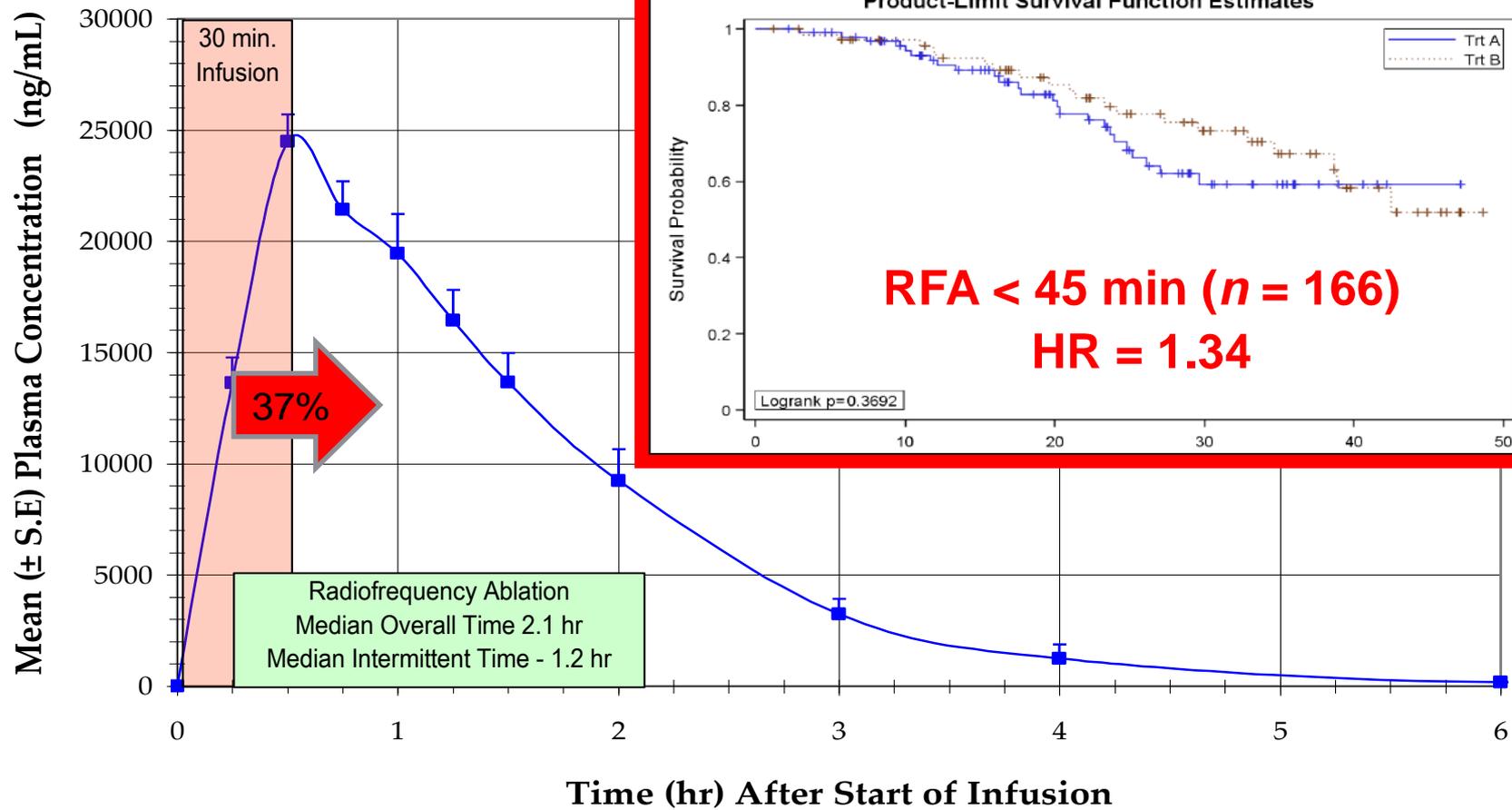
A Phase I Study of Heat Deployed Liposomal Doxorubicin during RFA for Liver Malignancies

In HCC



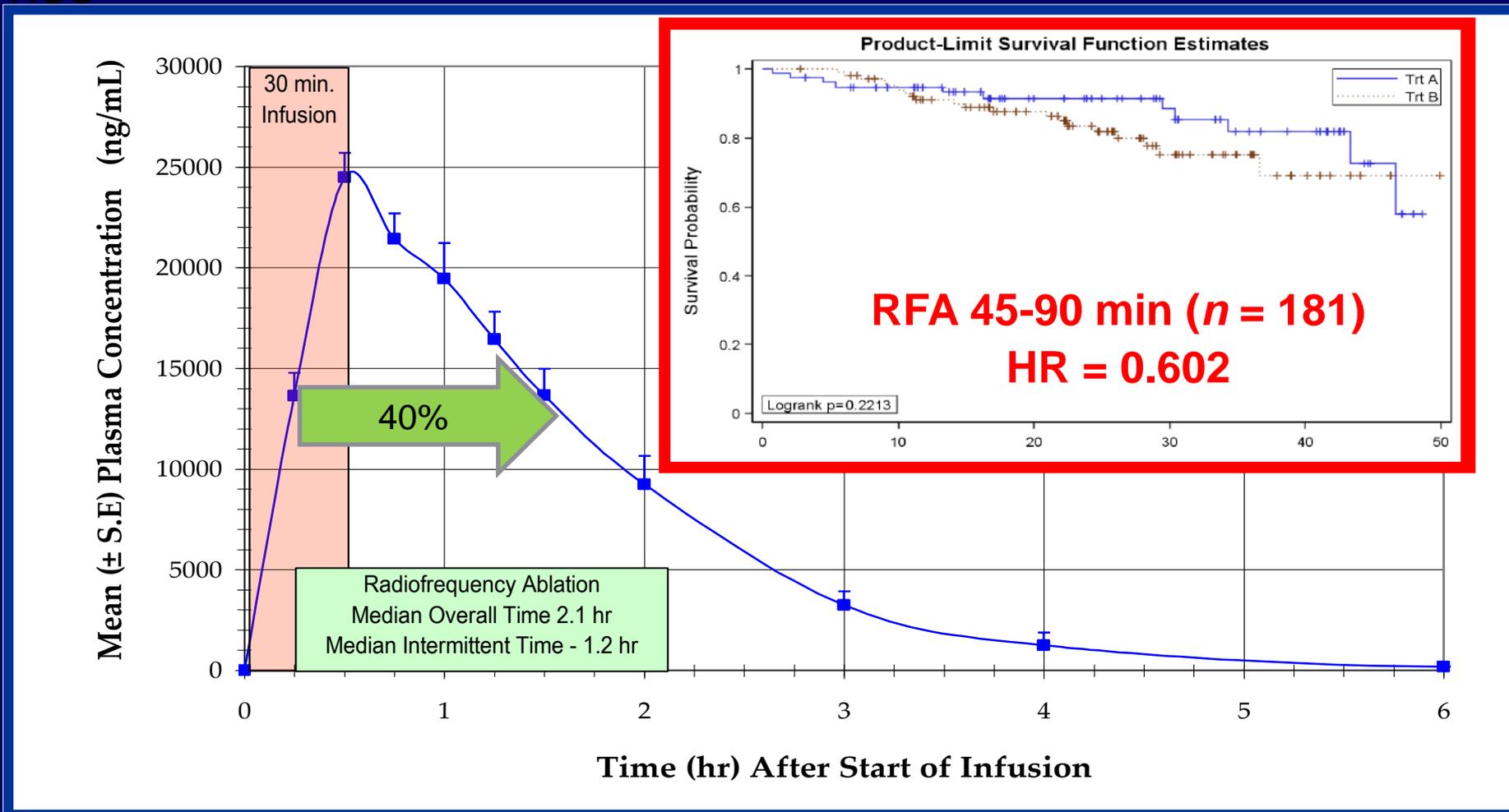
Overall Survival by RFA Heating Time in Single Lesions (Post-Hoc Analysis)

In HCC



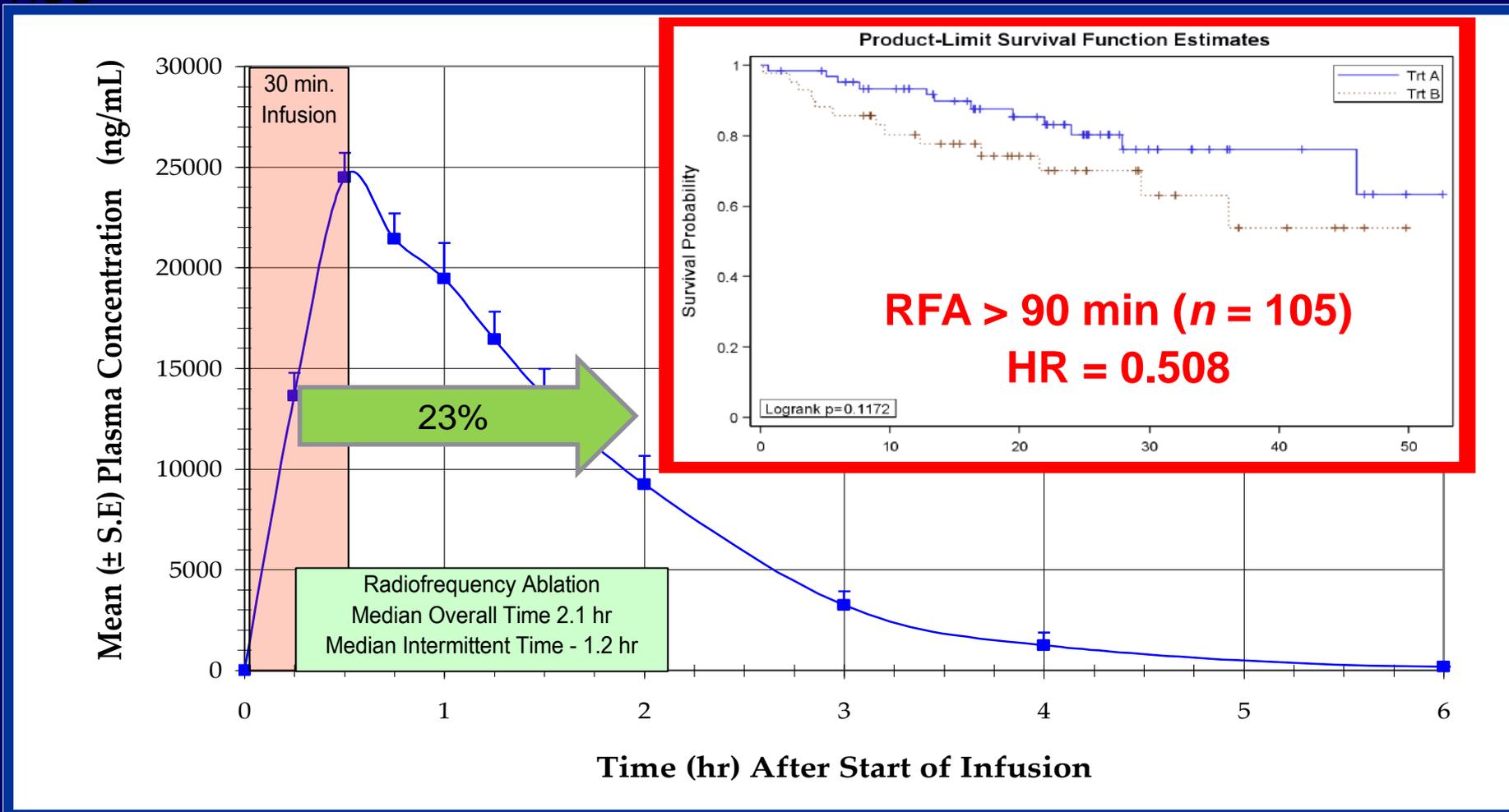
Overall Survival by RFA Heating Time in Single Lesions (Post-Hoc Analysis)

In HCC



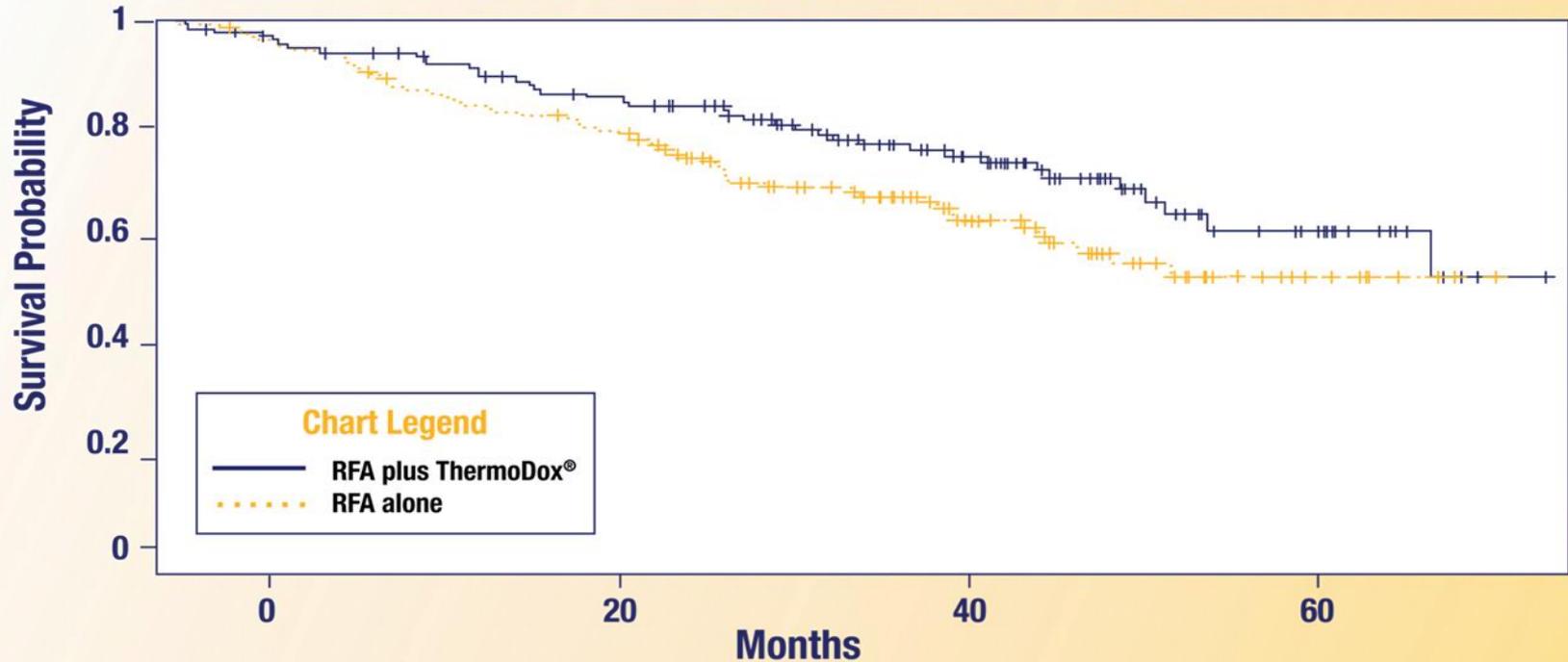
Overall Survival by RFA Heating Time in Single Lesions (Post-Hoc Analysis)

In HCC



Overall Survival in 285 Patients with Single HCC and RFA > 45 min (Post-Hoc Analysis)

Product-Limit Survival Function Estimates



Overall Survival as of 6/30/2014

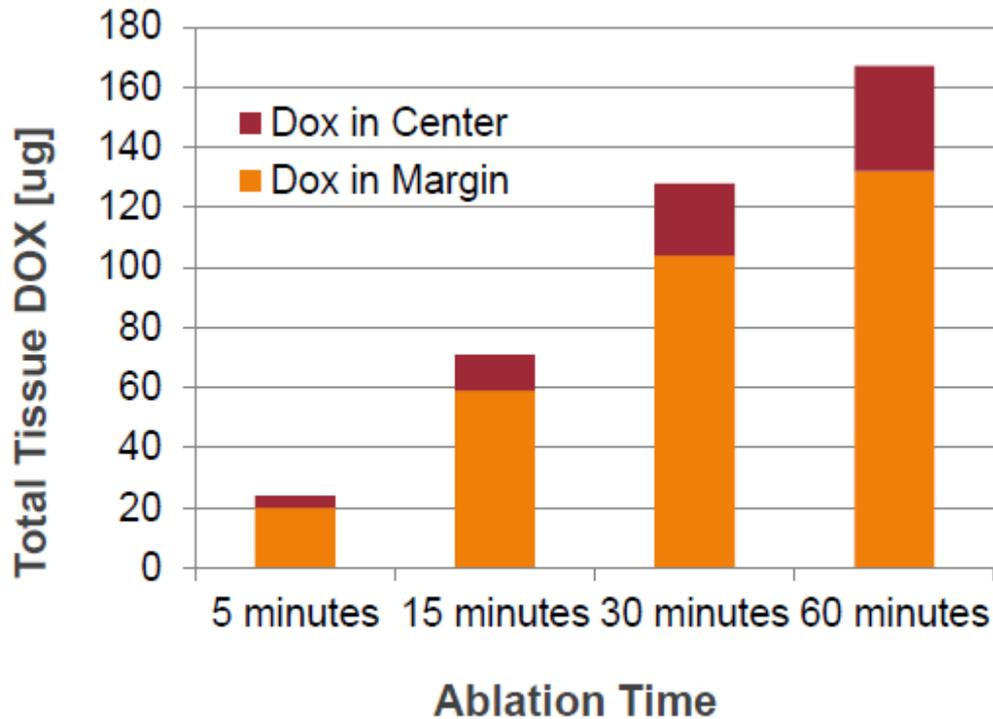
HR=0.639 (95% CI 0.419–0.974) P Value=0.037

Patients with Single HCC and RFA > 45 min: Baseline Characteristics (n = 285)

In HCC

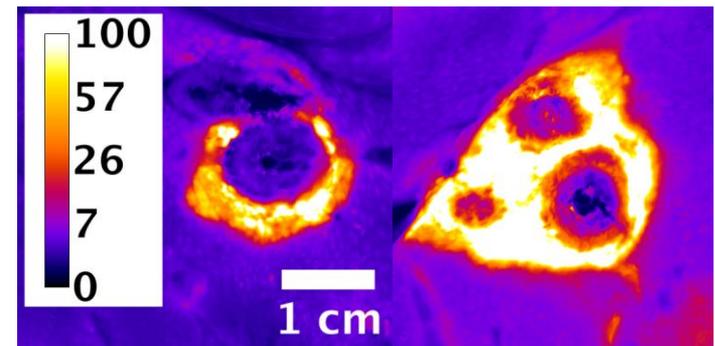
Parameter	RFA + LDLT (n = 138)	RFA (n = 147)	p-value
Male	99 (71.7%)	109 (74.1%)	NS
Female	39 (28.3%)	38 (25.9%)	
Age > 65	56 (40.6%)	53 (36.0%)	NS
Hepatitis B	89 (64.5%)	89 (60.5%)	NS
Hepatitis C	26 (18.8%)	33 (22.4%)	NS
Child class A	131 (94.9%)	140 (95.2%)	NS
Single tumor	138 (100.0%)	147 (100.0%)	NS
Max. size 3-5 cm	111 (80.4%)	122 (83.0%)	NS
Percutaneous route	123 (89.1%)	133 (90.5%)	NS

Experimental Animal Studies and Simulation Models Confirm the Key Role of Ablation Time



Prolonged heating achieves optimal doxorubicin tissue concentration

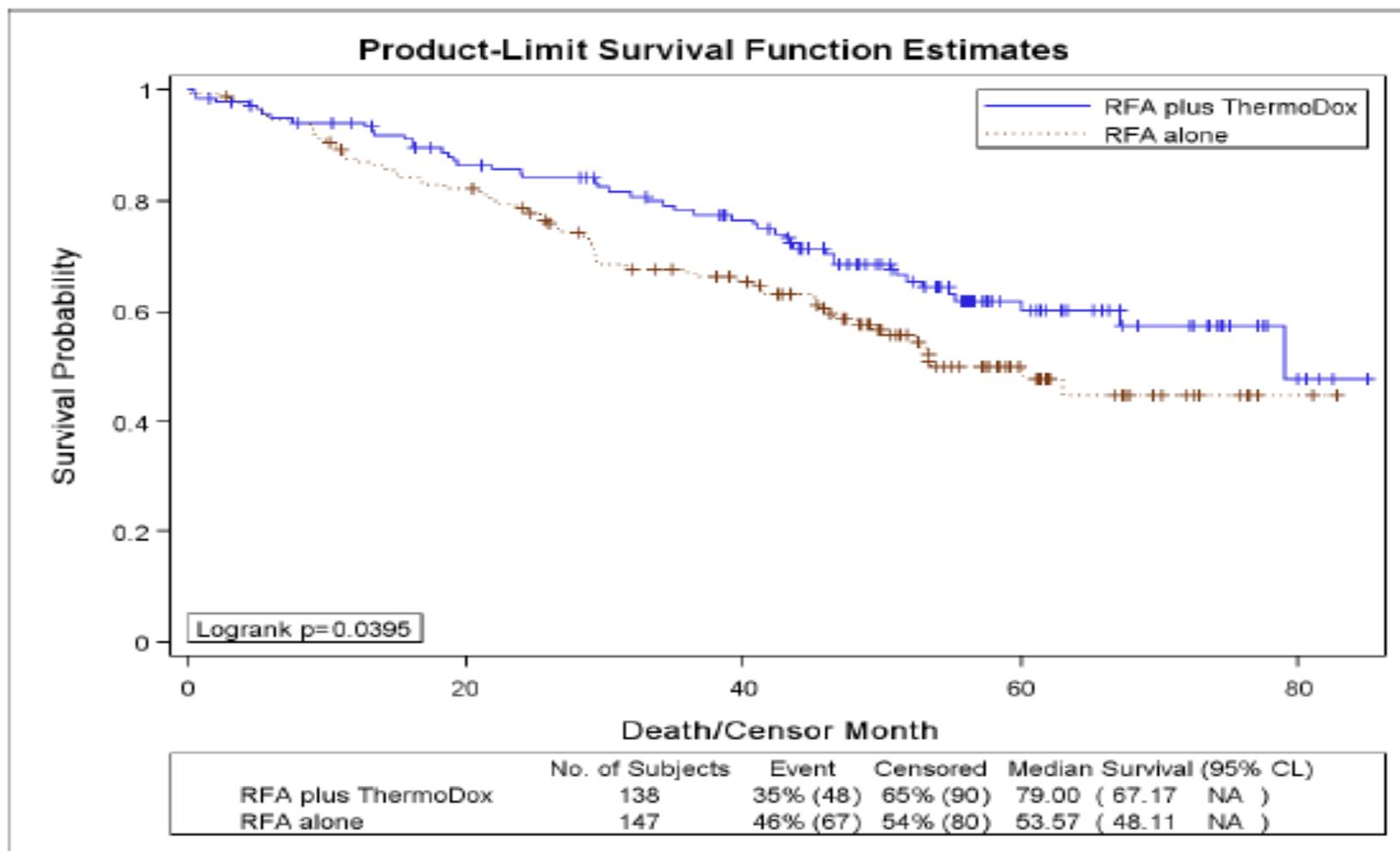
Fluorescence mapping of doxorubicin distribution in pigs treated with RFA plus ThermoDox



15 min

45 min

OS: 285 Pts with Single HCC and RFA > 45 min with and without ThermoDox (post-hoc analysis)



Multivariate Analysis of Prognostic Factors for Overall Survival in Pts with Single HCC (n = 446)

In HCC

Independent Variable [Reference Level (RL)]	Hazard Ratio	95% Confidence Interval	P-Value ¹
Treatment [RL: RFA Alone]	0.64	0.40 – 1.03	0.0668
RFA Dwell Time [RL: \geq 45 minutes]	1.02	0.62 – 1.69	0.9249
Treatment*Dwell Time Interaction [RFA Alone or \geq 45 minutes]	1.91	0.94 – 3.90	0.0749
Lesion Diameter [RL: 3-5 cm]	1.82	1.18 – 2.82	0.0071
Child-Pugh Score [RL: 5]			
6	1.40	0.93 – 2.12	0.1107
7+	3.55	2.05 – 6.15	< 0.0001
Age [RL: \geq 65]	1.07	0.72 – 1.57	0.7487
Region [RL: Taiwan/Korea]			
China/Hong Kong	1.23	0.76 – 1.98	0.3929
Rest of World	1.09	0.66 – 1.80	0.7264
Etiology [RL: Any Hepatitis B]	1.05	0.71 – 1.54	0.8174
RFA Device [RL: Covidien]	0.99	0.65 – 1.51	0.9751

The OPTIMA Study: A Phase III RCT of LTLD with Standardized RFA for the Treatment of HCC

A Phase III, Randomized, Double Blind, Dummy-Controlled Study of ThermoDox Using Standardized RFA for Single HCC 3-7 cm

PIs: R. Lencioni, R.T. Poon, M.H. Chen

Inclusion Criteria

- Single HCC 3-7 cm
- Child-Pugh A
- ECOG 0
- Candidate for RFA
- No prior treatment

Randomization

50 mg/m² ThermoDox

Dummy infusion

Primary Endpoint

- OS

Secondary Endpoints

- PFS

- Safety

- Others

n = 550

Lyso-Thermosensitive Liposomal Doxorubicin (LTLD): Conclusion

- **LTLD is the first product designed for image-guided drug delivery tested in a large multicenter phase III trial**
- **The HEAT study showed that LTLD is well-tolerated with no unexpected serious adverse events**
- **Post-hoc findings suggest that when target tissue is heated adequately (≥ 45 min), ThermoDox plus RFA increases overall survival**
 - **HR of 0.63 for OS in subgroup analysis ($p < 0.05$)**
 - **Treatment by ThermoDox independent prognostic factor at multivariate analysis**