Thermodox in HCC: Development Plan and Lessons Learned

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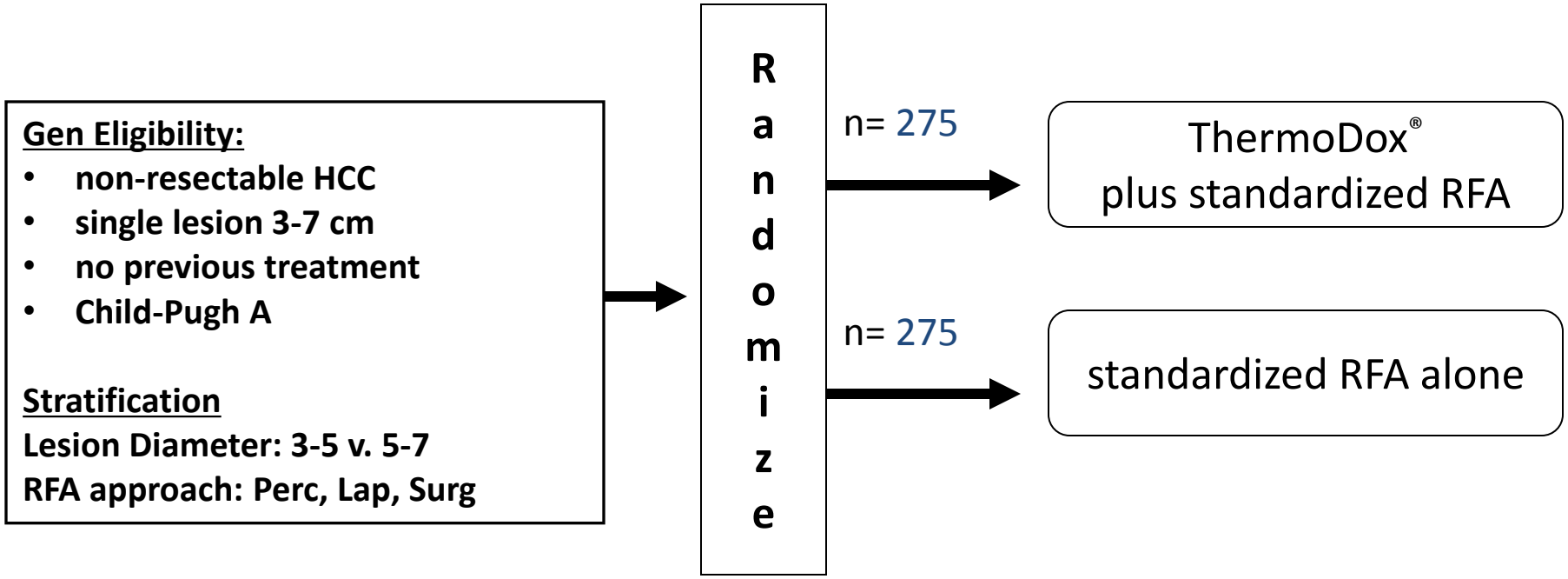
OPTIMA Phase 3 Design

Currently Being Initiated at 100 sites Throughout Asia, North America, and Europe



End Points

Primary: Overall Survival

Secondary: PFS, Safety

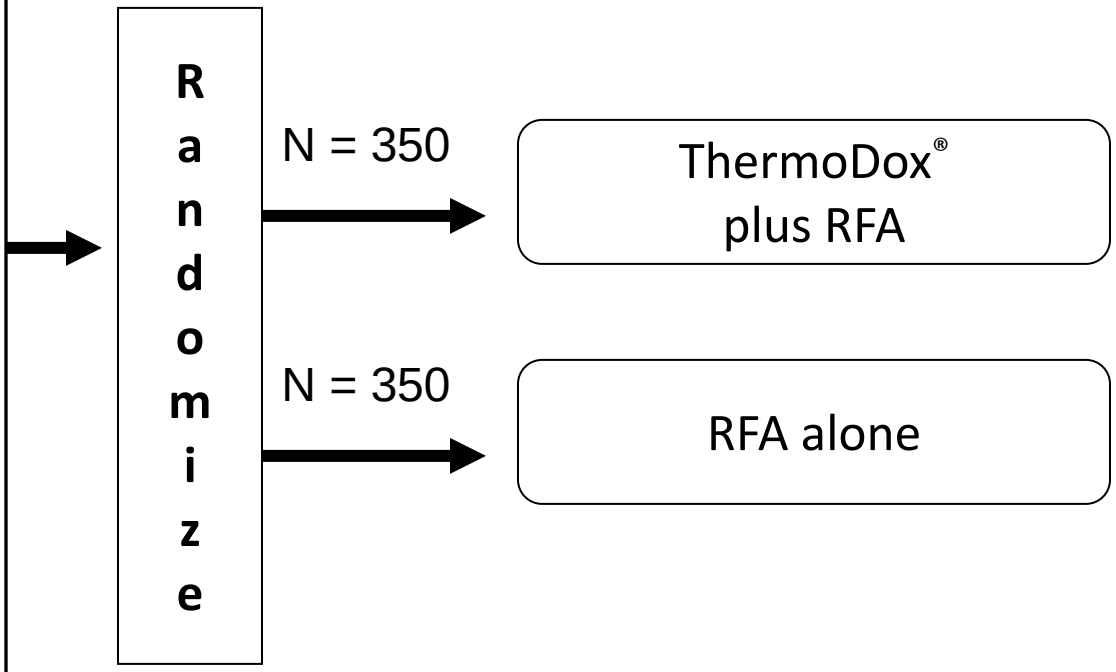
HEAT Study Design (n=701)

General Eligibility:

- Non-resectable HCC
- No more than 4 lesions
- At least 1 lesion ≥ 3cm and none > 7cm
- No previous treatment
- Child-Pugh A or B

Stratification:

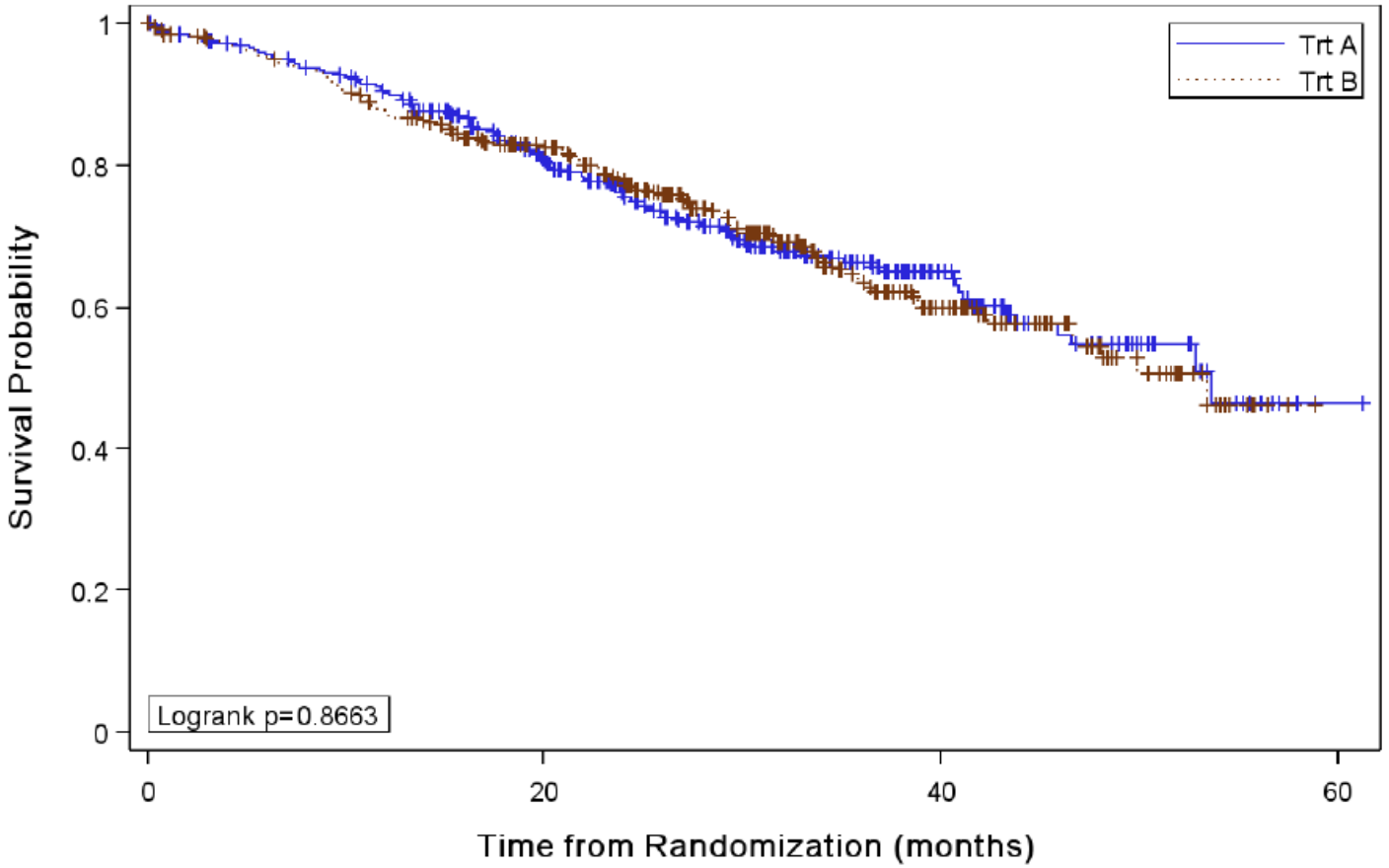
- Lesion size: 3-5 vs >5-7
- RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous



Endpoints

Primary: PFS (Progression Free Survival)
Secondary: OS (Overall Survival), TTLR (Time to Local Recurrence), Safety, PRO (Time to Definite Worsening)

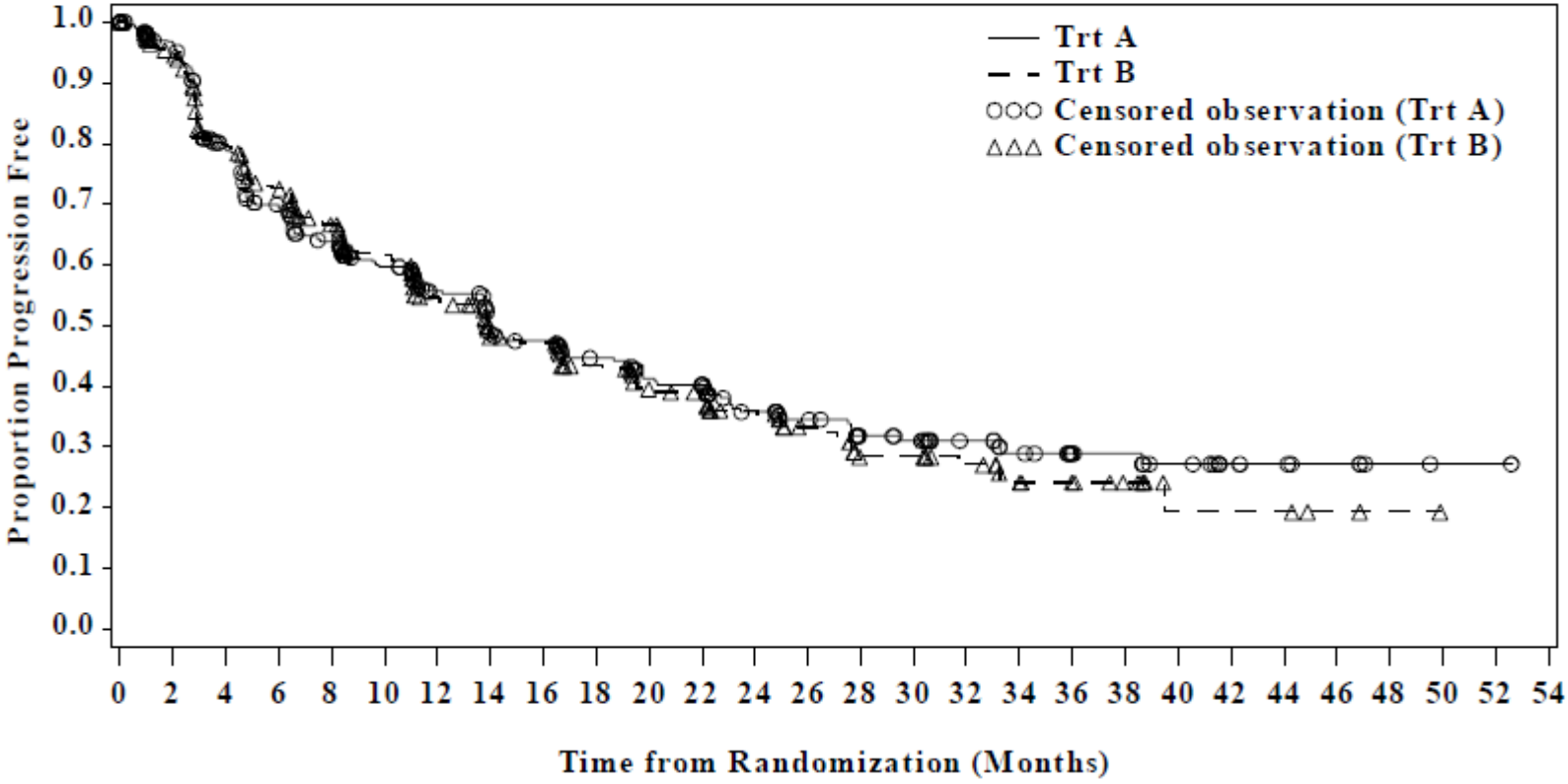
Overall Survival



Median Time to OS event RFA + TDox:	**53.66 mos.**
RFA Alone:	**53.40 mos.**
Hazard Ratio (Trt A/Trt B):	**1.011 (CI 0.761, 1.286)**

Overall Results: PFS

Figure 1.1
Kaplan-Meier: Cumulative Probability of Progression-Free Survival (PFS) by Treatment Group (IRRC)
Intent-to-Treat Population



When target tissue heated adequately (≥ 45 minutes), ThermoDox & RFA increases overall survival

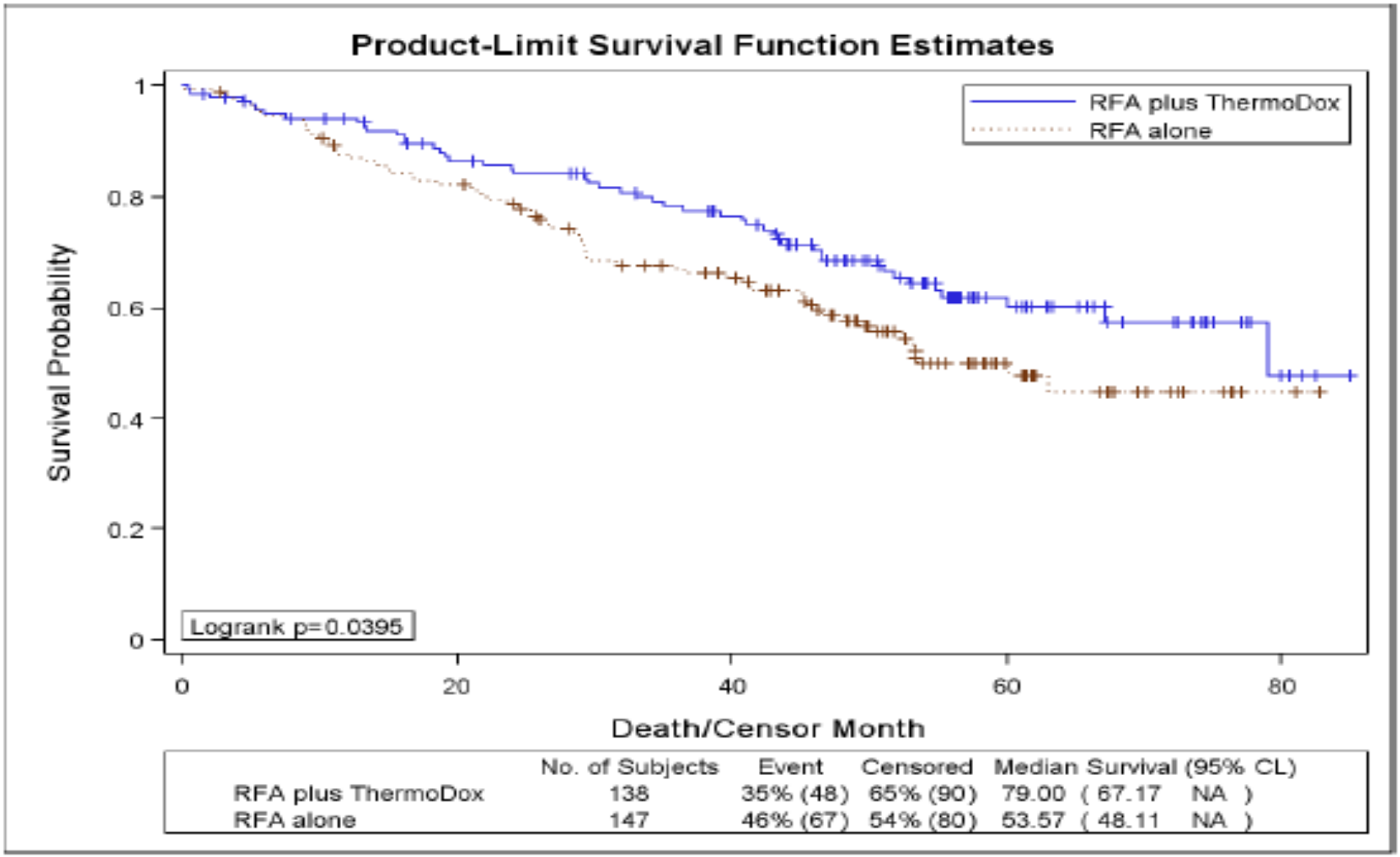
- Consistent with ThermoDox's heat-based mechanism of action
- All three preclinical studies found that doxorubicin tissue concentration increased with duration of heating
- HEAT Study subgroup analysis shows HR of 0.63 (95% CI: 0.41 to 0.96) for OS ($p < .05$)
- Clinical characteristics in the subgroup were balanced at baseline
- Multivariate analysis found a similar HR of 0.64 for overall survival

The Importance of Dwell Time

Lesion Size (Solitary)	OS (mos)			
	< 45 mins	≥ 45 mins	< 45 mins + LTLD	≥ 45 mins + LTLD
3-5 cm	57.9	63.0	55.0	79.0
5-7 cm	31.3	45.5	25.3	NE

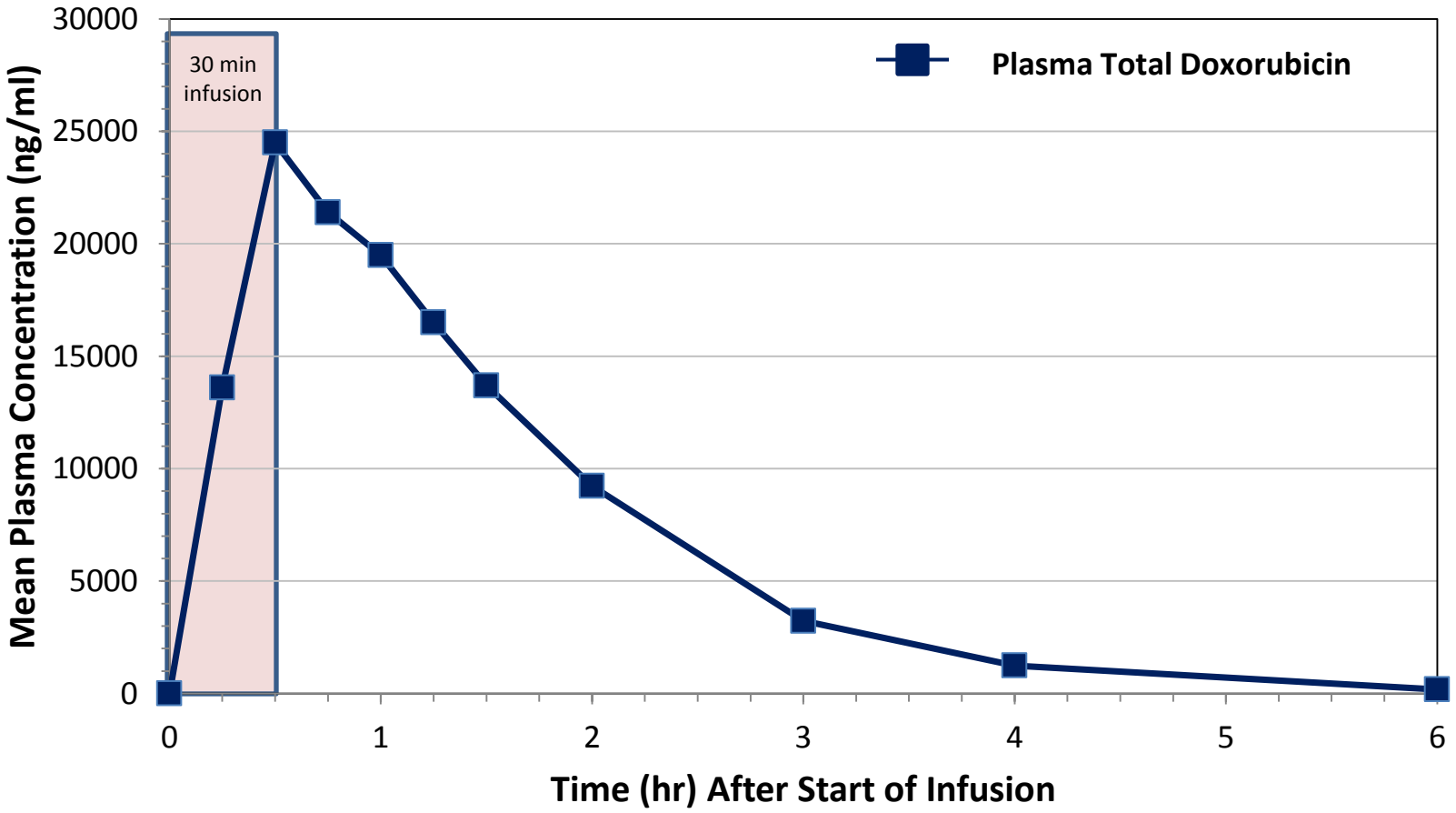
The importance of thorough RFA (> 45 mins) is also demonstrated without LTLD

Recent HEAT Data Sweep demonstrates improvement of over 24 months in median survival

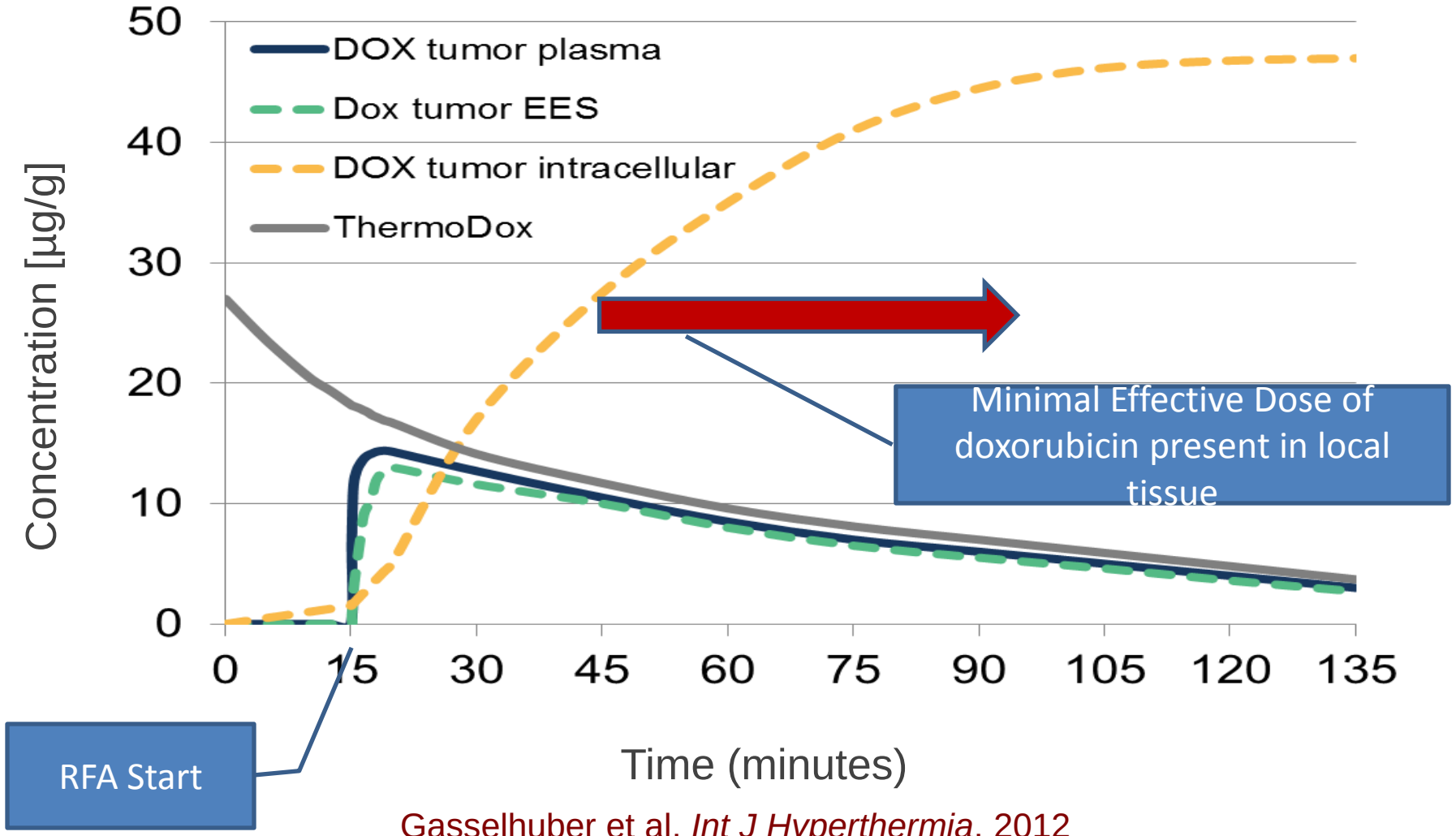


ThermoDox Human PK

Protocol 104-03-101: + Liver RFA @ 50 mg/m²
Mean Plasma Concentrations (n=6)



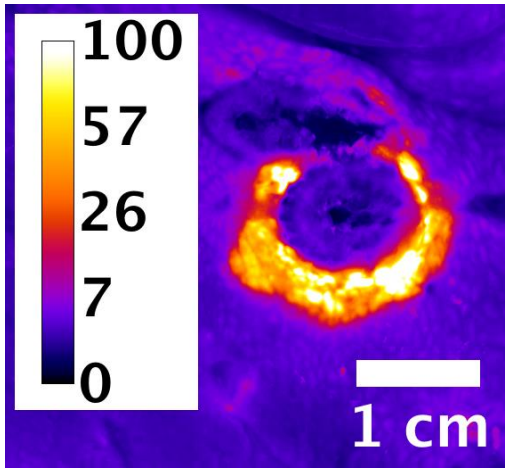
Impact of Mild Hyperthermia on Tissue Deposition



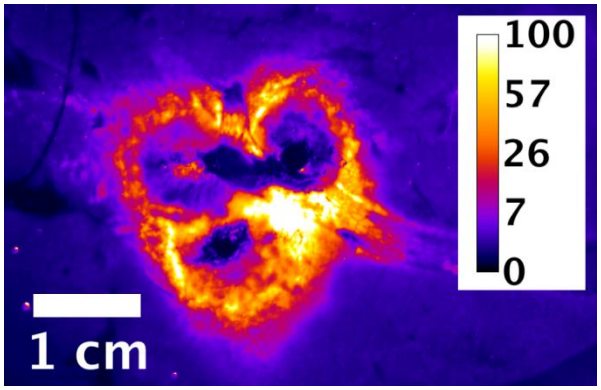
Gasselhuber et al, *Int J Hyperthermia*, 2012

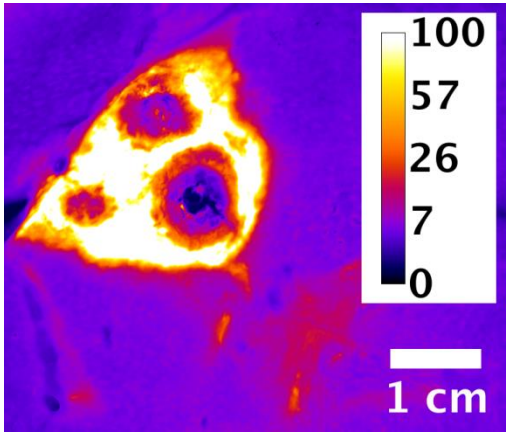
Two Dimensional Fluorescence Mapping of Doxorubicin Distribution in pigs treated with ThermoDox

15 minute

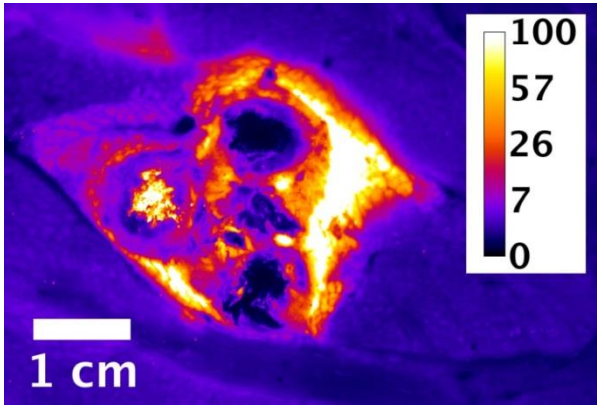


45 minute





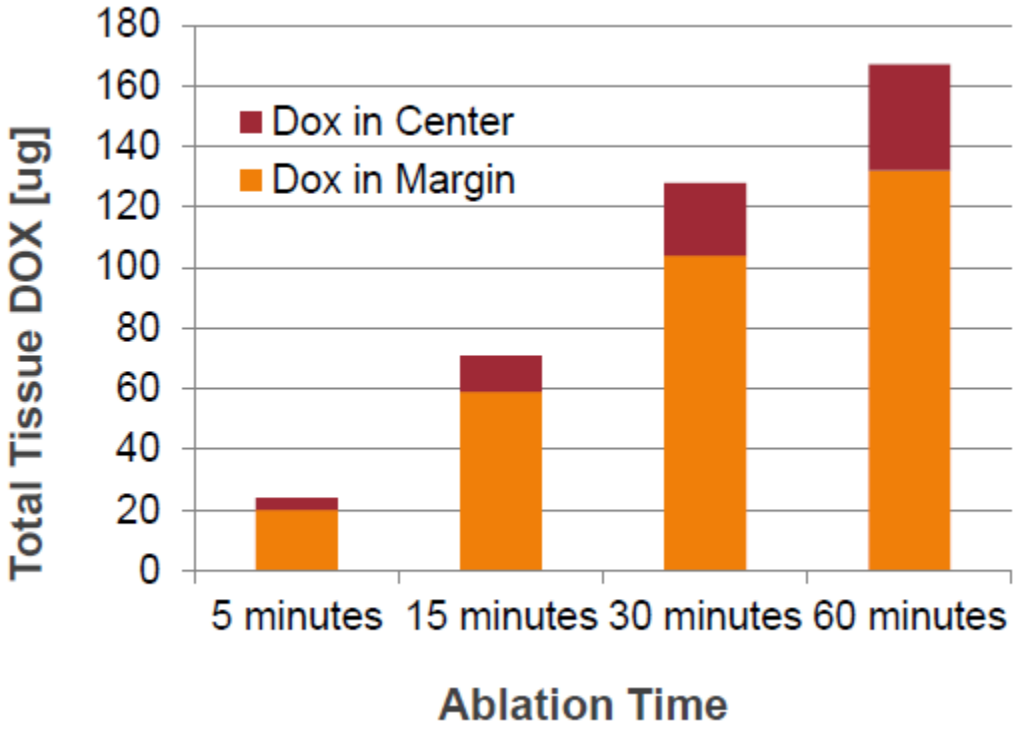
90 minute



Post Hoc Analysis

- Ablation time or strategy was not mandated in HEAT Study
  - High degree of variability exists with ablation cycles (burns) and treatment time by lesion size

- Recent simulation studies show that prolonged heating is required in order to achieve optimal tissue concentrations of doxorubicin



HEAT and Doxorubicin Concentration

Table 1: Computational Model of Doxorubicin Concentration in Liver Tumor Tissue following ThermoDox and Mild Hyperthermia

Duration of Heating	Doxorubicin Tumor Concentration
15 minutes	~ 16 µg/g
30 minutes	~ 28 µg/g
45 minutes	~ 35 µg/g
60 minutes	~ 40 µg/g
120 minutes	~ 47 µg/g

Subgroup Population is Balanced

Table 4: Baseline Clinical Characteristics in the 285-patient HEAT Study Subgroup with a Solitary Lesion and ≥ 45 minutes RFA Dwell Time

Characteristic	RFA Alone (n = 147)		RFA + LTLD (n = 138)	
	No. of Patients	%	No. of Patients	%
Age (years)				
18-64	93	63.3	80	58.0
65+	53	36.0	56	40.6
Missing	1	0.7	2	1.4
Sex				
Male	109	74.1	99	71.7
Female	38	25.9	39	28.3
Race				
Asian	142	96.6	132	95.7
Chinese	66	44.9	53	38.4
Korean	36	24.5	36	26.1
Taiwanese	20	13.6	21	15.2
Japanese	9	6.1	3	2.2
Other Asian	11	7.5	19	13.8
Caucasian	5	3.4	6	4.3
Black	0	0.0	0	0.0
Child-Pugh Class				
A	140	95.2	131	94.9
B	7	4.8	6	4.3
Missing	0	0.0	1	0.7

Subgroup Population is Balanced (cont)

HCC Etiology				
Hepatitis B	89	60.5	89	64.5
Cirrhosis	72	49.0	71	51.4
Hepatitis C	33	22.4	26	18.8
Other	14	9.5	17	12.3
Maximum Lesion Diameter				
3-5cm	122	83.0	111	80.4
>5-7cm	25	17.0	27	19.6
RFA Approach				
Percutaneous	133	90.5	123	89.1
Open Surgery	11	7.5	11	8.0
Laparoscopic	3	2.0	4	2.9
RFA Device				
Angiodynamics	43	29.2	42	30.4
Boston Scientific	22	15.0	19	13.8
Covidien	82	55.8	77	55.8

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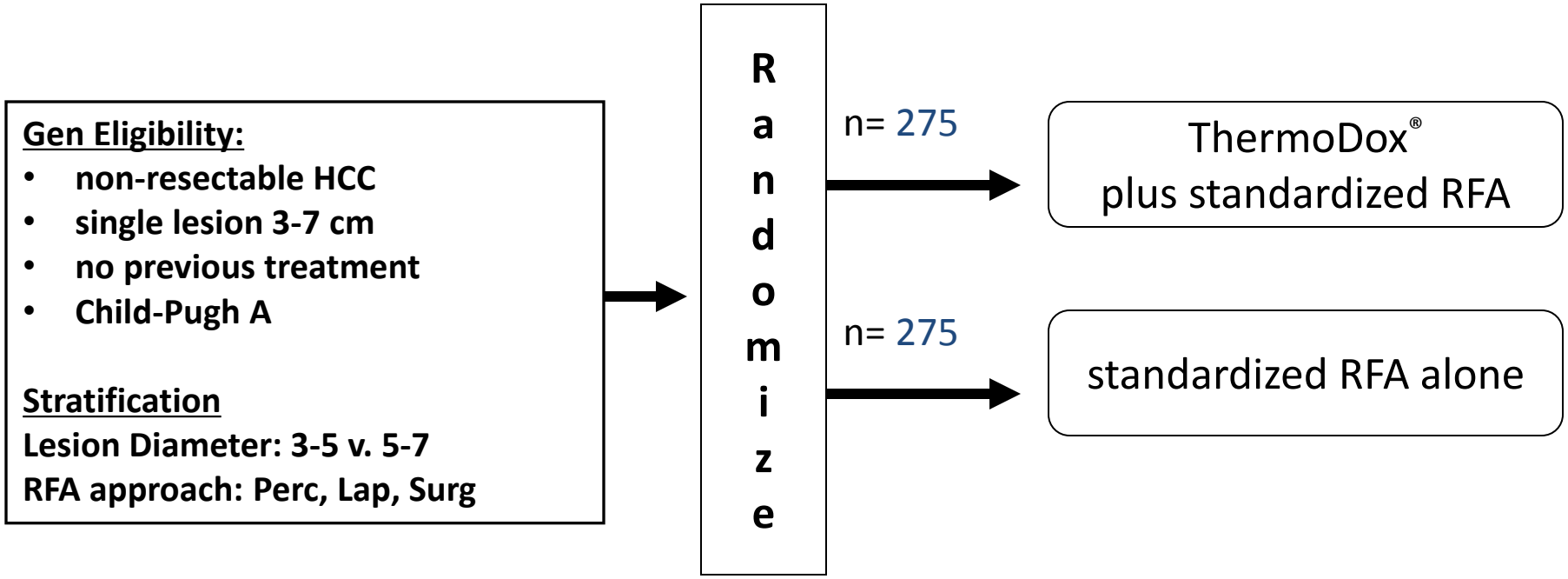

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