

**RFA Duration per Tumor Volume
May Correlate With Overall
Survival in Patients Treated with
RFA plus Lyso Thermosensitive
Liposomal Doxorubicin (LTLD)**

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Disclosures

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- Researcher, W. L. Gore & Associates, Inc
- Researcher, Cook Group Incorporated
- Patent agreement, VitalDyne, Inc
- Intellectual property, Koninklijke Philips NV
- Intellectual property, BTG International Ltd

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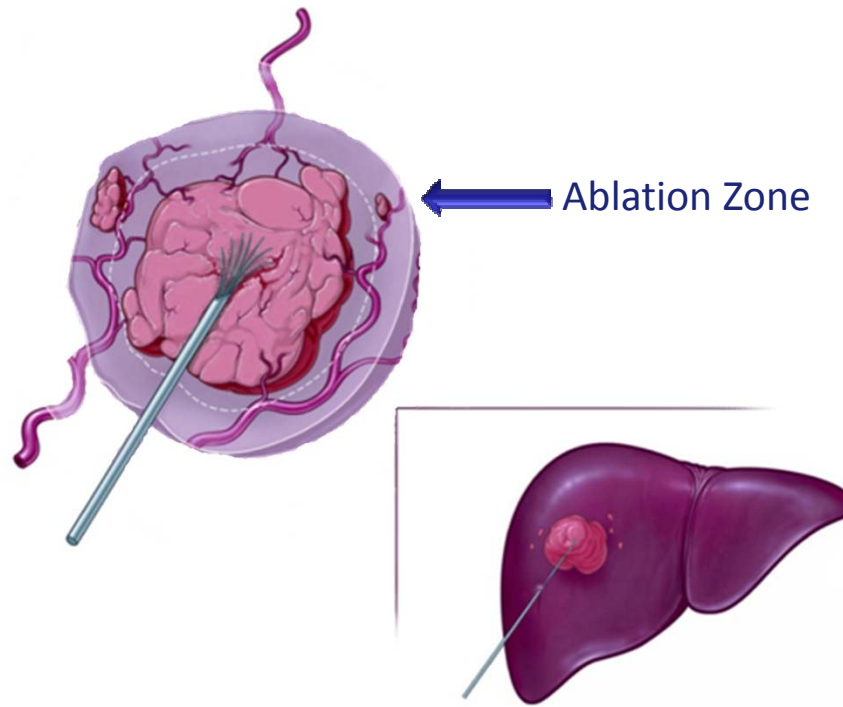
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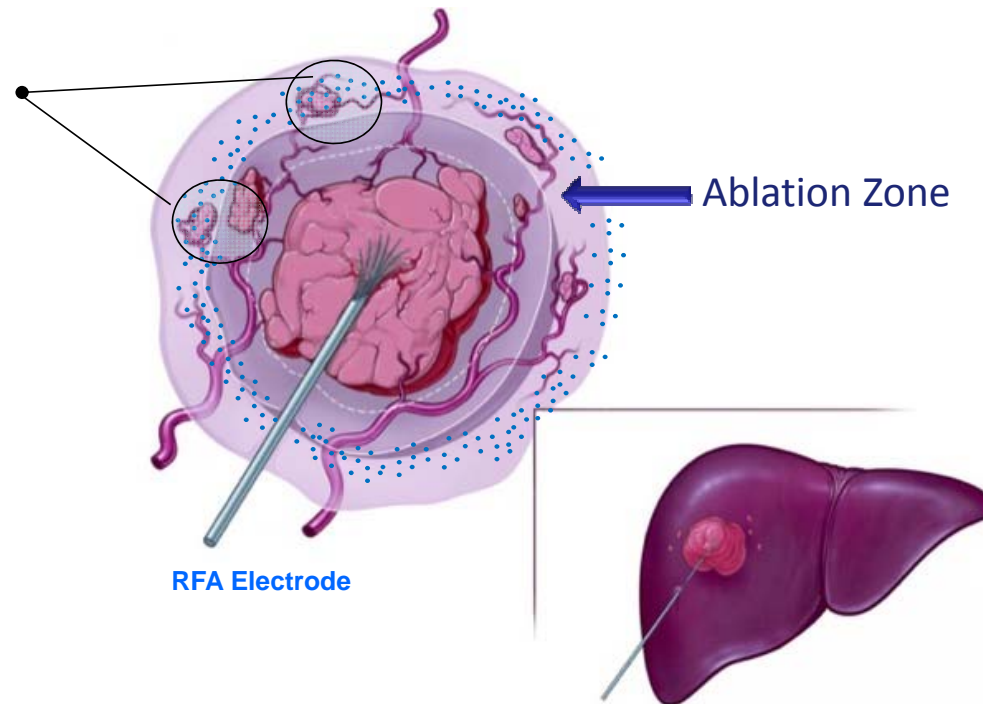


Background: RF Ablation of Liver Tumor



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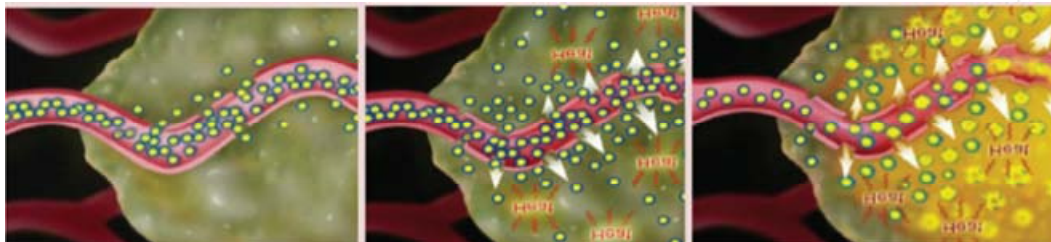
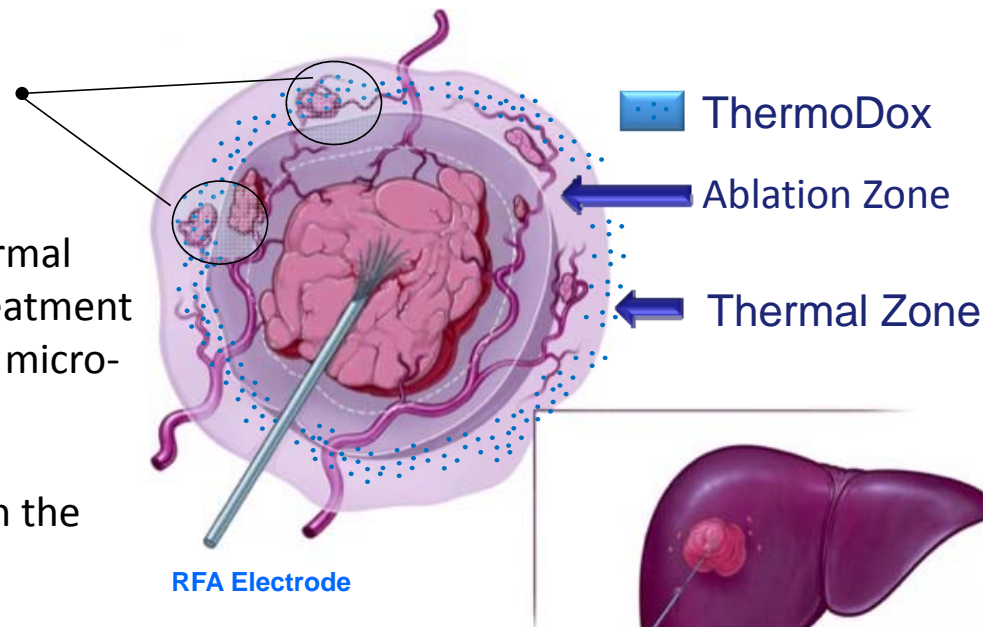
- RFA misses micro-metastases outside ablation zone



Background: RFA+LTLD (ThermoDox)

Expand the treatment zone to address RFA limitations

- RFA misses micro-metastases outside ablation zone
- Ablation releases doxorubicin in “Thermal Zone” expanding treatment area and destroying micro-metastases
- Drug concentrates in the “Thermal Zone”



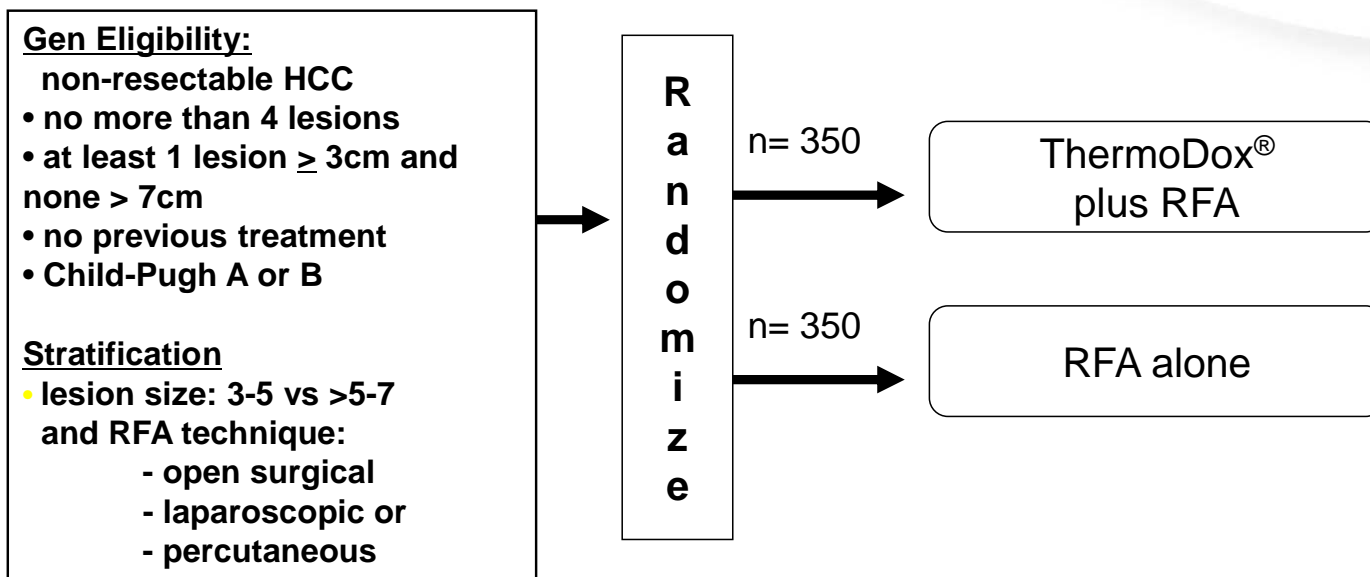
Phase III HEAT Study Design

HEAT Study

Hepatocellular Carcinoma Study
of RFA and ThermoDox[®]

Celsion
Corporation

**Started
in 2009**



End Points

Primary: PFS (Progression Free Survival)

Secondary: OS (Overall Survival), TTLR (time to local recurrence), Safety, PRO (Time to definite worsening).



National Institutes
of Health

Courtesy: Celsion

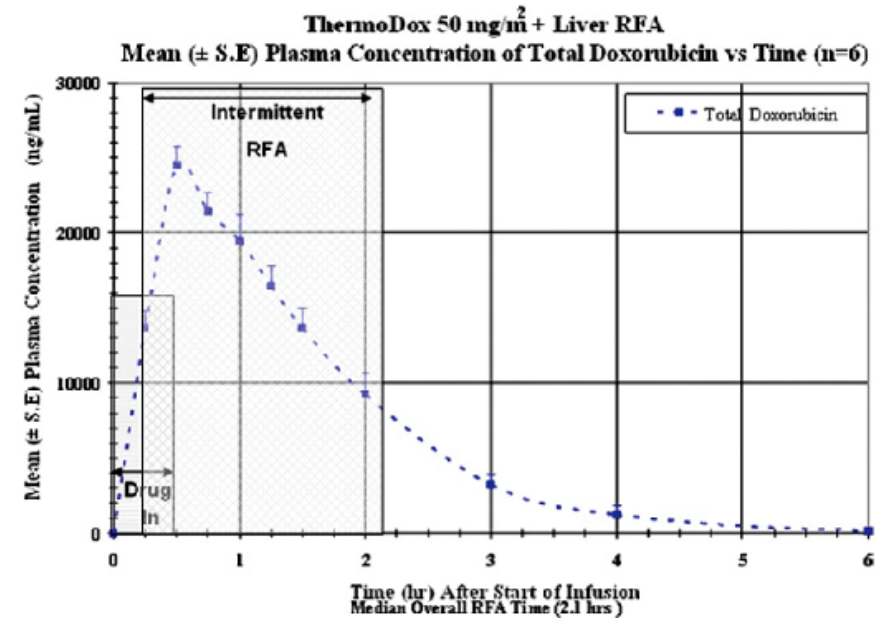
Results of HEAT Study

- **No statistical significant difference** between the treatment groups when PFS or OS considered
- 2014 Sub-group analysis report: Thermodox patients treated longer than 45 min dwell time benefited compared with RFA-only patients. **BUT**
 - **Dwell time includes repositioning of the needle, when RFA is off.**



Methods

- Details of our study:
 - Only single lesion patients were included (n=437)
 - One lesion can be under the peak of PK curve to maximize AUC = drug deposited
 - Two radiologists segmented volumes using CT images. Average was used.
 - Cox proportional hazard model used and proportionality was tested.
 - R Studio for statistical analysis



Wood et.al. 2012

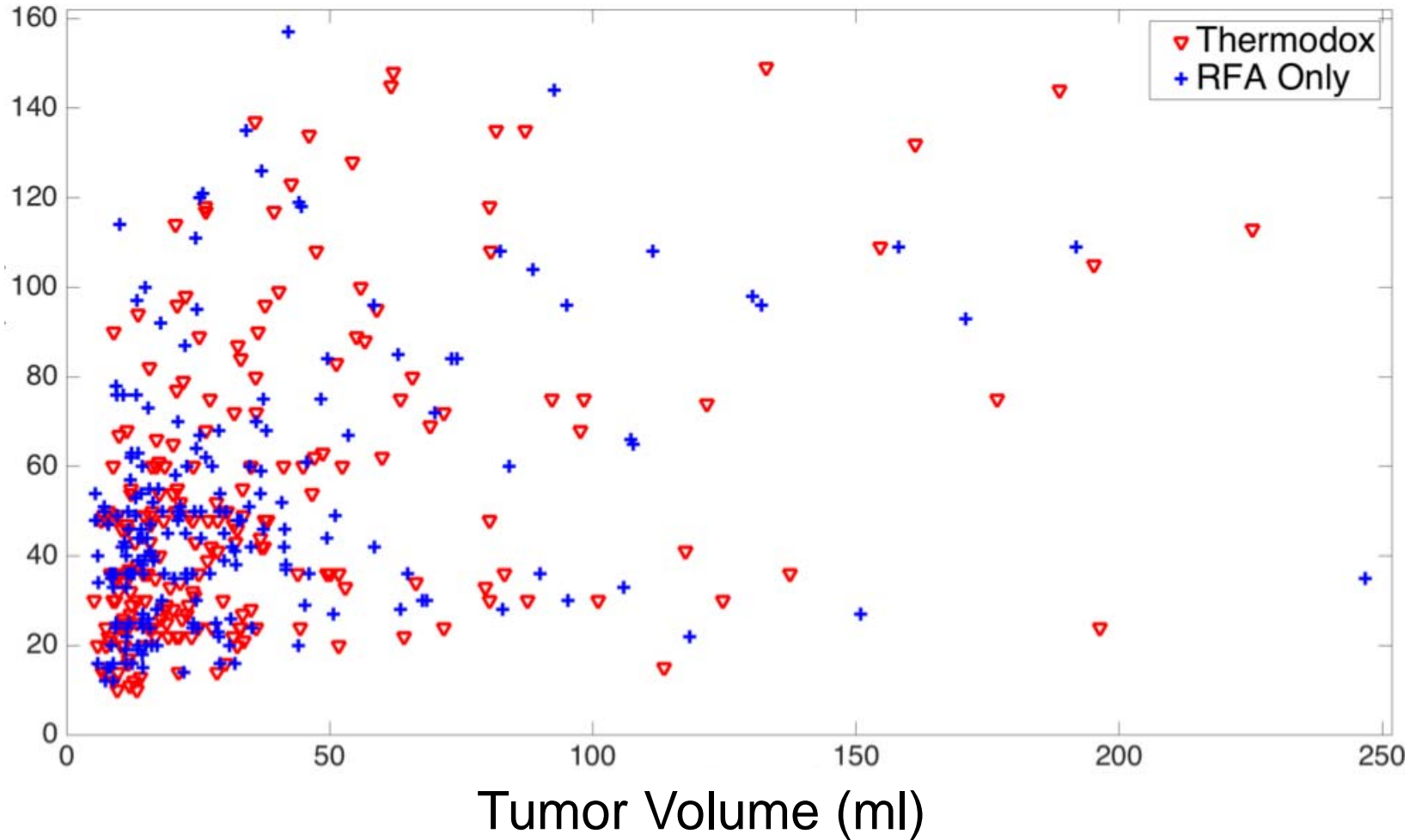
This is a post-hoc study!



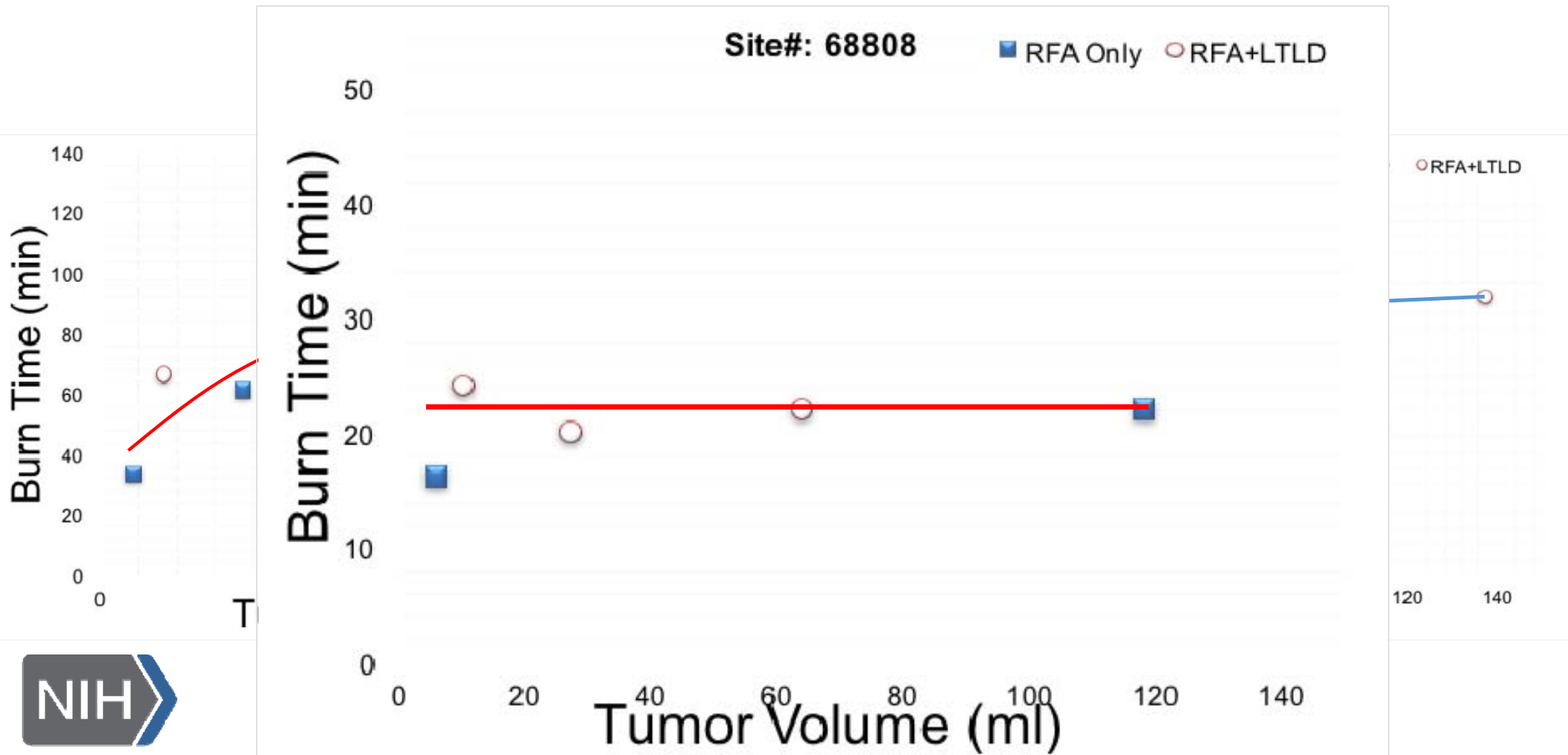
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Burn time vs. Tumor Volume of the HEAT Phase III Clinical Trial Patients

Burn Time
(min)

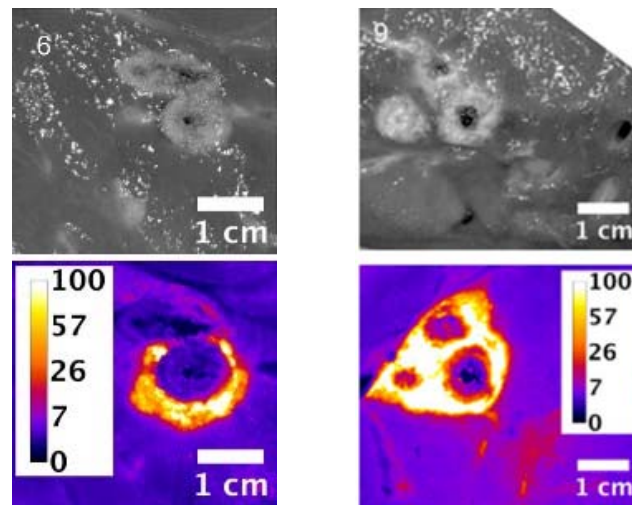


Individual Sites have Different Practice Patterns



Burn Time Per Tumor Volume for RFA

- ThermoDox deposition margin is directly affected by burn time



Burn Time:

15 min

45 min

Swenson et.al. 2015

- We introduce a **novel parameter** that represents burn time and tumor volume and better than the conventional parameters:

Burn Time per Tumor Volume (BTPTV)



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Cox Proportional Hazard Model

Input Covariates:

- Categorical (eg. RFA-only / 0 vs. RFA+ThermoDox / 1) *or*
- Continuous (eg. BTPTV)

Simple Cox Model

- Survival Duration in Months (Continuous)
- Censor information 0 or 1 (Categorical)

Output:

How the hazard ratio changes in response to unit increase in input covariate.

Input Covariates:

- Confounding (Treatment Groups + BTPTV) *or*
- Effect Modifier (Treatment Groups x BTPTV)

Multivariate Cox Model

- Survival Duration in Months (Continuous)
- Censor information 0 or 1 (Categorical)

Output:

BTPTV is a:

- Confounding
- Effect Modifier
- Neither



Cox Analysis Results

Covariates	Output	p-Val	Hazard Ratio	CI
Treatment Groups	Treatment Groups	0.445	0.895	0.674-1.189
Effect Modification (Treatment Groups (TG) vs BTPTV)	TG*BTPTV	<u>0.038</u>	<u>0.85</u>	0.728-0.991

n= 437, Events=191

- We confirmed the previous work, no statistical difference
- BTPTV is an **effect modifier** for the treatment groups: Depending on the group (RFA-only vs. RFA+ThermoDox) BTPTV improves survival
- BTPTV is **not confounding** (tested)
- Burn time per **tumor diameter** is not statistically significant

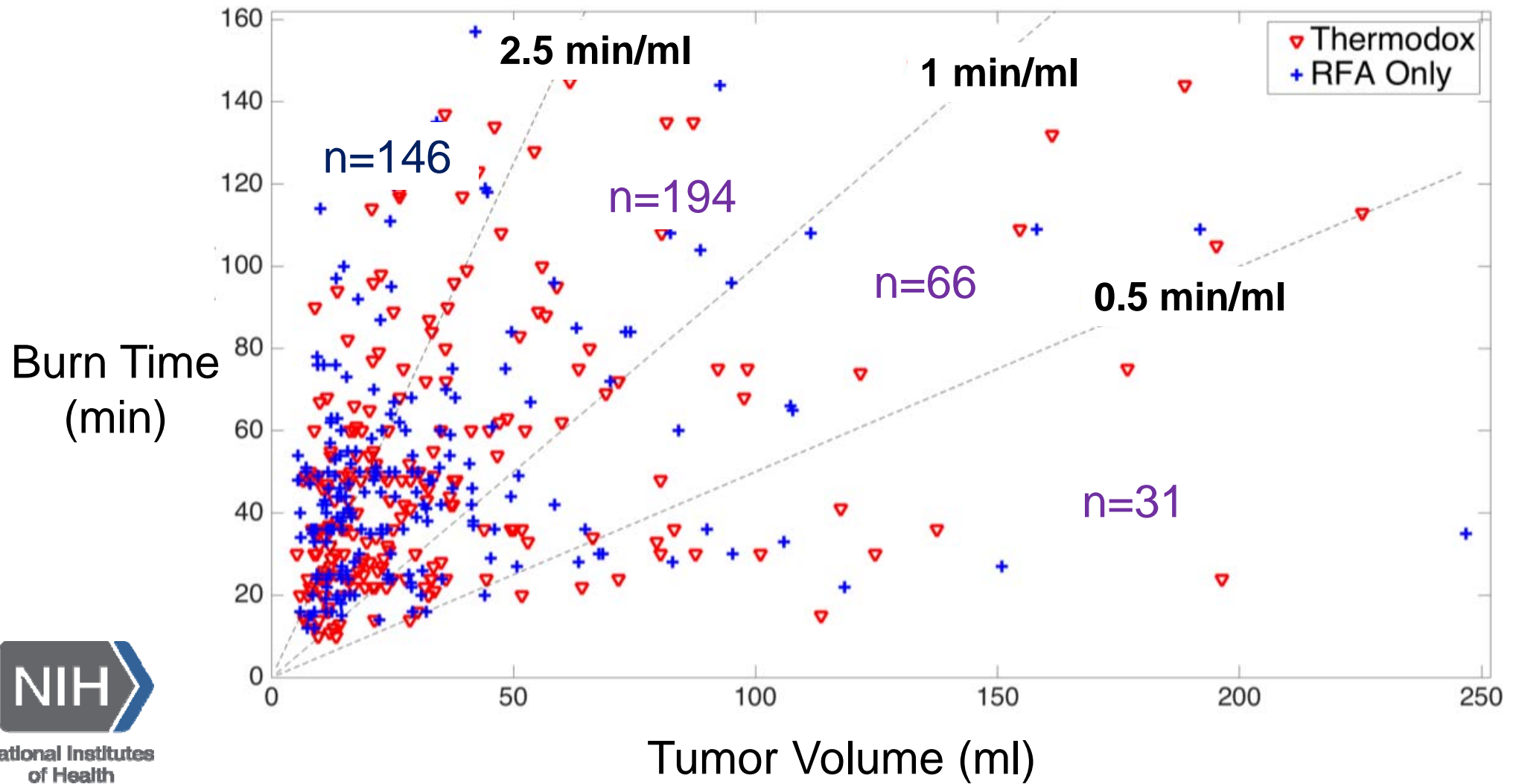
Cox Analysis on Individual Treatment Groups

Input Covariate: **BTPTV**

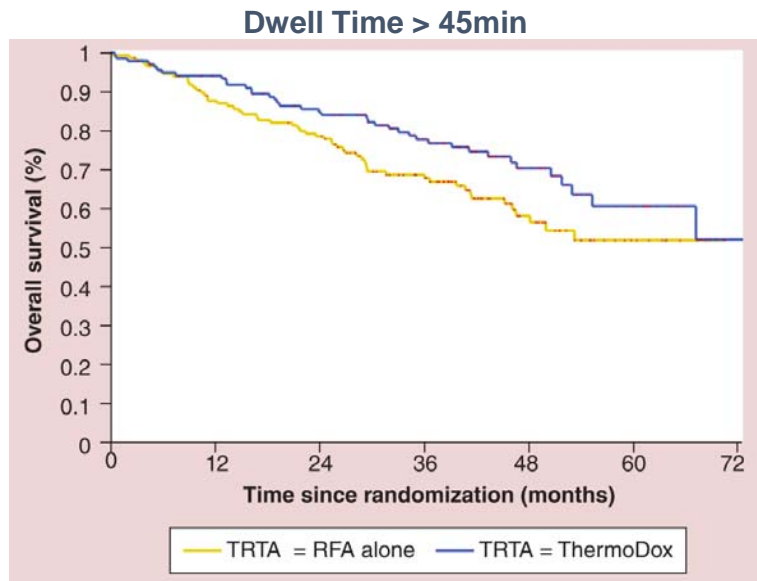
Groups	p-Val	Hazard Ratio	CI	# of Patients	Events (Deats)	R ²
RFA+ThermoDox	<u>0.017</u>	<u>0.836</u>	0.722-0.968	227	95	0.033
RFA-only	0.590	0.987	0.940-1.036	210	96	0.002

- Overall Survival of RFA+LTLD patients improved 20% from each unit increase of BTPTV
- BTPTV increase did not affect RFA-only patient survival
- PFS was not affected

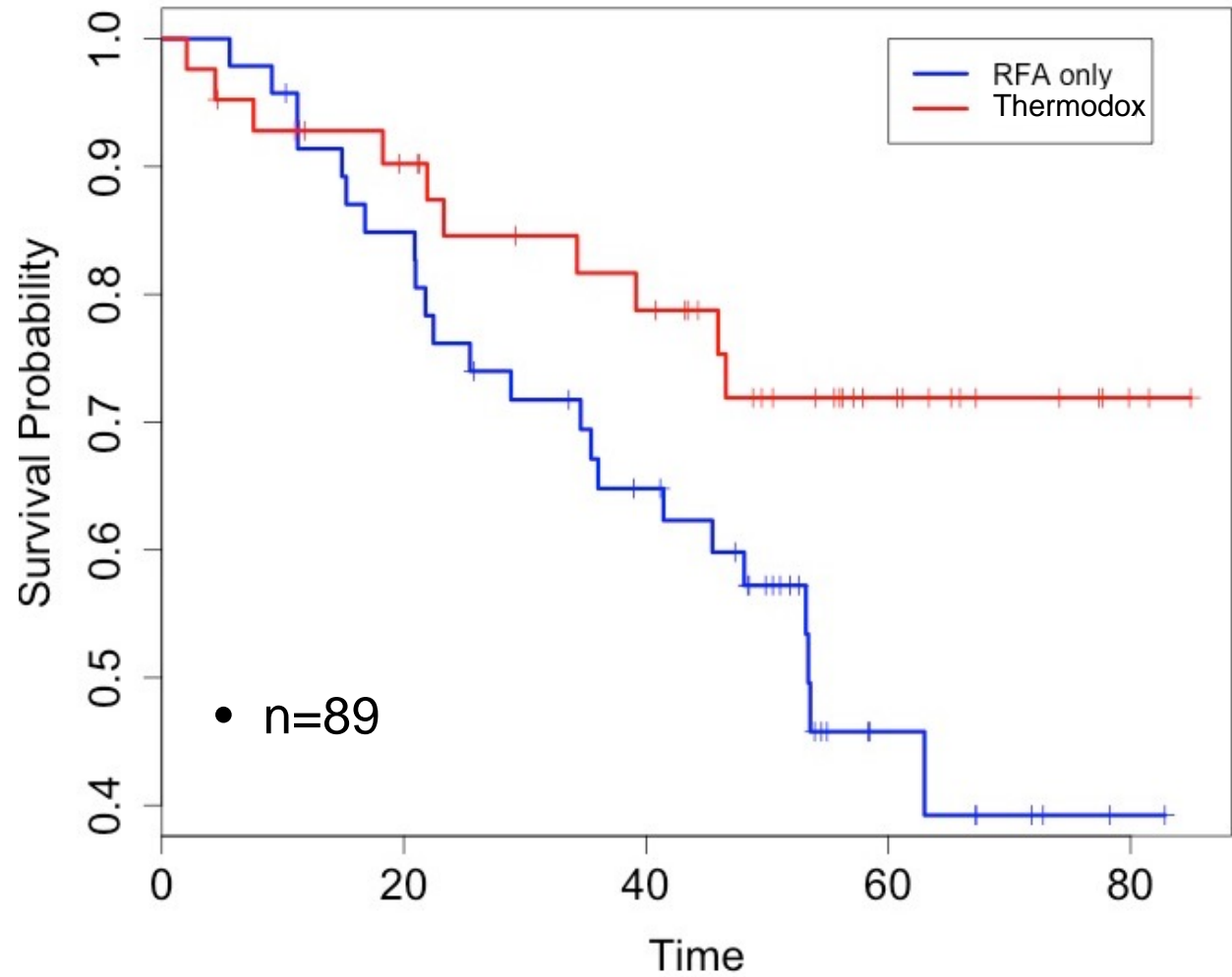
Different BTPTV Regions and Number of Patients



Kaplan Meier for BTPTV >3.41min/ml



Lencioni et.al. 2016



Conclusion

- **This is a post-hoc study**
- **Burn time and tumor size are both critical for Thermodox**
- **RFA practice patterns can be identified per location by phenotyping using BTPTV**
- **Device + Drug combinations are complex, studies need to be designed mechanistically**
- **New phase III study (OPTIMA), uses longer than 45 min burn time**



THANK YOU!