Thermo-sensitive Drug Assisted Ablation

Asian Conference on Tumor Ablation (ACTA 2016)

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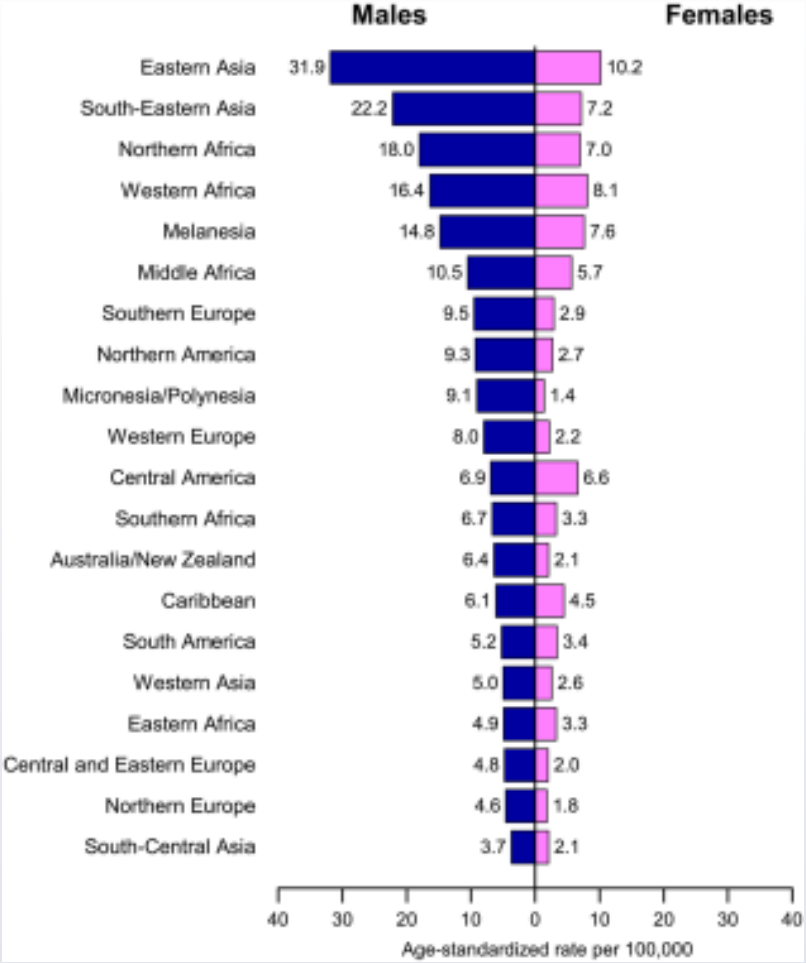
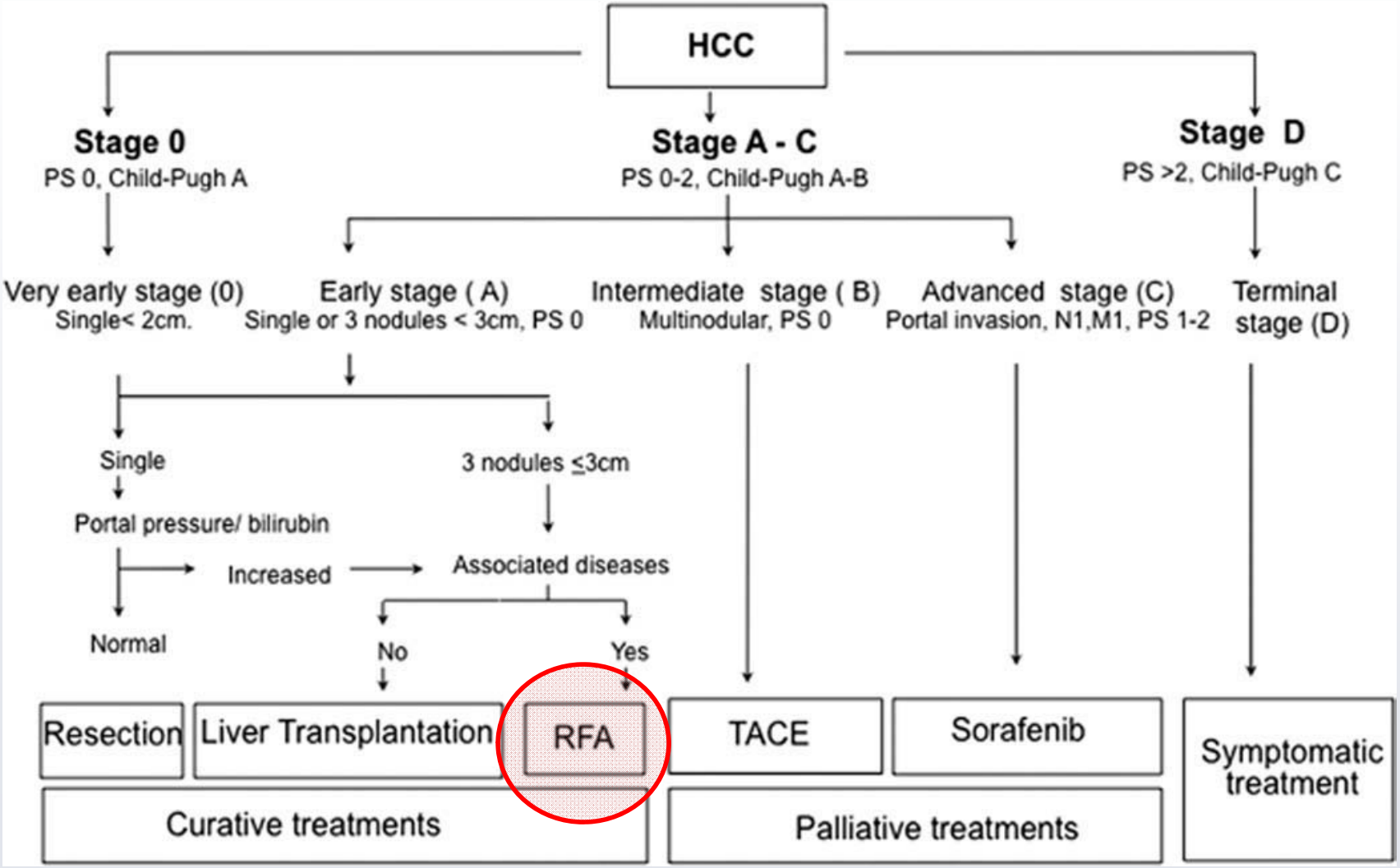
Global Liver Cancer Statistics, 2012



- 782,500 new cases and 745,500 deaths in 2012
- In men second leading cause of death worldwide
- China accounts for 50% total cases and deaths
- Rates are increasing in Oceania, Western Europe, Northern America due to increase in HCV & obesity
- Rates decreasing in China and Japan due to decrease in HCV and HBV

CA: A Cancer Journal for Clinicians
Volume 65, Issue 2, pages 87-108, 4 FEB 2015 DOI: 10.3322/caac.21262
http://onlinelibrary.wiley.com/doi/10.3322/caac.21262/full#caac21262-fig-0009

Barcelona Clinic Liver Cancer Staging System



RFA in Hepatocellular Carcinoma

- Standard Liver Cancer Staging Systems have recommended RFA for patients with early stage HCC

- However studies have shown that RFA can be safely used in early to intermediate sized tumors with comparable outcome to surgery (*Kudo et al, 2010; Hung et al, 2011; Hocquelet et al, 2015)*

RFA in Intermediate Size HCC

- HCC > 3cm are difficult to cure
  - Difficult to obtain adequate margin around tumor
- Post RFA recurrence rate high
  - Greater than 40%
  - Large lesions cannot be treated within a single ablation zone
  - Viable tumor cells may be left in margins or clefts of ablation zones
- Multi-modality approach may be beneficial

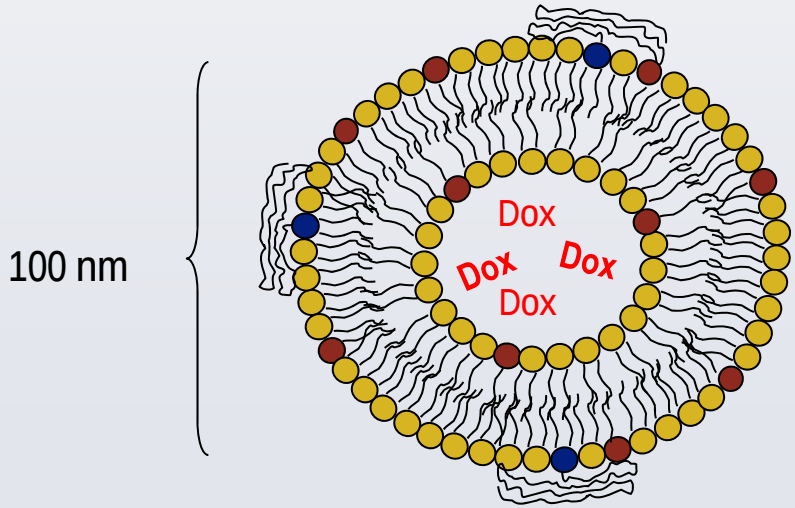
Radiofrequency ablation-based combination therapies

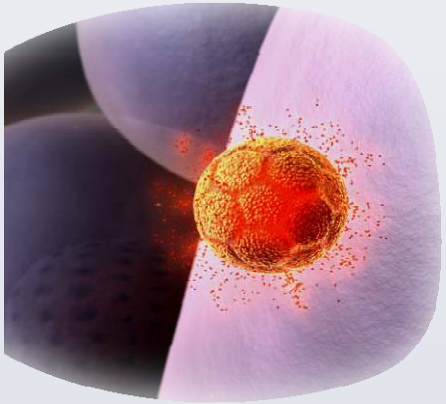
- Surgery for resectable tumors and for unresectable tumors (efficacy additive)
  - RFA + partial hepatectomy
- Precede RFA with local treatment to downsize tumor (efficacy additive)
  - TACE + RFA
- Follow RFA with systemic therapy to eradicate residual tumor (efficacy additive)
  - RFA + Interferon
  - RFA + Sorafenib (or new molecular targeted agents)
  - RFA + Vitamin analogue
- Simultaneous RFA and heat-enhaced, organ-specific chemotherapy (efficacy synergistic)
  - RFA + Lyso-thermosensitive liposomal doxorubicin

Poon RT, et al. Future Oncol. 2011 Aug;7(8):937-45.

ThermoDox Product Design Principles

- Near complete encapsulation of Doxorubicin HCl
- Release of the encapsulated Doxorubicin with mild thermal warming (> 39.5^{o}C)
- Ability to provide adequate systemic circulation to allow Mononuclear Phagocytic System (MPS) and Enhanced Permeation and Retention (EPR) to concentrate at tumor target
- Heat inducing medical devices to warm the target tumor - initiating a rapid drug release in the targeted tumor vasculature

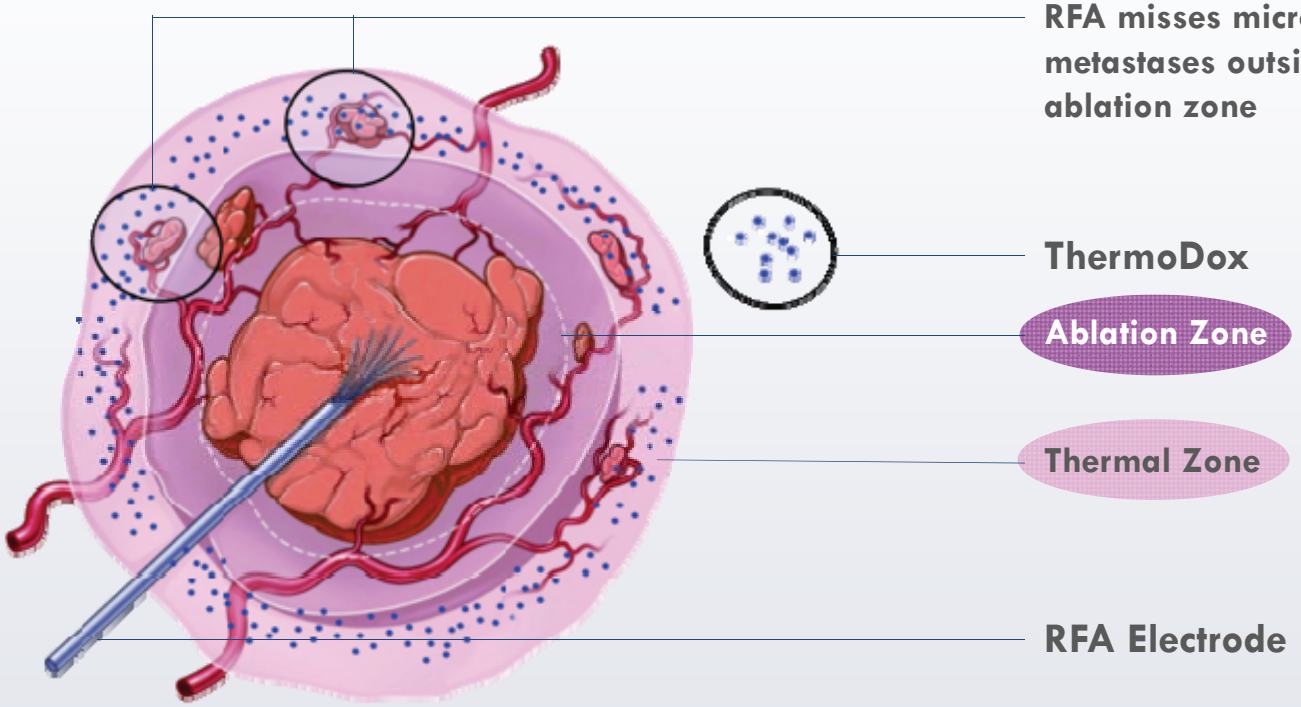




ThermoDox + RF Liver Ablation

Expanding the Treatment Zone Addresses RFA Limitations

- ThermoDox infused IV ~15 minutes prior to sRFA
- RFA ablates tumor and creates a "Thermal Zone" in margin surrounding the tumor
- Doxorubicin is released in the "Thermal Zone" expanding treatment area and killing the metastases outside the ablation zone



A Global Phase 3 Multi-Center Trial in HCC : HEAT Trial

RFA + ThermoDox for HCC

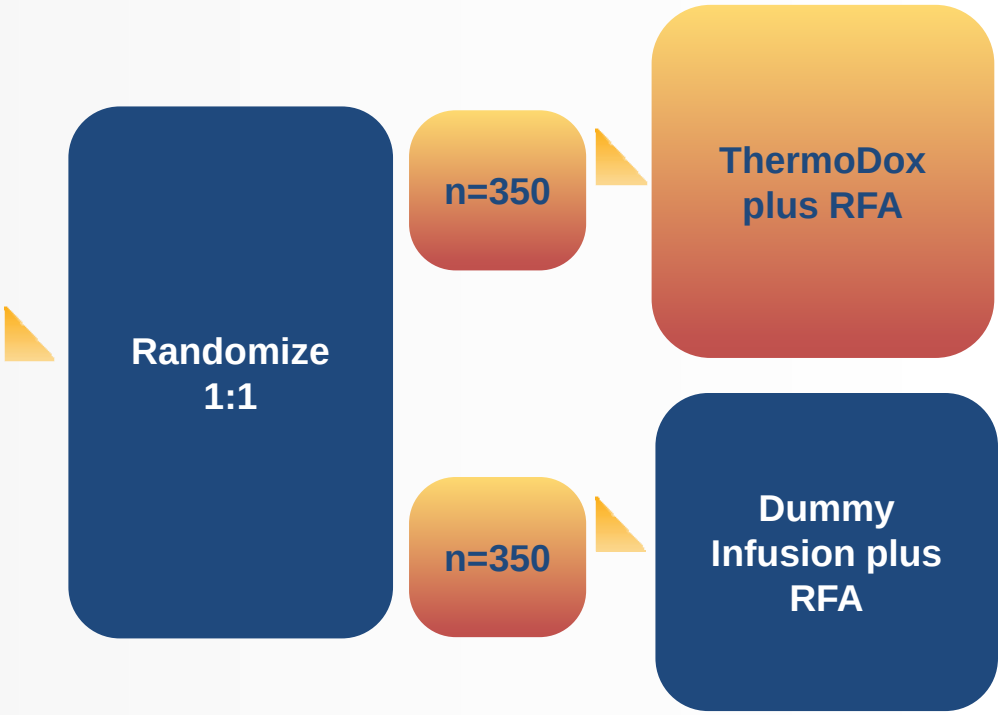
Primary Endpoint:	**Progression Free Survival**
Secondary Endpoints:	**Overall Survival, Time to Local Recurrence, Time to Definite Worsening and Safety**

General Eligibility:

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

Stratification:

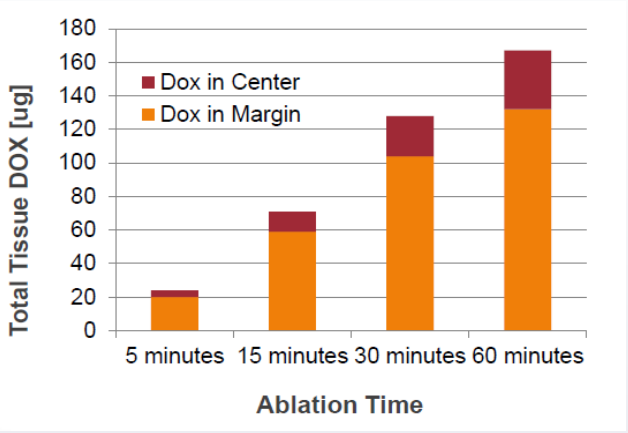
- Lesion size: 3-5 cm and 5-7 cm
- RFA technique:
  - Open surgical
  - Laparoscopic
  - Percutaneous

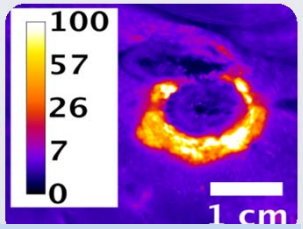


RFA Dwell Time Matters!

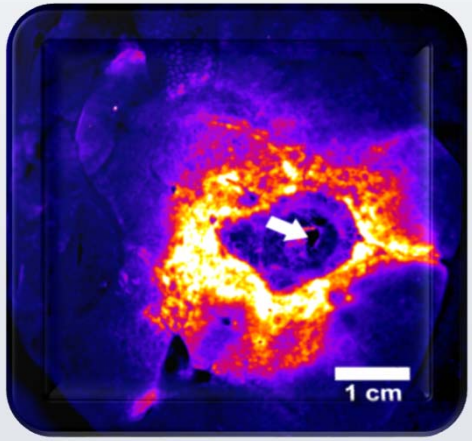
Learnings from the 700 patient HEAT Study

- When standardized for dwell time and lesion number, the ThermoDox patients demonstrated difference in Overall Survival
- The hypothesis that dwell time increases local doxorubicin concentration was then tested and demonstrated in computer simulation study
- The hypothesis was further tested and demonstrated in an in-vivo porcine model:





15 Min Dwell Time



45 Min Dwell Time

- Multivariate analysis points to RFA dwell time with ThermoDox as the factor correlating to significant improvement in survival

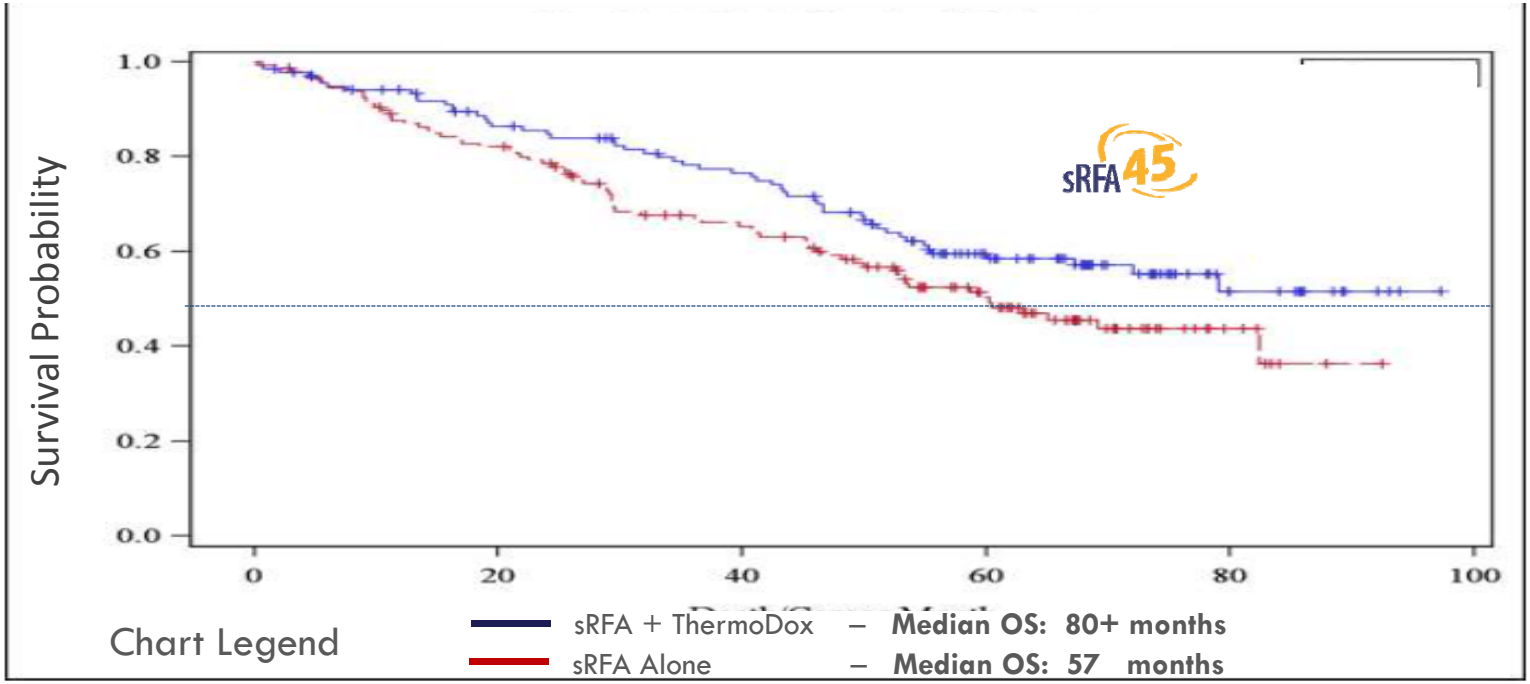
ThermoDox: HCC

Sub-Group Analysis of HEAT Study Data

Greater than Two Years Overall Survival Benefit

285 Patients Followed Quarterly for 3 ½ years

Standardized RFA > 45 minutes (sRFA)

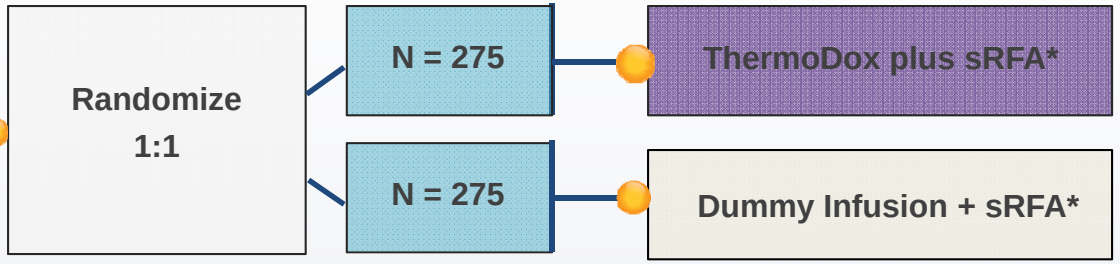


Overall Survival as of 7/15/2016	HR=0.65 (95% CI 0.43 - 0.93) *P* Value = 0.02

Phase III OPTIMA Study Design

General Eligibility
- Non-resectable HCC
- Single lesions
- Lesion > 3 cm but not > 7 cm
- Treatment naïve
- Child-Pugh A

Stratification
- Lesion size: 3-5 cm / 5-7 cm
- RFA Technique (Percutaneous, Laparoscopy, or Surgical)



Primary Endpoint	**Overall Survival (OS)**
Secondary Endpoints	**Progression Free Survival; Safety**
Interim Efficacy Analysis	**118 OS Events / HR < 0.61** **158 OS Events / HR < 0.70**
Final Efficacy	**197 OS Events / HR < 0.75**

First Patient Enrolled
Q3 – 2014

~80 Clinical Sites in
14 Countries

* sRFA45 Standardized Radiofrequency Ablation > 45 minutes

Conclusion

- It will be promising if LTLD is proved to play role in controlling micrometastases of the target HCC and enables to get larger safety margins to prevent future recurrences.

- Further results of phase III trial of LTLD are expected.

HEAT Investigators

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