CIRSE 2012 Lisbon Portugal

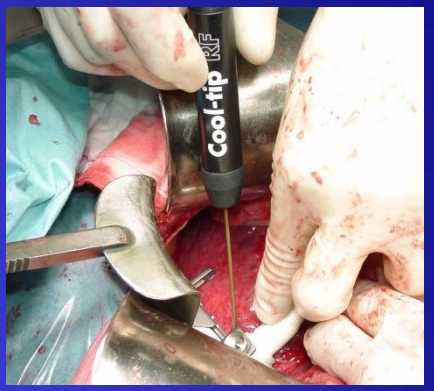
Combining Thermal Ablation with Thermosensitive Liposomes

Ronnie T.P. Poon, MD, PhD
Chair Professor & Chief of Hepatobiliary and Pancreatic Surgery
Department of Surgery
Queen Mary Hospital
The University of Hong Kong

Financial Disclosure

- Advisory Board member of Celsion Ltd.
- Asia-Pacific lead PI of Phase III Randomized Trial of Thermodox in Combination with RFA for HCC (HEAT study)

Local Ablative Therapies for Cancers



- Ethanol injection
- Cryotherapy
- Radiofrequency ablation
- Microwave
- High intensity focused ultrasound
- Electroporation

Thermal ablation

Indications for liver cancer:
< 5 cm tumor, </= 4 tumor nodules

RFA for HCC < 5 cm
Complete Ablation Rate

Study	No. of patients	Route of RFA	Complete ablation
Curley 2000	110	Percut (76) Lap (31) Open (3)	100%
Giovannini 03	53	Percut	92.8%
Vivarelli 04	79	Percut	87%
Poon 04	86	Percut (35) Lap (3) Open (48)	93%

Local Recurrence after RFA for HCC

Study	No. of patients	Median follow-up (months)	Local recurrence
Buscarini 01	88	34	14%
Giovannini 03	56	14	7%
Vivarelli 04	79	15.6	15%
Poon 04	86	11.5	6.2%
Lencioni 05	187	24	5.3%
Marchi 05	65	20	17%
Ng 08	207	26	14.5%

Local Recurrence after RFA for HCC

- Incomplete necrosis of tumor cells in ablated lesion
  - Complete necrosis only in 29 of 38 (83%) tumors ablated by RFA followed by liver transplantation based on histological examination of explants

Lu et al. Radiology 2005

- Untreated microsatellite nodules adjacent to tumor

Risk Factors for Local Recurrence

Independent risk factors of local recurrence by meta-analysis of 5224 liver tumors treated by RFA from 95 series in the literature:

- tumor size > 3 cm ($p < 0.001$)
- percutaneous vs. surgical approach ($p < 0.001$)

Mulier et al. Ann Surg 2005

RFA for Large HCC > 5 cm

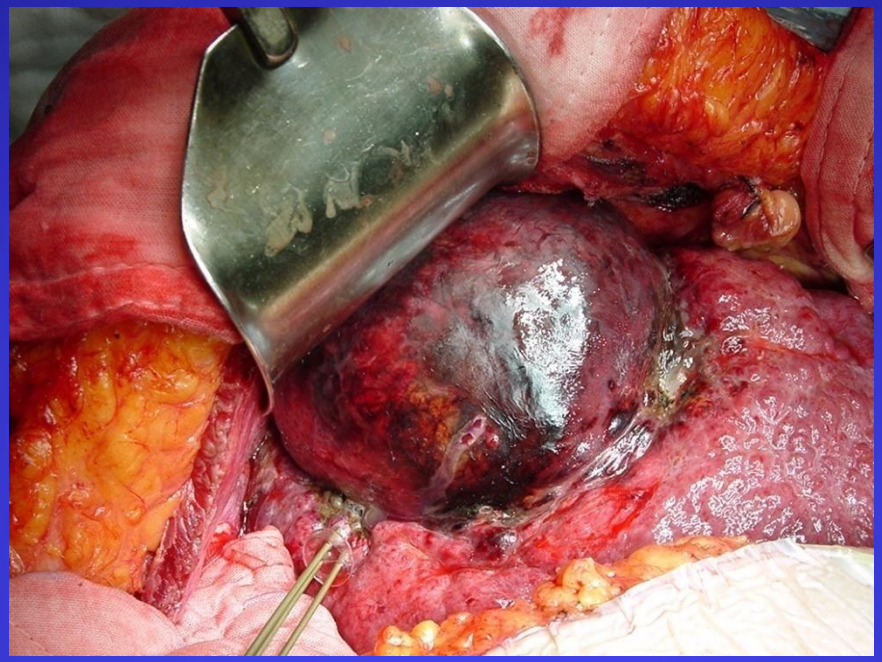
- Percutaneous RFA for HCC > 5 cm:
  Complete ablation rate < 50%
  (compared with 90% for HCC < 3 cm)

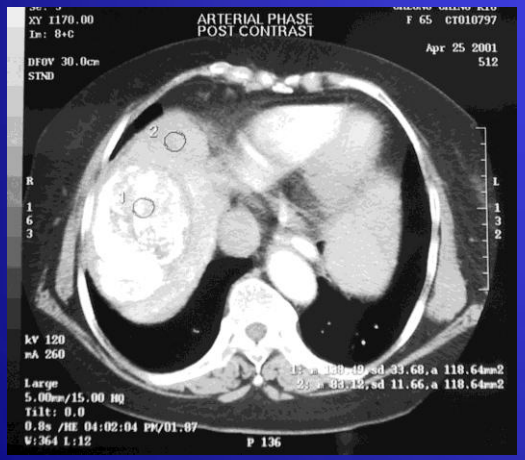
Livraghi et al. Radiology 2000

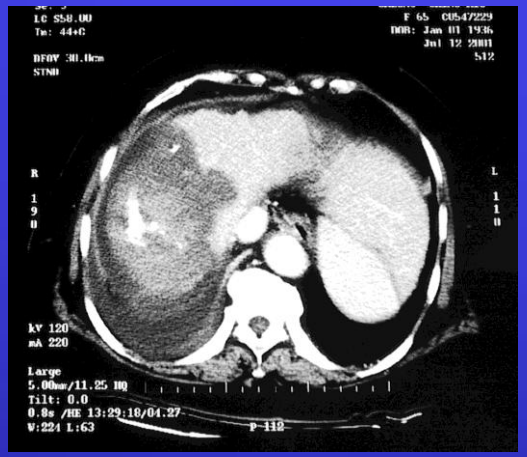
Guglielmi et al. Hepatogastroenterology 2003

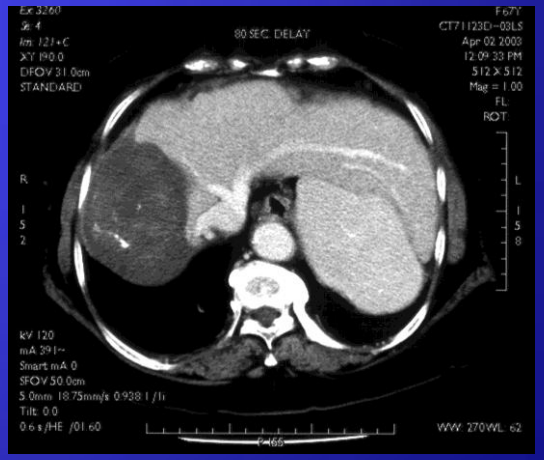
- Open RFA for HCC > 5 cm:
  Complete ablation rate 83% (vs. 96% for HCC < 3 cm)

Poon et al. Arch Surg 2004

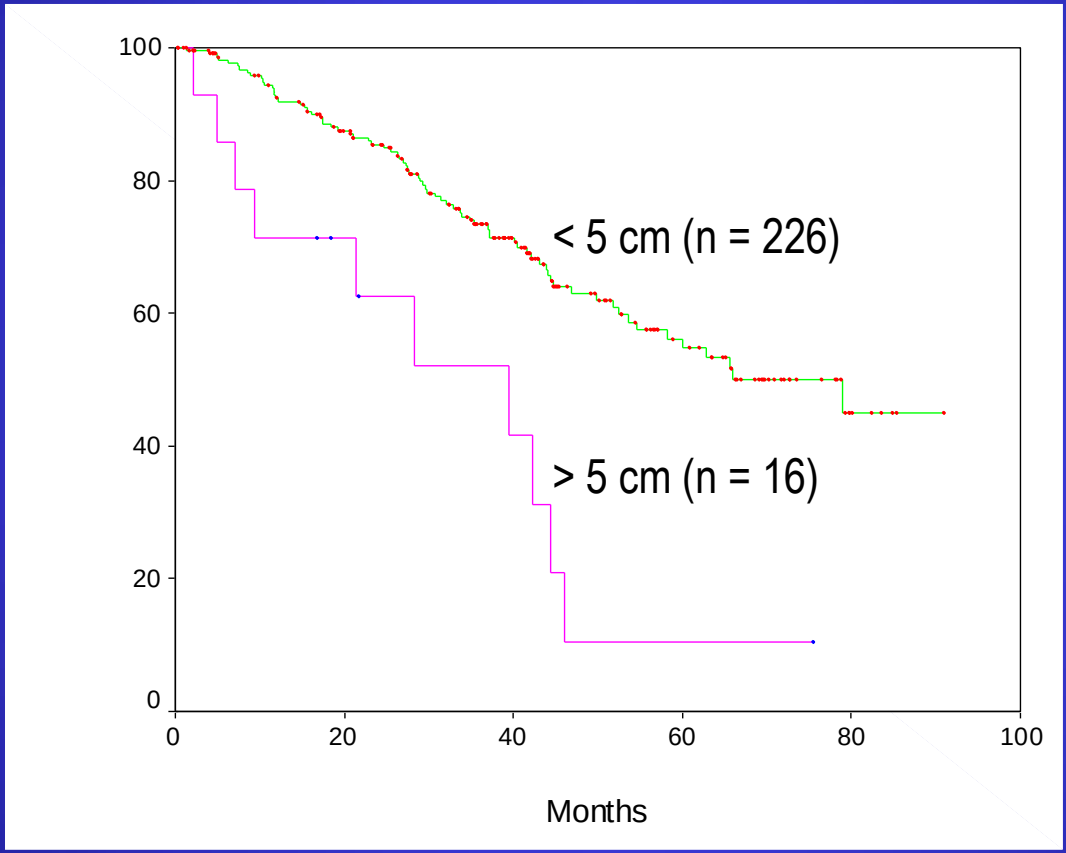



ARTERIAL PHASE
POST CONTRAST
Apr 25 2001
512
kV 120
mA 260
P 136


kV 120
mA 220
P 112


80 SEC. DELAY
kV 120
mA 391
Smart mA 0
SFOV 50.0cm
Tilt 0.0

Long-term Survival after RFA for HCC > 5 cm



3-year survival 73% vs. 52%
5-year survival 56% vs. 12%

P < 0.05

Potential Approaches to Reduce Recurrence after RFA for HCC > 3 cm

- Combination with transarterial chemoembolization

  - one more invasive procedure with potential serious complications

- Thermosensitive liposomes encapsulating cytotoxic drugs

  - a novel technology to deliver high concentrations of chemotherapy drugs to the tumor with lower systemic toxicity

  - simple intravenous injection prior to RFA procedure

Thermal Sensitive Liposomes

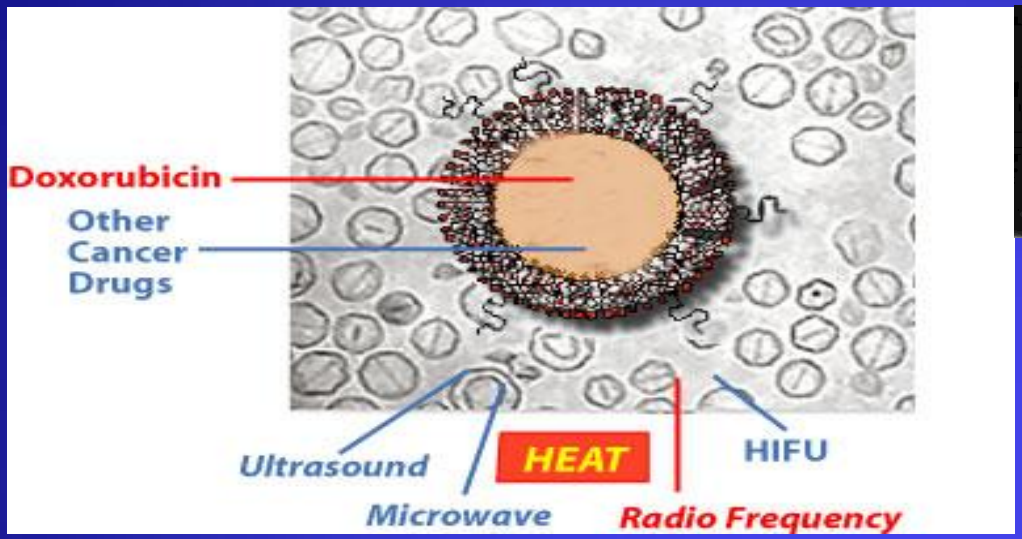
- Liposomal encapsulation can optimize and enhance the delivery of different cytotoxic agents with lower systemic toxicity and better drug cell internalization compared with free drug

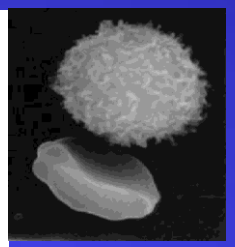
  (e.g. DOXIL - polyethylene glycolylated liposomes containing Doxorubicin)

- New generation of lyso-lipid heat-sensitive liposomes release drugs with hyperthermia and may further improve drug delivery to tumors

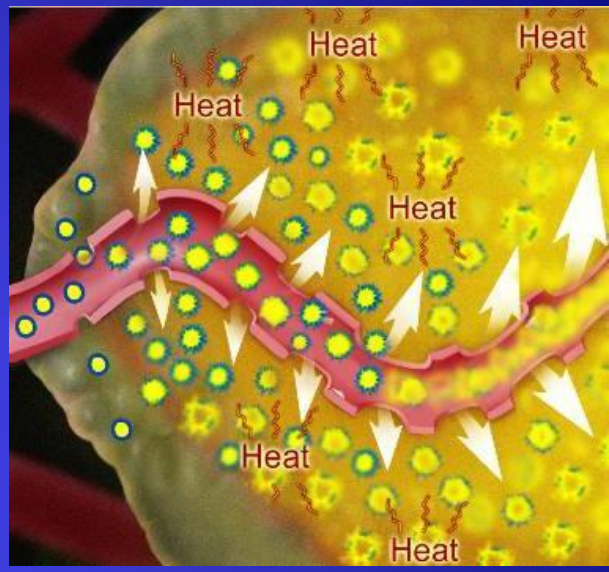
  (e.g. ThermoDox)

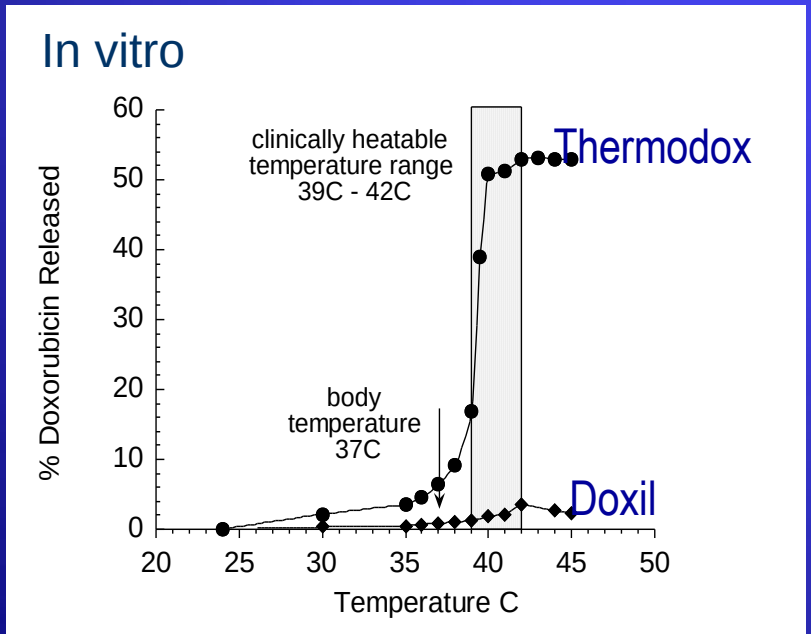
Thermosensitive Liposomal Doxorubicin (ThermoDox)

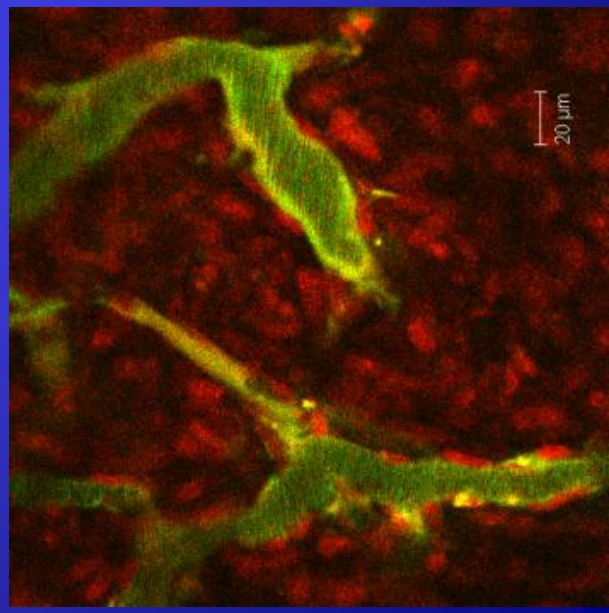




ThermoDox is 100 nm, a Fraction of RBC

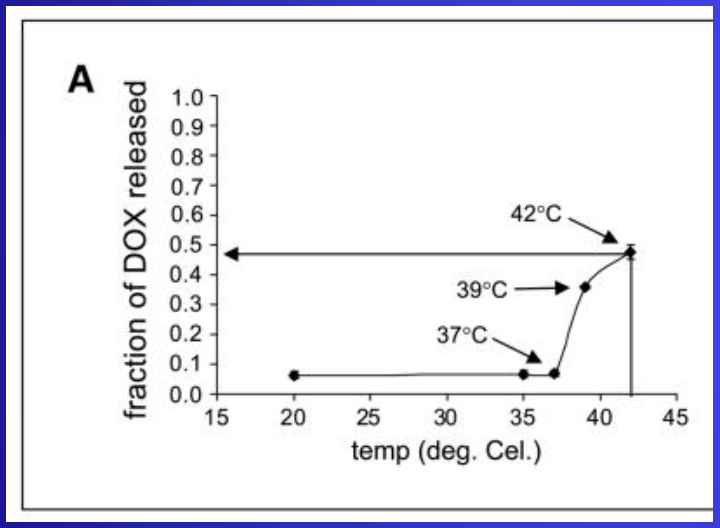




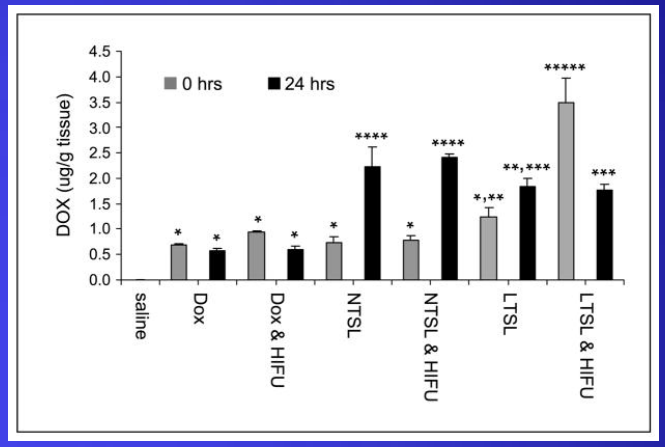


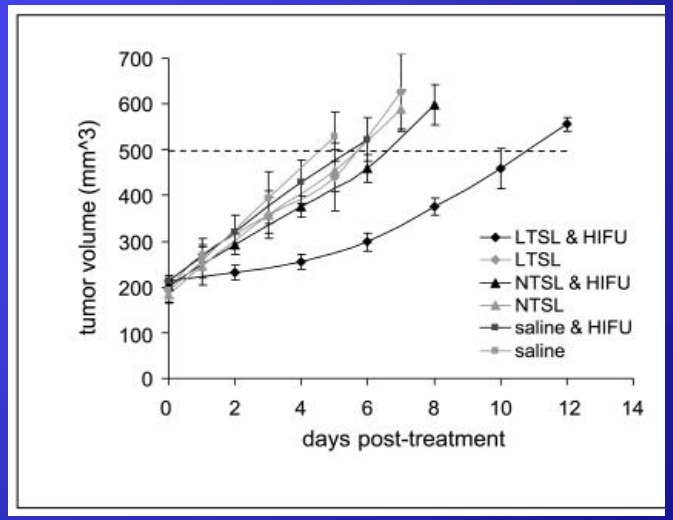
ThermoDox in Mice Tumor Study

Combining Thermodox with pulsed HIFU enhanced its delivery to tumor and its anti-tumor effects compared with Doxil



Thermodox started releasing doxorubicin at a temperature of 39°C. At a temperature of 42°C, release of doxorubicin at 2 min was ~ 50% and nearly 100% by 12 min





Dromi et al. Clin Cancer Res 2007

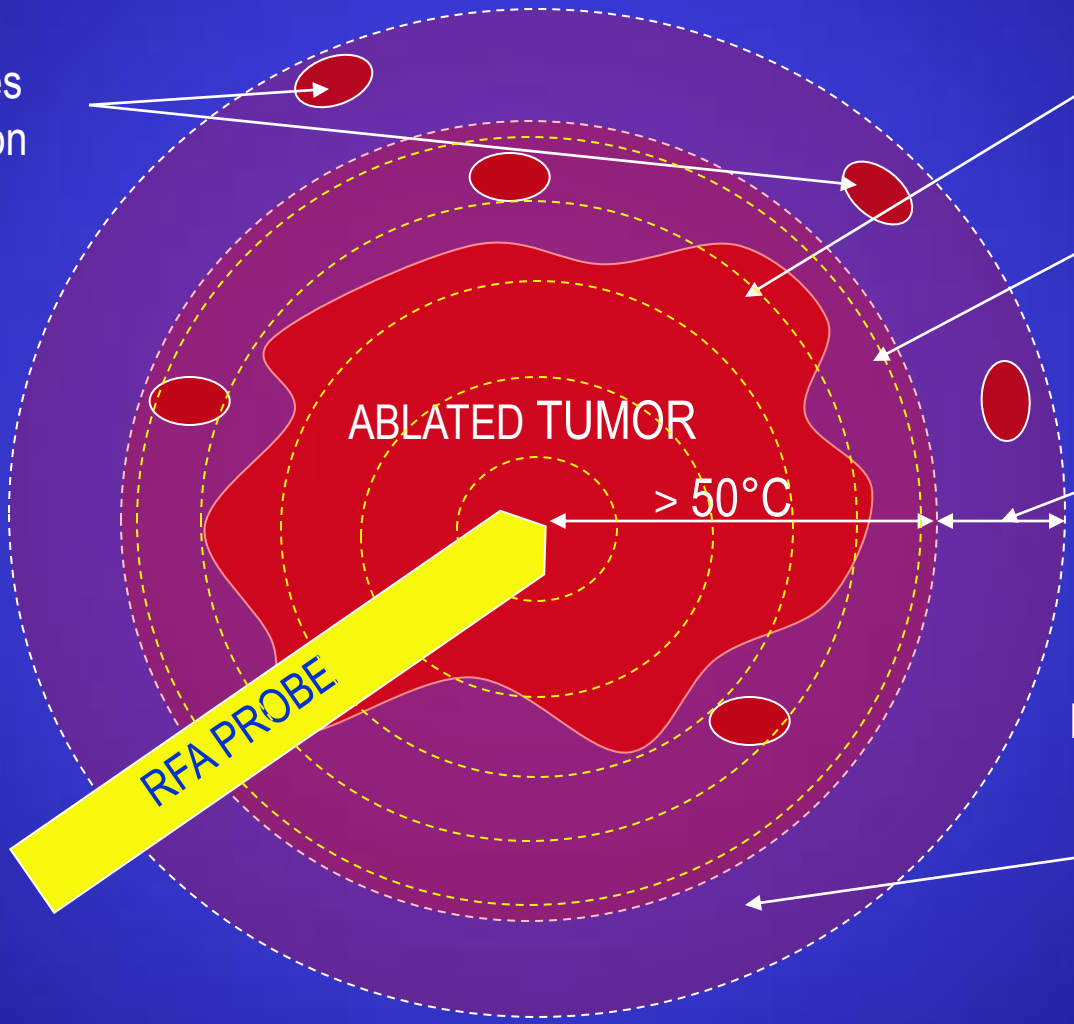
Mode of Action for ThermoDox

- Local tissue concentration ~ 10x that of standard free doxorubicin, achieving higher cancer cytotoxicity and reduced systemic toxicity
- Direct toxicity to tumor vasculature

Synergistic effects:

- Cytotoxic effect of doxorubicin enhanced by heat (doxorubicin binding to tumor DNA)
- Doxorubicin reduces ablation threshold temperature – enhanced lesion size

RF Ablation / ThermoDox Combination



Phase I Study at NCI (USA) and QMH (HK)

- Phase I, single dose, dose escalation study to evaluate tolerability of Thermodox in patients with liver tumors undergoing RFA
- Patients with primary or secondary liver cancer, 4 or fewer tumor nodules up to 7 cm, were enrolled following the dose escalation design
- Six ThermoDox dose levels were planned:

  20, 30, 40, 50, 60 and 70 mg/m^2
- Patients received a single dose of 30-min. IV infusion of ThermoDox starting 15 min. before percutaneous or surgical RFA
- Patients were monitored for safety up to 3 months, and contrast CT scan was performed at day 28 to assess treatment efficacy

Wood, et al. J Vasc Interv Radiol. 2012

Patient and Tumor Characteristics

- A total of 24 patients were treated (3, 6, 6, 6, 3 patients at doses of 20, 30, 40, 50 and 60 mg/m^2, respectively)
- Median age 58.5 years (range: 33 to 84), 17M / 7F
- Median tumor size 3.7 cm (range 1.7-6.5 cm), and totally 28 tumors treated
- Pathology:

  Hepatocellular carcinoma n = 9

  Metastatic carcinoma n = 15 (Primary sites: adrenal, colorectal, esophageal, breast, cervix uteri, kidney, pancreas)

Adverse Events and MTD

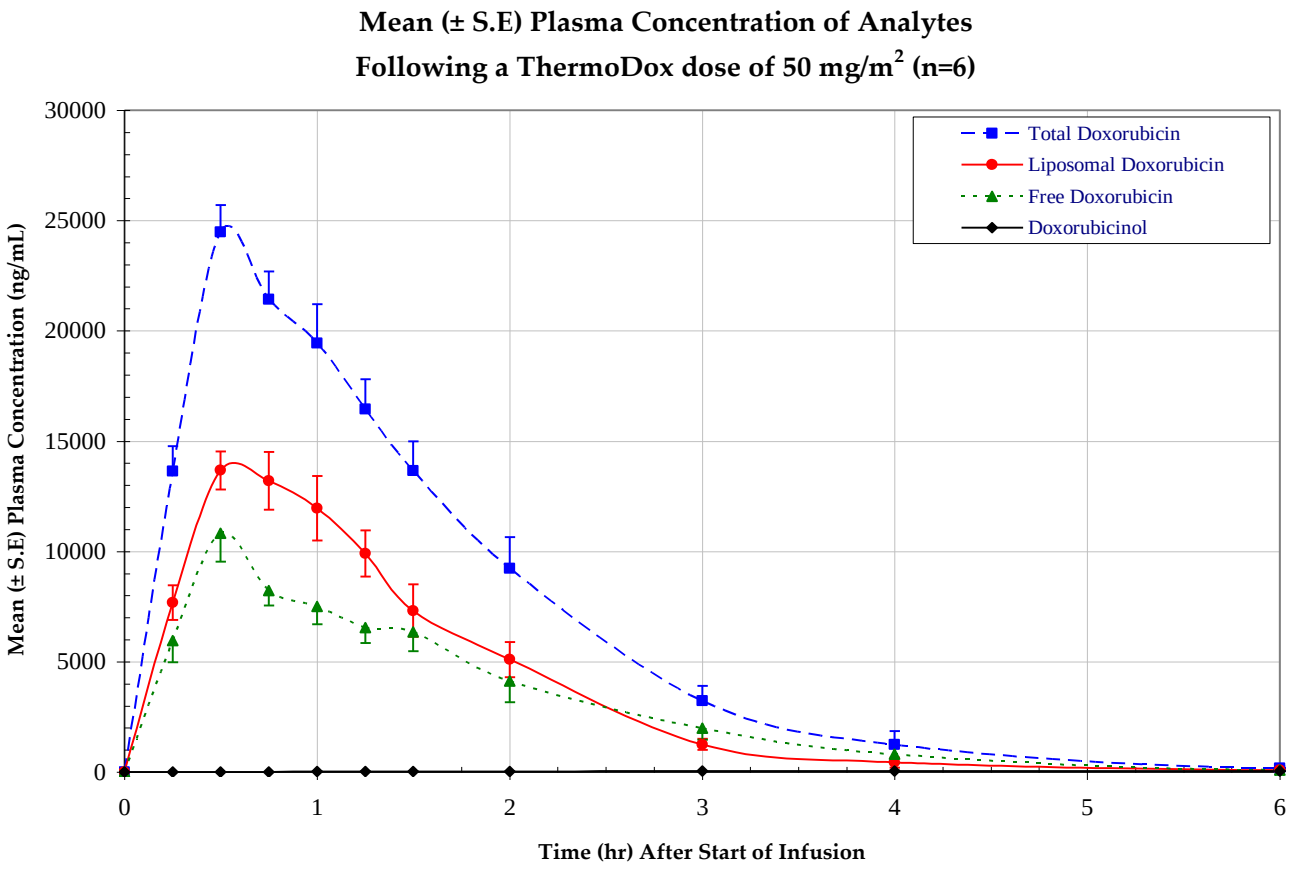
- Common drug-related adverse events included:
  - alopecia (grade 1 or 2 only, 66.7%)
  - reversible grade 3/4 neutropenia (50%, dose-dependent)

- No treatment death

- No renal toxicity, congestive heart failure, reduced ventricular ejection fraction or hand-foot reaction

- The maximum tolerated dose (MTD) was determined as 50 mg/m^2 based on two dose-limiting toxicities (a grade 3 alanine aminotransferase increase and a grade 4 neutropenia) occurring at 60 mg/m^2 dose

Pharmacokinetics



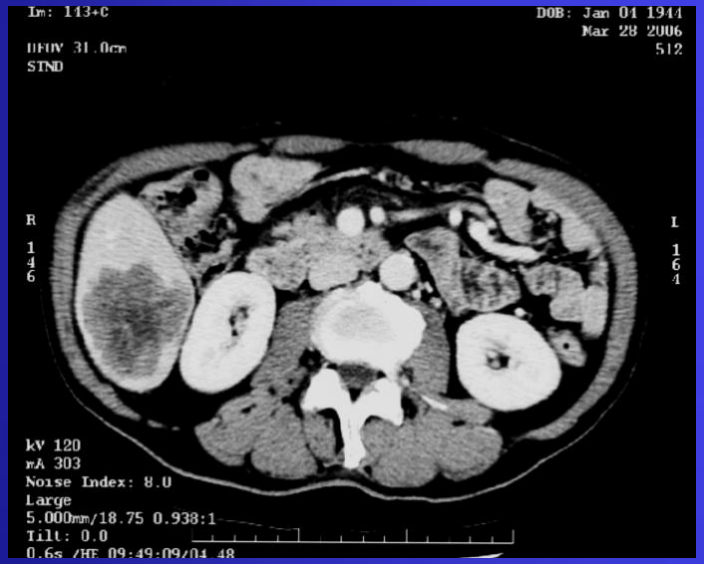
- The concentration of doxorubicin peaked at 30 minutes and then decreased as doxorubicin is cleared (initial half-life 0.92 hr.)
- A simple approach of initiating RFA halfway into a 30 minute IV infusion of Thermodox captured 51% of the AUC_0-∞ with RFA current on and 90% of the AUC_0-∞ with the overall RFA time.

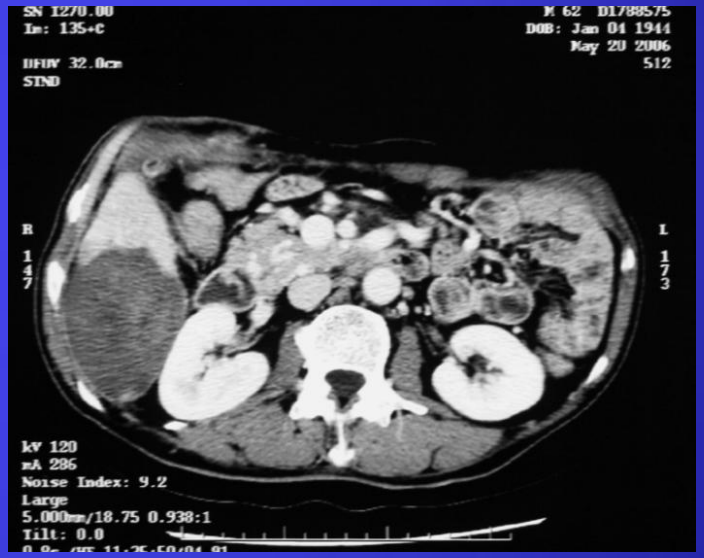
Tumor Control

- Totally 28 tumors were treated
- Three patients had local failure detected at 28 days post-treatment (12.5%)
- There was a statistically significant ThermoDox dose-response relationship in time to tumor progression (P = 0.011)

Illustrative Case - HCC

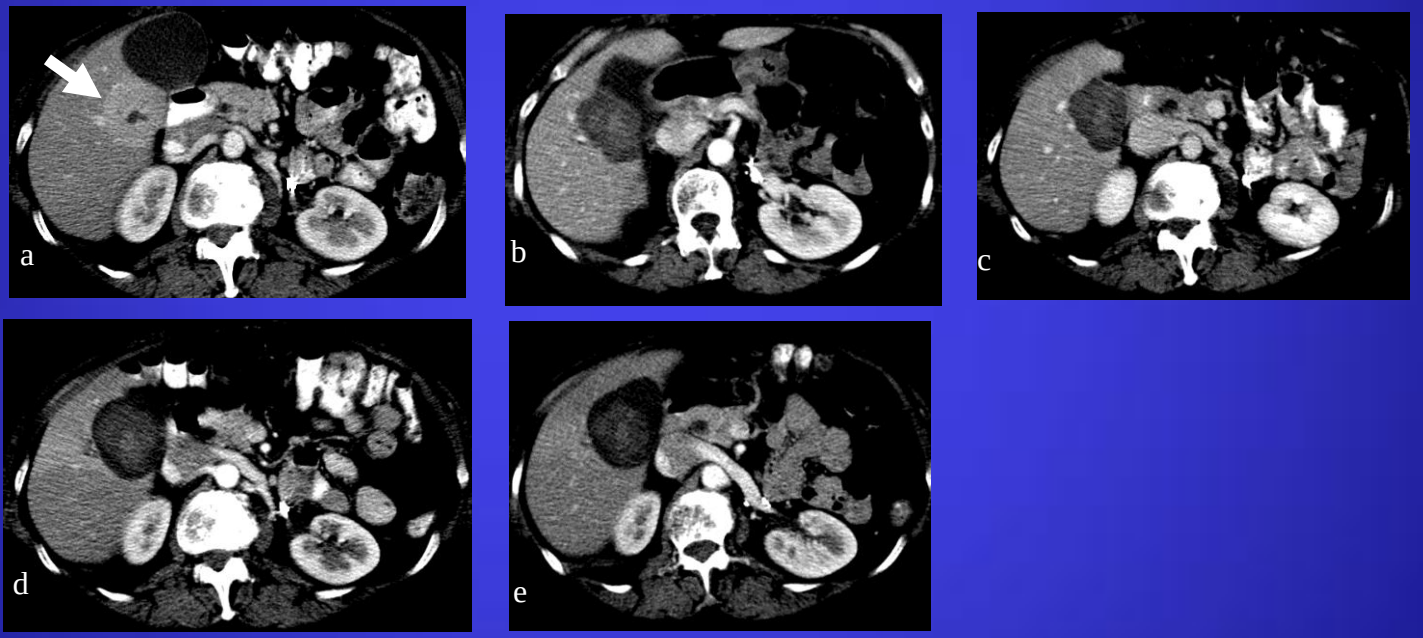
5.7 cm HCC





Illustrative Case - Metastasis

Adrenal cortical carcinoma metastasis

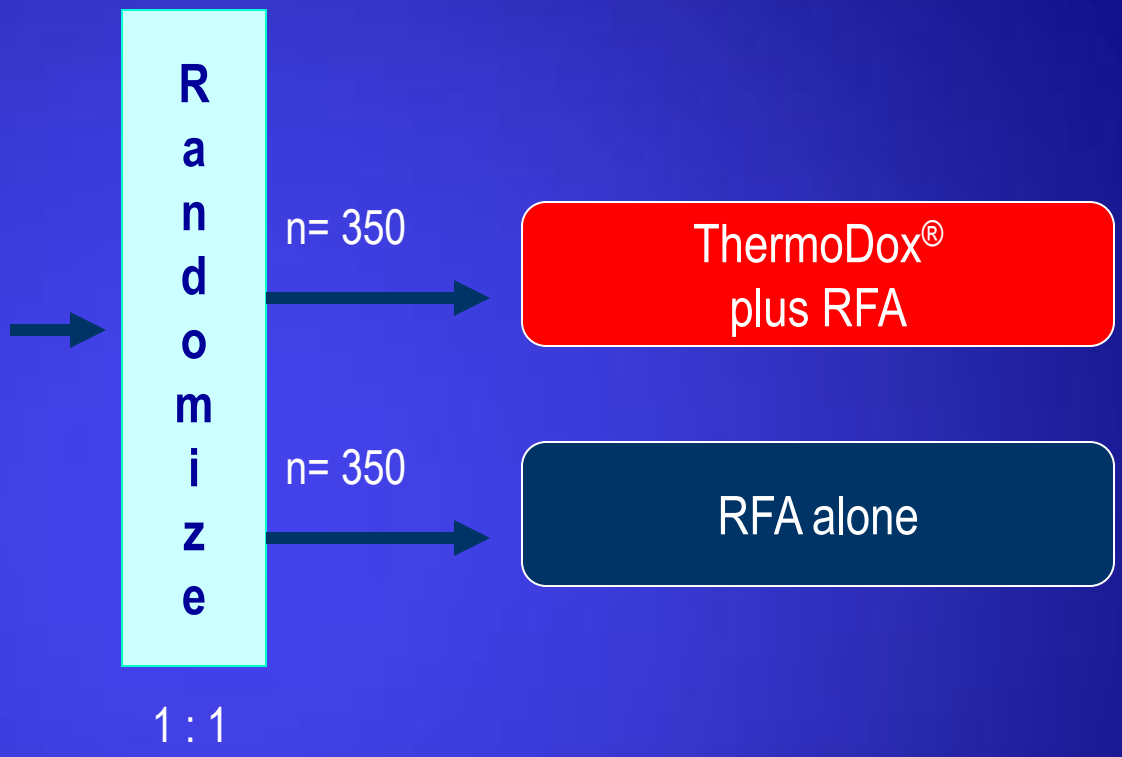


Pre-treatment (a, arrow), 3 days (b), 4weeks (c), 11 weeks (d), and 20 weeks (e) post treatment

Phase III Multi-center Randomized Trial

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 cm and RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous



End Points: Primary: PFS (Progression Free Survival)

Secondary: OS (Overall Survival), TTLR (time to local recurrence), Safety

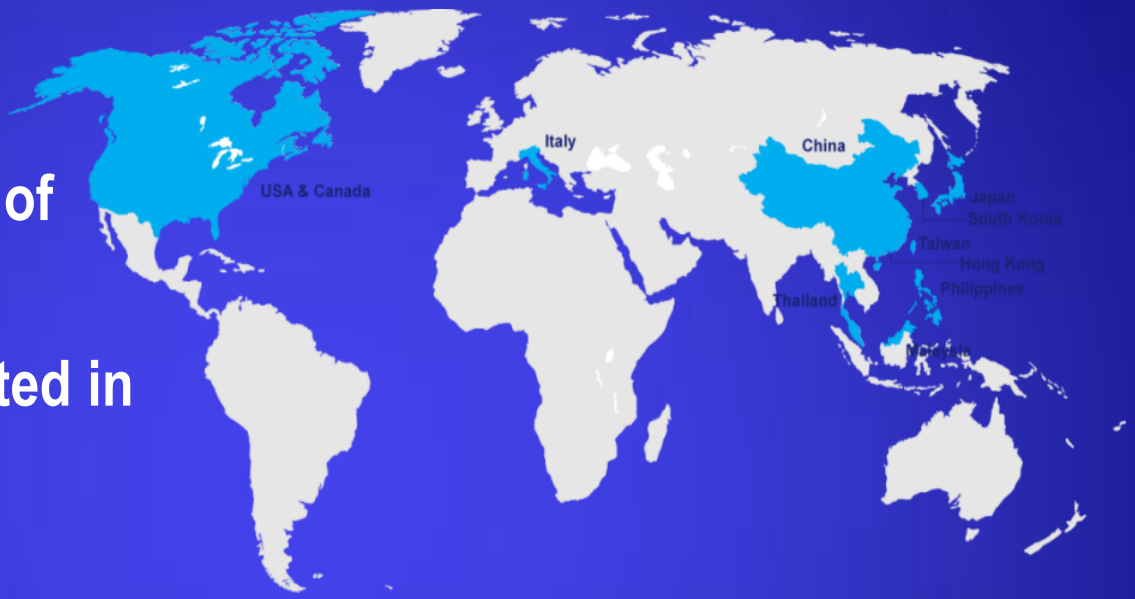
HEAT Study

Hepatocellular Carcinoma Study of RFA and ThermoDox®

Phase III HEAT Study

Status

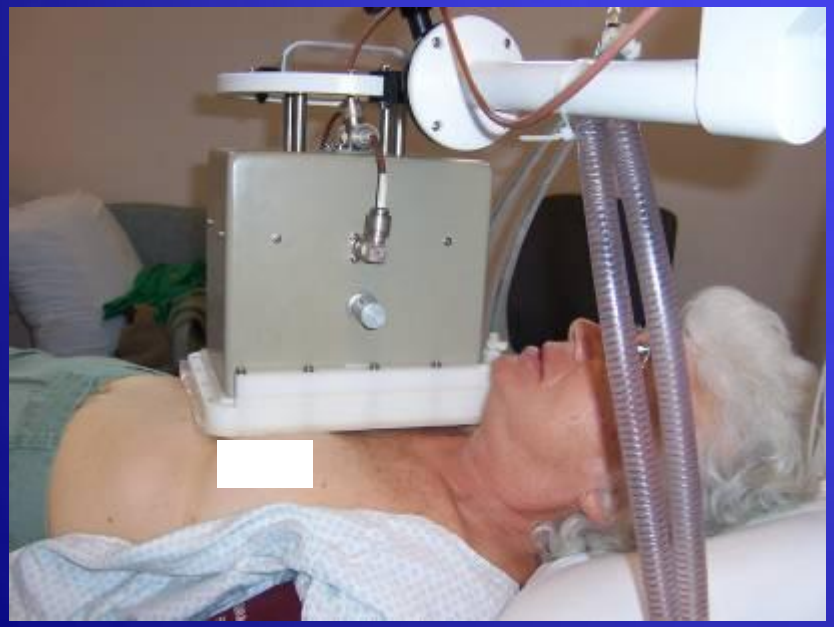
- 76 clinical sites in 11 countries/regions
- Completed enrollment of 700 by June, 2012
- Effiacy analysis expected in the end of 2012

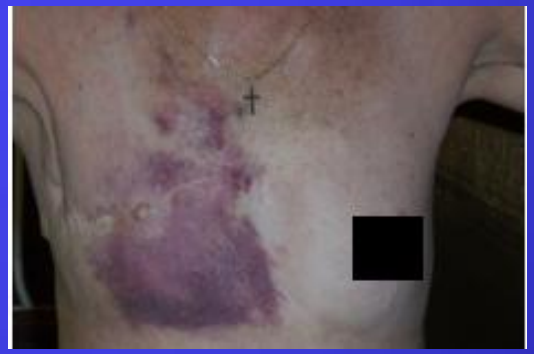


HEAT Study
Hepatocellular Carcinoma Study of RFA and ThermoDox®

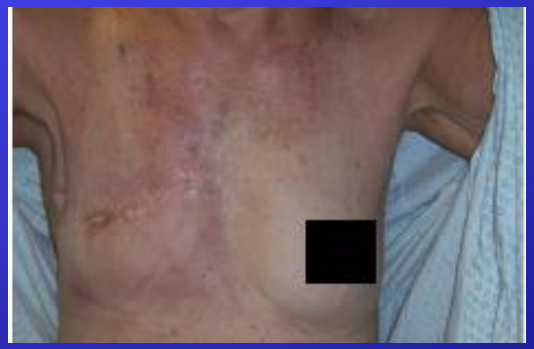
Other On-going Trials of ThermoDox

- Phase II Study of ThermoDox in colorectal MLC patients
  - 2 arm, randomized, RFA +/- ThermoDox; 88 patients
- Phase II trial of combination of Thermodox with HIFU for HCC
- Phase I/II trial for chest wall recurrence of breast cancer
- Potential use in other cancers e.g. pancreatic cancer, bone cancer





Pre-treatment



Post-treatment

MRI Monitoring of Tumoral Drug Delivery with Thermosensitive Liposomes

- A multifunctional HaT liposome co-encapsulating Gd-DTPA (an MRI probe) and doxorubicin (DOX), which simultaneously releases and reports on drug delivery in a locally heated tumor
- The temperature-dependent release profiles of DOX from HaT were closely related to the change in the MR T(1) relaxation time, in which DOX was 100% released at 40-42 °C in 3 min, accompanied by a 60% reduction in T(1)
- DOX uptake in the tumor was quantitatively correlated with T(1) response (R(2) = 0.98), predominantly detected in the highly perfused tumor periphery
- The extent of T(1) relaxation enhancement in the heated tumor successfully predicted the antitumor efficacy

Tagami et al, Biomaterials 2011

Conclusions

- Thermosensitive liposome is a novel technology of heat-activated delivery of cancer drugs
- Encouraging results from phase I trial of Thermodox combined with RFA in liver cancer; on-going randomized phase III trial will evaluate the benefit of Thermodox in reducing tumor recurrence and increasing survival after RFA
- Potential use in other cancers with other encapsulated drugs in combination with heat


Thank you!