EASL
The Home of Hepatology

THE INTERNATIONAL LIVER CONGRESS™ 2018
APRIL 11-15, PARIS, FRANCE

SATELLITE SYMPOSIUM

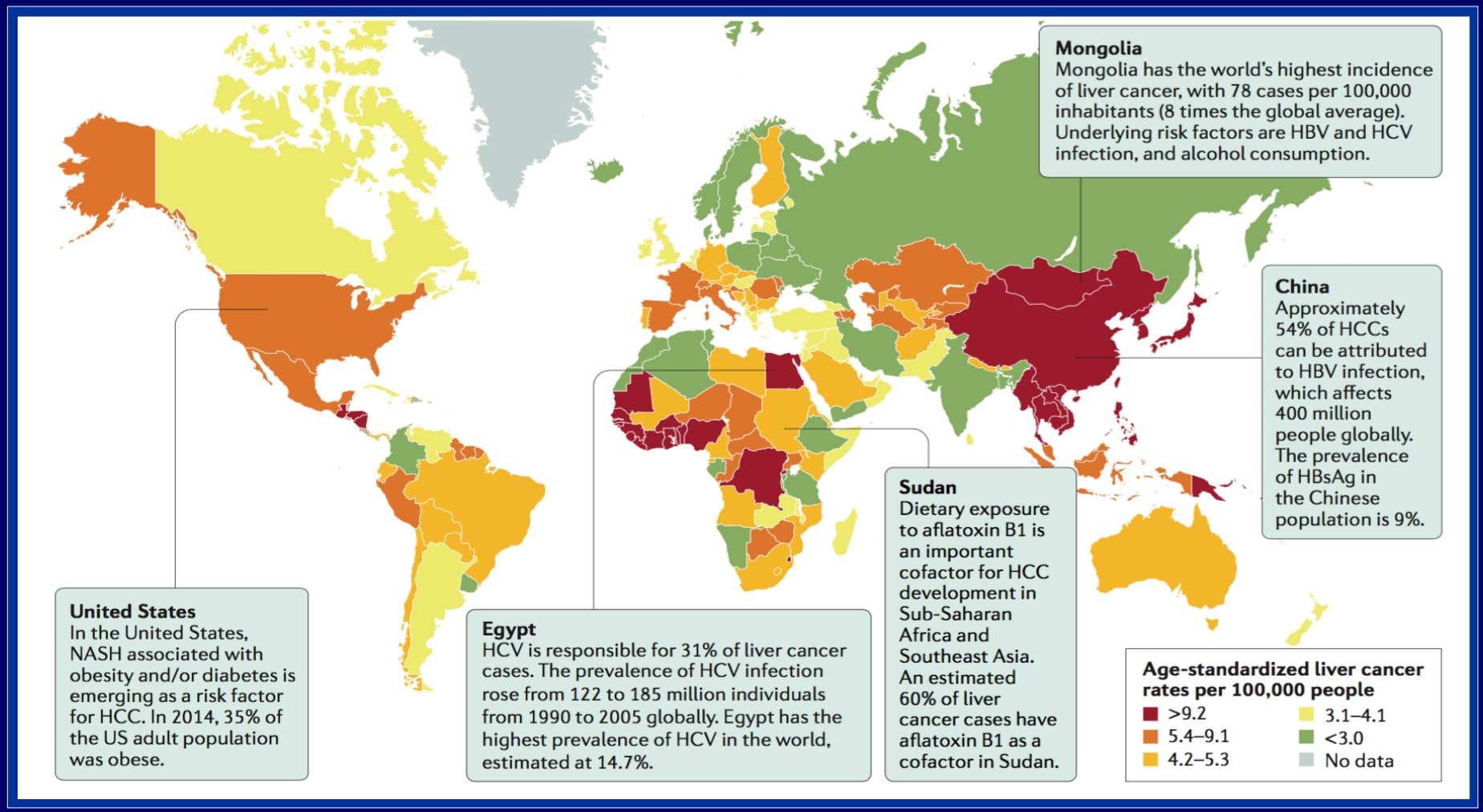
"Emerging Horizons in HCC: From Palliation to Cure"

RETHINKING OUR APPROACH TO INTERMEDIATE-SIZE HCC

Professor Riccardo Lencioni, MD, FSIR, EBIR

University of Pisa School of Medicine, Pisa, Italy

Hepatocellular Carcinoma (HCC): The Global Burden

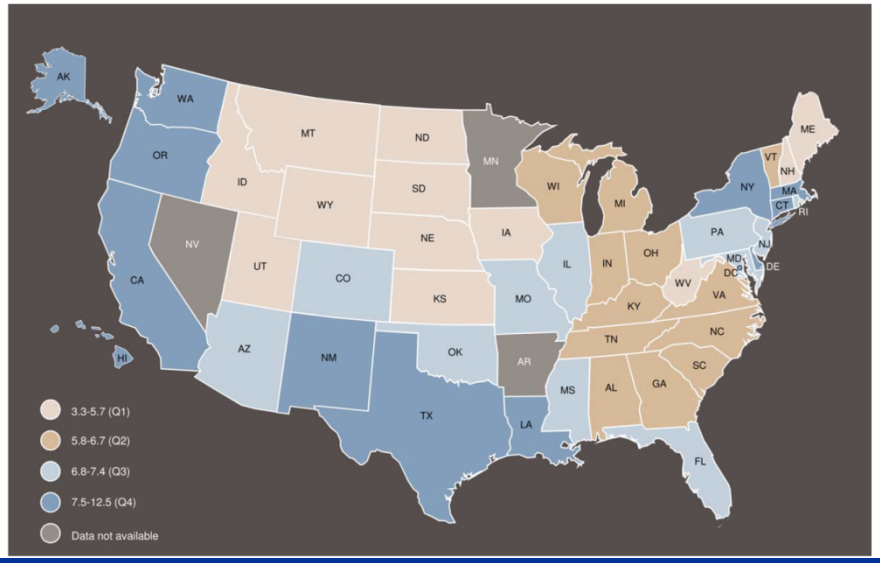


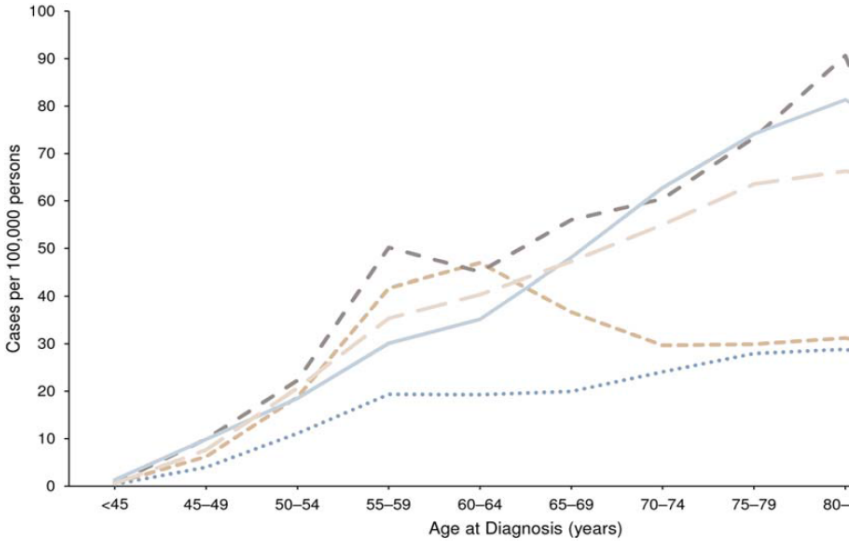
Llovet JM et al. Nat Rev Dis Primers 2016;2:16018

18th Annual Report to the Nation on the Status of Cancer (ACS – CDC – NCI – NAACCR)

Annual Report to the Nation on the Status of Cancer, 1975-2012, Featuring the Increasing Incidence of Liver Cancer

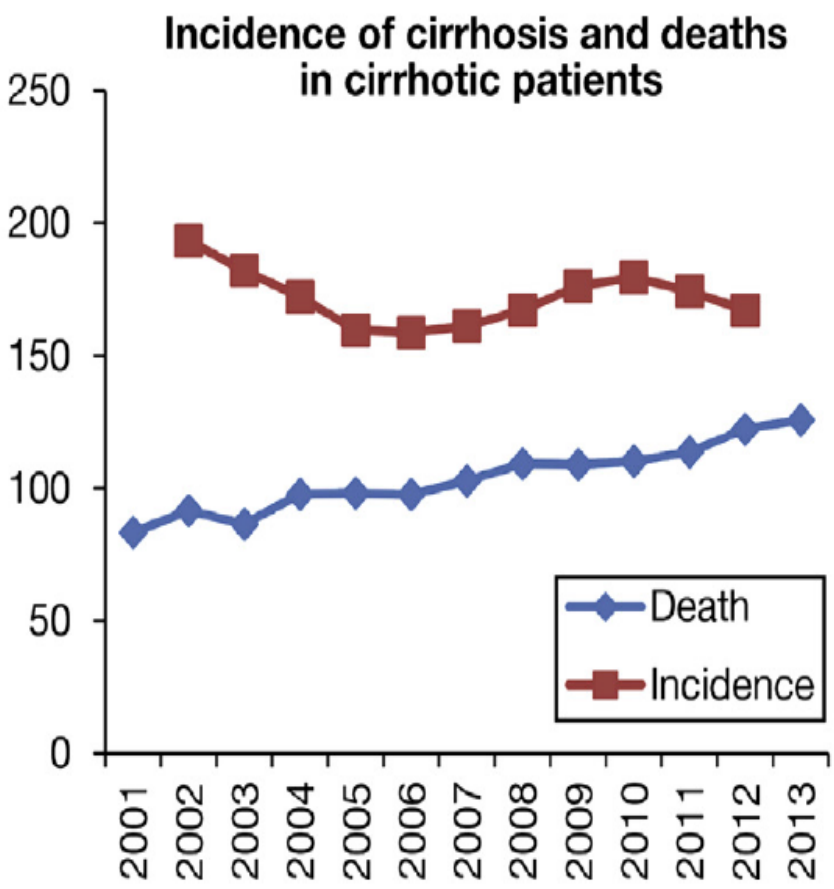
A. Blythe Ryerson, PhD, MPH[1]; Christie R. Eheman, PhD, MSHP[1]; Sean F. Altekruse, DVM, MPH, PhD[2]; John W. Ward, MD[3]; Ahmedin Jemal, DVM, PhD[4]; Recinda L. Sherman, MPH, PhD, CTR[5]; S. Jane Henley, MSPH[1]; Deborah Holtzman, PhD[3]; Andrew Lake, BS[6]; Anne-Michelle Noone, MS[2]; Robert N. Anderson, PhD[7]; Jiemin Ma, PhD, MHS[4]; Kathleen N. Ly, MPH[3]; Kathleen A. Cronin, PhD, MPH[2]; Lynne Penberthy, MD, MPH[2]; and Betsy A. Kohler, MPH[5]

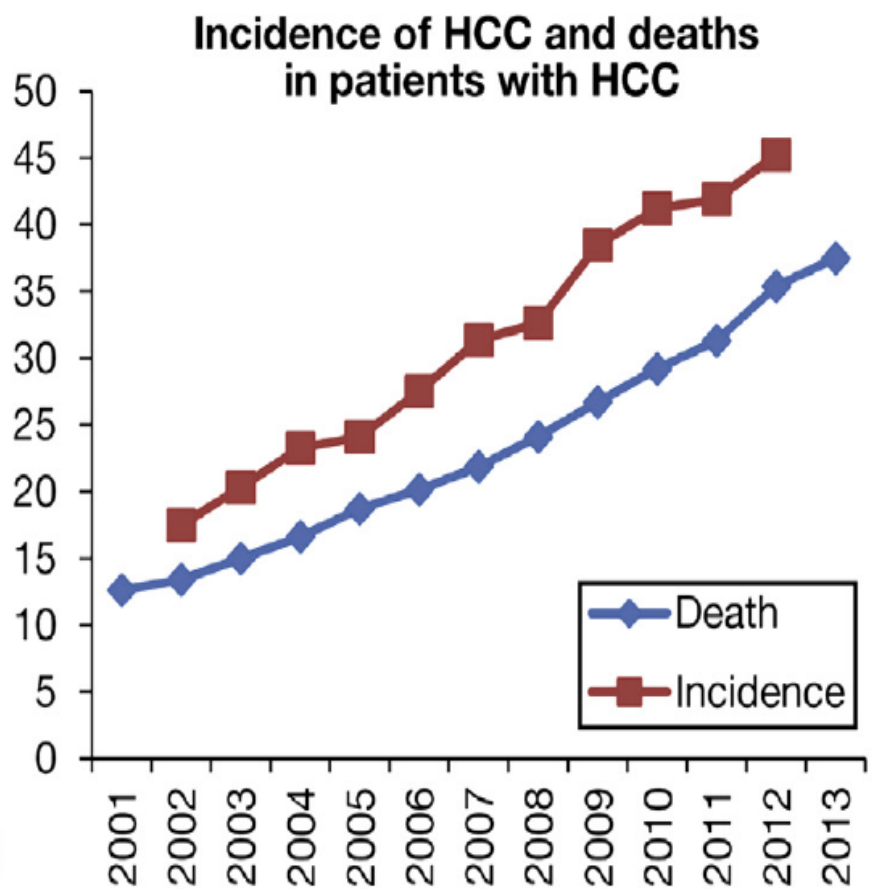




Ryerson AB et al. Cancer 2016;122:1312-37

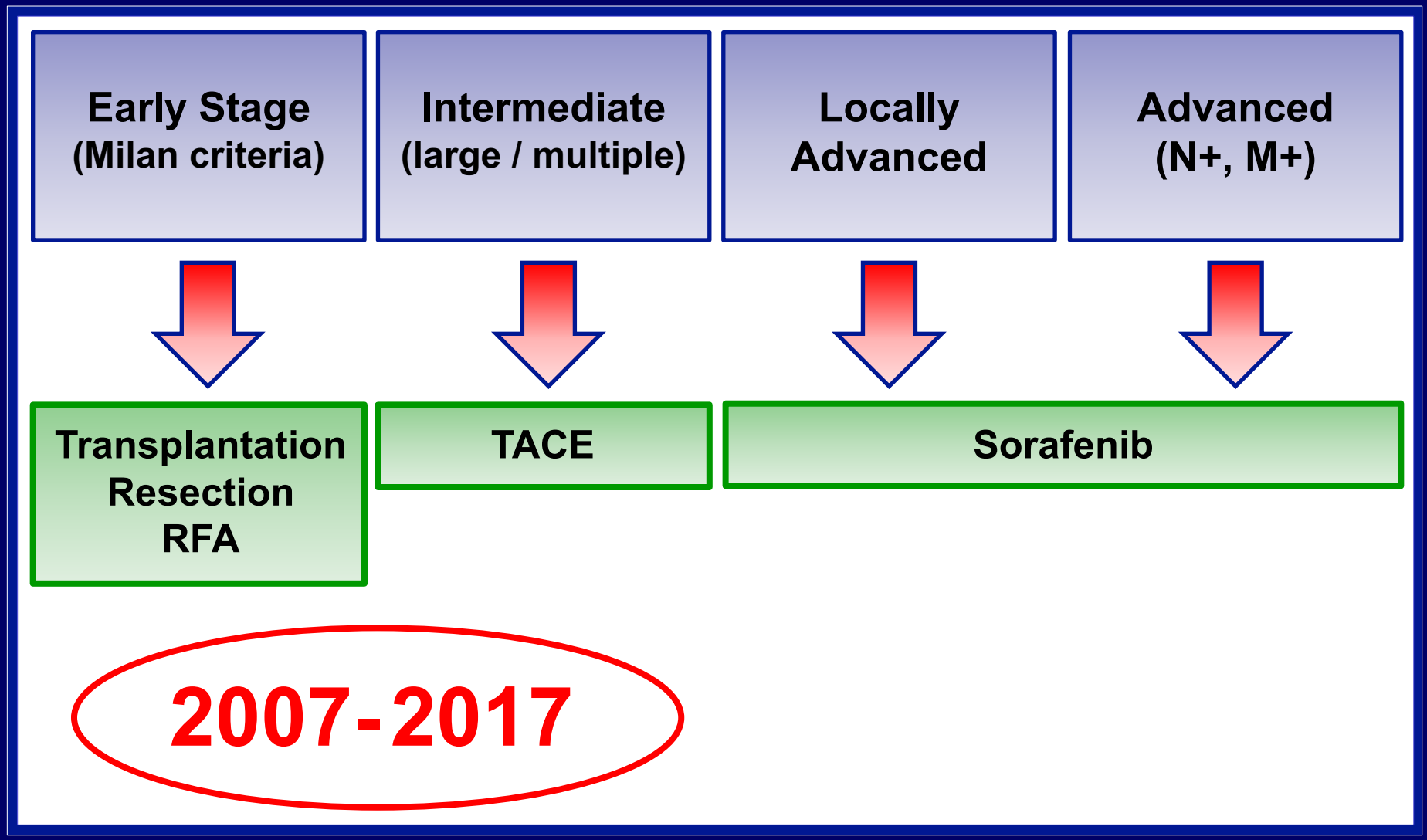
Trends in the Incidence and Mortality of Cirrhosis and HCC (United States)



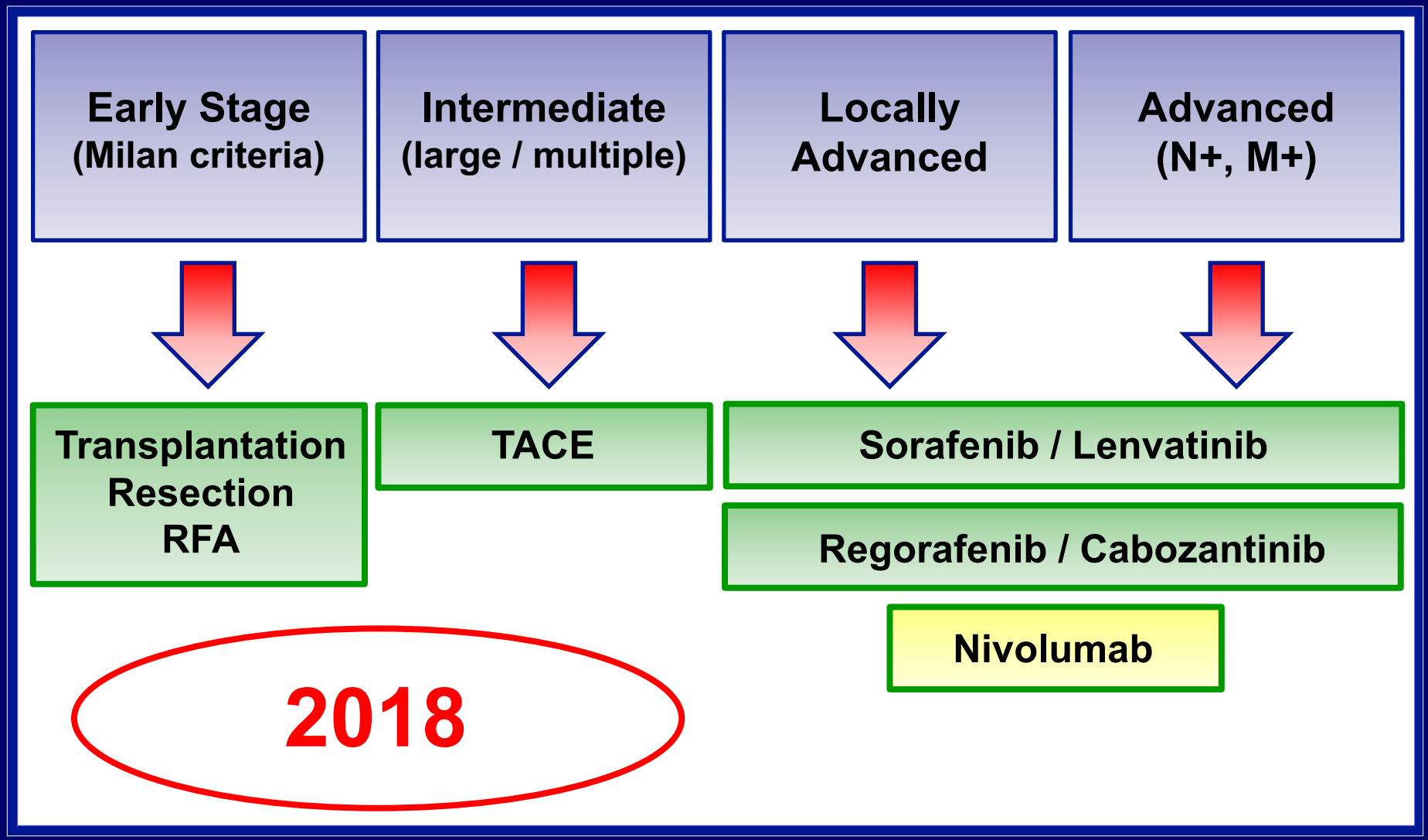


Beste LA et al. Gastroenterology 2015;149:1471-1482

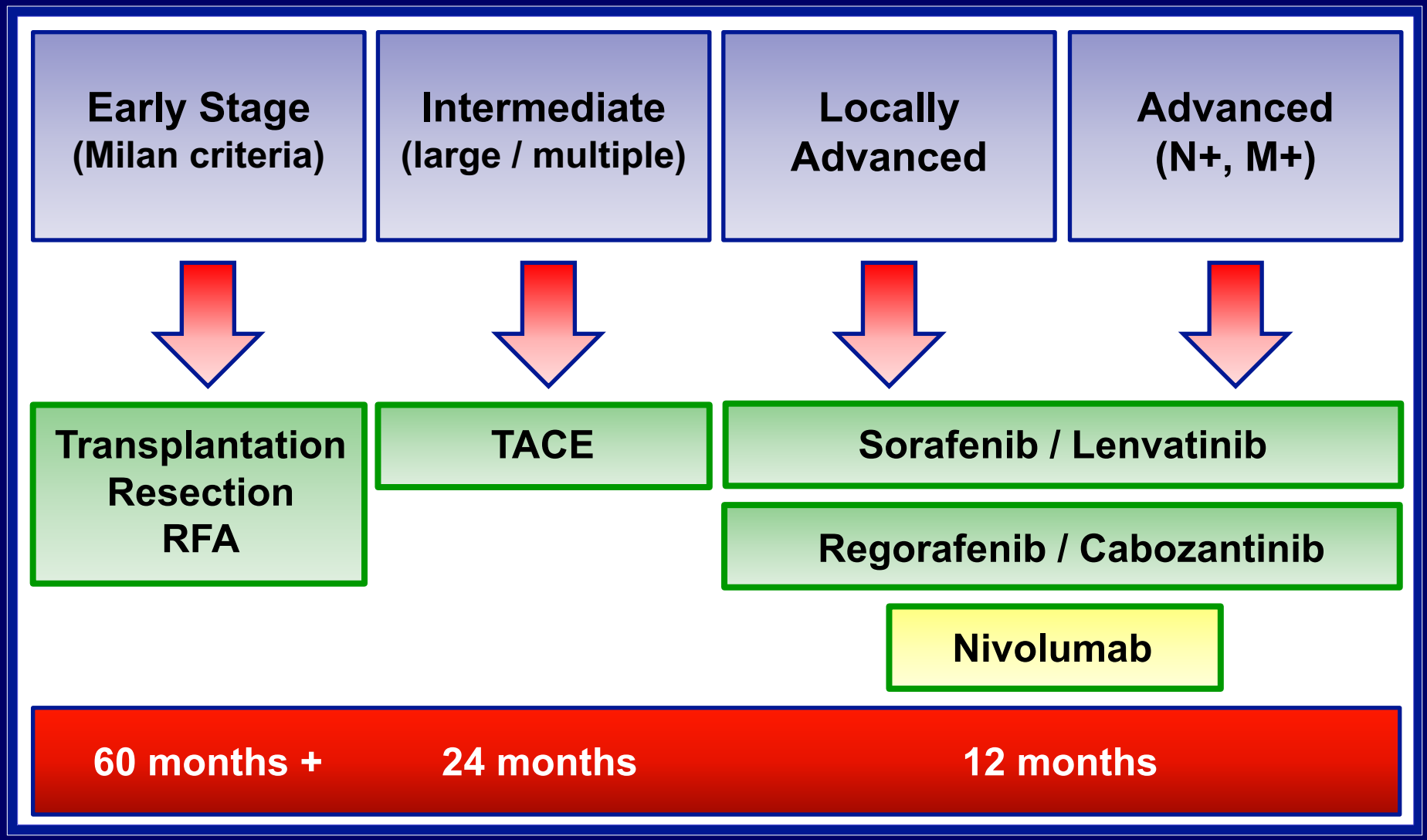
Clinical Management of Hepatocellular Carcinoma: Tumor Stages & Evidence-Based Treatment Options



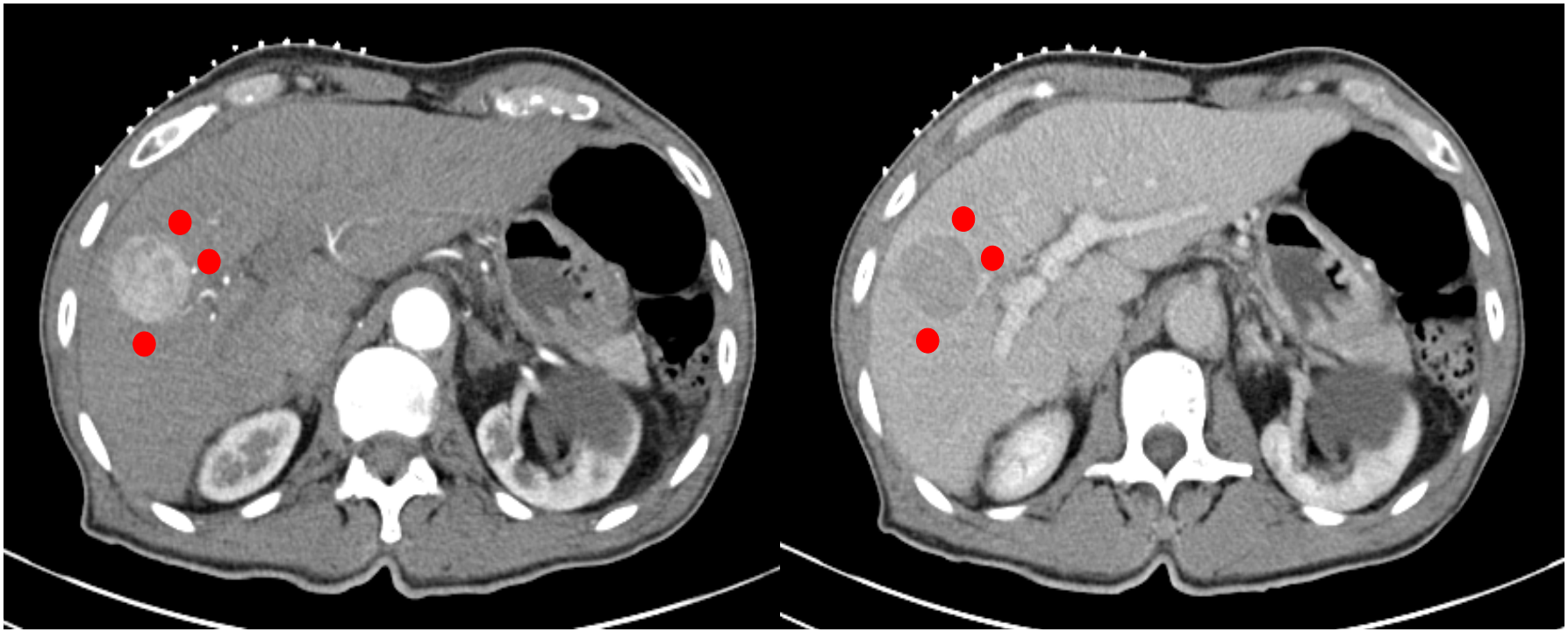
Clinical Management of Hepatocellular Carcinoma: Tumor Stages & Evidence-Based Treatment Options



Clinical Management of Hepatocellular Carcinoma: Tumor Stages & Evidence-Based Treatment Options



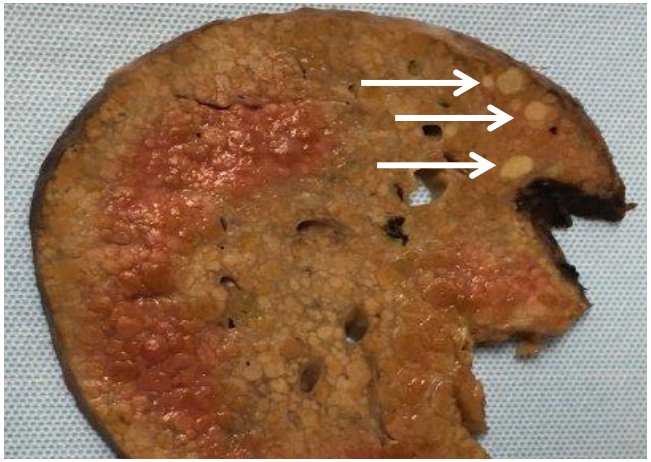
Microsatellites Distribution in HCC: Implications for Loco-Regional Treatment

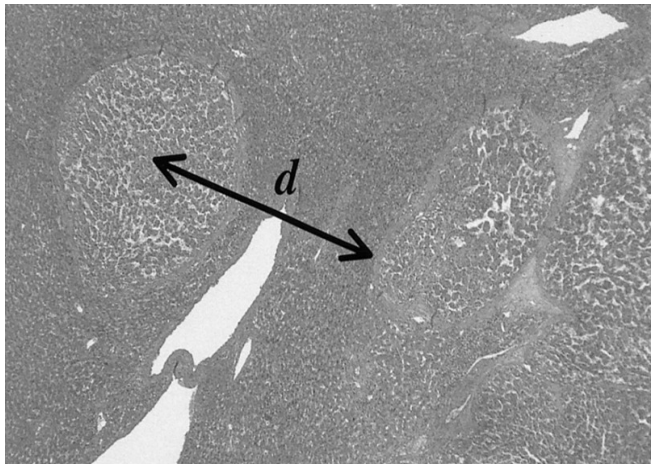


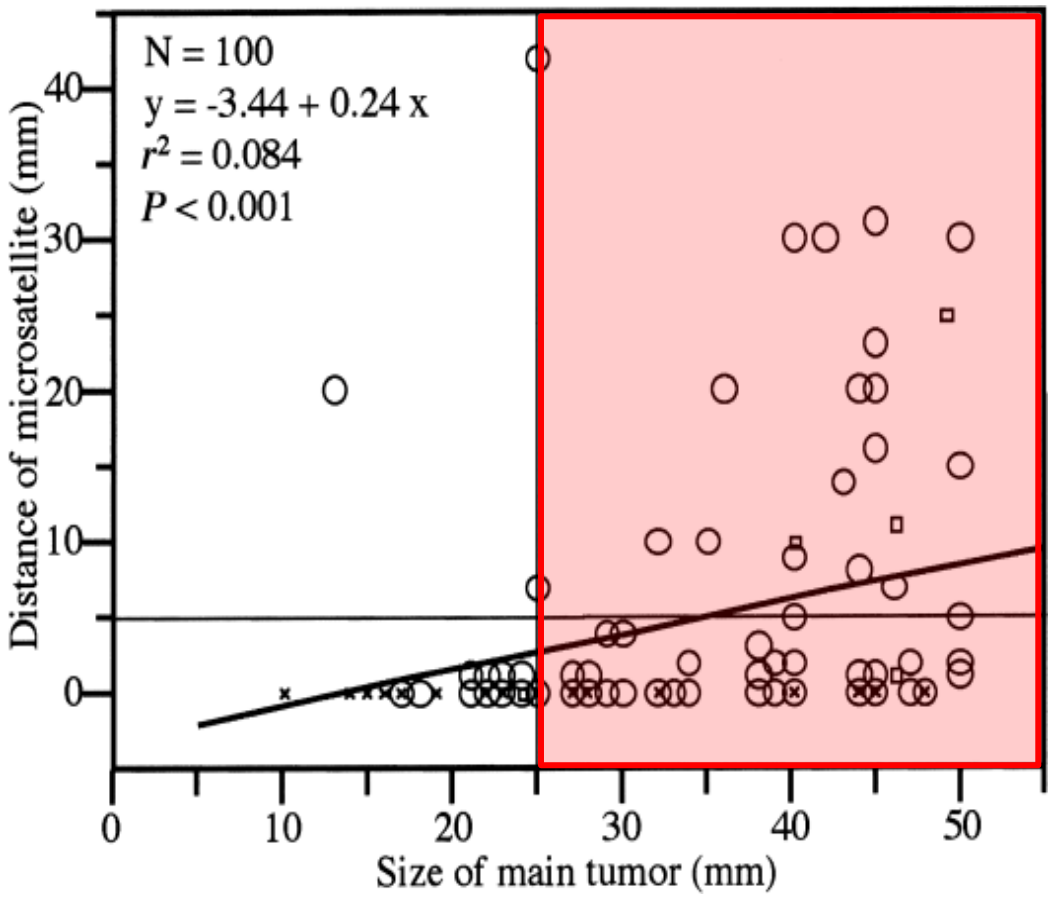
46% of patients with solitary HCC < 5 cm on imaging have microsatellites on histology

Sasaki A et al. Cancer 2005;103:299-306

Microsatellites Distribution in HCC: Implications for Loco-Regional Treatment

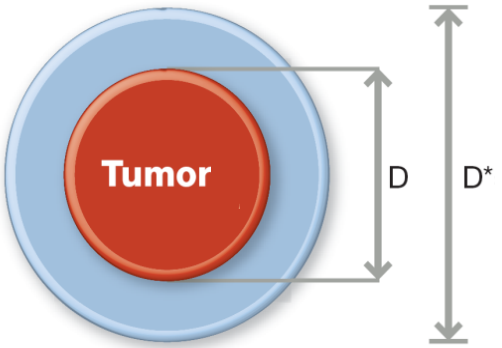


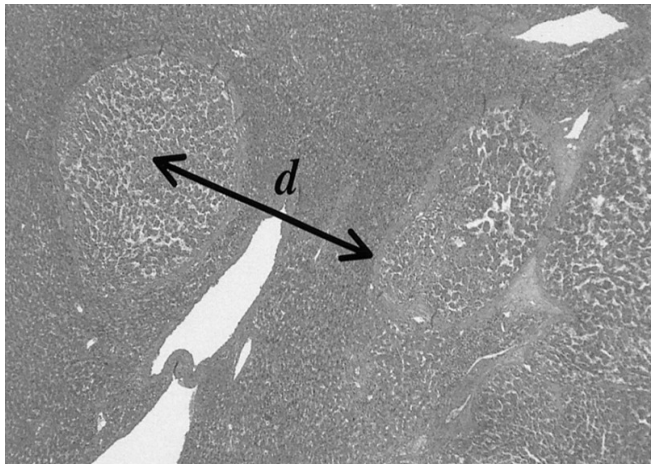


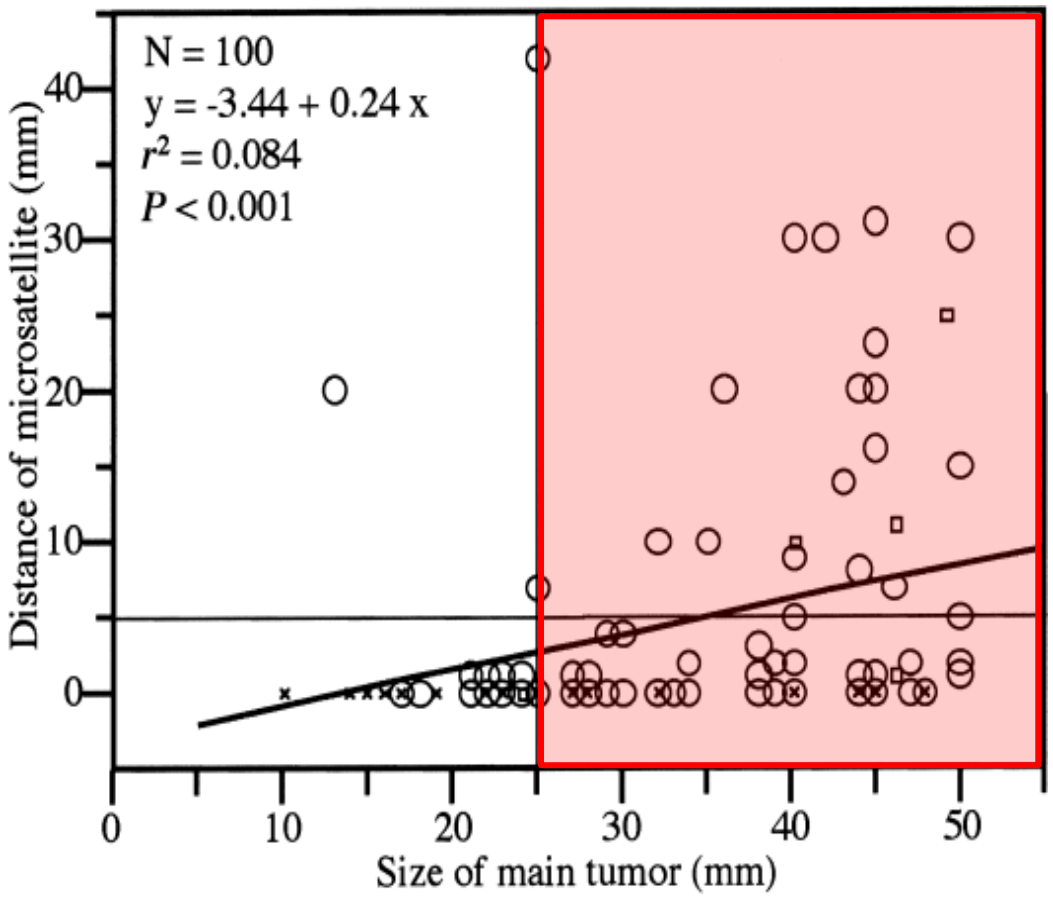


Sasaki A et al. Cancer 2005;103:299-306

Microsatellites Distribution in HCC: Implications for Loco-Regional Treatment

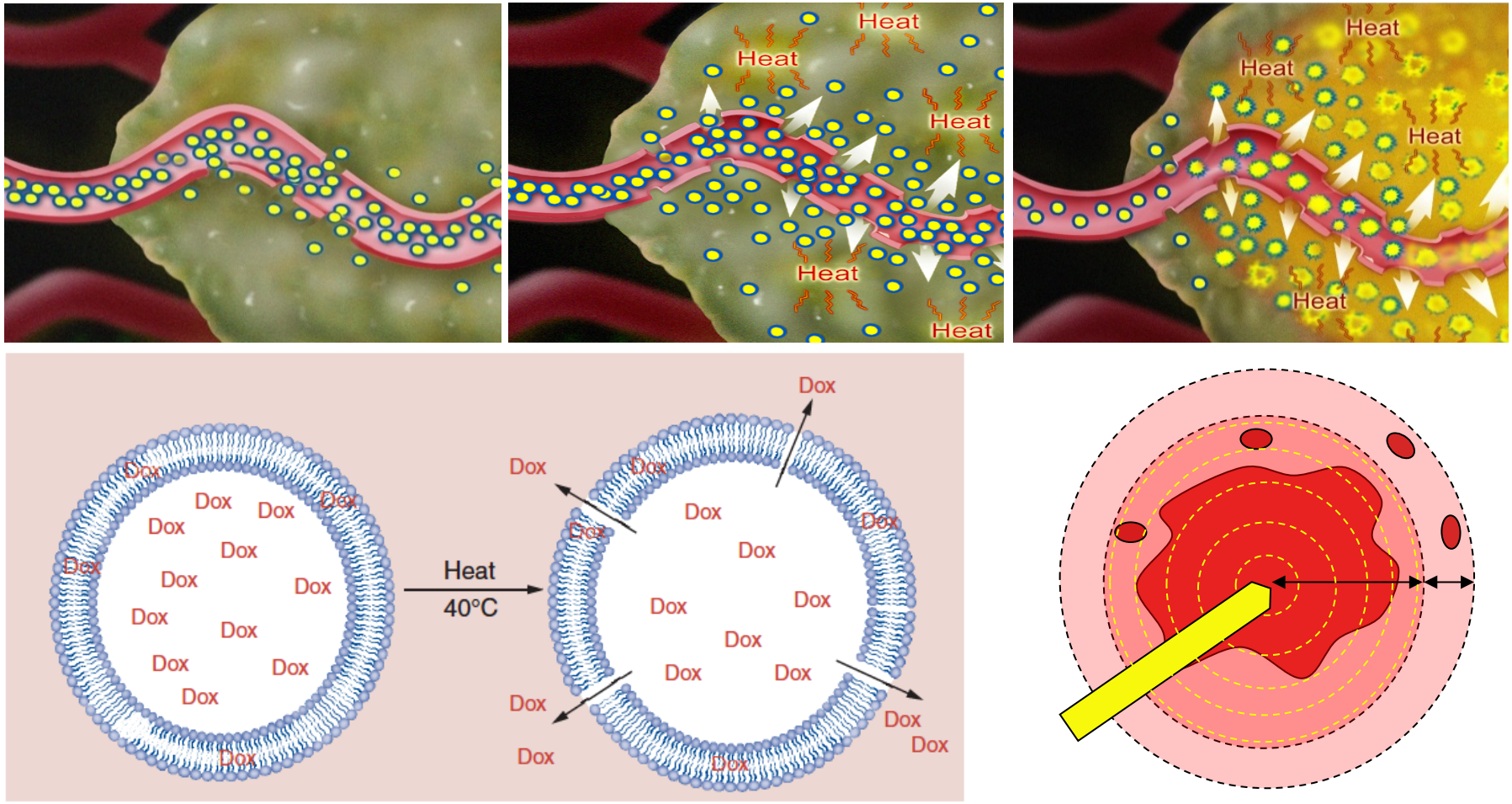






Sasaki A et al. Cancer 2005;103:299-306

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

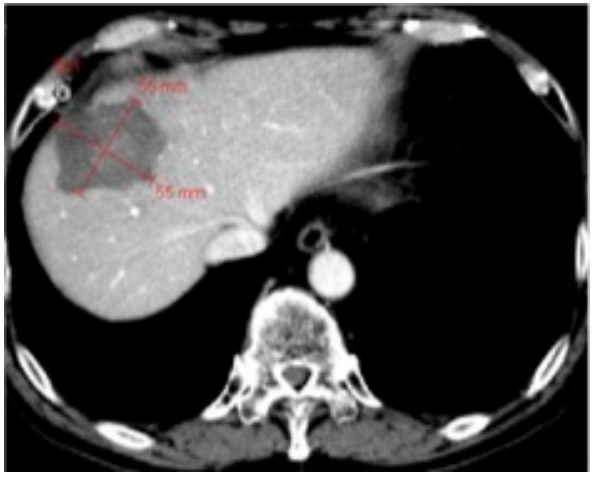


Lencioni R, Cioni D. Hepatic Oncol 2016;3:193-200

Lyso-Thermosensitive Liposomal Doxorubicin (LTLD): Case Example

Baseline CT Scan
(arterial & venous phases)

CT Scan after Treatment with RFA + LTLD
(5.5 x 5.5 cm ablation zone)



Lencioni R, Cioni D. Hepatic Oncol 2016;3:193-200

Enhancing the Effect of Image-Guided Ablation with Thermosensitive Liposomal Doxorubicin: the HEAT Study

Cancer Therapy: Clinical

Clinical Cancer Research

Phase III HEAT Study Adding Lyso-Thermosensitive Liposomal Doxorubicin to Radiofrequency Ablation in Patients with Unresectable Hepatocellular Carcinoma Lesions

Won Young Tak[1], Shi-Ming Lin[2], Yijun Wang[3], Jiasheng Zheng[4], Aldo Vecchione[5], Soo Young Park[1], Min Hua Chen[6], Stephen Wong[7], Ruocai Xu[8], Cheng-Yuan Peng[9], Yi-You Chiou[10], Guan-Tarn Huang[11], Jianqiang Cai[12], Basri Johan Jeet Abdullah[13], June Sung Lee[14], Jae Young Lee[15], Jong-Young Choi[16], Julieta Gopez-Cervantes[17], Morris Sherman[18], Richard S. Finn[19], Masao Omata[20], Michael O'Neal[21], Lukas Makris[22], Nicholas Borys[23], Ronnie Poon[24], and Riccardo Lencioni[25]

Tak WY et al. Clin Cancer Res 2018;24:73-83

The HEAT Study: CONSORT Flow Diagram and Baseline Characteristics

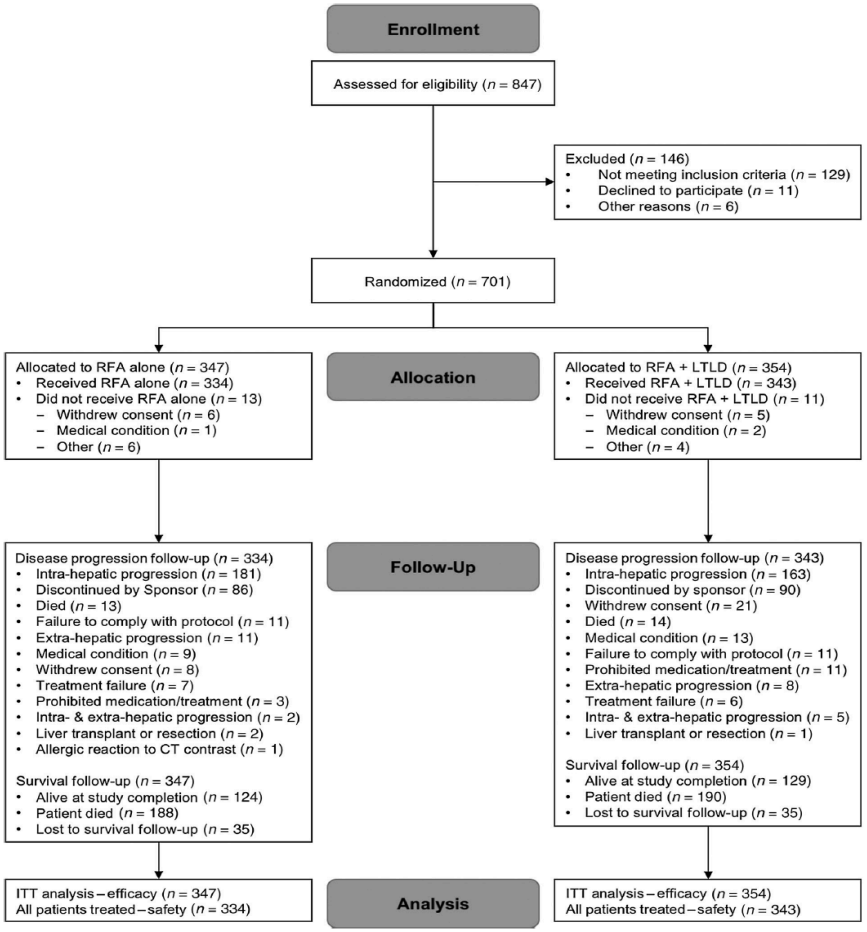


Table 1. Summary of demographics and baseline characteristics

	ITT Population	
	RFA alone (*n* = 347)	RFA + LTLD (*n* = 354)
Characteristics	***n*** **(%)**	***n*** **(%)**
Age, years		
18–64	207 (59.6)	202 (57.1)
65+	138 (39.8)	149 (42.1)
Missing	2 (0.6)	3 (0.8)
Sex		
Male	263 (75.8)	267 (75.4)
Female	84 (24.2)	87 (24.6)
Race		
Asian	321 (92.5)	312 (88.1)
Chinese	125 (36.0)	115 (32.5)
Korean	91 (26.2)	83 (23.4)
Taiwanese	62 (17.9)	66 (18.6)
Japanese	11 (3.2)	8 (2.3)
Other Asian	32 (9.2)	40 (11.3)
Caucasian	26 (7.5)	42 (11.9)
Child–Pugh class		
A	329 (94.8)	329 (92.9)
B	18 (5.2)	23 (6.5)
Missing	0 (0.0)	2 (0.6)
HCC etiology[a]		
Hepatitis B	203 (58.5)	207 (58.5)
Cirrhosis	196 (56.5)	205 (57.9)
Hepatitis C	89 (25.6)	92 (26.0)
Other/Unknown	25 (7.2)	33 (9.3)
Alpha-fetoprotein, ng/mL		
<200	241 (69.5)	232 (65.5)
≥200	86 (24.8)	97 (27.4)
Missing	20 (5.8)	25 (7.1)
BCLC stages		
A	219 (63.1)	234 (66.1)
B	116 (33.4)	109 (30.8)
Missing	12 (3.5)	11 (3.1)
Number of HCC lesions		
1	219 (63.1)	234 (66.1)
2	74 (21.3)	76 (21.5)
3	30 (8.6)	25 (7.1)
4	12 (3.5)	7 (2.0)
5	0 (0.0)	1 (0.3)
Missing	12 (3.5)	11 (3.1)
Maximum lesion diameter, cm		
3–5	286 (82.4)	289 (81.6)
>5–7	61 (17.6)	65 (18.4)

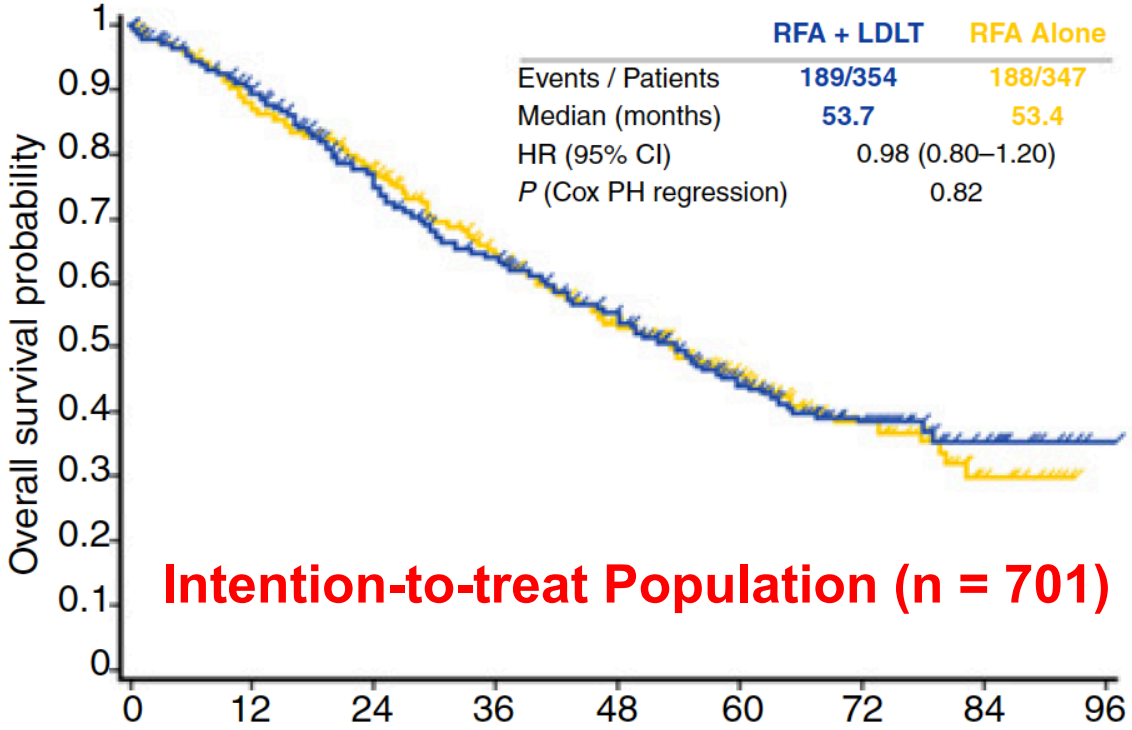
Tak WY et al. Clin Cancer Res 2018;24:73-83

The HEAT Study: Summary of RFA Treatment

Characteristic	RFA alone (n=347) n (%)	RFA + LTLD (n=354) n (%)
RFA approach		
Percutaneous	315 (90.8)	321 (90.7)
Open surgery	19 (5.5)	19 (5.4)
Laparoscopic	13 (3.7)	14 (4.0)
RFA device		
Angiodynamics	64 (18.4)	72 (20.3)
Boston Scientific	45 (13.0)	48 (13.6)
Covidien	225 (64.8)	223 (63.0)
Not treated	13 (3.8)	11 (3.1)
Treatment received		
Initial treatment	334 (96.3)	343 (96.9)
Completion treatment[a]	27 (7.8)	28 (7.9)
Retreatment 2[b]	23 (6.6)	26 (7.3)
Retreatment 3[b]	3 (0.9)	2 (0.6)
Retreatment 4[b]	1 (0.3)	0 (0.0)
Initial complete response[c]	327 (94.2)	337 (95.1)
Treatment failure[d]	7 (2.0)	6 (1.7)
RFA dwell time (initial treatment), minutes		
Median	65	60
Range	12-230	12-180

Tak WY et al. Clin Cancer Res 2018;24:73-83

The HEAT Study: Overall Survival (Intention-to-Treat Analysis)



Number at risk

RFA Alone	347	292	250	195	153	106	47	10	0
RFA + LDLT	354	303	244	200	160	102	59	18	2

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Tak WY et al. Clin Cancer Res 2018;24:73-83

The HEAT Study: Stepwise Multivariate Cox Modelling

Parameter	Model factor	Main factor P-value[a]	Hazard ratio [95% CI][b]
Overall Survival	Treatment	0.9147	0.99 [0.80, 1.22]
	Number of Tumors at Baseline [1 vs 2+]	<0.0001	
	RFA Duration [<45 min vs ≥45 min]	0.0116	
IRRC PFS	Treatment	0.7657	0.97 [0.79, 1.19]
	Number of Tumors at Baseline [1 vs 2+]	0.0001	
	RFA Duration [<45 min vs ≥45 min]	0.0506	
Investigator PFS	Treatment	0.5349	0.94 [0.78, 1.14]
	Number of Tumors at Baseline [1 vs 2+]	<0.0001	
	RFA Duration [<45 min vs ≥45 min]	0.0034	

Parameter/	Model factor	Treatment interaction P-value[c]
Overall Survival	Treatment	
	Number of Baseline Tumors [1 vs 2+]	0.1706
	RFA Duration [<45 min vs ≥45 min]	0.4379
IRRC PFS	Treatment	
	Number of Baseline Tumors [1 vs 2+]	0.5890
	RFA Duration [<45 min vs ≥45 min]	0.7154
Investigator PFS	Treatment	
	Number of Baseline Tumors [1 vs 2+]	0.1353
	RFA Duration [<45 min vs ≥45 min]	0.7297

Tak WY et al. Clin Cancer Res 2018;24:73-83

The HEAT Study: Stepwise Multivariate Cox Modelling

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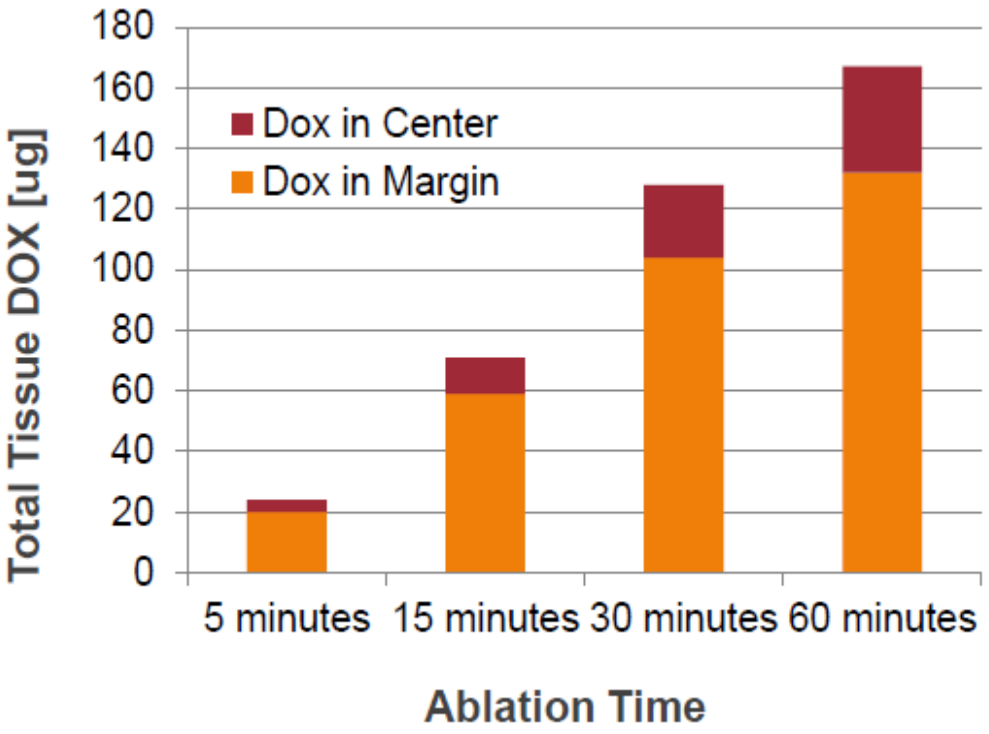
Parameter	Model factor	Main factor P-value[a]	Hazard ratio [95% CI][b]	Treatment interaction P-value[d]
Overall Survival	Treatment	0.9285	0.99 [0.81, 1.22]	
	Number of Baseline Tumors [1 vs 2+]	0.0627		0.1599
	RFA Duration [<45 min vs ≥45 min]	0.3944		0.4449
	Number of Baseline Tumors x RFA Duration	0.5501		0.0092
IRRC PFS	Treatment	0.7965	0.97 [0.79, 1.19]	
	Number of Baseline Tumors [1 vs 2+]	0.6011		0.5305
	RFA Duration [<45 min vs ≥45 min]	0.8304		0.7251
	Number of Baseline Tumors x RFA Duration	0.1645		0.1371
Investigator PFS	Treatment	0.5376	0.94 [0.78, 1.14]	
	Number of Baseline Tumors [1 vs 2+]	0.3478		0.1188
	RFA Duration [<45 min vs ≥45 min]	0.8064		0.7788
	Number of Baseline Tumors x RFA Duration	0.1442		0.0844

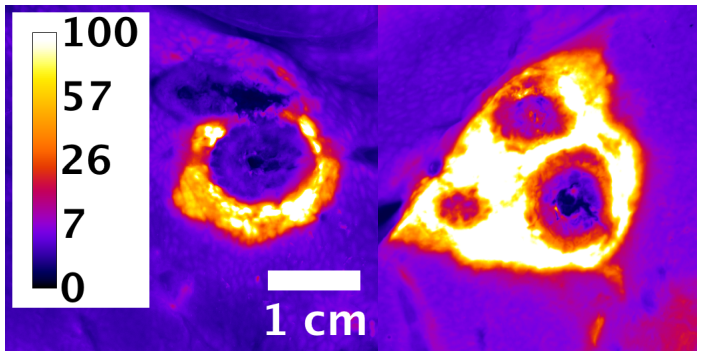
Tak WY et al. Clin Cancer Res 2018;24:73-83

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



Prolonged heating achieves optimal doxorubicin tissue concentration

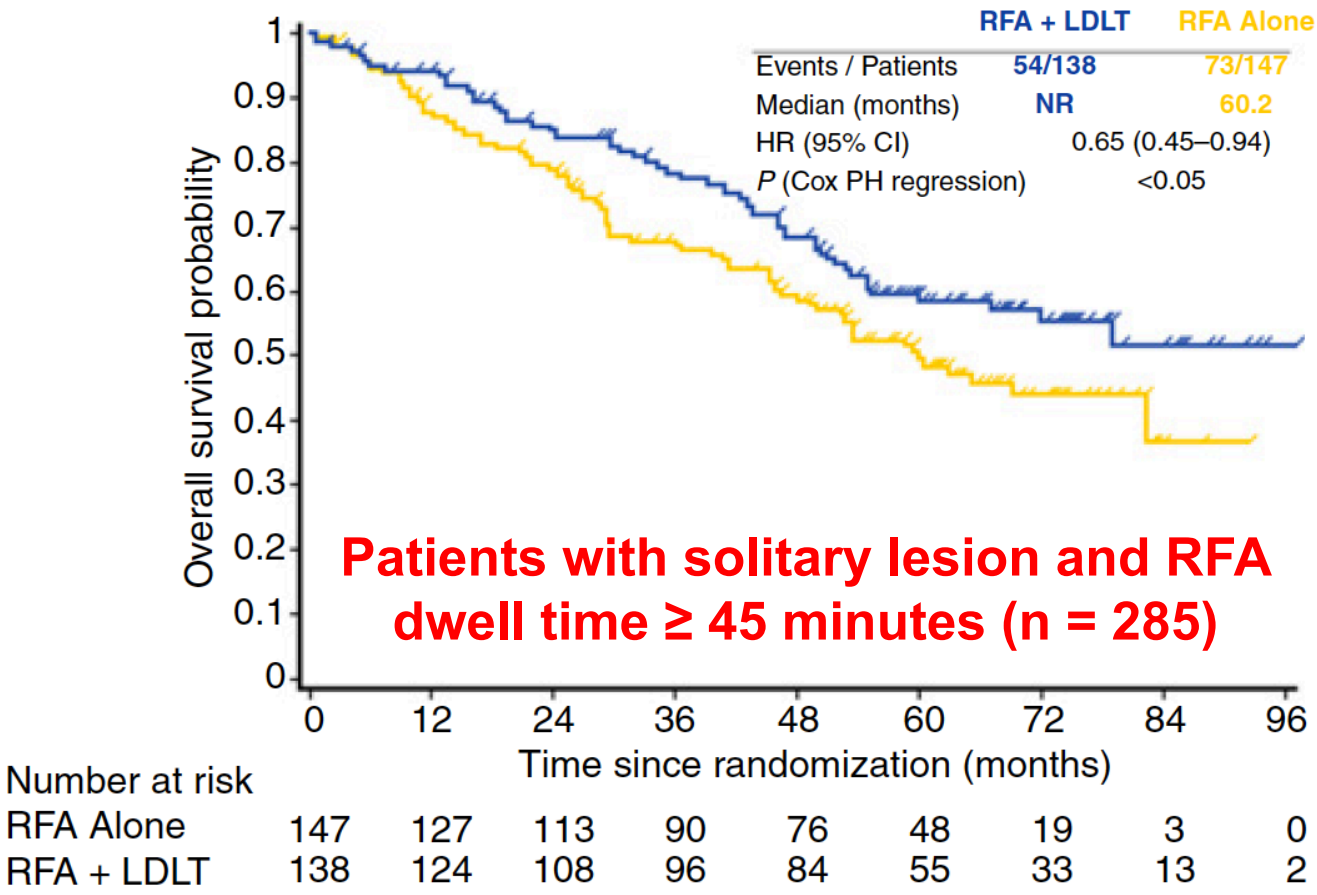
Fluorescence mapping of doxorubicin distribution in pigs treated with RFA plus ThermoDox



15 min **45 min**

Swenson CE et al. PLoS One 2015;10:e0139752

The HEAT Study: Overall Survival (Post-Hoc Analysis)



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Tak WY et al. Clin Cancer Res 2018;24:73-83

The HEAT Study: Treatment-Related Adverse Events (5% or more)

Table 3. Incidence of treatment-related[a] adverse events (≥5% of patients in either group; safety population)

	RFA alone (n = 334) %				RFA + LTLD (n = 343) %			
Preferred term	**All grades**	**Grade 3**	**Grade 4**	**Grade 5**	**All grades**	**Grade 3**	**Grade 4**	**Grade 5**
Overall incidence	35	12	<1	<1	83[b]	21	33	<1
Alopecia	<1	0	0	0	49[b]	3	0	0
Neutropenia	4	<1	<1	0	50[b]	13	29	0
Leukopenia	4	<1	0	0	38[b]	10	7	0
Thrombocytopenia	4	2	0	0	9[b]	4	<1	0
Aspartate aminotransferase increased	11	5	0	0	12	4	<1	0
Nausea	7	0	0	0	10	0	0	0
Alanine aminotransferase increased	10	3	0	0	10	3	0	0
Pyrexia	7	0	0	0	7	0	0	0
Blood bilirubin increased	8	1	<1	0	7	2	<1	0
Vomiting	2	0	0	0	6[b]	0	0	0
Decreased appetite	<1	0	0	0	5[b]	0	0	0

Abbreviation: AE, adverse event.

[a]Treatment-related AEs are defined as AEs that are recognized on or after the date of the first dose and throughout study duration AND related to study drug.

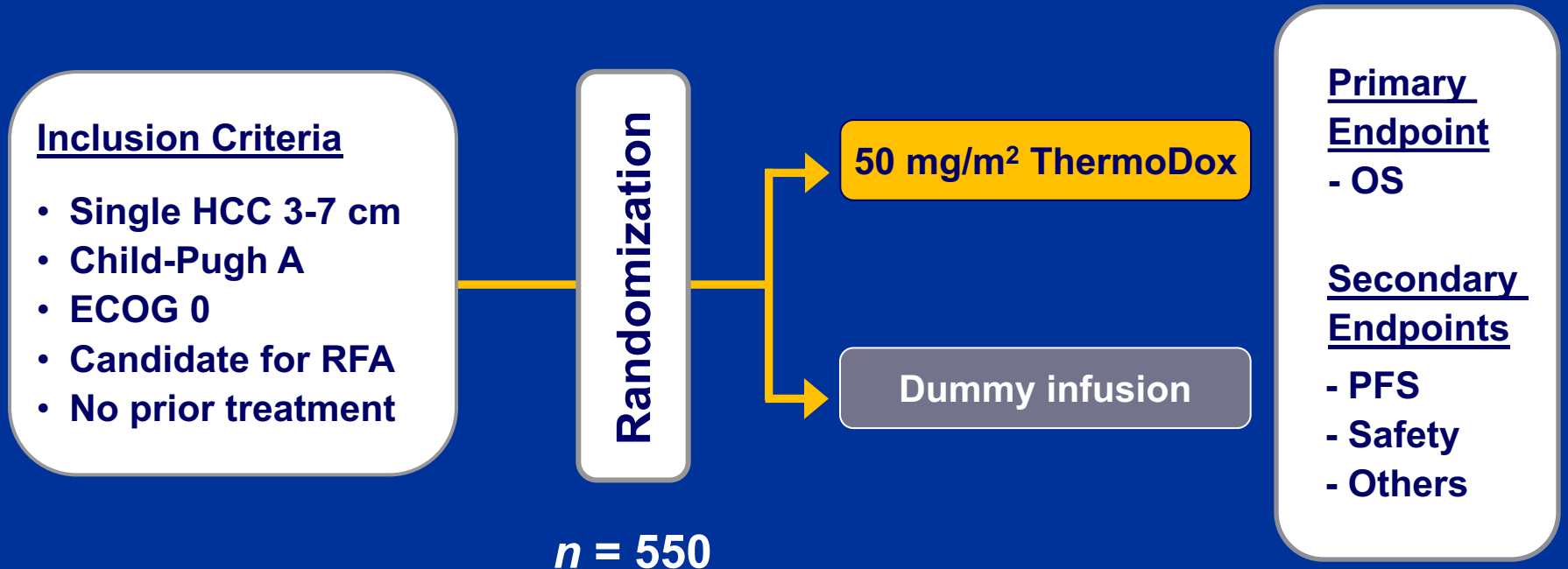
[b]Indicates a significant difference for the specific AE incidence between the two treatment groups at the 0.05 significance level, using Fisher exact test.

No difference in deaths resulting from any treatment-emergent SAE (2% in both arms: RFA alone n= 6; RFA+LTLD n= 7)

Tak WY et al. Clin Cancer Res 2018;24:73-83

The OPTIMA Study: A Phase III RCT of RFA plus LTLD vs RFA Alone Using a Standardized Ablation Protocol

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



www.clinicaltrials.gov - NCT02112656

Rethinking our Approach to Intermediate-Size HCC: From Palliation to Cure

- 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), LTLD plus RFA increases overall survival
  - HR of 0.65 for OS in subgroup analysis ($p < 0.05$)
- This hypothesis is now being tested in the ongoing OPTIMA study