Updates in Liver Directed Therapy for Liver Metastasis: The Surgical Perspective

Andrew D. Newton MD

Ochsner MD Anderson Multidisciplinary Cancer Update 2025

October 10, 2025

Ochsner MD Anderson Cancer Center

Making Cancer History®

Disclosures

- No disclosures

Overview

- Histotripsy
  - Explanation of the technology
  - Clinical data
  - Limitations
- Microwave Ablation for Colorectal Liver Metastases
  - COLLISION Trial
- Hepatic Artery Infusion Therapy for Colorectal Liver Metastases
  - Floxuridine Dosing

Histotripsy

- Short, high pressure ultrasound waves that cause local tissue pressure changes and mechanical tissue liquefaction.
- Can be visualized in real time
- Spares collagenous tissues including blood vessels and bile ducts

Histotripsy

Histotripsy

Radiology

ORIGINAL RESEARCH • VASCULAR AND INTERVENTIONAL RADIOLOGY

The #HOPE4LIVER Single-Arm Pivotal Trial for Histotripsy of Primary and Metastatic Liver Tumors

Mishal Mendiratta-Lala, MD • Philipp Wiggermann, MD • Maciej Pech, MD • Xavier Serres-Créixams, MD, PhD • Sarah B. White, MD • Clifford Davis, MD • Osman Ahmed, MD • Neehar D. Parikh, MD, MS • Mathis Planert, MD • Maximilian Thormann, MD • Zhen Xu, PhD • Zachary Collins, MD • Govindarajan Narayanan, MD • Guido Torzilli, MD • Clifford Cho, MD • Peter Littler, MD • Tze Min Wah, MD, PhD • Luigi Solbiati, MD • Timothy J. Ziemlewicz, MD**

Mediratta-Lal et al. Radiology. 2024.

Table 1: Participant Characteristics

Variable	Participants in United States (n = 21)	Participants in European Union and England (n = 23)	Combined (n = 44)
Age (y)*	64.0 ± 15.2	63.8 ± 9.3	63.9 ± 12.3
Sex			
Female	8 (38)	14 (61)	22 (50)
Participants with HCC	11 (52)	7 (30)	18 (41)
Total no. of liver tumors			
1–5	11 (100)	6 (86)	17 (94)
6–10	0	0	0
11–15	0	1 (14)	1 (6)
Participants with metastatic non-HCC	10 (48)	16 (70)	26 (59)
Total no. of liver tumors			
1–5	7 (70)	10/15 (67)	17/25 (68)
6–10	2 (20)	1/15 (7)	3/25 (12)
11–15	0	0	0
16–20	0	1/15 (7)	1/25 (4)
>20	1 (10)	3/15 (20)	4/25 (16)
Primary tumor location			
Colon	2 (20)	3 (19)	5 (19)
Rectum	3 (30)	2 (12)	5 (19)
Breast	1 (10)	3 (19)	4 (15)
Pancreas	2 (20)	3 (19)	5 (19)
Other‡	2 (20)	5 (31)	7 (27)

>20	1 (10)	3/15 (20)	4/25 (16)
Primary tumor location			
Colon	2 (20)	3 (19)	5 (19)
Rectum	3 (30)	2 (12)	5 (19)
Breast	1 (10)	3 (19)	4 (15)
Pancreas	2 (20)	3 (19)	5 (19)
Other‡	2 (20)	5 (31)	7 (27)

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Tumor Location and Size

Table 2: Target Tumor Characteristics and Histotripsy Treatment

Variable	Evaluated Tumors		
	United States (n = 23)	European Union and England (n = 21)	Combined (n = 44)
Tumor location segment			
2	1 (4)	5 (24)	6 (14)
3	12 (52)	12 (57)	24 (54)
4a	0	1 (5)	1 (2)
4b	6 (26)	1 (5)	7 (16)
5	2 (9)	1 (5)	3 (7)
6	2 (9)	1 (5)	3 (7)
7	0	0	0
8	0	0	0
Pretreatment tumor longest diameter (cm)	1.5 ± 0.6	1.4 ± 0.5	1.5 ± 0.6
Pretreatment tumor volume (cm^3)	1.8 ± 2.0	1.3 ± 2.0	1.6 ± 2.0
Post-histotripsy treatment zone longest diameter (cm)	3.7 ± 1.7	3.4 ± 1.2	3.6 ± 1.4
Post-histotripsy treatment zone volume (cm^3)	19.1 ± 19.7	15.7 ± 14.8	17.5 ± 17.4
Treatment zone volume greater than or equal to targeted tumor volume	22 (96)	21 (100)	43 (98)
Full tumor coverage	21 (91)	21 (100)	42 (95)
Technique efficacy at 30 days*	14/20 (70)	16/16 (100)	30/36 (83)

Note.—Unless otherwise specified, data are numbers of tumors; data in parentheses are percentages. Mean data are ± SDs. The parameters were reported by the core laboratory.

* Data are numerators/denominators; data in parentheses are percentages.

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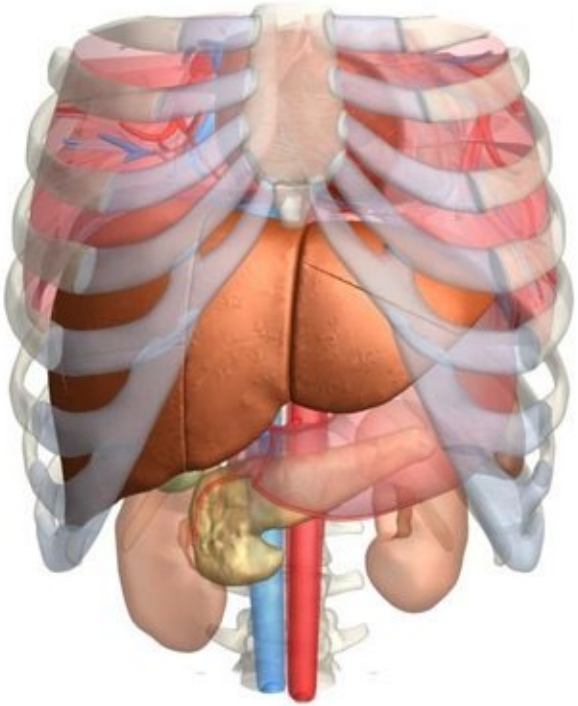
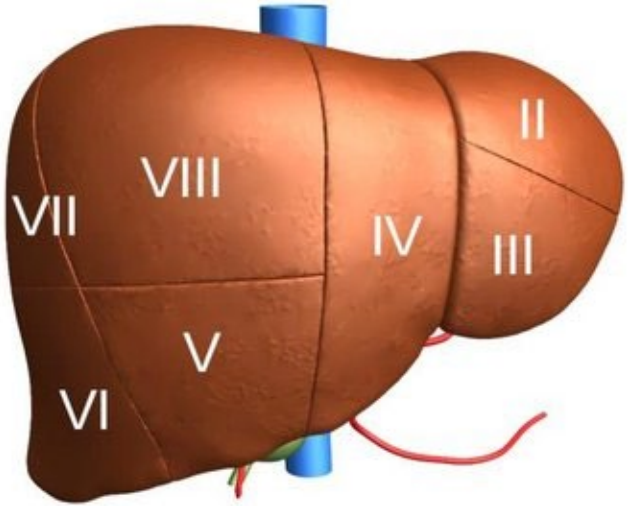
Anatomic Liver Segments





Outcomes

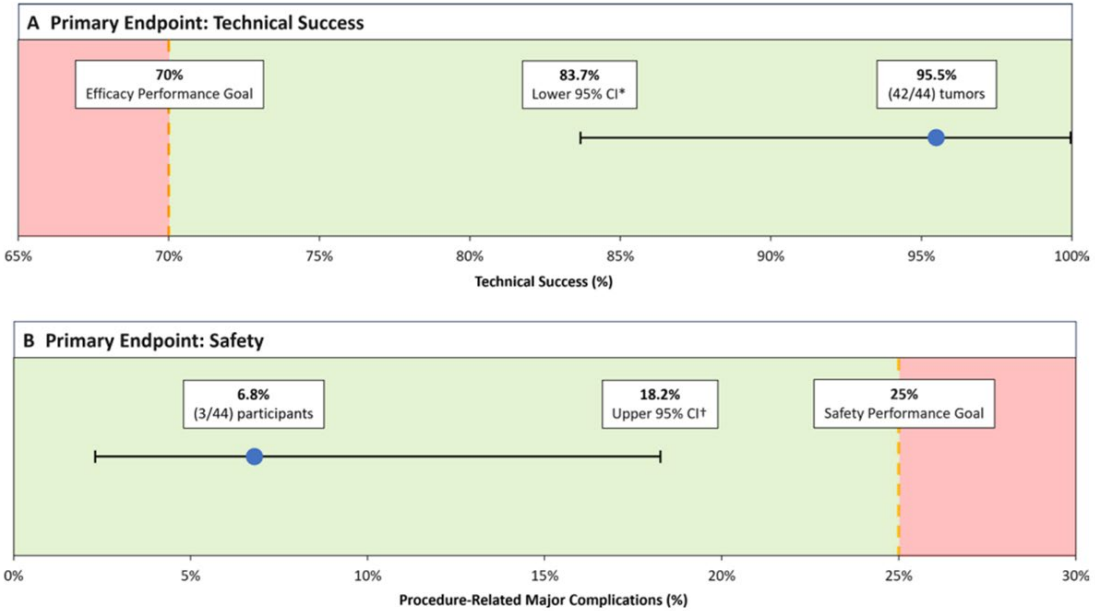


Figure 3: Graphs show primary end points of **(A)** technical success and **(B)** safety of procedure-related major complications. * = Estimated by bootstrap sampling with replacement method to account for potential within-subject lesion correlations. Subject was the bootstrap sampling unit, 1 000 000 iterations for bootstrap resampling were performed, and the bootstrap method was the bias-corrected and accelerated method. † = Two-sided 95% Wilson score CI.

Procedure related major complications

- Sepsis in setting of previous biliary stent
- 2-day admission for pleuritic pain
- Liver failure 12 days post-procedure in patient with innumerable metastatic breast tumors

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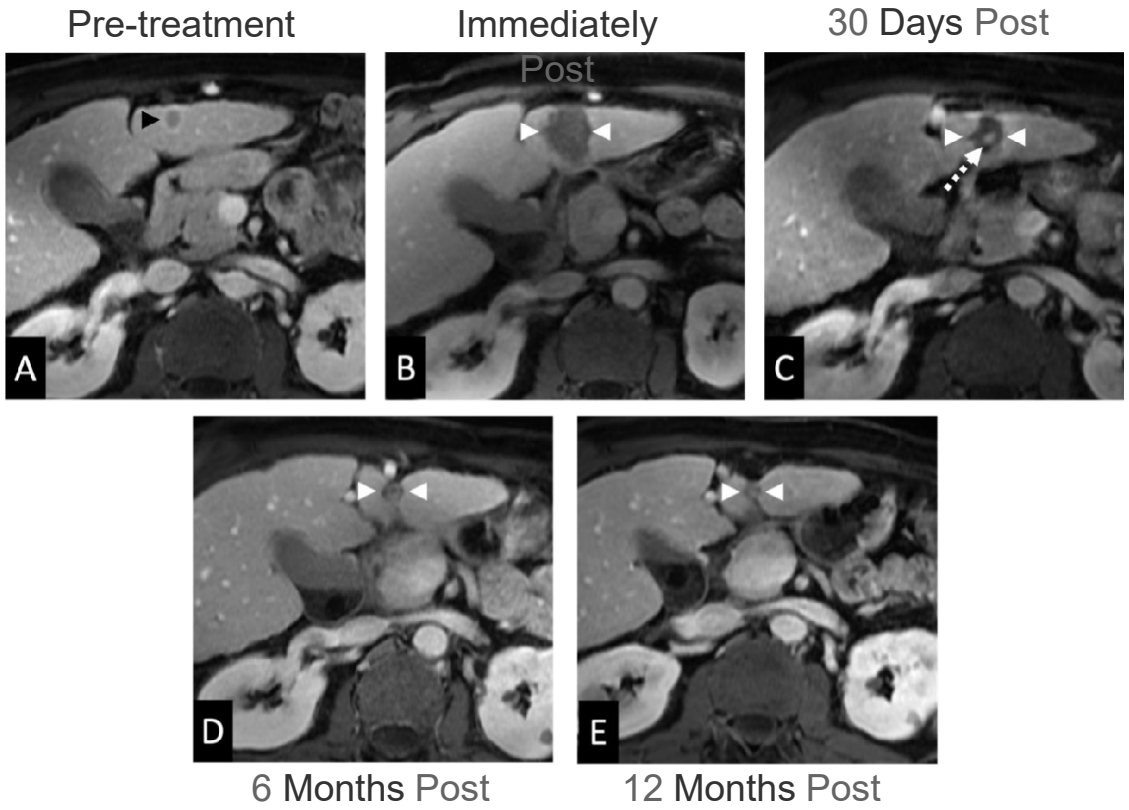
Histotripsy


The #HOPE4LIVER single-arm Pivotal Trial for Histotripsy of Primary and Metastatic Liver Tumors

Zieniewicz, Timothy J., Critchfield, Jeffrey J., Mendiratta-Lala, Mishal, Wiggermann, Philipp, Pech, Maciej, Sarwa-Crézeans, Xavier, Lubner, Meghan, Wah, Tze Min, Littler, Peter, Davis, Clifford R., Narayanan, Govindarajan; White, Sarah B.; Ahmed, Osman; Collins, Zach S.; Parikh, Neehar D.; Planert, Mathis; Thormann, Maximilian; Iezzi, Guido; Solbiati, Luigi A.; Cho, Clifford S.

- One year follow up for patients undergoing histotripsy in the HOPE4Liver trial
- Imaging assessment of nodular or mass-like enhancement along the treatment periphery at 30 days, 6 months, and 12 months
- Second post hoc analysis at each of those time points by “core lab”

Post-Histotripsy Imaging



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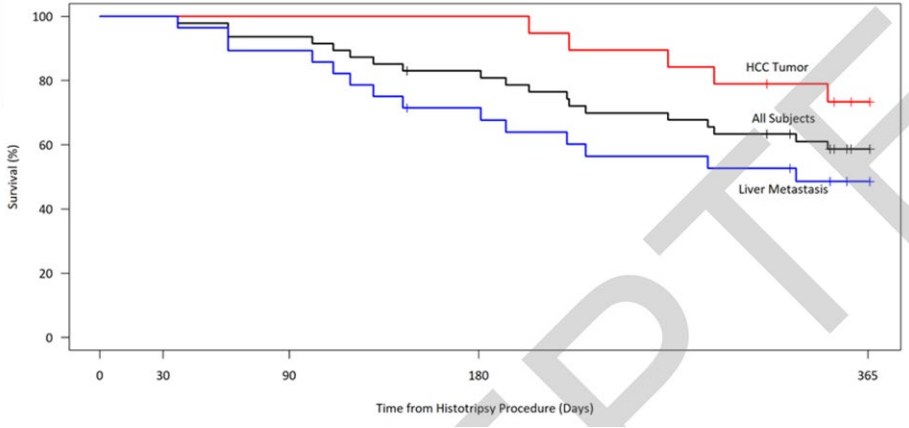
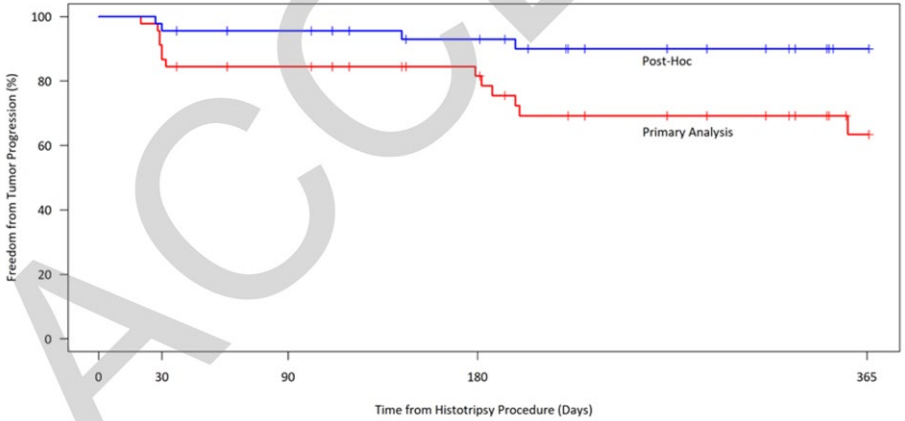
Overall and Progression Free Survival





Radiographic Success of Treatment

Table 3: Quantitative Tumor Assessments (Core Lab Assessed)

Variable	Post-Histotripsy	30-Day	6-Month	1-Year
Total tumors treated and followed	52	52	41	30
Total tumors with core lab assessable images*	51	47	35	23
Treatment zone longest diameter (cm)	3.4 (0.9, 8.8)	2.5 (0.8, 6.3)	1.8 (0.6, 6.9)	1.4 (0.6, 5.3)
Treatment zone involution by diameter (assessed)	-	46	34	22
Yes	-	41 (89.1)	27 (79.4)	18 (81.8)
No	-	5 (10.9)	7 (20.6)	4 (18.2)
If yes, treatment zone involution (%, by diameter)	-	28.8 (1.0, 62.6)	50.7 (4.4, 80.9)	65.0 (4.8, 86.2)
Treatment zone volume (cc)	11.6 (0.1, 75.9)	4.9 (0.1, 82.0)	1.5 (0.0, 96.3)	0.8 (0.0, 31.6)
Treatment zone involution by volume (assessed)	-	46	34	22
Yes	-	42 (91.3)	27 (79.4)	18 (81.8)
No	-	4 (8.7)	7 (20.6)	4 (18.2)
If yes, treatment zone involution (%, by volume)	-	64.2 (15.6, 94.8)	92.3 (10.4, 98.9)	96.4 (42.3, 99.7)

*Images were not assessable if deemed inadequate for review by the core laboratory or an image was not provided by the site.

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Radiographic Success of Treatment

Table 4: Qualitative Tumor Assessment (Core Lab Assessed)

Variable	30-Day	6-Month	1-Year
Tumors at follow-up	52	41	30
Primary Assessment	48	35	24
Nodular or mass-like area of enhancement along the edge or margin of the treatment volume			
Yes	8 (16.7)	7 (20)	2 (8.3)
No	38 (79.2)	28 (80)	22 (91.7)
Unknown	2 (4.2)	0 (0)	0 (0)
Post-Hoc Assessment	48	36	25
Treatment area of another locoregional therapy confounds the read			
Yes	5 (10.4)	3 (8.3)	1 (4)
No	41 (85.4)	32 (88.9)	23 (92)
Indeterminate	2 (4.2)	1 (2.8)	1 (4)
Area of enhancement that is representative of a vessel within the treated area			
Yes	10 (20.8)	9 (25)	5 (20)
No	36 (75)	26 (72.2)	20 (80)
Indeterminate	2 (4.2)	1 (2.8)	0 (0)
Nearby tumors that may introduce ingrowth into the targeted area			
Yes	11 (22.9)	7 (19.4)	4 (16)
No	37 (77.1)	29 (80.6)	21 (84)
Indeterminate	0 (0)	0 (0)	0 (0)
In your opinion, based on this visit's images, is there residual targeted tumor or progression of the targeted tumor?			
Yes	2 (4.2)	1 (2.8)	1 (4)
No	43 (89.6)	33 (91.7)	24 (96)
Indeterminate	3 (6.3)	2 (5.6)	0 (0)

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Histotripsy

Contents lists available at ScienceDirect

Journal of Gastrointestinal Surgery

journal homepage: www.jogs.org

Original Article

The first international experience with histotripsy: a safety analysis of 230 cases

Chase J. Wehrle [a,*], Kevin Burns [b], Evan Ong [c], Allison Couillard [d], Neehar D. Parikh [e], Elaine Caoili [f], JaeKeun Kim [a], Federico Aucejo [a], Andrea Schlegel [a], Emily Knott [a], Paul Laeseke [d], J. Philip Boudreaux [g], Philipp von Breitenbuch [h], Mikhail Silk [i], Mohamed Alassas [c], Andrew Guzowski [j], Brian Fuller [b], Erica Knavel Koepsel [d], Brock Hewitt [k], Mishal Mendiratta-Lala [f], David C.H. Kwon [a]

- 510 tumors in 295 patients in 18 centers
- Safety data from 230 patients

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Table 1
Information for included patients.

Variable	Total (N = 230)
Age, y	60 (58–67)
Male sex, n (%)	94 (41.0)
Number tumors treated, n (%)	
1	170 (58.0)
2	69 (23.0)
3	37 (13.0)
> 3	19 (6.0)
Size of tumor treated, cm	2.85
Tumor type/primary tumor site, n (%)	
Colorectal	117 (40.0)
Hepatocellular carcinoma	31 (11.0)
Neuroendocrine tumor	46 (16.0)
Cholangiocarcinoma	23 (8.0)
Breast	26 (9.0)
Pancreatic	30 (10.0)
Other	22 (7.0)
Time of treatment, min	22.6
Liver segments treated, n (%)	
I	9 (2.0)
II	60 (12.0)
III	140 (27.0)
IVA/B	99 (19.0)
V	79 (15.0)
VI	96 (18.0)
VII	29 (6.0)
VIII	8 (2.0)
	Outcomes of histotripsy (N = 230)
Any complication, n (%)	12 (5.2)
No complication, n (%)	218 (94.8)
Clavien-Dindo grade, n (%) [21]	
I	5 (2.2)
II	4 (1.7)
III	0 (0.0)
IV	0 (0.0)
V	3 (1.3)
CCI (points), median (IQR) [22]	0 (0–0)
Readmission, n (%)	6 (2.6)

CCI, Comprehensive Complication Index.

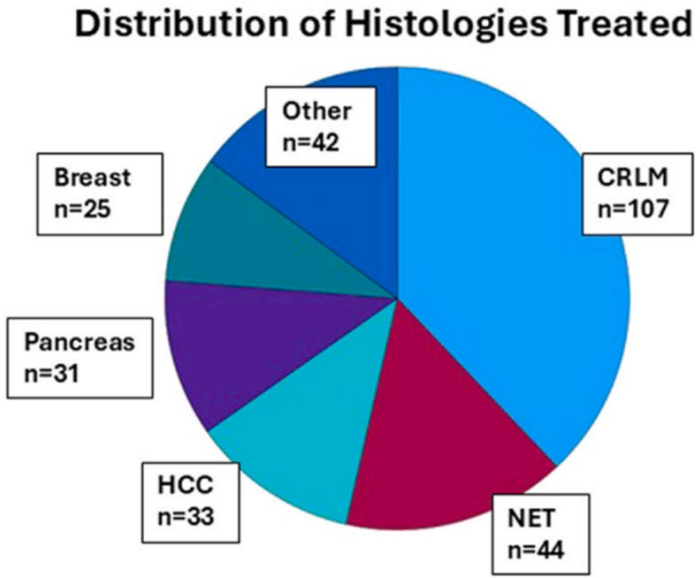

Figure 2. Treated lesions by liver segment. CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; NET, neuroendocrine tumor.

All grade 5 complications were related to progression of disease

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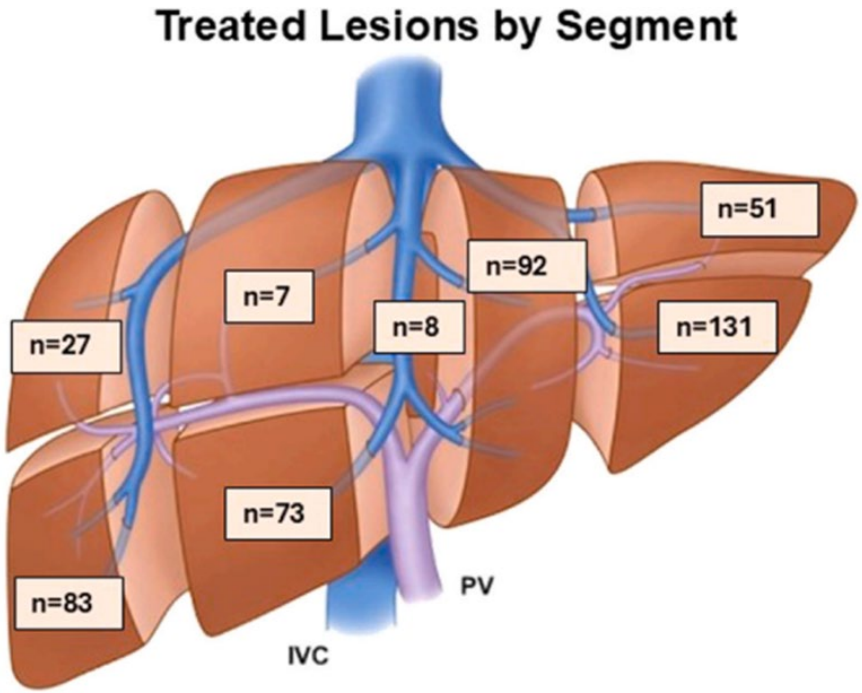

Figure 3. Treated lesions by histologic subtype. IVC, inferior vena cava; PV, portal vein.

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Histotripsy

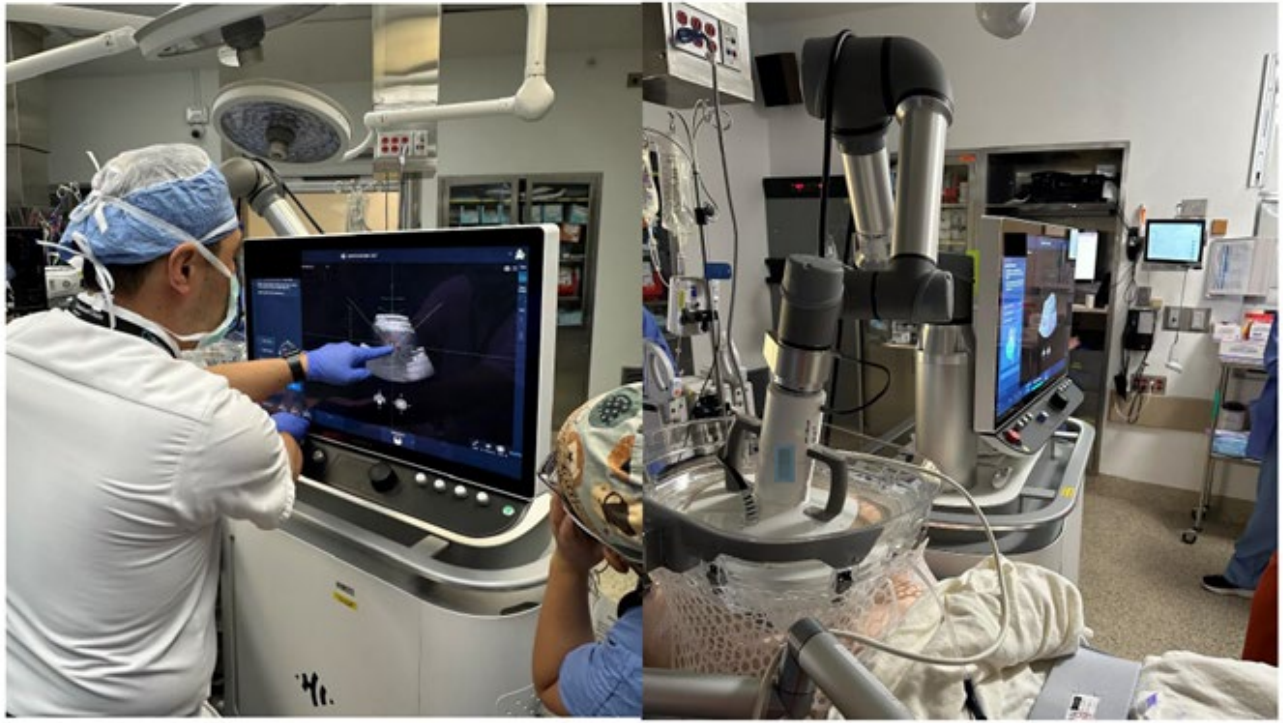
cancers

MDPI

Review

Histotripsy of Liver Tumors: Patient Selection, Ethical Discussions, and How We Do It

Melis Uysal †, Chase J. Wehrle †, Sangeeta Satish, Emily Knott, Hanna Hong, Erlind Allkushi, Andrea Schlegel, Eren Berber, Federico Aucejo, JaeKeun Kim and David C. H. Kwon *



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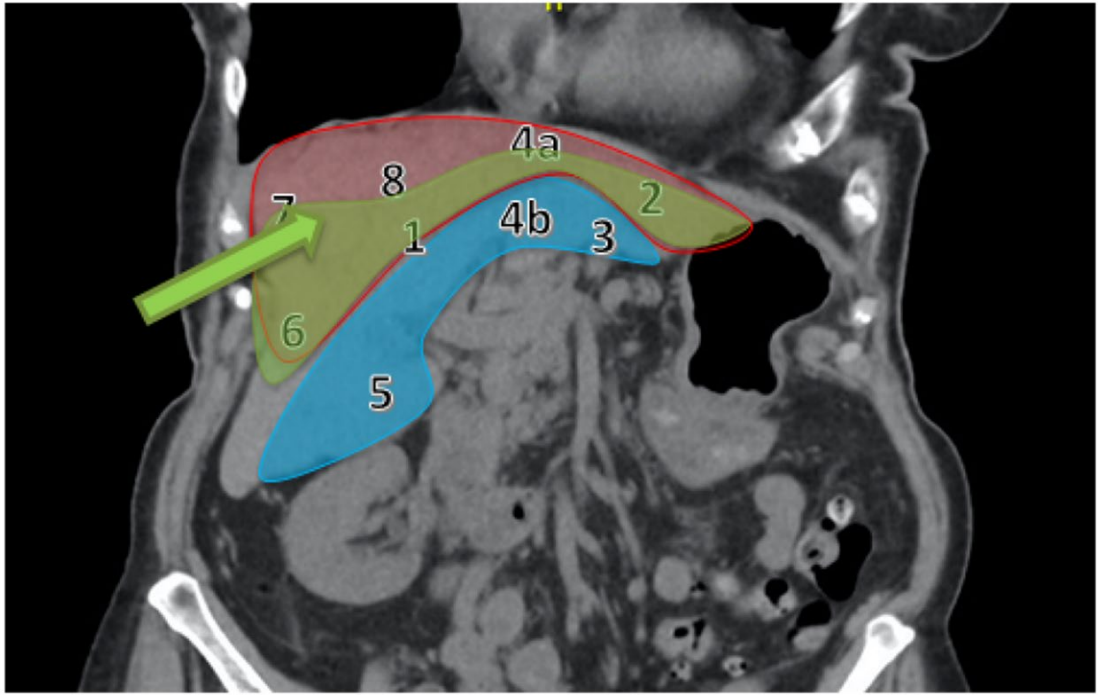
Likelihood of Technical Success



Likely

Moderately likely

Unlikely

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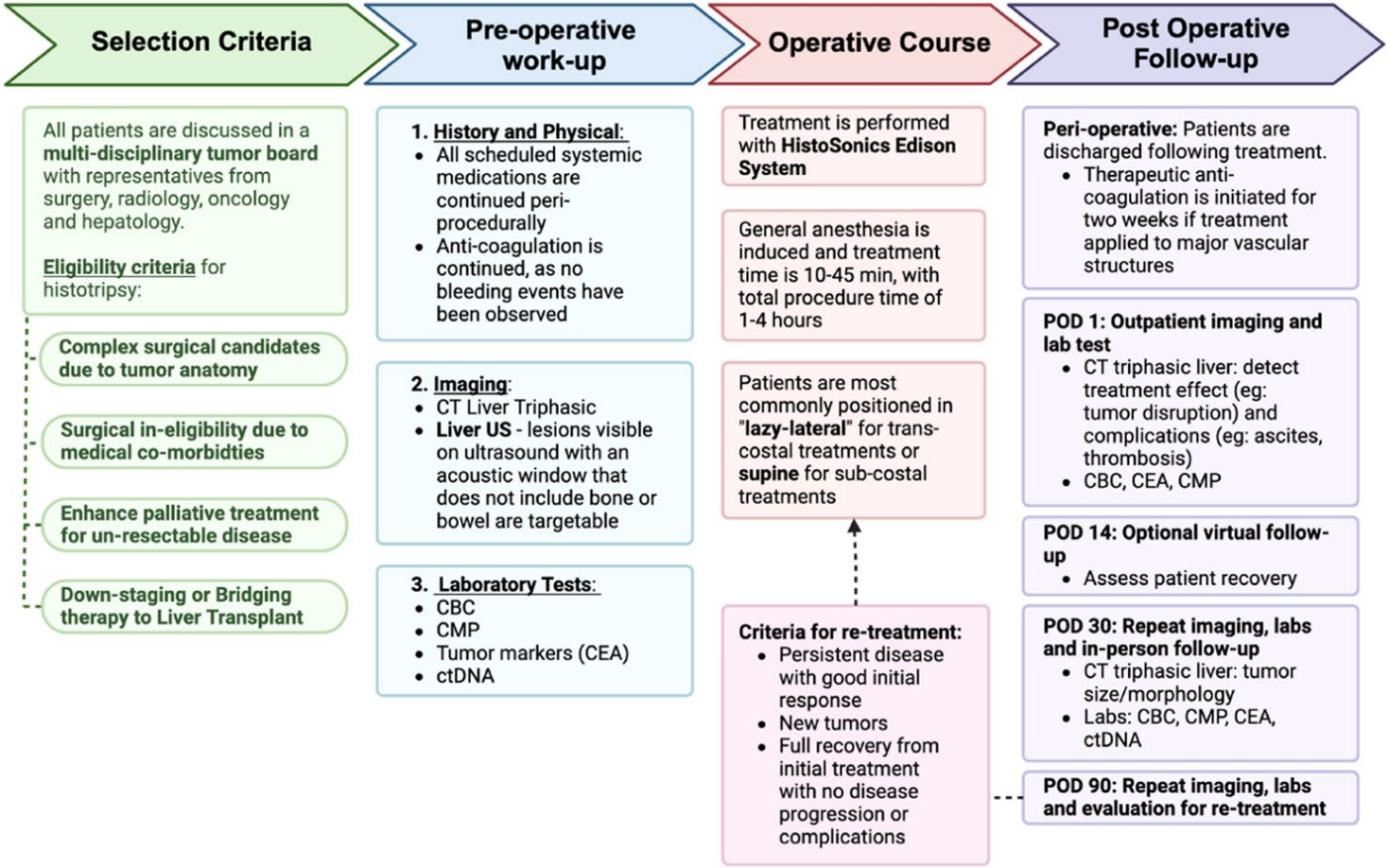

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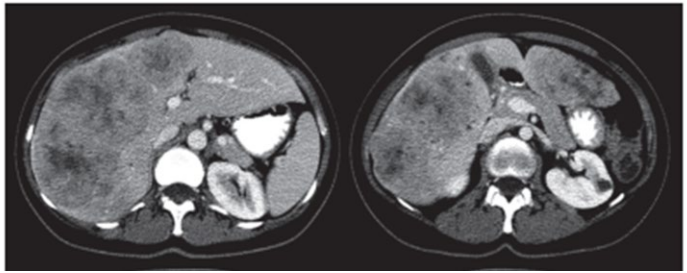
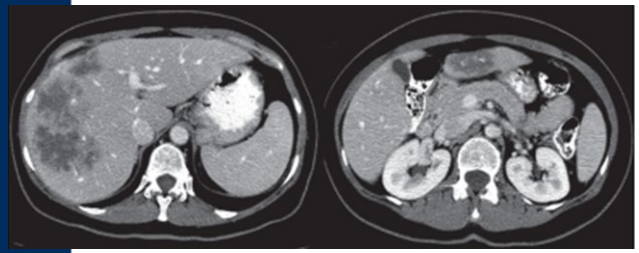
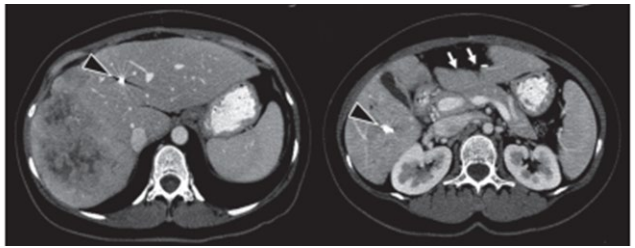
Two Stage Hepatectomy for Bilobar Colorectal Liver Metastases

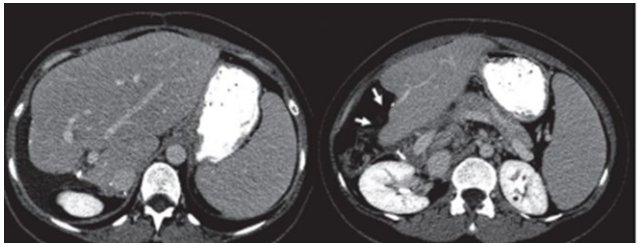
Bilobar Liver Metastases, Right Hepatectomy Needed



4-6 cycles of chemotherapy → 4 weeks → Clear Left Liver → 2 weeks → Portal Vein Embolization → 4-6 weeks → Right or extended right hepatectomy



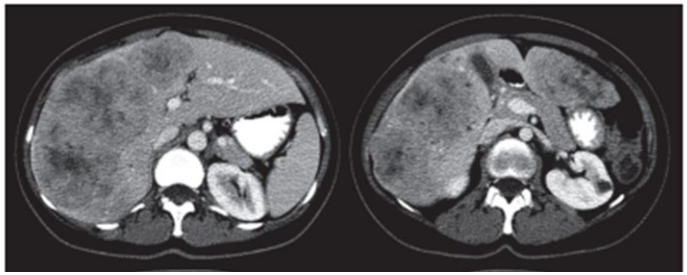




Broquet. JCO. 2011

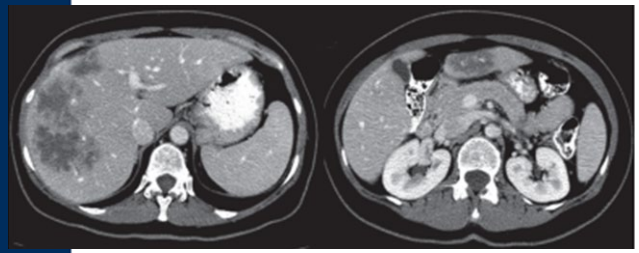
Histotripsy Followed by Right Hepatectomy for Bilobar Colorectal Liver Metastases

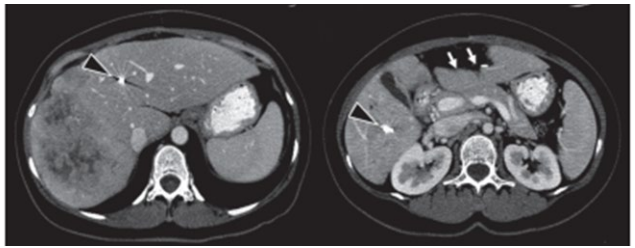
Bilobar Liver Metastases, Right Hepatectomy Needed

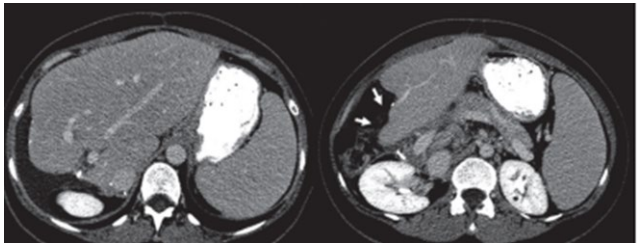


* Decrease time off chemotherapy by 2 months (2 vs. 4 months)
* 1 major operation rather than 2
* 2 procedures rather than 3
* Therapeutic failure due to progression less likely

4-6 cycles of chemotherapy → No Delay → Histotripsy, Portal Vein Embolization → 3-4 weeks → Right or extended right hepatectomy







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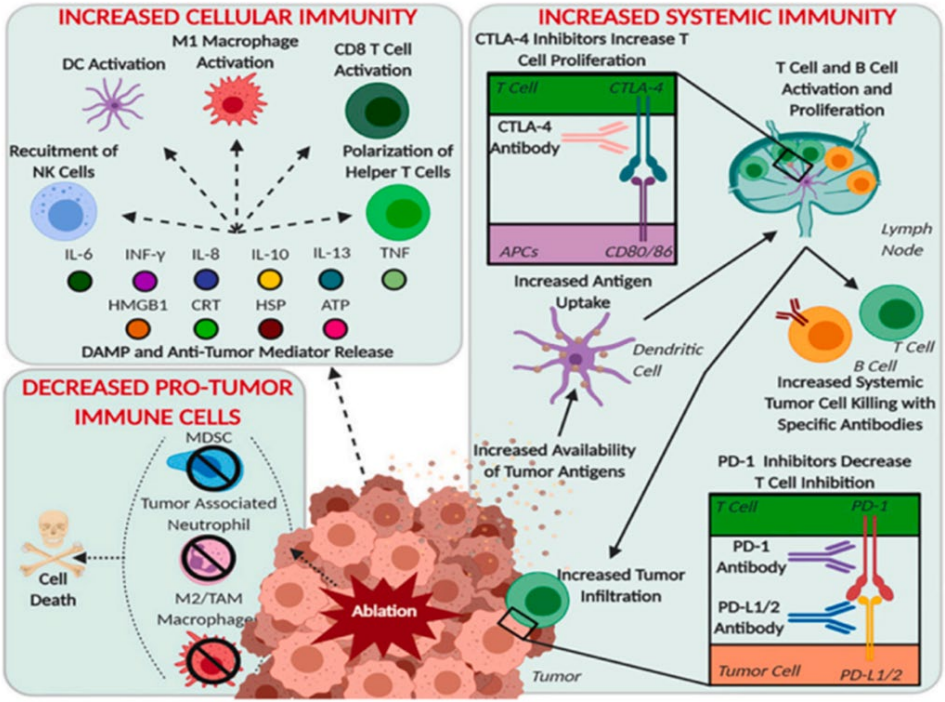
Abscopal Effect



- Immunogenic cell death with priming of host immune system
- Damage associated molecular patterns found by circulating lymphocytes
- Theoretical advantage over other ablative techniques due to precise margin and less damage to adjacent vasculature and lymphatics

Sandilos et al. JOGS 2024

Abscopal Effect

Spatiotemporal local and abscopal cell death and immune responses to histotripsy focused ultrasound tumor ablation

Ashley L. Pepple[1,2†], Joey L. Guy[1,2†], Reliza McGinnis[1,3], Amy E. Felsted[1], Brian Song[1,2], Ryan Hubbard[3], Tejaswi Worlikar[3], Hannah Garavaglia[1], Joe Dib[1], Hannah Chao[1], Nicoleen Boyle[1,2], Michal Olszewski[2], Zhen Xu[3], Anutosh Ganguly[1,2†] and Clifford S. Cho[1,2*†]

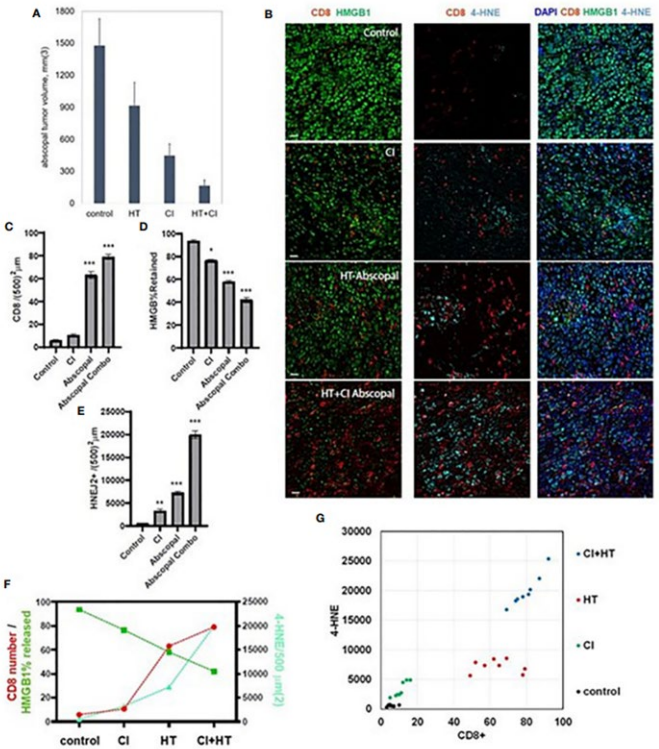
[1]Department of Surgery, University of Michigan Medical School, Ann Arbor, MI, United States, [2]Research Service, Ann Arbor VA Healthcare, Ann Arbor, MI, United States, [3]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, United States

Open access Original research

Journal for ImmunoTherapy of Cancer

Non-thermal histotripsy tumor ablation promotes abscopal immune responses that enhance cancer immunotherapy

Shibin Qu,[1,2] Tejaswi Worlikar,[3] Amy E Felsted,[1] Anutosh Ganguly,[1,4] Megan V Beems,[1] Ryan Hubbard,[3] Ashley L Pepple,[1] Alicia A Kevelin,[1] Hannah Garavaglia,[1] Joe Dib,[1] Mariam Toma,[1] Hai Huang,[5] Allan Tsung,[5] Zhen Xu,[3] Clifford Suhyun Cho[1,4]



Potential Current Uses and Future Directions

- Considerations for Use Now
  - Patients not a candidate for either surgery, ablation, or Y90 due to tumor anatomy
  - Patients at high risk for thrombotic events when stopping anticoagulation
  - To treat left liver disease in setting of bilobar liver metastases and future right hepatectomy
  - Local treatment of oligometastatic disease in a palliative setting (e.g. single liver metastasis from pancreatic cancer with long disease interval)
  - Downstaging or bridge to liver transplant

- Future directions
  - Small pancreatic neuroendocrine tumors or renal cell carcinoma metastases
  - Small renal tumors

Histotripsy Limitations

- The machine does not account for movement. Once a target is set, that is the area that will be treated.
- Requires jet ventilation or single lung ventilation
- There is no quantitative measurement as to how much power is being applied
- Many tumors cannot be treated based on location, especially in segments 7 and 8
- Very limited data on oncologic outcomes
- The abscopal effect has relatively weak evidence in mice and none in patients. It may be more relevant for patients also receiving immunotherapy.

Microwave Ablation

Thermal ablation versus surgical resection of small-size colorectal liver metastases (COLLISION): an international, randomised, controlled, phase 3 non-inferiority trial

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Inclusion Criteria:
- Patients with 10 or fewer colorectal liver metastases all ≤ 3 cm in size
- No extrahepatic metastases
- ECOG 0 – 2
- Patients were also included if < 50% of tumors were not amenable to resection but could be ablated or < 50% of tumors could not be ablated but could be resected.

Exclusion Criteria:
- Extrahepatic disease
- ECOG > 2
- Previous locoregional liver therapy
- 1-2 small but deep liver metastases that would require major hepatectomy and ablation was preferred
- Two-stage hepatectomy with portal vein embolization would be required but a single stage with resection and ablation would be preferred

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Subgroups:
- A (Low disease burden): ≤ 3 tumors all ≤ 3 cm in size
- B: 4 – 10 tumors or 1-3 tumors with at least 1 that could not be resected or ablated
- C: Same as B but resection of at least 1 of the tumors would require major hepatectomy

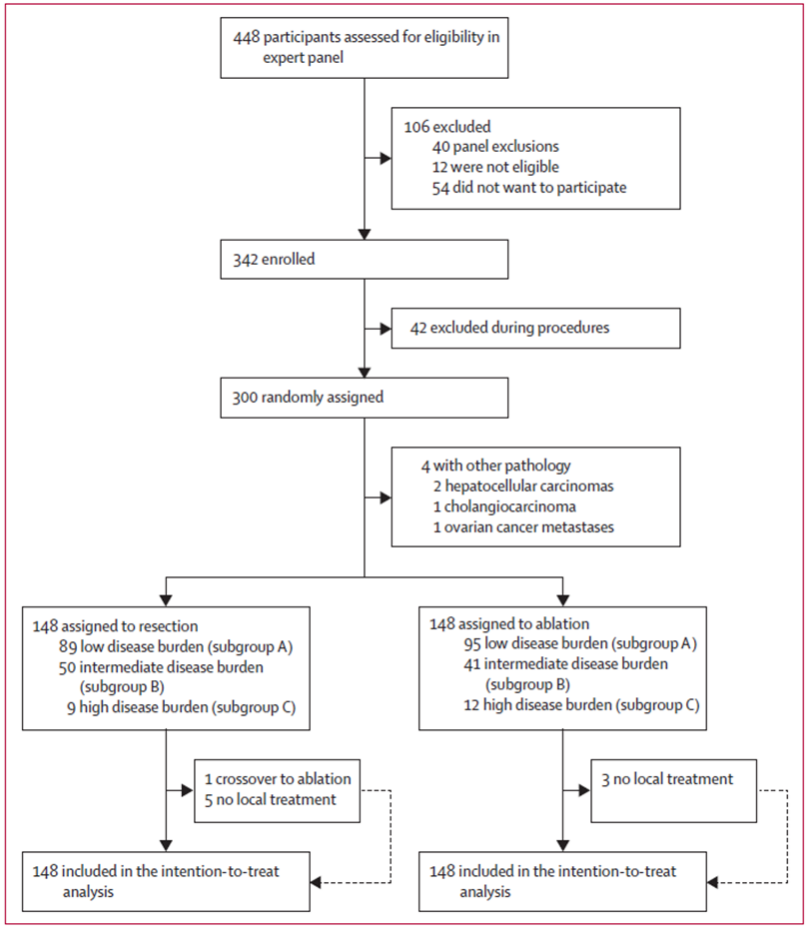

Figure 1: Trial profile

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Microwave Ablation

	Experimental group (n=148)	Control group (n=148)
Patient-related characteristics		
Age, years	67·9 (29·2–85·7)	65·1 (31·4–87·4)
Sex		
Male	100 (68%)	107 (72%)
Female	48 (32%)	41 (28%)
ASA score		
2	102 (69%)	121 (82%)
3	46 (31%)	27 (18%)
Charlson's comorbidity index		
None	53 (36%)	74 (50%)
Minor	69 (47%)	70 (47%)
Intermediate	26 (18%)	4 (3%)
BMI, kg/m²	26·5 (18·6–42·7)	26·1 (17·2–45·5)
Disease-related characteristics		
Primary tumour		
Right-sided	33 (22%)	40 (27%)
Left-sided	57 (39%)	50 (34%)
Rectum	58 (39%)	58 (39%)
T stage		
1	4 (3%)	3 (2%)
2	22 (15%)	15 (10%)
3	93 (63%)	97 (66%)
4	29 (20%)	33 (22%)
N stage		
0	55 (37%)	33 (22%)
1	61 (41%)	79 (53%)
2	32 (22%)	36 (24%)
M stage (at diagnosis of primary tumour)		
0	71 (48%)	79 (53%)
1	77 (52%)	69 (47%)
Extrahepatic disease at diagnosis of colorectal liver metastases		
No	147 (99%)	148 (100%)
Yes	1 (1%)	0
Molecular profile		
RAS status		
Wild type	25 (53%)	24 (47%)
Mutated	22 (47%)	27 (53%)
Missing	101	97

(Table 1 continues in next column)

	Experimental group (n=148)	Control group (n=148)
(Continued from previous column)		
BRAF status		
Wild type	41 (89%)	45 (88%)
Mutated	5 (11%)	
Missing	102	
MSS or MSI status		
MSS	98 (100%)	
MSI	0	
Missing	50	
Subgroup		
Subgroup A (low disease burden)	95 (64%)	
Subgroup B (intermediate disease burden)	41 (28%)	
Subgroup C (high disease burden)	12 (8%)	
Procedure-related characteristics		
Induction chemotherapy		
No	118 (80%)	
Yes	30 (20%)	
Capecitabine	2 (1%)	
CAPOX	3 (2%)	
CAPOX-B	21 (14%)	
FOLFOX-B	2 (1%)	
FOLFIRI-B	1 (1%)	
FOLFOXIRI-B	1 (1%)	
Missing	0	
Induction chemotherapy cycles		
Median (range)	6 (3–12)	
Procedure details		
Resection alone	0	90 (61%)
Ablation alone	118 (80%)	1 (1%)*
Resection with ablation	27 (18%)†	52 (35%)‡
No local treatment	3 (2%)	5 (3%)
Approach§		
Percutaneous	84 (57%)	1 (1%)*
Laparoscopic or robotic	10 (7%)	69 (47%)
Open	54 (36%)	76 (51%)

(Table 1 continues in next column)

Resection alone	0	90 (61%)
Ablation alone	118 (80%)	1 (1%)*
Resection with ablation	27 (18%)†	52 (35%)‡
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(Table 1 continues in next column)

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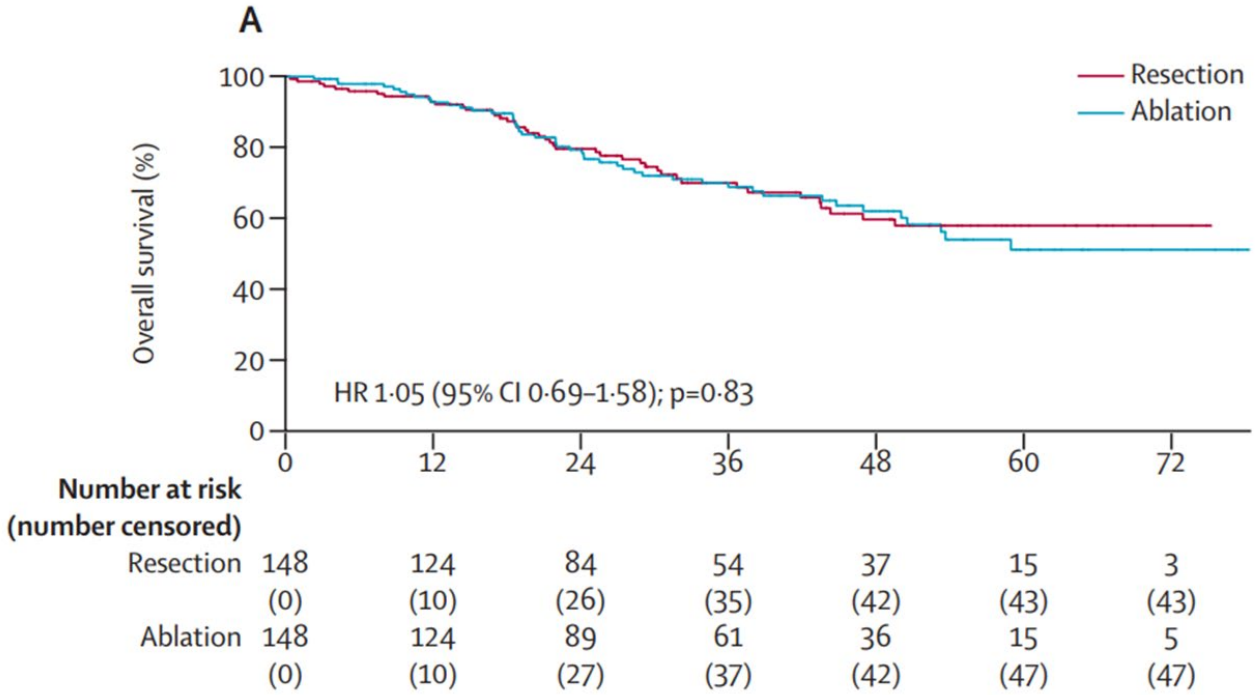
Overall Survival



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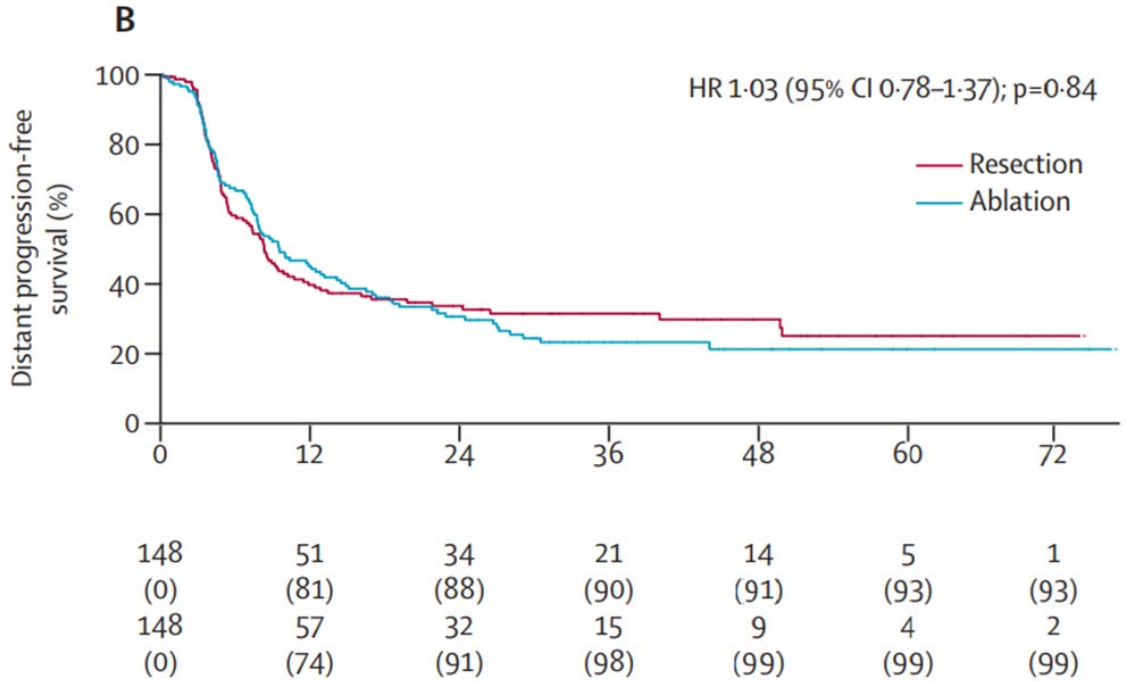
Overall Survival



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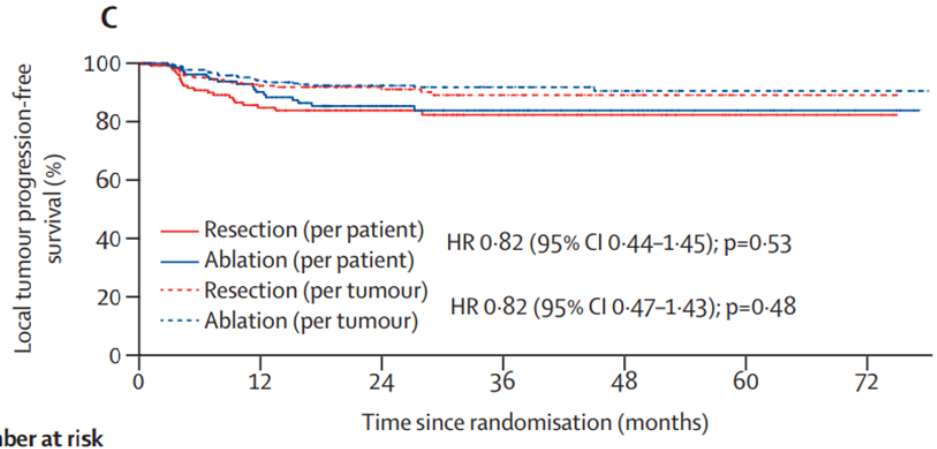
Local Progression Free Survival



Number at risk (number censored)							
Resection (per patient)	148	94	63	38	24	10	3
	(0)	(19)	(20)	(21)	(21)	(21)	(21)
Ablation (per patient)	148	99	65	40	22	10	4
	(0)	(12)	(17)	(18)	(18)	(18)	(18)
Resection (per tumour)	304	210	117	66	42	15	5
	(0)	(20)	(22)	(24)	(24)	(24)	(24)
Ablation (per tumour)	349	278	189	114	62	37	16
	(0)	(18)	(23)	(24)	(25)	(25)	(25)

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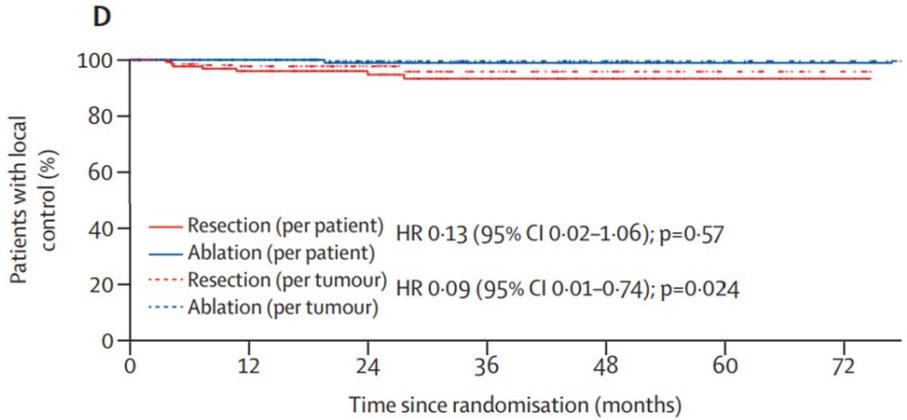
Patients with Local Control



148	109	74	47	31	13	3
(0)	(5)	(5)	(7)	(7)	(7)	(7)
148	121	83	56	33	14	5
(0)	(0)	(1)	(1)	(1)	(1)	(1)
304	220	125	70	45	16	5
(0)	(6)	(6)	(8)	(8)	(8)	(8)
349	295	208	129	74	40	16
(0)	(0)	(1)	(1)	(1)	(1)	(1)

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Microwave Ablation

	Experimental group (n=148)	Control group (n=146)*	p value
Adverse events	28 (19%)	67 (46%)	<0·0001†
Grade 1	9 (6%)	22 (15%)	..
Grade 2	8 (5%)	16 (11%)	..
Grade 3	8 (5%)	19 (13%)	..
Grade 4	2 (1%)	7 (5%)	..
Grade 5	1 (1%)	3 (2%)	..
All grades	..	..	<0·0001‡

Data are n (%). CTCAE=Common Terminology Criteria for Adverse Events.
*Two patients were randomly assigned, but their procedures were cancelled due to rapid disease progression. †Fisher's Exact test. ‡Pearson's χ^2 test.

Table 4: **Adverse events by CTCAE grade**

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Limitations

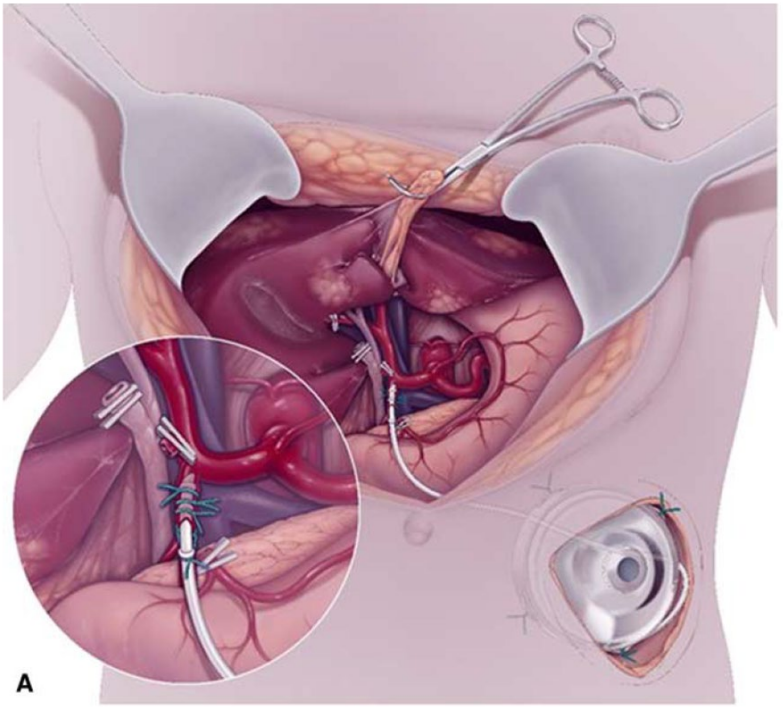
- Did not comment on why tumors could not be ablated
- A significant percentage of patients had both resection and ablation
- Included open, minimally invasive, and percutaneous ablations, which confounds the results and limits comparisons between techniques

Conclusions

- Microwave ablation can be considered non-inferior to resection for small (≤ 3 mm) colorectal cancer liver metastases
- The decision to resect, ablate, or do a combination of resection and ablation should be based on tumor location and patient factors and not number of tumors alone
- Suggests these cases should be reviewed in a multidisciplinary tumor board that includes both surgeons and interventional radiologists

Hepatic Artery Infusion Pump Chemotherapy

- Program at Ochsner started in February 2024
- Have now placed 17 HAI pumps all for unresectable colorectal liver metastases
- The overall complication rate has been similar to what is reported in the literature, but the biliary sclerosis rate has been higher – 4/17 (24%) - compared to what is generally reported (5-10%)



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Ann Surg Oncol (2024) 31:6537–6545
https://doi.org/10.1245/s10434-024-15729-4

Annals of
SURGICAL ONCOLOGY
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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

A Modified Floxuridine Reduced-Dose Protocol for Patients with Unresectable Colorectal Liver Metastases Treated with Hepatic Arterial Infusion

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Hepatic Artery Infusion Pump Chemotherapy

TABLE 2 HAI therapy details

Variable	Standard dose protocol $n = 15$	Modified dose protocol $n = 18$	*P*-value
HAI Floxuridine			
Number of total cycles; median (IQR)	5 (3.5–6.5)	7.5 (5.25–11)	$P = 0.033$
Number of full dose cycles; median (IQR)	2 (1.5–2.5)	6 (3–11.25)	$P < 0.001$
% Full dose cycles; mean (95% CI)	81% (70%–92%)	49% (35%–63%)	$P < 0.001$
Original intended floxuridine treatment (mg); median (IQR)	904 (738–1281)	650 (438–908)	$P = 0.023$
Total cumulative floxuridine dose (mg); median (IQR)	397 (262–443)	356 (288–635)	$P = 0.772$
Total days of active HAI infusion; mean (95% CI)	76 (56–97)	115 (87–141)	$P = 0.025$
Number of dose holds; mean (95% CI)	1.2 (0.41–1.98)	0.2 (0–0.43)	$P = 0.004$
Number of dose reductions; mean (95% CI)	1.4 (0.90–1.90)	0.6 (0.36–0.86)	$P = 0.007$
Total treatment intensity floxuridine received; mean (95% CI)	65% (53–76%)	91% (82–99%)	$P < 0.001$
Three-cycle treatment intensity; median (IQR)	83% (76%–95%)	100% (94%–100%)	$P = 0.019$
Six-cycle treatment intensity; median (IQR)	65% (53%–75%)	100% (91–100%)	$P = 0.005$
Dose holds in first three-cycles; mean (95% CI)	0.42 (0.05–0.80)	0.06 (0–0.18)	$P = 0.038$
Dose holds in first six-cycles; mean (95% CI)	0.67 (0–1.52)	0.08 (0–0.27)	$P = 0.038$
Dose reductions in first three-cycles; mean (95% CI)	0.86 (0.47–1.24)	0.29 (0.05–0.20)	$P = 0.010$
Dose reductions in first six-cycles; mean (95% CI)	1.33 (0.25–2.42)	0.5 (0.17–0.83)	$P = 0.062$
Number of completed HAI cycles prior to first treatment disruption; mean (95% CI)	2 (1.32–2.67)	4.23 (2.24–6.22)	$P = 0.025$
Patients with one or less treatment disruptions	6 (40%)	16 (89%)	$P = 0.008$
Treatment ending biliary toxicity (biliary sclerosis)	4 (27%)	1 (6%)	$P = 0.152$
Biliary sclerosis requiring stent placement	2 (13%)	1 (6%)	$P = 0.99$
Conversion to hepatic resection for complete disease clearance	3 (20%)	6 (33%)	$P = 0.459$
Potential conversion (Not Classified as Destination Therapy)	3/13 (23%)	6/17 (35%)	$P = 0.691$
Months of HAI treatment before conversion; median (IQR)	12.9 (12.8–20.8)	9.3 (8.3–10.7)	$P = 0.019$

Treatment disruption = dose hold or dose reduction

Treatment intensity= mg floxuridine received divided by floxuridine originally intended (cycles * first dose floxuridine)

CRLM colorectal liver metastases, = interquartile range, *HAI* hepatic arterial infusion, *CI* confidence interval

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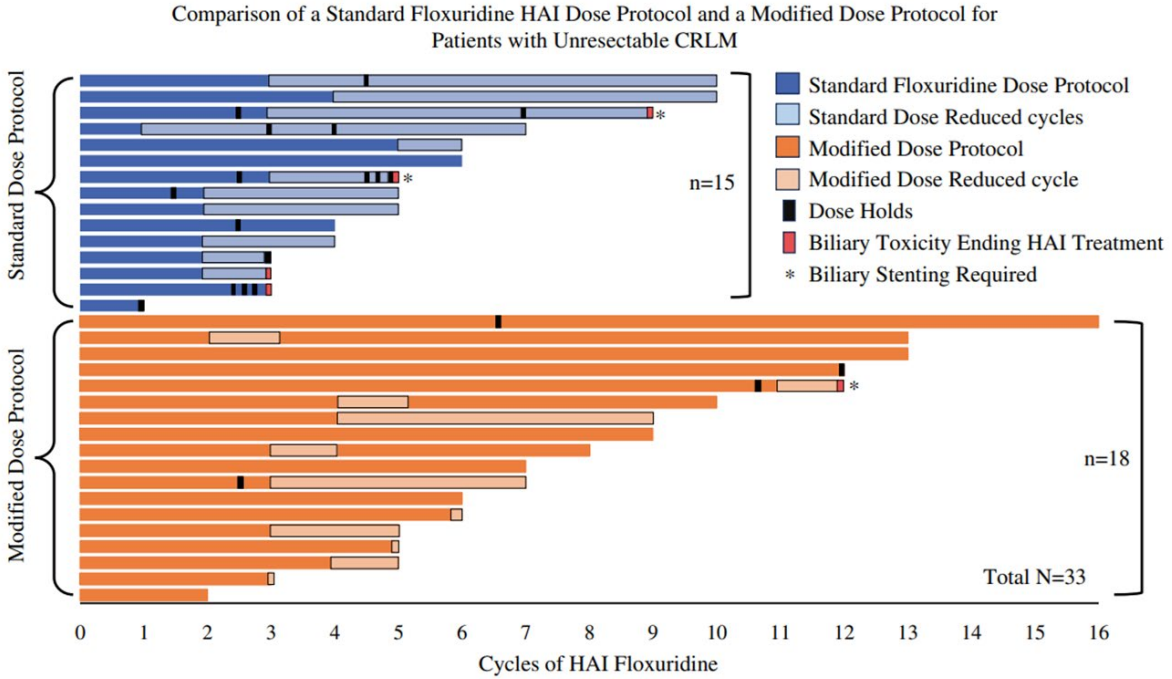

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Ann Surg Oncol
https://doi.org/10.1245/s10434-025-17783-y

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Reduced Floxuridine Dose Limits Hepatobiliary Toxicity Without Negatively Impacting Survival After Resection of Colorectal Cancer Liver Metastases

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Characteristic	All patients N = 71	Standard dose n = 40	Reduced dose n = 29	*p*
Age (median, range)	52 (24–76)	49 (34–76)	53.5 (38–72)	0.03
Female sex (n, %)	31 (44%)	18 (46%)	12 (40%)	0.63
Comorbidities (n, %)	55 (77%)	29 (74%)	24 (80%)	0.77
BMI (median, IQR)	25 (23–31)	25 (23–31)	25 (22–31)	0.64
Location of primary tumor				
Right colon	8 (11%)	4 (10%)	4 (13%)	0.72
Left colon	63 (88%)	35 (90%)	26 (87%)	0.72
CEA at dx (ng/mL, median, IQR)	54 (8–99)	21 (8–72)	29 (4–88)	0.89
Synchronous presentation (n, %)	61 (86%)	33 (83%)	26 (90%)	>0.99
pT3/4 primary tumor (n, %)	53 (75%)	30 (75%)	20 (69%)	0.32
pN+ primary tumor (n, %)	45 (63%)	25 (63%)	18 (62%)	0.99
RAS mutant (n, %)	28 (39%)	18 (46%)	9 (30%)	0.22
Clinical risk score (median, IQR)	2 (2–3)	3 (2–3)	3 (2–3)	0.57
Tumor burden score (median, IQR)	8.3 (5.8–11.3)	9.1 (6.4–11.6)	7.3 (5.4–10.8)	0.17
Zone 1 (<3) (n, %)	1 (1%)	1 (2.5%)	0 (0%)	>0.99
Zone 2 (≥3 – 9)	41 (58%)	18 (46%)	21 (70%)	0.05
Zone 3 (≥9)	29 (41%)	20 (51%)	9 (30%)	0.09
Recurrent hepatic metastases (n, %)	7 (10%)	4 (10%)	2 (7%)	0.69
No. liver tumors at dx (median, range)	7 (1–30)	7 (1–30)	6 (2–30)	0.21
>10 liver tumors at dx (n, %)	21 (30%)	13 (33%)	8 (27%)	0.60
Size of largest liver tumor in cm (median, IQR)	2.6 (1.6–3.7)	2.6 (1.8, 5)	2.6 (1.9–3.4)	0.71
Bilobar disease (n, %)	67 (94%)	35 (90%)	29 (97%)	0.38
Extrahepatic disease (n, %)	14 (20%)	6 (15%)	6 (20%)	0.75
Peritoneum	1 (1%)	0 (0%)	1 (3%)	0.43
Retroperitoneal lymph nodes	5 (7%)	1 (2.5%)	3 (10%)	0.31
Lung	9 (13%)	5 (13%)	3 (10%)	>0.99
Multiple	1 (1%)	0 (0%)	3 (10%)	0.08
Receipt of neoadjuvant tx (n, %)	70 (99%)	40 (100%)	29 (100%)	>0.99
No. cycles of NAT (median, IQR)	8 (6–11)	9 (8–12)	8 (6–10)	0.14
Major hepatectomy (n, %)	21(30%)	8 (21%)	13 (43%)	0.06
Partial hepatectomy (n, %)	50 (70%)	32 (80%)	16 (55%)	0.04
Segments resected (median, IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.76
Concurrent hepatic ablation (n, %)	57 (80%)	34 (85%)	21 (72%)	0.23
Segments ablated (median, IQR)	3 (2–5)	3 (2–4)	3 (2–4)	0.71
Simultaneous colon resection (n,%)	38 (54%)	19 (49%)	18 (60%)	0.47
R0 resection, colectomy (n, %)	71 (100%)	39 (100%)	30 (100%)	>0.99
R0 resection, hepatectomy (n, %)	64 (90%)	33 (85%)	29 (97%)	0.13
Receipt of adjuvant therapy (n, %)	71 (100%)	39 (100%)	30 (100%)	>0.99
Floxuridine dose used in first 34 cases (n, %)	–	32 (80%)	2 (7%)	<0.001
Floxuridine dose use in last 35 cases (n, %)	–	8 (20%)	27 (93%)	<0.001

IQR interquartile range

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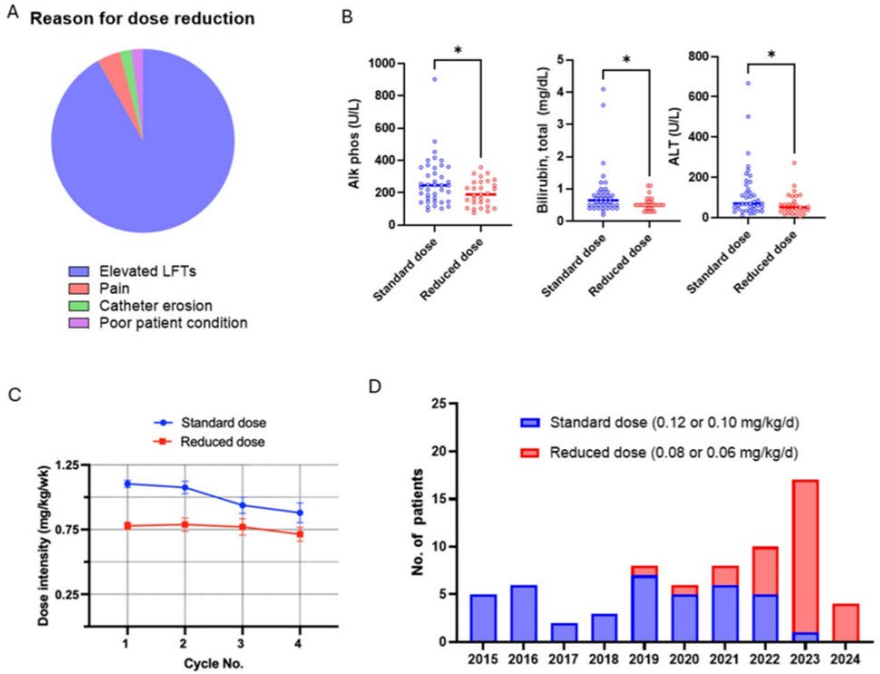

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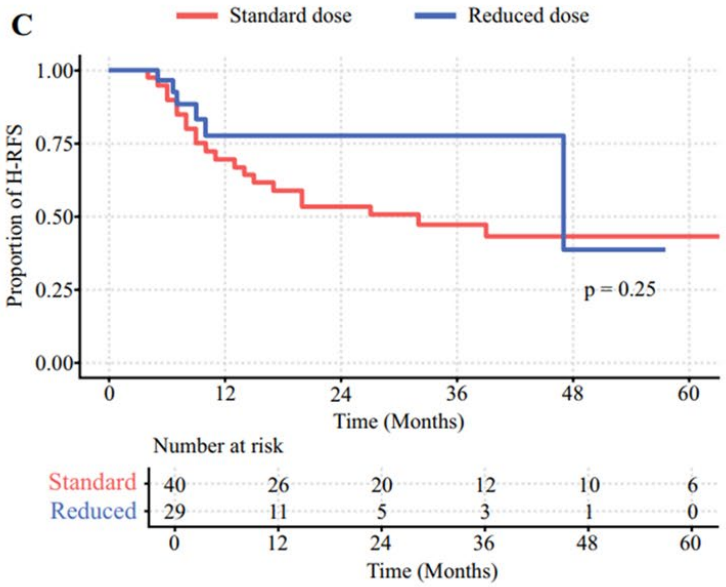

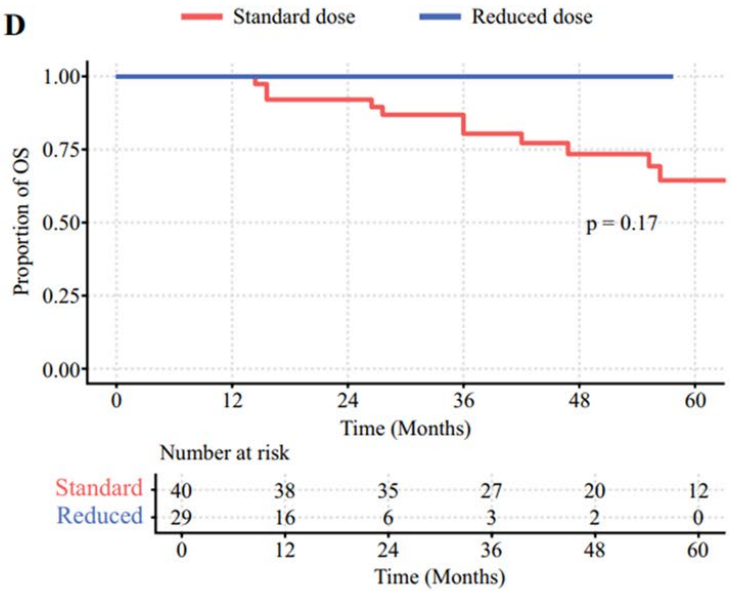

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Conclusions and Future Directions

- Rates of biliary toxicity are probably under reported in the literature
- It is critical to publish real world outcomes, especially from institutions new to the procedure, as more HAI programs continue to open
- A reduced dose of floxuridine may limit biliary toxicity, decrease the rate of biliary sclerosis, and allow for more total cycles of floxuridine
- We are now using 0.06 mg/kg as the starting floxuridine dose compared to the traditional dose of 0.12 mg/kg