Liver Metastases: A year in review 2020

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- **Research Support:**

- National Institute of Health (NIH)
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  R01 CA240569-01

- Industry:

SIRTEX Medical Inc: Phase I Trial Y90 Post HAI: Clinical CRC 2013

Angiodynamics/ Neuwave/ SOTA Medical/ HS Medical/ Perseon

BTG: EPOCH Trial

- Consultant, Advisory Boards:

- J&J/ Ethicon
- Terumo
- BTG/Boston Scientific
- SIRTEX
- Varian

Disease Related: Focus CRC

Impact of patient, primary tumor and metastatic pattern including tumor location on survival in patients undergoing ablation or resection for colorectal liver metastases: A population-based national cohort study

Peter Scherman [a, b, *], Ingvar Syk [c, d], Erik Holmberg [e], Peter Naredi [a, f], Magnus Rizell [a, g]

European Journal of Surgical Oncology xxx (xxxx) xxx

Prospective Swedish registries:

CRC registry (SCRCR) with diagnosis between 2009-2013 cross checked for the presence of liver tumor (SweLiv):

1325 Patients: 300 (22.6%): 75 yo or older.

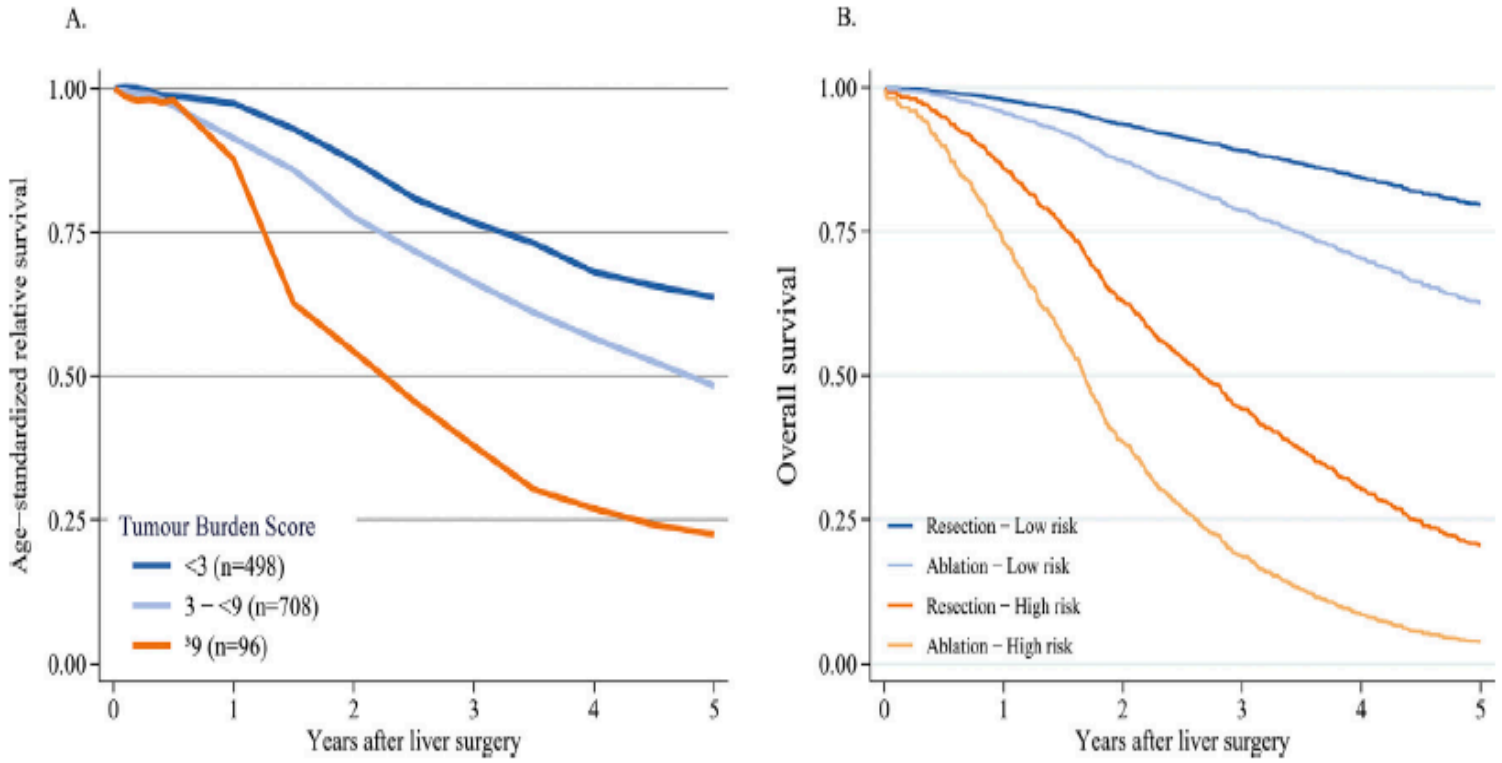
1098 (82.9%) treated by surgery only, 125 (9.4%) ablation only and 102 (7.7%) by Resection and ablation.

731/1325 (55.2%): synchronous and 594/1325 (44.8%) metachronous.

Impact of patient, primary tumor and metastatic pattern including tumor location on survival in patients undergoing ablation or resection for colorectal liver metastases: A population-based national cohort study

Peter Scherman [a, b, *], Ingvar Syk [c, d], Erik Holmberg [e], Peter Naredi [a, f], Magnus Rizell [a, g]

[a] Department of Surgery, Institute of Clinical Sciences, University of Gothenburg, Gothenburg, Sweden



No Margin Assessment and stratification

Increasing age-related survival gap among patients with colorectal cancer: a population-based retrospective study

Yang Feng[1,2] · Shaobo Mo[1,2] · Weixing Dai[1,2] · Qingguo Li[1,2] · Guoxiang Cai[1,2] · Sanjun Cai[1,2]

International Journal of Clinical Oncology (2020) 25:100–109
https://doi.org/10.1007/s10147-019-01538-3

The Surveillance, Epidemiology and end Results (SEER) 9 registries for CRC diagnosis between 1975-2009

SEER 18: CRC diagnosis: 1973-2014:

CSS for patients < 54, 55-64, 65-74 and 75-84: Robust Increase in survival

BUT: for patients > 85 yo: No difference in OS between 1990-99 and 2000-12

Despite improved outcomes in OS during last 40 years this did not change in elderely patients.

PRINCIPLES OF SURGERY
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization[13] or staged liver resection[14]

- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

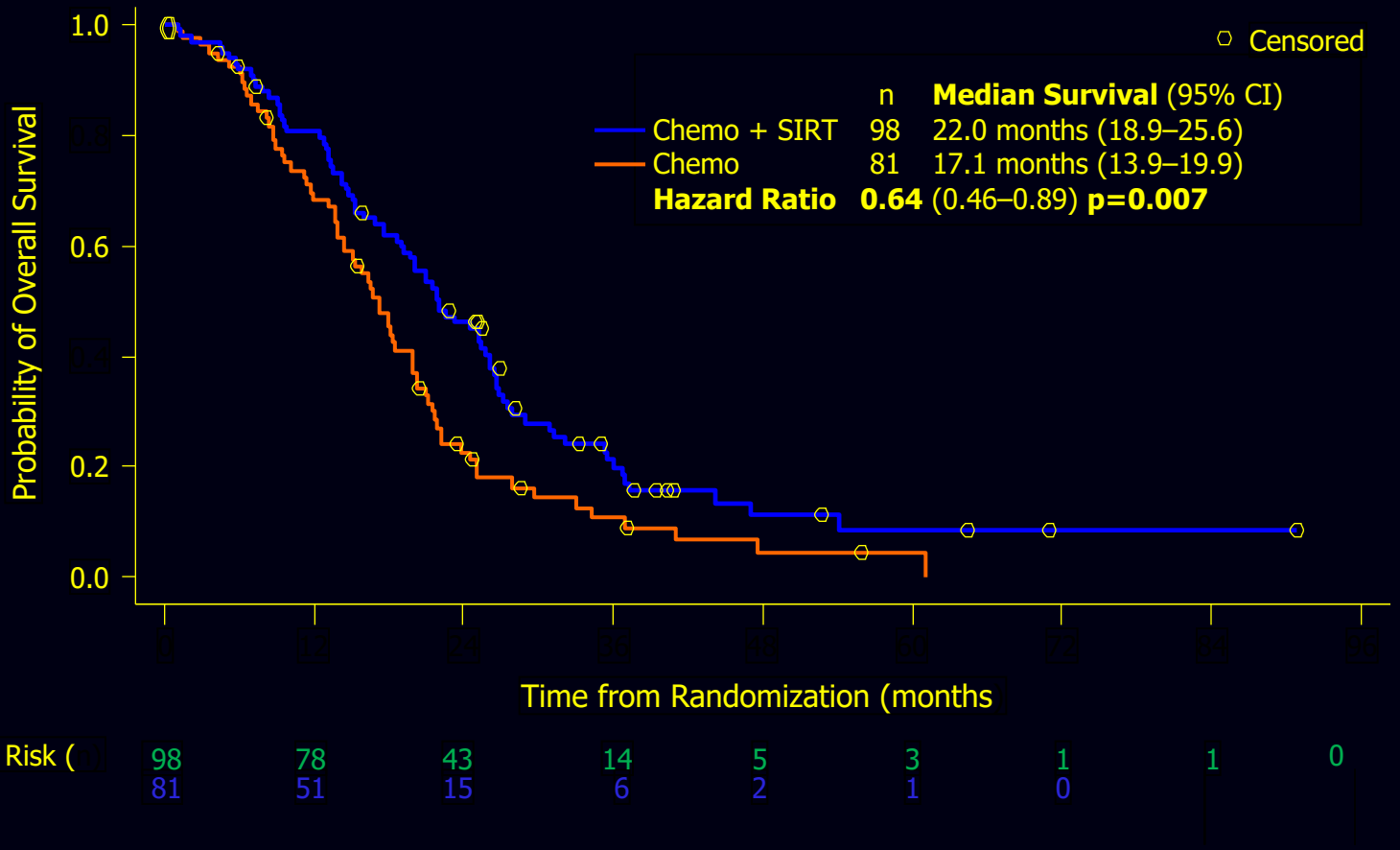
in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.

- Re-resection can be considered in selected patients.[15]

Y90

OS for RCP/ mCRC Patients with Right-Sided Primary Tumours

For the 179/739 patients (24.2%) with a RSP tumor, OS was improved with the addition of SIRT (median, 22.0 vs. 17.1 months HR, 0.641; P: .008).

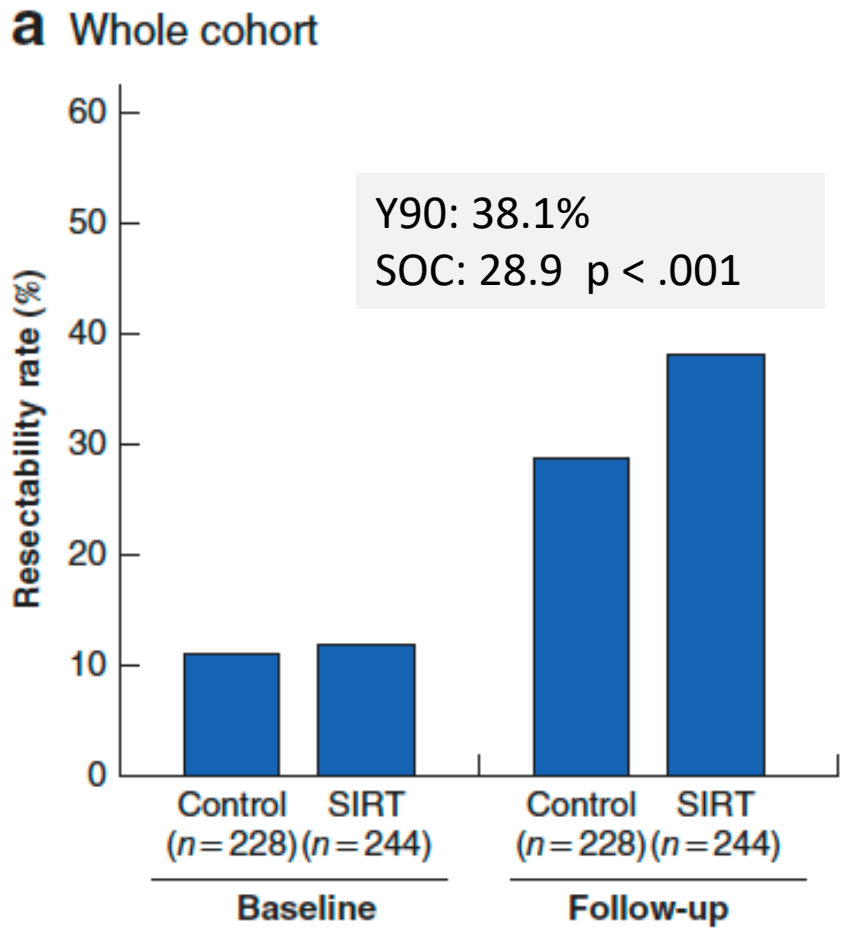


5 months prolongation of Median Survival and 36% protective effect against death

Gibbs et al: Clinical Colorectal Cancer December 2018

Secondary technical resectability of colorectal cancer liver metastases after chemotherapy with or without selective internal radiotherapy in the randomized SIRFLOX trial

Fig. 3 Resectability of colorectal liver metastases



B. Gerlipp, P. Gibbs, G. A. Van Hazel, R. Jayaraijah, R. C. G. Martin, C. J. Bruns *et al.*

BJS 2019; **106**: 1837–1846

Contralateral liver hypertrophy and oncological outcome following Y90 TARE

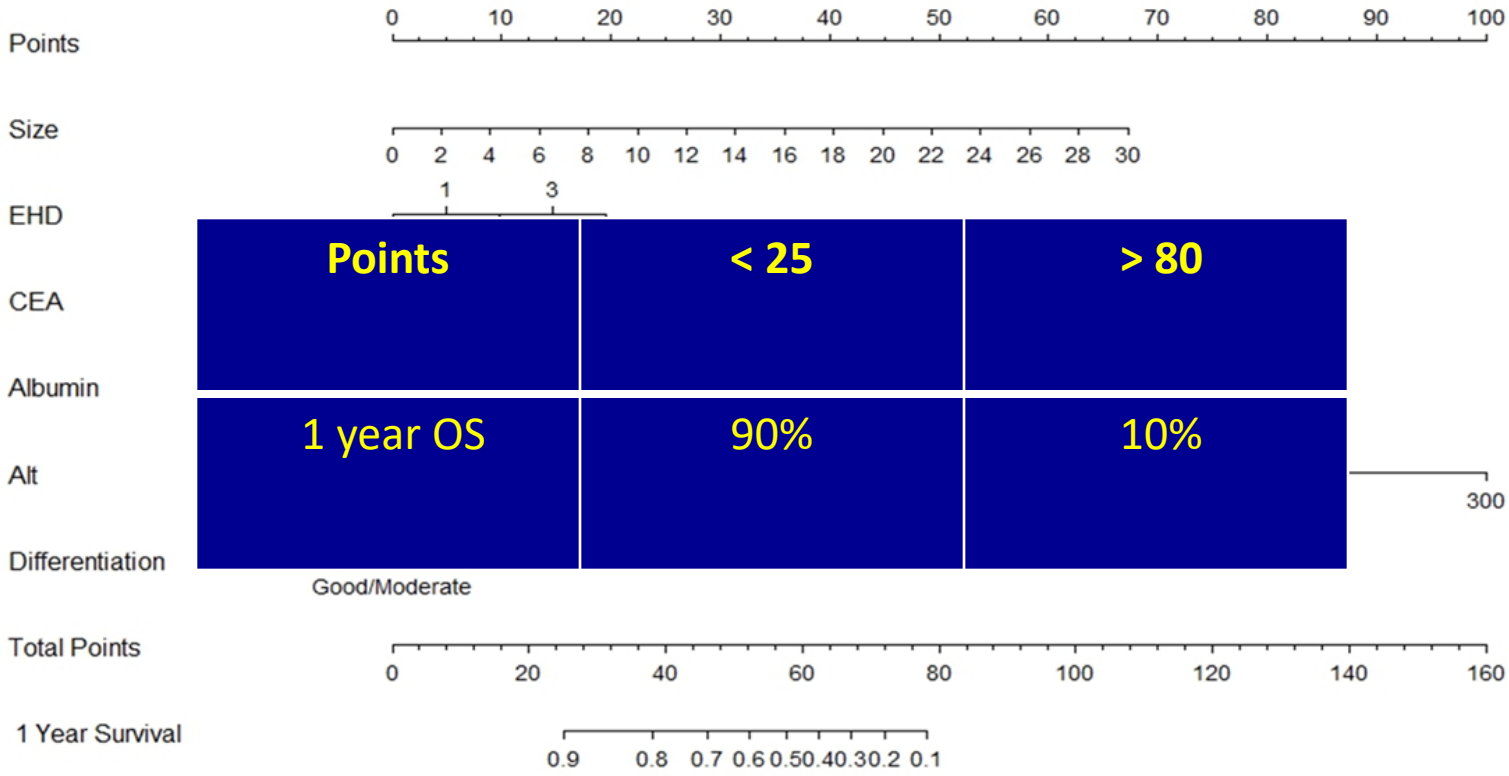
- Systematic literature search using the MEDLINE, EMBASE, and Cochrane libraries for studies published between 2008-2020 identified 16 studies, comprising 602 patients.
- Median kinetic growth rate per week of the contralateral liver lobe: 0.7%
- Local tumor control was 84%.
- Surgical resection after Y90 was carried out in 109/362 patients (30%).

Further work needed for the Role of Y90 as a means of Local control and liver remnant Hypertrophy in borderline resectable patients

Contralateral liver hypertrophy and oncological outcome following radioembolization with90 y-microspheres: A systematic review (2020) Cancers, 12 (2), art. no. 294,

Factors Affecting Oncologic Outcomes of 90Y Radioembolization of Heavily Pre-Treated Patients With Colon Cancer Liver Metastases

103 patients; 77% EHD, Median OS: 11.4 months



NOMOGRAM: 1-year OS of patients with total points of **<25 vs. >80 was 90% and 10%,** respectively

Bootstrap resampling showed **good discrimination** (optimism corrected c-index=0.745) and **calibration** (mean absolute prediction error=0.299) of the nomogram

Kurilova I, Gonen M, Cercek A, Kemeny NA, Sofocleous CT: Clinical Colorectal Cancer September 2019

Thermal Ablation

A new sequential treatment strategy for multiple colorectal liver metastases: Planned incomplete resection and postoperative completion ablation for intentionally-untreated tumors under guidance of cross-sectional imaging☆

Masayuki Okuno [a,1], Yoshikuni Kawaguchi [a,1], Mario De Bellis [a], Eduardo A. Vega [a], Steven Y. Huang [b], Kamran Ahrar [b], Sanjay Gupta [b], Jean-Nicolas Vauthey [a], Bruno C. Odisio [b,*]

Multiple CLM undergoing planned incomplete resection and Post-operative percutaneous image guided completion TA

Completion percutaneous TA: 23 vs IOP TA: 92 MWA more common in percutaneous Group (p: .001)

Complication rate PercTA vs IOP ablation: 21% vs 48% (p: 0.033)

5 year LTP: 31.7% vs 62.4% (p: 0.03)

5 year OS : PercTA; 53% vs 42% (P:.407)

M. Okuno et al. / European Journal of Surgical Oncology xxx (xxxx) xxx

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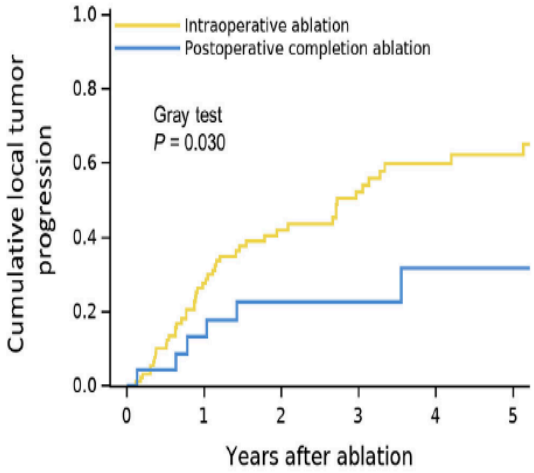
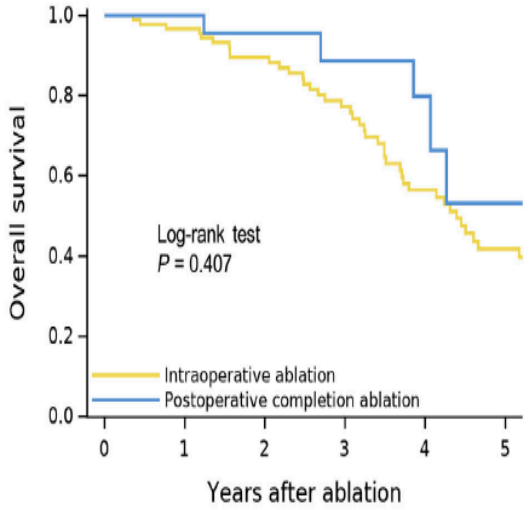
A

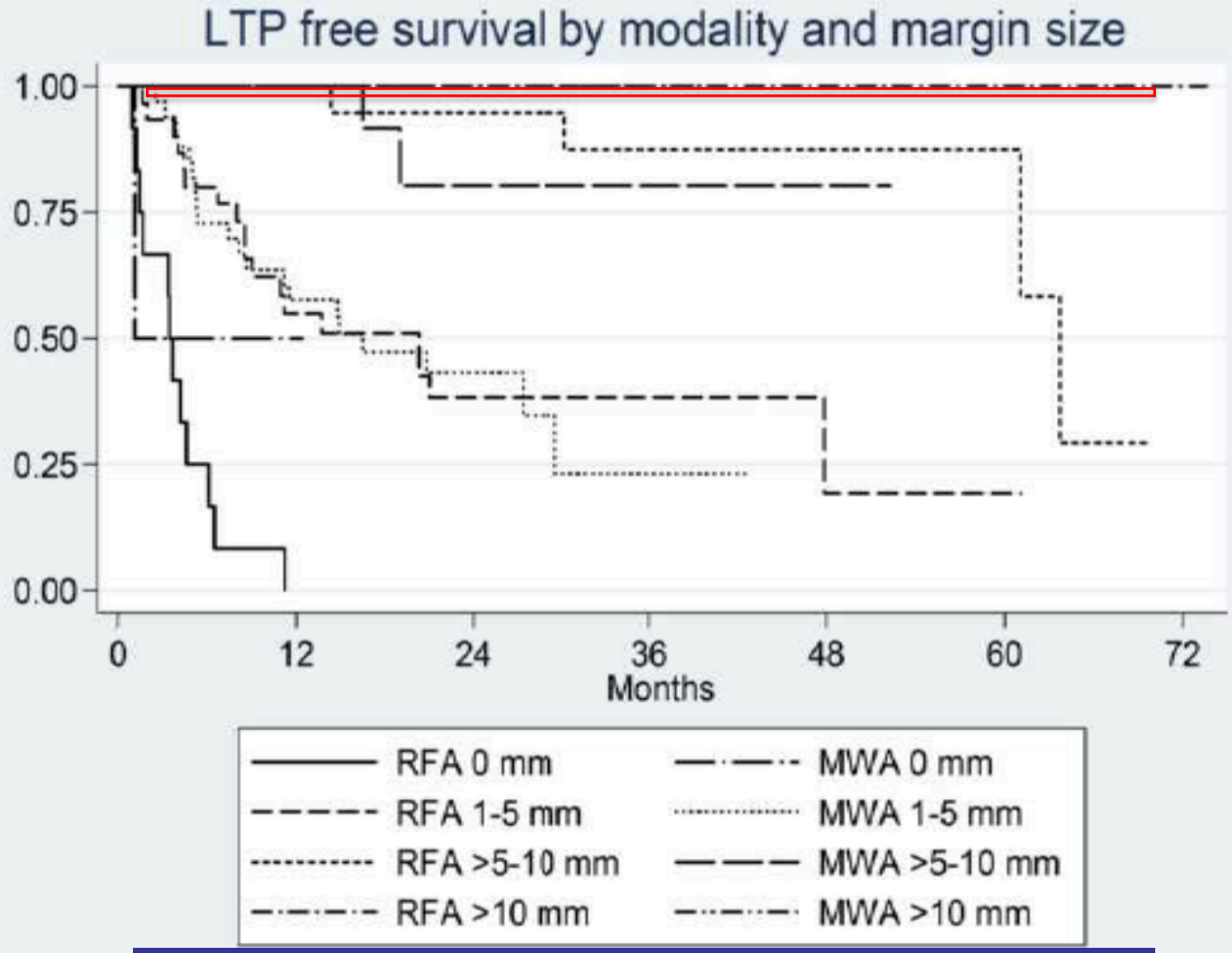


Patients at risk							5-year cumulative local recurrence rate
Intraoperative ablation	92	60	36	26	16	13	62.4%
Postoperative completion ablation	23	19	12	10	5	1	31.7%



Patients at risk							5-year OS rate
Intraoperative ablation	92	87	69	53	33	20	41.8%
Postoperative completion ablation	23	22	18	13	6	3	53.2%

NO LTP FOR MARGIN OVER 10 mm!



77 CLM RFA vs 60 MWA; Up to 5 cm

Shady W, Solomon SB, Kemeny NE, Sofocleous CT: Comparison of RFA and MWA in the treatment of CLM; JVIR 2018

Factors Associated with Local Tumor Control and Complications after Thermal Ablation of Colorectal Cancer Liver Metastases: a 15-year Retrospective Cohort Study

2003-2017: 286 patients 415 CLM treated within 378 session (RFA: 213 and MWA: 165)

HAC 140/286

Post Liver Resection: 275/378: 73%

Recurrence after hepatectomy: (100), Hepatectomy+HAC (175)

Median F-U: 31 months

NO LTP for MM >10mm

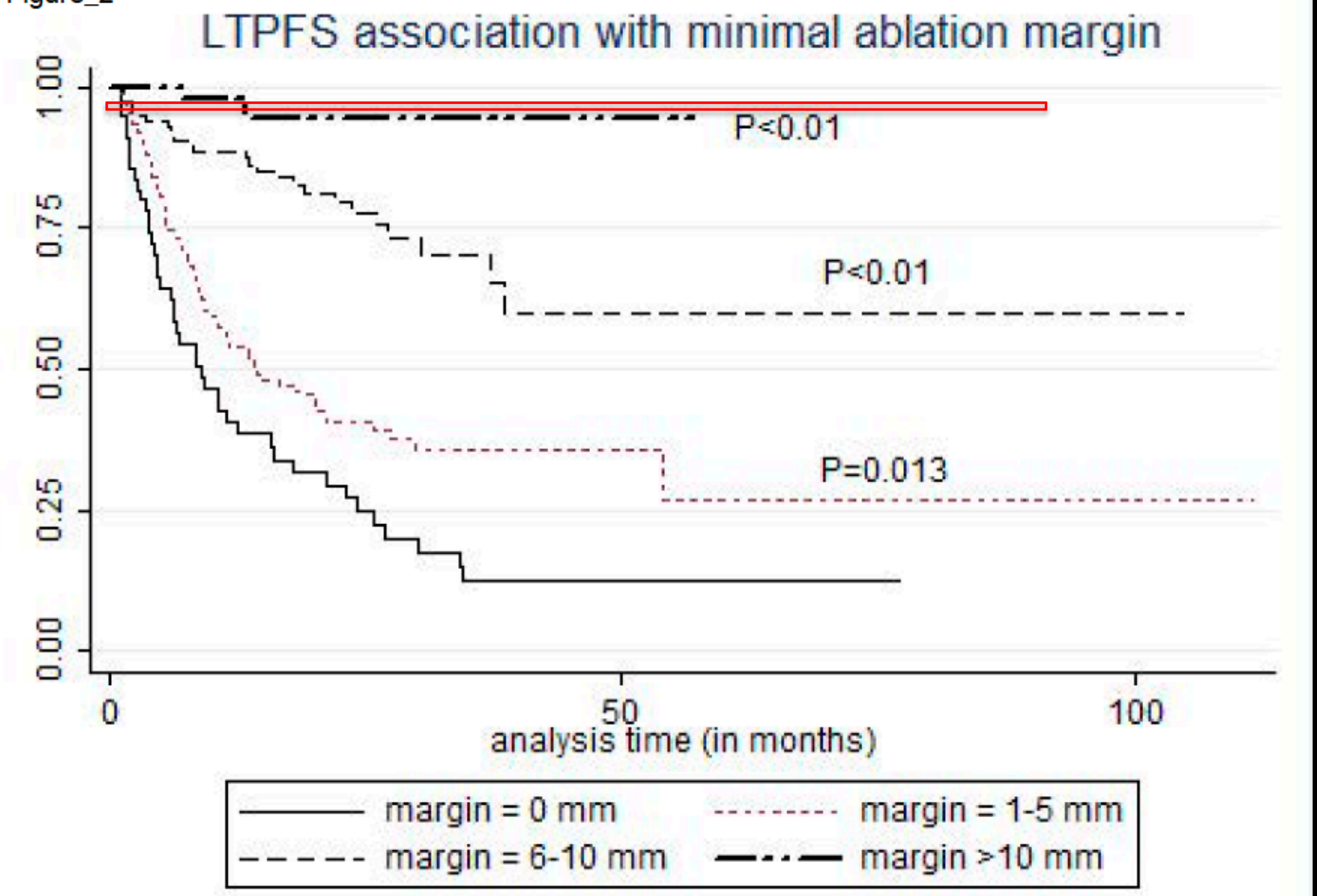
Total Major Complications: 7.4%

Biliary complications ONLY in patients with Prior Hepatic Arterial Chemotherapy (HAC).

Kurilova I et al: Clinical Colorectal Cancer 2020 In Press

Factors Associated with Local Tumor Control and Complications after Thermal Ablation of Colorectal Cancer Liver Metastases: a 15-year Retrospective Cohort Study

Figure_2



Factors Associated with Local Tumor Control and Complications after Thermal Ablation of Colorectal Cancer Liver Metastases: a 15-year Retrospective Cohort Study

Major complications post-liver thermal ablation	
Complication type/description (n=378 procedures)	**Incidence**
Biliary	**15 (4%)**
Intrahepatic biloma, requiring drainage with additional sequelae: abscess (1) / abscess+ secondary biliary stricture + biliary leak (1)/ bacteremia (1)/ biliary fistula to abdominal wall (1) or biliary fistula to m. ileopsoas (1)	6
Secondary biliary stenosis, requiring intervention	3
Hyperbilirubinemia, requiring stenting (1)/ requiring intervention and prolonged hospitalization (1)/ resulting in bacteremia, requiring drainage (1)	3
Bilioenteric/biliogastric fistula with recurrent bacteremia or requiring intervention	2
Extrahepatic biloma + infection + bile leak, requiring intervention	1
Liver vascular complications	**7 (1.9%)**
Arterioportal fistula, requiring embolization	2
Hepatic pseudoaneurysm ± hematoma, requiring embolization	3
Retroperitoneal hematoma, requiring drainage	1
Bleeding into biliary tree	1
Pulmonary complications	**9 (2.4%)**
Pulmonary embolism ± pneumonia/bronchiolitis	2
Pneumothorax ± pleural effusion, requiring prolonged admission	2
SVC thrombosis/syndrome + pulmonary vein thrombosis + pulmonary embolism	1
Hemothorax, requiring thoracostomy and prolonged hospitalization	1
Pleural effusion + desaturation, requiring thoracentesis + prolonged hospitalization	1
Diaphragm injury + abscess + hydropneumothorax, requiring >48 h hospitalization	1
Pneumothorax + pneumomediastinum + pneumoperitoneum + subcutaneous emphysema due artificial hydropneumoperitoneum, requiring >48h hospitalization	1
Other	**2 (0.5%)**
In alcohol abuse patient SIADH+ Alcohol withdrawal syndrome + epistaxis, requiring intervention and prolonged hospitalization	1
Grade 3 abdominal pain + opioid-induced agitation/delirium with prolonged hospitalization	1
Total number of major complications	**33**
Total number of procedures with major complication(s)*	**28 (7.4%)**

*After five procedures patients developed two different major complications per procedure, this is why

Kurilova I et al: Clinical Colorectal Cancer 2020 In Press

Table 3. Factors associated with biliary and hepatic vascular complications

Complication risk factors	Biliary complications				Vascular complications		Local tumor progression			
	UVA		**MVA**		**UVA**		**UVA**		**MVA**	
	p	OR	*p*	OR	*p*	OR	*p*	SHR	*p*	SHR
Prior HAI therapy	**0.003**	20.0**	-	-	0.2	2.0	**0.032**	0.7	0.86	0.96
Pre-existing biliary dilatation*	**0.002**	7.2	**0.005**	5.8	-	-	-	-	-	-
Bevacizumab within 1 month*	**0.001**	9.5	**0.017**	14	0.07	4.6	-	-	-	-
Minimal ablation margins*	**0.007**	2.1	**0.015**	2.1	0.24	1.5	**<0.001**	0.38	**<0.001**	0.37
modality*			-	-	0.77	1.16	0.18	0.79	-	-
Tumor size (cm)*	0.33	1.25	-	-	0.57	0.82	**<0.001**	1.39	**0.001**	1.3
Tumor number *	0.63	1.19	-	-	0.24	1.62	-	-	-	-
History of liver resection*	0.14	0.40	-	-	0.86	0.90	**0.017**	0.67	**0.039**	0.64
Number of FUDR infusions* (range, 1-40)	0.37	1.03	-	-	-	-	-	-	-	-
KRAS mutation status	-	-	-	-	-	-	0.49	1.15	-	-

*These factors association with biliary complications analysis was made only for the HAI patients' subgroup, since biliary complications occurred only in HAI patient population. **Result is based on exact logistic regression analysis. In bold-statistically significant values. UVA - univariate analysis, MVA - multivariate analysis, HAI - hepatic artery infusion pump therapy; FUDR – fluoxuridine, OR - odds ratio; SHR - sub-hazard ratio.

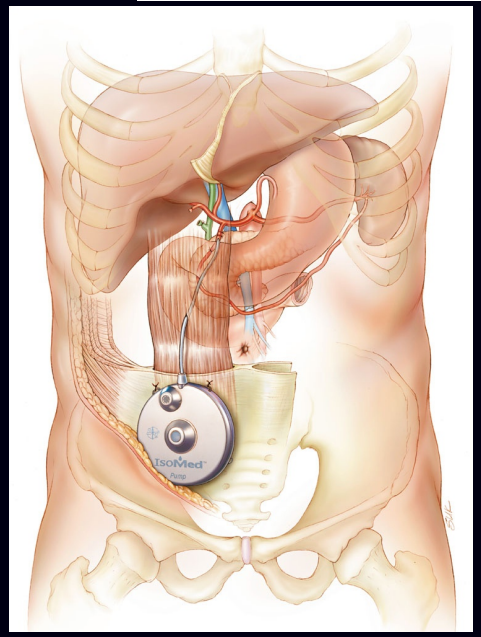
Factors Associated with Local Tumor Control and Complications after Thermal Ablation of Colorectal Cancer Liver Metastases: a 15-year Retrospective Cohort Study

Table 4. Biliary complications and local tumor progression rate, stratified based on minimal ablation margin size and HAI history.

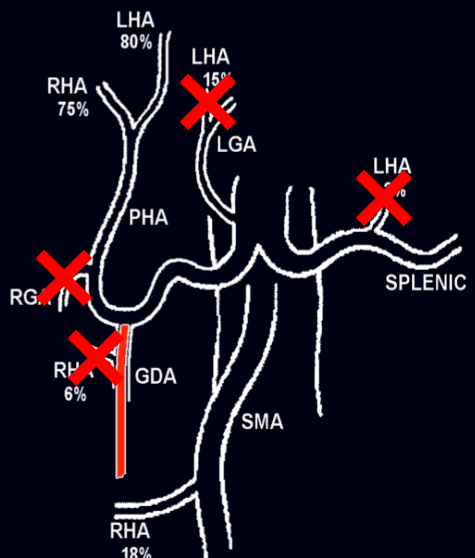
Minimal ablation margin	0 mm	1-5 mm	6-10 mm	>10 mm
Whole patients cohort*				
Minor biliary complications	0/50 (0%)	4/128 (3%)	0/96 (0%)	3/40 (8%)
Major biliary complications	0/50 (0%)	6/128 (5%)	2/96 (2%)	6/40 (15%)
Total biliary complications incidence	0/50 (0%)	8/128 (6%)**	2/96 (2%)	9/40 (23%)
Local tumor progression rate	41/52 (79%)	79/132 (60%)	25/98 (26%)	0/39 (0%)
Prior-HAI patients subgroup analysis				
Minor biliary complications	0/22 (0%)	4/71 (6%)	0/53 (0%)	3/29 (10%)
Major biliary complications	0/22 (0%)	6/71 (8%)	2/53 (4%)	6/29 (21%)
Total biliary complications incidence	0/22 (0%)	8/71 (11%)**	2/53 (4%)	9/29 (31%)
Local tumor progression rate	18/22 (82%)	38/72 (53%)	13/54 (24%)	0/28 (0%)
HAI-naïve patients subgroup analysis				
Total biliary complication incidence	0/28 (0%)	0/57 (0%)	0/43 (0%)	0/11 (0%)
Local tumor progression rate	23/30 (77%)	41/60 (68%)	12/44 (27%)	0/11 (0%)

* Total of 64 procedures were excluded from analysis: 33 due absence of imaging for minimal ablation margin assessment (contrast-enhanced CT within 6 weeks before treatment and/or at 4-8 weeks after treatment), 22 - due to multiple differing minimal ablation margins present following ablation of multiple tumors per procedure, 5 – due to coalescent ablation zones, 4 - due no follow-up).** patient(s) had both minor and major complications per procedure. HAI-hepatic artery infusion

Factors Associated with Local Tumor Control and Complications after Thermal Ablation of Colorectal Cancer Liver Metastases: a 15-year Retrospective Cohort Study



Hepatic Arterial Chemotherapy Group		
MM	LTP	Biliary Complications
6-10 mm	24%	4%
> 10 mm	0	21%
P value	.0033	.0011



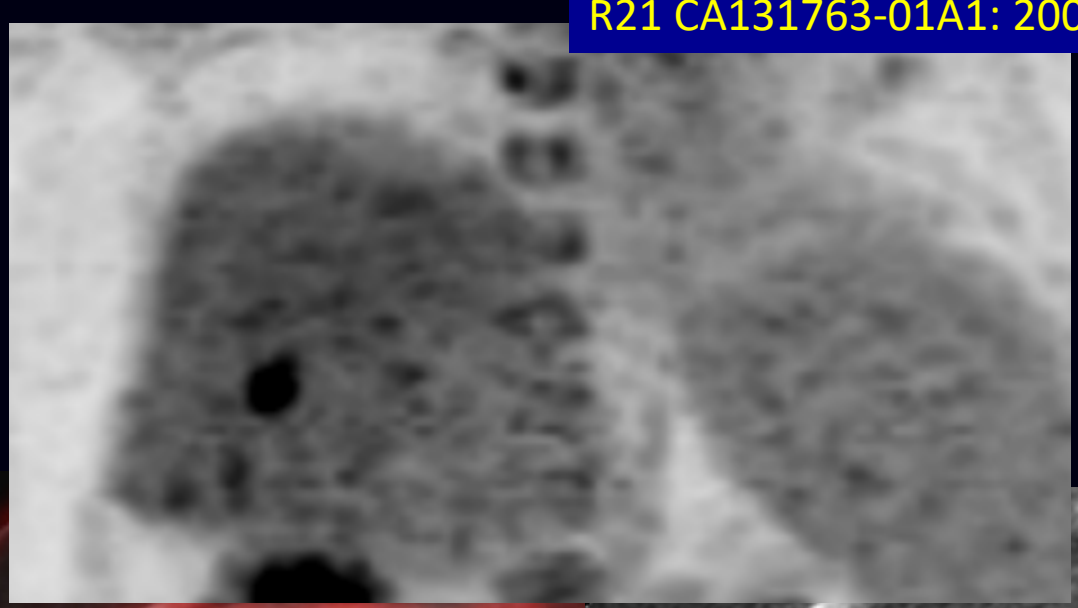
Hepatic Arterial Chemotherapy Group Predictors of Complications

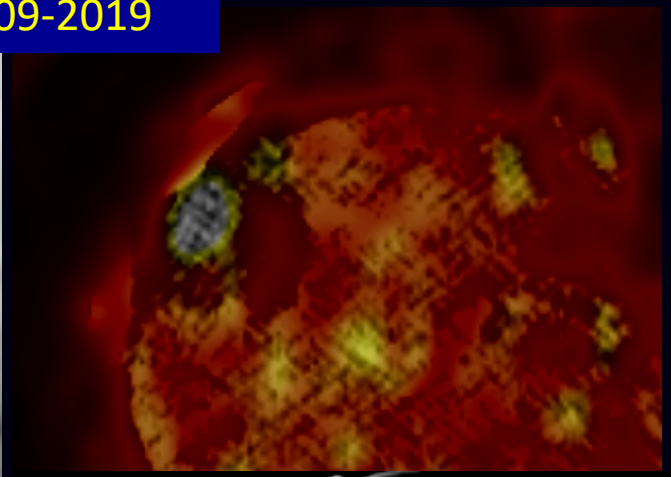
Prior Bevacuzimab,
Pre-existing Biliary Dilatation
MM > 10mm

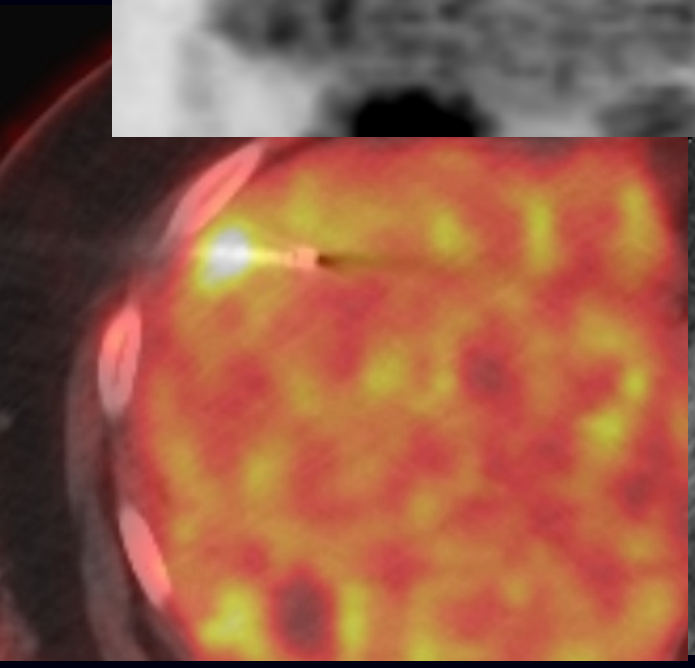
Kurilova I et al: Clinical Colorectal Cancer 2020 In Press

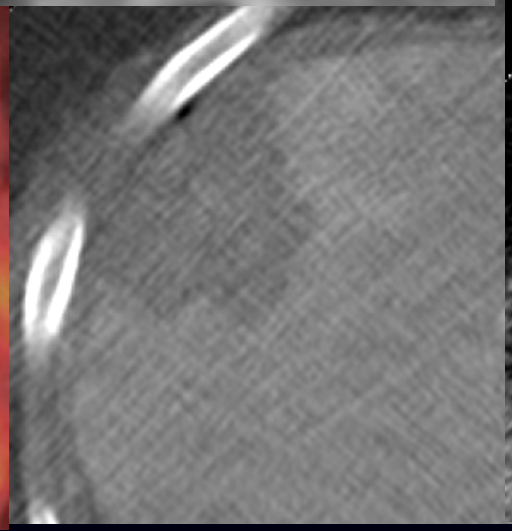
PET /Fusion capabilities improve targeting and can be used to demonstrate and Biopsy the minimal Margin

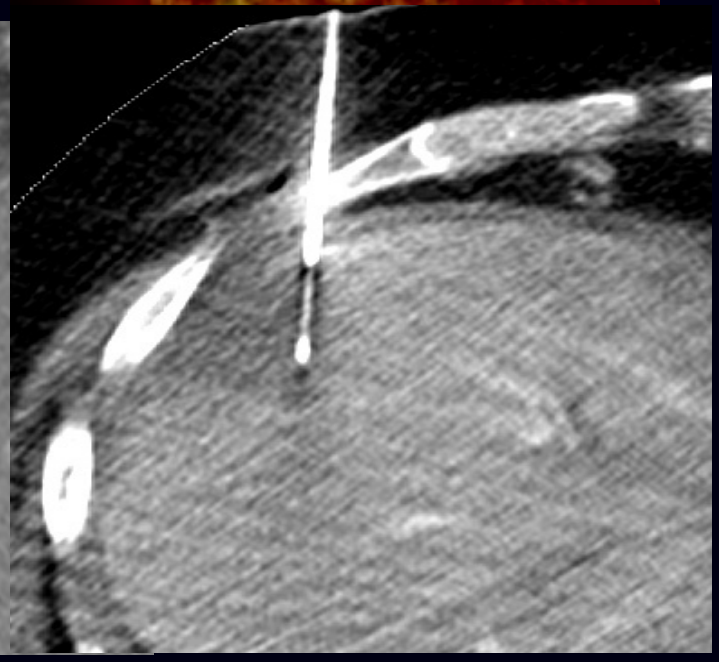
R21 CA131763-01A1: 2009-2019





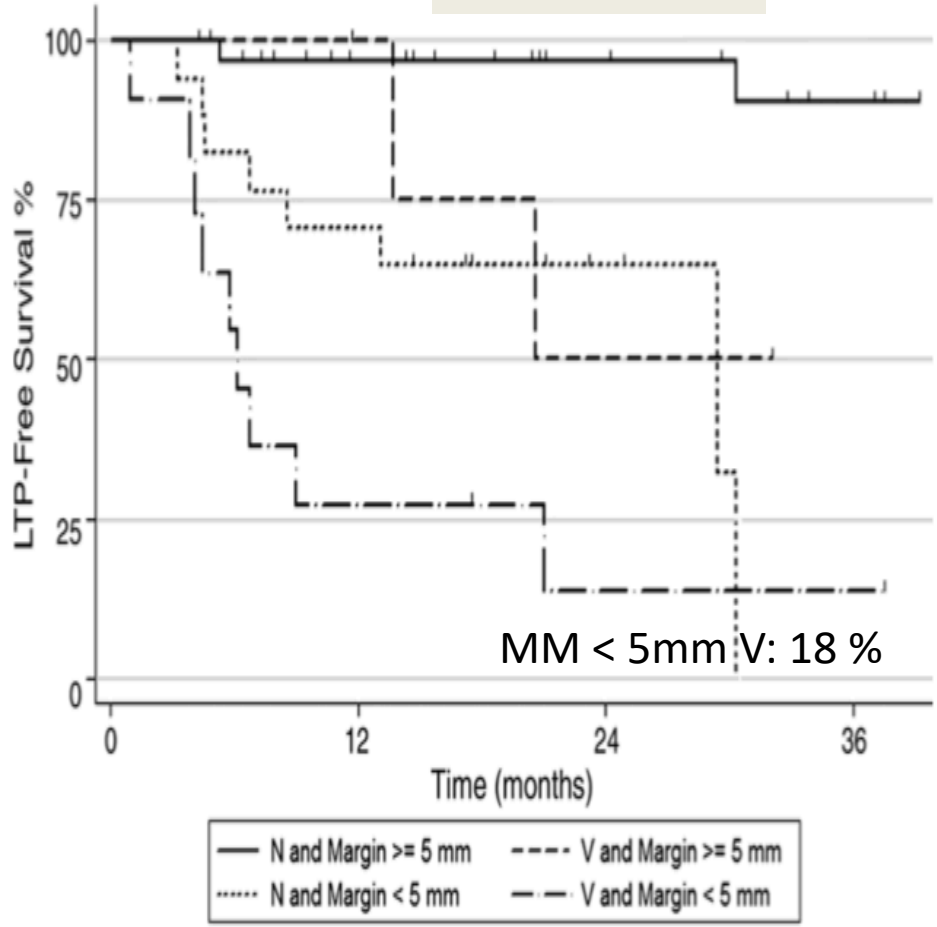






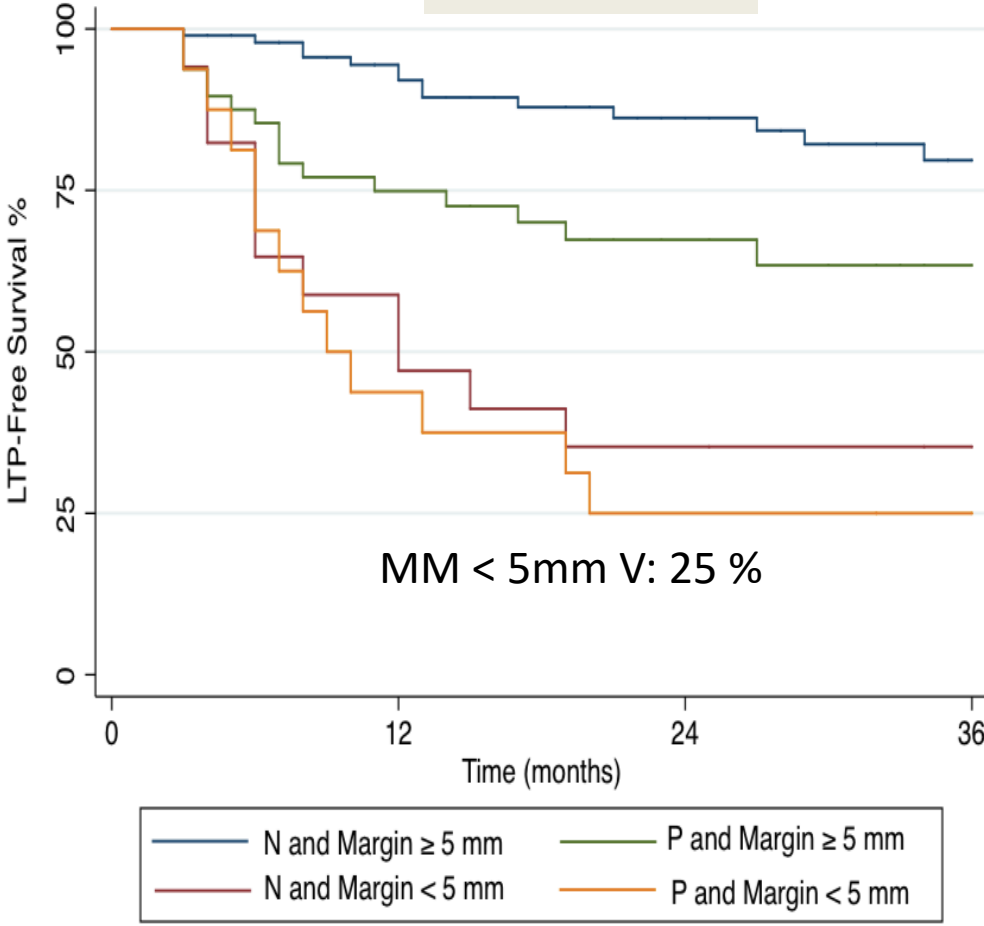
12 month-LTP of tumor-negative biopsy and margins ≥5 mm: 7%

MM> 5 CN97%



Sotirchos VS et al: Radiology. 2016 Sep;280(3):949-59

MM> 5 CN93%



New data Vasiniotis Kamarinos N et al: ASCO 2020

HR of LTP for narrow margins and positive tissue biopsy was 20.3

Optimizing Thermal Ablation for Colon Cancer Liver Metastases:

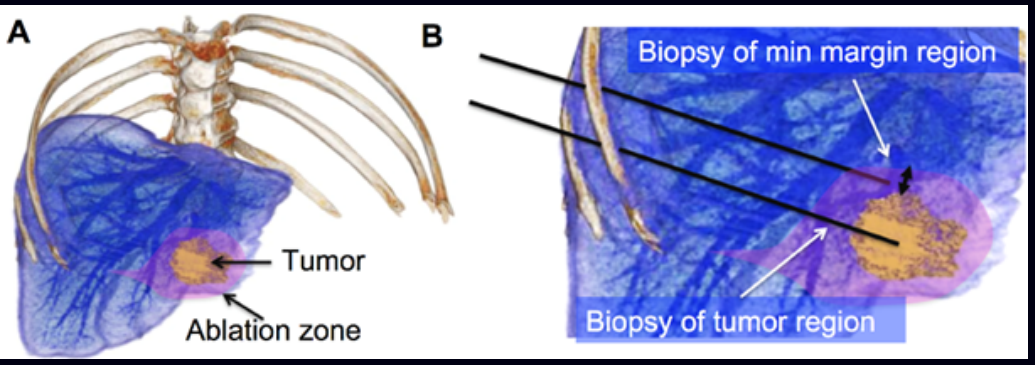
Rapid Tissue Analysis Allowing for Immediate Retreatment; Metabolic Imaging Biomarker Validation; and Predictive Genetic Signatures

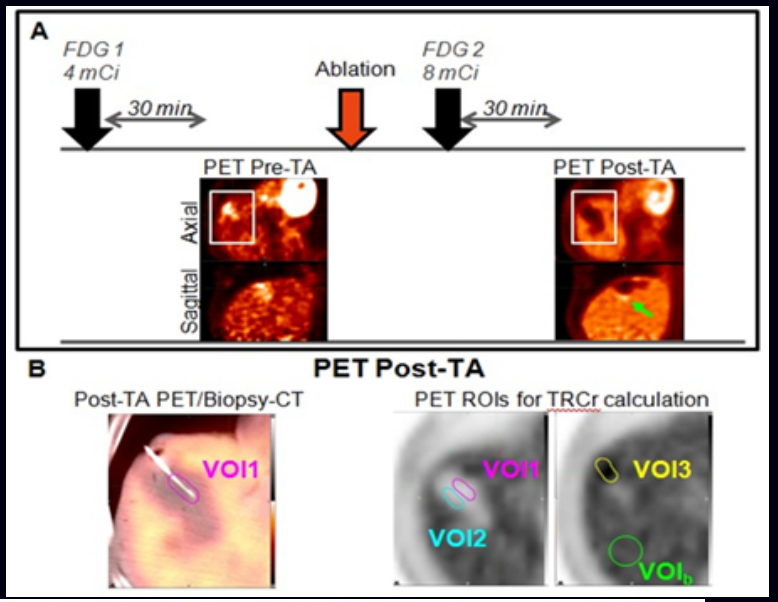
R01 CA240569-01

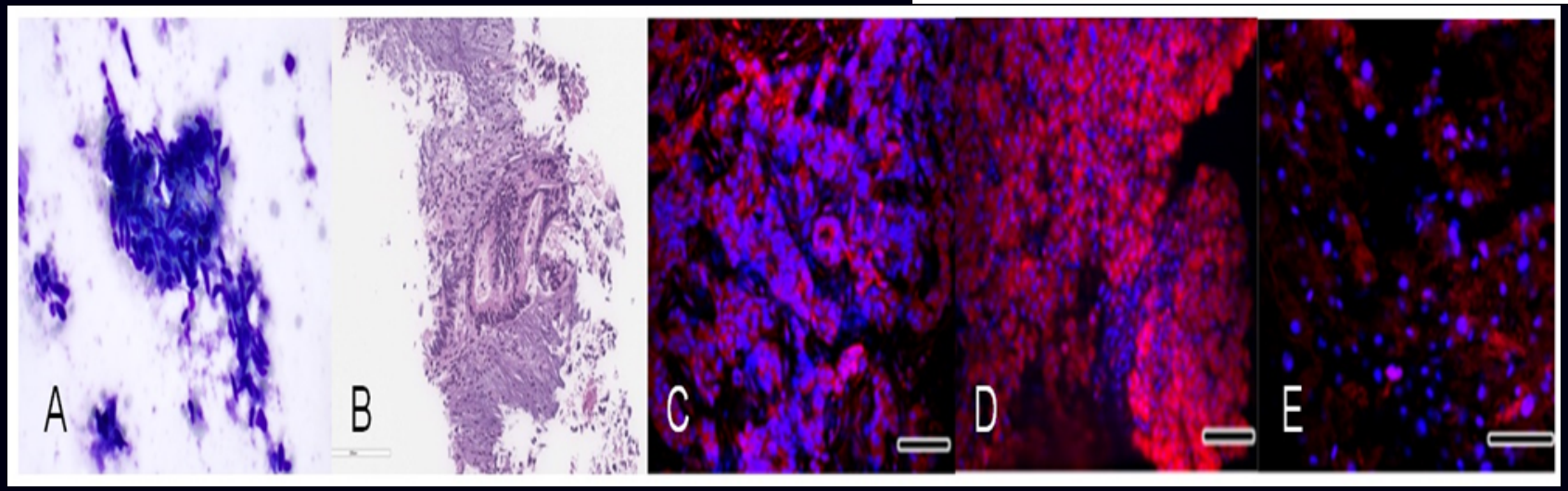
IRB 19-332

Optimizing Thermal Ablation for Colon Cancer Liver Metastases

R01 CA240569-01
IRB 19-332







Sotirchos VS, et al. Ann Surg Oncol. 2019 Jun;26(6):1833-1840

Liver Metastases Year in Review 2020

- Disease Biology critical Factor Impacting Outcomes after IO for CLM
- Y90 may prolong Survival in those CLM with Right Side primary Origin
- Y90 may provide liver remnant hypertrophy in addition to local control
- MM >10 mm (A0) is established as the optimal goal for CLM ablation, offering over 95% local tumor control
- A MM > 5 mm is the absolute minimum Requirement for acceptable Local Tumor Control
- When Combined with biopsy proven complete tumor necrosis a MM of 6-10 mm may provide same control as a 10 mm MM .
- For patients at high risk for biliary complications:

  A 6-10 MM margin, biopsy proven complete ablation and close follow-up may provide the safest strategy for long term Local tumor control