Contemporary Management of Colorectal Liver Mets

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Making Cancer History®

Surgical Oncology Cancer Symposium

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Disclosures

- No financial disclosures relevant to this talk

- PanTher – consultant for device company

What Defines Contemporary Management?

- **Multidisciplinary**
- **Treatment sequencing**
- **Increasing # patients getting resections**
  - Portal (+hepatic) vein embolization
  - Two-stage hepatectomy
  - Liver-first sequencing

(Dis)agreement Among Surgeons for Treatment Plans

ESA PAPER

Choices of Therapeutic Strategies for Colorectal Liver Metastases Among Expert Liver Surgeons

A Throw of the Dice?

Povilas Ignatavicius, MD, Christian E. Oberkofler, MD,* William C. Chapman, MD,†*
Ronald P. DeMatteo, MD,‡ Bryan M. Clary, MD,§ Michael I. D'Angelica, MD,¶ Kenneth K. Tanabe, MD,||
*Johnny C. Hong, MD,** Thomas A. Aloia, MD,†† Timothy M. Pawlik, MD, MPH, PhD,††*

TABLE 1. Agreement (Percentage) Among Experts for Each Clinical Case

Easy → Complex scenarios

	1*	2*	3*	4*	5	6	7	8	9	10	All (IRQ)
Resectability (Yes/No)	100	100	100	100	95	95	97	84	89	63	96 (88–100)
Initial treatment (surgery, chemotherapy)	53	84	97	97	82	86	58	83	86	68	84 (66–89)
Approach (open, minimally invasive)	71	63	58	46	92	89	95	94	100	96	91 (62–95)
Portal vein embolization (Yes/No)	92	100	79	100	89	68	95	75	57	52	84 (65–96)
Preoperative volumetry (Yes/No)	71	97	66	95	79	57	84	56	81	67	75 (64–87)
Type of surgery (2-stage, 1-stage)	100	100	95	100	89	62	92	62	44	44	91 (58–100)
Type of resection (anatomical, parenchyma sparing)	47	82	47	61	81	49	51	56	79	60	58 (49–80)
Ablation in combination with resection (Yes/No)	97	97	76	92	50	62	55	51	65	56	64 (54–93)

*Low complexity cases.

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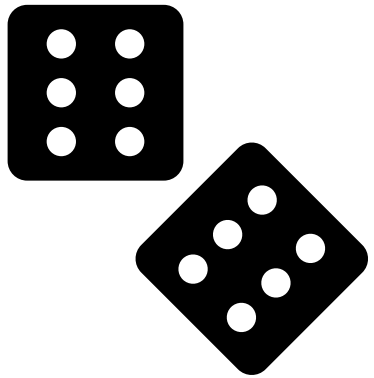
Ignatavicius, Ann Surg 2020

Disagreement is Either Comical or Scary…

- From this “expert” survey:
  - “In conclusion, choices of therapeutic strategies among expert liver surgeons actually look like ‘***a throw of the dice***.’”



Ignatavicius, Ann Surg 2020

Synchronous Colorectal Liver Mets (CLM)

- **Combination** (*Simultaneous* Colorectal and Liver Surgery)
- **Staged**
  - *Classic* Approach (Colorectal Surgery 1st)
  - *Liver-First* (formerly known as “Reverse Approach”)

Staged vs. Combo: Not Simple Yes vs. No

- ❑ Minor hepatectomy + proctectomy?
- ❑ Major hepatectomy + right colectomy?
- ❑ Major hepatectomy + proctectomy?
- ❑ Bilateral liver mets?

Cumulative Burden of Simultaneous Surgery

https://doi.org/10.1016/j.hpb.2022.12.008 HPB

ORIGINAL ARTICLE

Impact of cumulative operative time on postoperative complication risk in simultaneous resections of colorectal liver metastases and primary tumors

Allison N. Martin[1], Ching-Wei D. Tzeng[1], Elsa M. Arvide[1], John M. Skibber[2], George J. Chang[2], Yi-Qian Nancy You[2], Brian K. Bednarski[2], Abhineet Uppal[2], Whitney L. Dewhurst[1], Jenilette V. Cristo[1], Yun S. Chun[1], Hop S. Tran Cao[1], Jean-Nicolas Vauthey[1] & Timothy E. Newhook[1]

Predictors of Grade ≥2 Complications

Variable	Odds ratio	95% CI min	95% CI max	*p* value
Multivariable[a]				
OR time (in minutes)				
1st quartile (<325 min)	Ref	Ref	Ref	Ref
2nd quartile (325–416 min)	1.78	0.48	6.65	0.39
3rd quartile (416–506 min)	3.54	0.92	13.6	0.07
4th quartile (>506 min)	7.28	1.73	30.6	0.007

23% to 57%

Carefully consider if your patient can really handle the sequelae of 8-hr combo case

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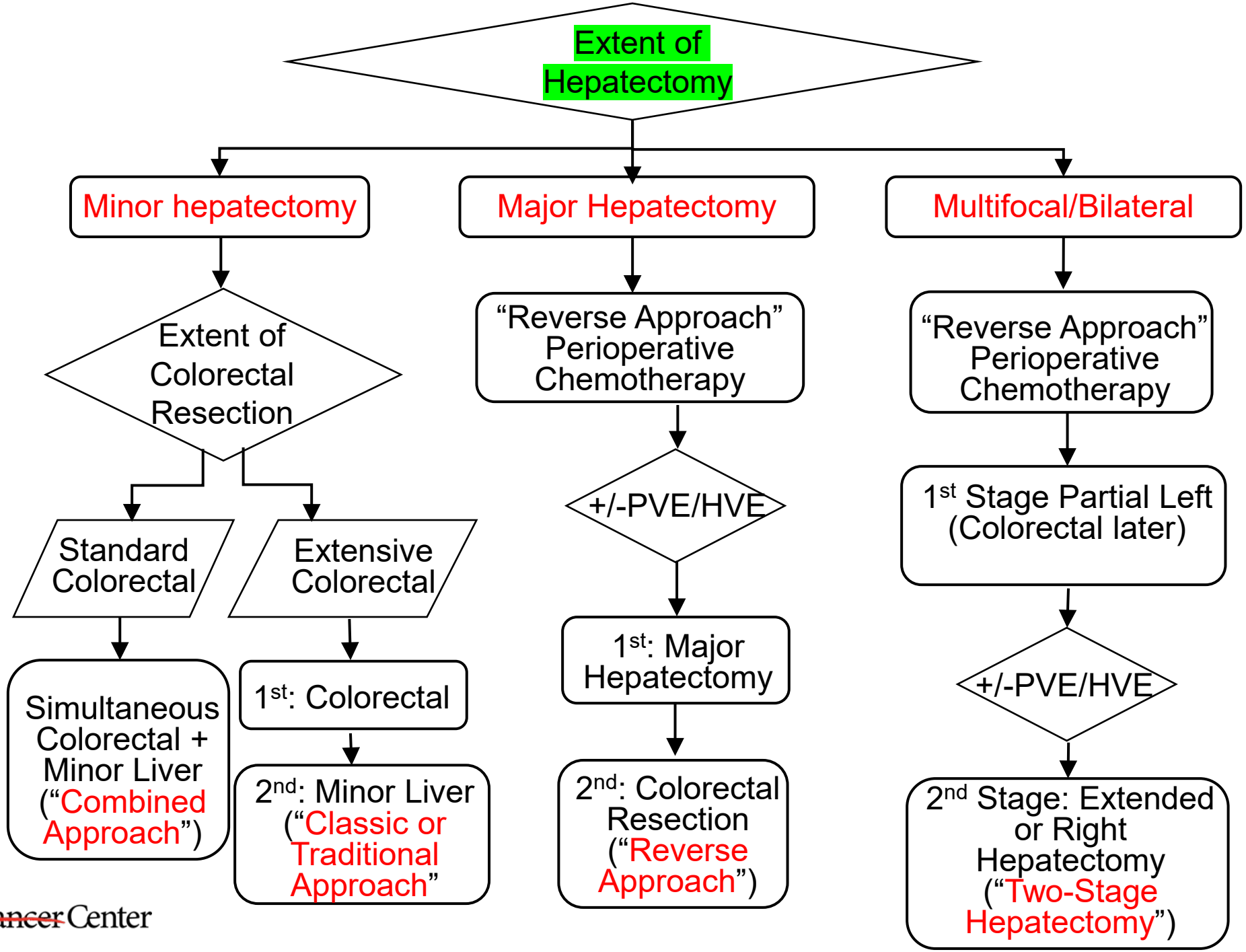
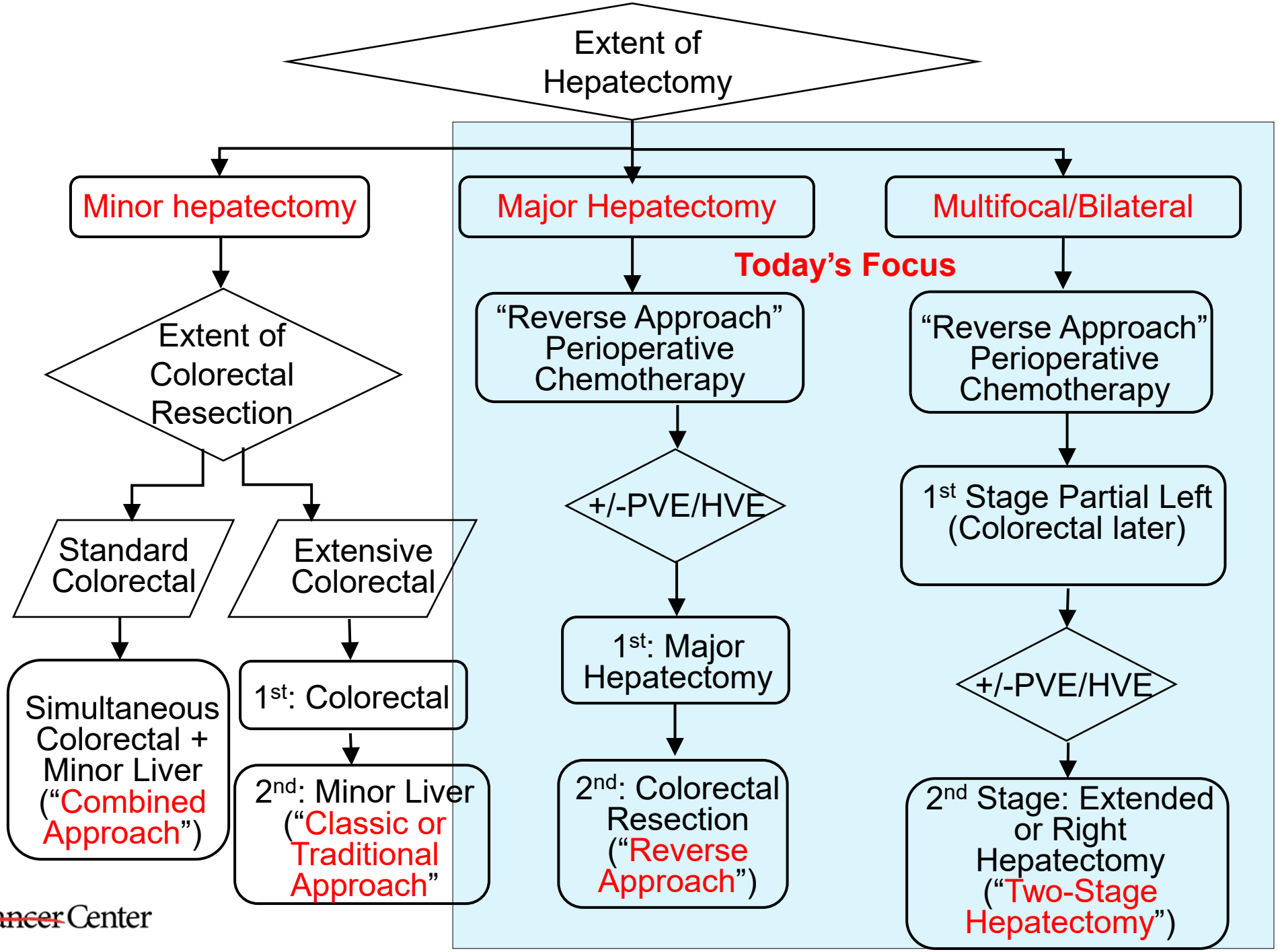
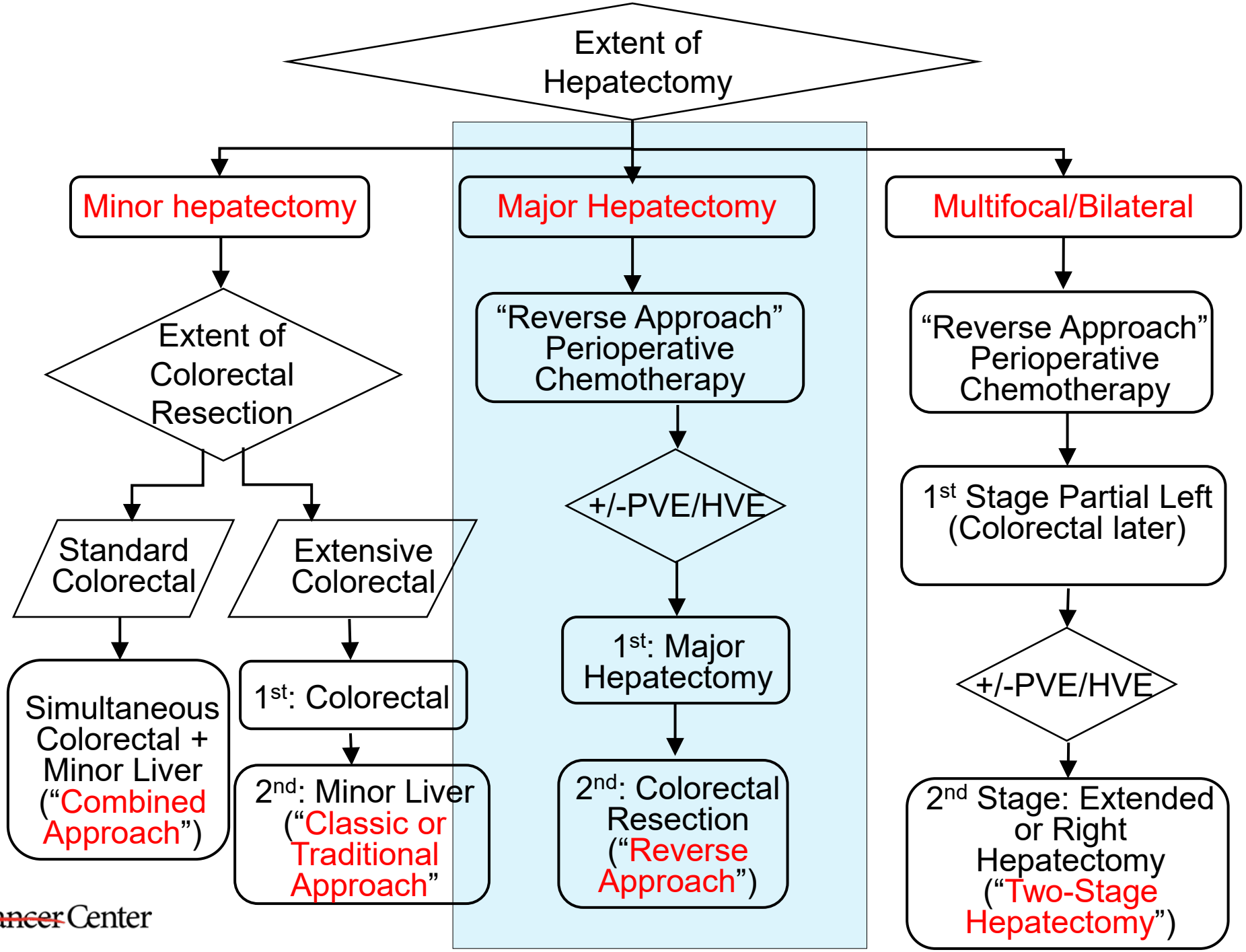
Martin, HPB 2023

Staged CLM Resection

- (Dis)agreement among surgeons in treatment decisions
- Safety of Major Hepatectomy is Paramount in 2023
- Borderline/Unresectable CLM
- Oncologic Outcomes of Liver-First Approach




Extent of Hepatectomy
Minor hepatectomy
Major Hepatectomy
Multifocal/Bilateral
Today's Focus
Extent of Colorectal Resection
Standard Colorectal
Extensive Colorectal
Simultaneous Colorectal + Minor Liver ("Combined Approach")
1st: Colorectal
2nd: Minor Liver ("Classic or Traditional Approach"
"Reverse Approach" Perioperative Chemotherapy
+/-PVE/HVE
1st: Major Hepatectomy
2nd: Colorectal Resection ("Reverse Approach")
"Reverse Approach" Perioperative Chemotherapy
1st Stage Partial Left (Colorectal later)
+/-PVE/HVE
2nd Stage: Extended or Right Hepatectomy ("Two-Stage Hepatectomy")



Staged CLM Resection

- (Dis)agreement among surgeons in treatment decisions
- Safety of Major Hepatectomy is Paramount in 2023
- Borderline/Unresectable CLM
- Oncologic Outcomes of Liver-First Approach

What is our goal? Speed or Safety?

RANDOMIZED CONTROLLED TRIAL

OPEN

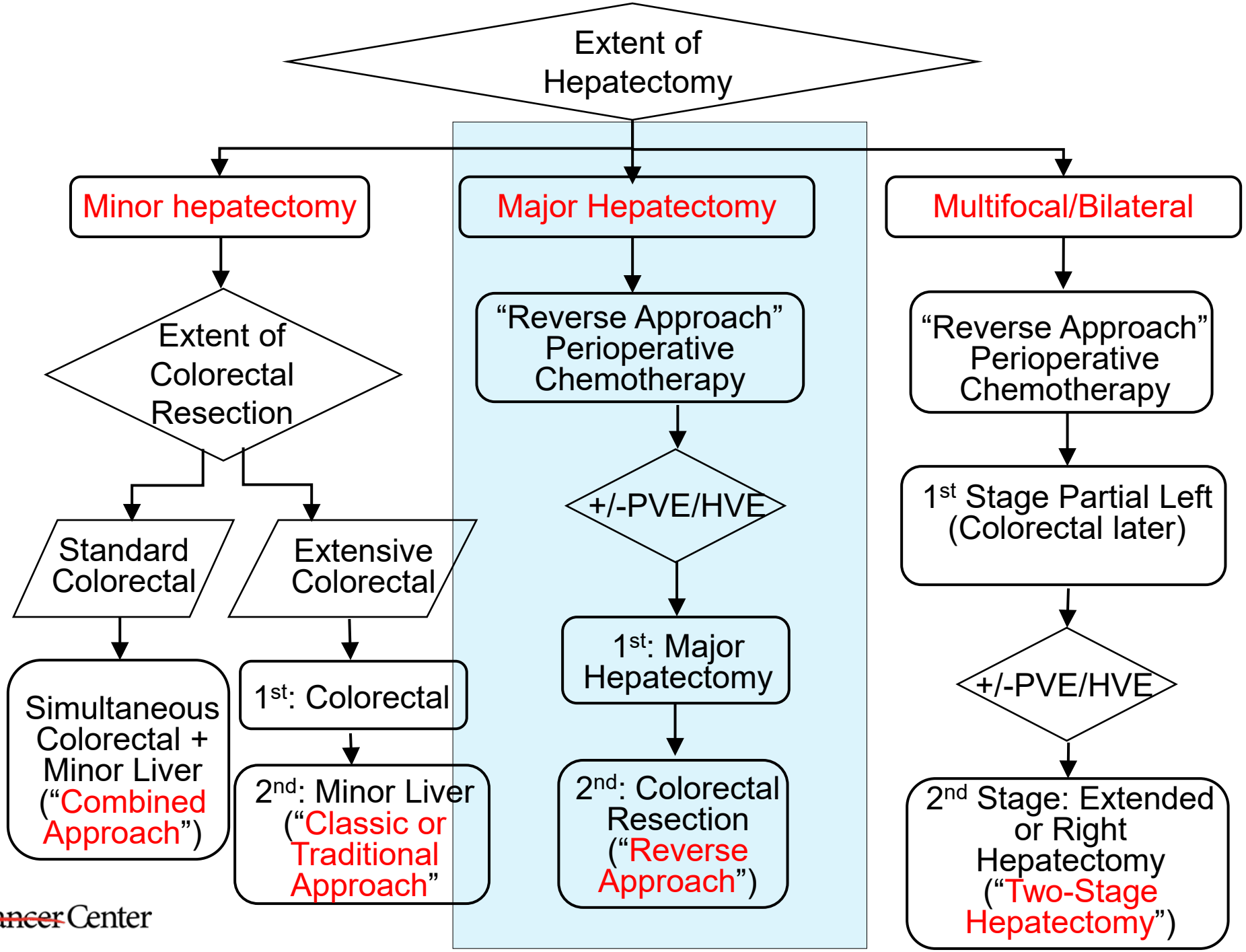
ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis

Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial)

Per Sandström, MD, PhD, Bård I. Røsok, MD, PhD,|| Ernesto Sparrelid, MD, PhD,‡ Peter N. Larsen, MD, PhD,¶ Anna L. Larsson, RN,* Gert Lindell, MD, PhD,§ Nicolai A. Schultz, MD, PhD,¶ Bjorn A. Bjørnbeth, MD, PhD,|| Bengt Isaksson, MD, PhD,‡ Magnus Rizell, MD, PhD,† and Bergthor Björnsson, MD, PhD**

- 8.3% surgical mortality in this RCT (best-selected patients)
- Real-world mortality always worse than RCT
- USA databases: 90d mortality after major hepatectomy: 5-15% (!)
- Europe: >10% in national databases

Sandstrom, Ann Surg 2018



Staged CLM Resection

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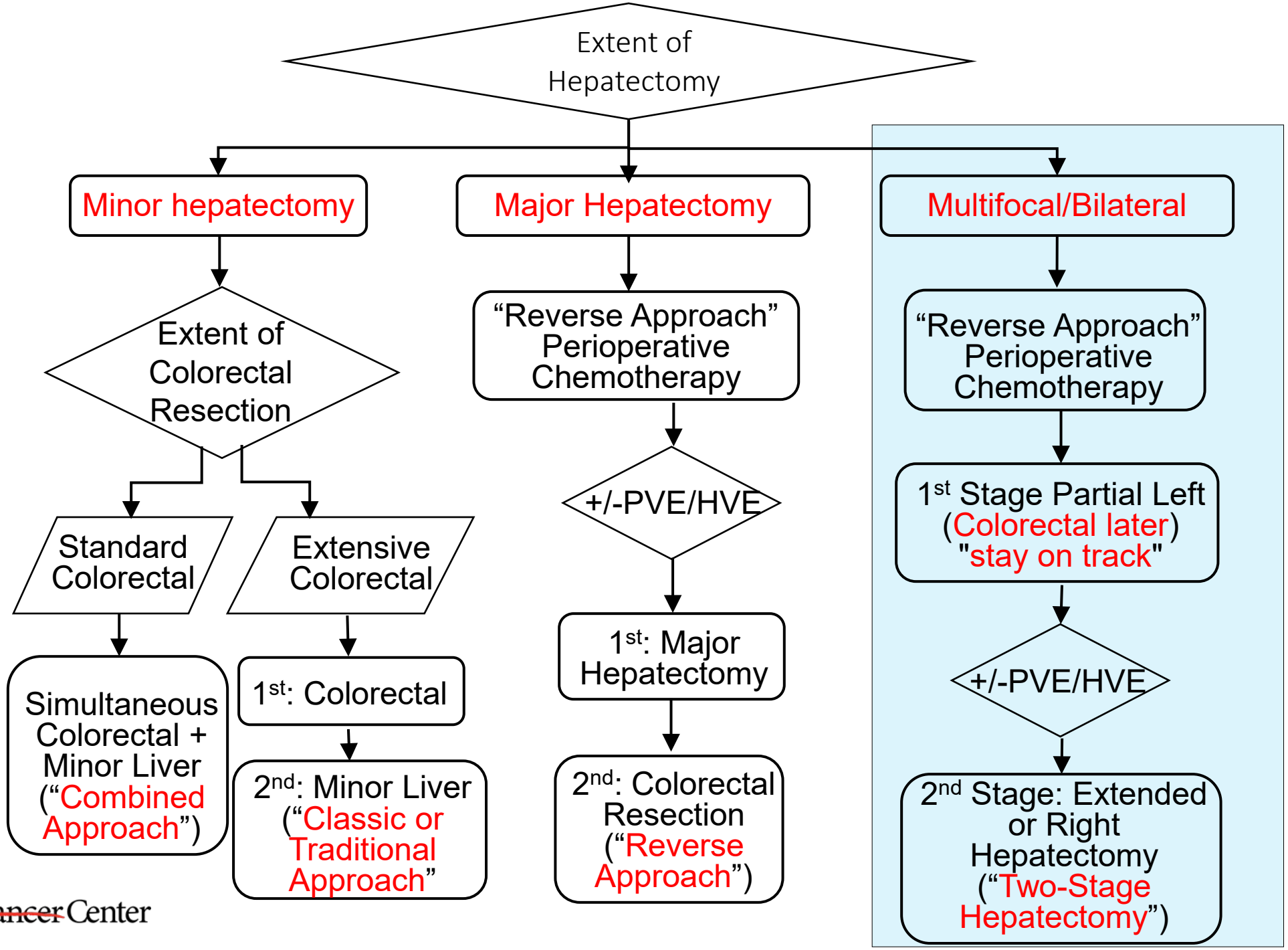

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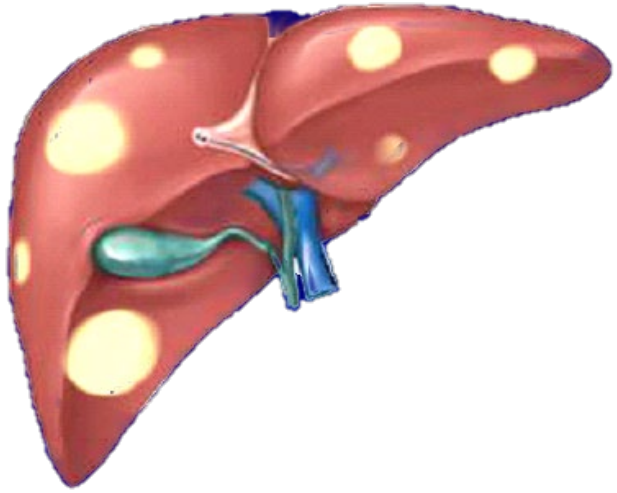
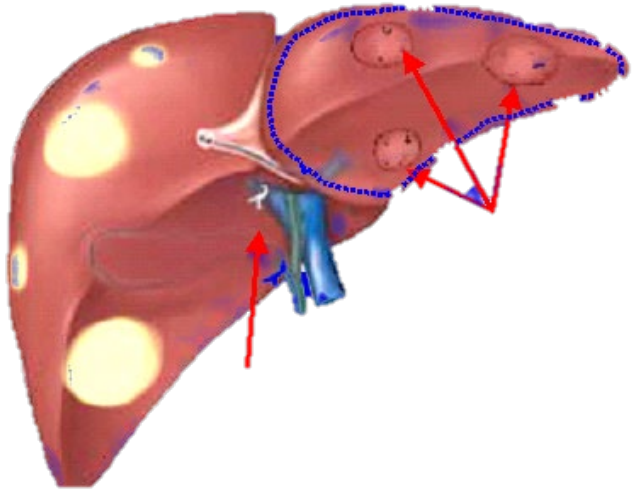
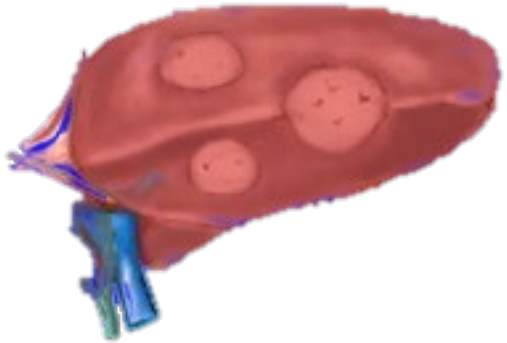
Must Stage: Bilateral (Initially Unresectable) Due to Small Future Liver Remnant



Multiple Bilateral CLM (with small sFLR)



1st Stage: Partial Resection + PVE/HVE



2nd Stage: Major Hepatectomy

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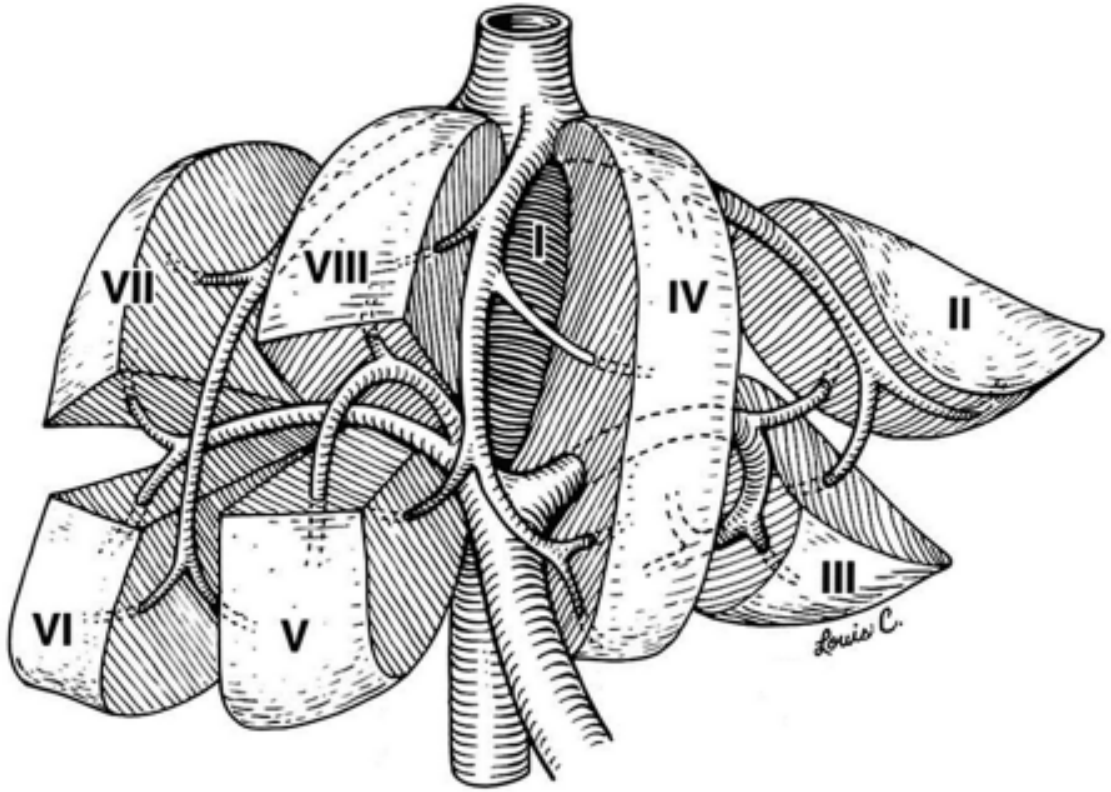
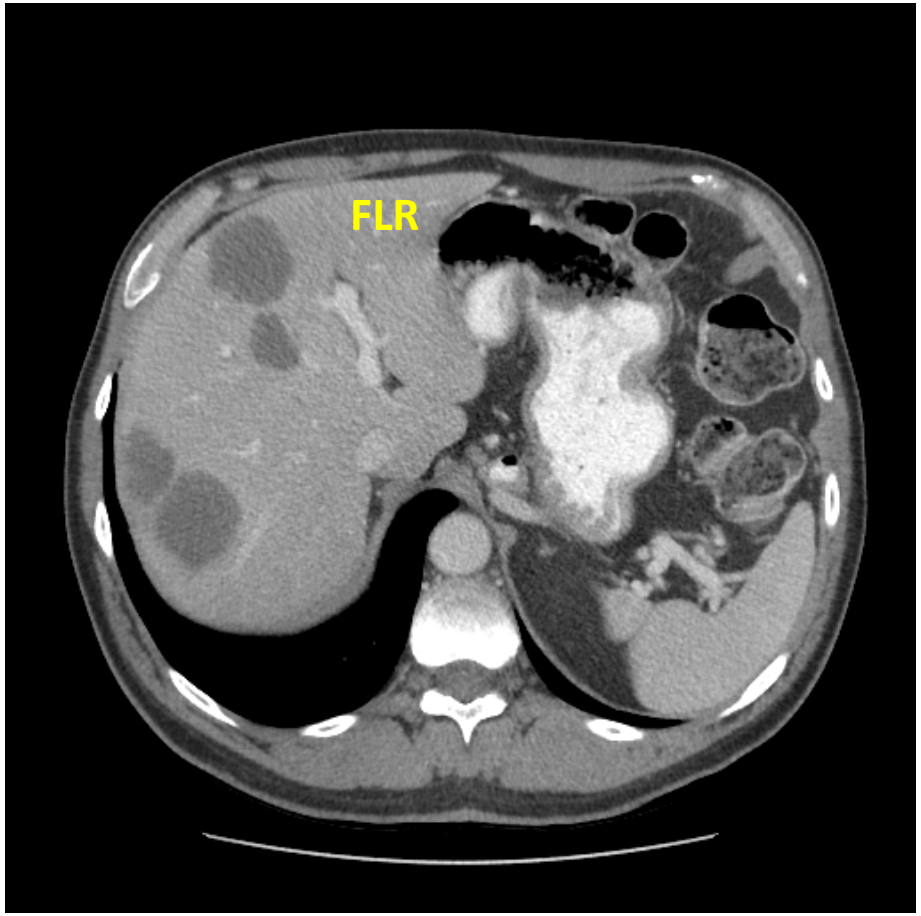
Adam. *Ann Surg* 2000
Jaeck. *Ann Surg* 2004
Brouquet. *J Clin Oncol* 2011

What Is Considered “Resectable” in 2023?



- Not the number of lesions or tumor size
- All about % leftover liver volume
- Must have adequate future liver remnant (FLR)

Case 1: 55 yo male with metastatic rectal cancer. PS 0. Small FLR.



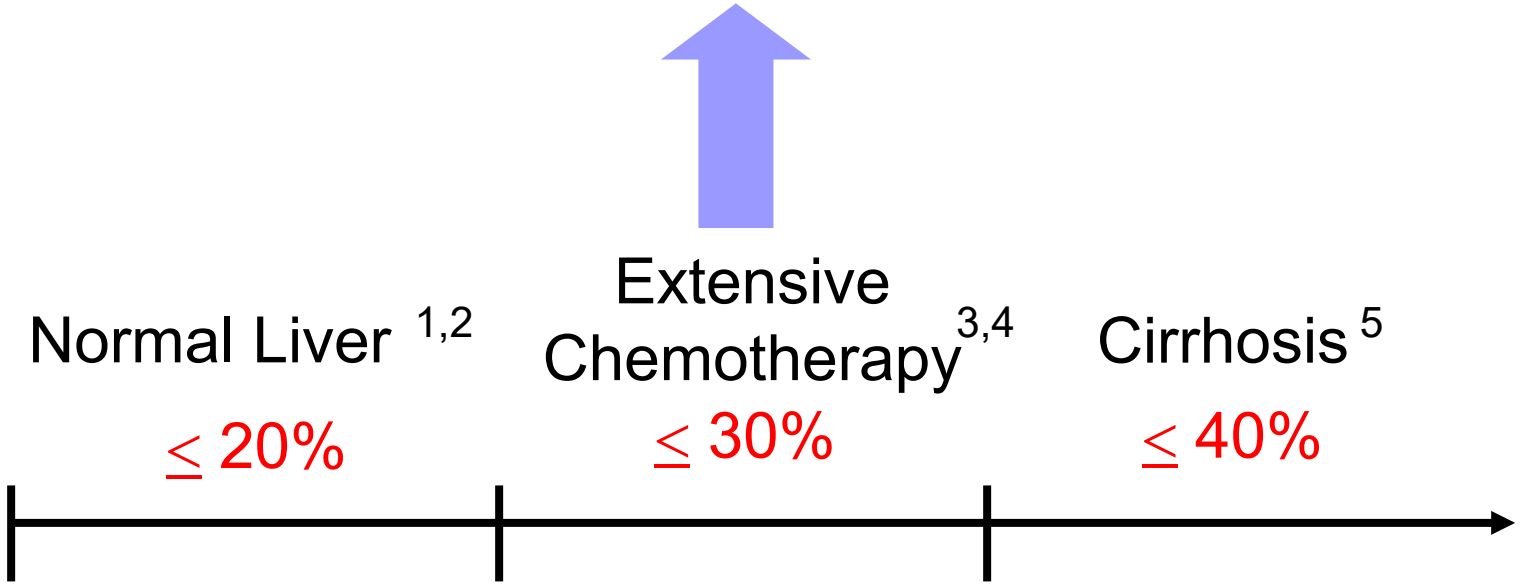
Insufficient FLR: options?

1. **Chemotherapy for life**
2. **Attempt resection (high risk of PHI and/or death)**
3. **PVE**

Baseline with 17% FLR (segments I, II, III)

Indications for PVE?

- Extended duration chemo
- High BMI/fatty liver?
- Chemo-associated liver injury (CALI)?



1. Vauthey JN *Ann Surg* 2004
2. Ribero D *Br J Surg* 2007
3. Shindoh J Gastrointest Surg 2013
4. Azoulay D *Ann Surg* 2000
5. Kubota K *Hepatology* 1997

Manipulate Liver and Lose Excess Weight

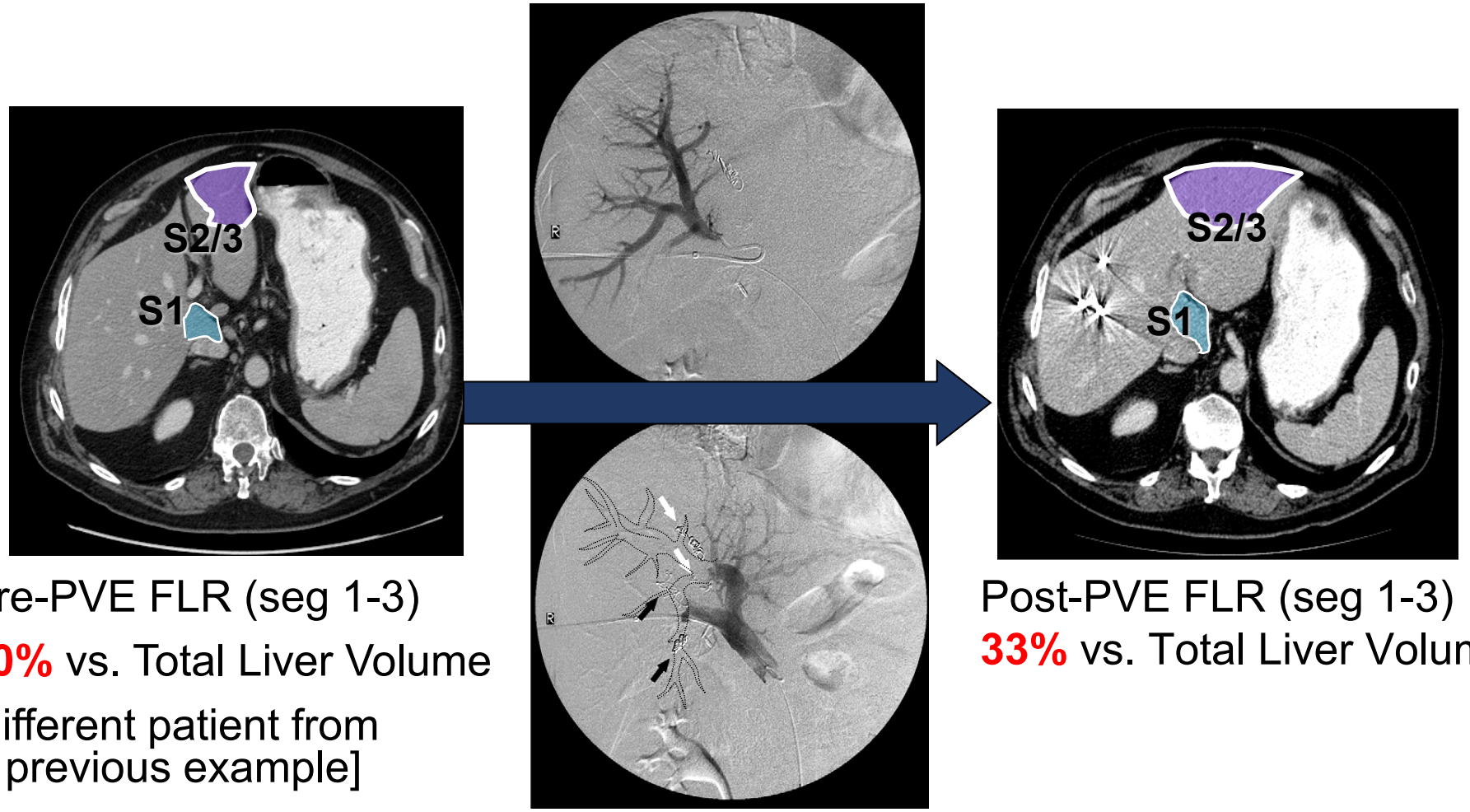
Liver size divided by body size…

Can reduce wt to reduce absolute liver volume that is needed

PVE DATE:			
	Pre Embo LIVER VOLUME		
	CT DATE	Pre-Embo	
	9/24/2020		
		%TLV	%TLV
Liver	1560.00		
Segment 1	16.48		
Segment 2	124.23		
Segment 3	176.15		
Segment 4	169.15		
Seg's 1,2,3	316.85		
Seg's 1,2,3,4	486.00		
Seg's 2,3	300.38		
Ht	161.50		
Wt	87.30		
BSA	1.98		
BMI	33.47		
T.E.L.	1399.96		
Segments 1,2,3		**0.226331072**	22.6%
Segments 1,2,3,4		**0.347153266**	34.7%
Whole Liver		**1.114316982**	111.4%
New Formula 2			
T.E.L.	1713.75347		
Segments 1,2,3		**0.184888904**	18.5%
Segments 1,2,3,4		**0.283588048**	28.4%
Segments 2,3		**0.175273169**	17.5%
Whole Liver		**0.910280872**	91.0%

Not quite enough for right hepatectomy

Portal Vein Embolization (PVE)



Pre-PVE FLR (seg 1-3)

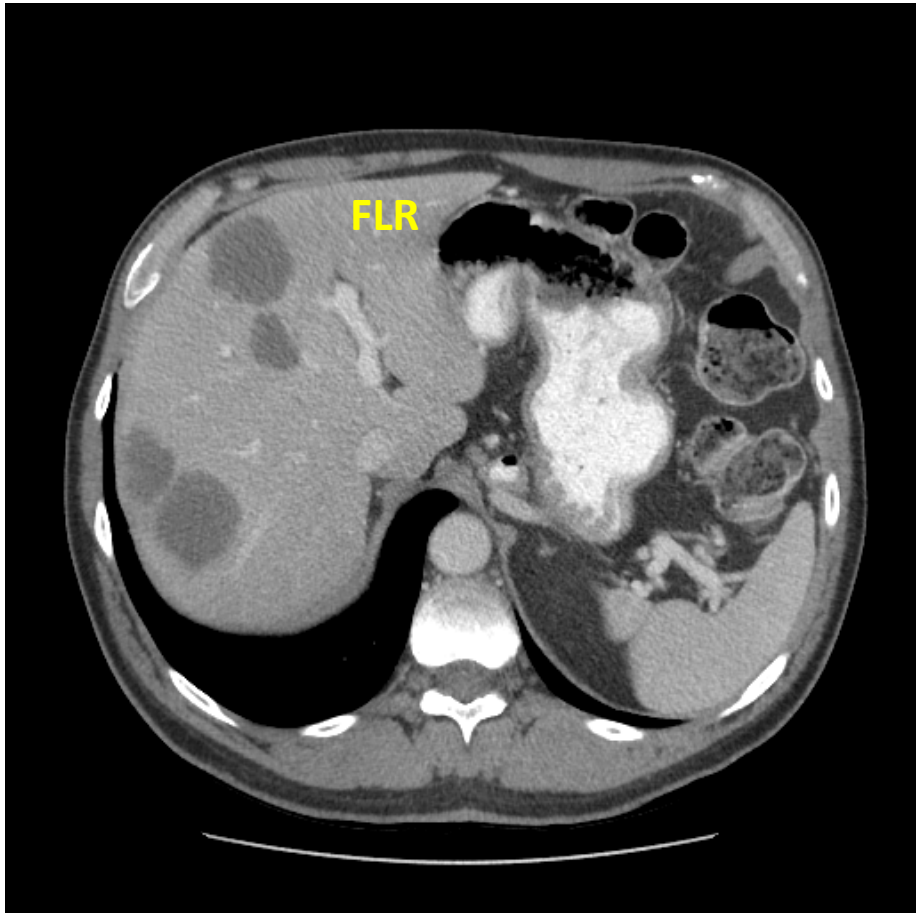
10% vs. Total Liver Volume

[different patient from previous example]

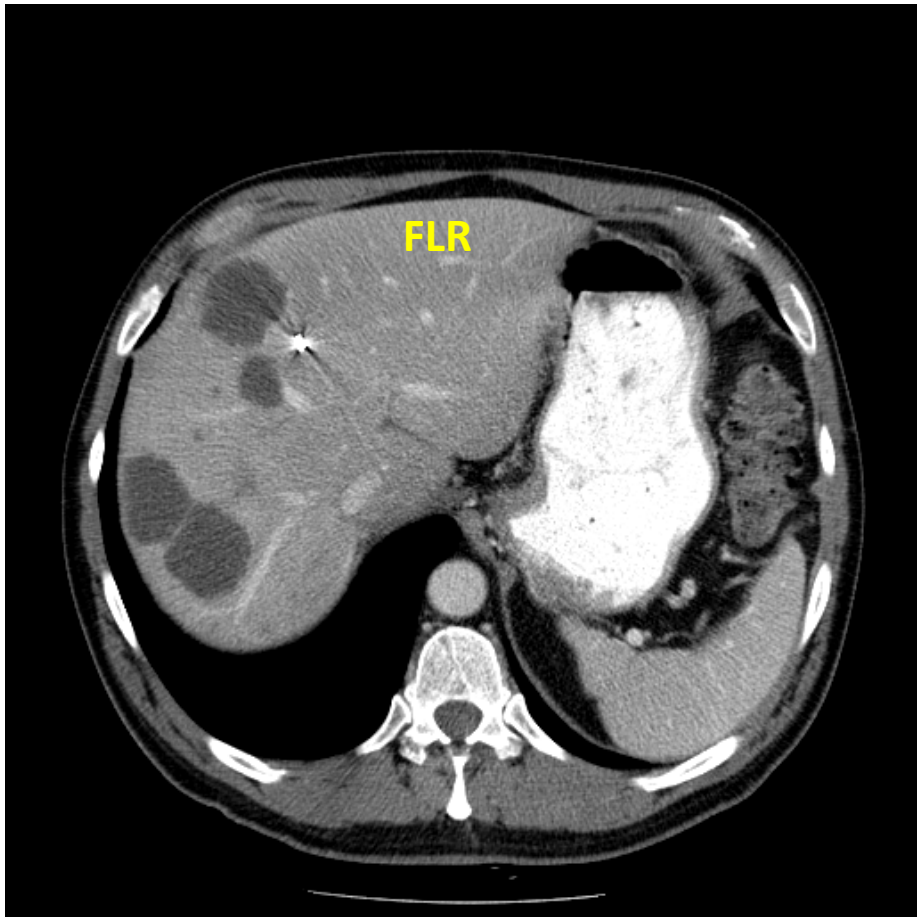
Post-PVE FLR (seg 1-3)

33% vs. Total Liver Volume

Case 1: 55 yo male with metastatic rectal cancer. PS 0. Small FLR.



Before R PVE with 17% sFLR



After RPVE with 33% sFLR

Staged CLM Resection

- (Dis)agreement among surgeons in treatment decisions
- Safety of Major Hepatectomy is Paramount in 2022
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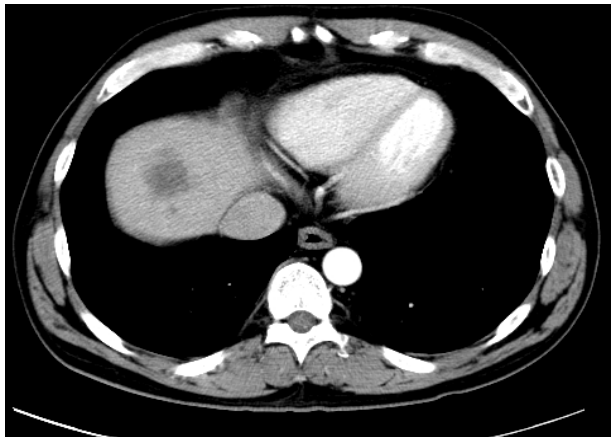
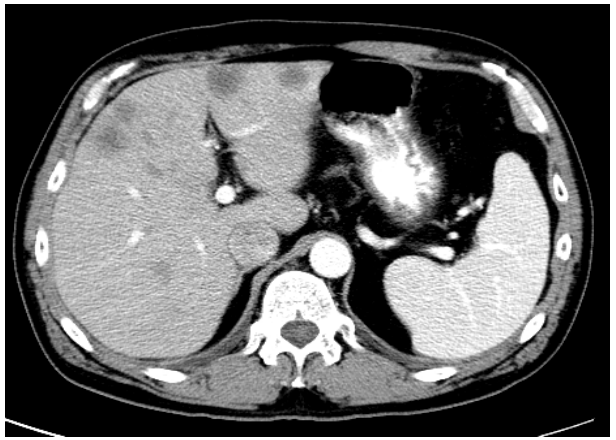
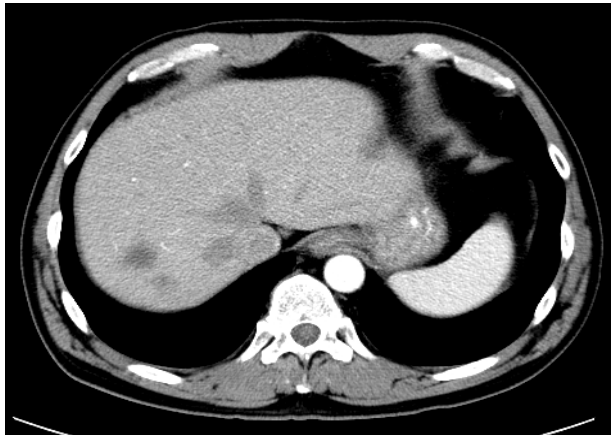
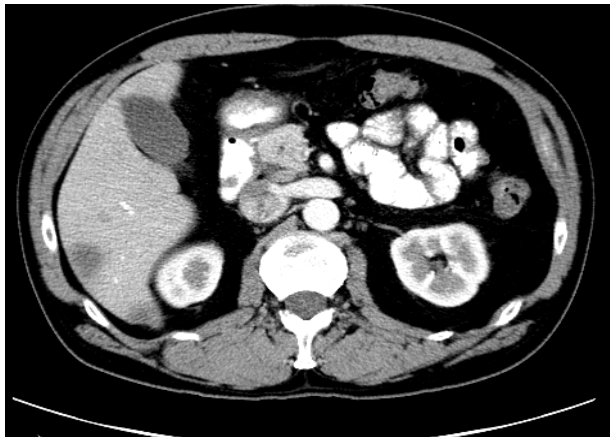
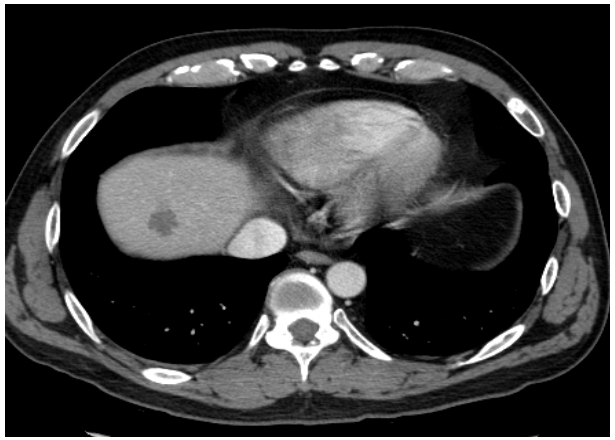
- Oncologic Outcomes of Liver-First Approach

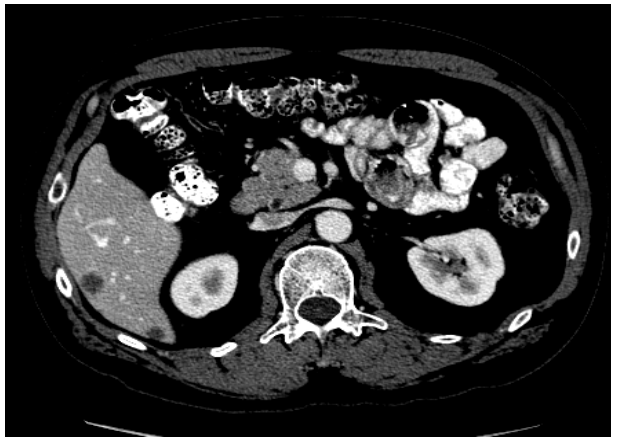
Case 2: 51 yo male with synchronous liver metastases and rectal cancer

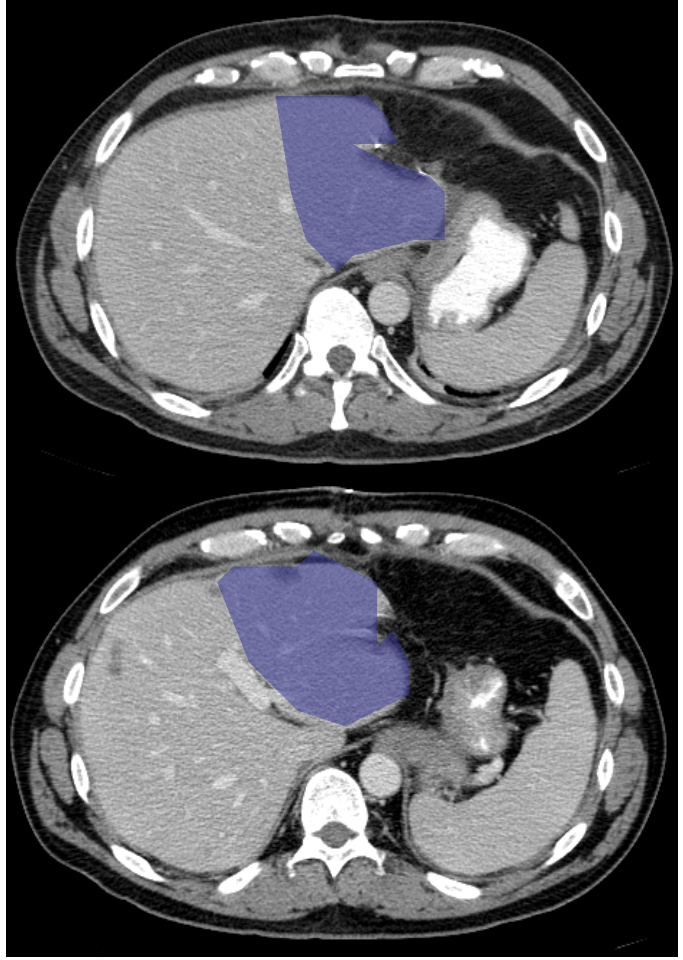
- 13 synchronous CLM, involving 7 of 8 liver segments
  - initially unresectable → no surgical referral?

After FOLFOX Bevacizumab x4

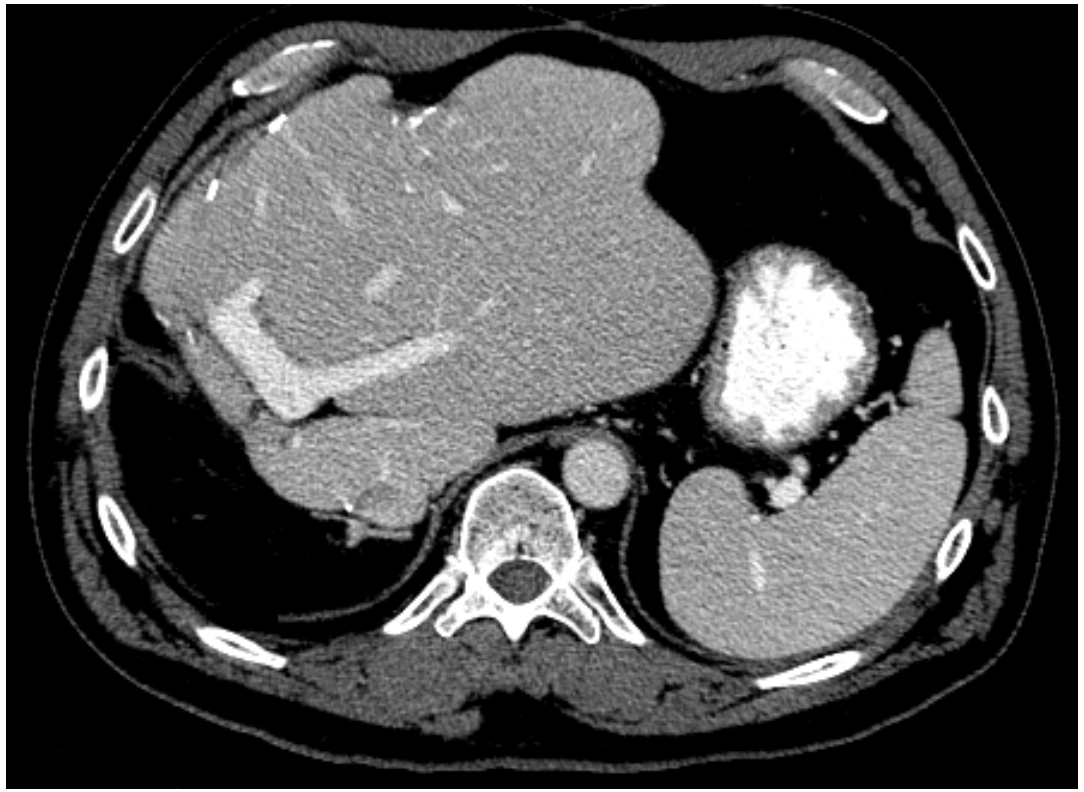




Type I Morph Response (sharp margin, no enhancement, probably RAS-WT)

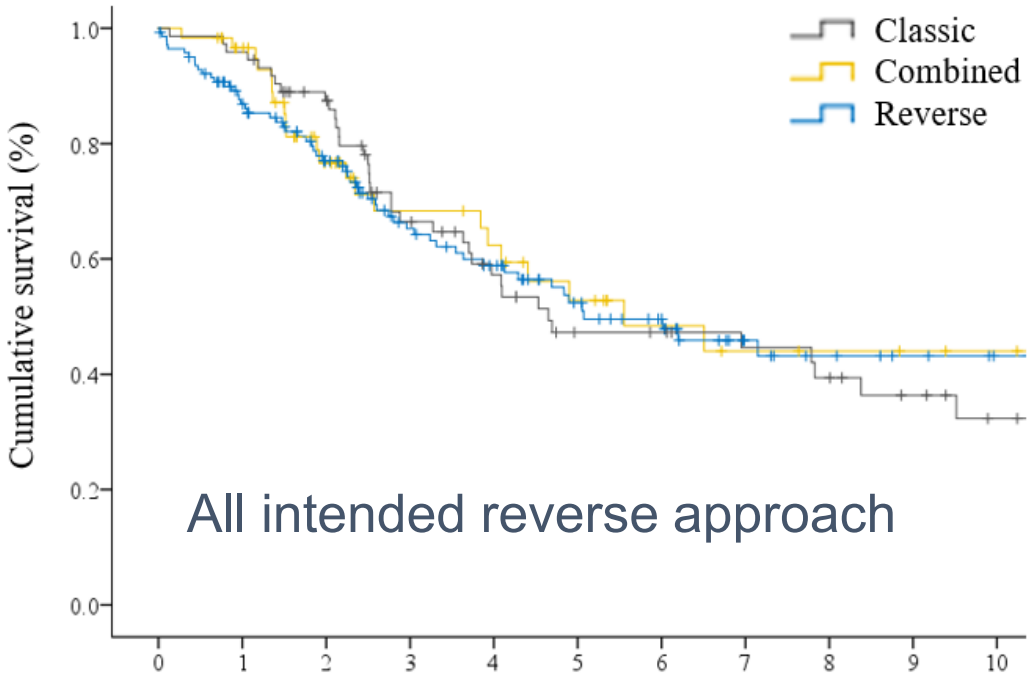


After first stage partial left hepatectomy



- Second Stage: Extended Right Hepatectomy
- Finished last 8 of 12 cycles of chemo
- Alive NED 5 years later (probably a RAS-WT pt)

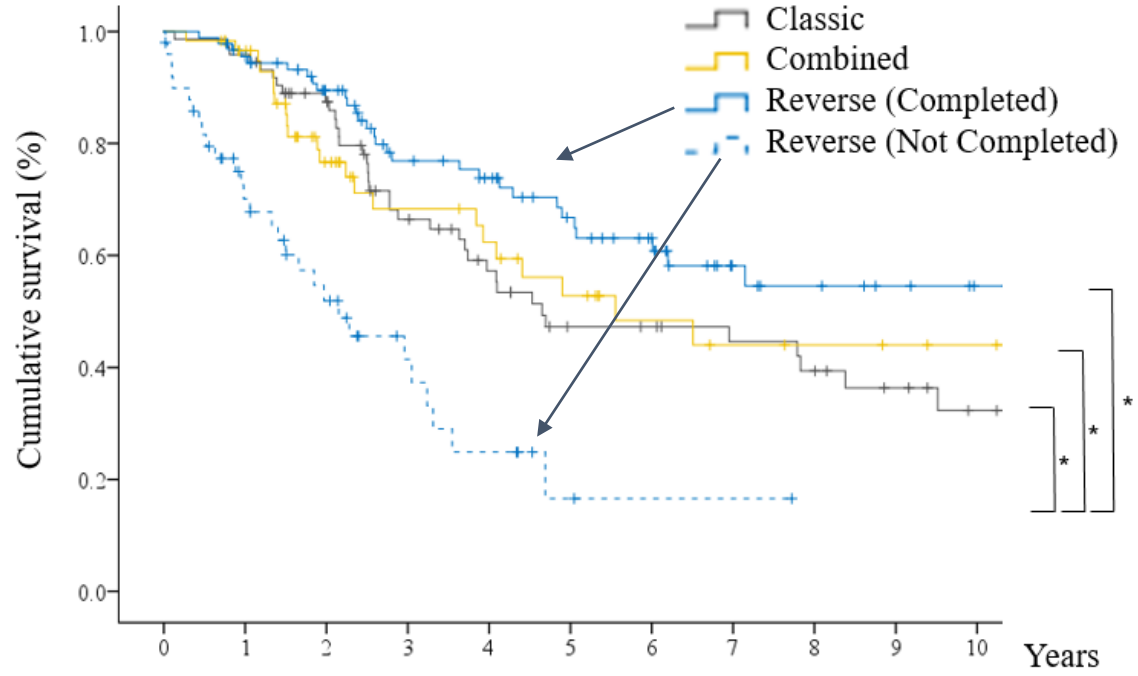
No Oncologic Downside to Reverse (Liver-First) Approach



All intended reverse approach

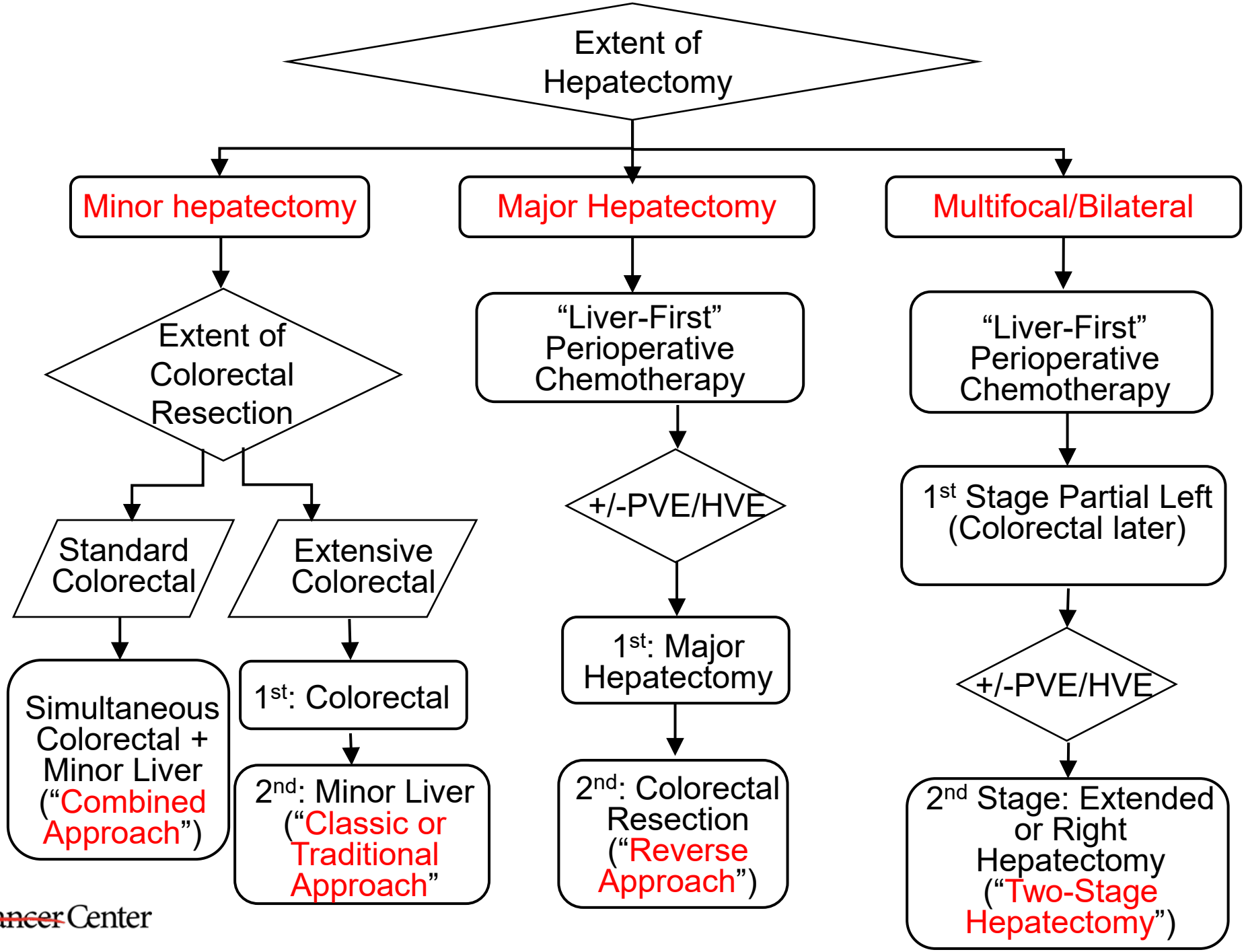
No. at risk	0	1	2	3	4	5	6	7	8	9	10
Classic	73	69	57	38	30	21	19	17	14	11	7
Combined	60	52	33	24	21	16	11	9	8	7	5
Reverse	141	106	81	59	44	33	23	15	11	9	6

B.



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Classic	73	69	57	38	30	21	19	17	14	11	7
Combined	60	52	33	24	21	16	11	9	8	7	5
Reverse (Completed)	91	76	61	49	39	31	21	14	11	9	6
Reverse (Not completed)	50	29	19	10	5	1	1	0			

Maki Ann Surg Oncol 2023



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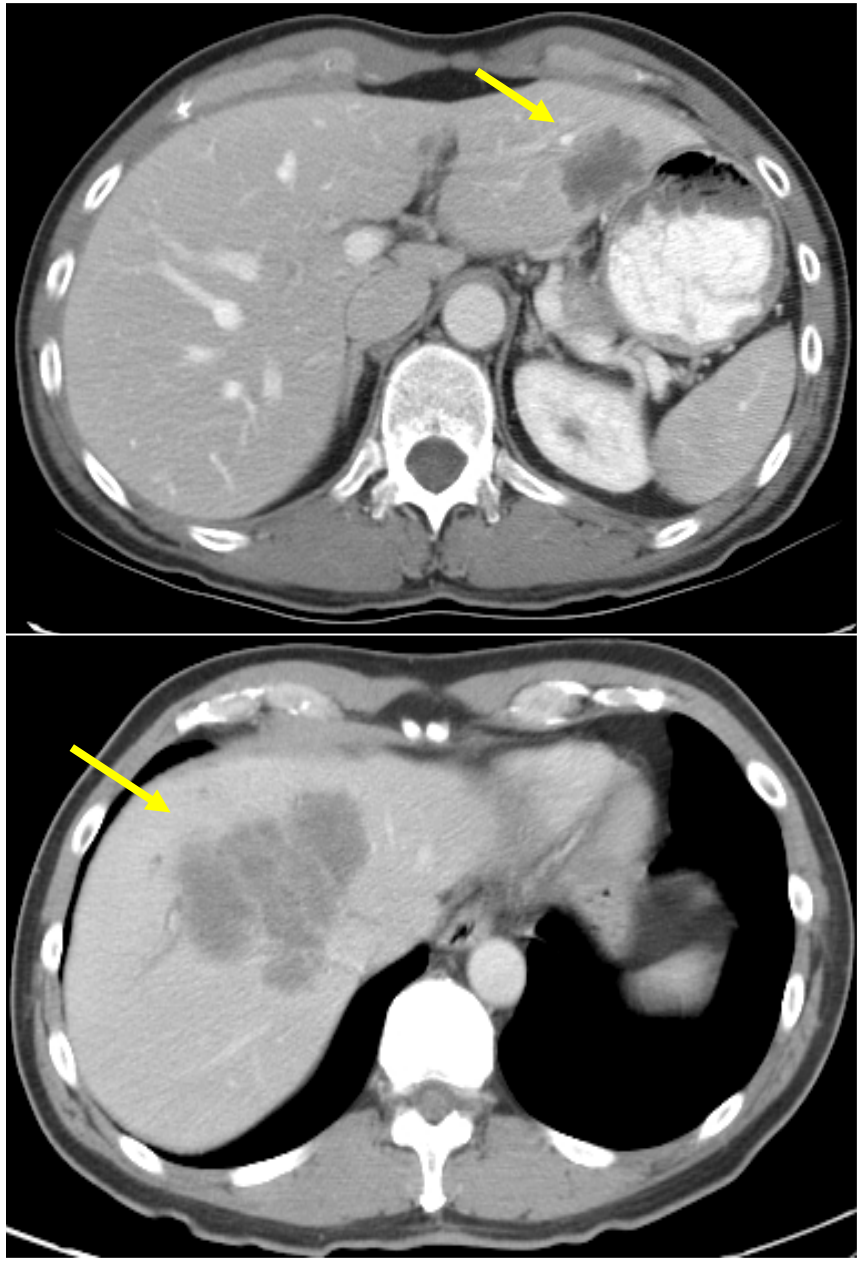
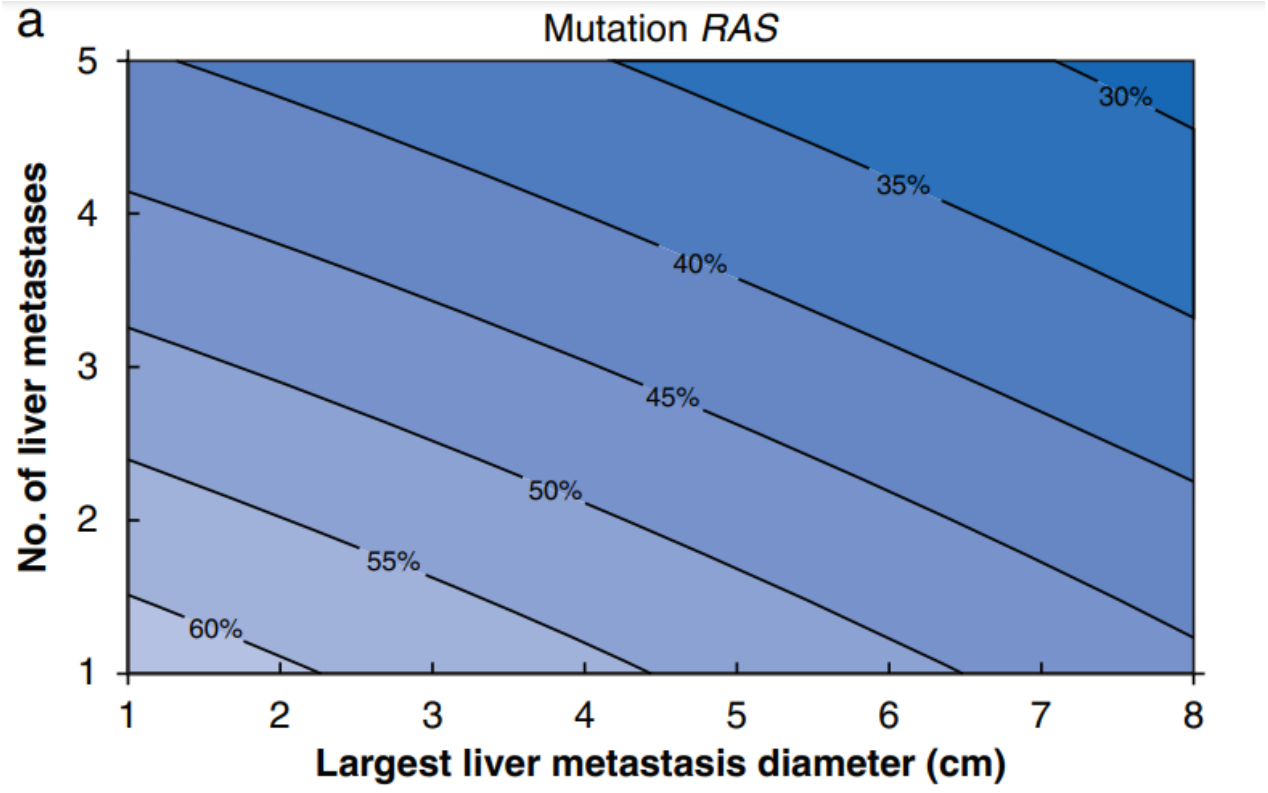


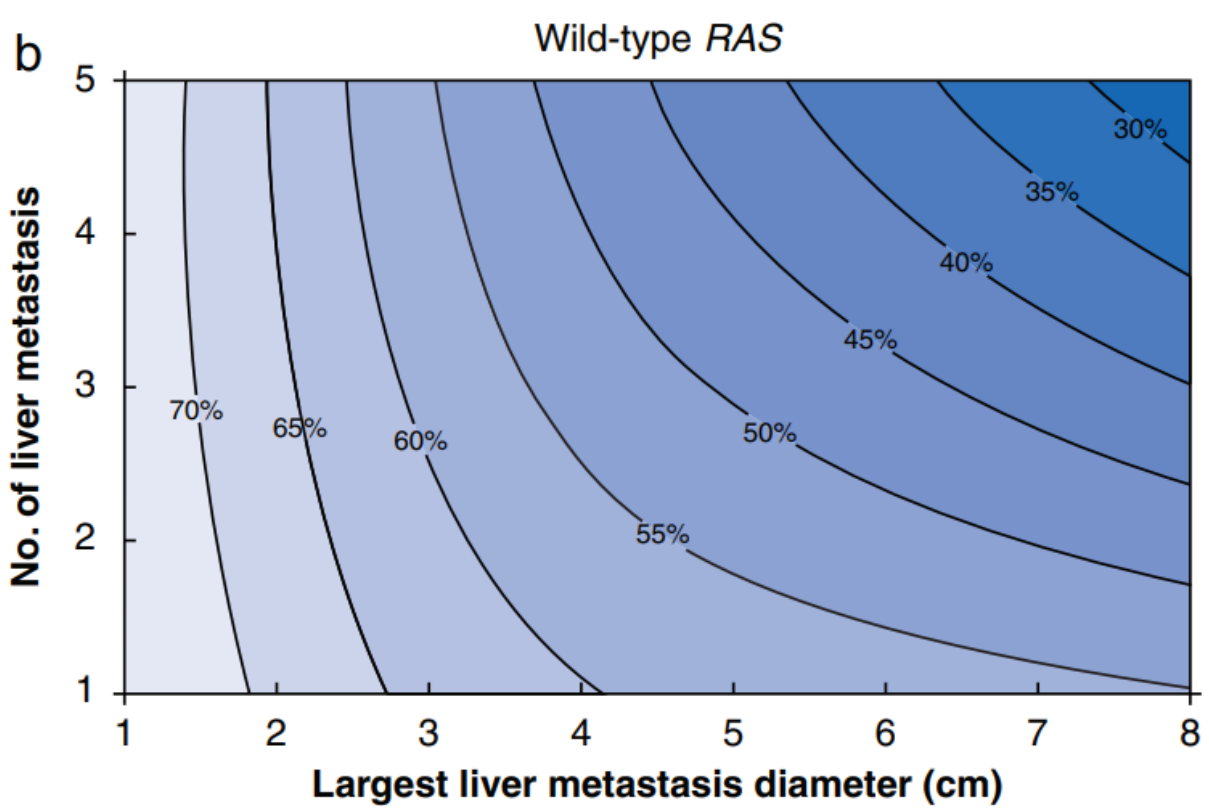
Mrs. X

Mrs. Y

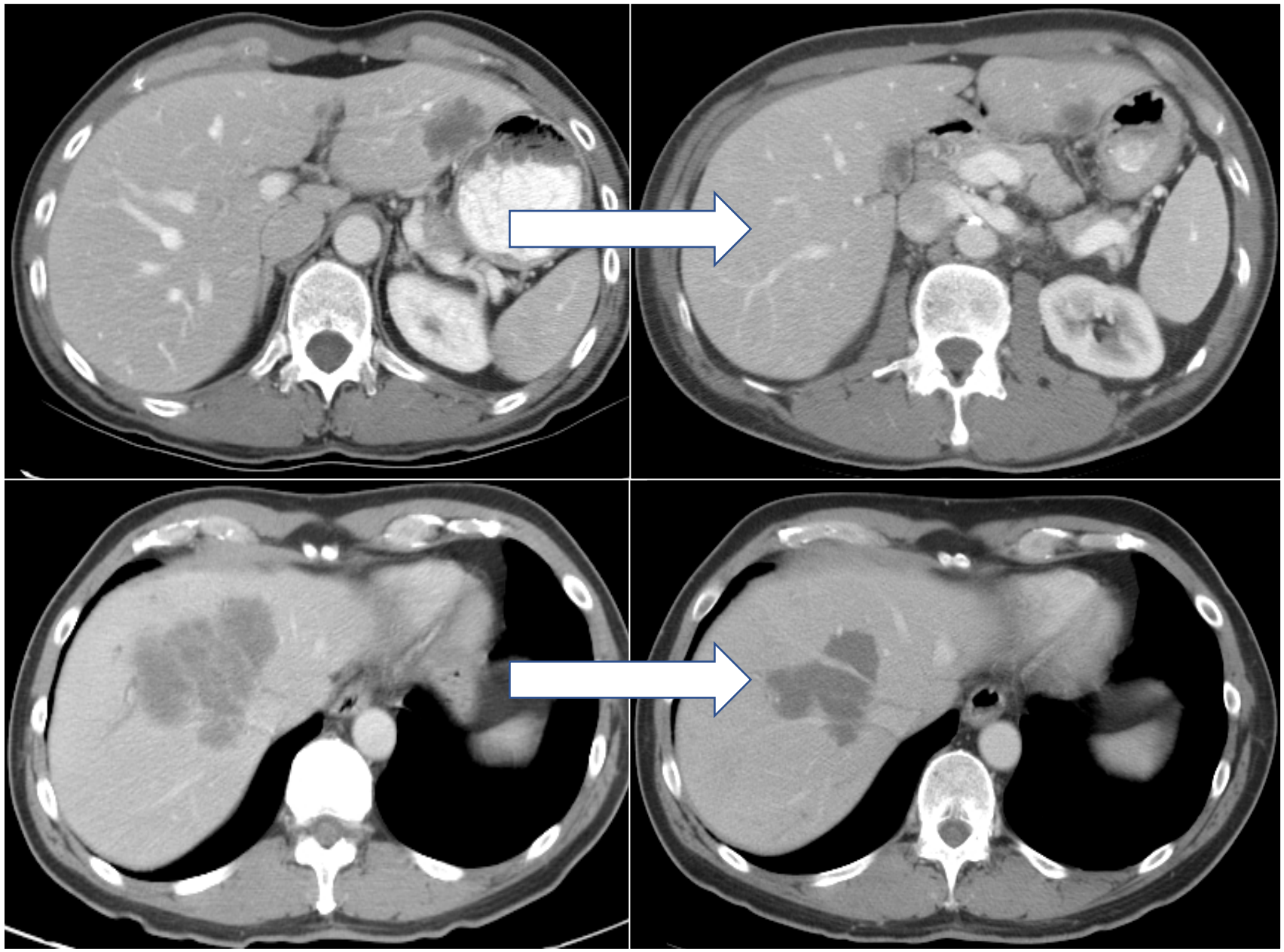
The Future is Now: Look Beyond Radiographic Calipers

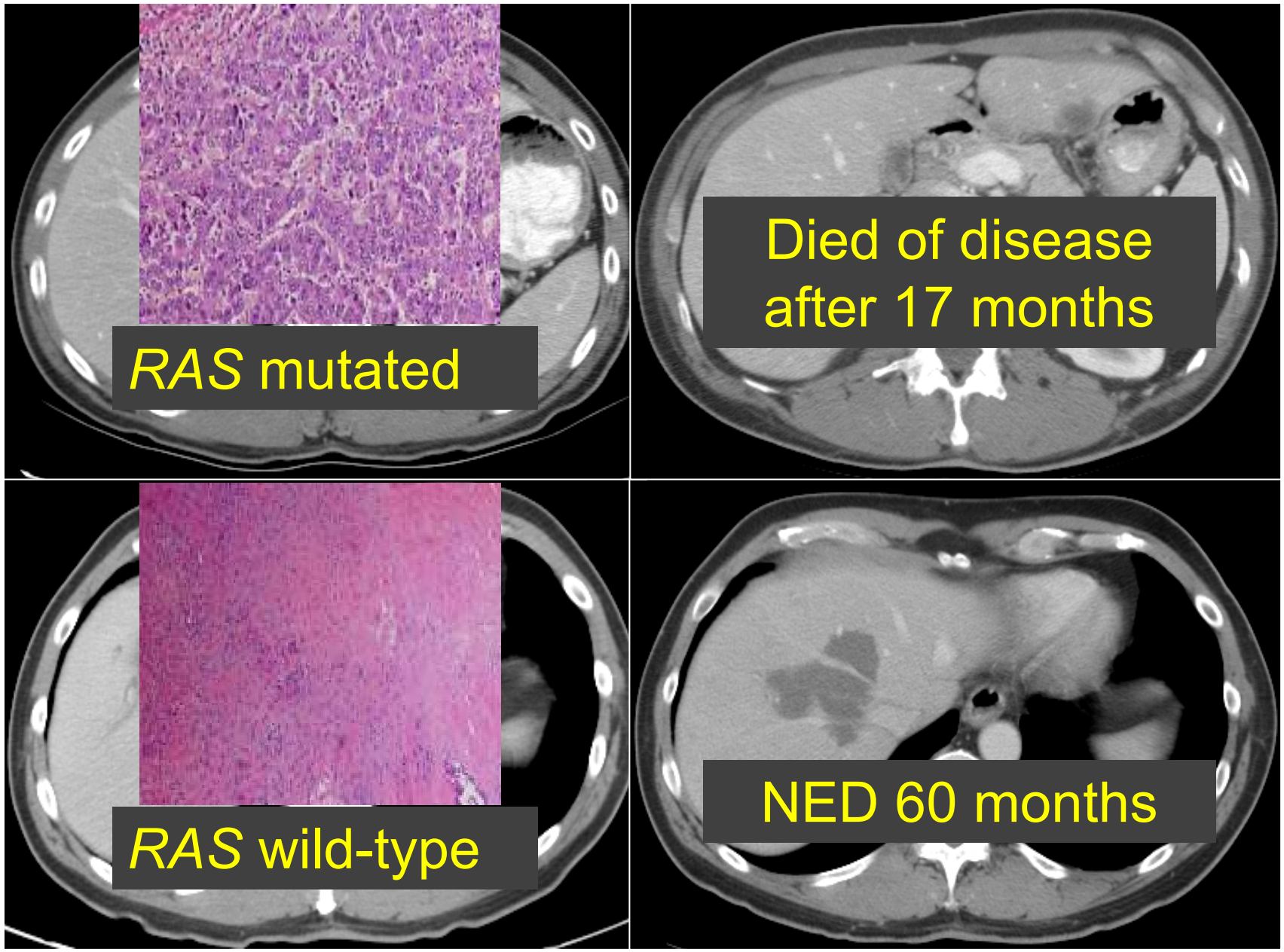
Biology Predicts the “Mileage” Derived from Big Operations





Kawaguchi, Br J Surg 2021




RAS mutated
Died of disease after 17 months
RAS wild-type
NED 60 months

FOLFOX+Bev
4 cycles

Molecular Diagnostics

AKT1	CCND1	ESR1	HRAS	MAPK3	NPM1	RB1
ALK	CCND2	EZH2	IDH1	MET	NRAS	RET
APC	CCNE1	FBXW7	IDH2	MLH1	NTRK1	ROS1
AR	CDK4	FGFR1	JAK2	MPL	NTRK3	SMAD4
ARAF	CDK6	FGFR2	JAK3	MTOR	PDGFRA	SMO
ARID1A	CDKN2A	FGFR3	KIT	MYC	**PIK3CA**	STK11
ATM	CTNNB1	GNA11	**KRAS**	NF1	PTEN	TERT
BRAF	DDR2	GNAQ	MAP2K1	NFE2L2	PTPN11	**TP53**
BRCA1	EGFR	GNAS	MAP2K2	NOTCH1	RAD51	TSC1
BRCA2	ERBB2	HNF1A	MAPK1	NOTCH2	RAF1	VHL

Somatic Mutations

Gene	Standardized Nomenclature (HGVS)	Location	DNA change	Protein change	COSMIC ID	Computed VAF†
APC	NM_000038.5(APC):c.4666dupA p.T1556fs	Exon 16	Duplication	Frameshift	COSM1969[illegible]	5.5%
KRAS	NM_004985.3(KRAS):c.35G>T p.G12V	Exon 2	SNV	Missense	COSM520	10.7%
PIK3CA	NM_006218.2(PIK3CA):c.1633G>A p.E545K	Exon 10	SNV	Missense	COSM763	5.2%
TP53	NM_000546.5(TP53):c.817C>T p.R273C	Exon 8	SNV	Missense	COSM1065[illegible]	<0.3%

Molecular Diagnostics

AKT1	CCND1	ESR1	HRAS	MAPK3	NPM1	RB1
ALK	CCND2	EZH2	IDH1	MET	NRAS	RET
APC	CCNE1	FBXW7	IDH2	MLH1	NTRK1	ROS1
AR	CDK4	FGFR1	JAK2	MPL	NTRK3	SMAD4
ARAF	CDK6	FGFR2	JAK3	MTOR	PDGFRA	SMO
ARID1A	CDKN2A	FGFR3	KIT	MYC	**PIK3CA**	STK11
ATM	CTNNB1	GNA11	**KRAS**	NF1	PTEN	TERT
BRAF	DDR2	GNAQ	MAP2K1	NFE2L2	PTPN11	TP53
BRCA1	EGFR	GNAS	MAP2K2	NOTCH1	RAD51	TSC1
BRCA2	ERBB2	HNF1A	MAPK1	NOTCH2	RAF1	VHL

Somatic Mutations

Gene	Standardized Nomenclature (HGVS)	Location	DNA change	Protein change	COSMIC ID	Computed VAF†
KRAS	NM_004985.5(KRAS):c.35G>T p.G12V	Exon 2	SNV	Missense	COSM520	<0.2%
PIK3CA	NM_006218.4(PIK3CA):c.1633G>A p.E545K	Exon 10	SNV	Missense	COSM763	<0.2%

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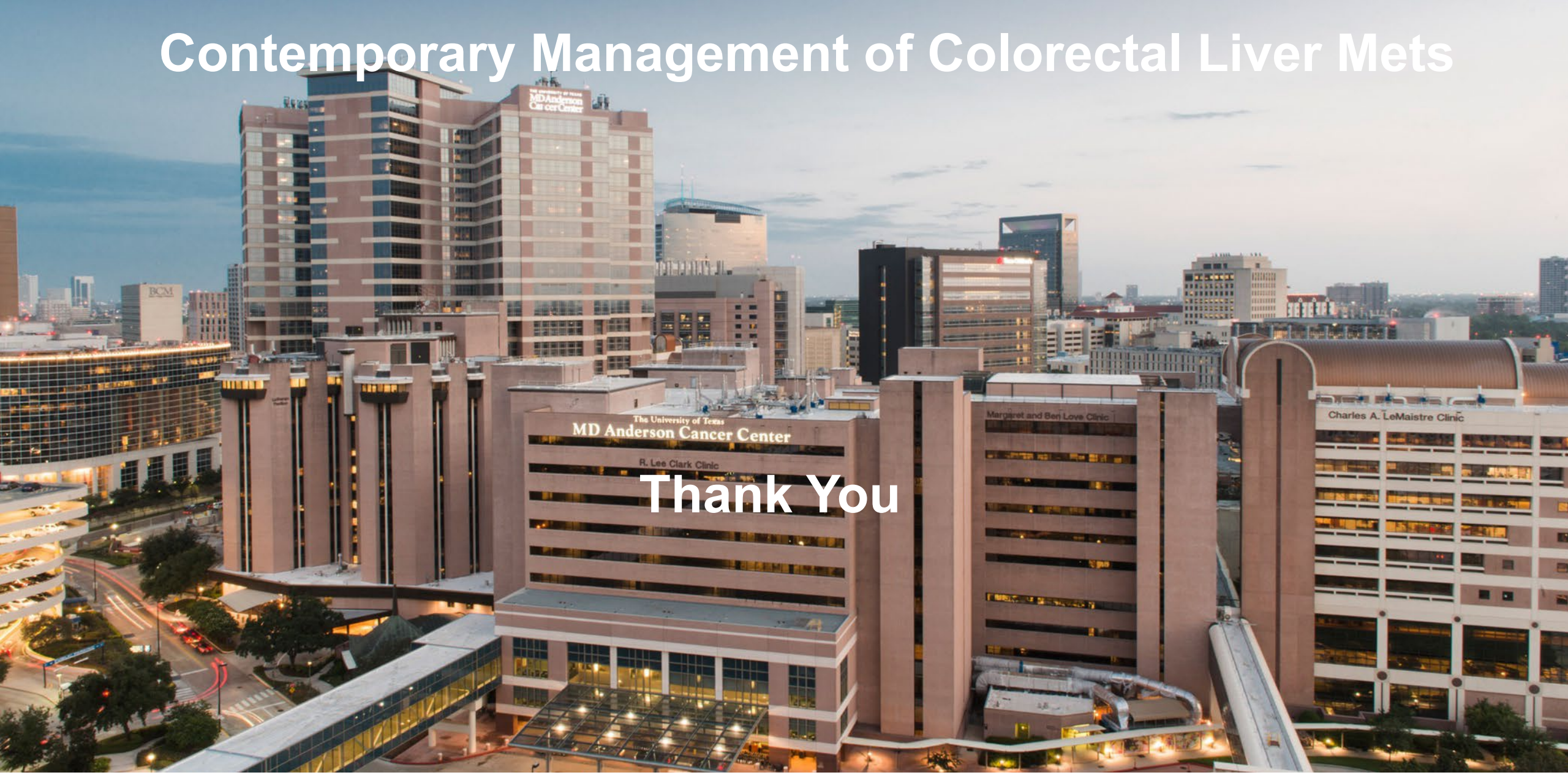
Summary: “Contemporary” Management

- Resectable liver mets → resected
- PVE/HVE prevents liver failure
- Two-stage hepatectomy separates surgical risk
- Liver-first sequencing is preferred for asymptomatic primary tumors
- Tumor genomic sequencing helps inform prognosis but is not a pure veto for surgery

Contemporary Management of Colorectal Liver Mets



Thank You

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Contemporary Management of Colorectal Liver Mets

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Surgical Oncology Cancer Symposium

University of Tennessee Health Science Center

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