



Colorectal Cancer with Liver Metastases: A Multidisciplinary Perspective





Panel

- **Surgical Oncology**
 - Dr. Daniel Anaya Moffitt Cancer Center
- **Medical Oncology**
 - Dr. Craig Lockhart, University of Miami
- **Pathology**
 - Dr. Gregory Lauwers, Moffitt Cancer Center
- **Radiation Oncology**
 - Dr. Kathryn Hitchcock, University of Florida
- **Interventional Radiology**
 - Dr. Beau Toskich, Mayo Clinic



Learning Objectives

Metastatic disease is resectable until proven otherwise

- Understand how multidisciplinary evaluation at first contact contributes to treatment planning, sequencing and identifying curable disease
- Recognize when surgery is indicated and what steps lead to surgical candidacy
- Outline the role of chemotherapy
 - Regimen
 - Timeline
 - Toxicity management



- Outline the role of radiation therapy
 - High dose treatment for local control
 - SBRT
 - Palliation of symptoms
- Outline the role of Interventional Radiology
 - Surgical optimization techniques
 - Palliative interventions for nonsurgical patients
- Understand the role of pathology review after surgery
 - Post chemotherapy response
 - Quality of liver after chemotherapy



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- **Multidisciplinary team approach for GI malignancies has become routine over the past two decades**
 - NCCN Guidelines
- **Impacts staging decisions**
 - MDT rectify 20% of the referral diagnoses
- **Impacts treatment and adherence to guidelines**
 - Pretreatment plan certainty is high, but changes are made in up to 1/3 of patients after MDT review
- **More timely implementation of the treatment plan**
 - Median number of days from first visit to treatment initiation changes from 24 days to 17 days
- **Potential impact on outcomes**
 - 3-year survival rate increasing from 25.6 to 38.2 % ($P < 0.001$) due to increase in surgical referral

Basta et al. *Ann Surg Oncol*. 2017;24(9):2669-2678.

Basta et al. *Ann Surg Oncol*. 2016;23(8):2430-7.

Oxenberg et al. *Ann Surg Oncol*. 2014;22(5):1533-9.

Lan et al. *Int J Colorectal Dis* (2016) 31: 403.

Ehab et al. AHBPA 2019



Case 1: Dr. Sofia Palacio

Hematology/Medical Oncology
Fellow, University of Miami



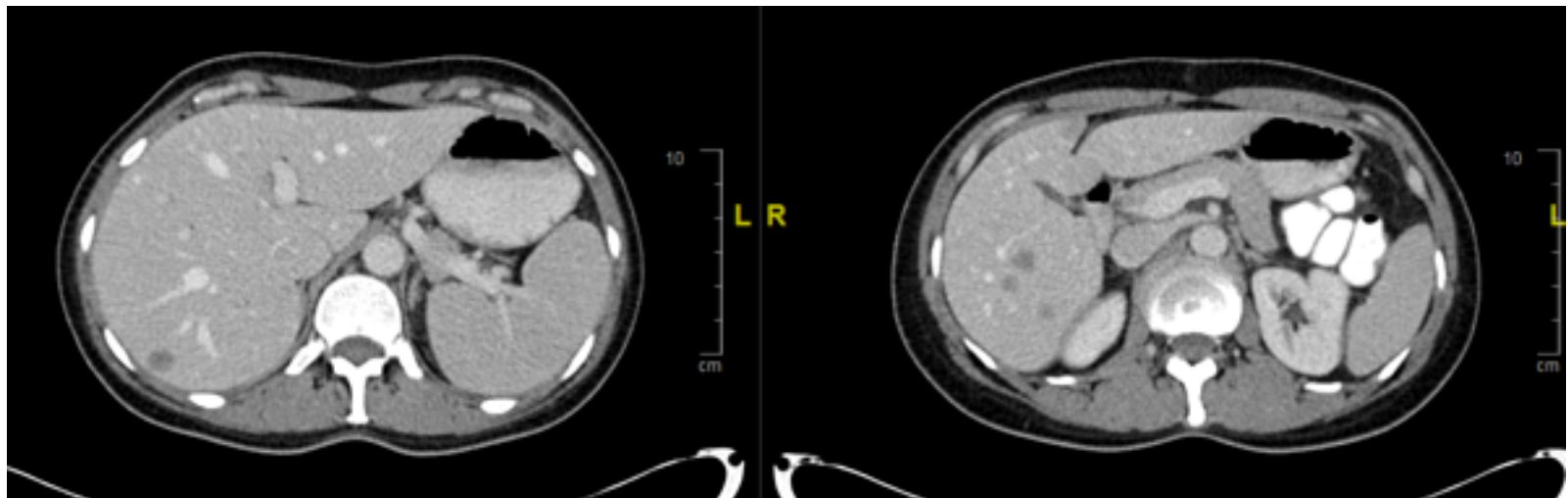
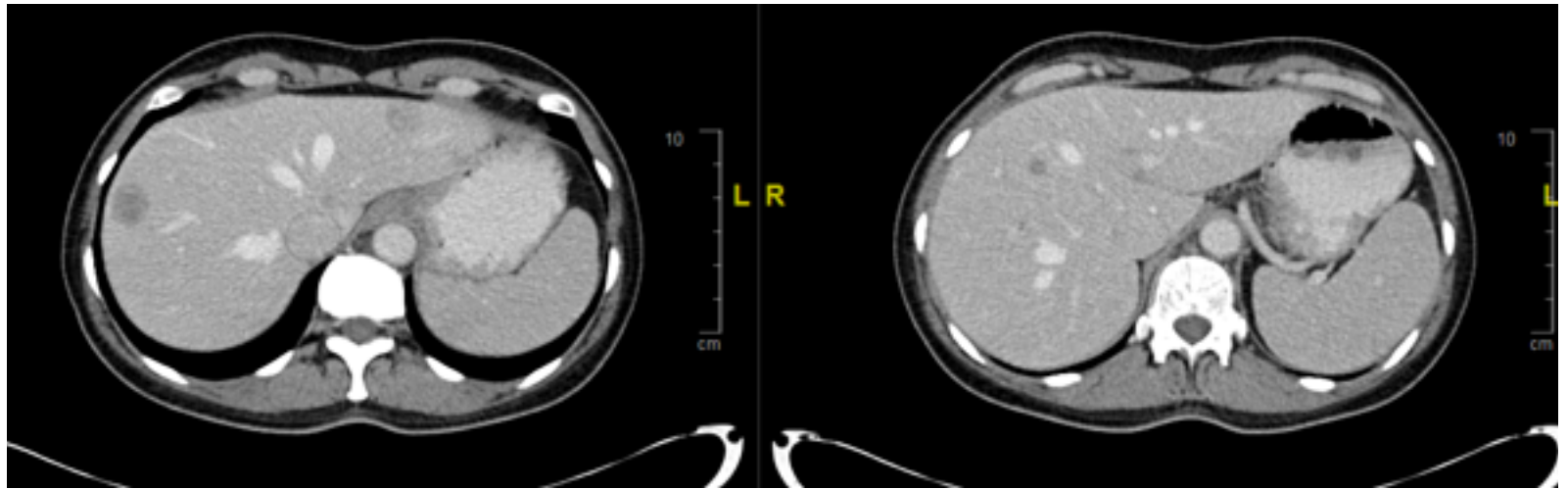
A 54 year old woman presented with progressive abdominal pain

- Initial evaluation
 - CT revealed ‘colitis’
- Readmitted within 2 weeks with worsening pain
 - Repeat CT abdomen/pelvis
 - Multiple liver lesions, likely hemangiomas
 - Inflammatory bowel disease at terminal ileum but cannot exclude tumor at IC valve
 - Distended proximal bowel
 - Worsening ascites
 - Unable to tolerate bowel prep for colonoscopy
 - Taken to OR for laparoscopic right hemicolectomy
- **CBC, CMP normal**
- **CEA post operatively - 22.1**



Surgical pathology

- Right colon, appendix, ileum
 - Low grade colonic adenocarcinoma, 6.5 cm
 - LVI, PNI present
 - 8/14 LN positive
 - T3N2Mx
- MLH1, PMS2, MSH2 and MSH6 intact
- KRAS mutated (p.G13R)

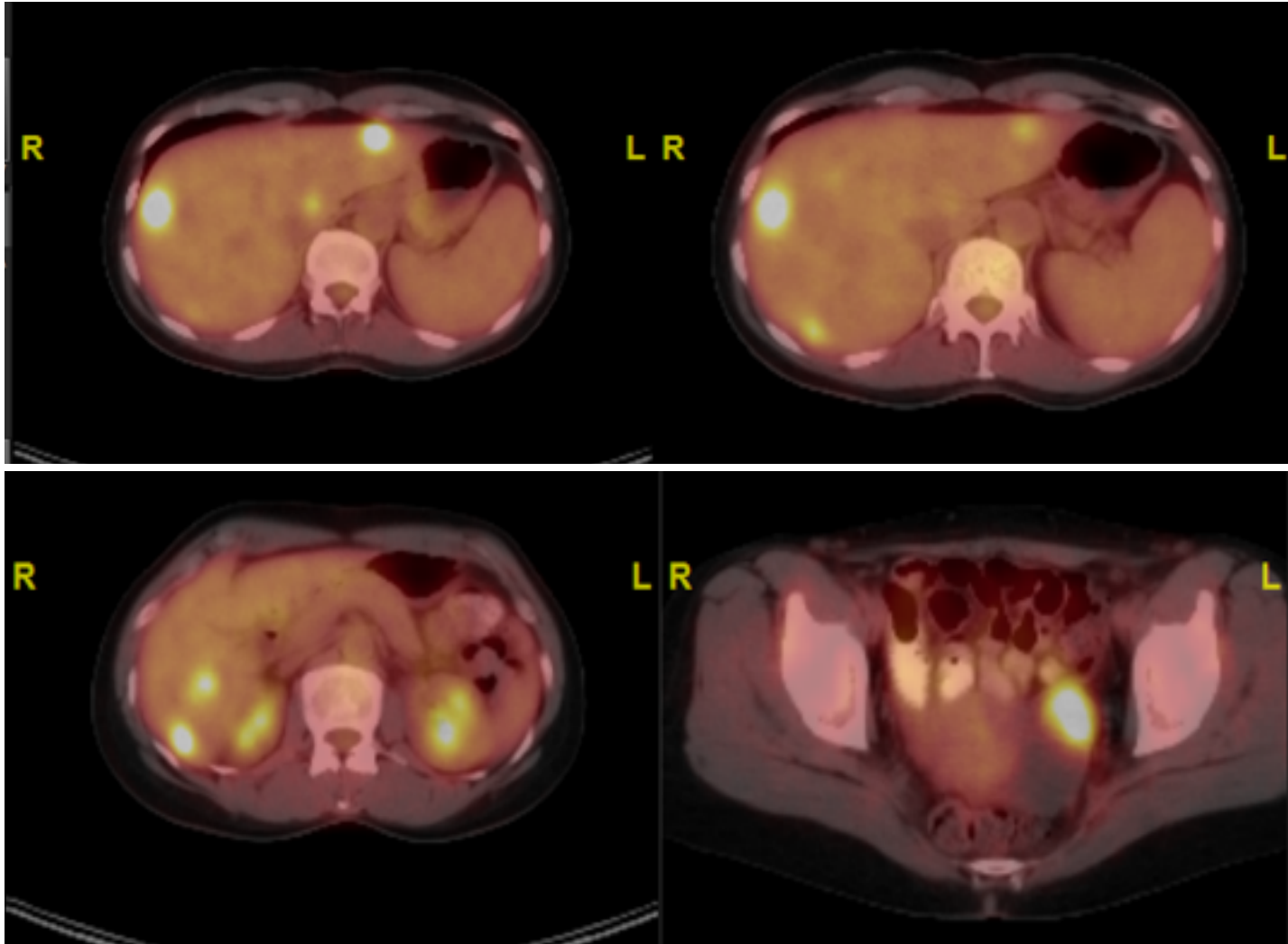




- Panel: what would you consider next:
 - Are these lesions worrisome for metastatic disease?
 - Is there a role for more imaging?



- **PET**





- Panel, can you comment on the role of biopsy at this point?
 - Second primary in ovaries?
 - Residual disease at surgical site?
 - Liver biopsy?
- Are these areas important to biopsy for surgical assessment?



- **Patient had colonoscopy with biopsy**
 - Enteric mucosa with erosion, no dysplasia or tumor
- **Ovarian FNA**
 - Adenocarcinoma, favor colorectal primary (PAX-8 negative)
- **Liver biopsy**
 - Metastatic adenocarcinoma



- **Patient presented for MDT discussion**
- **Options**
 - Systemic chemotherapy with palliative intent
 - Multi-step treatment with onco-surgical strategies with curative intent



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MEDICAL ONCOLOGY PERSPECTIVE

CRAIG LOCKHART, M.D.M.H.S

**Professor of Medicine
Chief, Division of Medical Oncology
Sylvester Comprehensive Cancer Center
Miller School of Medicine
University of Miami**

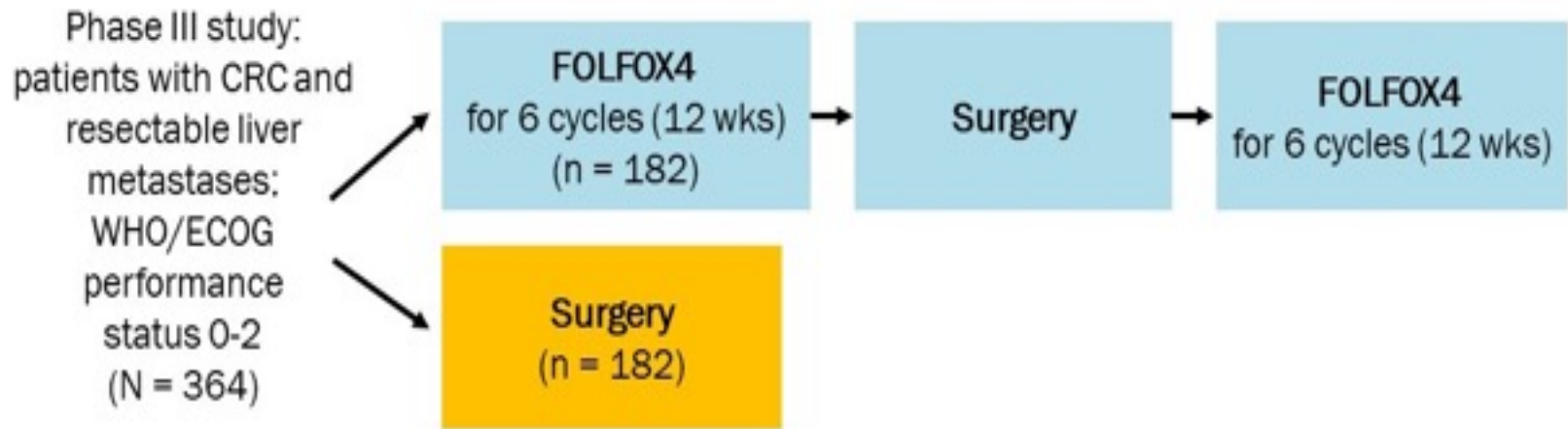


Approach to a New Patient

- **Resectable metastatic disease - Curative potential**
 - Oligometastatic liver or lung mets
- **“Borderline” resectable disease - Curative potential**
 - Usually only refers to conversion of unresectable liver mets to resectability
 - ORR is critical in these cases
- **Unresectable disease - Palliative therapy**
 - Multiple lung mets
 - Extensive bilobar liver mets
 - Extensive lymph node disease
 - Bone, subcutaneous mets



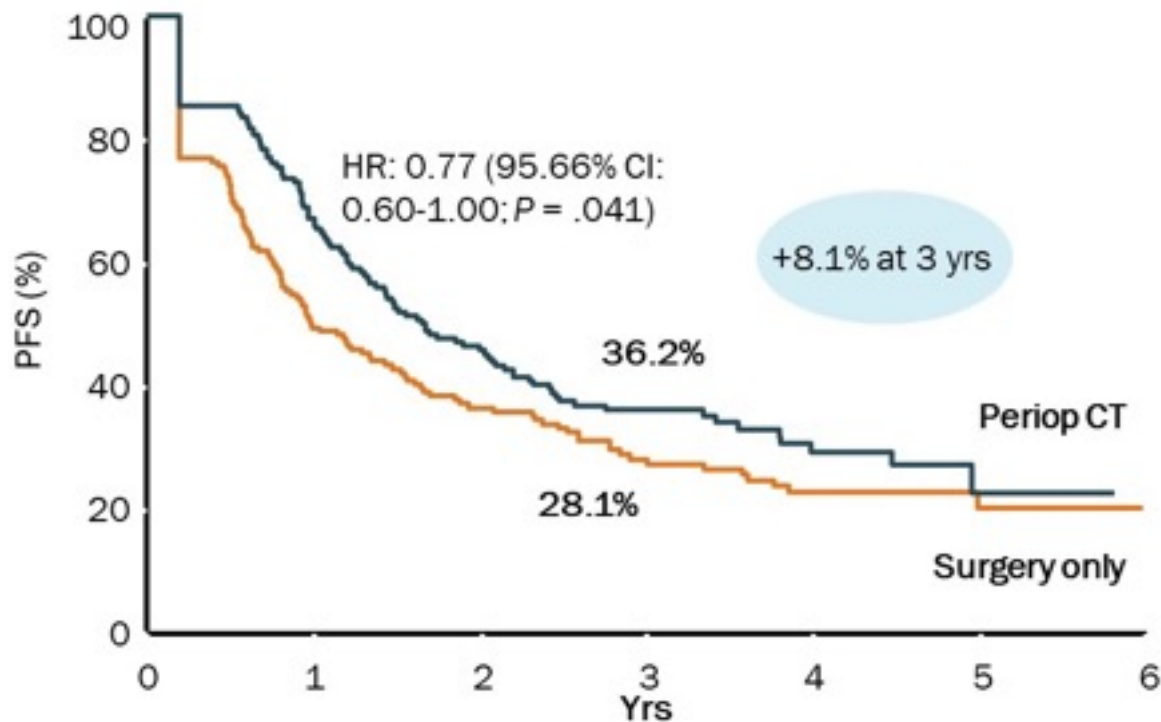
EORTC 40983



- **Primary endpoint: PFS**
- **Secondary endpoints: OS, complete resection**



EORTC 40983: PFS



- 5-yr OS rate was not significantly different (51.2% vs 47.8%; P = 0.34)

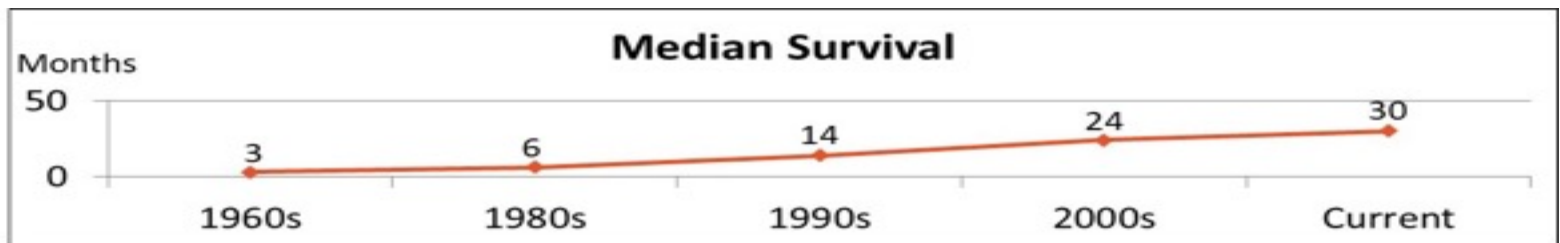
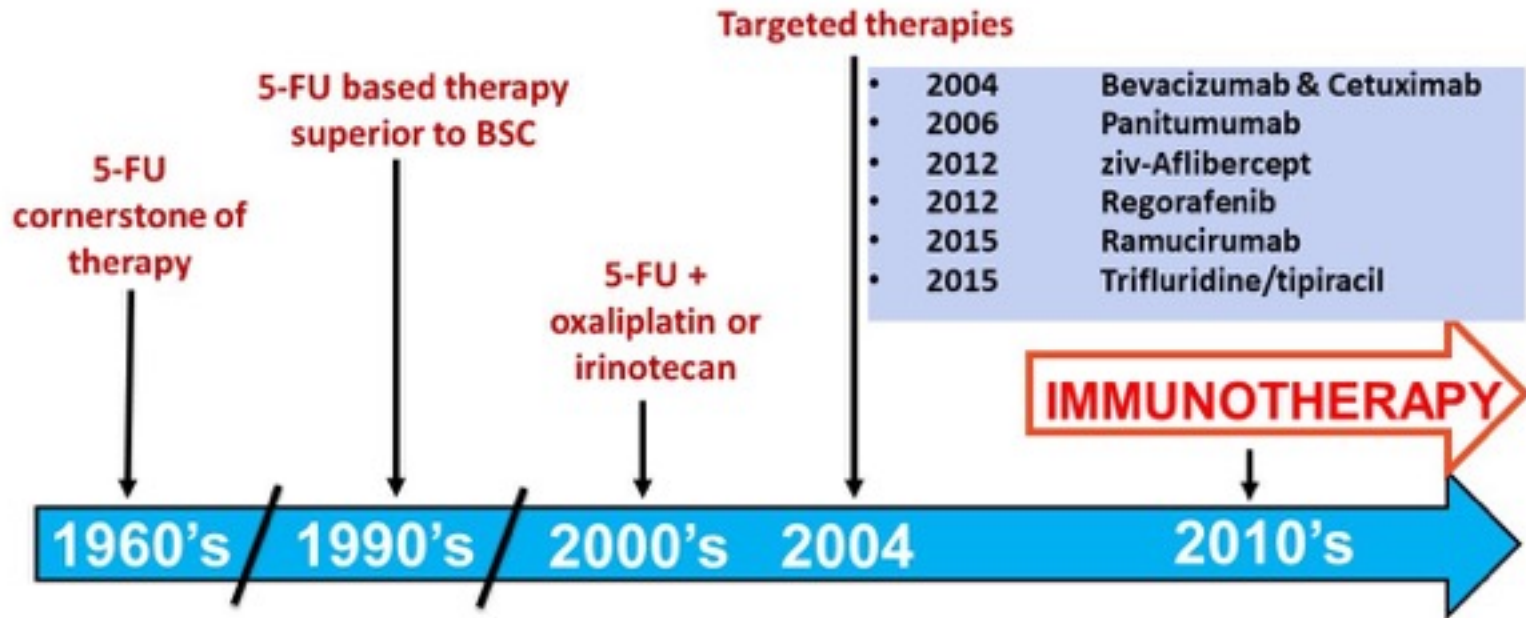
Nordlinger B, et al. Lancet. 2008;371:1007-1016

Nordlinger B, et al. Lancet Oncol. 2013;14:1208-1215



Progress with Treatment

Treatment of Advanced CRC



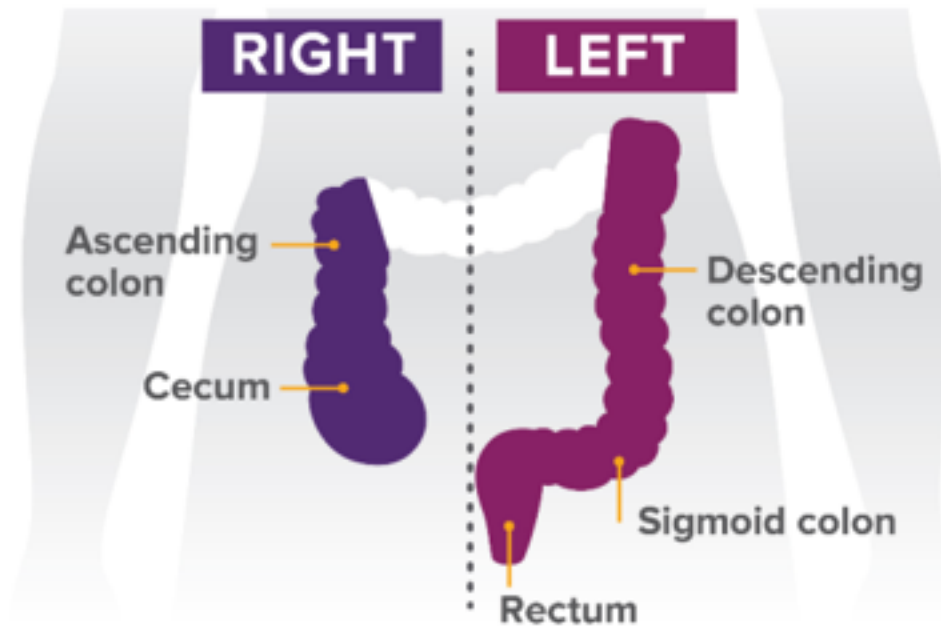


ORR with Common Regimens

TRIAL	REGIMEN	N	ORR (%)	PFS (mo.)	OS (mo.)
BICC-C	FOLFIRI + Bev	57	57.9	11.2	28.0
TREE 1/2	FOLFOX + Bev	71	52	9.9	26.1
TRIBE	FOLFOXIRI + Bev	252	65.1	12.1	31.0
CRYSTAL	FOLFIRI + Cetux	599	46.9	8.9	19.9
OPUS	FOLFOX + Cetux	344	46	9.0	—
CAIRO-2	CAPOX + Bev + Cetux	755	52.7	9.4	19.4



Sidedness Matters?



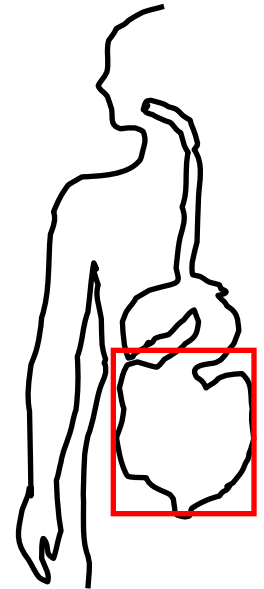
Right → Bevacizumab Left → Cetuximab

- Left-sided primary tumors are associated with longer OS
- Location may help to make therapeutic decisions



Conclusions

- We need to consider eventual surgical resectability when evaluating a new patient with metastatic CRC – Multidisciplinary Tumor Board
- Targeted therapies in CRC combine well with and improve chemotherapy outcomes
- Toxicities of targeted therapy are mostly predictable
- Develop comfort with management and mitigation of common, non-serious, AEs





Case 1

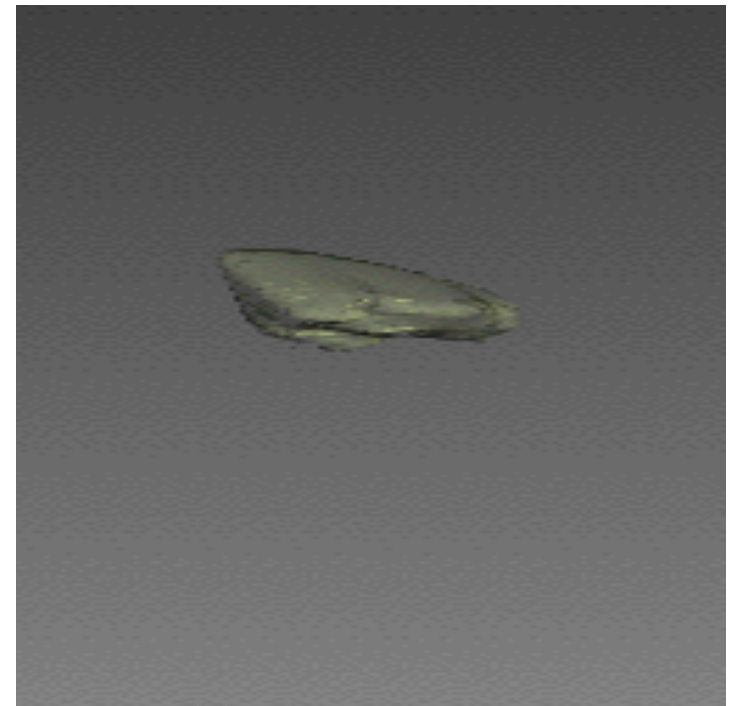
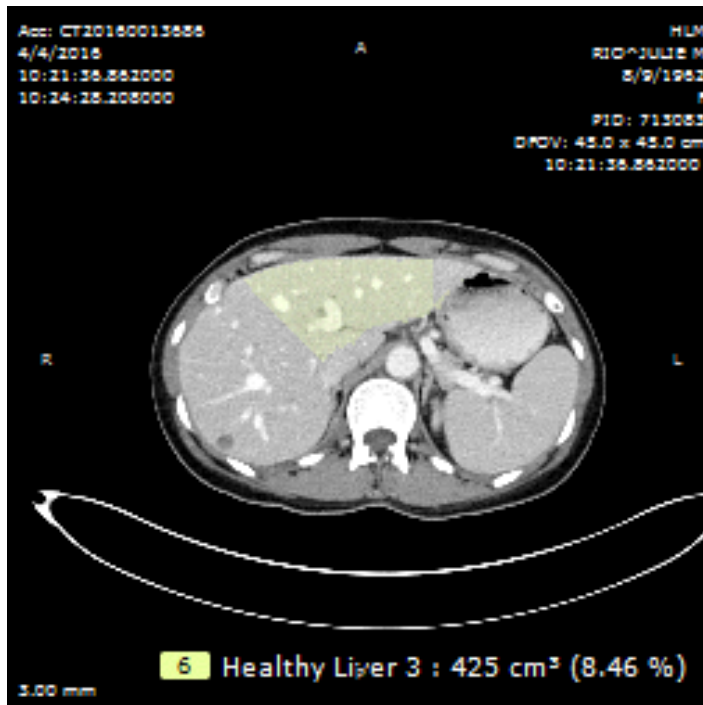
- **MDT discussion recommended neoadjuvant chemotherapy**



- **Completed 7 cycles of treatment**
 - Oxaliplatin removed at cycle 5
- **Restaging CT TAP**
 - Interval decrease in size and enhancement of hepatic metastases
 - No new metastatic disease

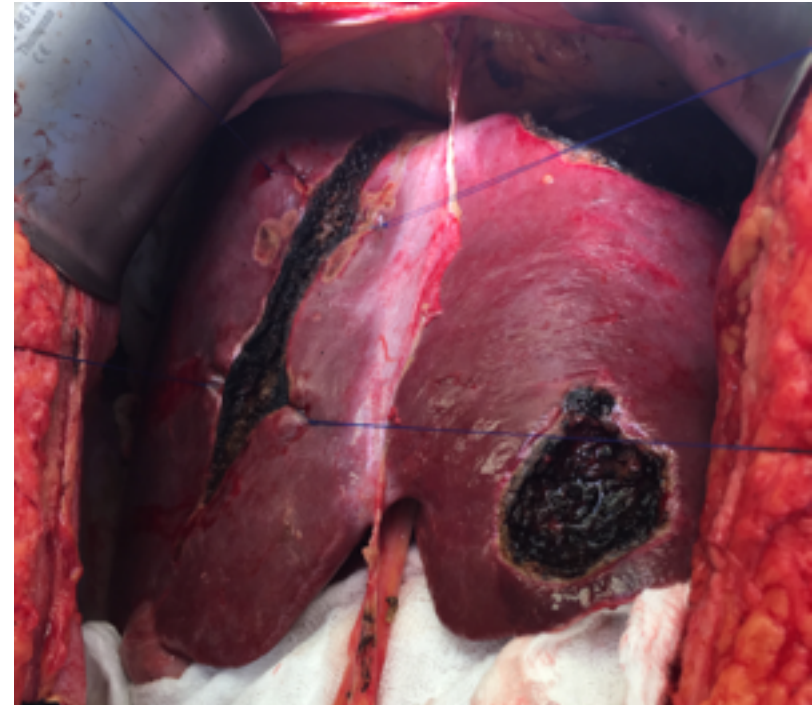
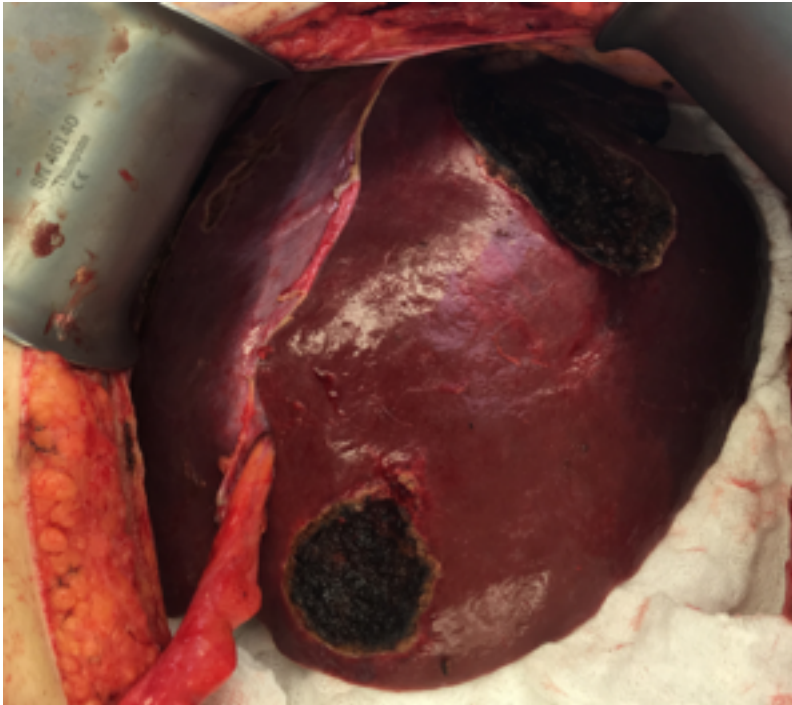


- In preparation for surgery, the patient underwent right portal vein embolization



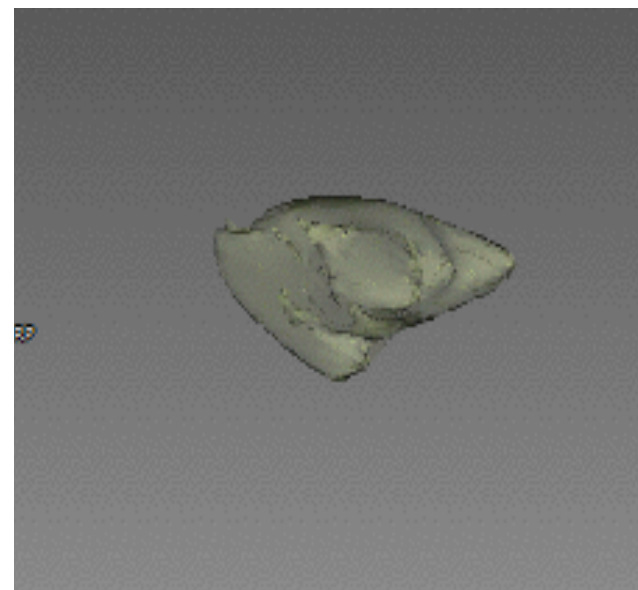
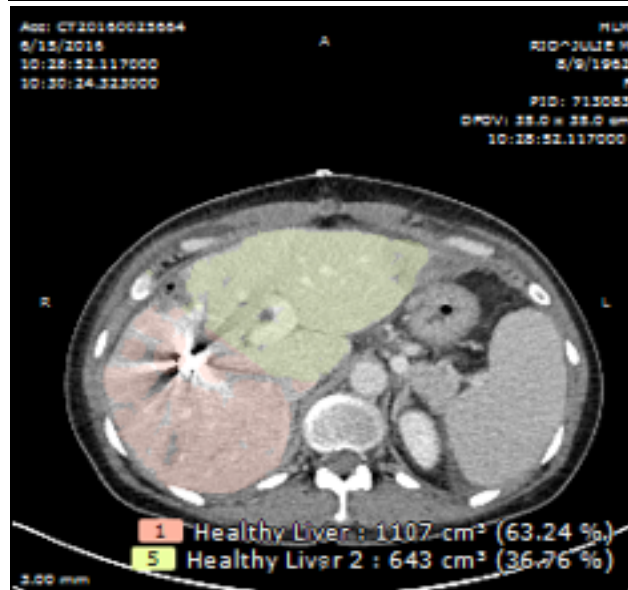
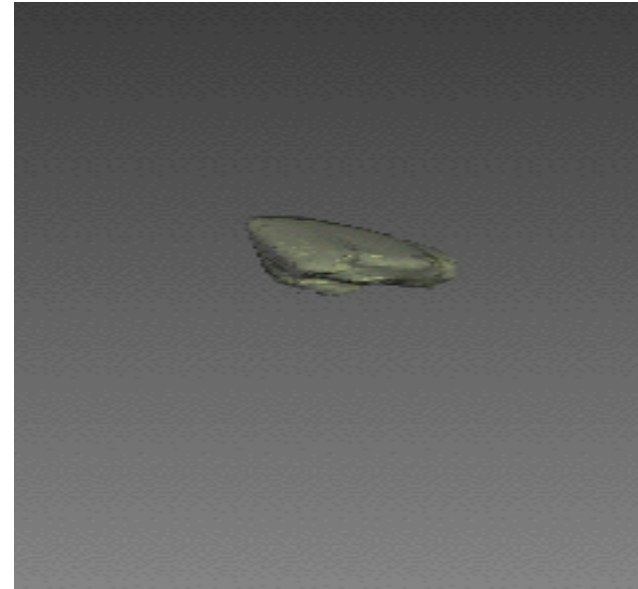
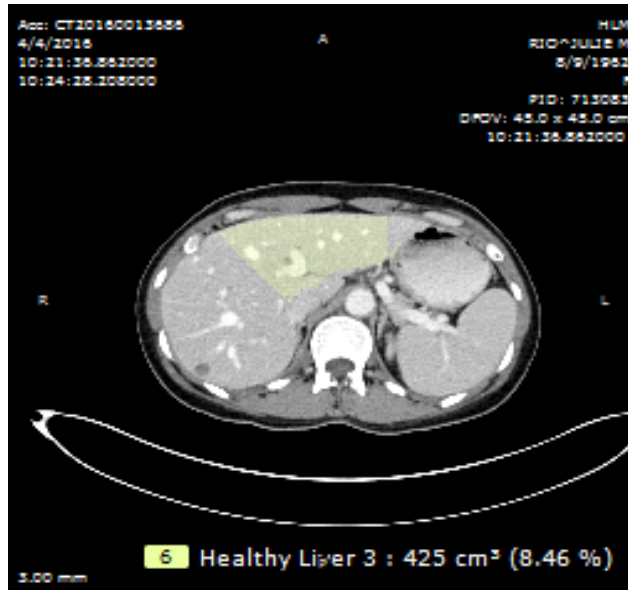


- **Next day**
 - Exploratory laparotomy, IOUS
 - Partial liver resection segment 2, wedge resection segment 2, wedge resection segment 3, microwave ablation of caudate
 - Linear hepatotomy
 - TAH-BSO, left ureterolysis





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**Liver Volumetry / Hypertrophy - Report Form
- Moffitt Liver Group -**

Name: _____ MRN: _____
Age: 53 Gender: female

Diagnosis:

Metastatic CRCLM bilobar > 10 + ovary w good response to chemo (4-7cycles)

1. Baseline information

Height (cm)	Weight (Kg)	BMI	BSA	sTLV (794 +1267xBSA)
173	65	21	1.77	1448

2. Embolization procedure

Strategy used	Date	Approach	Embolized target	Embolization material
PVE (mini-ALPSS)	6/7	Percutaneous	Right	

3. Hypertrophy of sFLR

FLR	Baseline sFLR** (4/04/16 - CT)		Post-embolization baseline s1*** (6/15/16 / CT)				Post-embolization baseline s2**** (Date / imaging)			
	Volume	sFLR	Volume	sFLR	DH	%	Volume	sFLR	DH	KG
Scgs 1-4	418	28.0%	643	44.4%	16	54%				
Scp 1-4										
Scp 1-3										
Scp 1-2										
Scp 2-3										
Scp 2-2										

PVE 6/7
1st stage hepatectomy, + ovary + hepatectomy 6/8
2nd stage hepatectomy (right hepatectomy) pending

---MINI-ALPSS



- POD 9
- Return to OR
 - Right hepatectomy and cholecystectomy



- **All lesions - CRCLM, negative margins**
 - **Segment 2, partial resection**
 - Metastatic adenocarcinoma; TRG 5
 - **Segment 2, wedge resection**
 - Metastatic adenocarcinoma; TRG 5
 - **Segment 3, wedge resection**
 - Metastatic adenocarcinoma; TRG 5
 - **Ovary and fallopian tube R and L**
 - Ovary with metastatic adenocarcinoma
 - Fallopian tube with no evidence of malignancy



- **Right hepatectomy**
 - Metastatic adenocarcinoma; TRG 4
 - Negative margins

- **Gallbladder, cholecystectomy**
 - Mild chronic cholecystitis



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PATHOLOGY OF COLORECTAL LIVER METASTASES

Gregory Y. Lauwers, M.D.

**Senior Member & Director GI Pathology Service
H. Lee Moffitt Cancer Center & Research Institute
Departments of Pathology & Cell Biology and Oncologic Sciences
University of South Florida**



Pathologic evaluation of Colorectal Liver Metastases [CRLM]:

1. Identification of the tumor.
- ② Status of the resection margin.
- ③ Response to therapy.
- ④ Chemotherapy adverse effect.



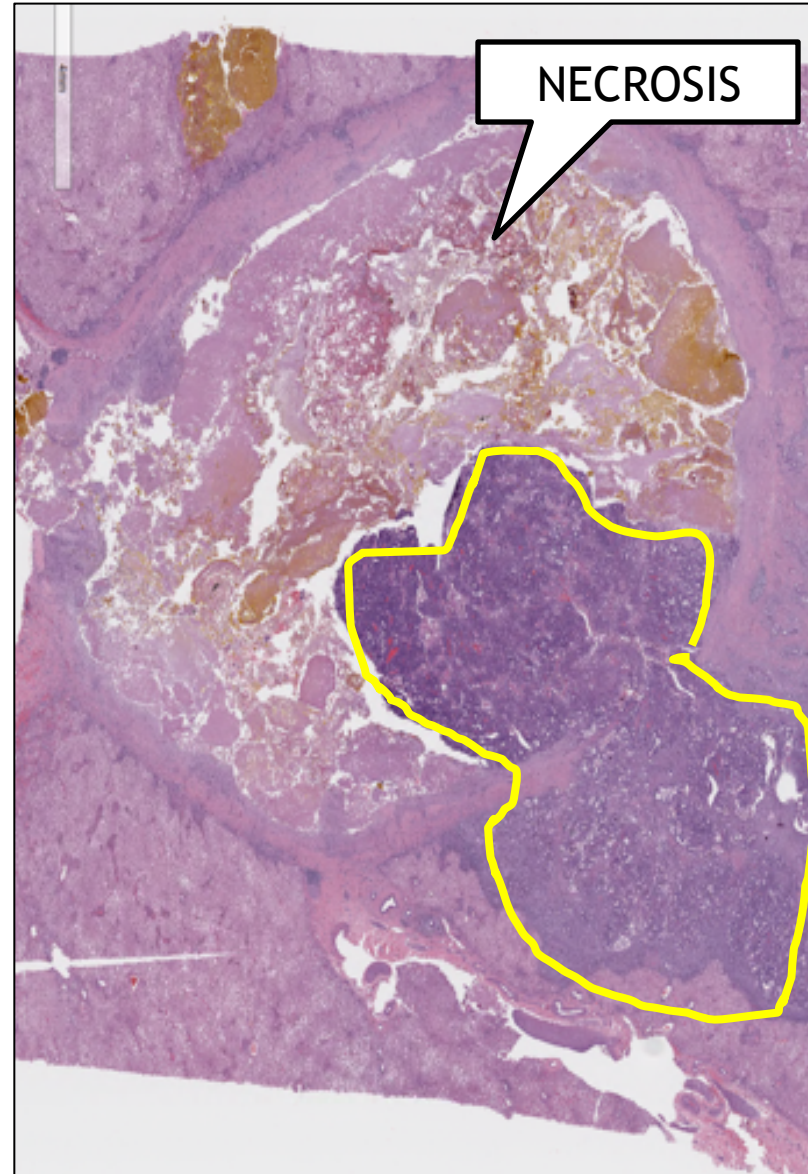
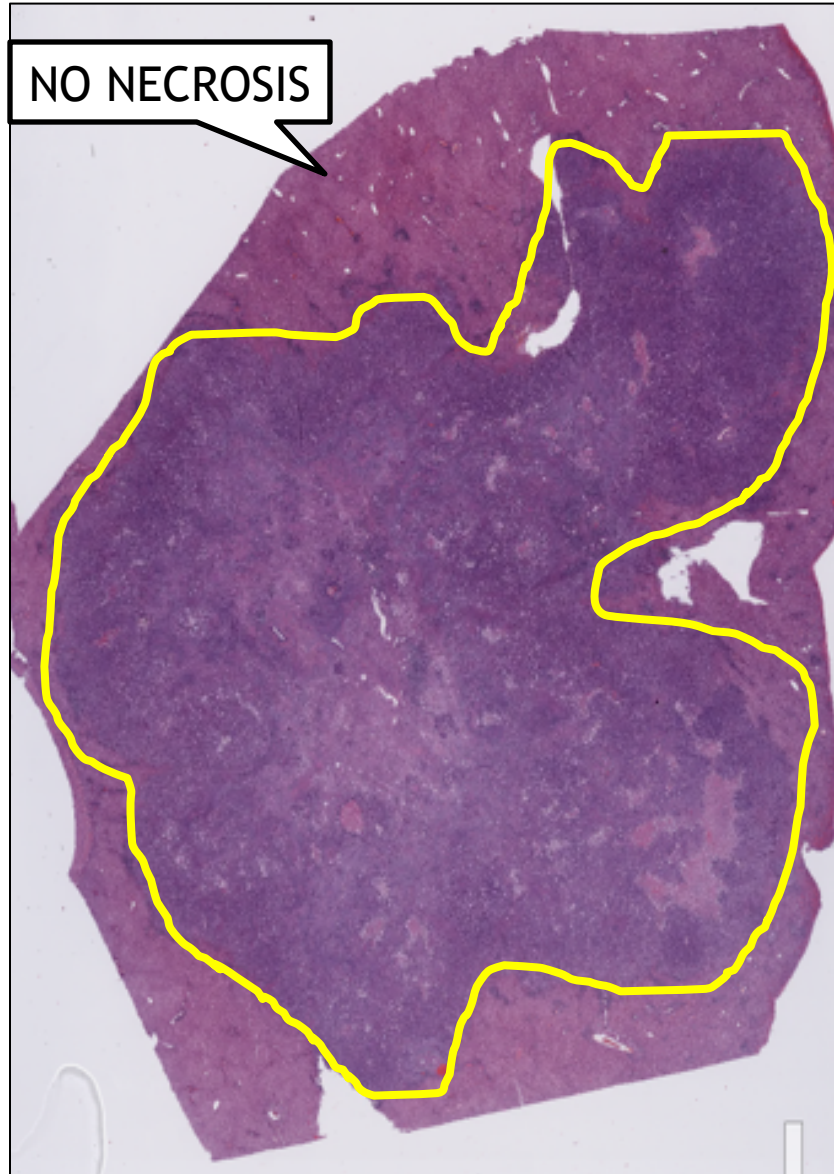
Resection margins of CRLM

- A margin is positive if a tumor is microscopically present at the margin.
- Dictate a worse outcome.
- Clearance to be recorded.
 - Significance is not entirely clear.
 - Surgical / anatomic limitation



Response to Neo-adjuvant therapy

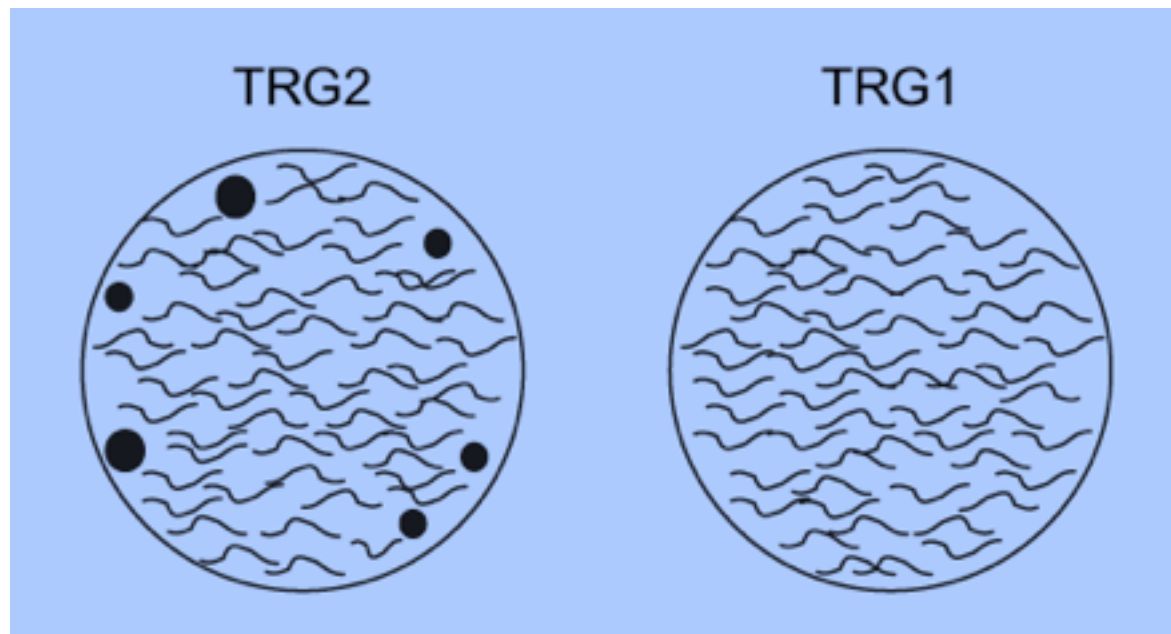
- Complete pathologic response is associated with improved survival.
 - 76% 5-year overall survival vs. 45% for those with residual tumor
 - Achieved only in 4% of the cases (n=767)
 - Regimens were non uniform.
 - Newer regimens may increase the response rate.

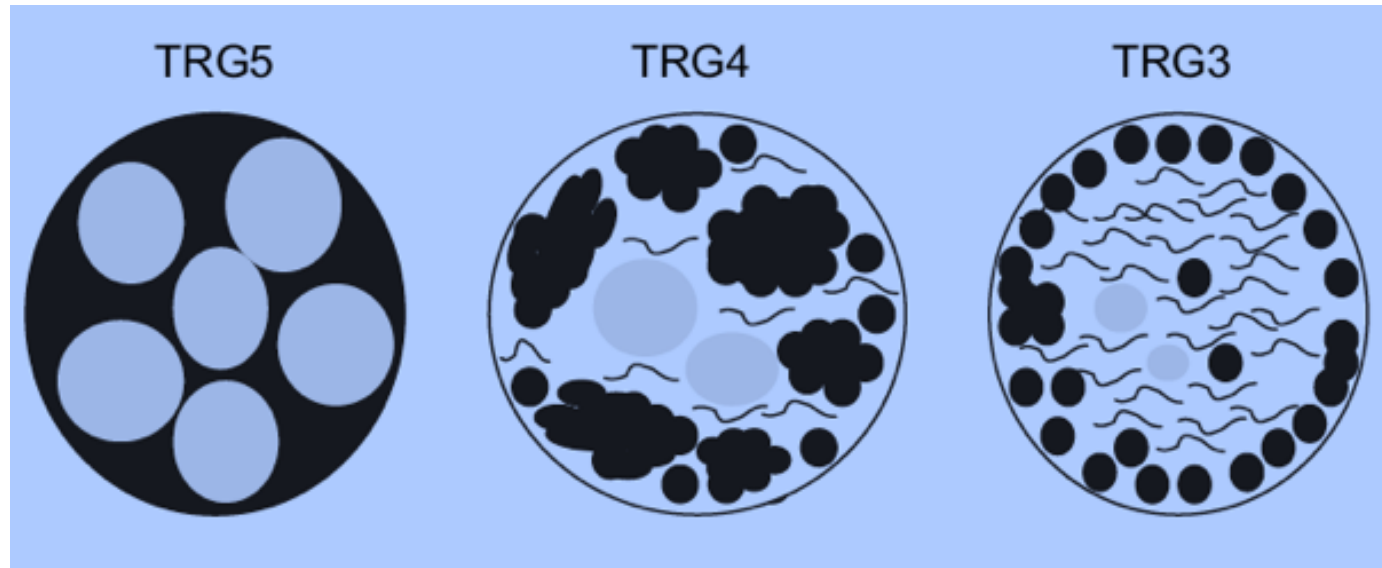




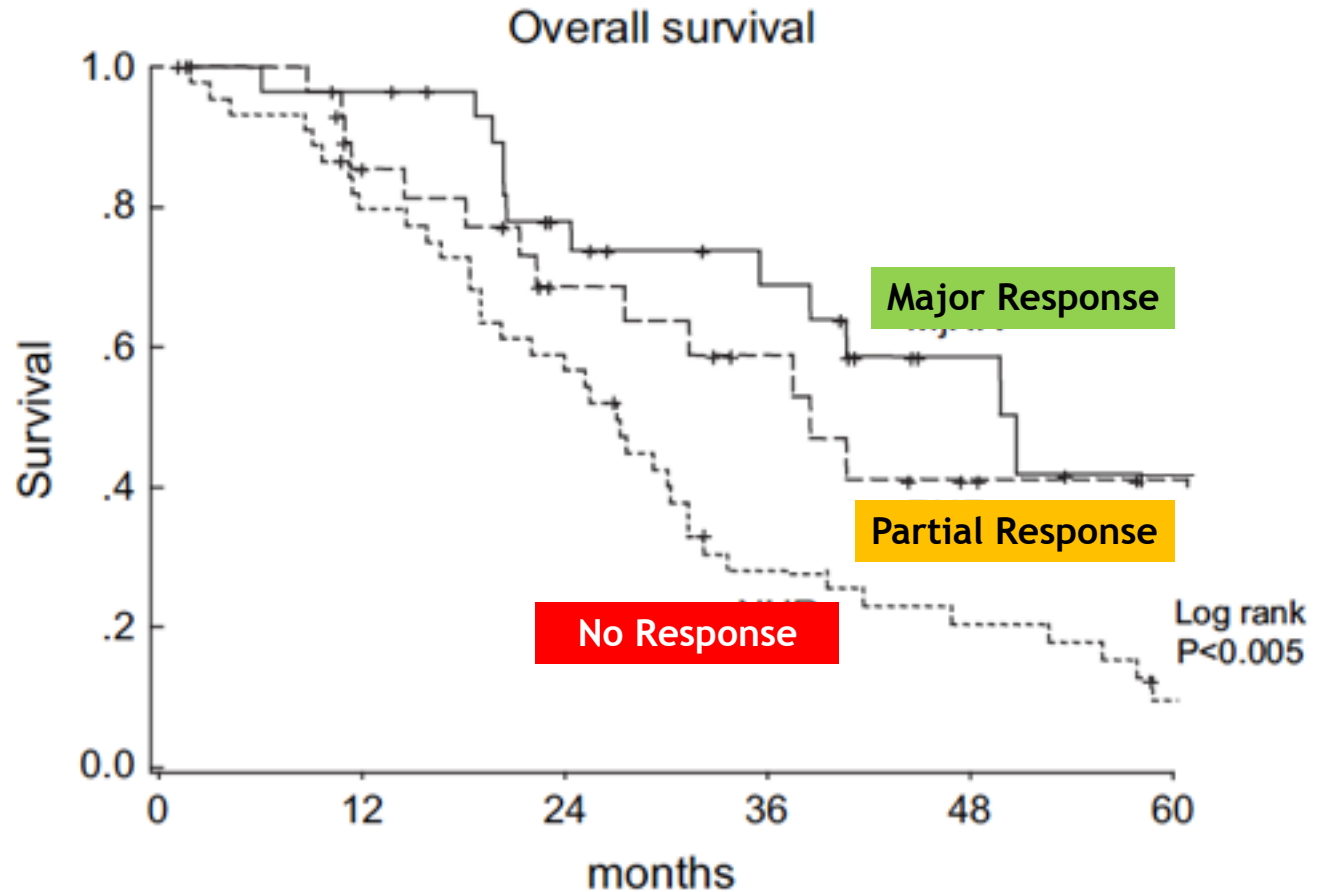
Tumor regression grade (TRG) scoring system

- TRG1, absence of residual cancer;
- TRG2, rare residual cancer cells scattered throughout the fibrosis;





- TRG3, more residual tumor cells but fibrosis predominates;
- TRG4, residual cancer cells predominate over fibrosis;
- TRG5, no signs of regression.



Patients at risk

No Response	47	36	26	11	8	2
Partial Response	30	22	24	10	4	2
Major Response	29	28	19	14	7	1



SIGNIFICANCE OF OTHERS CHARACTERISTICS

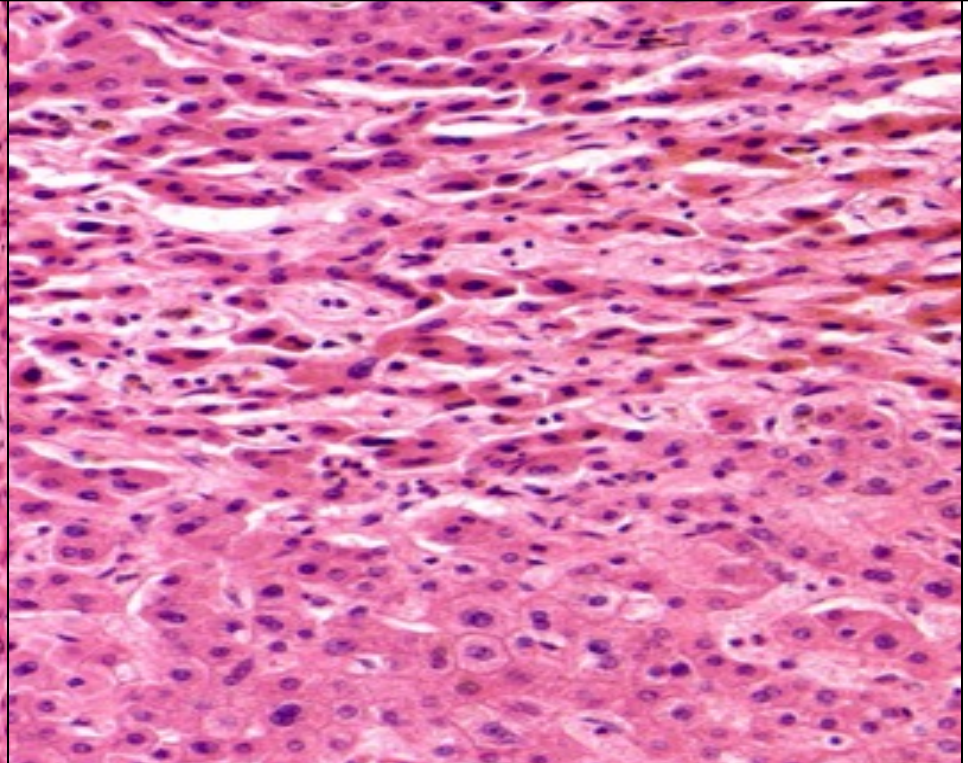
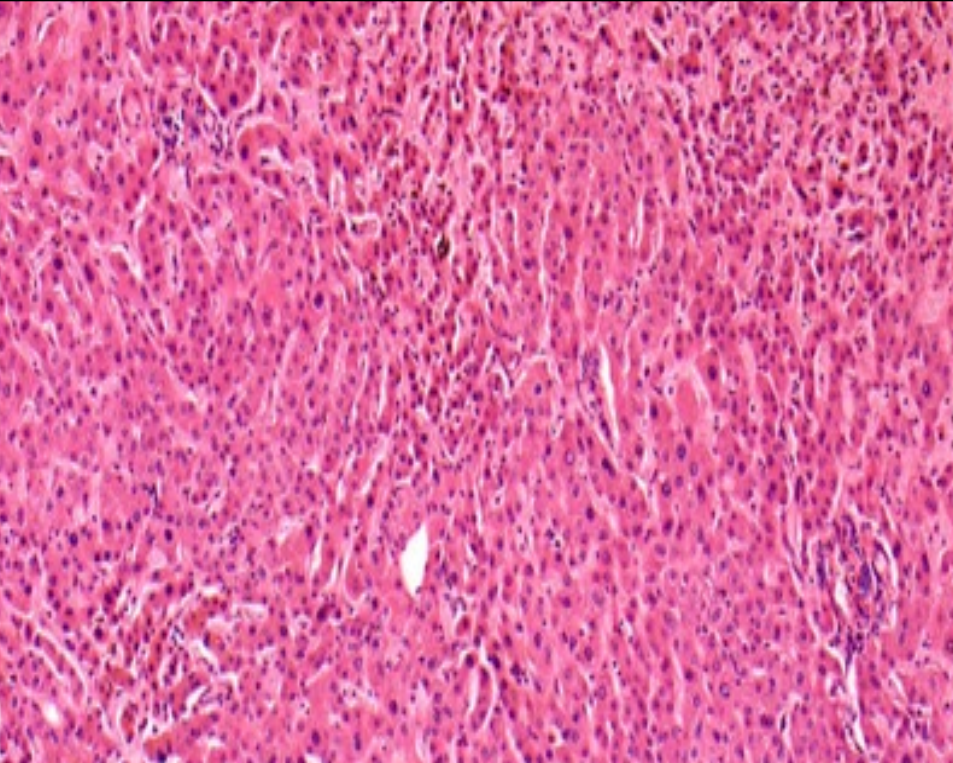
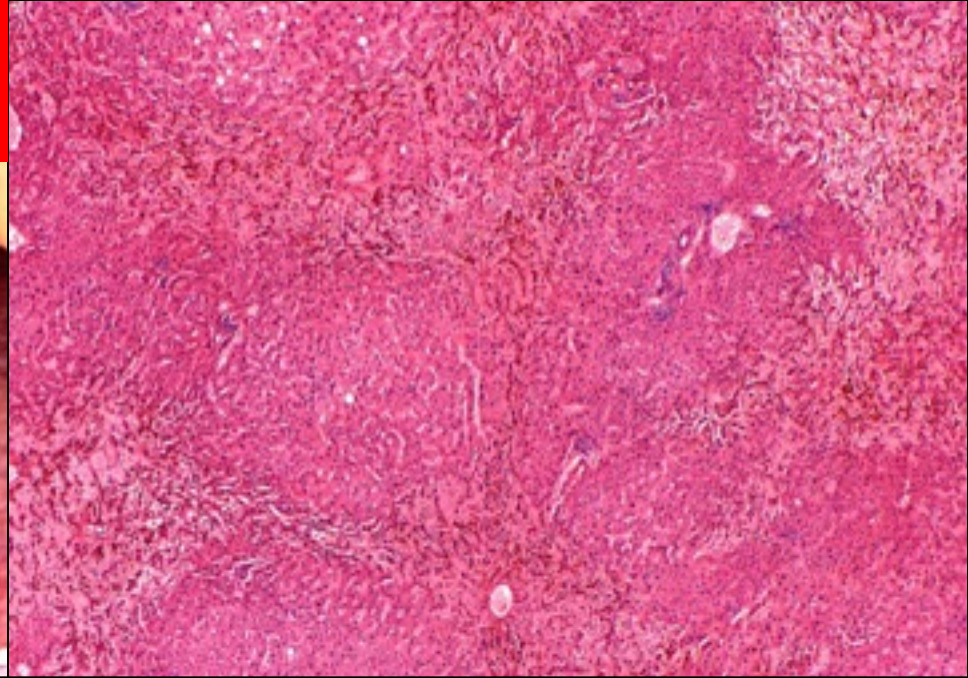
FEATURES	CONSEQUENCE
Portal vein invasion	Decreased survival
Bile duct invasion	Not definitive
Lymphatic invasion	Not definitive
Hepatic vein invasion	Not definitive

A histological section of a liver stained with Masson's trichrome. The image shows a cross-section of a liver lobule. The central vein is stained blue, while the surrounding hepatocytes are stained red. A prominent feature is the fibrous capsule, which is a thick layer of connective tissue that encloses the liver. This capsule is stained blue and is visible as a distinct boundary between the liver tissue and the surrounding structures. The thickness of the capsule is a key feature in the image.

**Fibrous
Capsule**

Thickness of the fibrous capsule improves survival

Sinusoidal Obstruction Syndrome





- *Sinusoidal distention [sinusoidal obstruction syndrome]*
 - Oxaliplatin
 - Increased risk of major morbidity
- *Nodular Regenerative Hyperplasia*
 - 5FU
- *Steatosis*
 - Irinotecan, 5-FU and others
 - Increased risk of liver surgery specific complications
- *Hepatitis*
 - Regorafenib
 - Idiosyncratic hepatitis-rarely fatal (0.33%)



Chemotherapy Related Toxicity

- Chemotherapy- related injury should be reported.
- However, liver injury does not appear to affect long-term outcomes.
- Yet, treatment response is decreased in patients with more severe sinusoidal lesions.



Case 2: Dr. Bilal Farooqi

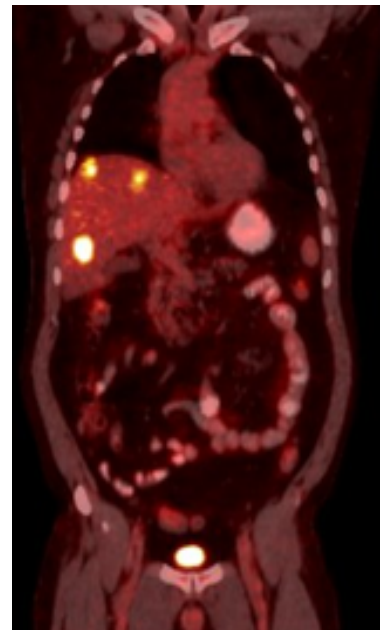
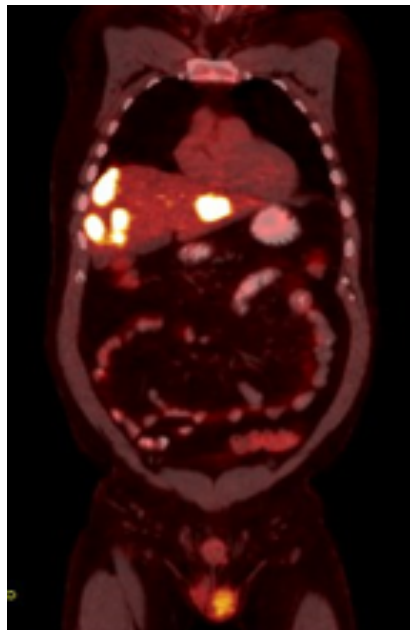
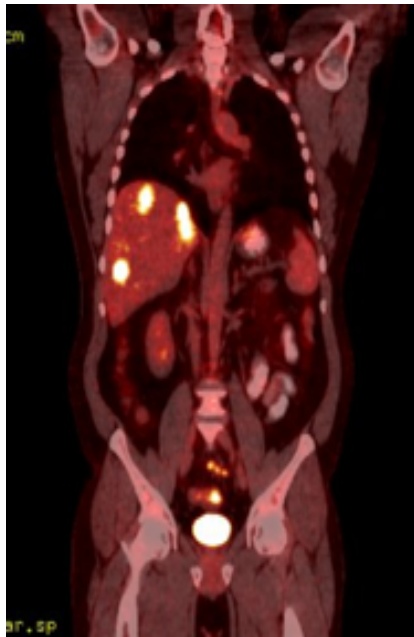
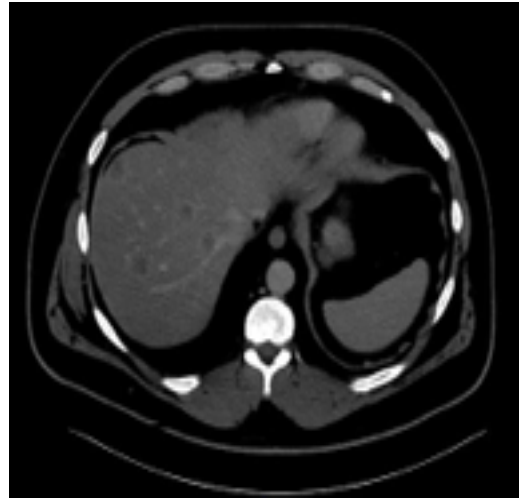
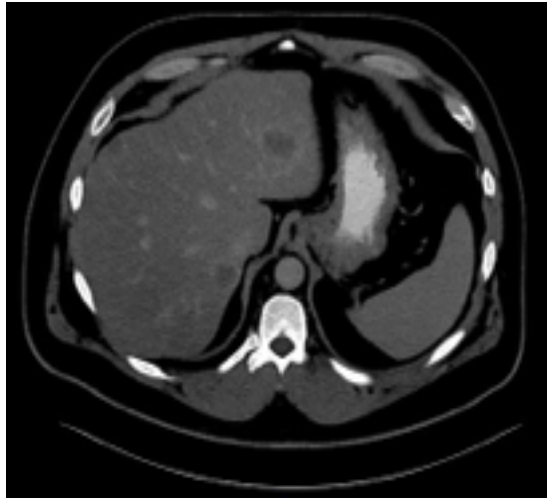
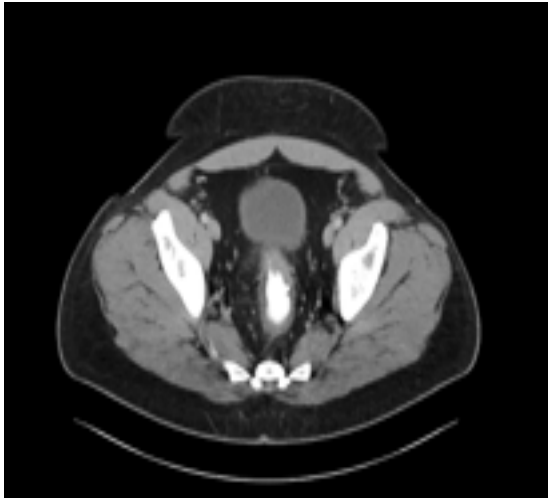
Hematology/Medical Oncology
Fellow, University of Florida



- A 53 year old man presented to his primary care physician with rectal bleeding. No prior colonoscopies.
- PCP did not palpate any masses on exam and referred to Gastroenterology for evaluation
- Colonoscopy identified fungating, non-obstructive mass located 14-18 cm from anal verge
- Biopsied as adenocarcinoma, moderately differentiated
- CBC, CMP normal. CEA elevated at 16.1



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- Dr. Anaya, this patient resectable?
- Dr. Lockhart, is systemic treatment first line treatment reasonable? Does bleeding tumor concern your decisions?
- Dr. Hitchcock, is there a role for radiation treatment in this bleeding patient?



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RADIATION ONCOLOGY PERSPECTIVE

Kathryn Hitchcock, M.D.

**Assistant Professor
Division of Radiation Oncology
Shands Hospital
College Of Medicine
University of Florida**



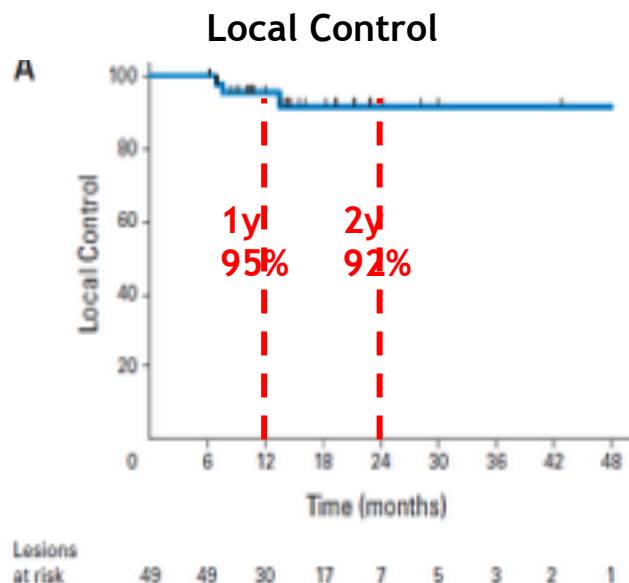
Roles of RT in metastatic colorectal ca:

1. Stereotactic RT to liver to obliterate one/few mets

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

JCO 2009

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenas, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter



100% LC for tumors < 3 cm

Toxicity:

- 0 RILD
- 0 G4-5
- Before modern computing, used few beams, hard on skin



- Roles of RT in metastatic colorectal ca:
 2. In rectal cancer, neoadjuvant to resection of primary if considered after strong chemo response
 3. To palliate, especially primary tumor

[Acta Oncol](#). 2014 Feb;53(2):164-73. doi: 10.3109/0284186X.2013.837582. Epub 2013 Nov 6.

Palliative pelvic radiotherapy of symptomatic incurable rectal cancer - a systematic review.

[Cameron MG](#)¹, [Kersten C](#), [Vistad I](#), [Fosså S](#), [Guren MG](#).

27 studies

Pooled . . . positive responses were reported for pain (78%), bleeding and discharge (81%), mass effect (71%) and other pelvic symptoms (72%).



Case 2

- Short-course stereotactic radiation - 5 Gray per fraction x 5 days
- Systemic chemotherapy
 - FOLFOX x 8 cycles
 - 5-FU/leucovorin and bevacizumab x 2 cycles
 - 5-FU/leucovorin x 8 cycles
- CEA decline to 3.7





- Exlap
- Right hepatectomy
- Wedge resection segment 3

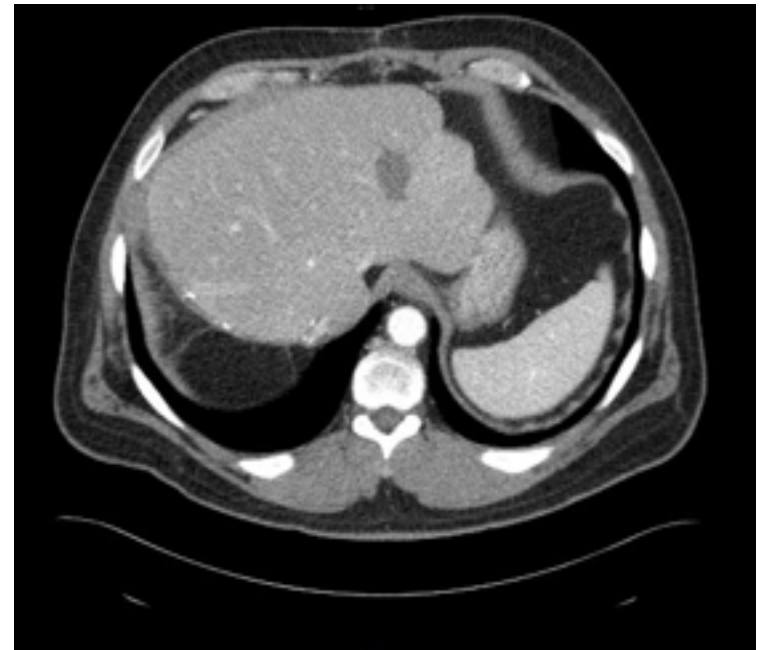


Pathology

- **6 lesions**
 - Fibrosis
 - No viable cells - complete pathologic response
 - Tumor Response Grade 1
- **Margin - 1.5cm**
- **Mild steatosis**



- **Adjuvant therapy**
 - 3 cycles of 5-FU/leucovorin
- **Restaging with no evidence of disease**





- **Panel:** Primary is still in place, what is the next step?



- 6 weeks after completion of adjuvant therapy - hand-assisted laparoscopic low anterior resection with diverting loop ileostomy
- **Pathology report**
 - Scar tissue with no viable cancer cells (Tumor Response Grade 1)
 - Complete pathologic response
 - Intact mesorectum - 4 lymph nodes, all negative



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SURGICAL ONCOLOGY PERSPECTIVE

Daniel Anaya, M.D.

**Senior Member and Chief of GI Surgery
Head of Hepatobiliary Section
Department of Gastrointestinal Oncology
Moffitt Cancer Center**

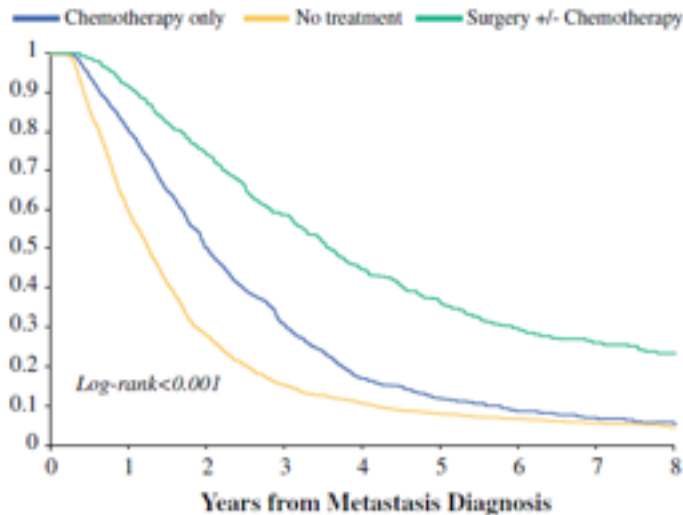
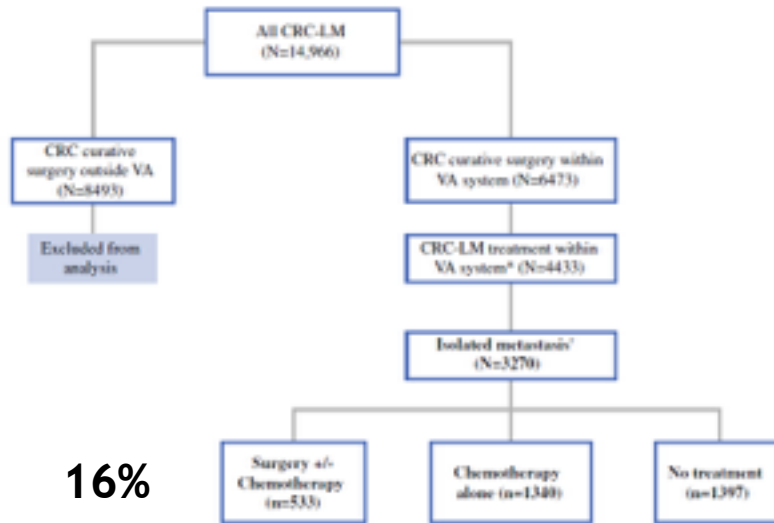


CRCLM - Treatment & Outcomes

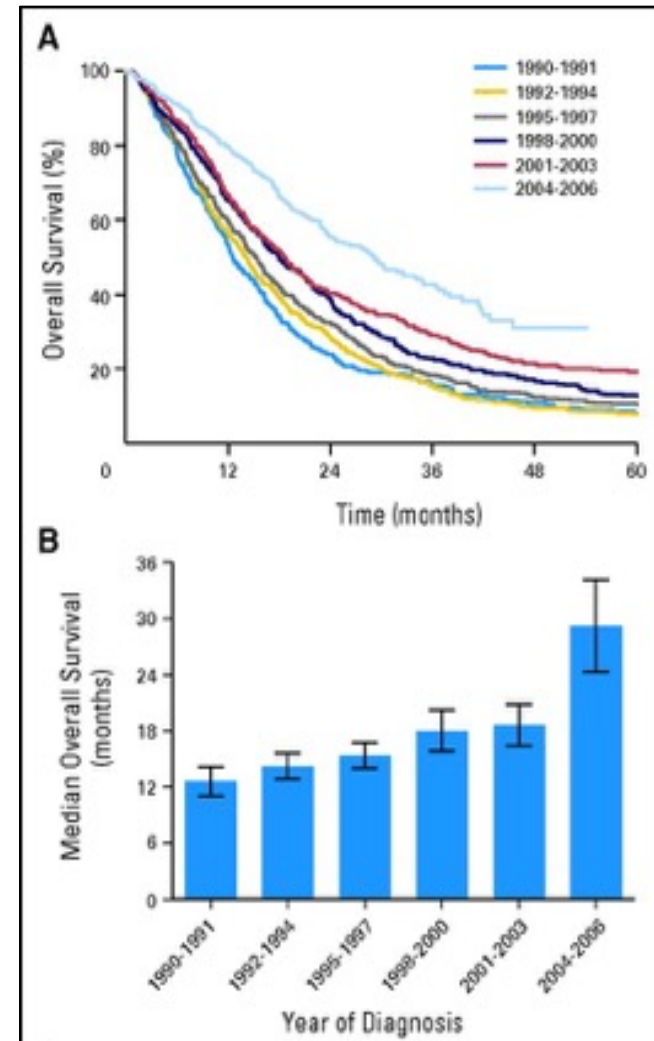
Treatment	Median OS	5-year OS
Supportive care	6-9 months	0%
Historic reports (1960-1990)		
Chemotherapy (5FU/LV)	12-14 months	< 5%
Liver resection	35 months	20-30%
Current reports (2000-2016)		
Chemotherapy (FOLFOX/ FOLFIRI +/- Bio)	24+ months	<10%
Ablation	30 months	20%
Chemotherapy + ablation	35-40 months	?
Liver resection	74 months	58% 25% (10-year OS = cure)



CRCLM - Liver Resection



Orcutt & Anaya et al. ASO 2017



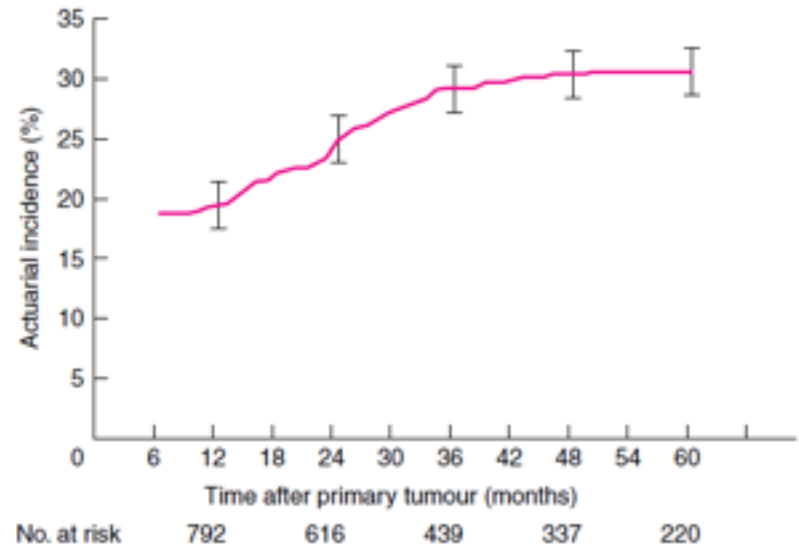
Kopetz S et al. JCO 2009



CRCLM - Presentation

**Incidence
Liver metastasis**

30-50%



Leporrier J et al. BJS 2006

Resectable

5-20%

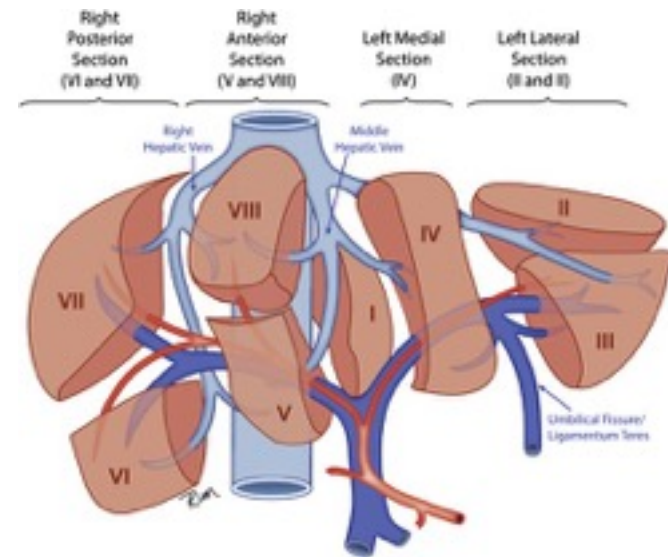
Unresectable

80-95%



CRCLM - Treatment Goals

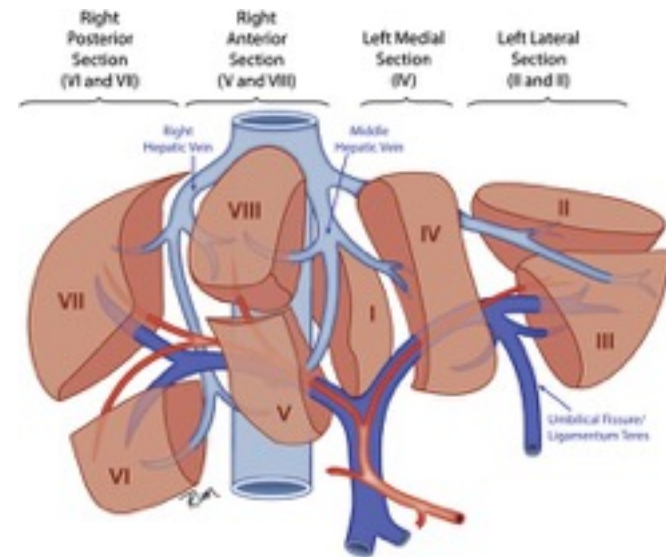
- Complete - R0 resection
- Adequate residual liver
 - 2 contiguous segments with adequate inflow/outflow and biliary drainage
 - Functional liver remnant (volume/function)





CRCLM - Treatment Goals

- Complete - R0 resection
- Adequate residual liver
 - 2 contiguous segments with adequate inflow/outflow and biliary drainage
 - Functional liver remnant (volume/function)



****Surgery/resection = oncologic benefit***



CRCLM - Presentation

Multiple lesions

Larger lesions

Bilobar tumors

Synchronous disease

Geriatric population



Resectable

Unresectable

15-30%

70-85%



Technically unresectable

Close margins

Vein involvement

Small liver remnant

High burden disease

Multiple-bilobar disease
(liver)

Extrahepatic disease

Recurrent CRCLM

Biologic markers

Other scores



Resectable

Borderline

Unresectable

15-30%

10-20%

50-75%



Technically unresectable

Close margins

Vein involvement

Small liver remnant

High burden disease

Multiple-bilobar disease
(liver)

Extrahepatic disease

Recurrent CRCLM

Biologic markers

Other scores

All other
Progressive disease
Poor biology

No surgical candidates

Multiple lesions
Larger lesions
Bilobar tumors
Synchronous disease
Geriatric population

Resectable

Borderline

Unresectable

15-30%

10-20%

50-75%



Liver Resection for CRCLM

- Good surgery - results
 - Postoperative morbidity/mortality
 - Negative margins
- Surgical strategy - long-term
 - Parenchyma-sparing* / Combined resection
- Multimodality treatment (chemo)
 - Sequence / # cycles
- Oncosurgical strategies***



Liver Resection for CRCLM

- **Oncosurgical strategies**
 1. Conversion chemotherapy
 2. Preoperative portal vein embolization
 3. Staged hepatectomies
 4. ALPPS
 5. Oncologic considerations
 6. Future: immunotherapy, chemo delivery



1. Conversion Chemotherapy

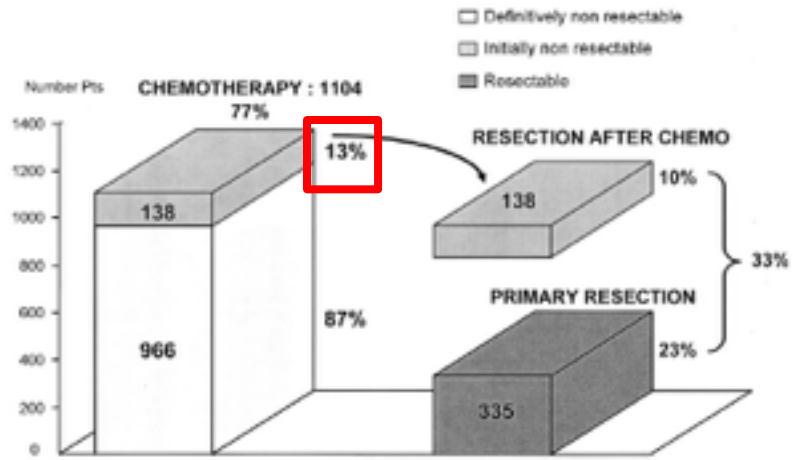
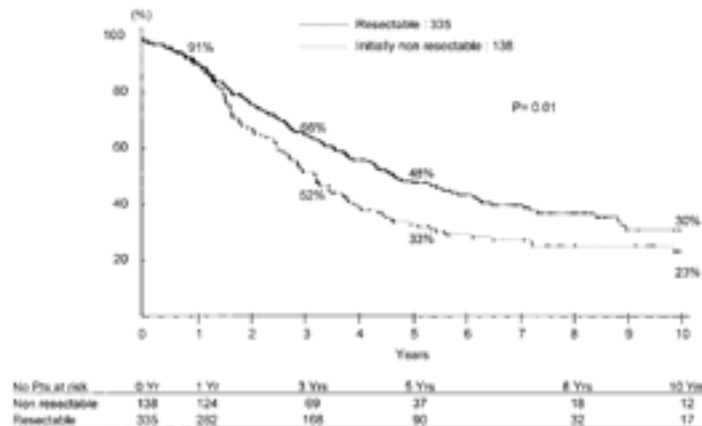


FIGURE 1. Paul Brousse Experience (1988–1999) in the management of colorectal liver metastases.



- Unresectable (mixed)
 - Large burden - liver
 - EH disease (38%)
 - Small liver remnant
- Chemotherapy
 - Median 10 cycles
- Other therapies (30%)
 - PVE
 - Staged hepatectomy
 - +/- RFA
- Outcomes
 - 7% CR
 - Survival



1. Conversion Chemotherapy

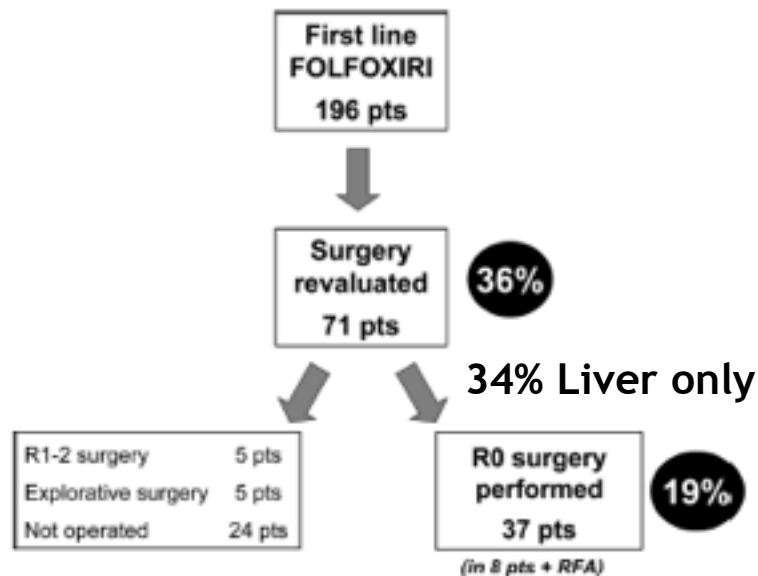
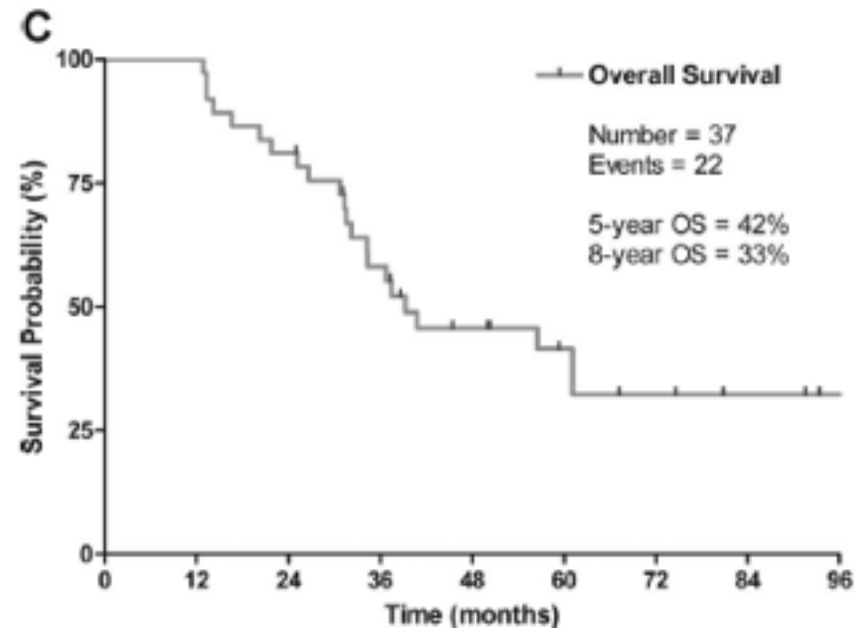


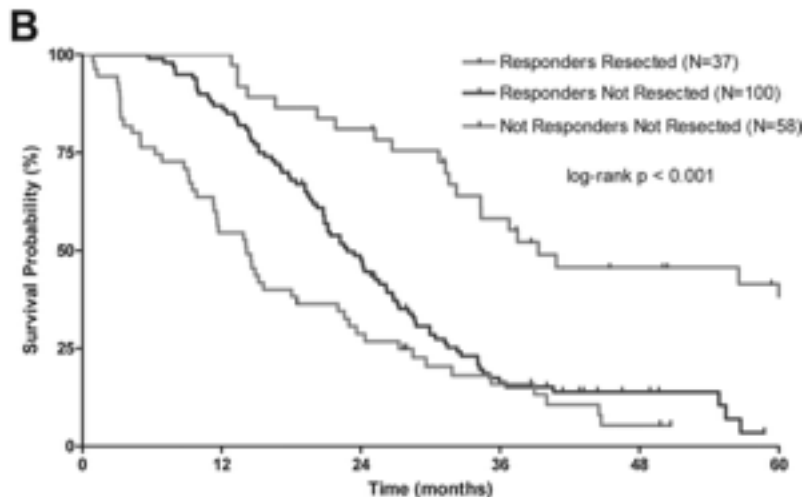
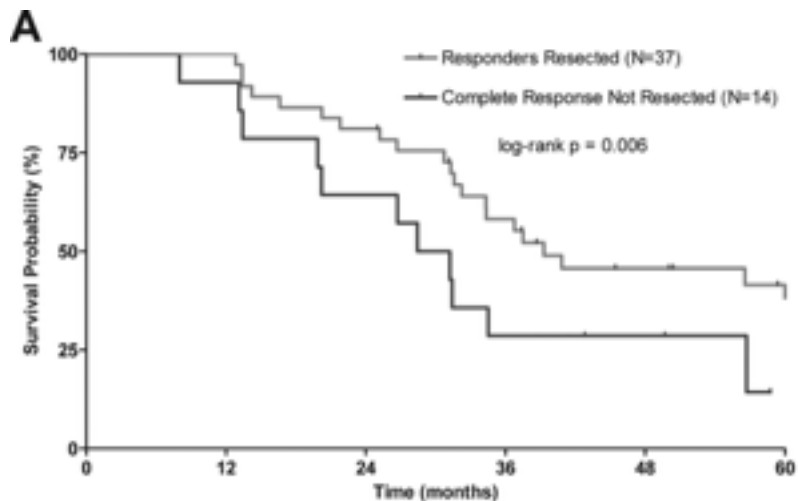
FIGURE 2. Treatments flow-chart.



- Pooled analysis - phase II/III studies / unresectable
- Median cycles 11 - RR 70% - CR 11% (resected)
- Outcomes: higher resection / OS



1. Conversion Chemotherapy



- Differential benefit in long-term survivors
- Liver toxicity: SOS, steatosis, steatohepatitis



1. Conversion Chemotherapy

- Which chemotherapy / regimen to use
 - Efficacy - Survival outcomes
 - RR / “downstaging”
 - Curative-intent surgery
 - Liver toxicity
- Tumor features - location / biomarkers



1. Conversion Chemotherapy

- Liver Toxicity - CALI
 - Steatosis
 - Sinusoidal Obstructive Syndrome (SOS)
 - Steatohepatitis



1. Conversion Chemotherapy

Regimen	RR	Conversion / Resection	5-year OS (median)	Comments
5FU/LV	~40%	11%		
FOLFIRI	~40-50%	3-12	33%	-9 cycles -Steatohepatitis
FOLFOX	~50-60%	4-40%	33% (26-42m)	-10 cycles -SOS
FOLFOXIRI	~70%	19 (34%*)	42% (40-60m*)	-11 Cycles -More toxic
+ Bevacizumab	↑ ~10%	49-60%*		-FOLFOXIRI > FOLFOX / FOLFIRI
+ Cetuximab	↑ ~10-20%	16-34%	(54m)	-RAS wt -FOLFOX / FOLFIRI

* Liver-only metastatic disease



2. Portal Vein Embolization

- Small - future liver remnant (FLR)
 - Common cause of unresectability
 - Multifocal/bilateral, large, poorly located
 - Major resection
 - Small FLR
 - Extensive chemotherapy



2. Portal Vein Embolization

- Primary goal - Hypertrophy FLR
 - Allows for (safe) operation - outcomes
 - “Sufficient” residual liver - FLR

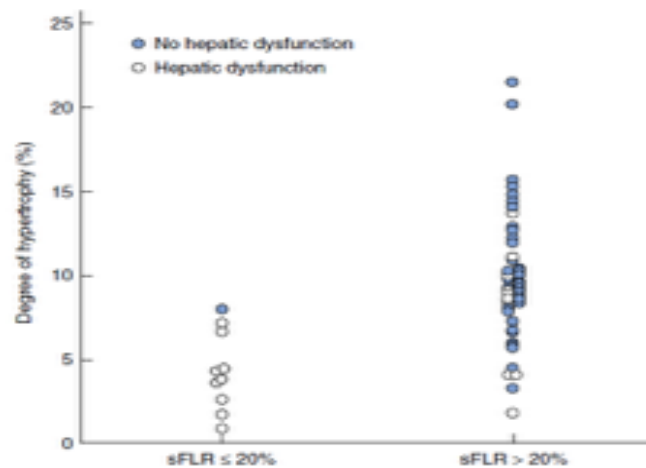
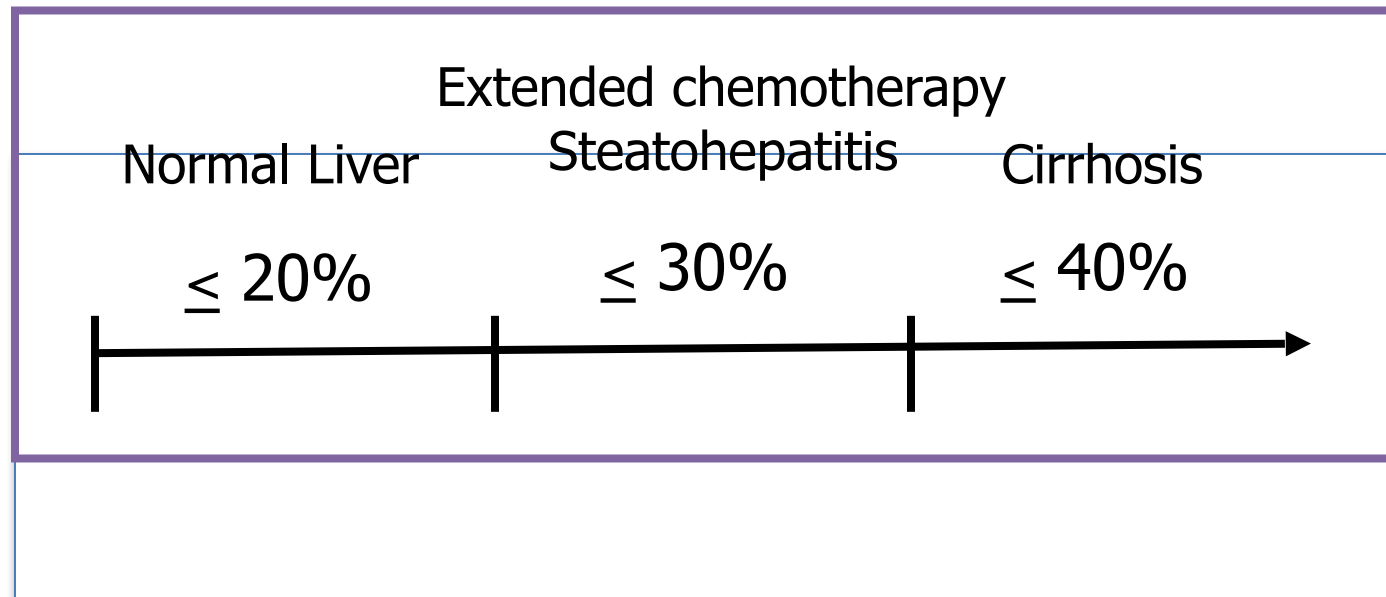


Fig. 3 Scatter plot of the incidence of hepatic dysfunction according to degree of hypertrophy, stratified by standardized future liver remnant (sFLR)

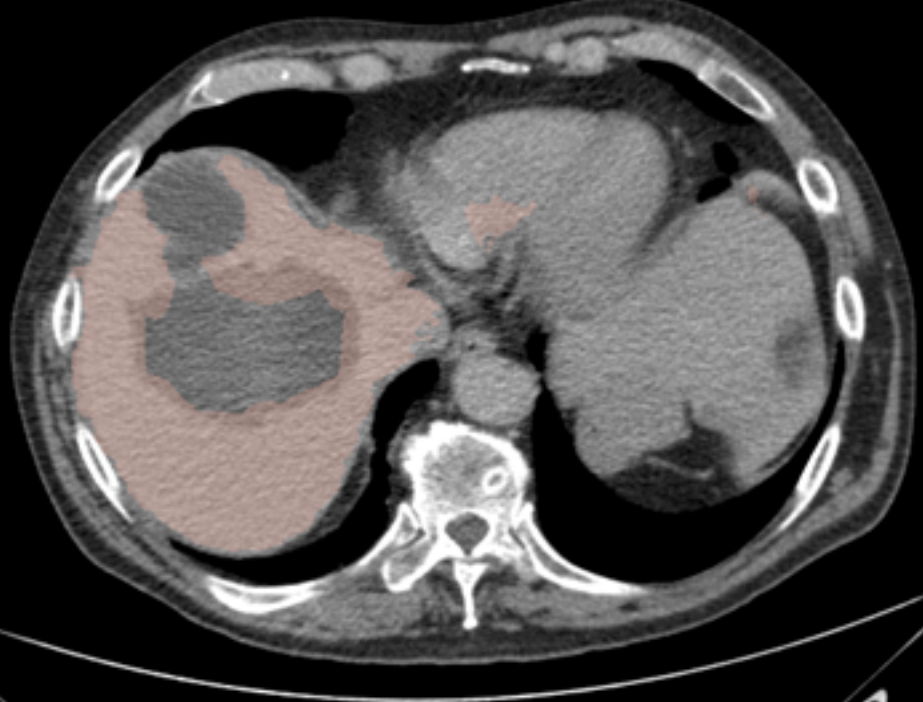


2. Portal Vein Embolization

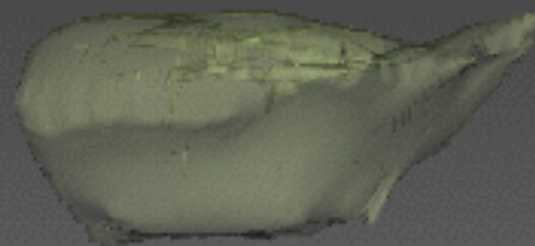
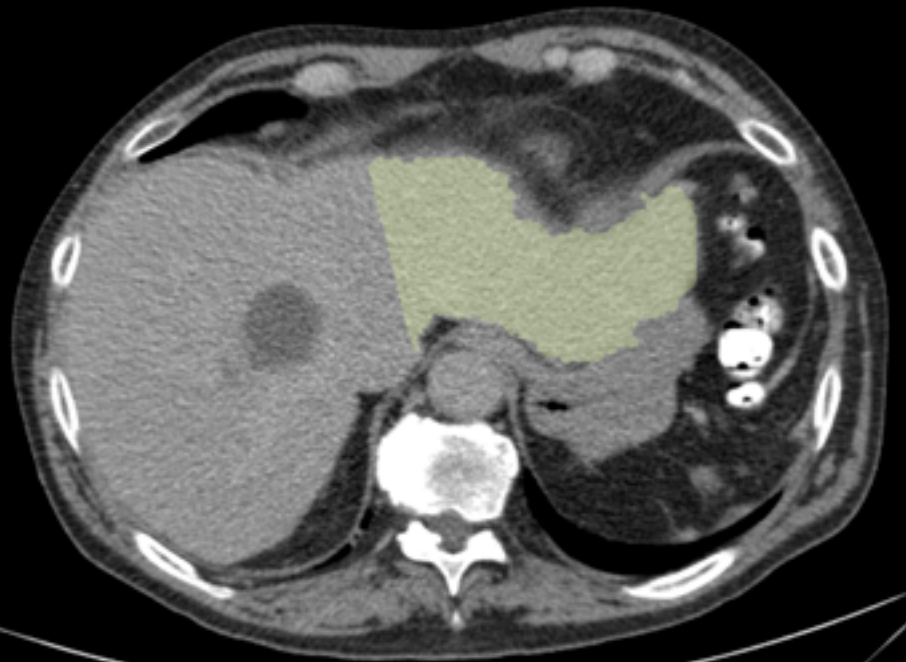
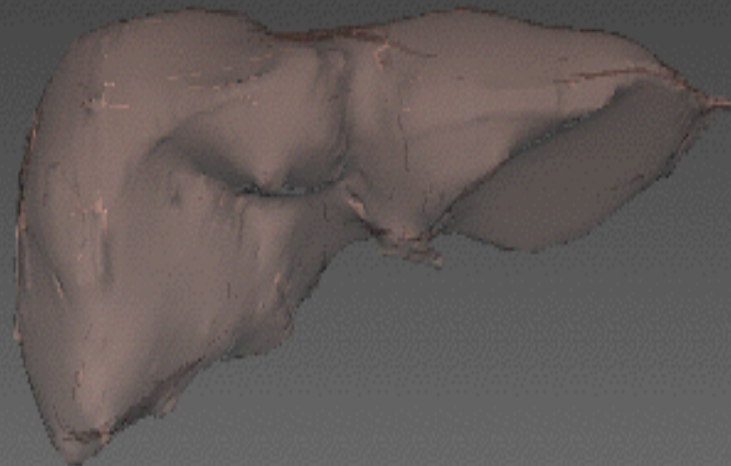
- FLR volume - Indications



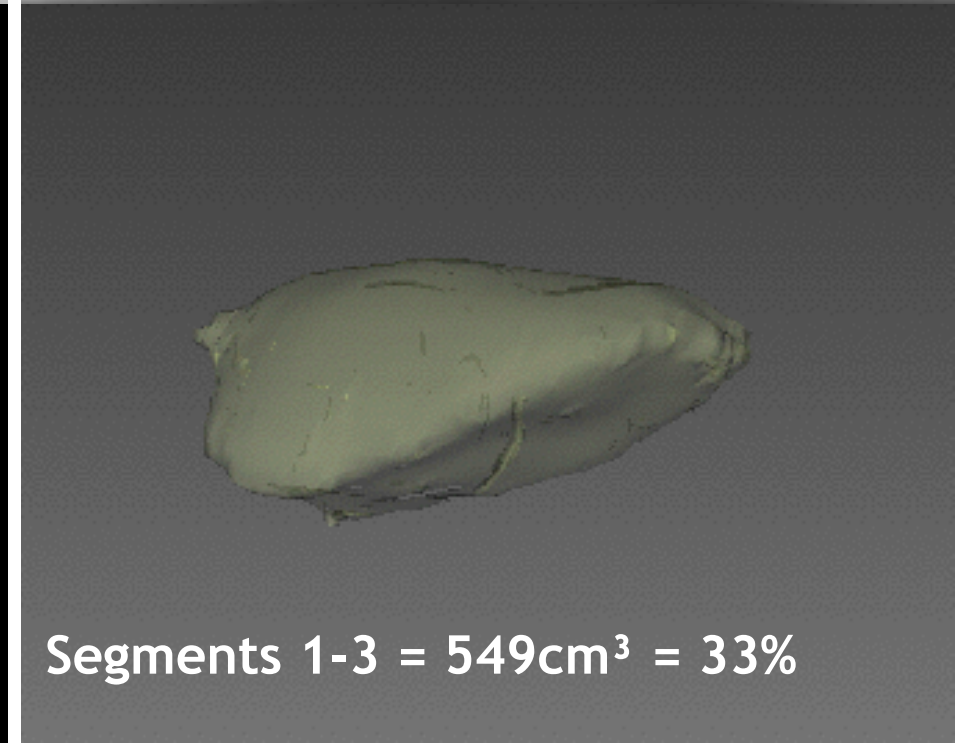
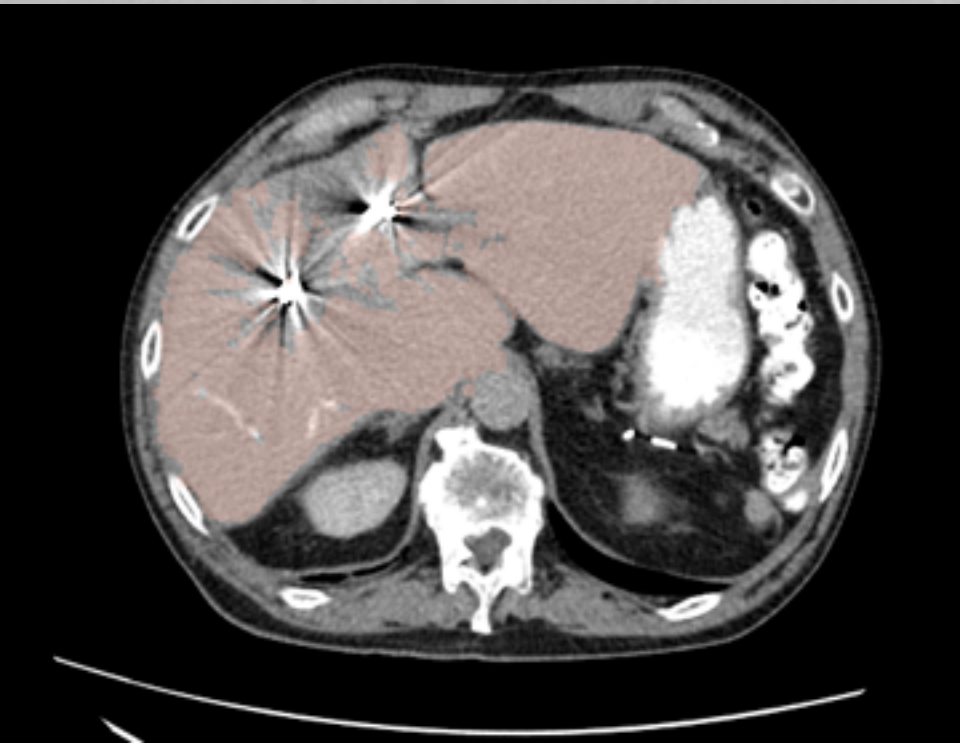
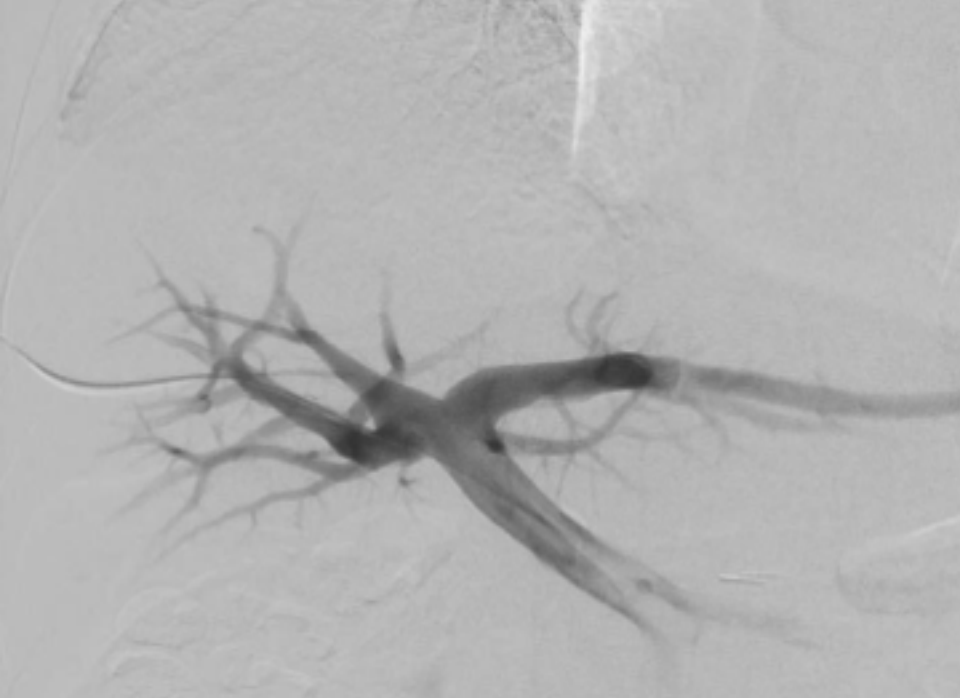
Abdalla EK. *Arch Surg.* 2002.
Consensus Statement. *Ann Surg Onc.*
2006
Anaya DA et al. *Semin Intervent Radiol*
2008



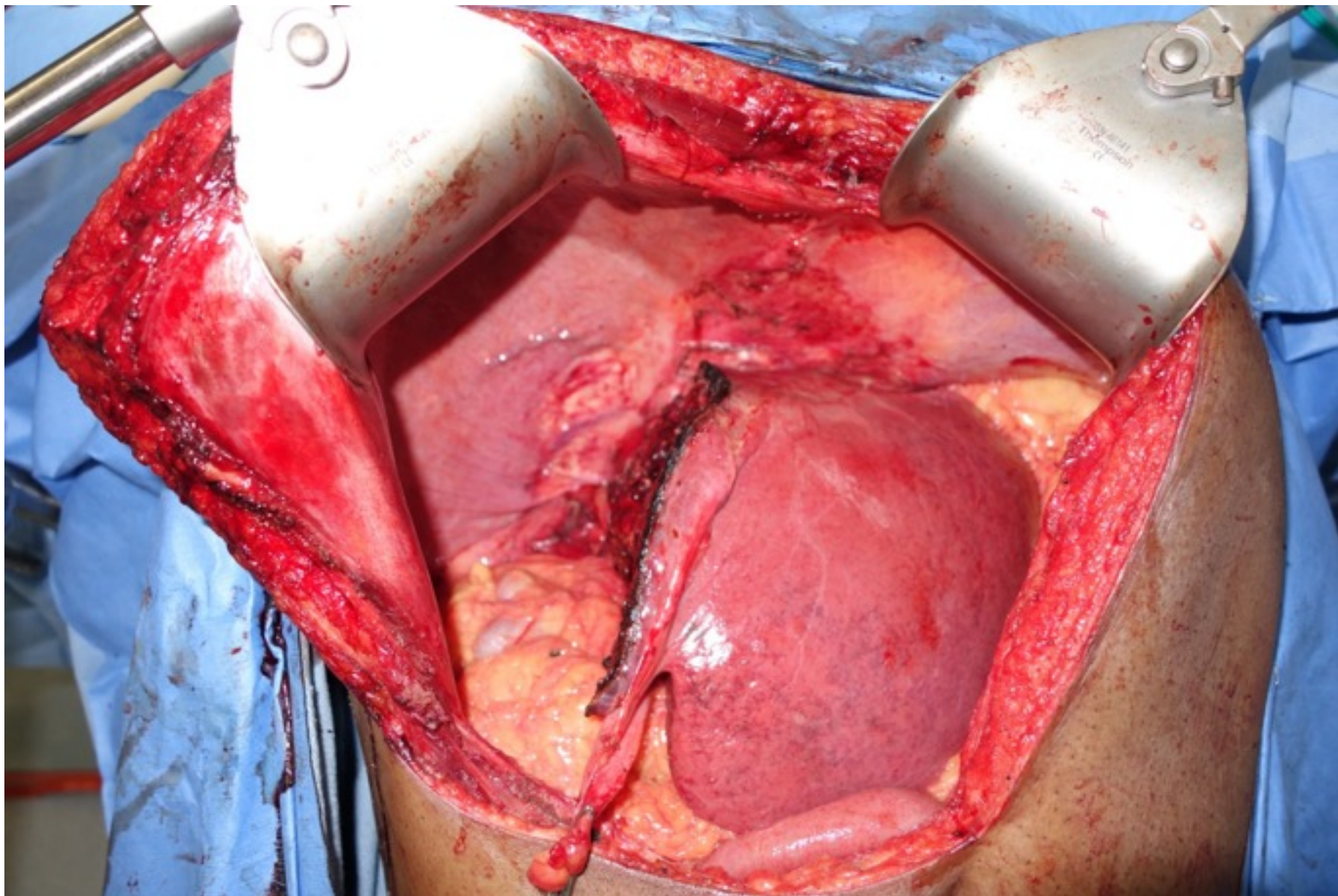
Healthy Liver : 1542 cm³



Segments 1-3 = 420cm³ = 25%



Segments 1-3 = 549cm^3 = 33%



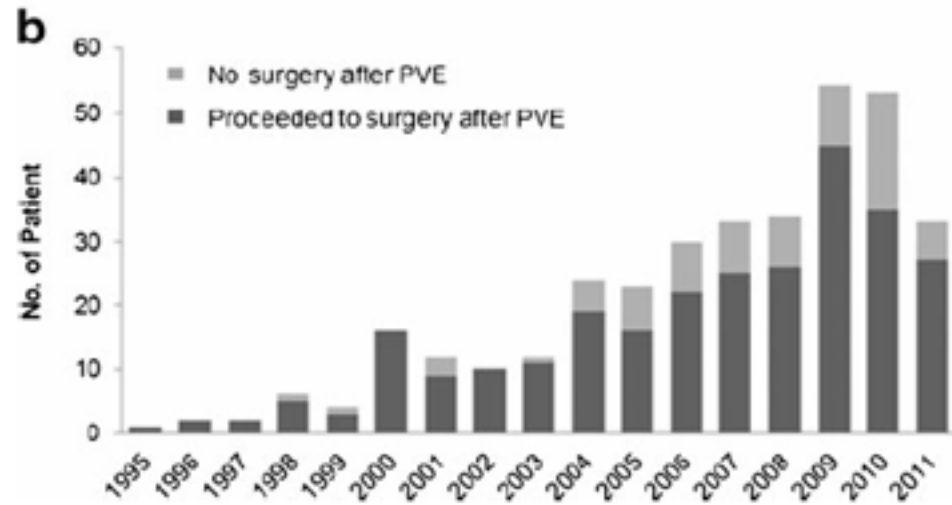


2. Portal Vein Embolization

• Outcomes - Efficacy of PVE

TABLE 1. Summary 37 Publications on Portal Vein Embolization

Details	No. (%)
Total no. patients	1088
Pathology	
HCC ^{10-15,18,20,22-26,28-37}	265 (24)
ChC ^{2,5,15-18,19,21-25,28,29-31,33-45}	430 (39)
Others ^{3,5,12,13,17-19,20,22,23,25,26,28-31,34-37,39-41,46-49}	393 (36)
Embolization method	
PTPE ^{2,3,5,10-15,18,21-25,28,29,31-42,44,46-49}	784 (72)
TIPE ^{2,14,26,30,37,39,40,43,45,45}	304 (28)
Embolization materials	
Cyanoacrylate + lipiodol ^{7,22,29,36,47,48}	169
Gelfoam + thrombin + urografin ^{26,30,31,42,45}	309
PVA + coil + lipiodol + fibrin glue ^{12,25,34}	66
Fibrin glue + lipiodol + PVA ^{14,19,21,24,32,41,44,46}	80
Gelfoam + urografin + gentamicin ^{2,37,39,40,43}	123
Embol-78 ¹⁰	51
Gelfoam + coils ^{15,20,28,35,49}	137
PVA + micro coils ^{5,18,23,47}	153
Volumetric change	
Pre-PVE	16-44
Post-PVE	24-69
Percentage increase (%)	8-27
Timing of CT scan post-PVE (week)	2-6
Length of time post-PVE to operation (day)	2-60
Resection post-PVE	930 (85)
No resection post-PVE	158 (14)



Abulkhir A et al. Ann Surg 2008
 Shindoh J et al. J GastroIntest Surg 2013

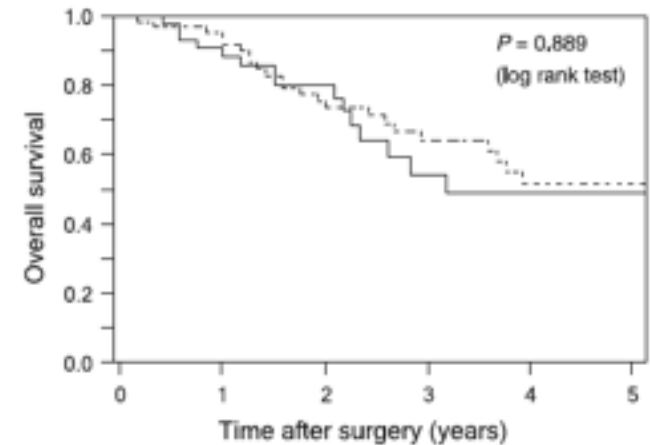


2. Portal Vein Embolization

- Outcomes - short-term outcomes / OS

Table 2 Short-term outcomes

Outcome parameter	Non-PVE group (n = 66)	PVE group (n = 49)	p*
Mortality ^c	0	0	–
Morbidity ^b	16 (25.0 %)	17 (34.7 %)	0.263
General complication ^{b,d}	11 (17.2 %)	2 (4.1 %)	0.022
Biliary leakage ^b	1 (1.6 %)	7 (14.3 %)	0.007
Accumulation of pleural or ascitic fluid ^b	4 (6.3 %)	9 (18.4 %)	0.045
Relaparotomy ^b	1 (1.6 %)	1 (2.0 %)	0.849



Patients at risk

Non-PVE	66	56	39	26	16	14
PVE	49	38	24	12	9	7

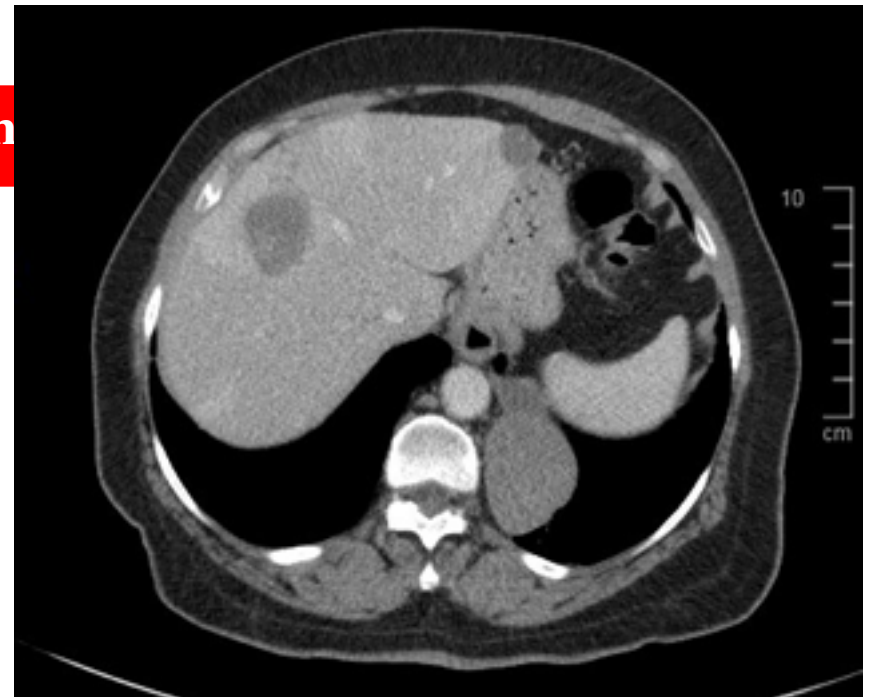
Fig. 2 Overall survival curves for the PVE group (solid line) and the non-PVE group (dotted line)



3. Staged Hepatectomy

- 2-stage liver resection
- Bilateral liver metastasis
- Not amenable to one-stage approach
 - 1st stage - resect one side disease +/- primary
 - +/- PVE contralateral tumor-bearing liver
 - Adequate recovery
 - Re-image: hypertrophy + no progression
 - 2nd stage - resect tumor-bearing liver (larger)

cal On



69 y/o F - rectal cancer and CRCLM

- **Bilobar - unresectable CRCLM**
- **Small FLR**
- **Biologic behavior ?**



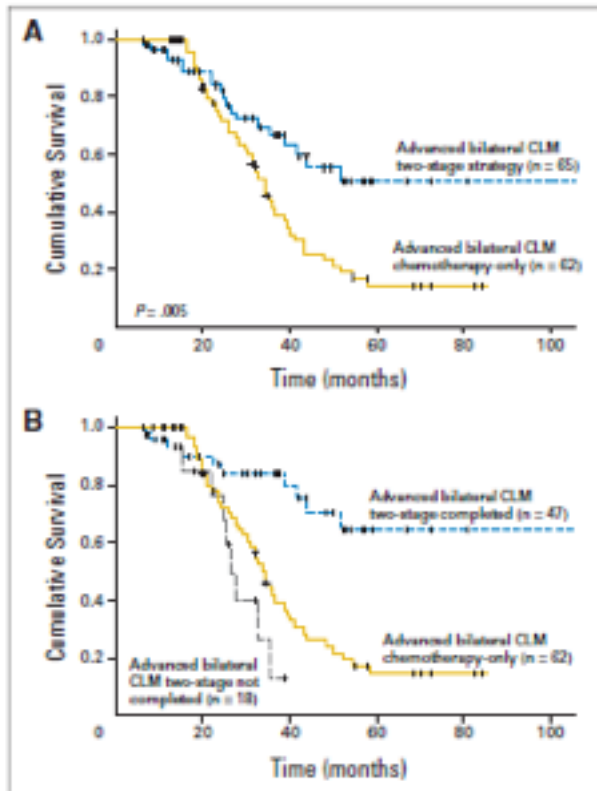
3. Staged Hepatectomy

- Combined strategies
 - Preoperative chemotherapy - 88%
 - PVE 76%
- Success rate - 77% complete 2-stage
- Major hepatectomy - 84%
 - Morbidity - 17% & 40%
 - Mortality - 0.5% & 3%

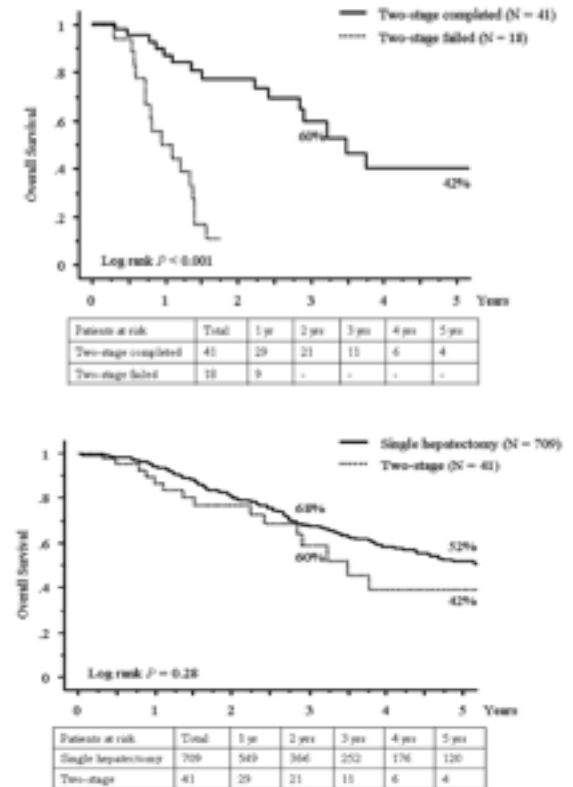


3. Staged Hepatectomy

- Outcomes - Overall survival



Brouquet A, et al. JCO 2011
2008



Wicherts DA, et al. Ann Surg

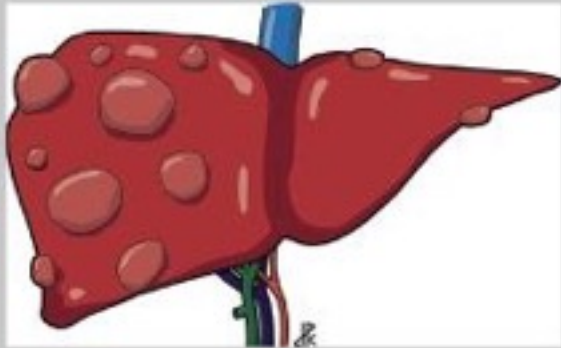


4. ALPPS

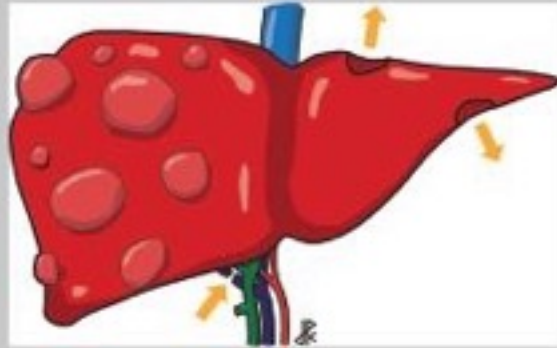
- “Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy”
 - Two-stages within 1-2 weeks
 - First stage with PV ligation and hepatotomy
 - Faster and Higher hypertrophy



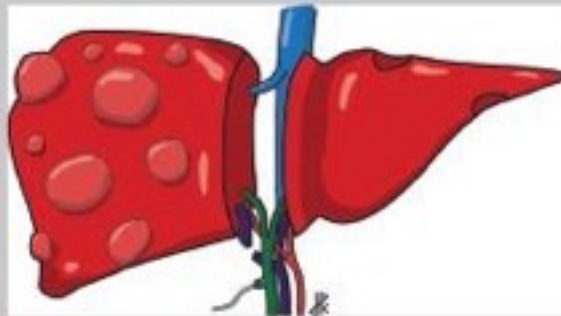
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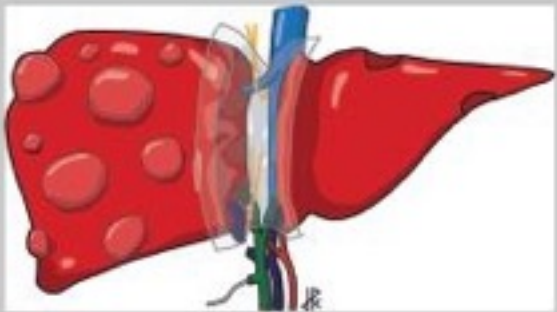
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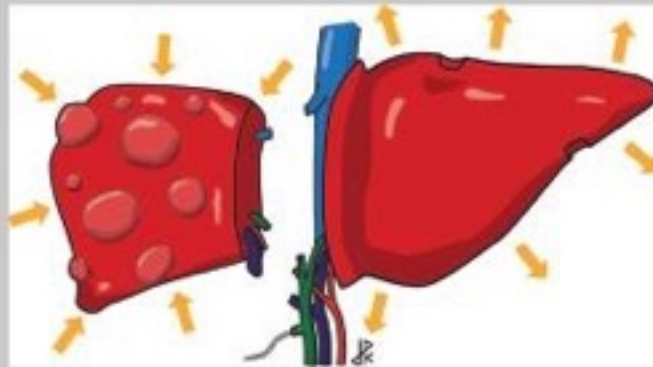
3



4



5





**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)*

N= 100 (49 vs. 48)

	ALPSS	TSH	<i>p</i>
Median # lesions	8+/-4	8+/-5	0.48
% FLR growth reached	92%	47%	<0.001
Resections rate	92%	57%	<0.001

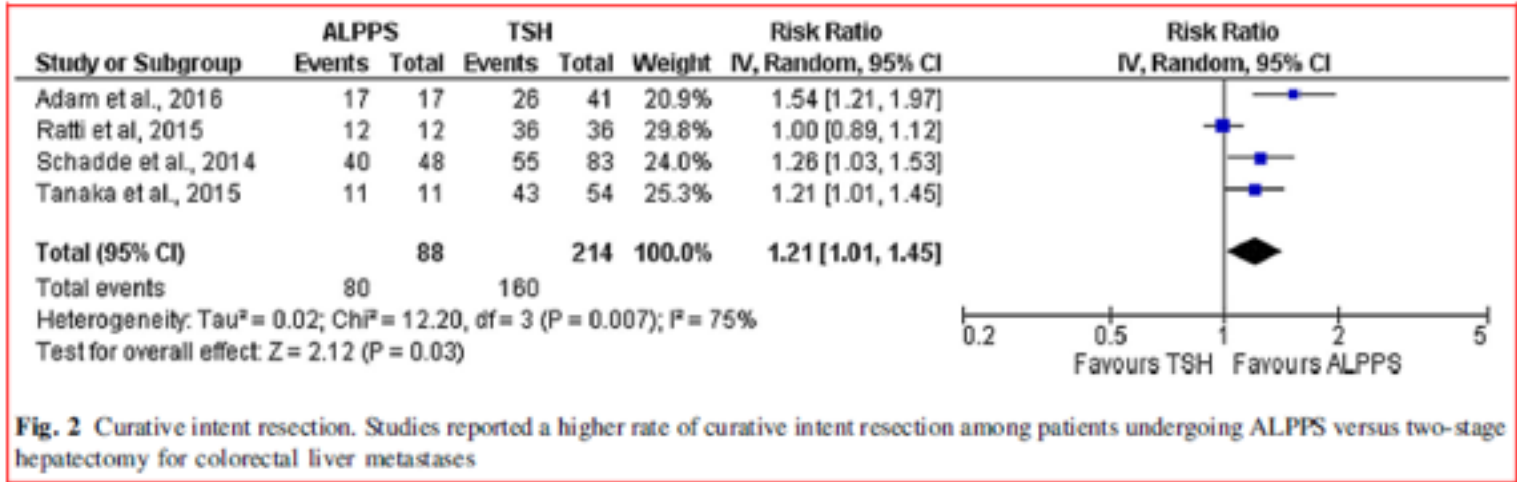
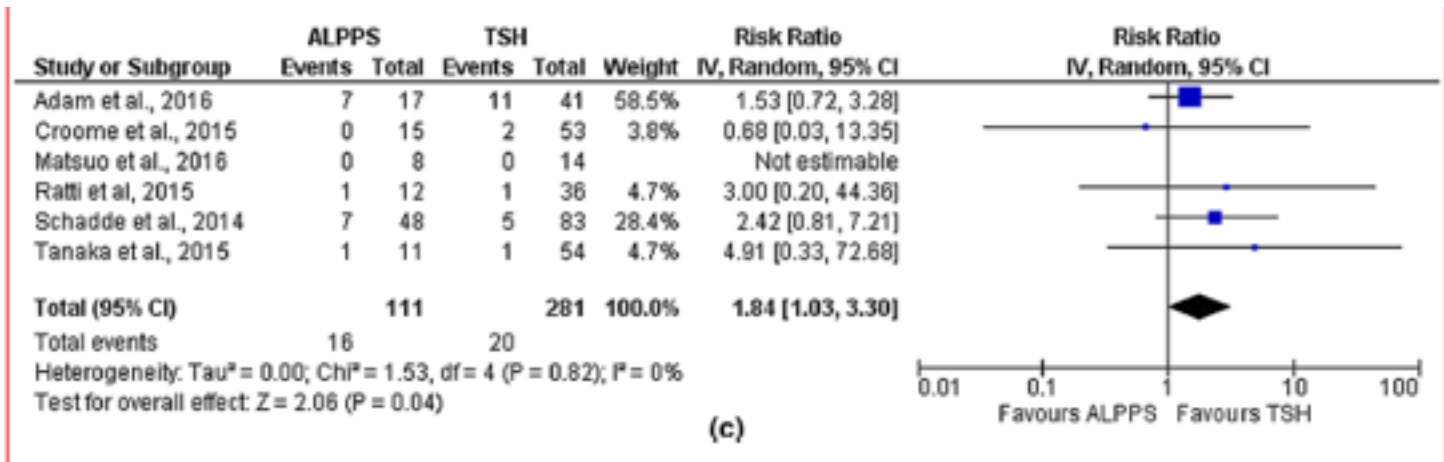


Fig. 2 Curative intent resection. Studies reported a higher rate of curative intent resection among patients undergoing ALPPS versus two-stage hepatectomy for colorectal liver metastases





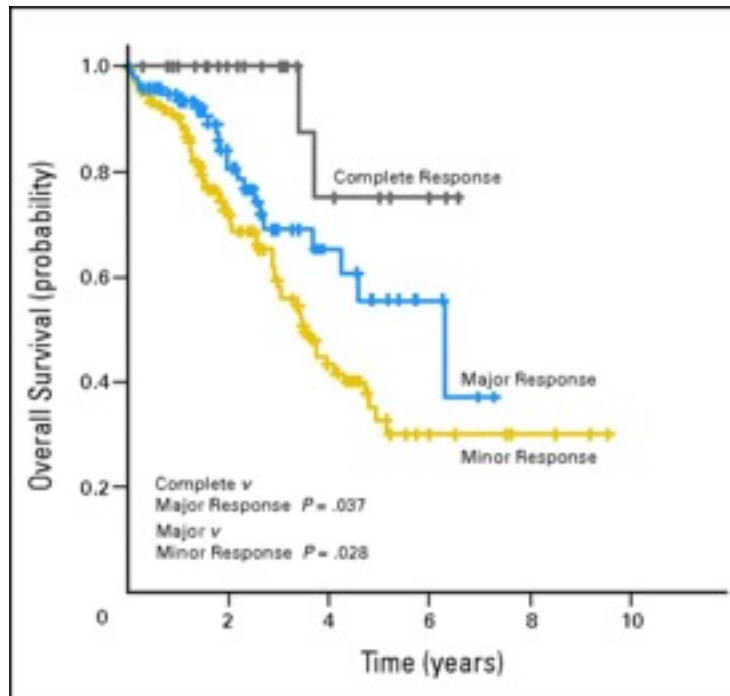
5. Oncologic Considerations

- Predictive and prognostic factors
 - Anatomic and tumor-burden (CRS - other)
- Molecular markers
 - Extent / site of EH disease
 - Kras/BRAF/MMR, other
- Novel markers - biology

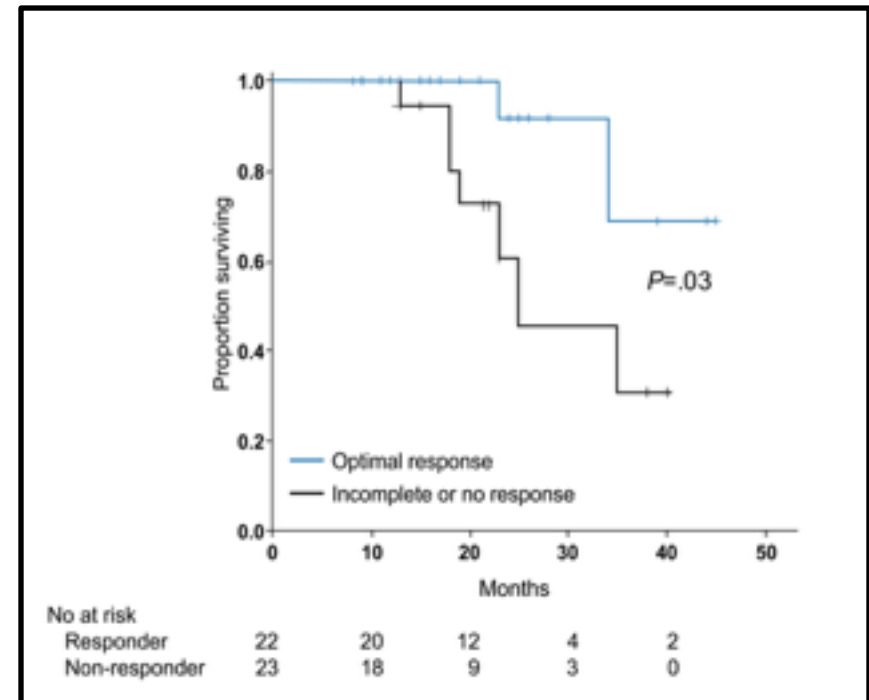
*****RESPONSE TO CHEMOTHERAPY*****



Response to chemotherapy and survival



Blazer 3rd DG, et al. *JCO* 2008



Chun YS, et al. *JAMA* 2009



6. Future (examples)

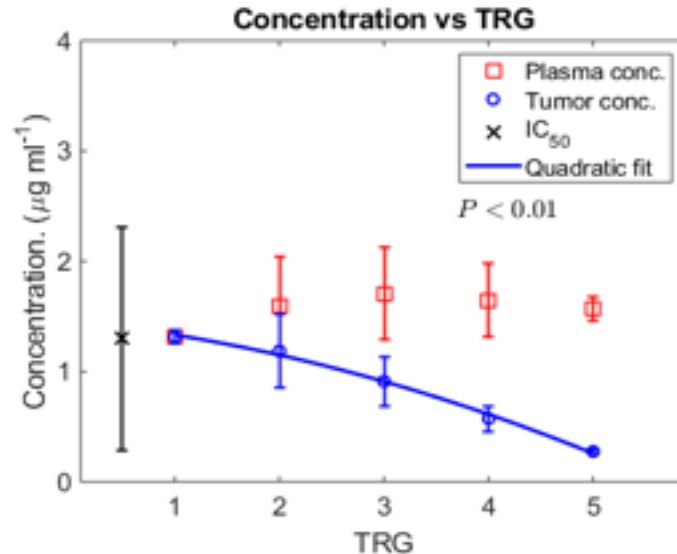
- Multimodality therapies - immunotherapy
 - Preoperative vaccine injection CRCLM
 - Direct kill effect
 - Abscopal effect
- Chemotherapy modeling
 - Tumor-site chemotherapy concentration



6. Future (examples)

- Chemotherapy modeling

$$f_{kill} = 2 \cdot f_{kill}^0 \cdot BVF \cdot \frac{BVF^{1/2} \cdot K_1(r_b/L) - K_1(BVF^{-1/2} \cdot r_b/L)}{BVF^{1/2} \cdot r_b/L - K_0(r_b/L) \cdot (1 - BVF)}$$



- Predict response
- Guides regimen/dose
- Alternative models of delivery



Summary and Conclusions

- **Liver surgery and systemic treatment of CRCLM have improved outcomes**
- **Goal = multimodal treatment**
 - Includes surgery
 - Outcomes critical but not sufficient
 - **Appropriate use of combined therapies is essential**



Summary and Conclusions

- **Borderline - Conversion to resectable**
- **Oncosurgical strategies**
 - Understanding of biologic behavior
 - Chemotherapy / PVE
 - Surgical approaches
- **Evolving / novel approaches**
 - Molecular profiling
 - Immunotherapy / chemotherapy modeling



Case 3: Sonikpreet Aulakh

Hematology/Medical Oncology
Fellow, Mayo Clinic



- A 49 year old woman presented to local ER with severe abdominal pain and distention
- CT abdomen/ pelvis:
 1. obstructing rectosigmoid mass
 2. multiple presumed liver metastases
- Underwent palliative resection rectosigmoid colon with end colostomy



Pathology

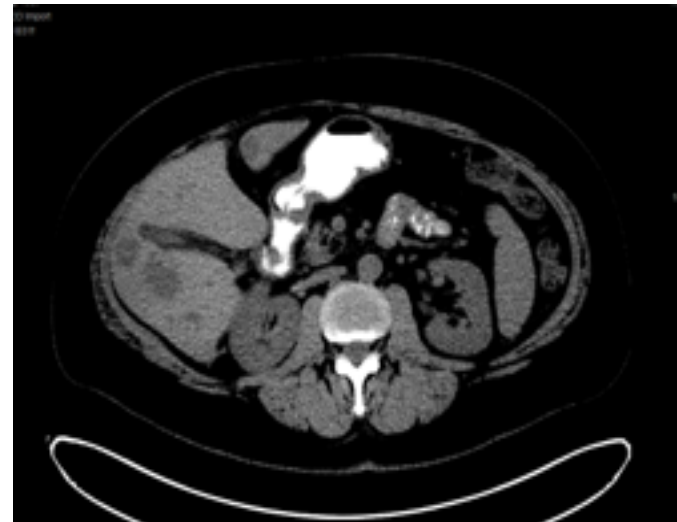
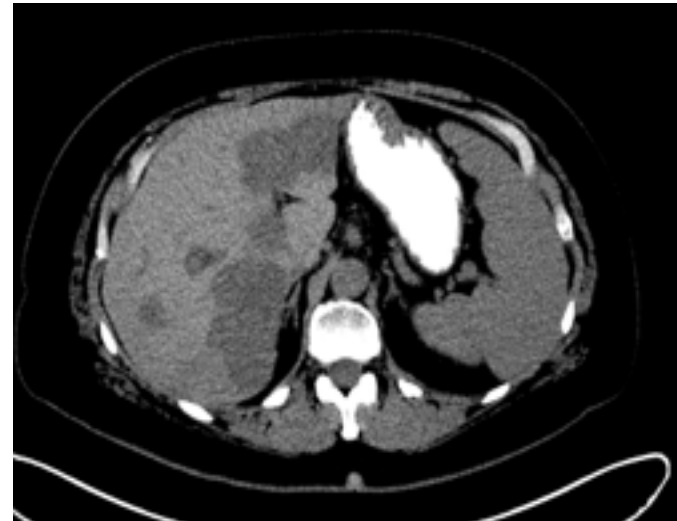
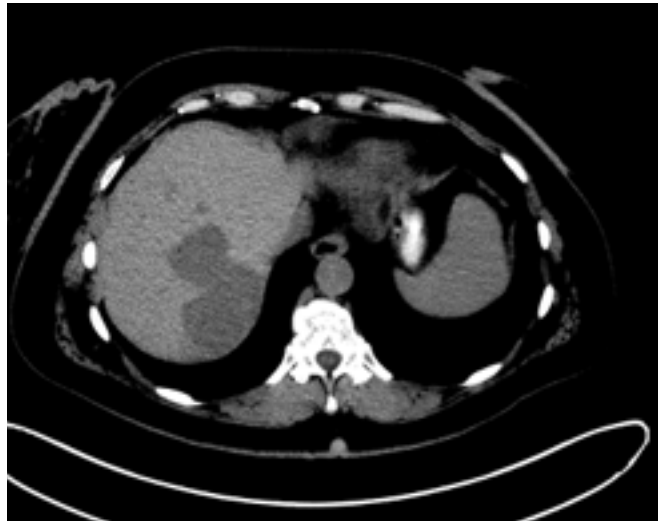
- 5.5 X 4.5 cm low grade colonic adenocarcinoma w serosal penetration
- Lymphovascular invasion present
- Perineural invasion indeterminate
- 5/12 nodes involved
- Margins clear

Mutational analysis:

- BRAF WT
- KRAS WT
- NRAS WT
- Microsatellite instability negative by PCR



- CT Chest: Tiny pulmonary nodules
- PET: Hypermetabolic abdominal adenopathy
- 3 phase Liver CT: Multiple bilobar liver metastases occupying approximately 2/3 hepatic parenchyma





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INTERVENTIONAL RADIOLOGY PERSPECTIVE

Beau Toskitch, M.D.

**Assistant Professor
Division of Interventional Radiology
The Mayo Clinic, Jacksonville**



Ablation for mCRC



O – 018

Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomised phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC)

T. Ruers¹, C.J.A. Punt², F. van Coevorden¹, J.-P. Pierie³, I. Borel Rinkes⁴, J. Ledermann⁵, G. Poston⁶, W. Bechstein⁷, M.-A. Lentz⁸, M. Mauer⁸, E. Van Cutsem⁹, M. Lutz¹⁰, B. Nordlinger¹¹

- **Phase II study, only of its kind:**
- **119** Patients randomized to CT (FOLFOX *plus* Avastin from 2005) vs CT + RFA for up to 9 lesions
- Conversion to resection 11% vs 45%
- *Median OS was mos 40.5 vs 45.6 mos (p .010)*
- **8 year OS was 8.9% vs 35.9% (p .010)**
- **8 year PFS was 2% vs 22% (p .005)**
- *...likely never to be repeated*



Eur J Cancer. 2014 Mar;50(5):912-9. doi: 10.1016/j.ejca.2013.12.008. Epub 2014 Jan 7.

Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983.

Tanis E¹, Nordlinger B², Mauer M³, Sorbye H⁴, van Coevorden F⁵, Gruenberger T⁶, Schlag PM⁷, Punt CJ⁸, Ledermann J⁹, Ruers TJ⁵.

Author information

Abstract

AIM: The aim of this study is to describe local tumour control after radiofrequency ablation (RFA) and surgical resection (RES) of colorectal liver metastases (CLM) in two independent European Organisations for Research and Treatment of Cancer (EORTC) studies.

BACKGROUND: Only 10-20% of patients with newly diagnosed CLM are eligible for curative RES. RFA has found a place in daily practice for unresectable CLM. There are no prospective trials comparing RFA to RES for resectable CLM.

METHODS: The CLOCC trial randomised 119 patients with unresectable CLM between RFA (\pm RES)+adjuvant FOLFOX (\pm bevacizumab) versus FOLFOX (\pm bevacizumab) alone. The EPOC trial randomised 364 patients with resectable CLM between RES \pm perioperative FOLFOX. We describe the local control of resected patients with lesions \leq 4 cm in the perioperative chemotherapy arm of the EPOC trial (N=81) and the RFA arm of the CLOCC trial (N=55).

RESULTS: Local recurrence (LR) rate for RES was 7.4% per patient and 5.5% per lesion. LR rate for RFA was 14.5% per patient and 6.0% per lesion. When lesion size was limited to 30 mm, LR rate for RFA lesions was 2.9% per lesion. Non-local hepatic recurrences were more often observed in RFA patients than in RES patients, 30.9% and 22.3% respectively. Patients receiving RFA had a more advanced disease.

CONCLUSIONS: LR rate after RFA for lesions with a limited size is low. The local control per lesion does not appear to differ greatly between RFA and surgical resection. This study supports the local control of RFA in patients with limited liver metastases. Future studies should evaluate in which patients RFA could be an equal alternative to liver resection.

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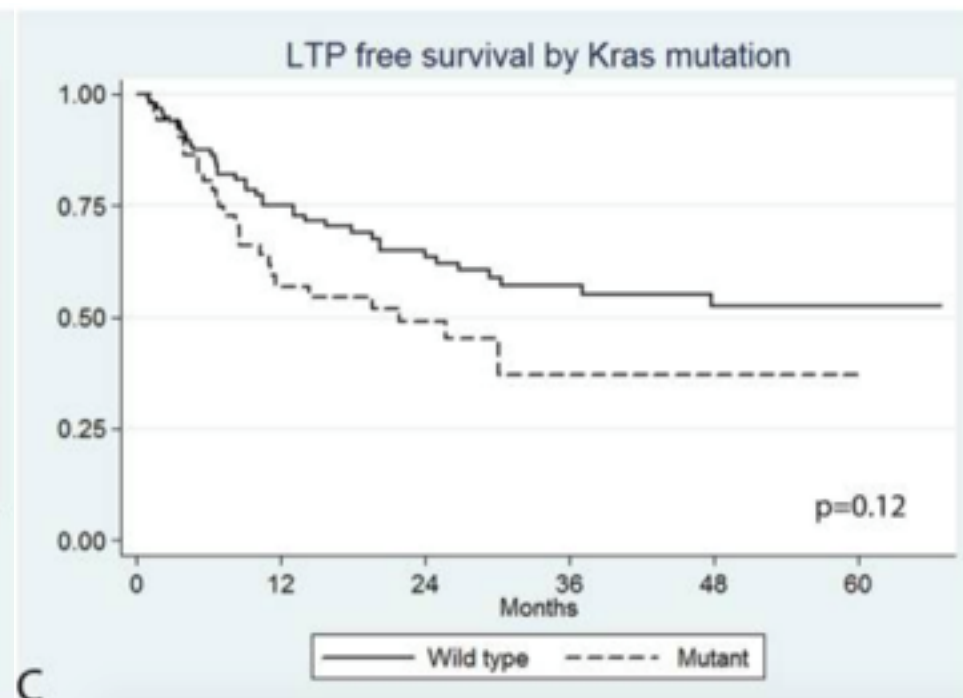
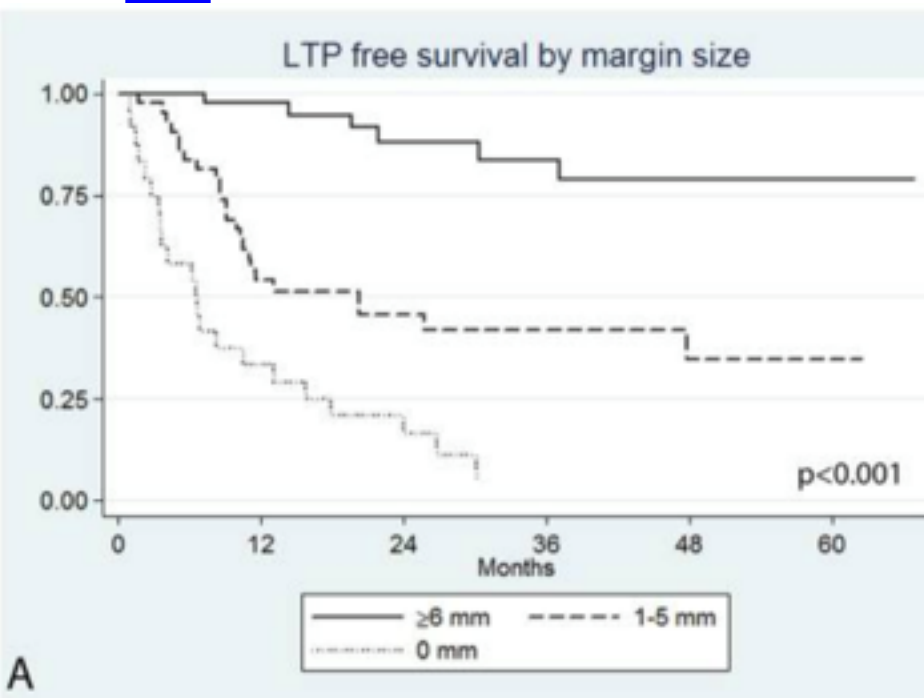
... local control per lesion did not differ greatly between RFA and surgical resection.

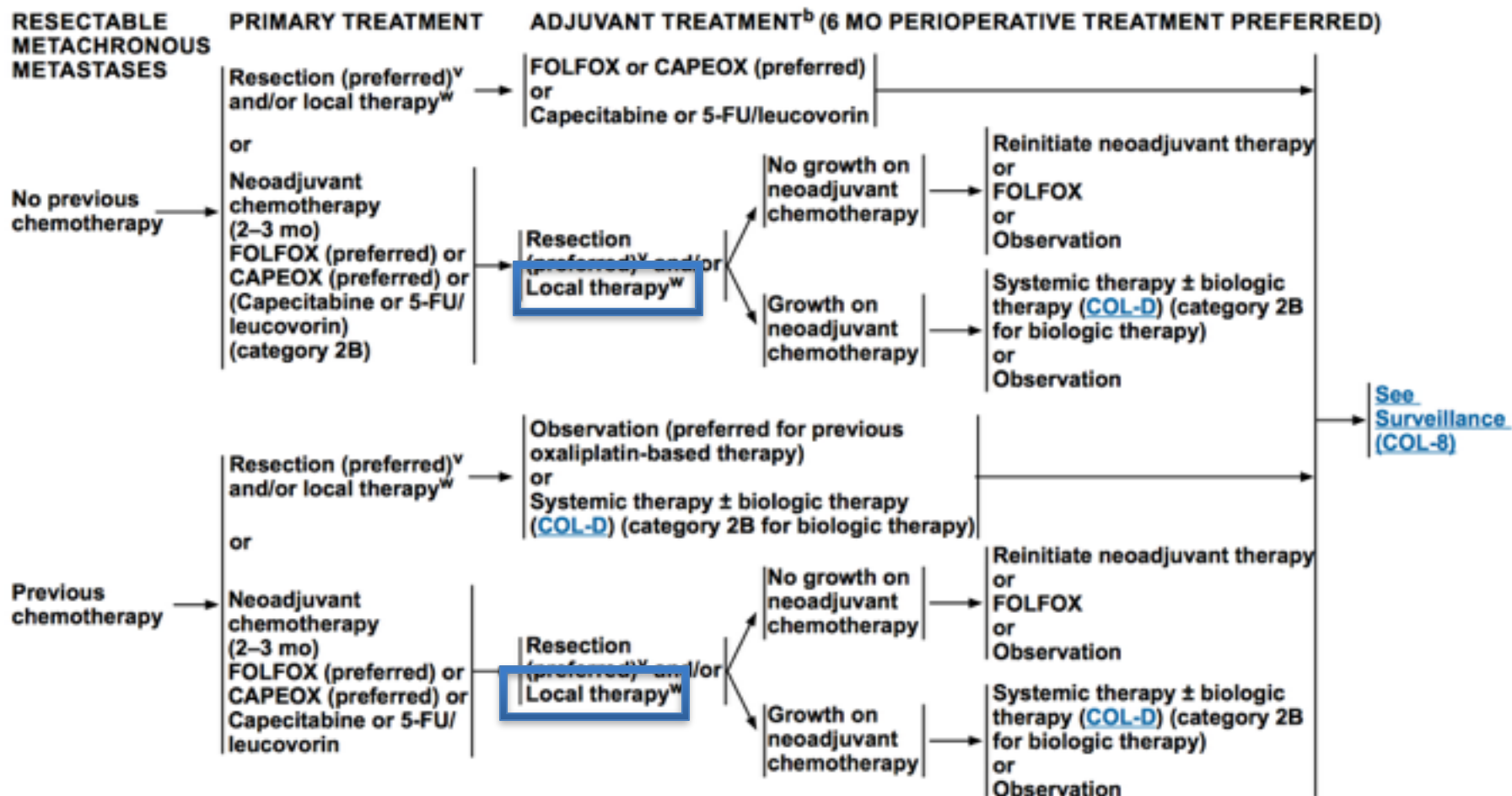


Oncotarget. 2017 Aug 2;8(39):66117-66127. doi: 10.18632/oncotarget.19806. eCollection 2017 Sep 12.

Kras mutation is a marker of worse oncologic outcomes after percutaneous radiofrequency ablation of colorectal liver metastases.

Shady W¹, Petre EN¹, Vakiani E², Ziv E¹, Gonen M³, Brown KT¹, Kemeny NE⁴, Solomon SB¹, Solit DB⁴, Sofocleous CT¹.





^bSee Principles of Imaging (COL-A).

^vHepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

^wResection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).





Ablation is a well tolerated, curative intent, therapy when applied to the *correct candidate* for many malignancies

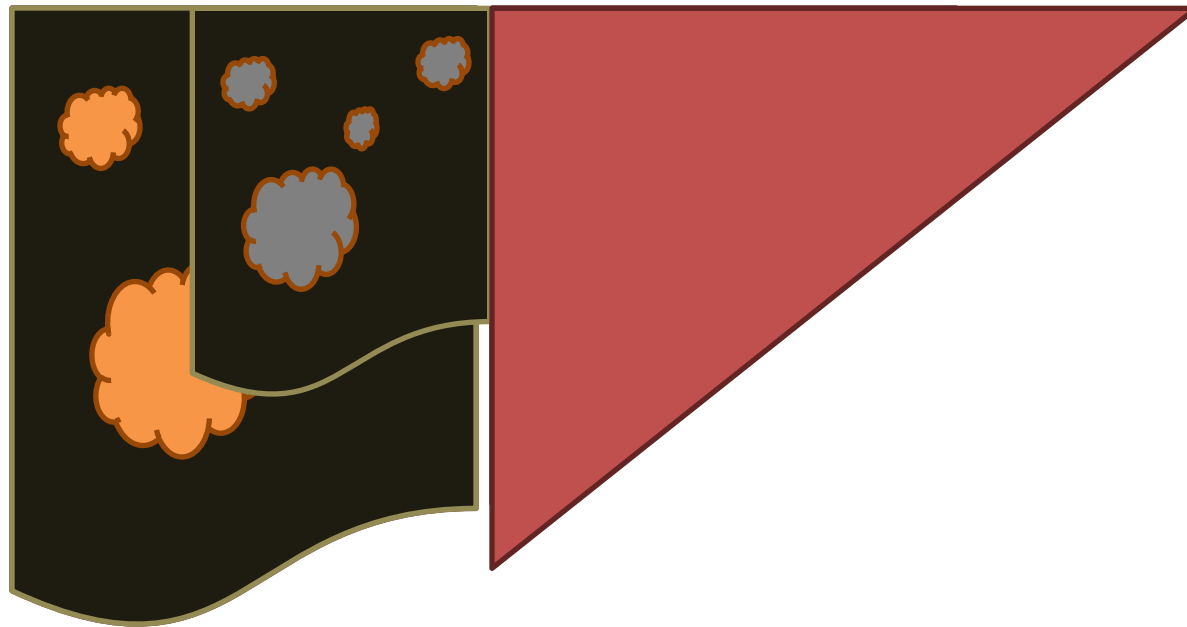


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Neoadjuvant Ablative Radioembolization



Neoadjuvant “Radiation Lobectomy”



Neoadjuvant transarterial radiation lobectomy for colorectal hepatic metastases: a small cohort analysis on safety, efficacy, and radiopathologic correlation.

Shah JL¹, Zendejas-Ruiz IR², Thornton LM¹, Geller BS¹, Grajo JR¹, Collinsworth A³, George TJ Jr⁴, Toskich B^{1,5}.

- Synchronous mCRC
- Neoadjuvant RL with doses ranging from
- 50-392 Gy (3 glass, 1 resin)
- No systemic therapy toxicity or > G1 CTCAE AW
- Right hepatectomy from 2.5 to 9 months post RL
- 50% CPN
- No postoperative liver failure in cohort



Synchronous presentation:
51 y/o female with sigmoid junction primary and 10
cm
hepatic mass

Right hepatic lobe radiation lobectomy with concurrent FOLFOX / dBev



May 16 CEA = 154.4

Path report:

“Extended right lobectomy:

- Liver with necrotic nodules, 5.2cm and 2.4cm.***
- No viable tumor is seen.***
- Background liver with no significant steatosis or fibrosis.”***



July 7 CEA = 1.8

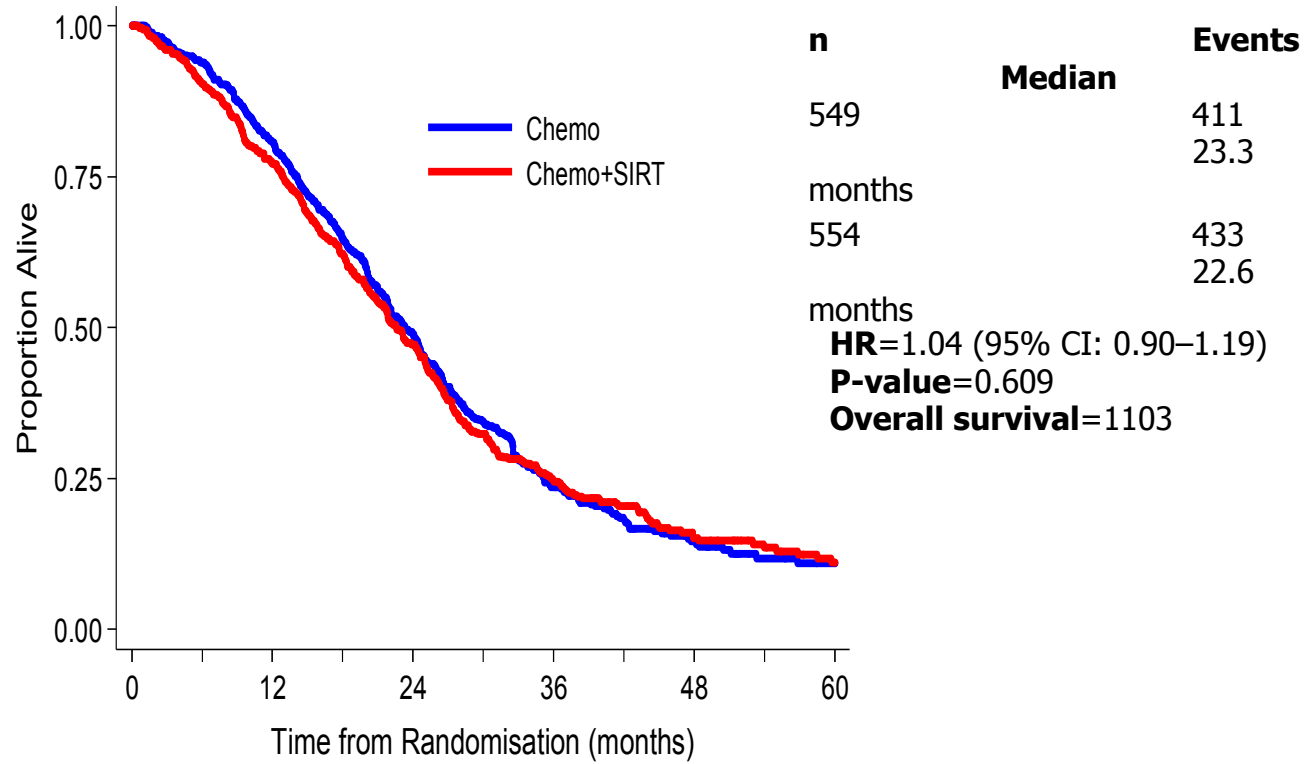


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Palliative radioembolization for mCRC



SIRFLOX, FOXFIRE, and FOXFIRE-Global Combined Analysis: Response (Per Protocol Population)



No. at Risk		0	12	24	36	48	60
Chemo	549	419	242	88	33	12	
Chemo+SIRT	554	417	247	91	35	17	

PRINCIPLES OF SURGERY

CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.⁶
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.⁷
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.⁸⁻¹¹ Having a plan for a debulking resection (less than an R0 resection) is not recommended.⁷
- Patients with resectable metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.¹²
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization¹³ or staged liver resection¹⁴ can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to

- 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.

Conformal external beam radiation therapy may be considered 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

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.¹⁶⁻¹⁹
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.²⁰⁻²³
- Re-resection can be considered in selected patients.²⁴
- Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to ablation or resection.
- Ablative techniques can also be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered 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.

Evaluation for Conversion to Resectable Disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.²⁵⁻²⁸
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.²⁹
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.³⁰



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SIRT Salvage Options

Author	N	Treatment	ORR, %	SD%	‡TTP or †PFS, mo	Survival, mo
Hendlisz ¹ Level 1	44	Resin microspheres* + 5-FU 5-FU (Resin microspheres* @PD)	10 0 (P=.22)	76 35 (P=.001)	5.5‡/4.5 2.1 (HR: 0.38‡/0.51, P=.003‡/. 03)	10 7.3
Seidensticker ² Level 3	29	Resin microspheres* BSC (matched-pairs)	41 NR	17 NR	5.5 [†] 2.1 [†]	8.3 3.5 (HR: 0.26, P<.001)
Cosimelli ³ Level 2	50	Resin microspheres*	24	24	4 [†]	12.6

Systematic Salvage Options

Author	N	Treatment	ORR, %	SD%	‡TTP or †PFS, mo	Survival, mo
Grothey ⁴ Level 1	505 255	Regorafenib BSC	1 0.4	41 15	1.9 1.7 (HR:0.49, P<0.001)	6.4 5 (HR: 0.77, P.0052)
Mayer ⁵ Level 1	534 266	TAS-102 BSC	1.6 0.4	44 16	2.0 1.7 (HR: 0.48, P<0.001)	7.1 5.3 (HR: 0.77, P.0052)

*Y-90 resin microspheres cross-over was allowed upon progression;
 †PFS, Progression free survival;
 ‡TTP liver;
 §retrospective data.

PD=progressive disease;
SD=stable disease;
ORR=objective response rate;
TTP=time to progression

1. Hendlisz A et al. J Clin Oncol. 2010;28(23):3687-3694. 2. Seidensticker R et al. Cardiovasc Intervent Radiol. 2012;35(5):1066-1073. 3. Cosimelli M et al. Br J Cancer. 2010;103(3):324-331.
 4. Grothey et al. Lancet. 2013;381:303-312. 5. Mayer et al. NEJM. 2015;372:1914-1919.



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Thank You