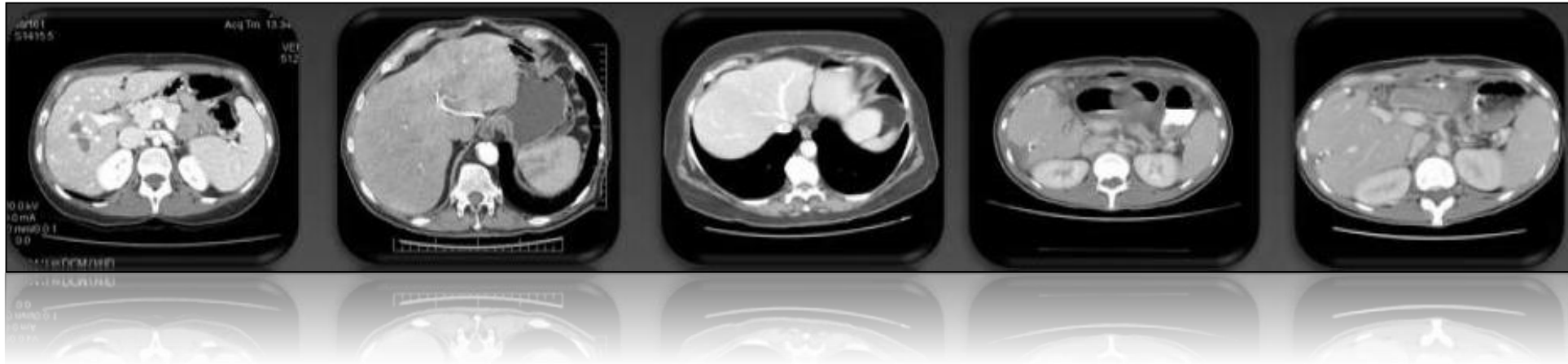


Oncologic & Technical Considerations with Stage IV Liver Disease *Sequencing & Synchrony*



Sean Cleary

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Case Presentation

- 63 yo female investigated for mild constipation and abdominal discomfort
 - Marked circumferential wall thickening of the recto- sigmoid colon
 - Transmural invasion (T3)
 - “innumerable bilateral liver metastases”
- Biopsy: Mod Diff AdenoCa
Kras mut+ Braf wt



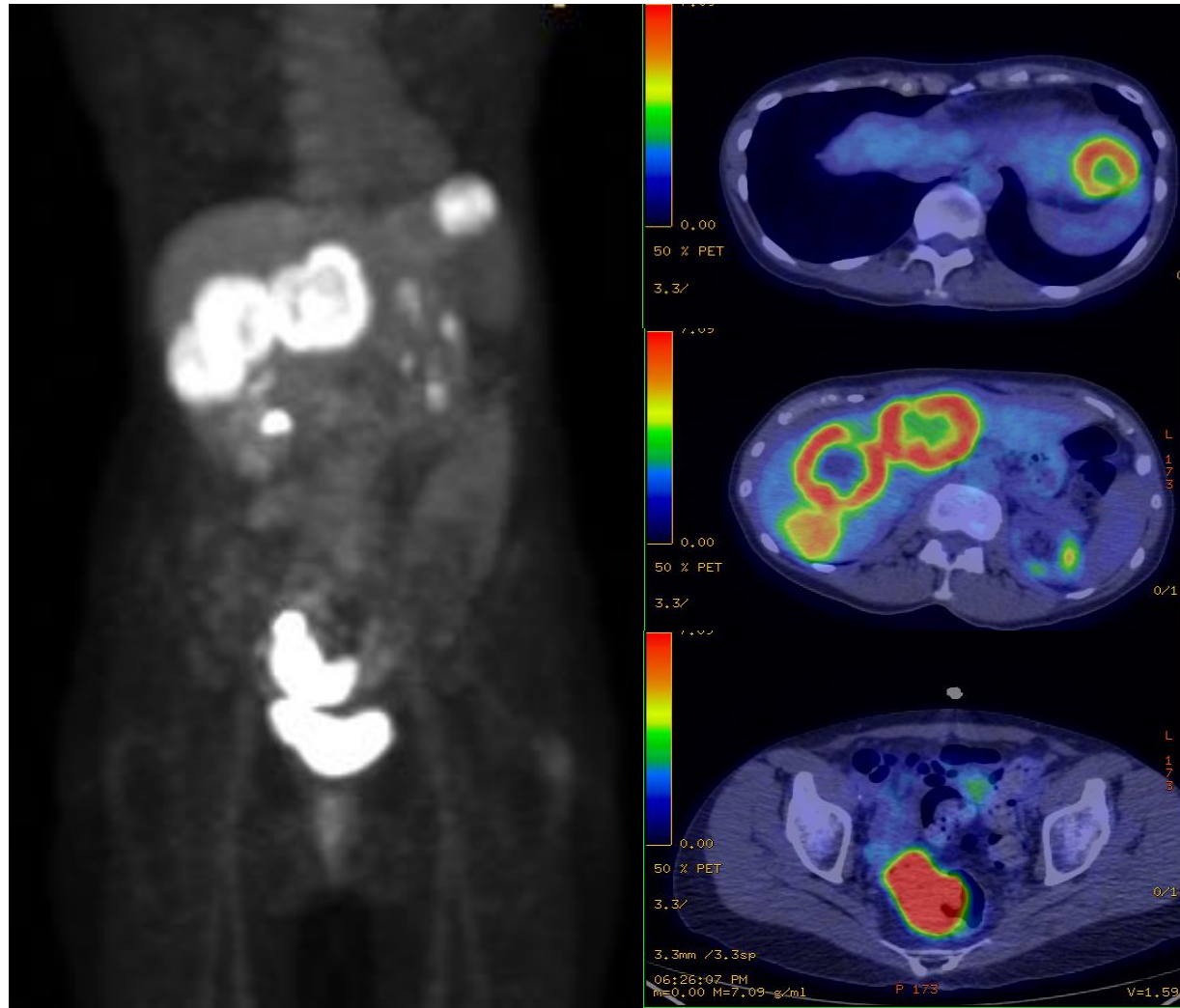












Clinical Options

1. Resect the rectal lesion, start systemic chemotherapy
2. Resect the rectal lesion, resect the liver lesions, start chemotherapy
3. Chemoradiotherapy, resect rectal lesion, systemic chemotherapy, resect liver lesions
4. Systemic chemotherapy, resect liver and rectal lesions, complete systemic chemotherapy

Liver metastases in colorectal cancer

CRC-LM develop in ~ 30% of patients

50% synchronous

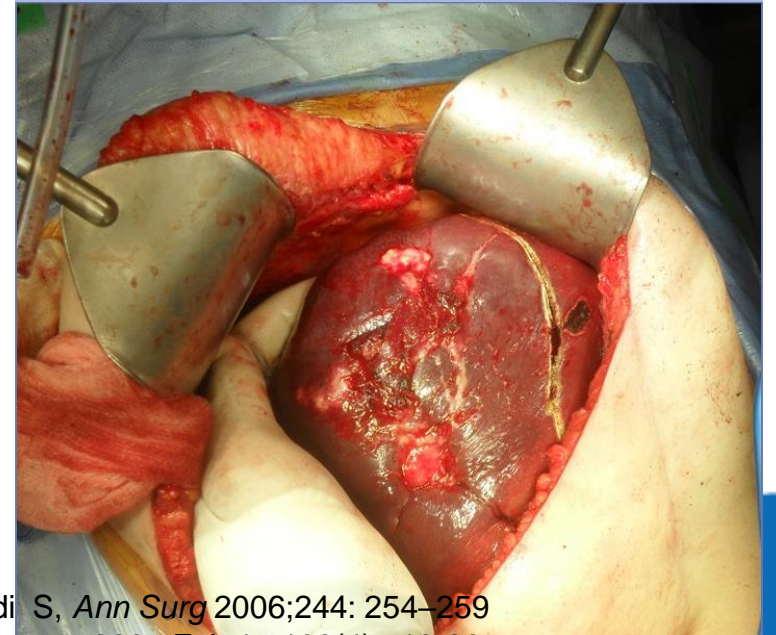
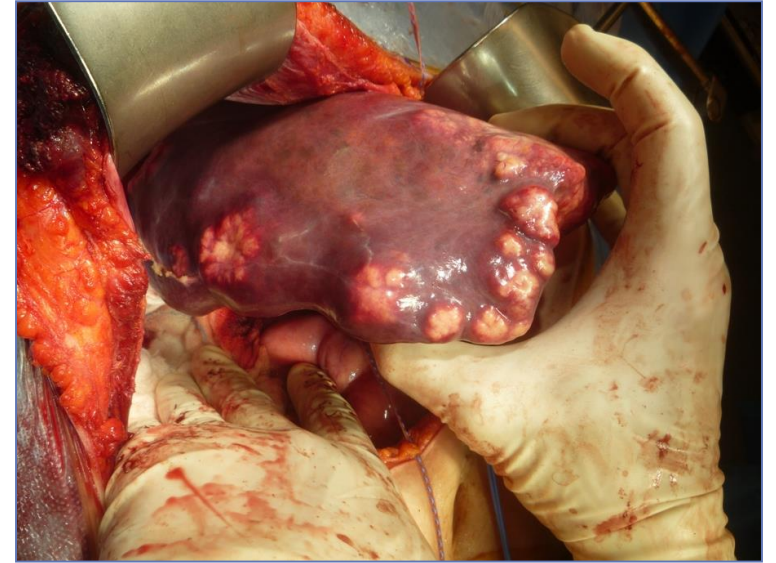
higher risk in Stage III disease (OR 8.3)

Best treatment is multi-modal

surgery + chemotherapy

< 5-10% 5-year OS if untreated^{1,2}

Surgery remains underutilized



Resectability

The Past

By What Comes Out

Now

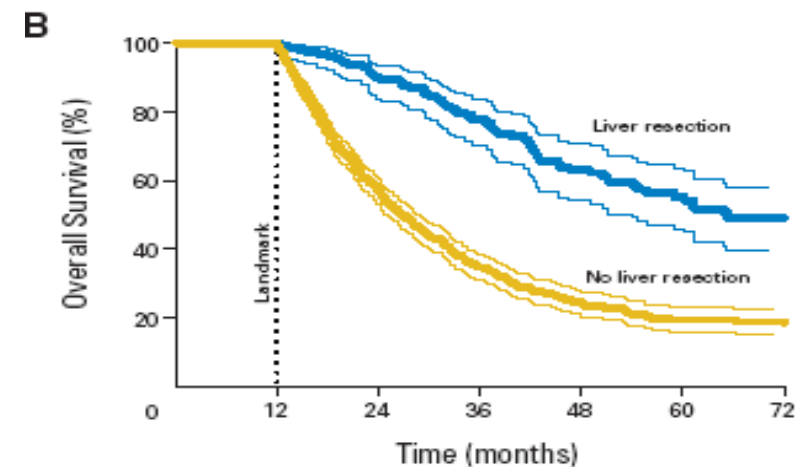
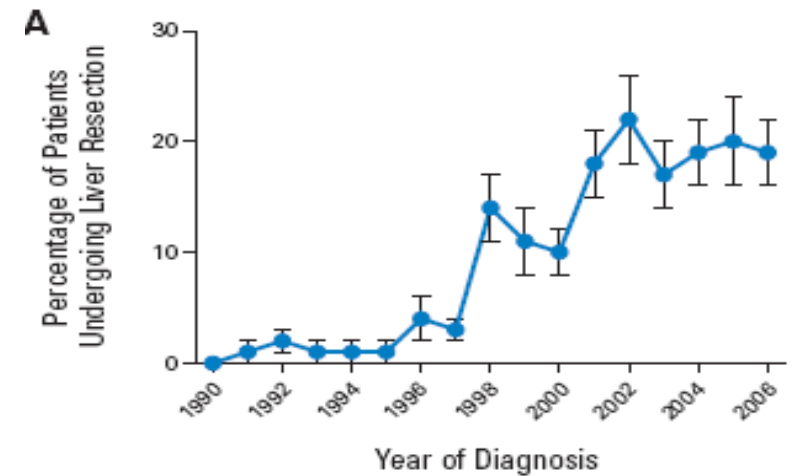
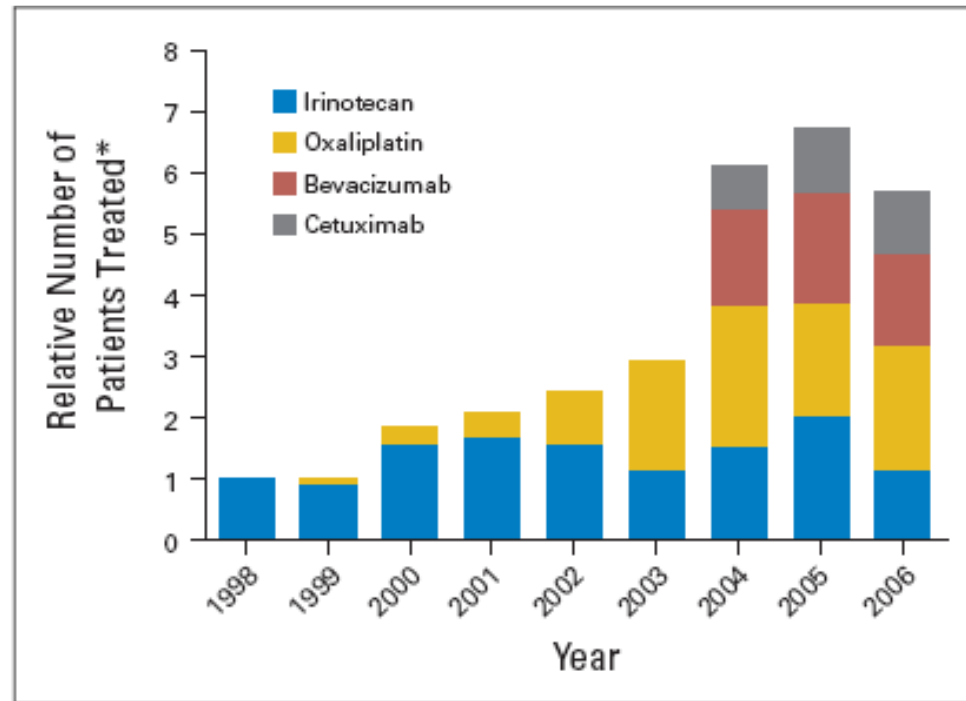
By What Stays In

AHPBA/SSO/SSAT Consensus criteria for resectability ²

<i>Disease characteristics</i>	<i>Liver characteristics</i>	<i>Extra-hepatic disease</i>
Any number	R0 margin anticipated	Lung Mets
Any size	Liver parenchyma >20-30%	? Lymph nodes?
Any TNM	Maintain vascular supply	? Other sites
Any CEA	Preserve biliary outflow	

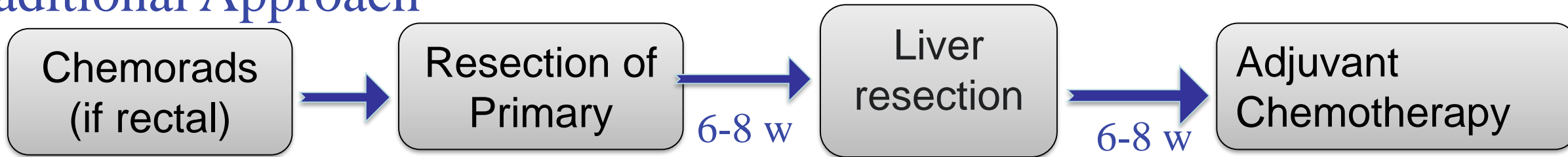
Improved Survival in Metastatic Colorectal Cancer Is Associated With Adoption of Hepatic Resection and Improved Chemotherapy

Scott Kopetz, George J. Chang, Michael J. Overman, Cathy Eng, Daniel J. Sargent, David W. Larson, Axel Grothey, Jean-Nicolas Vauthey, David M. Nagorney, and Robert R. McWilliams

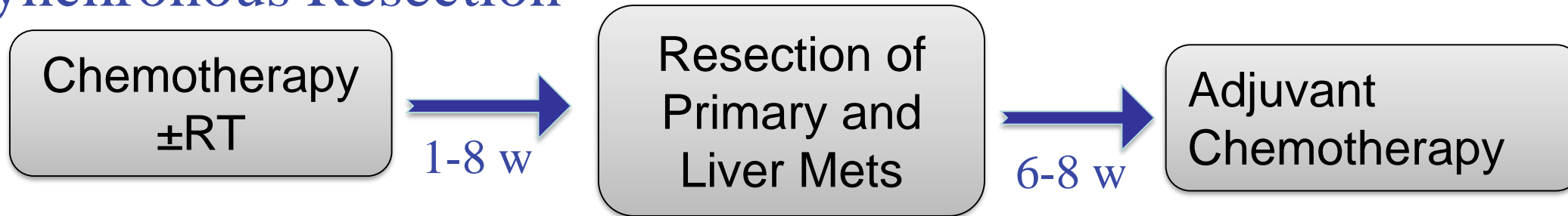


Timing of surgery and chemotherapy

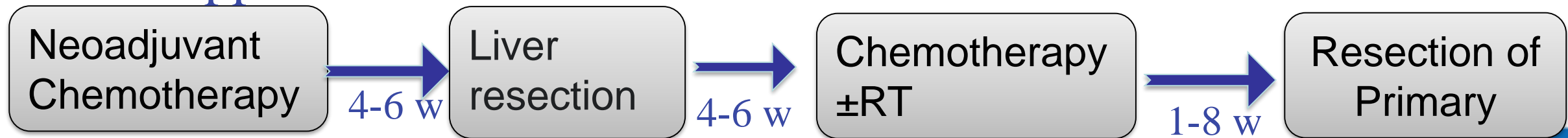
Traditional Approach



Synchronous Resection



Reverse Approach



Timing of Resection and Chemotherapy

- Traditional Approach
 - Surgery First
 - Chemotherapy (Pseudoadjuvant)
- Perioperative Approach
 - 4-6 cycles of chemotherapy
 - Liver resection
 - Completion of chemotherapy



Traditional (surgery first) approach

- **Advantages**
 - Early resection of primary
 - Eliminates bleeding, obstruction
 - Removes source of metastases
 - Plan liver surgery on original size/location
- **Disadvantages**
 - Significant delay (>3months) in Systemic chemotherapy
 - Primary symptoms are uncommon
 - Complications may cause future delays
 - Liver mets may progress
 - Less likely if chemo rads includes oxaliplatin
 - Less appealing for advanced LM



ChemoRT
(if rectal)

Resection of
Primary

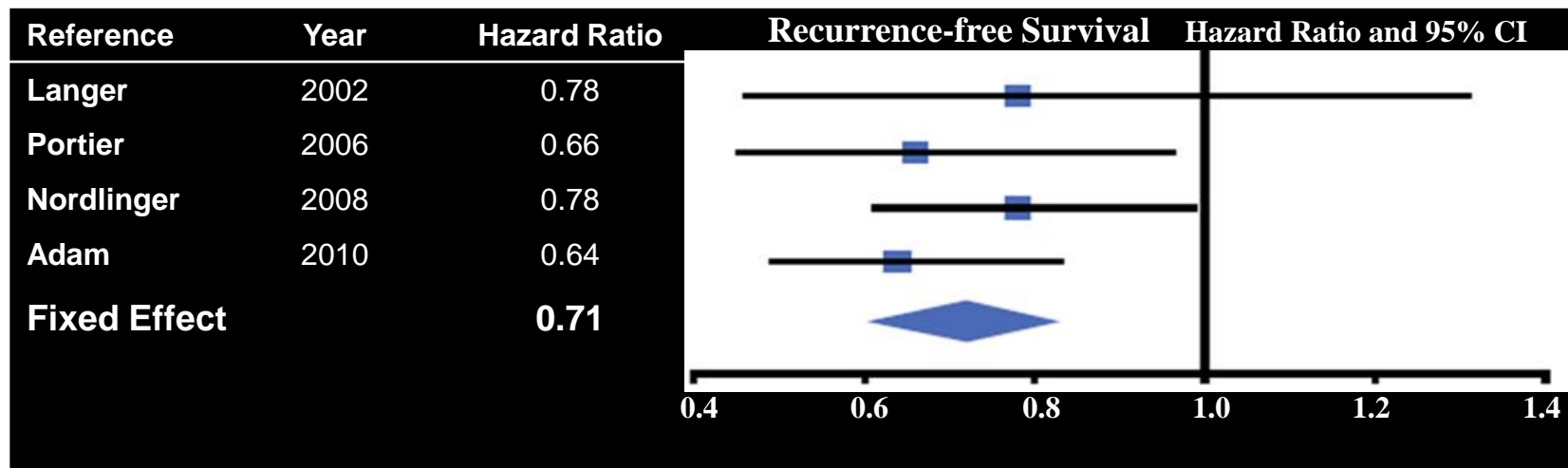
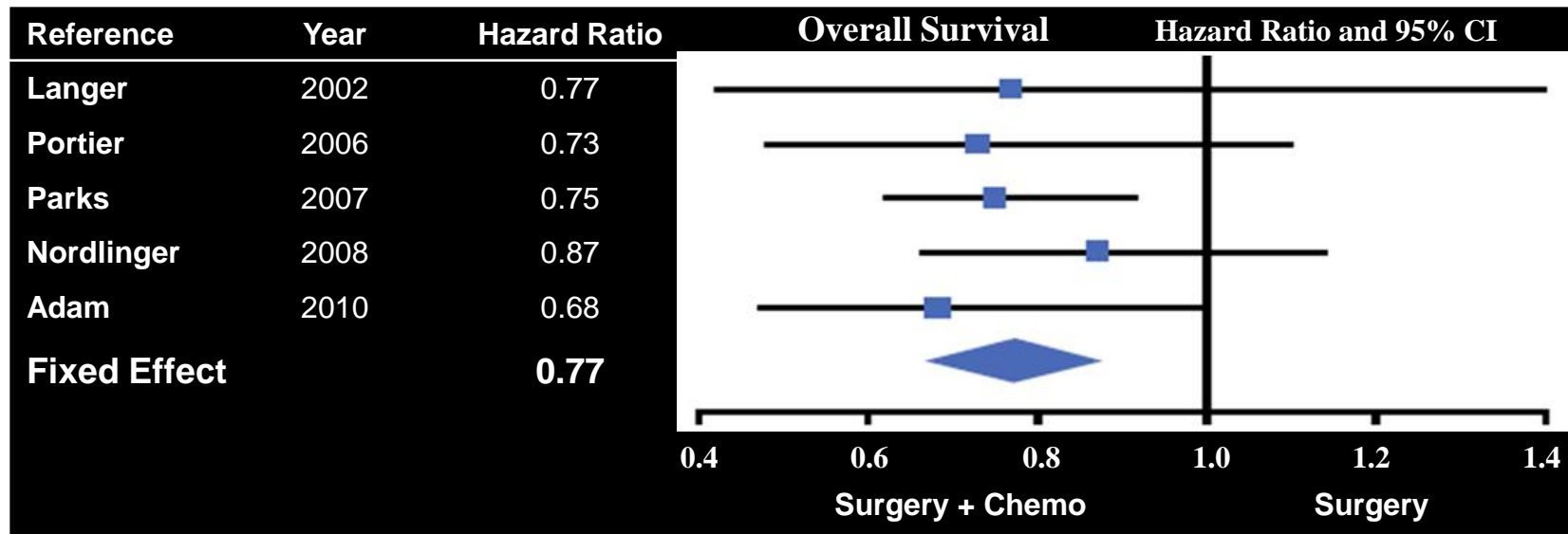
6-8 w

Liver
resection

6-8 w

Adjuvant
Chemotherapy

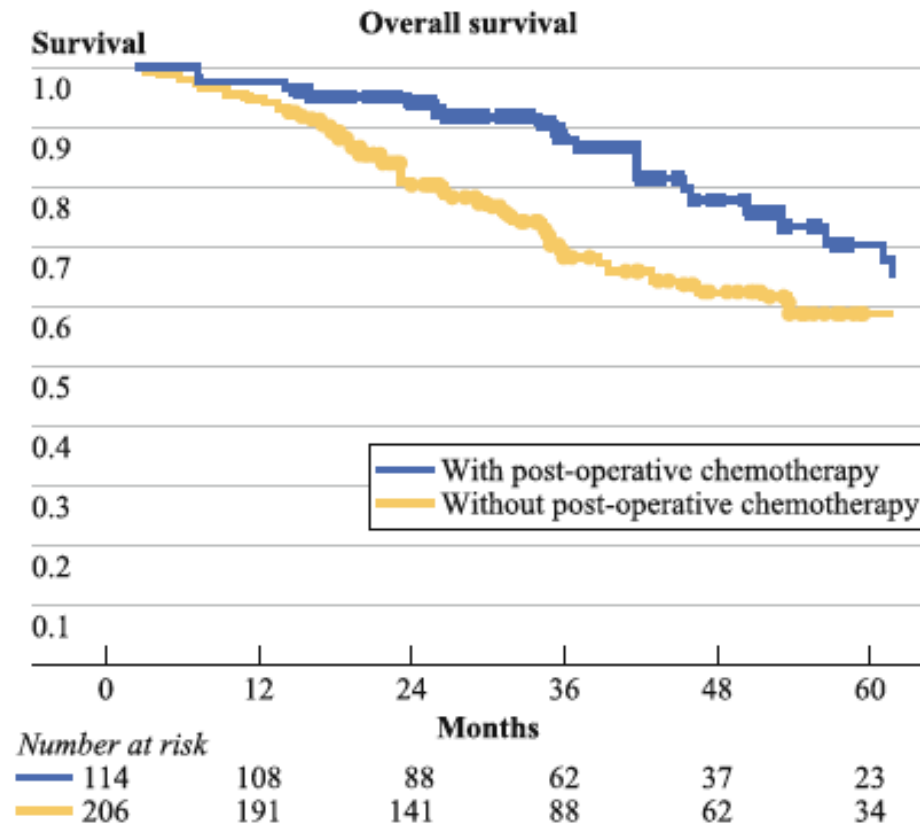
Chemotherapy post Liver Rx (pseudo-adj)



Up-front Hepatic Resection for Metastatic Colorectal Cancer Results in Favorable Long-term Survival

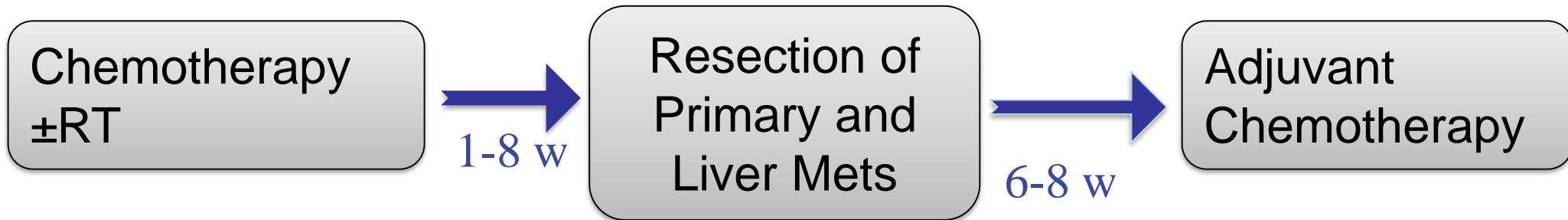
Sulaiman Nanji, MD, PhD¹, Sean Cleary, MD, MSc², Paul Ryan, MD³, Maha Guindi, MD⁴, Subani Selvarajah, MD², Paul Grieg, MD², Ian McGilvary, MD, PhD², Bryce Taylor, MD², Alice Wei, MD, MSc², Carol-Anne Moulton, MD, PhD², and Steven Gallinger, MD, MSc²

- 320 pts (2002-07)
- 40% synchronous
- 114 (35%) had chemo after Liver Rx
- Disease-Free Survival
 - 3yr: 46%; 5yr: 42%
- Overall Survival
 - 3yr: 64%; 5yr: 55%
- Predictors of OS
 - Synchronous mets
 - Size of largest lesion
 - LN +ve primary
 - Post-op chemotherapy
 - HR=0.42 (0.23-0.75)



Perioperative Chemotherapy Approach

- 4-6 cycles of chemotherapy prior to liver resection
 - Limit toxicity
- Potential advantages
 - Assess tumour biology
 - Response to chemotherapy
 - Potential downsizing



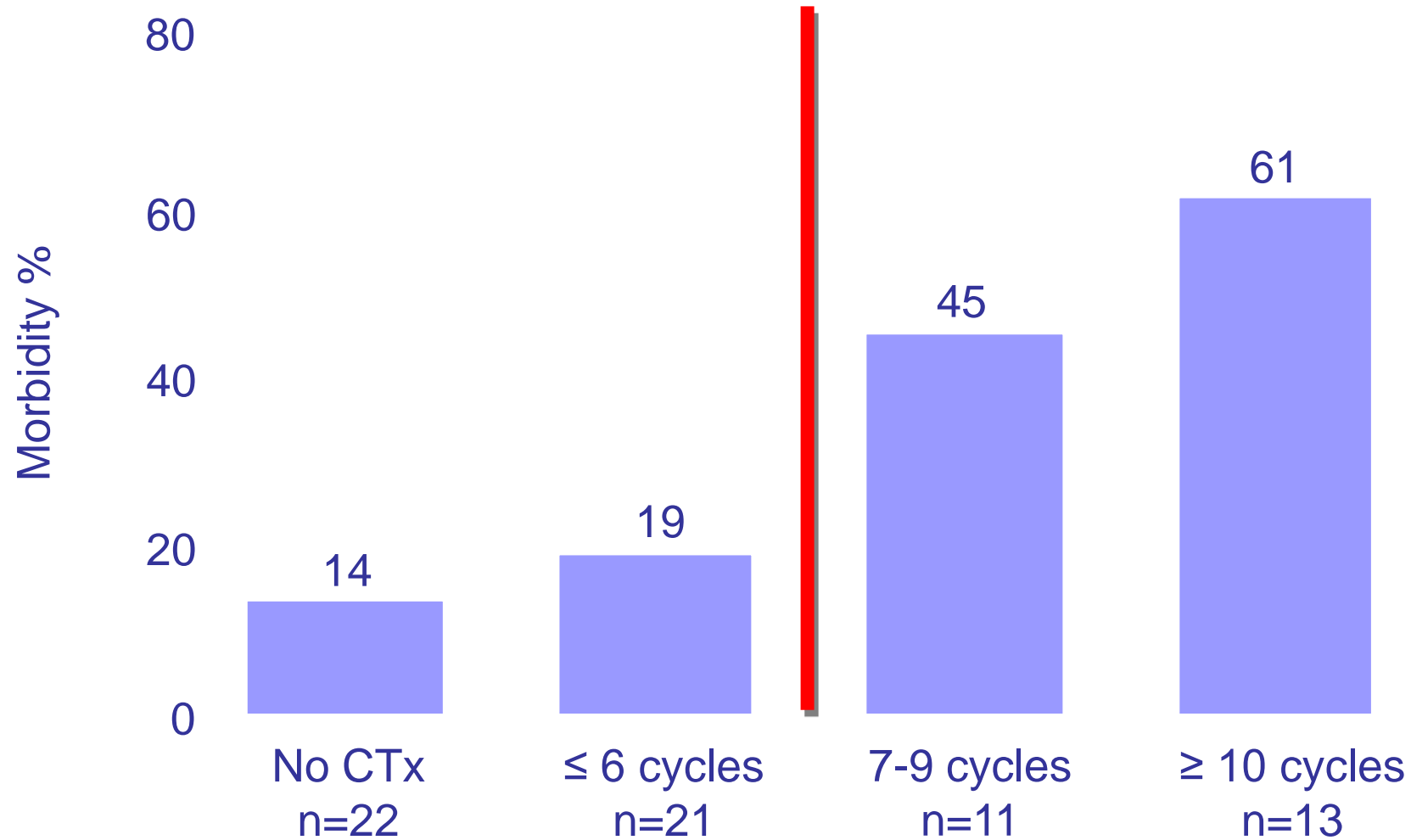
Chemotherapy effects

Irinotecan= Steatohepatitis

Oxaliplatin= Sinusoidal Obstruction



Chemotx Duration and Surgical Morbidity

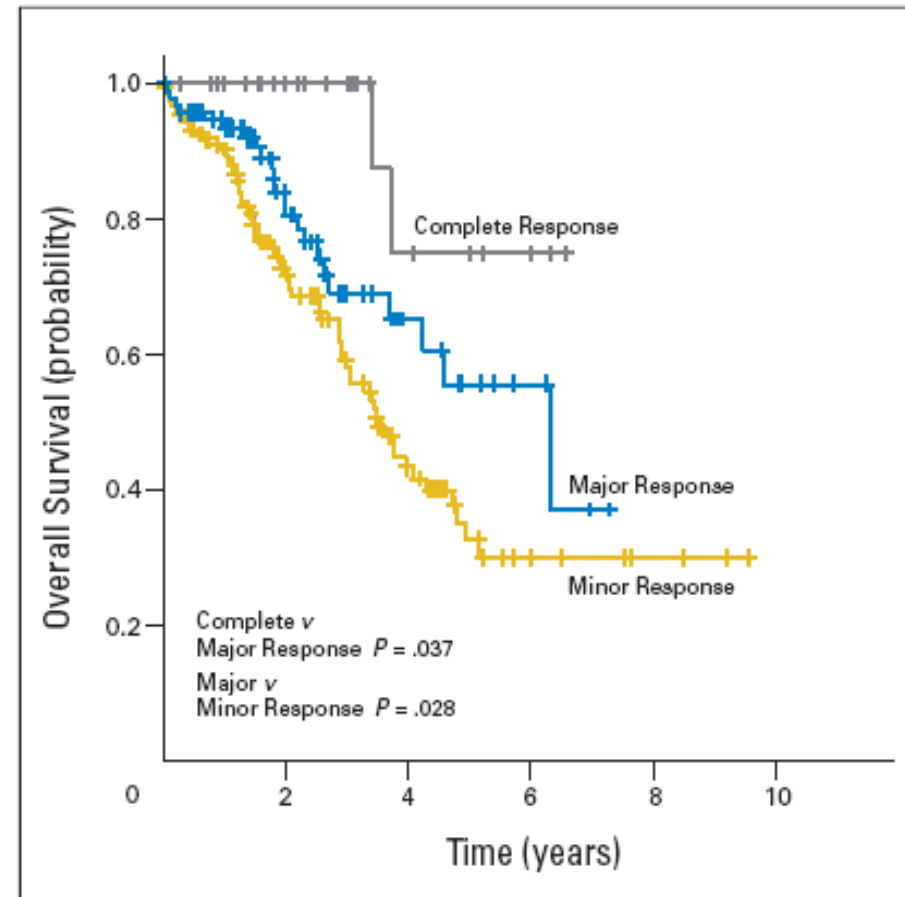
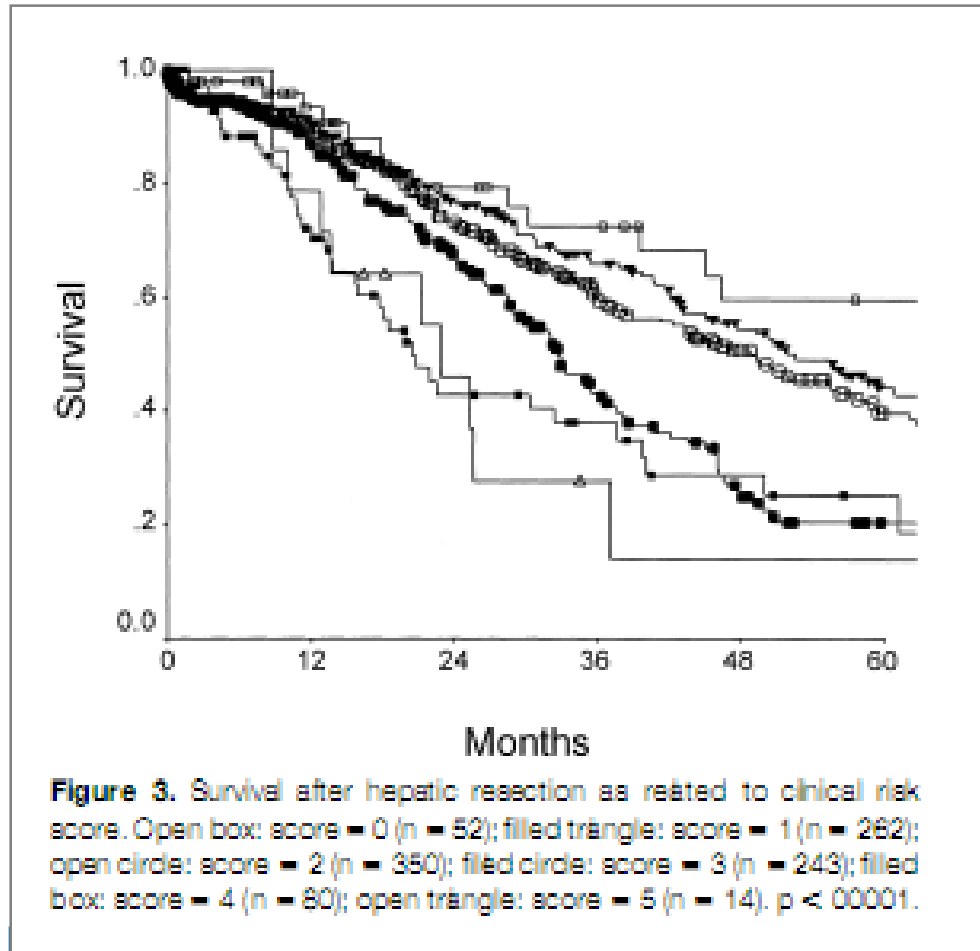


Response to Chemotherapy

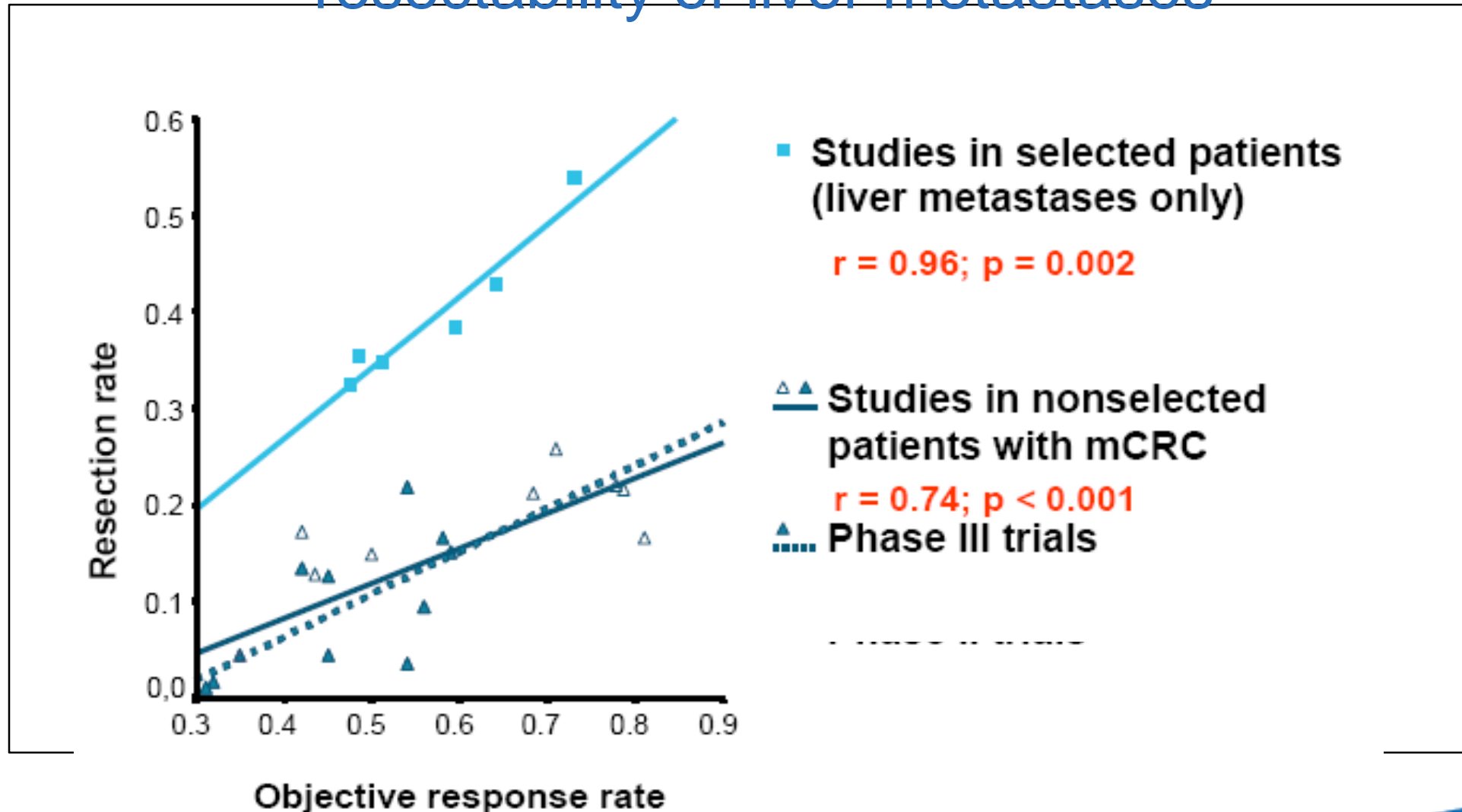
Fong 1999



Blazer, Vauthey 2008



Tumour response to preoperative therapy predicts resectability of liver metastases

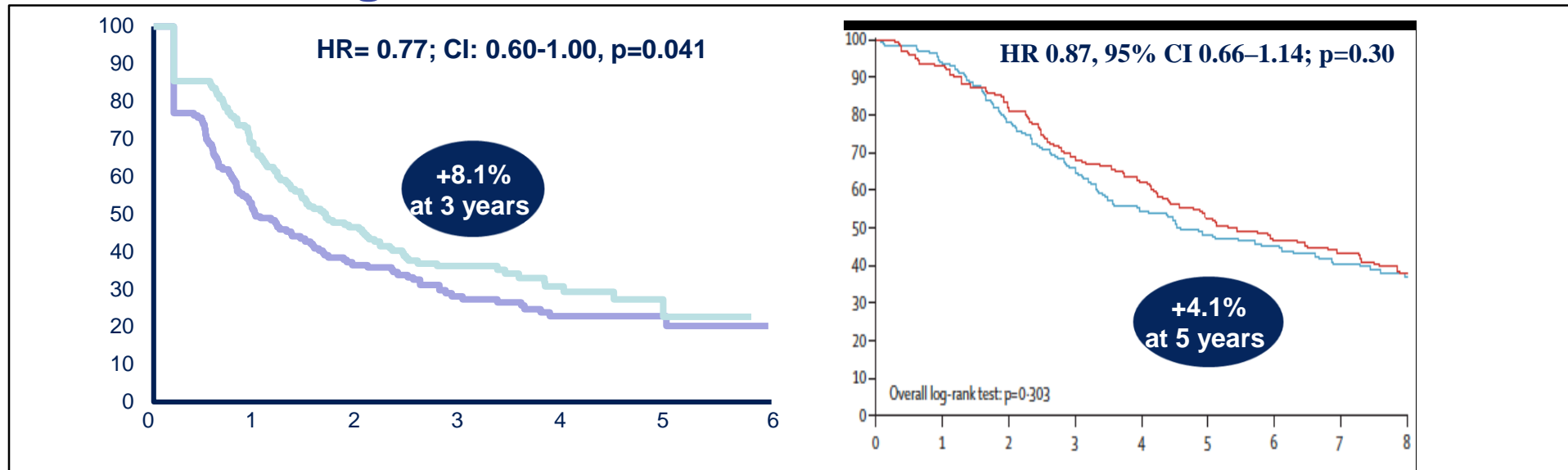


EORTC 40983: EPOC

Patient Population	Primary Endpoint	Secondary Endpoints	Result
mCRC patients with resectable CLM	PFS	OS, Tumour resectability, Tumour response	<p>Perioperative chemotherapy with FOLFOX4 increased PFS vs. surgery alone</p> <p>OS was numerically increased, but not significant</p>

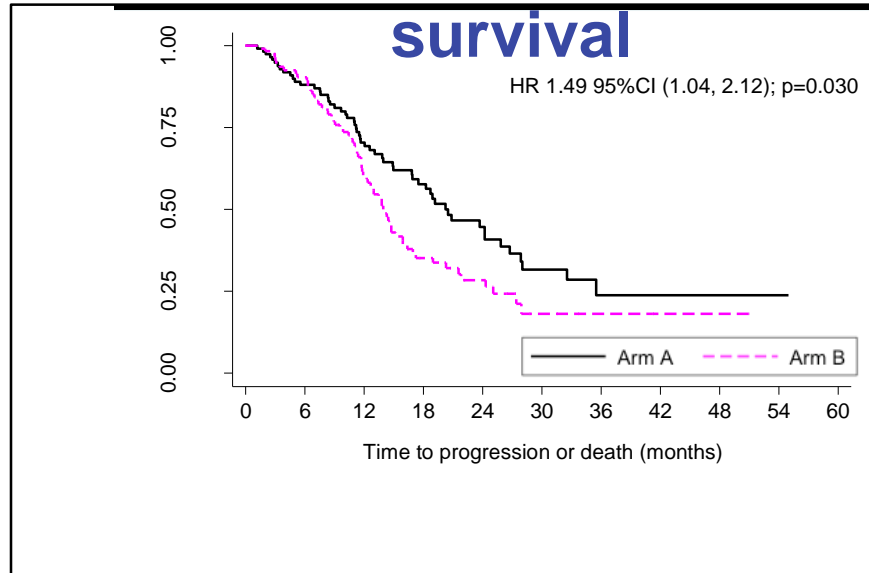
Progression-free survival

Overall survival

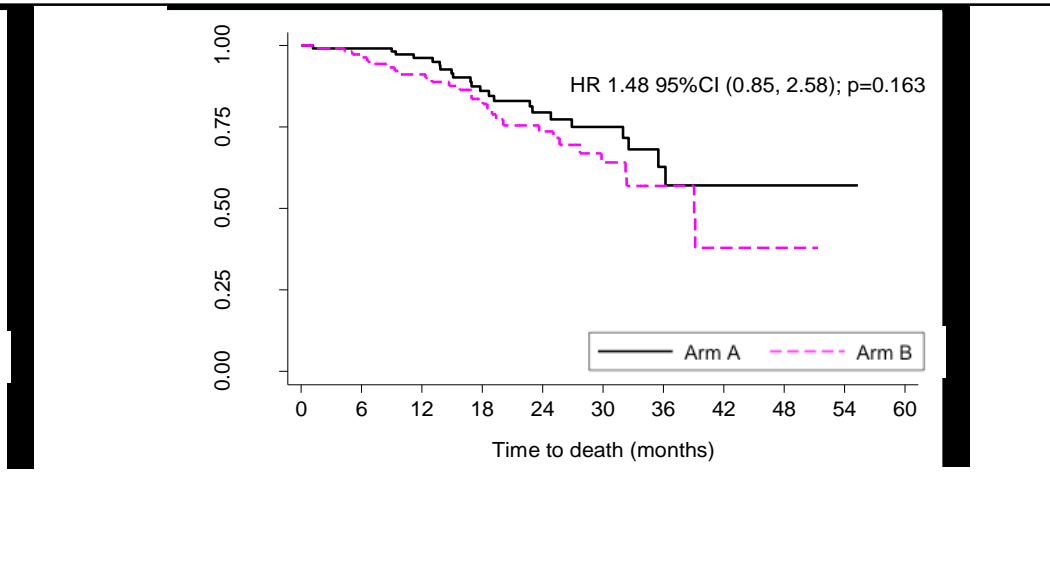


New EPOC: Cetuximab + chemotherapy

Progression-free survival



Overall survival



Arm A = Chemo
Arm B = Chemo + cetuximab

All randomised KRAS wild-type patients.
Median PFS: Arm A vs. Arm B = 20.5 vs. 14.1 months

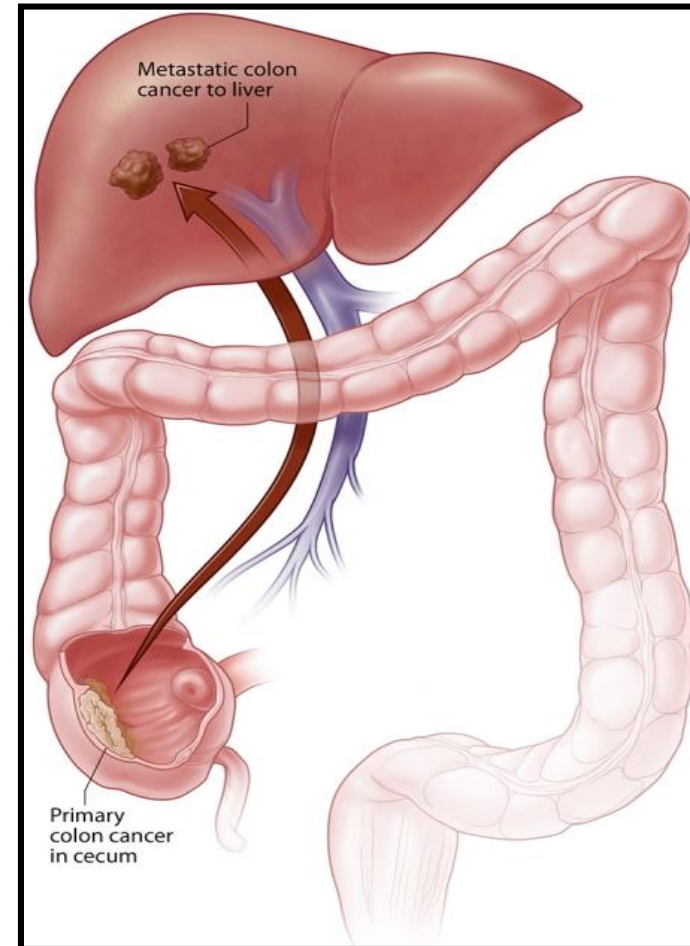
All randomised KRAS wild-type patients.
Median OS: Arm A not reached vs. Arm B = 39.1 months

Addition of cetuximab to FOLFIRI/FOLFOX had significant detriment on survival

in KRAS wild-type patients (PFS = 14.1 months vs. 20.5 months)

Perioperative Approach

- Advantages
 - Early systemic therapy
 - Assess response to chemotherapy
 - Downsizing, improved R0
- Disadvantages
 - Evidence is inconclusive
 - Progression on chemotherapy
 - Management of disappearing lesions



Optimizing Resection in CRC Liver mets

Liver preserving approach

Parenchymal sparing surgery

Maximal FRL

Avoid chemotherapy associated toxicity

Options for future resection

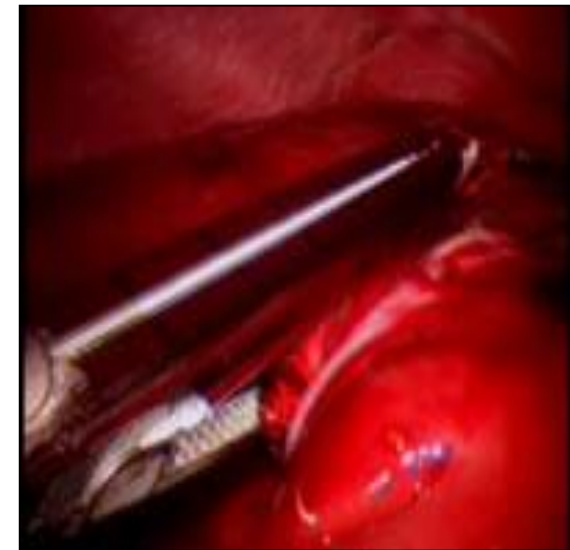


Planned sequential surgery

2-stage liver resections

Modified sequence → liver first approach

ALLPS

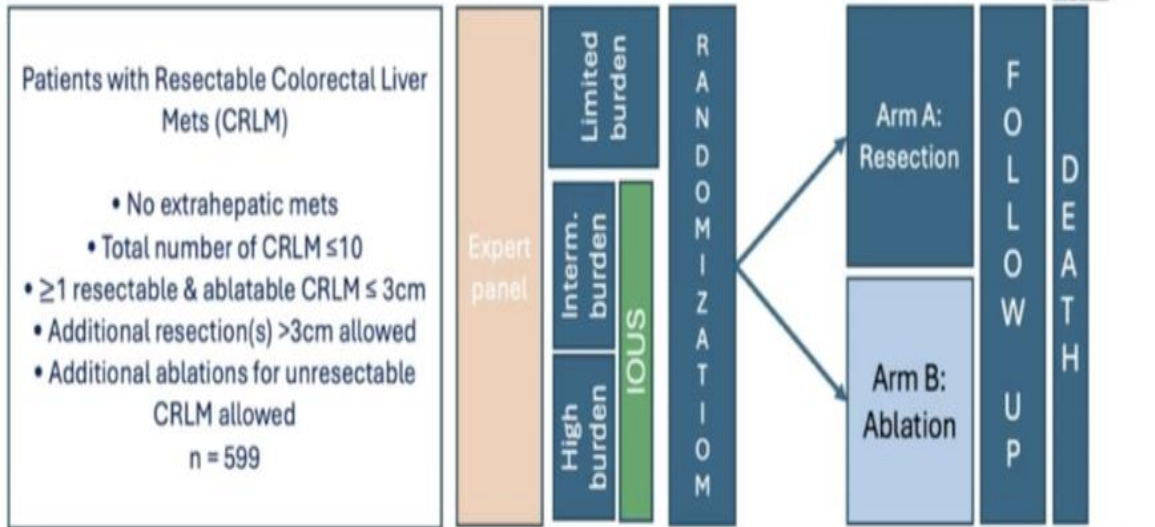


Adjuncts to increase resectability

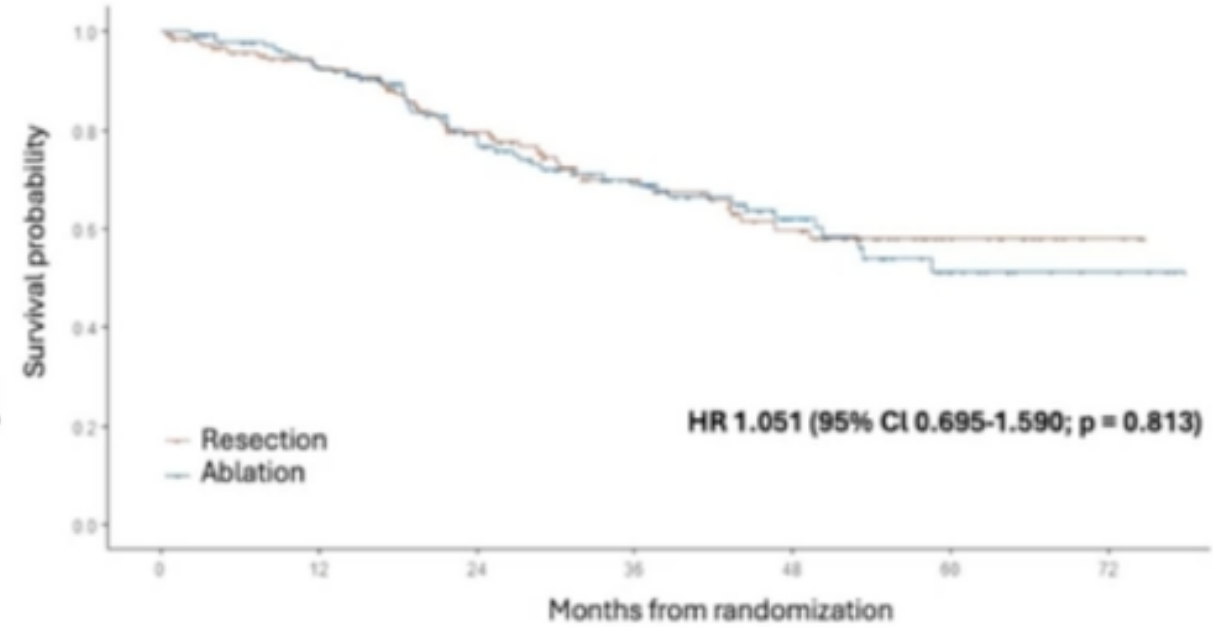
Portal Vein embolization

Ablation

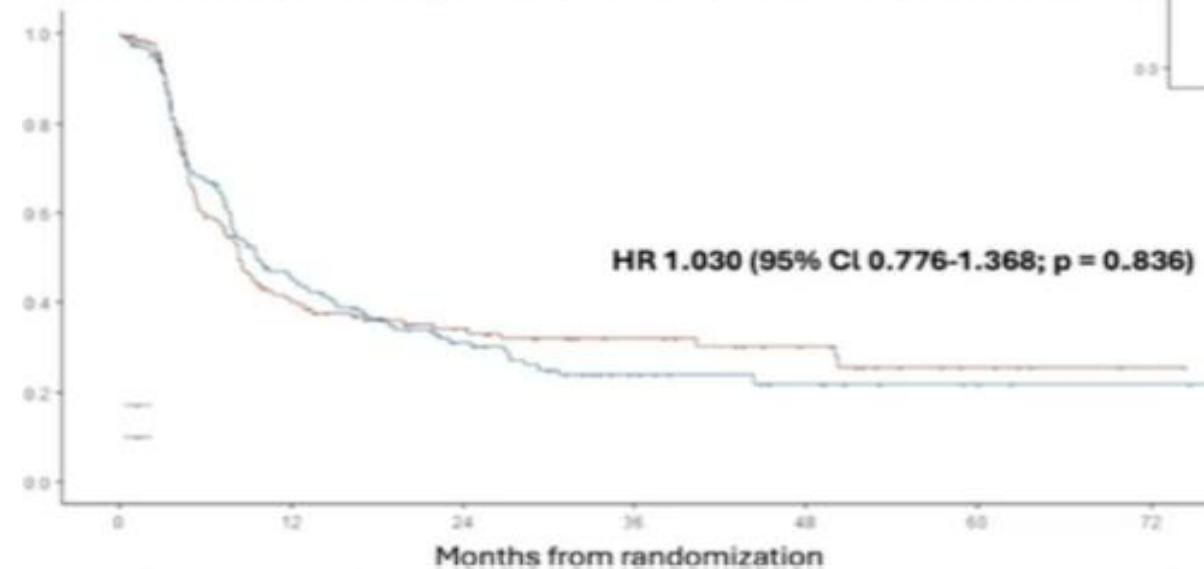
COLLISION: Surgery vs. thermal ablation for small-size colorectal liver mets



Overall survival

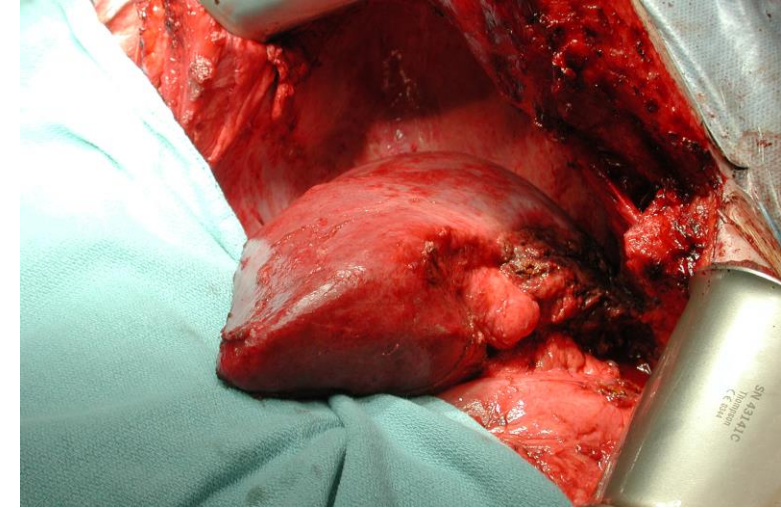


Distant Progression-free Survival



Synchronous resection

- **Advantages**
 - Single anesthetic
 - Early systemic chemotherapy
 - Decreased length of stay and costs compared to 2 ORs
- **Disadvantages**
 - Higher complication rate
 - Anastamotic leaks, infectious complications
 - Intra-op low CVP, post op high portal pressures
 - Major hepatic resections



Synchronous resection of colorectal cancer primary and liver metastases: an outcomes analysis

Michael R. Driedger¹, Thomas S. Yamashita¹, Patrick Starlinger¹, Kellie L. Mathis², Rory L. Smoot¹, Sean P. Cleary¹ & David M. Nagorney¹

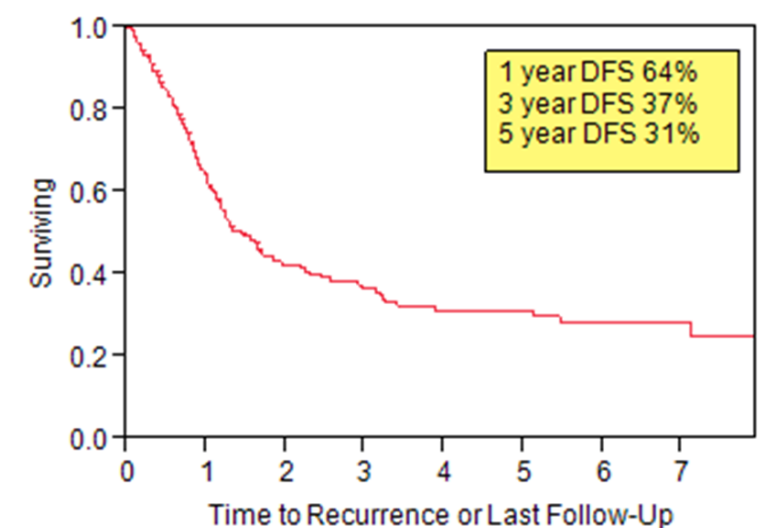
273 Patients (2000-2017)

- 52% colon, 48% rectum
- 62% neoadjuvant Tx
 - 22% SD, 62% PR
- Median 3.4 mets
 - 47% bilobar

- 70% received adjuvant Tx
- Receipt of adjuvant therapy and major morbidity associated with OS

Table 4 Postoperative outcomes stratified by extent of surgery

	N	30-day Mortality	90-day Mortality	Colorectal	Liver	Major Morbidity	Total Morbidity	Reoperation
Major liver/Major colorectal	24	1 (4.2%)	4 (16.7%)	11 (45.8%)	7 (29.2%)	13 (54.2%)	14 (58.3%)	4 (16.7%)
Major liver/Minor colorectal	43	0	2 (4.7%)	7 (16.3%)	8 (18.6%)	10 (23.3%)	19 (44.2%)	2 (4.7%)
Minor liver/Major colorectal	92	1 (1.1%)	1 (1.1%)	27 (29.3%)	2 (2.2%)	13 (14.1%)	37 (40.2%)	6 (6.5%)
Minor liver/Minor colorectal	114	1 (0.9%)	4 (3.5%)	20 (17.5%)	6 (5.3%)	16 (14.0%)	37 (32.5%)	6 (5.3%)
Total	273	3 (1.1%)	11 (4.0%)	65 (23.8%)	23 (8.4%)	52 (19.0%)	107 (39.2%)	18 (6.6%)



Minimally invasive vs. open approach to the simultaneous treatment of colorectal tumors with synchronous liver metastasis: a single center, propensity-score matched analysis from Mayo clinic

Guido Fiorentini¹, Andrea Zironda¹, Giacomo Calini², Solafah Abdalla², David M. Nagomey¹, Susanne G. Warner¹, Rory L. Smoot¹, Kevin T. Behm², Sherief F. Shawki², Kellie L. Mathis², Robert A. Vierkant³, David W. Larson² & Sean P. Cleary¹

Table 1 Characteristics of the study population

	Before matching			After matching		
	MIS (n = 43)	Open (n = 341)	P-value	MIS (n = 43)	Open (n = 86)	P-value
Gender, M, n (%)	24 (55.8)	197 (57.8)	0.743	24 (55.8)	52 (60.5)	0.705
Age, median (IQR), year	57 (49, 63)	55 (48, 64)	0.841	57 (49, 63)	55 (47, 63)	0.691
BMI, median (IQR), kg/m ²	28.0 (25.2, 32.4)	27.0 (23.9, 30.0)	0.102	28.0 (25.2, 31.5)	28.8 (25.4, 32.4)	0.520
ASA score, n (%)	20 (46.5)	225 (66.0)	0.019	20 (46.5)	45 (52.3)	0.578
	23 (53.5)	116 (34.0)		23 (53.5)	41 (47.7)	
Localization, n (%)	23 (53.5)	187 (54.8)	0.745	23 (53.5)	56 (65.1)	0.251
	20 (46.5)	154 (45.2)		20 (46.5)	30 (34.9)	
• Colon						
• Rectum						
Neoadjuvant chemotherapy, n (%)	40 (93.0)	235 (68.9)	<0.001	40 (93.0)	54 (62.8)	<0.001
Neoadjuvant radiotherapy, n (%)	14 (32.5)	76 (22.3)	0.125	14 (32.5)	15 (17.4)	0.075
Type of liver resection, n(%)	6 (14.0)	134 (39.0)	<0.001	6 (14)	12 (14)	1
• Major	37 (86.0)	207 (61.0)		37 (86)	74 (86)	
• Minor						

Table 3 Postoperative morbidity and mortality

	MIS (n = 43)	Open (n = 86)	P-value
Duration of hospital stay, median (IQR), days	4 (3-5)	6 (5-8)	0.001
Overall complications, n (%)	16 (37.2)	32 (37.2)	1.000
Overall complications CD ≥ 3, n (%)	5 (11.6)	13 (15.1)	0.187
Liver specific complications CD ≥ 3, n (%)	3 (7.0)	4 (4.7)	0.859
• Bile leak	1 (2.3)	2 (2.3)	
• Perihepatic abscess	1 (2.3)	2 (2.3)	
• Ascites	0 (0.0)	0 (0.0)	
• Transient liver failure	0 (0.0)	0 (0.0)	
Bowel specific complications CD ≥ 3, n (%)	2 (4.7)	8 (9.3)	0.494
• Ileus	0 (0.0)	2 (2.3)	
• Abscess	1 (2.3)	6 (6.9)	
• Anastomotic leak	1 (2.3)	0 (0.0)	
Reoperation due to complications, n (%)	0 (0.0)	5 (6.1)	0.132
Delay of adjuvant therapy due to complications, n (%)	3 (7.1)	10 (11.9)	0.555
30-days mortality, n (%)	0 (0.0)	0 (0.0)	NA
90-days mortality, n (%)	1 (2.3)	2 (2.3)	1.000

Synchronous Hepatic Metastases

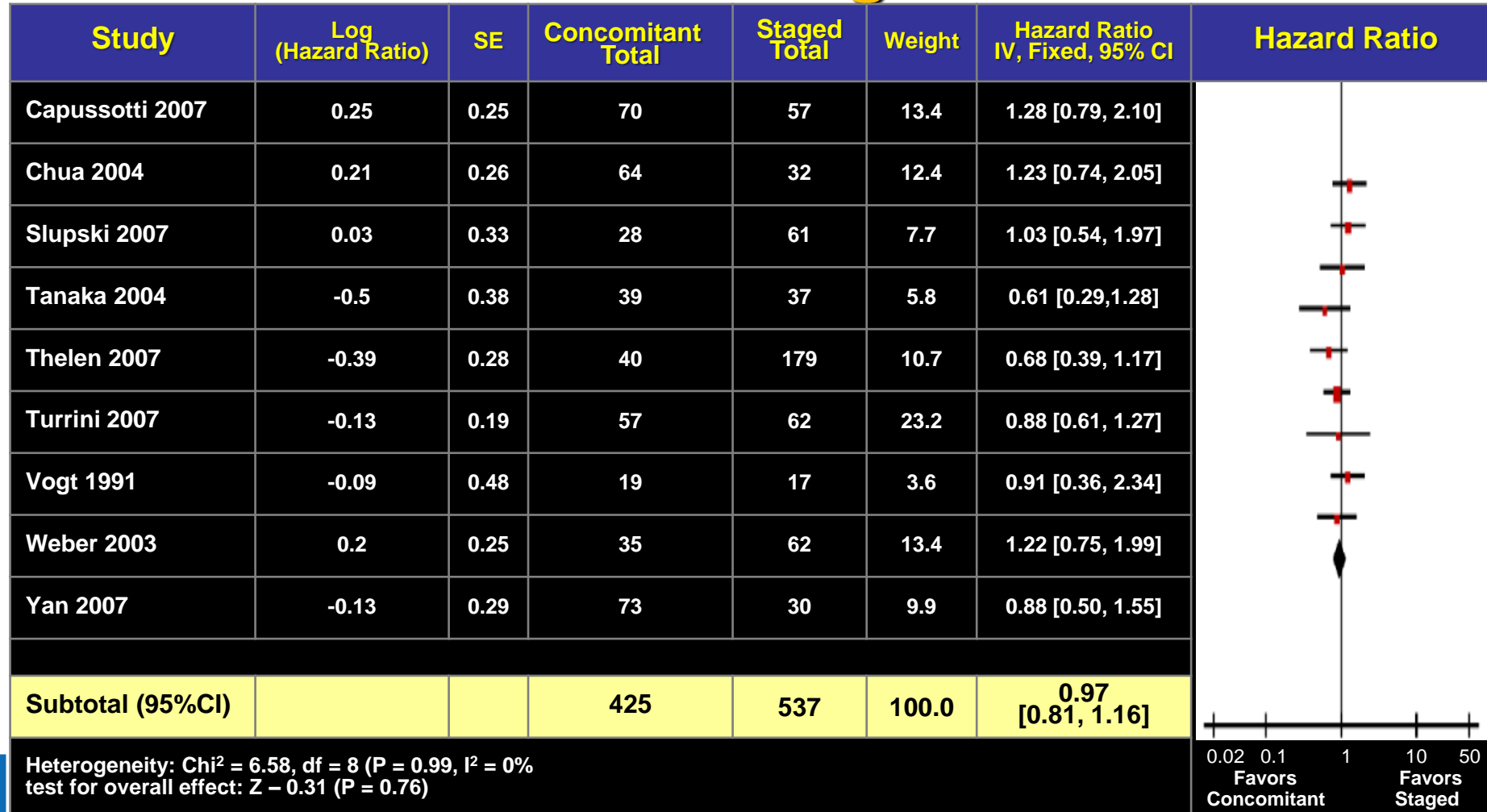
Length of Hospitalization - Concomitant vs Staged Resection

Study	Concomitant			Staged			Weight (%)	Mean Difference IV, Random 95% CI [days]	Mean Difference
	Mean [days]	SD [days]	Total	Mean [days]	SD [days]	Total			
Chua 2004	11.4	6.7	64	22.4	17.6	32	4.2	-11.00 [-17.32, -4.68]	
Jaeck 1999	17	10	28	15	5	31	6.1	2.00 [-2.10, 6.10]	
Luo 2010	8	2	129	14	2.75	276	9.2	-6.00 [-6.47, -5.53]	
Martin 2003	10	8.25	134	18	8.5	106	8.1	-8.00 [-10.14, -5.86]	
Martin 2009	10	14.5	70	18	8	160	6.6	-8.00 [-11.62, -4.38]	
Petri 2010	13.1	7	14	11.7	6	29	5.9	1.40 [-2.87, 5.67]	
Reddy 2007	8.6	1.8	135	12.6	2.5	475	9.2	-4.00 [-4.38, -3.62]	
Slupski 2009	12	4	28	15	3.5	61	8.5	-3.00 [-4.72, -1.28]	
Tanaka 2004	25.6	10.4	39	23.1	10.3	37	5.6	2.50 [-2.15, 7.15]	
Thelen 2007	20.05	8	40	19.85	30.7	179	5.1	0.20 [-4.94, 5.34]	
Vassillou 2007	12	6	25	20	8	78	7.3	-8.00 [-10.95, -5.05]	
Vogt 1991	15	1.3	19	26	1.2	17	9.0	-11.00 [-11.82, -10.18]	
Weber 2003	17	9	35	16	7	62	6.8	1.00 [-2.45, 4.45]	
Yan 2007	7	2.3	73	15	4.5	30	8.5	-8.00 [-9.69, -6.31]	
Total (95%CI)			833			1573	100	-4.64 [-6.38, -2.90]	

Heterogeneity: $\tau^2 = 8.53$ $\chi^2 = 320.66$, $df = 13$ ($p < 0.00001$); $I^2 = 96\%$
 Test for overall effect: $Z = 5.23$ ($P < 0.00001$)

Synchronous Hepatic Metastases

5-Year Overall Survival Concomitant vs Staged Resection



Liver First Approach

- **Advantages**

- Metastatic disease is primary determinant of outcome
- Early systemic chemotherapy
- Symptoms/progression of primary is uncommon (5%)
- Most advantageous for rectal primary and advanced LM
- Long course radiation

- **Disadvantages**

- 20% will not have primary resection
 - Disease progression or complications

Surgical Management of Patients with Synchronous Colorectal Liver Metastasis: A Multicenter International Analysis

Skye C Mayo, MD, MPH, Carlo Pulitano, MD, Hugo Marques, MD, Jorge Lencinas, MD,

JACS 2013

- 1004 Pts synchronous liver mets, 4 centres
- 64% Traditional, 33% Synchronous, 3% Liver first
 - Liver first-higher rates of Rectal Ca, bilateral LM and pre-op chemo
- No difference in morbidity or mortality
- Multivariate analysis: male sex, rectal primary and RFA associated with worse OS
- 5yr OS 44%

Thirty-Day Morbidity after Simultaneous Resection of Colorectal Cancer and Colorectal Liver Metastasis: American College of Surgeons NSQIP Analysis

Rebecca A Snyder, MD, MPH, FACS, Scarlett Hao, MD, William Irish, PhD, MSc, Emmanuel E Zervos, MD, FACS, Janet E Tuttle-Newhall, MD, FACS, Alexander A Parikh, MD, MPH, FACS

JACS 2020 ePub

Table 2. Thirty-day Morbidity for Overall Cohort

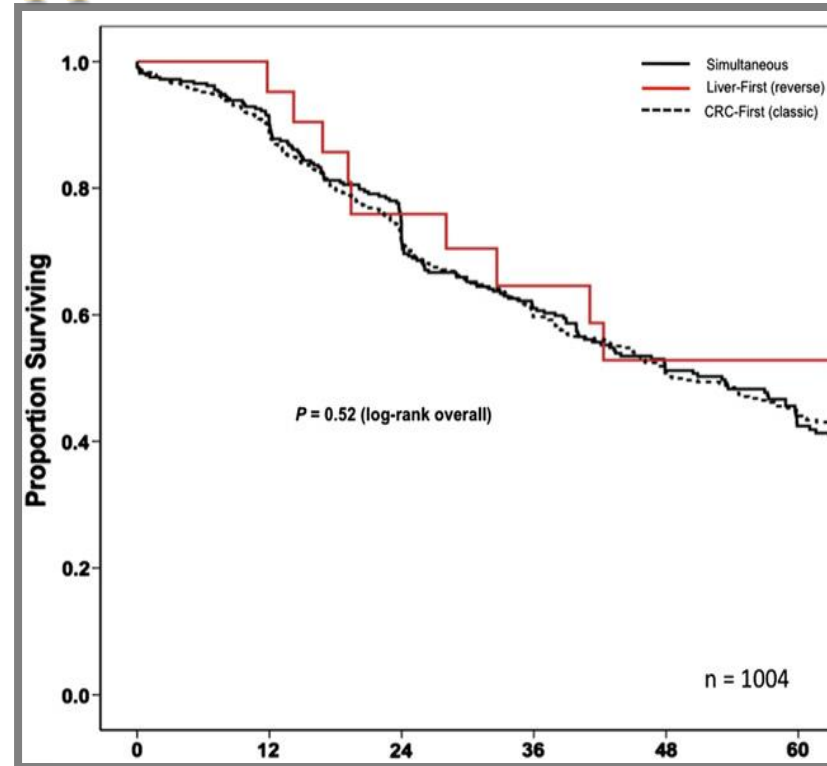
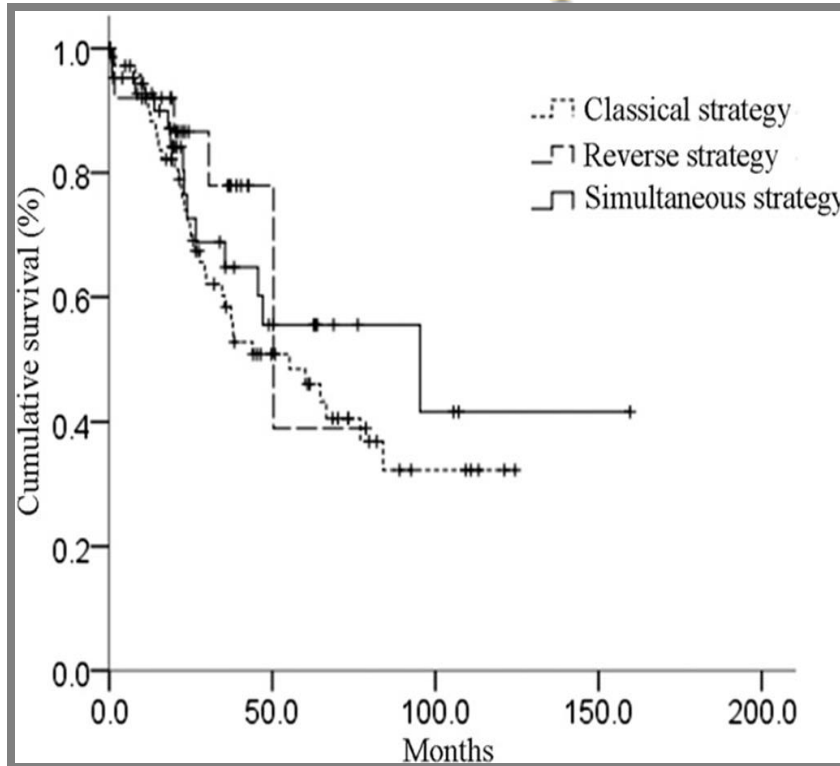
Variable	Isolated colon resection, n = 23,643	Isolated liver resection, n = 7,462	Simultaneous resection, n = 592	p Value
Overall composite 30-day morbidity, n (%)	5,249 (22.2)	1,275 (17.1)	177 (29.9)	<0.001
95% CI	21.7–22.8	16.2–18.0	26.2–33.8	
LOS > 30 d, n (%)	246 (1.0)	42 (0.6)	12 (2.0)	<0.001
Readmission, n (%)	2,938 (12.4)	710 (9.5)	87 (14.7)	<0.001
Median LOS, d, (IQR)	6 (4, 8)	5 (4, 7)	7 (6, 10)	<0.001
Mortality within 30 d, n (%)	291 (1.2)	73 (1.0)	7 (1.2)	0.209

Table 3. Postoperative Complication Rates for Targeted Colectomy and Hepatectomy Cohorts

Variable	Isolated colon resection: colectomy module, n = 9,774	Simultaneous resection: colectomy module, n = 140	p Value	Isolated liver resection: hepatectomy module, n = 5,479	Simultaneous resection: hepatectomy module n = 265	p Value
Procedure-specific complication, n (%)	2,025 (20.7)	52 (37.1)	<0.001	524 (9.1)	38 (14.3)	0.007
Anastomotic leak	372 (3.8)	11 (7.9)	0.024	–	–	–
Postoperative ileus	1,864 (19.1)	51 (36.4)	<0.001	–	–	–
Postoperative bile leak	–	–	–	359 (6.2)	22 (8.3)	0.195
Postoperative liver failure	–	–	–	219 (3.8)	23 (8.7)	<0.001
Grade A	–	–	–	96 (1.7)	16 (6.0)	
Grade B	–	–	–	89 (1.5)	5 (1.9)	
Grade C	–	–	–	34 (0.6)	2 (0.8)	

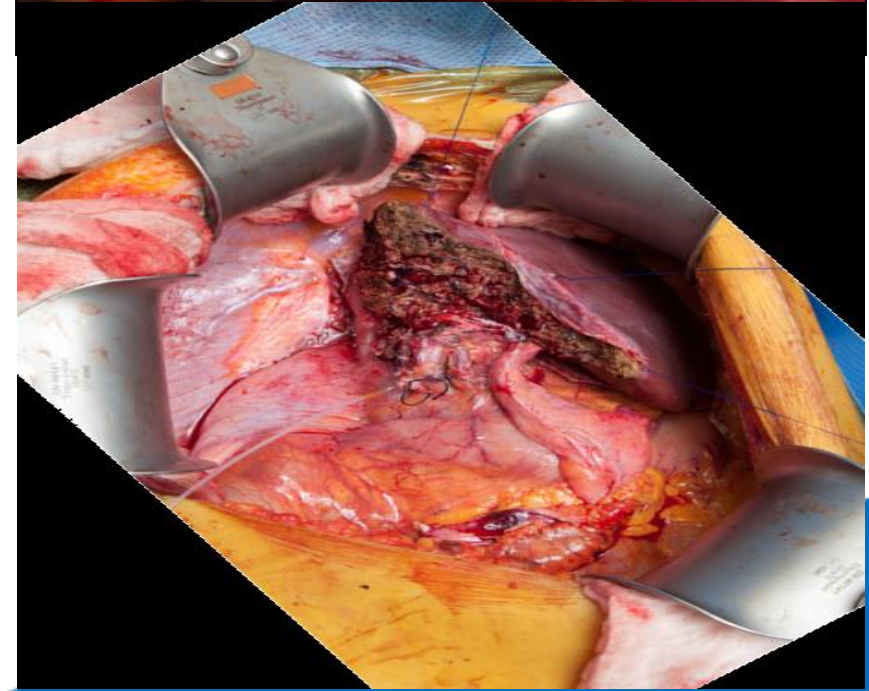
Synchronous Hepatic Metastases

Survival after Liver-Directed Operations (mo) Three Operative Approaches



Summary

- Different approaches based on timing of surgery, chemotherapy and radiation
 - CRC first
 - Simultaneous resection
 - Liver first
- Metastatic disease and systemic chemotherapy are main determinants of outcome
- Selection of approach depends on:
 - Location of primary and need for ChemoRT
 - short vs long course
 - Extent of LM and hepatic resection required.



THANK YOU.....



Rank	Hospital name	Country	City	State (US only)	PROMs survey
1	Mayo Clinic - Rochester	U.S.	Rochester	Minnesota	
2	Cleveland Clinic	U.S.	Cleveland	Ohio	
3	Toronto General - University Health Network	Canada	Toronto		
4	The Johns Hopkins Hospital	U.S.	Baltimore	Maryland	
5	Massachusetts General Hospital	U.S.	Boston	Massachusetts	



UHN Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
Michener Institute