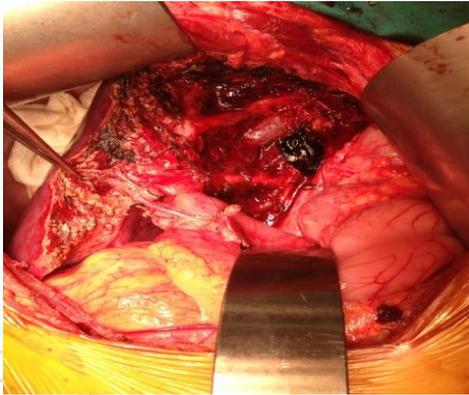


Resection of liver limited resectable metastases – Upfront, neoadjuvant and repeat hepatectomy



Dr Chan Chung Yip

MBBS, M.Med(Surgery), MD, FAMS, FRCSEd

Senior Consultant and Head

Department of Hepatopancreatobiliary and Transplant Surgery
Singapore General Hospital

Associate Professor (Adj), Duke-NUS Medical School

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Introduction

- Resection of colorectal liver metastasis (CRLM) is required for long term survival
- 15-25% will present with synchronous CRLM
- 40-50% will develop CRLM within 3 years of resection of primary tumour
- 25% of patients with CRLM are eligible for surgical extirpation

Chronology of chemotherapy for mCRC

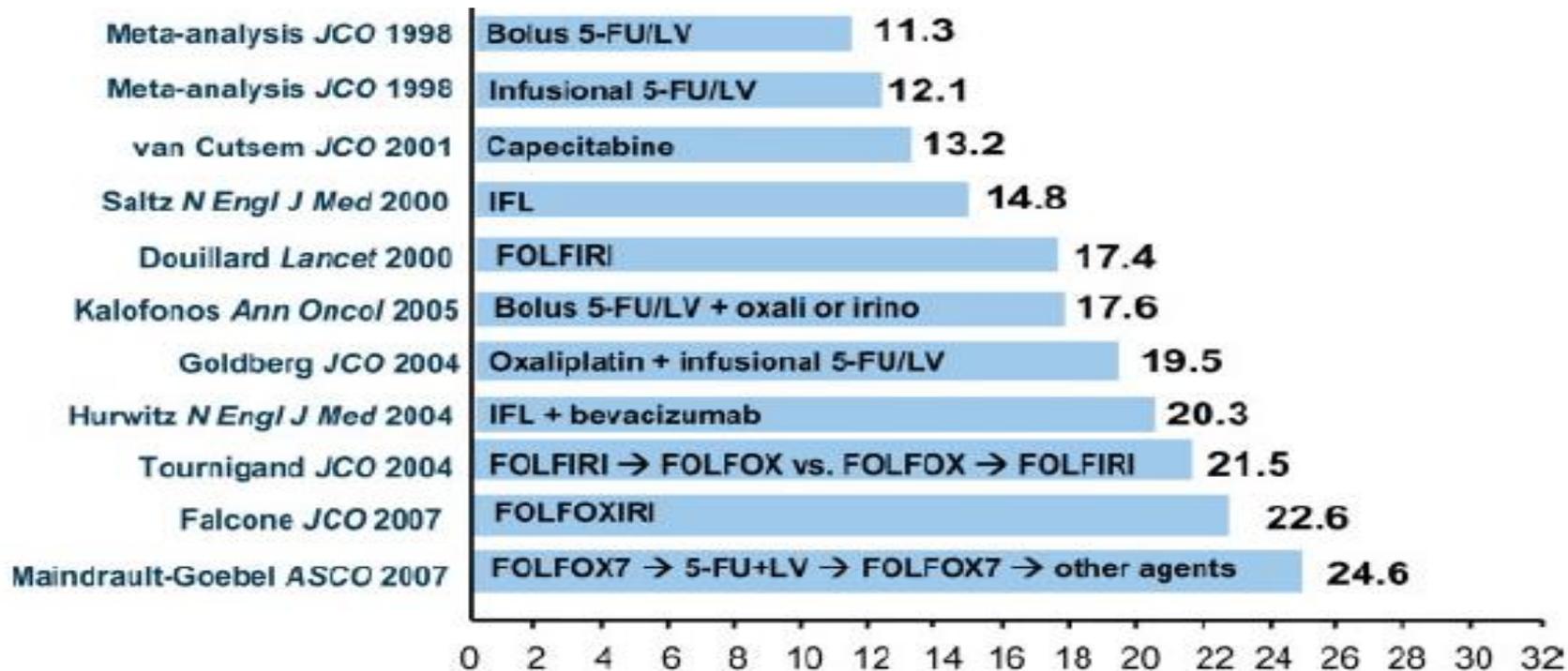


Table 2 Results of Liver Resection for Colorectal Metastases

Study	N	Operative Mortality %	1-yr Survival %	3-yr Survival %	5-yr Survival %	10-yr Survival %	Median Survival (mo)
Gayowski 1994[10]	204	0	91	–	32	–	33
Scheele 1995[5]	434	4	85	45	33	20	40
Nordlinger 1996[6]	1568	2	80	–	28	–	40
Fong 1999[7]	1001	2.8	89	57	36	22	42
Minagawa 2000[11]	235	0.85	–	51	38	26	–
Adam 2001[14]	335	1	91	66	48	30	52
Choti 2002[12]	226	1	93	57	40	26	46
Kato 2003[13]	585	0	–	–	33	–	–
Figueras 2007[17]	501	4	88	67	42	36	44
Tomlinson 2007[18]	612	–	–	–	–	17	44
Rees 2008[19]	929	1.5	–	–	36	23	43
House 2010[15]	563	1	–	69	51	37 ^a	64
Nathan 2010[20]	949	0.9	–	65	45	22	52

^a 8-yr survival.

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Surgical resection of colorectal liver metastasis in patients with expanded indications: a single-center experience with 501 patients.

Figueras J et al. Dis Colon Rectum, 2007

- 501 patients with 545 liver resections over 15 year period comparing classic with expanded indications
- Expanded indications: lesions > 10cm (n=14), bilateral deposits (n=194), ≥ 4 metastasis (n=140), extra-hepatic disease (n=73)
- 52% of patients
- 5 year survival: 45% vs 34%, 10 year survival: 36 vs 24% (p=0.0009)
- ≥ 4 metastases and extra-hepatic disease predict poor outcome

Can we improve survival with chemotherapy?

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Role of adjuvant chemotherapy in resectable CRLM

- Robust data on role of systemic chemotherapy for resected stage III and unresectable stage IV cancer
- Data on role of adjuvant chemotherapy for resected CRLM is scant
- 4 randomized trials, 2 published
 - Langer B et al. Proc Amer Soc Clin Oncol 2002
 - Portier G et al. J Clin Oncol 2006
- Both did not show difference in overall survival, Portier et al trial showed disease free survival benefit
- Poor accrual, small sample size

Role of adjuvant chemotherapy in resectable CRLM

- Several large retrospective studies
 - Parks R et al. J Am Coll Surg 2007
 - Figueras J et al. Dis Colon Rectum 2007
 - Wang X et al. Br J Cancer 2007
- All reported overall and DF survival benefit for adjuvant 5-FU
- A randomized phase II study comparing adjuvant 5-FU/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. [Ychou M et al. Ann Oncol 2009.](#)
- No difference in overall or DF survival

Peri-operative and Neoadjuvant Chemotherapy

- Survival benefits from pre-hepatectomy chemotherapy have not been established
- Retrospective studies show improved survival with adjuvant therapy but not with neoadjuvant therapy. Increased post operative complications
 - Adam R et al. Ann Surg 2010.
 - Reddy SK et al. Ann Surg Oncol 2009.
- Only 1 randomized trial (EORTC Intergroup trial 40983)
 - Norlinger B et al. Lancet 2008.
 - Norlinger B et al. Lancet Oncol 2013

EORTC Intergroup Trial 40983

- 364 patients randomized to surgery alone or surgery with perioperative FOLFOX 4 chemotherapy
- Median follow-up 8.5yrs
- Non-statistically significant trend in 5yr PFS favouring chemotherapy group (38% vs 30%, HR 0.81, p=0.068)
- 5yr OS similar: 51% vs 48% (HR 0.88, 95% CI 0.68-1.14)

Peri-operative and Neoadjuvant Chemotherapy

- Early treatment of systemic disease
- Allow biology of disease to declare itself
- In vivo assessment of response to chemotherapy
- While already resectable, lesions treated with neoadjuvant chemotherapy may benefit from further downsizing to facilitate increased rates of margin negative as well as parenchymal sparing resections

Progression on chemotherapy

- Marker for aggressive tumour biology
- Uncommon, 5-15% of patients
- Development of new lesions strongest predictor of poor post-hepatectomy outcome
- 5 yr survival in pts with >3 mets that progressed – 8%
- Prognostic impact of progression in form of growth of pre-existing lesion less clear

Allen et al. J Gastrointest Surg 2003

Adam et al. Ann Surg 2004

Can prehepatectomy chemotherapy identify pts who will unlikely benefit from hepatectomy?

- Relatively few patients experience disease progression while receiving short duration of contemporary chemotherapy
 - 11/171 pts (7%) exhibited progressive disease in response to FOLFOX (EORTC Intergroup Trial 40983. Lancet 2008)
 - Does neoadjuvant chemotherapy reveal disease precluding surgical treatment of initially resectable CRLM? Reddy SK, Tsung A, Marsh JM, Geller D. JSO 2012
- Median progression-free survival for metastatic unresectable cancer exceeds 6 months in most phase III trials
- Extended durations of chemotherapy treatment would be required to identify those patients with interval disease progression

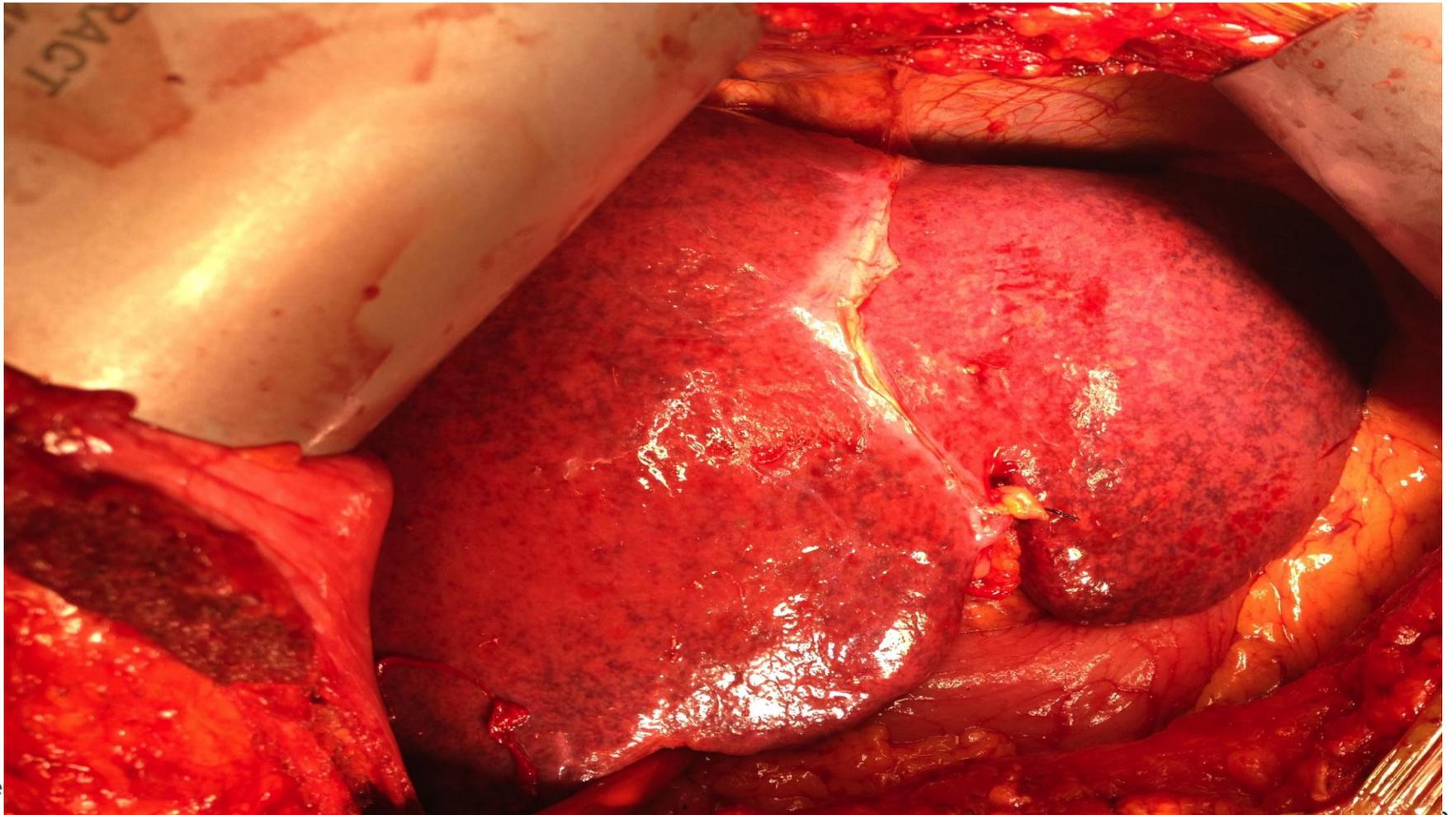
How useful is prehepatectomy chemotherapy an in-vivo test of response?

- Response to chemotherapy before hepatic resection will help determine optimal post hepatectomy chemotherapy
- 14% and 9% of patients whose disease was downsized from unresectable to resectable CLM responded to second and third lines of treatment when first-line chemotherapy failed.

[Adam R et al. Ann Surg 2004](#)

Disease progression on pre-hepatectomy chemotherapy may render previously resectable CLM unresectable, thereby preventing opportunity for long term survival ?

- EORTC 40983: 364 pts \leq 4 mets assigned to liver resection with or without perioperative chemotherapy
- 67/182 pts assigned to chemo had objective response
- 11 progressed, 8 of whom no longer resectable
- 83% resected vs 84% in surgery alone group



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Chemotherapy induced liver injury

- Irinotecan – Steatosis, Chemotherapy Associated SteatoHepatitis (CASH)
- Oxaliplatin: Sinusoidal injury (Sinusoidal Obstruction Syndrome- SOS, “blue liver syndrome”)
- Bevacizumab: Impairment of liver regeneration (anti-VEGF)

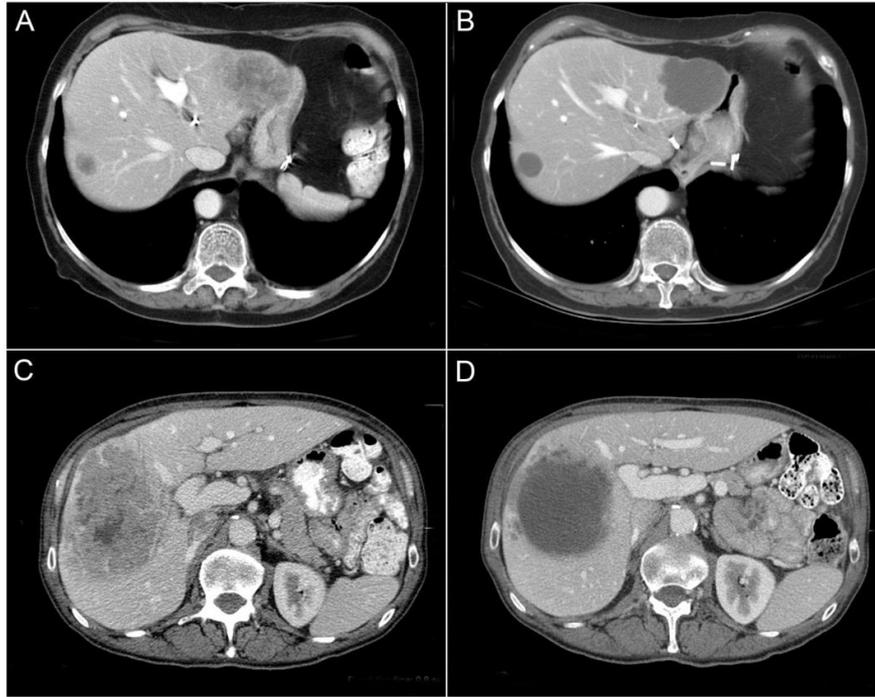
Does preoperative chemotherapy increase the morbidity and mortality after surgery?

- EORTC Intergroup trial 40983, overall complication increased from 16-25%, rate of hepatic complications from 9-15%. No change in mortality. [Norlinger et al, Lancet 2008](#)
- Multicentric cohort study showing significantly higher complication rate 24% vs 37% in patients subjected to neoadjuvant chemotherapy for resectable lesions. [Adam R et al. Ann Surg 2010](#)
- In the setting of extended surgical resection, may contribute to development of small for size syndrome and fatal liver failure

Can neoadjuvant chemotherapy help select patient for type of surgical resection?

- Recurrence following liver resection is expected
- Shift from anatomical resection to parenchymal sparing strategies to improve subsequent resectability
- Trade off: Higher risk of margin positive resection

Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. *Vauthey JN et al. Ann Surg 2013*



Optimal morphological response

Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. *Vauthey JN et al. Ann Surg 2013*

- Pathological response: Area of residual viable tumour cells within each metastatic lesion as percentage of total tumour surface area
- Minor response: 0-49%
- Major response: $\geq 50\%$
- Multiple nodules: Mean of response in each individual nodule

Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. *Vauthey JN et al. Ann Surg 2013*

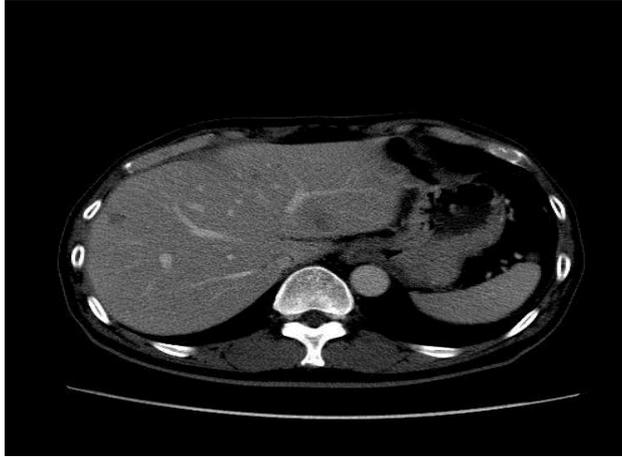
- 52 of 378 resections (14%) R1 resections.
- 246 (65%) synchronous lesions. No of mets median=2, mean=3
- 5yr OS R0 vs R1 resection: 55% and 26%
- Survival benefit a/w negative margins greater in patients with suboptimal morphological response (5yr OS: 62% vs 11%, $P=0.007$); patients with optimal response (3yr OS rate: 92% vs 88%, $P=0.917$)
- Greater in patients with minor pathological response (5yr OS: 46% vs 0%, $P=0.002$); patients with major response (5yr OS: 63% vs 67%, $P=0.587$)

Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy.

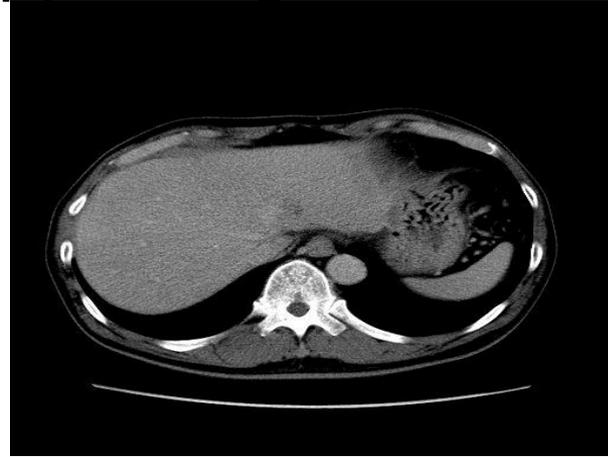
Vauthey JN et al. Ann Surg 2013

- Optimal radiological response : Multiple wedge resections (parenchymal sparing)
- Suboptimal radiological response : Anatomical resections

Dilemma - The disappearing metastasis



Nov 2011



Feb 2012



The disappearing metastases

- Complete clinical response from chemotherapy to sites of CLM obviates the need for surgical extirpation of these sites?
- Benoist S et al reported the recurrence of disease at site of unresected disappearing lesions in 23 of 31 lesions (74%). [J Clin Oncol 2004.](#)
- Tanaka et al reported similar findings with recurrence in 11 of 27 lesions (41%) at median of 14 months f/u. [Ann Surg 2009.](#)

Predictors of patient with at least one metastases that disappears

- Small size <3cm
 - Multiple lesions > 3
 - Longer duration of chemotherapy
-
- Benoist S et al. J Clin Oncol 2006
 - Van Vledder MG et al. J Gastrointest Surg 2010.

The disappearing metastases

- PET does not reliably predict pathological response
- 34 lesions in 14 patients had resolution of PET positivity after prehepatectomy chemotherapy. 29 (85%) had viable tumour on microscopic examination
 - Tan MCB et al. J Gastrointest Surg 2007.
- 40% of complete pathological response have radiologically evident lesions

The disappearing metastases

- Good quality MRI to identify “missing metastases”
- <10% of pts have complete radiological response of all liver metastases, hence most patients will undergo surgery for residual disease
- IOUS identifies additional lesions that alter surgical planning in a substantial number of patients
- Extended prehepatectomy chemotherapy induces pathological changes in surrounding non-tumour bearing liver that reduces sensitivity of both IOUS and visual examination to detect small lesions

Fong Clinical Risk Score

Ann Surg 1999

- Nodal status of primary
- DFI from primary to discovery of liver mets <12mths
- Number of tumours >1
- Preop CEA > 200ng/ml
- Largest tumor > 5cm

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Effect of neoadjuvant chemotherapy in patients with resectable colorectal liver metastases

Zhu DX et al. PlosOne 2014

- Retrospective analysis of 466pts between 2000 and 2010
- Pts divided into pts who received neoadj chemo (n=121) and pts who had adj chemo (n=345)
- No diff in morbidity, 30-day mortality and 5yr survival (52% vs 48%)
- Risk factors: Primary tumour T4, ≥ 4 mets, largest met ≥ 5 cm, serum CEA ≥ 5 ng/ml
- Low risk 0-2 factors, high risk 3-4 factors
- Low risk group no survival benefit from neoadjuvant chemo, high risk group survival benefit (5yr 39% vs 33%, $p=0.028$)

Liver resection for multiple colorectal liver metastases with surgery upfront approach: Bi-institutional analysis of 736 cases.

Saiura A et al. World J Surg 2012

- 625 resectable pts and 111 initially unresectable (ie converted) – 1993 to 2008
- Upfront resectable pts did not receive any preop-chemotherapy and few had adjuvant chemotherapy
- Patients divided into 3 groups: Group A 1-3 tumours (n=493), Group B 4-7 tumours (n=141), Group C 8 or more tumours (n=102)
- 5 year overall and recurrence free survival: Group A: 51% and 21%, Group B: 56% and 29%, Group C: 33% and 1.7%
- Prognostic factors for DFS: Extrahepatic disease, positive surgical margin, nodal involvement of primary, tumour number ≥ 4 , size $> 5\text{cm}$, CEA $> 200\text{ng/mL}$, primary site (rectum)
- Prognostic factors for OS: Node positive primary tumour, EHD, size $\geq 5\text{cm}$, positive margin

Should neoadjuvant chemotherapy be given in resectable colorectal liver metastases?

- Are there sufficient risks of possible poor tumor biology such that addition of one additional factor (ie progression on chemotherapy) would be sufficient to not offer resection?
- Does the patient have diabetes, obesity or other factors that compromise liver health, such that any degree of liver injury from preoperative chemotherapy might be significantly deleterious?
- Though resectable, will a minor response make the operation significantly less difficult (eg more easily achieving negative margins, avoid a critical vein, or lessen likelihood of conversion of laparoscopic resection)?

Recommendations based on available evidence

- Surgery upfront followed by adjuvant chemotherapy
- If need be, limit chemotherapy to 2-4 cycles before performing surgery
- Avoid pre-operative chemotherapy altogether in cases of small limited lesions (<3cm), else use fiduciary or consider ablation of small lesions pre-chemotherapy

Pattern of recurrence following hepatectomy

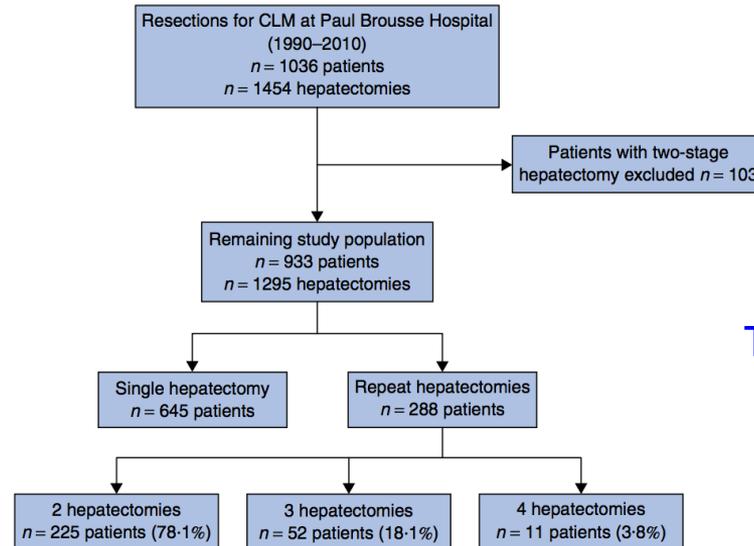
- Most patients with multiple, bilobar disease will ultimately recur
- Half will recur within 3 years, half of these recurrences isolated to the liver
- Extra-hepatic metastases most common form of disease recurrence among patients with multiple metastases, liver recurrence most common in patients with small number of mets
- More extrahepatic than intrahepatic recurrence for initially unresectable metastases downstaged by chemotherapy

Repeat hepatectomy for recurrent colorectal metastases

D. A. Wicherts¹, R. J. de Haas¹, C. Salloum¹, P. Andreani¹, G. Pascal¹, D. Sotirov¹, R. Adam^{1,2,3},
D. Castaing^{1,2,3} and D. Azoulay^{1,4}

¹Department of Surgery, Assistance Publique – Hôpitaux de Paris (AP-HP) Hôpital Paul Brousse, Centre Hépato-Biliaire, ²Institut National de la Santé et de la Recherche Médicale (INSERM), Unit 785, ³Unité Mixte de Recherche en Santé 785, Université Paris-Sud, and ⁴INSERM, Unit 1004, Villejuif, France

BJS
2013



Total = 650 hepatectomies

Repeat hepatectomy – Tumour characteristics

Wicherts et al. BJS 2013

	First hepatectomy (n = 288)	Second hepatectomy (n = 288)	Third hepatectomy (n = 63)	Fourth hepatectomy (n = 11)	P*
Liver metastases at diagnosis					
Mean(s.d.) no. of CLM	3(3)	2(2)	2(2)	2(2)	< 0.001†
No. of CLM categorized					< 0.001
1	75 (28.0)	136 (51.7)	32 (51)	6 (60)	
2–3	94 (35.1)	82 (31.2)	27 (43)	3 (30)	
> 3	99 (36.9)	45 (17.1)	4 (6)	1 (10)	
Maximum size (mm)					< 0.001
< 30	103 (44.2)	139 (62.1)	38 (70)	4 (57)	
≥ 30	130 (55.8)	85 (37.9)	16 (30)	3 (43)	
Bilobar distribution	145 (50.3)	60 (20.8)	7 (11)	0 (0)	< 0.001
Initial unresectability	114 (39.6)	42 (14.6)	8 (13)	0 (0)	< 0.001
Cause of unresectability					0.136
Multinodular	59 (51.8)	15 (36)	0 (0)	–	
Large size	32 (28.1)	15 (36)	5 (63)	–	
Close vascular relation	17 (14.9)	10 (24)	3 (37)	–	
Extrahepatic disease	6 (5.3)	2 (5)	0 (0)	–	
Concomitant extrahepatic disease	47 (16.3)	33 (11.5)	5 (8)	0 (0)	0.092
Location					0.288
Lung	16	16	0	–	
Lymph node	11	6	2	–	
Other	20	11	3	–	
Resection	33	17	5	–	0.043
Preoperative chemotherapy	218 (75.7)	162 (56.3)	31 (49)	5 (45)	< 0.001
No. of lines					0.020
1	149 (68.3)	129 (79.6)	25 (81)	3 (60)	
> 1	69 (31.7)	33 (20.4)	6 (19)	2 (40)	

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Repeat hepatectomy - Histopathology

Wicherts et al. BJS 2013

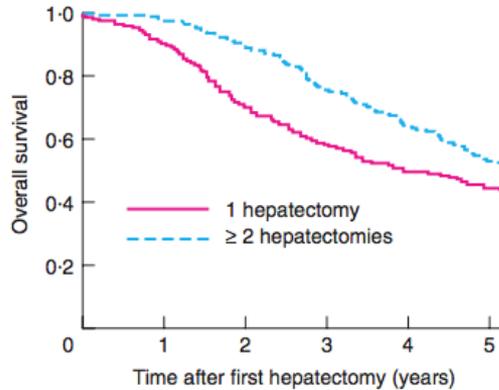
	First hepatectomy (n = 288)	Second hepatectomy (n = 288)	Third hepatectomy (n = 63)	Fourth hepatectomy (n = 11)	P§
Time interval between operations (months)*					
Colectomy to first hepatectomy	13 (0-113)	-	-	-	-
First to second hepatectomy	-	18 (5-146)	-	-	
Second to third hepatectomy	-	-	16 (6-59)	-	
Third to fourth hepatectomy	-	-	-	21 (4-103)	
No. of metastases detected					< 0.001
1	72 (27.8)	118 (47.0)	17 (61)	2 (67)	
2-3	93 (35.9)	94 (37.5)	11 (39)	1 (33)	
> 3	94 (36.3)	39 (15.5)	0 (0)	0 (0)	
PVE	15 (5.2)	6 (2.1)	2 (3)	0 (0)	0.364
Major resection (≥ 3 segments)	97 (33.7)	49 (17.0)	3 (5)	1 (9)	< 0.001
Type of resection					< 0.001
Anatomical	89 (31.0)	74 (27.9)	14 (23)	1 (9)	
Non-anatomical	98 (34.1)	138 (52.1)	42 (68)	9 (82)	
Both	100 (34.8)	53 (20.0)	6 (10)	1 (9)	
Vascular occlusion					< 0.001
None	77 (33.5)	36 (16.0)	6 (21)	9 (82)	
Selective	16 (7.0)	8 (3.6)	1 (4)	0 (0)	
Total pedicular	116 (50.4)	166 (73.8)	16 (57)	1 (9)	



Overall survival

Wichert et al. BJS 2013

P=0.003



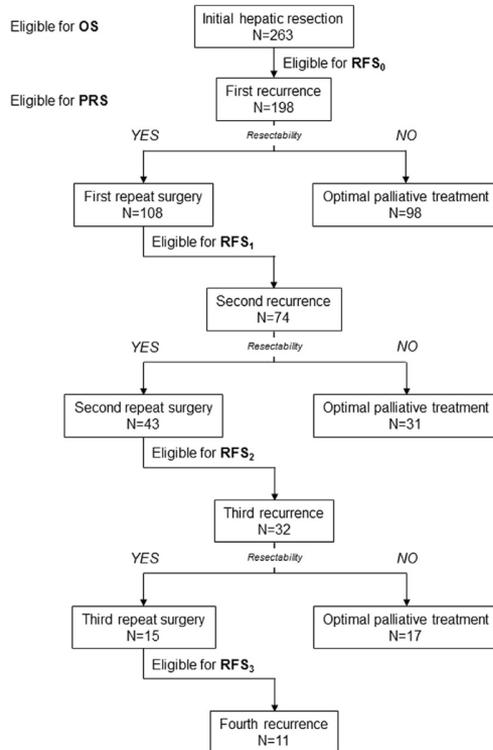
No. at risk

1 hepatectomy	645	493	325	236	174	131
≥ 2 hepatectomies	288	272	234	176	133	96

- Similar postoperative morbidity and mortality
- 3 and 5yr OS:
76% and 54% with repeat hepatectomy
58% and 45% with one hepatectomy

Survival benefit of repeat resection of successive recurrences after the initial hepatic resection for colorectal liver metastases

Oba M, Makuuchi M, Kokudo N et al. Surgery 2016

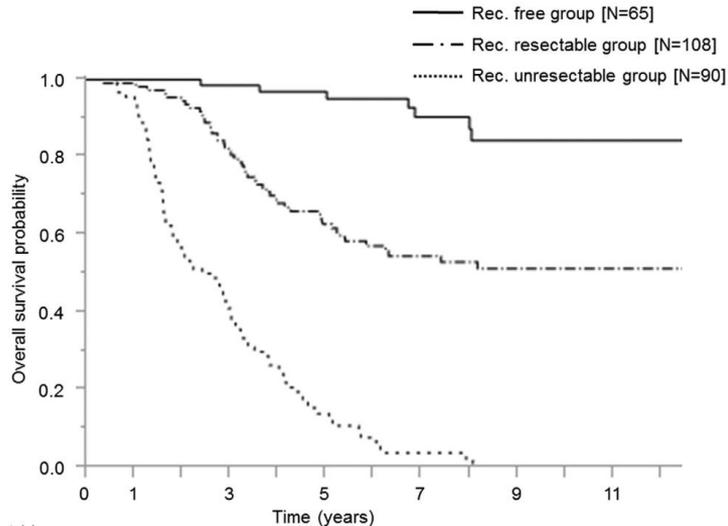


- 1996-2010: 336 pts upfront liver resection
- Adjuvant chemotherapy not standard of care; 77 pts receiving chemotherapy excluded
- Surgical management: Upfront resection regardless of number, distribution or extent

Survival benefit of repeat resection of successive recurrences after the initial hepatic resection for colorectal liver metastases.

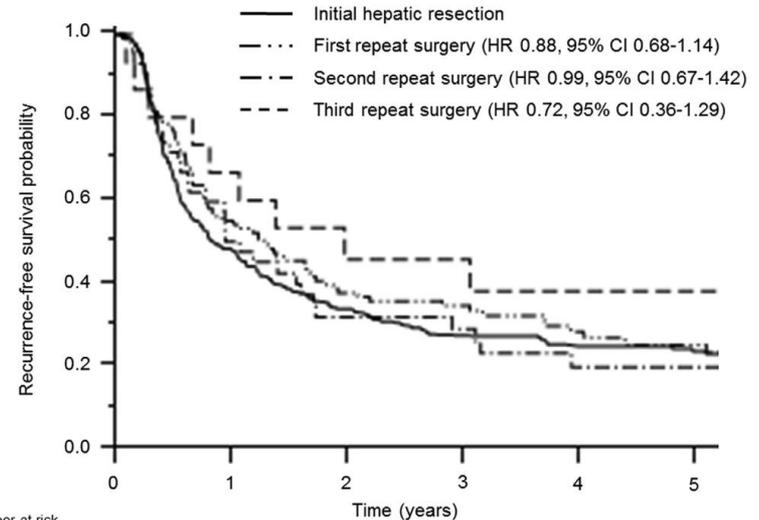
Oba M, Makuuchi M, Kokudo N et al. Surgery 2016

Overall survival



Number at risk	0	1	3	5	7	9	11
Rec. free	65	65	65	65	54	37	25
Rec. resectable	108	108	88	59	40	24	13
Rec. unresectable	90	86	37	10	3	0	0

Recurrence free survival



Number at risk	0	1	2	3	4	5
Initial hepatic resection	263	126	90	72	55	40
1 st repeat surgery	108	58	39	31	22	15
2 nd repeat surgery	43	23	13	11	7	4
3 rd repeat surgery	15	11	7	7	6	4

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Survival benefit of repeat resection of successive recurrences after the initial hepatic resection for colorectal liver metastases.

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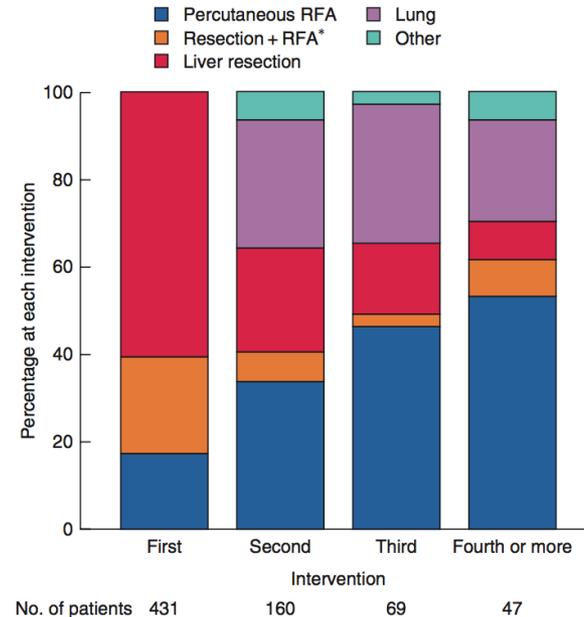
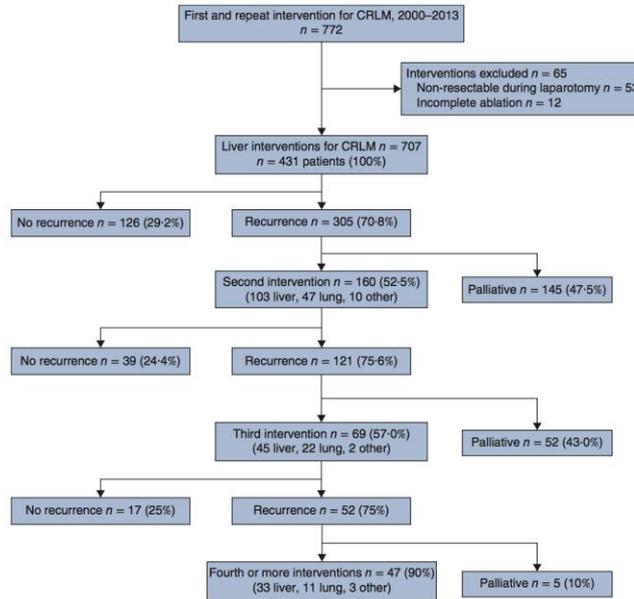
- At each repeat resection, approx 1/3 recurrence free
- Of those recurred, approx half suitable for further resection
- Survival benefit of repeat resections maintained regardless of number of previous resections
- Sequential repeat resections offer possibility of cure

Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases

J. Hof¹, M. W. J. L. A. E. Wertenbroek¹, P. M. J. G. Peeters¹, J. Widder², E. Sieders¹ and K. P. de Jong¹

BJS 2016

Departments of ¹Hepatopancreatobiliary Surgery and Liver Transplantation and ²Radiation Oncology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands



Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases

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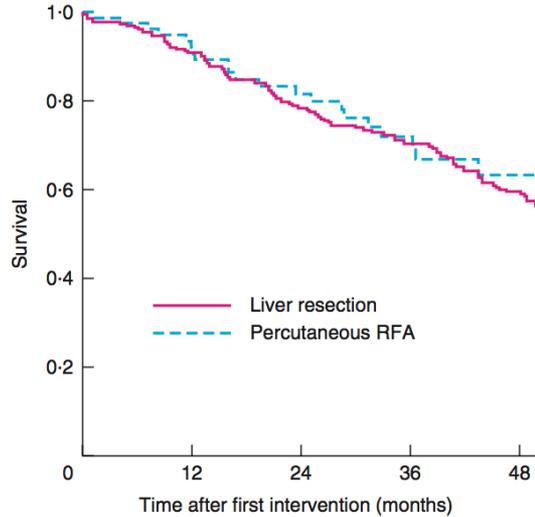
- Overall recurrence rate 83.5% (152/182) for percutaneous RFA cf 66.6% (201/302) for liver resection (P<0.001)
- Intra-hepatic recurrence 59.9% in RFA vs 23.9% in liver resection (P<0.001)
- Risk of ablation-site recurrence after RFA 26.9% (50/186pts, 250 lesions)
- 92% (46/50) of ablation site recurrence treated with curative intent (41 repeat RFA, 5 resection)

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Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases

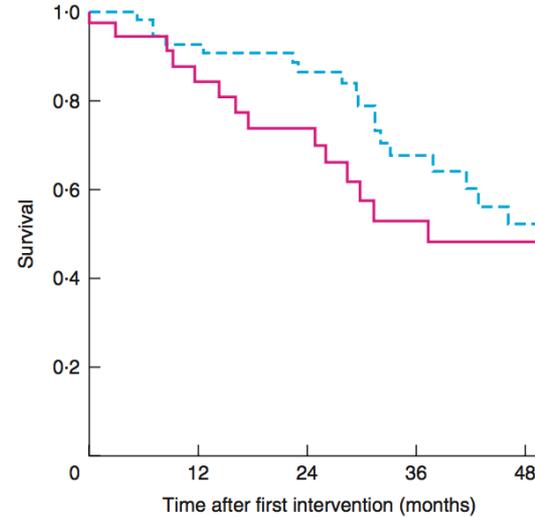
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No. at risk					
Resection	261	231	177	151	109
RFA	75	68	48	29	16

a Overall survival after first intervention



No. at risk					
Resection	37	24	19	11	9
RFA	54	47	40	22	13

b Overall survival after second intervention

Selecting patients for a second hepatectomy for colorectal metastases: A systemic review and meta-analysis.

Luo LX et al. EJSO 2014

- 7226 pts from 27 studies
- Recurrent CRLM more likely solitary, unilobar and smaller
- Better survival after second hepatectomy in high quality studies
- Predictors of better survival after second hepatectomy: DFI>1yr, solitary met, unilobar, size ≤ 5 cm, lack of EHD and R0 resection

Conclusion – repeat hepatectomy

- Morbidity and mortality similar to first time hepatectomy
- Progression free survival maintained with each hepatectomy
- Possible better survival
- Increasing indication for ablative approaches

Evaluating agreement regarding the resectability of colorectal liver metastases: a national case-based survey of hepatic surgeons.

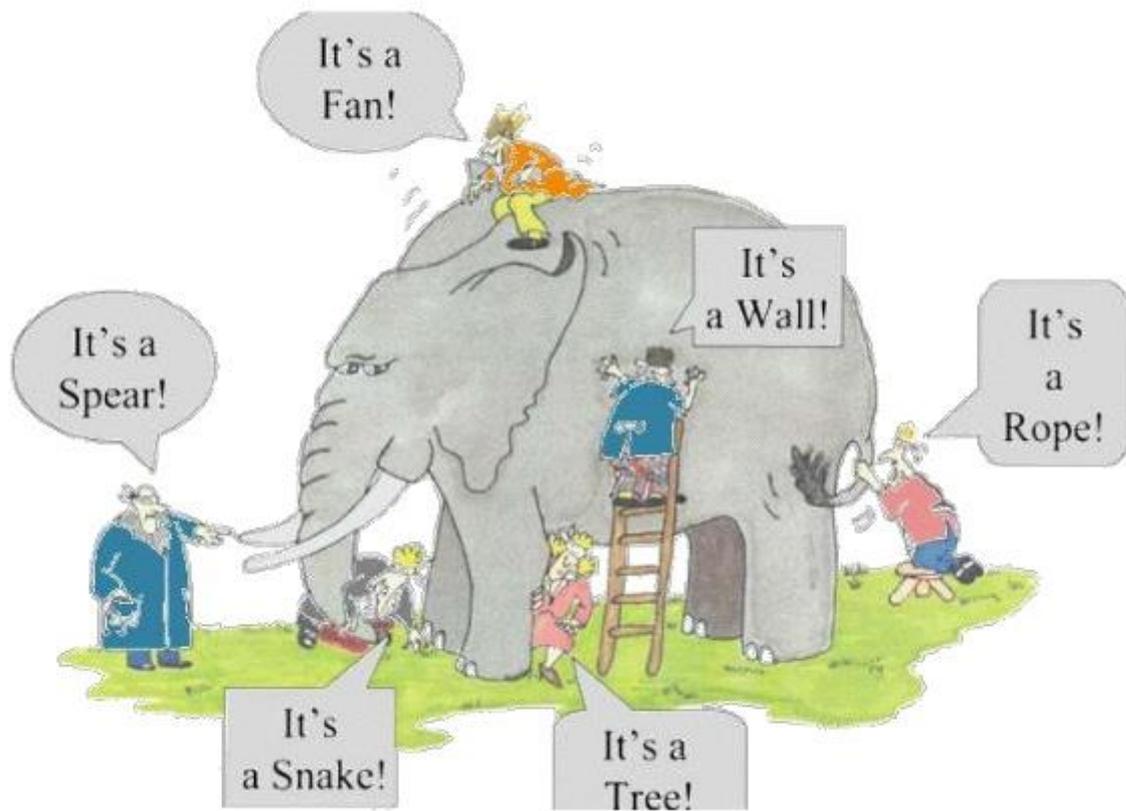
Mohammad WM et al. HPB 2012

- Investigates contemporary hepatic surgeon perceptions of resectability of CLM
- 10 scenarios ranging from a solitary, peripheral lesion to extensive bilobar involvement
- Evaluate CT images to determine if amenable to resection with or without adjunctive therapies such as radiofrequency ablation, PVE and staged resection

Evaluating agreement regarding the resectability of colorectal liver metastases: a national case-based survey of hepatic surgeons

Mohammad WM et al. HPB 2012

- Consensus only in 2 scenarios with clearly resectable and unresectable disease
- Marked divergence in opinion on the remainder of cases
- Little agreement on type and number of non-resectional adjuncts to surgery



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Conclusions

- Significant heterogeneity in approaches to patient with CLM
- Lack of randomized trials
- Rapidly changing management paradigms
- Imperative CLM patients to be evaluated in multidisciplinary setting by all surgical and oncologic specialties

Thank You



chan.chung.yip@singhealth.com.sg

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